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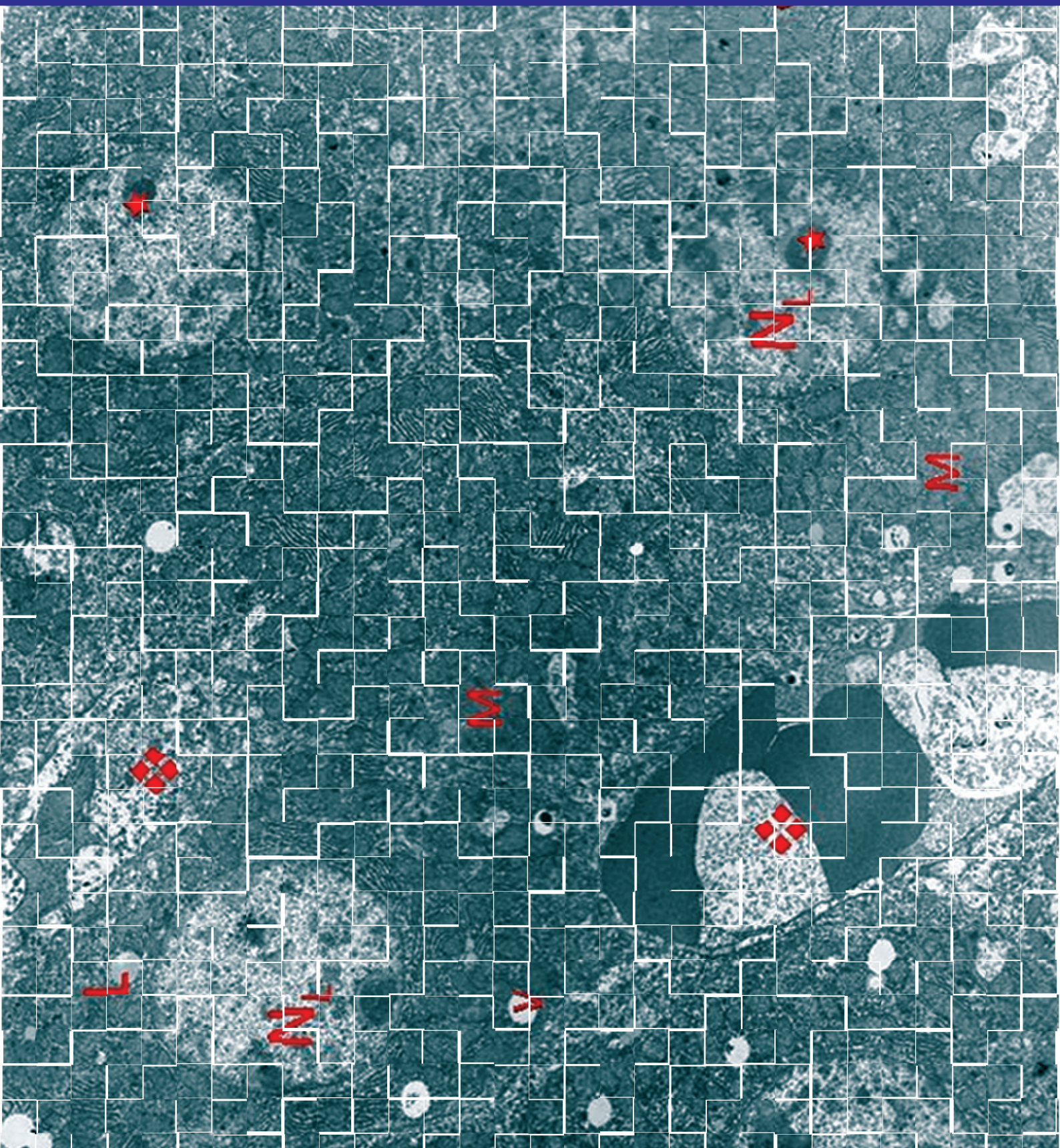

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The effects of a combined treatment of lipid emulsion and conventional therapy on tissues of rats poisoned with methyl parathion

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Abstract

Study Objective: The aim of this study was to determine the effects of a combined treatment of atropine, pralidoxime, and a lipid emulsion in rats poisoned with methyl parathion, which is an organophosphate with lipophilic properties.

Methods: A total of 21 Sprague-Dawley rats were used in the study and were divided equally into three groups. The first group was given 0.24 mg/kg methyl parathion orally, the second group was given 0.24 mg/kg methyl parathion followed by a repeated dose of 0.05 mg/kg atropine (2.2 mg total) and 40 mg/kg pralidoxime, and the third group received 0.24 mg/kg methyl parathion followed by 3 ml/kg lipid emulsion, and then this group was given the same dose of atropine and pralidoxime as was the second group. At the end of the study, tissue samples from the blood, brain, parotid gland, heart, kidney, liver, pancreas, ovary and stomach were taken for examination by electron microscopy.

Results: The rats that were treated with the lipid emulsion had a decreased expansion of glial feet involved in the structure of the blood-brain barrier when compared to the rats that were given only methyl parathion. In addition, the microvilli were preserved in the bile canaliculi and Disse's space in the rats that were treated with the lipid emulsion, while they were effaced in the other two groups. Also, the edema was not observed in the connective tissue between the pancreatic acini in the group treated with the lipid emulsion.

Conclusion: Rats poisoned with methyl parathion and treated with a lipid emulsion had a greater decrease in toxicity in the liver, brain and pancreas when compared to rats receiving only conventional therapy.

Key words: Emergency Medicine, lipid emulsion, lipophilic organophosphate

Introduction

A lipophilic compound refers to a compound that is lipid soluble.[1] There have been numerous studies published regarding the use of lipophilic agents such as verapamil, metoprolol, atenolol, bupivacaine, clomipramine, propranolol, amitriptyline, ropivacaine-lidocaine, lamotrigine, haloperidol, dothiepin, cocaine, venlafaxine-lamotrigine-diazepam and the organophosphate pesticide-paraoxon, which has been treated with a a lipid emulsion. [1-21]

The main ingredients of a lipid emulsion previously only used for parenteral nutrition, are 20% olive oil, soybean oil and egg yolk phosphatides. [22]

Organophosphates are in the sub-group of pesticides known as insecticides, which work by inhibiting the phosphorylation of acetylcholinesterase. This leads to an increase in acetylcholine levels in both muscarinic and nicotinic cholinergic receptors. [3,23-25]

Parathion is a commonly studied organophosphate. The highest levels of parathion have been detected in the salivary glands and in the cervical brown adipose tissue, which is also known as the hibernation gland. Parathion has also been found to be highly absorbed in organs such as the kidneys, liver, and adipose tissue, while the stomach and spleen have been reported to have the highest parathion activity. [23,26]

Clinical toxicologists have recently focused on the use of lipid emulsions to treat poisoning by li-

pophilic agents. The aim of this study was to determine the effects of a combined treatment of atropine, pralidoxime, and a lipid emulsion in rats poisoned with the lipophilic agent methyl parathion.

Materials and Methods

This study was approved by the Medical and Health Sciences Research Ethics Committee of Baskent University and was supported by the Baskent University Research Fund. All of the animals used in this study were obtained from Baskent University Experimental Animal Production and Research Center laboratory, and all of the experiments were carried out at the same center. More than one researcher observed and recorded the rats' fasciculation, convulsions, respiratory arrest, exitus, and clinical symptoms.

A total of 21 female albino Sprague-Dawley rats with average body weight of 250 grams were included in the study. All rats undergoing treatment were placed into separate cages. Intravenous (IV) access was first attempted with a 20G, 32 mm cannula. In rats where this did not work, a 22G, 25 mm cannula was used to gain vascular access. All IV lines were fixed with a patch. Rats with attached IV lines were placed into prepared separate cages on the laboratory bench. None of the rats were deprived of food and water.

The 21 rats included in the study were equally divided into three groups. The first group was assigned as a control group, and rats in this group were given 0.24mg/kg methyl parathion via intragastric gavage. The rats in the second group were given 0.24mg/kg methyl parathion, followed by treatment with 40mg/kg pralidoxime and 44 doses of 0.05mg/kg atropine over a 12 hour period.[27] The rats in the third group were given 0.24mg/kg methyl parathion, and then were treated with 3 ml/kg 20% lipid emulsion, which was immediately followed by the same dose of atropine and pralidoxime as the second group.

For all groups, the drugs were administered to the rats intravenously via the tail vein for the first 30 minutes of treatment, and later, the treatment was continued intraperitoneally.

Six mg/kg xylazine and 60mg/kg ketamine were administered prior to sacrificing. After the anesthesia, approximately 5 cc of blood was obtained from each rat by cardiac puncture. Blood samples were centrifuged for 10 minutes at 4000 rev/min, stored at 2-8 °C and were analyzed in the biochemistry laboratory within 12 hours.

Pseudocholinesterase enzyme activity was analyzed on the Roche Hitachi 912 analyzer (Roche Diagnostics, Mannheim, Germany) using the Roche cholinesterase kit (ChE, EC 3.1.1.8). Tissue samples from the brain, parotid gland, heart, kidney, liver, pancreas, ovary, and stomach were examined by electron microscopy. Tissues were stored in phosphate-buffered 2% glutaraldehyde solution (pH 7.4) prior to the examination. Thin sections (70-90 nm) were stained with uranyl acetate and lead citrate, and they were evaluated and photographed with a Carl Zeiss LEO 906E (Carl Zeiss Meditec, Oberkochen, Germany) transmission electron microscope.[28,29]

The SPSS 18.0 software program was used for statistical analysis. The descriptive statistics for pseudocholinesterase levels are presented as mean and standard deviation. The Kruskal-Wallis test was used to analyze the differences in pseudocholinesterase levels between the three groups. P values less than 0.05 were considered to be statistically significant. The Mann-Whitney U test was used for analyses between the groups. In addition, the Fisher's exact test was used to analyze the differences in the 8 symptoms that were observed between the groups.

Results

Table 1 summarizes the dose of each agent that was applied to the rats, the duration of their application, and the methods by which they were applied. Comparisons of the clinical findings that were observed in the rats are shown in Table 2. The measured pseudocholinesterase levels and the comparisons of these levels between the groups are shown in Table 3. The histopathological findings of the tissue samples are in summarized in Table 4.

Table 1. Agent, dose, duration of application, and application method

Duration	Methyl parathion 0.24 mg/kg	Atropine 0.05 mg/kg	Pralidoxime 40 mg/kg/day	Lipid Emulsion 3 ml/kg
0 min via gavage	+			
*15th min IV		+	+	+
15 –30 min IV 30-60 min IP 1 time/every 3 min		+		
60th min – 4th hour IP 1 time/every 15 min		+		
4th – 8th hour IP 1 time/every 30 min		+		
8th – 12th hour IP 1 time/every 60 min		+		

Application sequence: lipid emulsion, pralidoxime, atropine

Table 2. Comparison of the clinical findings observed in rats

Group (n=7)	Pollakiuria (n)	Hematuria (n)	Irritability (n)	Reduced response (n)	Changes in breathing pattern (n)	Tremor (n)	Difficulty in walking (n)	Big red eyes (n)
1	-	-	-	1	1	1	-	-
2	6	3	2	-	1	4	1	4
3	3	-	4	1	-	-	-	-

Table 3. Pseudocholinesterase levels and their comparisons between the groups

	Group 1	Group 2	Group 3	P
Pseudocholinesterase levels (U/L)	945.4±180.9 (678 – 1188)	1165.4±178.5 (937 – 1414)	907.6±334.7 (312 – 1262)	0.152 G1-2: p=0.064 G1-3: p=0.949 G2-3: p=0.142

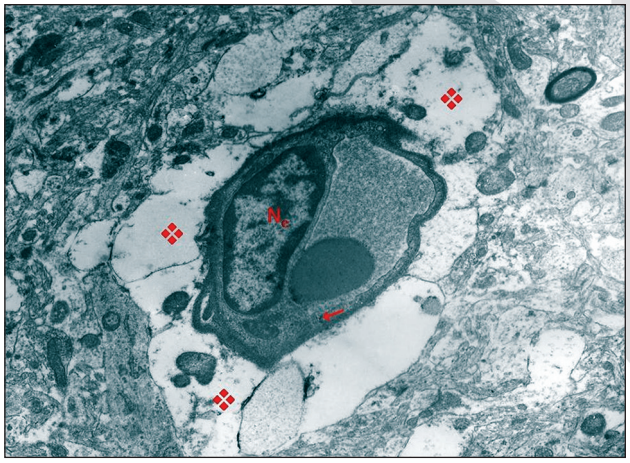

Figure 1. The brain tissue and the blood-brain barrier from the second group (Methyl parathion + Atropine - Pralidoxime Group): The vascular endothelial cell nucleus (N_c), the connection between the cells (→), the expansion in the glial feet (❖) (uranyl acetate - lead citrate X 6000).

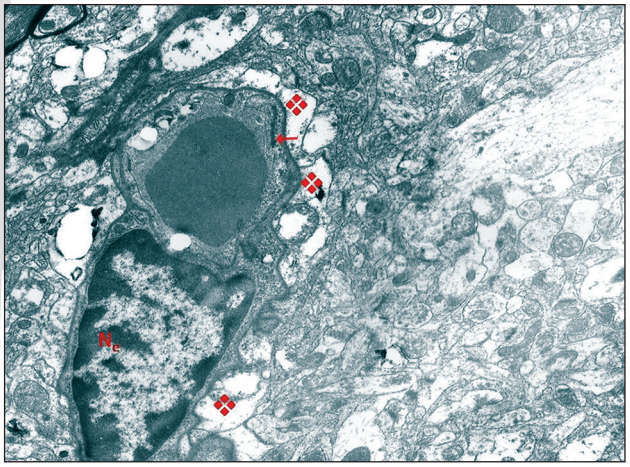

Figure 2. The brain tissue and the blood-brain barrier from the third group (Methyl parathion + Atropine - Pralidoxime + Lipid Emulsion Group): The vascular endothelial cell nucleus (N_c), the connection between the cells (→), the expansion in the glial feet (❖) (uranyl acetate - lead citrate X 6000).

Table 4. Histopathological findings of the tissues

	MP (Group 1)	MP + atropine-PAM (Group 2)	MP + atropine –PAM +Lipid emulsion (Group 3)
Heart	-Myofibrils effaced -Mitochondrial fusion -Formation of giant mitochondria -Significant fluid accumulation in the cytoplasm of the cell	- Myofibrils effaced - Mitochondrial fusion - Formation of giant mitochondria **-Suppression of fluid accumulation in the cytoplasm of the cell**	- Myofibrils effaced - Mitochondrial fusion - Formation of giant mitochondria - Significant fluid accumulation in the cytoplasm of the cell
Brain	-Significant expansion of glial feet at the blood-brain barrier	- Significant expansion of glial feet at the blood-brain barrier (Figure 1)	-**A significant decrease in the blood-brain barrier glial feet expansion** (Figure 2)
Kidney	-Damage in the structure of glomerular endothelium -Degeneration of the cells forming tubules -Loss of continuity of the structure of the basement membrane -Degeneration of pedicel pattern	-**The normal structure was preserved throughout the glomerular basement membrane** -**Pedicels pattern was more regular**	-**Normal pedicel pattern was preserved** -**Natural structure of tubules were relatively protected**
Liver	- Significant expansion of the bile canaliculi -Expansion in the Disse's space -Significant effacement of microvilli	-**Bile canaliculi and Disse's space are narrower** -Microvillus structure cannot be distinguished (Figure 3)	-**Bile canaliculi and Disse's space are narrower** -**Hepatocyte microvilli are prominent** -Lipid droplets and vacuoles in the cytoplasm of the cell (Figure 4)
Parotid	-Expansion in the lumen of the secretory duct -Significant effacement of microvilli on the apical side of the cells	-**The lumen in the secretory channel is narrow** -**Microvilli are preserved in the upper side of the cell**	-Expansion in the lumen of the secretory duct - Significant effacement of microvilli
Pancreas	-Liquid build up in the cytoplasm of the cell -Prominent edema in the connective tissue between the acini -Karyolysis in the centroacinar cell nucleus	-**No evidence of degeneration except for a few vacuoles in the cytoplasm of the cell** -**Edema of connective tissue between the acini smaller than in group 1** -**The centroacinar cell nucleus at the lumen of acini has normal cellular features** (Figure 5)	-Prominent vacuolization in the cytoplasm of acinar cell -**No edema at the connective tissue between the acini** (Figure 6)
Stomach	-Expansion of the GER tubuli from place to place -Eosinophils in connective tissue	- Expansion of the GER tubuli from place to place - Eosinophils in connective tissue -Vacuolization from place to place	- Eosinophils in connective tissue - Autophagic vacuoles containing degenerative connective tissue cells
Ovary	-Interruption in connections between granulosa cells and zona pellucida -Some vacuoles in the granulosa cells -Large number of lipid droplets in cytoplasm of theca interna cells	-Oocyte cytoplasm richer than granular endoplasmic reticulum -More common vacuolization in granulosa cells -Fragmentation of lipid droplets in cytoplasm of theca interna cells	-Overall structure of primary follicles more protected than in other groups - Nucleoli in granulosa cells at the cell division stage

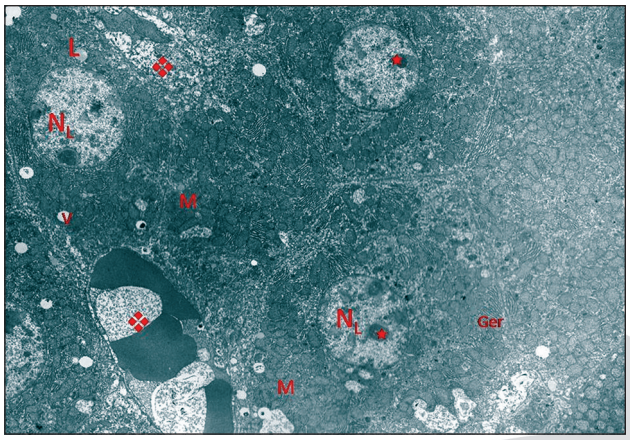

Figure 3. Liver tissue section from the second group (Methyl parathion + Atropine - Pralidoxime Group): Hepatocyte nuclei (N_L) are seen as prominent nuclei (★) structures. Dense matrix mitochondria (M), GER tubuli (GER), vacuoles (v), and lipid droplets (L) are seen in the cytoplasm of the cell. The cytoplasmic granular appearance can be distinguished in the enlarged sinusoidal lumen (uranyl acetate-lead citrate X 1670).

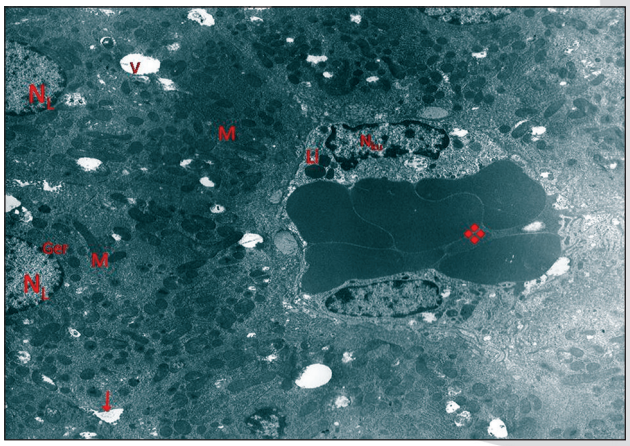

Figure 4. Liver tissue section from the third group (Methyl parathion + Atropine - Pralidoxime + Lipid Emulsion Group): Magnification of hepatocyte nuclei (N_L). Dense matrix mitochondria (M), GER tubuli (GER), vacuoles (v), and lipid droplets (L) are seen in the cytoplasm of the cell. The microvilli are seen in the normal structured bile cananiculi (→) located in the intercellular area. Lysosomes can be seen in the Kuppfer cells in the sinusoidal lumen and erythrocyte stasis (❖) is distinctive (uranyl acetate-lead citrate X 1670).

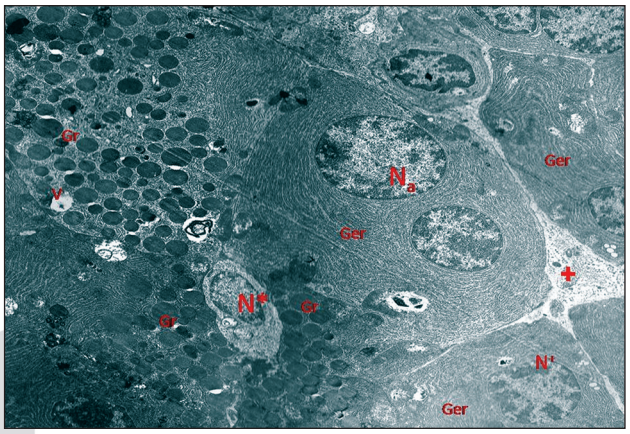

Figure 5. Pancreatic acini thin section from the second group (Methyl parathion + Atropine - Pralidoxime Group): Acinar wall euchromatin rich cell nucleus (Na), active GER tubuli (GER), secretory granules (Gr) and vacuoles (V) covering the cytoplasm are observed. The normally structured centroacinar cell nucleus (N) is seen in the lumen of the acini. Distinctive edema (+) in the connective tissue surrounding the acinus (uranyl acetate - lead citrate X 2784)*

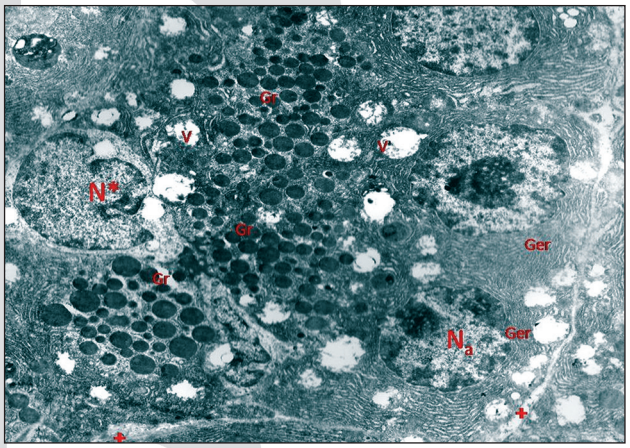

Figure 6. Pancreatic acini thin section from the third group (Methyl parathion + Atropine - Pralidoxime Group + Lipid Emulsion): The cell nucleus (Na) forming the acinus, GER tubuli (GER), secretory granules (Gr) and vacuoles (V) covering the cytoplasm are seen. The centroacinar cell nucleus (N) is seen in the lumen of the acini. The edema (+) in the connective tissue surrounding the acini is more prominent as compared to other groups (Uranyl Acetate - Lead Citrate X 2784).*

Discussion

Lipid emulsions are widely used as nutritional solvents. The effects of lipid emulsions on lipo-

philic substance poisoning have been reported in recent studies. [2-21] Lipophilic substances are eliminated from the circulation via "lipid sinking" in intravenous lipid emulsions. [30]

Organophosphates increase acetylcholine in muscarinic-nicotinic cholinergic receptors. [23-25] Methyl parathion is a lipophilic organophosphate that acts in this way. [31]

The histopathological effects of organophosphates on tissues from several organs have been reported. Kalender et al. reported that 7 weeks of diazinon administration (a synthetic organophosphate) resulted in unusual swelling of the mitochondria, mild swelling in the endoplasmic reticulum, separation of the mitochondrial cristae, and deterioration of the homogeneity of the chromatin density in the nucleus. [32] Kerem et al. reported swelling, vacuolization and central lobular damage (seen with light microscopy) in the hepatocytes of rats given 75 or 100 mg/kg fenthion after 24 hours. [33] Another study by Tos-Luty et al. reported thin subcapsular infiltrations in the liver, degeneration of diffused parenchymatous in single hepatocytes, lipid vacuoles and swelling of the mitochondria in rats given oral malathion. [34] Furthermore, Ulusoy et al. administered 15mg/kg/day diazinon in corn oil to rats for a total of 5 weeks and evaluated the hepatocytes with electron microscopy. There were no pathological changes 1 week after the administration, but they observed pyknotic nucleus, swelling of the mitochondria and vacuolization by the end of the 5th week. [35] In our study, the group that was treated with the lipid emulsion had less mitochondrial distribution in the hepatocytes as compared to the other groups. In addition, the group receiving the lipid emulsion also had narrower bile canaliculi and Disse's space. They also had prominent microvilli in those areas of the hepatocytes, while in the other groups, the microvilli were effaced. All of these observations suggest that the lipid emulsion had positive effects.

Yurumez et al. and İkizceli et al. detected (by light microscopy) edema, inflammation, vacuolization and necrosis in the pancreatic tissue of rats given 0.8 gr/kg fenthion. [36,37] Goodale et al. detected ultrastructural changes, such as zymogen granules, in the pancreatic acinar cells of rats poisoned with diazinon. [38] In our study, the group treated with the lipid emulsion had significant vacuolization, although edema was not detected. Therefore, we suggest that the lipid emulsion was effective in the treatment of edema in the connective tissue between the pancreatic acini due to organophosphate poisoning.

Finkelstein et al. evaluated the brain tissue of rats that were administered the organophosphate compound soman and found that there was serious damage in the amygdala, thalamus, and hippocampus, as well as massive neuronal loss in the piriform cortex. They also reported that there was a significant neuronal loss in the piriform cortex in the brain tissue of rats given a less neurotoxic organophosphate compound (paraoxon). [39] A study by Grange-Messent confirmed that soman alters the integrity of the blood-brain barrier. [40] In our study, we detected an accumulation of intracellular fluid that resulted in the significant expansion of the glial feet that are involved in the structure of the blood-brain barrier in rats that were treated with conventional therapy after methyl parathion poisoning. However, there was a significant reduction in the expansion of glial feet in the group that was treated with the lipid emulsion, which suggests that the lipid emulsion protects the blood-brain barrier.

Weinberg et al. administered 3 ml/kg/min lipid emulsions via infusion with a right internal jugular catheter to rats under general anesthesia that were poisoned with bupivacaine, another lipophilic substance. [30] The total duration of the treatment was 5 minutes, and they were able to obtain positive results. [30] We applied the same dose, but administered it peripherally. Bania et al. administered a lipid emulsion intraperitoneally into mice after a lethal dose of 15 ml/kg paraoxon. They reported that it did not have any effect on their survival. [20]

The measurement of serum cholinesterase levels is one of the parameters that helps with the diagnosis of organophosphate poisoning and is suggested to have at least some prognostic value. [24] Abdullat et al. evaluated symptomatic patients that had been exposed to acetylcholinesterase inhibitor insecticides. They reported that the butyrylcholinesterase activity in these patients increased significantly 2-4 hours after oxime treatment, and that this increase was accompanied with improvement in their clinical symptoms and other findings. [41] However, Nouri et al. state that cholinesterase levels are to be considered only as a marker of intoxication. [42] Na Jiang et al. and Yuan Du et

al. reported that they could achieve significant inhibition in rats with a single dose of intragastric 15 mg/kg methyl parathion. [43,44] In another study, rats were divided into three groups as follows: a control group that was not treated with any organophosphate, a toxic group that was administered 0.12 mg/kg methyl parathion, and a therapy group that was administered 0.12 mg/kg methyl parathion and was treated with conventional therapy. In that study, doses were administered based on the modified Ellman method and pseudocholinesterase levels were measured. The pseudocholinesterase level was 638 U/ml in the control rats that were not poisoned and was 210 U/ml in rats from the toxic group. In the group that was treated with conventional therapy, the pseudocholinesterase level was 287 U/ml after 24 hours of treatment and was 284 U/ml after 96 hours of treatment. In addition, different results were obtained with light microscopy between the groups mentioned above. [27] In the study by Yuan Du et al., the pseudocholinesterase level was 13,980 ± 4080 U/L in rats that were administered a single lethal intragastric dose of 15 mg/kg methyl parathion after 24 hours. [44] In our study, none of the treatment groups were able to reach such a high pseudocholinesterase level. This might be because the treatment duration was limited to 12 hours and the rats were administered a nonlethal toxic dose in our study.

When our clinical findings were evaluated, the most unexpected result was that there was a significant hematuria in three rats from the conventional treatment group. This may be due to the influence of the drugs and should be evaluated in further studies. The rats were extremely agitated during the application of the lipid emulsion, which we interpreted as irritation in the vascular way. In contrast to the study by Yürümez et al., our subjects did not receive a lethal dose of methyl parathion. Therefore, we did not observe cardiac arrest, respiratory failure, convulsions, diarrhea, loss of consciousness or fasciculation. [45]

One limitation of our study is that we did not determine pseudocholinesterase levels in healthy rats. Other limitations may be that the rats were exposed to a single toxic dose of methyl parathion and the treatment duration was only 12 hours.

Conclusion

An application of lipid emulsion prior to atropine-pralidoxime treatment in cases with organophosphate poisoning could have a preventive effect on toxicity in the liver, brain, and pancreatic tissue. However, further studies using non-peripheral vascular ways and a lethal dose of organophosphates are needed to explain those characteristics of the lipid emulsion.

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Body mass index, blood pressure and arteriography variables in a middle and aged population

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Abstract

Objectives: To explore the influence of body mass index and its interaction with blood pressure, on endothelial function, arterial stiffness, coronary blood flow and arterial age.

Methods: A total of 108 middle and aged patients, with normal, high normal blood pressure, and hypertension underwent arteriography. Endothelial function, arterial stiffness, coronary blood flow and arterial age were assessed.

Results: Body mass index (BMI), brachial augmentation index (Aix brach), pulse wave velocity (PWV), diastolic reflection area (DRA), diastolic area index (DAI) and arterial age (AA) were: 27±5.3 kg/m^2, -35±28 %, 8.55±1.94 m/s, 52±14, 51±5.48% and 43±16 years, respectively. Significant correlations and associations were found between BMI and arteriography variables. A negative interaction was found between elevated blood pressure and body mass index (BMI) on endothelial function, coronary perfusion, vascular age and arterial stiffness (synergy index: 0.703, 0.815, 0.651 and 0.582, respectively).

Conclusions: Overweight and obesity predict endothelial dysfunction, arterial stiffness, impaired coronary perfusion and early arterial aging in patients with normal and high normal blood pressure, grade 1 and 2 hypertension. Elevated BMI and blood pressure have less than additive effects on endothelial dysfunction, arterial stiffness, early vascular aging and coronary perfusion.

Key words: Arteriography, Body mass index, Blood pressure, Early vascular aging.

Introduction

Obesity, a complex condition of excessive fat accumulation, is a major public health problem, affecting children and adults in developing and developed countries (1, 2). In Europe, more than half of the population is overweight or obese. For both women and men aged 18 years and over, the prevalence of obesity in Romania in 2008/2009 was 8% and 7.6%, respectively, according to Eurostat statistics from November 2011 and continues to grow. Obesity has reached epidemic proportions and overwhelming evidence support the importance of obesity in the pathophysiology of chronic diseases, especially cardiovascular diseases (3).

Cardiovascular pathology, the leading cause of mortality in developed countries, is linked to atherosclerosis and its complications, very often after a long latency time (4). Arterial stiffness and endothelial dysfunction are markers of subclinical atherosclerosis and cardiovascular risk. Arterial age is a useful clinical tool for the investigation and guidance of individuals at increased cardiovascular risk, especially those with marginal elevation of classic risk factors (5, 6). Arteriography is considered an objective, noninvasive, availabil, portable, operator-independent, reproducible and convenient oscillometric method for early diagnosis and follow-up of atherosclerosis (7). It enables measurement of aortic pulse wave velocity (PWV), the speed at which the waveforms travel along the aorta and large arteries. PWV has a better predictive value for cardiovascular events than the classical risk factors, because it reflects the cumulative effect of cardiovascular risk factors (8, 9). Arteriography enables also measurement of augmentation indices (markers of endothelial dysfunction) and central blood pressure, reflecting different pathophysiological aspects of vascular damage. Assessing the mentioned parameters of vascular structure and function can improve risk stratification (9).

Obesity-related increase in cardiovascular risk is a multifactorial process, involving metabolic factors, activation of renin – angiotensin and sympathe-

tic nervous system, endothelial dysfunction, oxidative stress, inflammation, renal dysfunction and obstructive sleep apnea (10). Obesity accelerates the progression of atherosclerosis via dyslipidemia, is associated with metabolic syndrome, hypertension, coronary heart disease, left ventricular hypertrophy, systolic and diastolic dysfunction, heart failure, left atrial enlargement, atrial fibrillation and complex ventricular arrhythmias (1, 3, 10, 11, 12).

In light of the worldwide obesity epidemic and high cardiovascular morbidity and mortality, prophylactic measures must be given special attention and they should begin as soon as possible. Prevention and treatment of obesity could represent a cornerstone for the prevention of cardiovascular disease (12). It is of great clinical interest to have noninvasive methods and functional markers, which may detect vascular injury in the subclinical phase, as endothelial dysfunction and during the first histological changes (13).

The objectives of the present study were to explore the influence of body mass index, and its interaction with blood pressure, on endothelial function, arterial stiffness, coronary blood flow and arterial age, respectively.

Methods

Selection and description of the participants

A total of 108 consecutive patients from a family medicine practice, from Timisoara, Romania, were included in the study.

Patients with diabetes mellitus, atrial fibrillation, history of major cardiovascular events (stroke, myocardial infarction), peripheral artery disease, cholesterol lowering, antihypertensive, antipsychotic or vasoactive medication use, malignant diseases, psychiatric illnesses, as well as bed-ridden and disabled wheelchair individuals were not included in the study.

Ethical approvals

The investigations conformed to the principles of the Declaration of Helsinki (14) and were approved by the Ethics Committee of the "Victor Babes" University. Each patient was informed about the nature of the study and a written consent was obtained.

Arteriography

Arteriography was performed by the authors using a noninvasive automated oscillometric analyzer (TensioMed Ltd, Budapest, Hungary). The same device was used for all tests. Systolic and diastolic blood pressure, mean arterial pressure, brachial and aortic augmentation index (Aix brach and Aix ao, respectively), aortic pulse wave velocity (PWV), the diastolic reflection area (DRA), diastolic and systolic area index (DAI and SAI), and arterial age (AA) were assessed (5).

Measurements were made after 10 minutes rest, using an appropriate upper arm cuff considering the arm circumferences, in supine position, with extended arms, in a quiet room, with normal temperature (22±1 °C). The participants were previously asked not to smoke, eat or drink coffee or alcohol 4 hours before arteriography, to keep their eyes closed and to do not move or speak during the recording (5).

Arterial stiffness was considered if the pulse wave velocity >10 m/s, and endothelial dysfunction if the brachial augmentation index >-10%. Early vascular aging (EAA) was associated with a vascular age which was higher than the chronological age (5). Accelerated vascular aging was defined by a difference between biological and arterial age > 10 year). If automatic quality control showed less than 1 standard deviation for aortic PWV, the recording was considered valid.

Anthropometric measurements

Body weight was measured in kilogram, while subjects were dressed in light clothing (to the nearest 0.1 kg) (15), using a balance scale. A wall mounted stadiometer was used to measure height, to the nearest 0.5 cm (15). Body mass index (BMI) was calculated using the Quetelet index, dividing the weight (kg) by the height squared (m^2).

The BMI cut off values for overweight and obesity were: ≥25 kg/m^2 and ≥30 kg/m^2, respectively.

Statistical methods

Categorical variables are given as numbers (frequency) and percentages, continuous data are given as means ± standard deviation. Linear and multiple regression analysis, Bravais-Pearson correlations and synergy index were used as statistical methods. For all studies, $p<0.05$ was considered statistically significant.

Sample size

A power analysis was conducted to determine the number of participants needed in the present study and the minimum sample size required for regression analysis was 54 (16) and 30 for Bravais Pearson correlations (r = 0.5, one-tailed probability = 0.0024, two-tailed probability = 0.0048).

Results

Table 1. Characteristics of the study population and arteriography variables

Variable	Reference range (Means±SD) or N(%)
Chronological age	44±16 years
Gender (Male)	71 (65%)
Positive cardiovascular family history	26 (24%)
Current smokers	45 (42%)
Regular physical activity	13 (12%)
Body mass index	27±5.3 kg/m^2
Overweight	39 (36%)
Obese	26 (24%)
Systolic blood pressure	126±15 mmHg
Diastolic blood pressure	76±10 mmHg
Systolic blood pressure in the aorta	119±17 mmHg
Optimal blood pressure	39 (36%)
Normal blood pressure	25 (23%)
High normal blood pressure	22 (20%)
Grade 1 hypertension	14 (13%)
Grade 2 hypertension	8 (8%)
Pulse pressure	50±11 mmHg
Pulse pressure in the aorta	42±14 mmHg
Mean arterial pressure	93±11 mmHg
Heart rate	73±11 beats/minute
Brachial augmentation index (Aix brach)	-35±28%
Aix brach > -10%	23 (21%)
Aortic augmentation index (Aix ao)	20±14%
Pulse wave velocity (PWV)	8.55±1.94 m/s
DRA (diastolic reflection area)	52±14
DRA<50	52 (48%)
DAI (diastolic area index)	51±5.48%
DAI<50%	50 (46%)
PWV>9.7 m/s	82 (76%)
Arterial age	43±16 years
Difference between arterial and biological age (Dif AA)	7.63±9.43 years
Early arterial aging (%)	61 (56%)

The characteristics of the study population and arteriography variables are included in table 1. Aix brach, PWV, DRA, DAI and AA were: -35±28 %, 8.55±1.94 m/s, 52±14, 51±5.48% and 43±16 years, respectively.

Correlations

Significant correlations were found between BMI and the following arteriography variables: Aix brach and Aix ao, systolic blood pressure in the aorta, pulse pressure in the aorta, PWV and arterial age (AA) (table 2).

Table 2. Correlations between body mass index (BMI) and arteriography variables

Correlations of BMI with:	r (p)
Aix brach	0.268 (0.0025)
SBP ao	0.388 (<0.001)
PP ao	0.344 (<0.001)
Aix ao	0,278 (0.0017)
PWV	0.295 (<0.001)
AA	0.335 (<0.001)

Aix brach = brachial augmentation index, Aix ao = aortic augmentation index, SBP ao = systolic blood pressure in the aorta, PP ao = pulse pressure in the aorta, AA = arterial age, PWV = pulse wave velocity, r = Bravais-Pearson correlations coefficient

Regression analysis

Linear regression analysis revealed significant associations between BMI and the difference between chronological and arterial age, and accelerated arterial aging, respectively (table 3). Stepwise multiple regression analysis showed significant associations between BMI and systolic and diastolic blood pressure, mean arterial pressure and pulse pressure, systolic blood pressure and pulse pressure in the aorta, and arterial age and DAI, respectively (table 3).

Synergy index

Elevated blood pressure (high normal blood pressure and hypertension) and increased body mass index (overweight and obesity) impair endothelial function (Aix brach < -10%), but their effect is not synergistic (table 4). No additive effect was detected for elevated blood pressure and BMI on coronary perfusion, as well (table 4).

Hypertension, overweight and obesity have no additive effects on arterial age and arterial stiffness, respectively (table 4).

Table 3. Linear and multiple regression analysis. Factors significantly associated with the body mass index (BMI)

Variables associated with BMI	Multiple R	R square	Adjusted R	Significance F
SBP (p<0.01) **DBP** (p<0.01)	0.982	0.965	0.956	<0.01
PP (p = 0.008) **MAP** (p<0.01)	0.982	0.965	0.955	<0.01
SBP ao (p<0.01) **PP ao** (p<0.01)	0.982	0.964	0.955	<0.01
AA (p<0.01) **DAI** (p<0.01)	0.984	0.967	0.957	<0.01
Dif AA (p<0.01)	0.614	0.377	0.367	<0.01
AAA (p<0.01)	0.542	0.294	0.284	<0.01

Multiple R = multiple correlation coefficient, R square = coefficient of determination, Adjusted R = the coefficient of determination adjusted for the number of independent variables in the regression model, SBP = systolic blood pressure, DBP = diastolic blood pressure, PP = pulse pressure, MAP = mean arterial pressure, SBP ao = systolic blood pressure in the aorta, PP ao = pulse pressure in the aorta, AA = arterial age, DAI = diastolic area index, Dif AA = the difference between arterial and biological age, AAA = accelerated arterial aging (the difference between arterial and biological age > 10 years) (dichotomous variable).

Table 4. Negative interaction between elevated blood pressure and body mass index (BMI) on endothelial dysfunction, coronary perfusion, early vascular aging and arterial stiffness

Patients with	Effect on	AR1	AR2	Synergy index
1. BMI≥25 kg/m^2 2. SBP>130 mmHg and DBP>85 mmHg	Endothelial dysfunction	0.067	0.024	0.703
1. BMI≥25 kg/m^2 2. SBP>130 mmHg and DBP>85 mmHg	Coronary perfusion	0.072	0.101	0.815
1. BMI≥25 kg/m^2 2. Hypertension	Early vascular aging	0.068	0.107	0.651
1. BMI≥25 kg/m^2 2. Hypertension	Arterial stiffness	0.033	0.271	0.582

SBP = systolic blood pressure, DBP = diastolic blood pressure, AR = attributable risk

Discussion

The most important findings of the present study are the associations between body mass index and endothelial function, arterial stiffness, coronary perfusion and early arterial aging. Elevated BMI and blood pressure do not have additive effects on endothelial function, pulse wave velocity, arterial aging and coronary perfusion.

Obesity has been previously associated with increased arterial stiffness, endothelial dysfunction, early vascular aging and remodeling of large arteries (1, 10, 17, 18, 19). Kudo et. al. reported an increase of PWV and systolic blood pressure with increased BMI in teenage girls (11), and Miyai et. al. suggested that obesity and its associated metabolic abnormalities are important factors in the increased brachial-ankle pulse wave velocity of

adolescents (20). The onset of changes in arterial elasticity occurs sooner in obese children than in those with dyslipidemia (13). BMI, systolic blood pressure and triglycerides were significantly correlated with arterial stiffness indices, measured using high-resolution ultrasound, in a study published by Nunez et. al., indicating adiposity as trigger of vascular injury (13). Pena et al demonstrated similar degrees of vascular dysfunction in children with mild to moderate degrees of obesity and type 1 diabetes mellitus, using flow-mediated dilatation, and suggested that total cholesterol and inflammation have an important role in vascular dysfunction in obesity (17). Visceral fat is a stronger predictor of aortic stiffness than general obesity (2), which may explain the weak correlation between BMI and aortic PWV obtained in the present study. Body fat measures were among the strongest independent predictors of aortic stiffness in a study including young and older African Americans, and the strength of the association indicated that excess weight begins to affect the vascular system at a very early stage of vascular aging (19).

Weight loss is associated with a "destiffening" in overweight or obese young adults, independent of cardiometabolic and hemodynamic factors and common carotid artery geometry (21). Weight loss causes a reduction in brachial augmentation index, as well, associated by concurrent changes in heart rate and inflammatory status (21).

The relation between BMI and arterial stiffness is still controversial, considering that several studies did not find significant associations between BMI and arterial stiffness (6, 22). The explanation is based on differences in statistical methodology and characteristics of study populations. Most previous studies were conducted among diseased populations, and the present study, on Romanian, apparently healthy subjects, with few comorbidities, adds valuable information in evaluating the impact of general obesity on arterial stiffness.

Aortic stiffness has independent predictive value for fatal and nonfatal cardiovascular events in hypertensive patients (23) and is positively associated with systolic hypertension (9), but arterial distensibility may be impaired in the early stage of hypertension, as well. Sympathetic overactivity, structural changes in the vascular wall (inflammation, degradation of elastin by metalloproteinases, growth of vascular muscle, fibrosis) and endothelial dysfunction are involved in the development of arterial stiffness in hypertensive patients (9, 18, 24). Insulin resistance, stimulation of the sympathetic nervous system, promotion of smooth muscle cell growth, glycation of the proteins in the arterial wall, low grade inflammation and increased leptin levels are the main mechanisms by which obesity might contribute to aortic stiffening (19).

Obesity is the most important risk factor for the development of hypertension; obesity-related hypertension is very prevalent and affects the response to antihypertensive therapy (10, 25). The mechanisms are: hemodynamic (increased plasma volume and cardiac output), increased vascular peripheral resistance (due to increased sympathetic nervous system and renin-angiotensin-aldosterone system activity), increased insulin level and resistance (insulin stimulates the sympathetic nervous system and sodium retention in the kidney), decrease in natriuretic peptides and impaired pressure natriuresis, obstructive sleep apnea (stimulates the sympathetic nervous system), endothelial dysfunction (blunting of physiological vasodilatation), a low grade systemic inflammatory state, fatty acid metabolism and the secretory products of adipocytes (hormones, growth factors and cytokines) (2, 3, 10, 12, 25, 26). The link between obesity and hypertension is bidirectional: obese subjects are prone to hypertension and hypertensive subjects appear to be prone to weight gain, especially when there is genetically susceptibility (2, 10). Obesity that develops without genetic predisposition is related to blood pressure components but not to parameters of arterial compliance (2).

Obesity was also mentioned as a risk factor for the development of cardiac, vascular and renal subclinical target organ damage. Epicardial fat could play a direct functional and mechanical role in obesity-related left ventricular abnormalities (10).

Obesity is a risk factor for coronary heart disease, as well. The mechanisms by which obesity leads to atherosclerotic coronary artery disease include: the association of obesity with several other risk factors for atherosclerosis (insulin resistance, type 2 diabetes mellitus), atherogenic dyslipidemia (high triglycerides, low HDL cholesterol), adipokines generated by the adipose tissue, inflammation, oxidative stress, hypertension, the

imbalance between oxygen demand and supply (due to left ventricular hypertrophy: an adaptative change, appearing even in the absence of hypertension and coronary vasoconstriction due to the activation of the renin-angiotensin-aldosterone and sympathetic nervous system) (1, 12). Both increased BMI and waist circumference were associated with coronary vasoreactivity in overweight and obese men (27). A reduction of agonist-induced coronary dilations was mentioned in obese patients (28). Acute coronary syndromes are triggered by the rupture or erosion of the atheromatous plaque, with subsequent thrombus formation (1). Recent data have also shown an obesity paradox, considering that the mortality is lower in overweight and obese, compared to underweight and normal-weight patients with coronary heart disease, which means a cardioprotective effect of obesity (3). Impaired coronary perfusion, detected by decreased DAI and DRA was noticed in obese and overweight participants, in the present study. Obesity was previously mentioned as an independent predictor of coronary artery disease (10), and arteriography could serve as a screening tool for coronary involvement in patients with an elevated BMI. Greater arterial stiffness can lead to increased cardiac afterload, impaired coronary blood flow and increased arterial wall stress (22). Significant negative correlations were found in the present study between PWV and DAI ($r = -0.291$) and DRA ($r = -0.403$), respectively.

Endothelial dysfunction is an early event in atherogenesis, a vasoconstrictive, growth-promoting, procoagulant and proinflammatory state (26). It is considered an early marker of cardiovascular disease and contributes to cardiovascular events (12). Increased BMI predicts endothelial dysfunction, especially in patients with visceral obesity and insulin resistance (12). Obesity affects endothelial function due to comorbidities (insulin resistance, dyslipidemia, hyperglycemia), adiponectin deficiency, a leptin-resistant state, cytokines from the adipocytes and adipose-derived components of the renin-angiotensin-aldosteron system, functional abnormalities of the endoplasmic reticulum and mitochondria which contribute to the proinflammatory state, high production of free fatty acids, reduced synthesis of nitric oxide and increased generation of reactive oxygen species (1, 12). Some studies have reported a negative association between BMI and brachial and aortic augmentation indices (2). It has been suggested that volume overload could blunt the effect of the reflecting waves on pulse wave, reducing the elevation of the systolic peak over the wave shoulder (2).

Overweight and obesity impair endothelial function, arterial stiffness, coronary perfusion and favor early arterial aging. Hypertension and high normal blood pressure are also known to cause endothelial dysfunction, increase arterial stiffness and arterial age. Yet, the associations of elevated BMI and blood pressure values do not have additive effects on endothelial function, PWV, coronary perfusion and arterial age, according to the present study. The explanation for this new paradox, are, probably, mechanisms involved in different proportions, including microstructural changes of the arterial wall in different aortic and arterial segments, changes in nitric oxide bioavailability, sympathovagal imbalance, local renin-angiotensin-aldosterone activity, chronic inflammation in obese individuals, adiponectin levels, genetic factors and coronary microvascular adaptation in obesity (2, 21, 22, 28). It has been previously demonstrated that blood pressure is not the primary mechanism linking weight loss to improvements in central or peripheral arterial stiffness in healthy normotensive young adults (21). Obese hypertensives have a "paradoxically" lower risk of cardiovascular events than lean hypertensives, probably due to a relatively weaker impact of obesity on arterial structure and function in hypertensive than in normotensive subjects (18). Genetic factors seem to have an important role in individual differences in blood pressure and arterial stiffness components and explain the relation of these measures to BMI , and etiologies of obesity and hypertension are only partly shared (2). Fulop et al found that, in the simultaneous presence of hypertension and obesity, coronary arteriolar dilations to bradykinin and the NO donor sodium nitroprusside were markedly enhanced and positively correlated with BMI (29). It is possible that vascular oxidative stress and low grade vascular inflammation contribute to coronary microvascular adaptation in obesity (30). According to the present study, a lower impact of hypertension on arterial structure and function could be conside-

red in overweight and obese, than in lean patients, which may be a new obesity paradox.

PWV and augmentation indices are valuable, reliable, simple and inexpensive markers of arterial stiffness and vascular function, suitable for clinical and epidemiological studies. Detection of functional vascular alterations in overweight and obese patients would enable early lifestyle and therapeutic measures, delaying the development of cardiovascular disease. Efforts should be made, not only to loose weight and control other cardiovascular risk factors in obese patients, but also to evaluate vascular and cardiac function.

Strengths of the study

All the tests were performed by the same trained researchers, using the same device, in order to minimize intra- and inter-observer variations. The methodology is simple, time-saving, and suitable for population studies and ambulatory arterial stiffness assessment, with a higher reproducibility of the results compared to other techniques (30).

The present study included predominant apparently healthy subjects, with little comorbidity, which may provide additional insights in evaluating the impact of obesity on arterial stiffness, endothelial dysfunction and arterial aging.

The present study shows, for the first time, as far as we know, a significant association between an elevated BMI and impaired coronary perfusion, which could represent a preclinical stage of atherosclerotic coronary heart disease, enabling pharmaceutical intervention that may restore proper coronary arterial perfusion. Arteriography can serve as a screening tool for coronary involvement in patients with an elevated BMI. Elevated BMI and blood pressure have less than additive effects on endothelial function, pulse wave velocity, vascular age and coronary perfusion.

Study limitations

The most important limitations refer to lack of data about central obesity, salt intake, daily coffee and alcohol consumption, the cross-sectional study design, the characteristics of the study population and recording technique (30).

Body mass index has been used to define nutritional status, although waist circumference, waist-to-hip ratio and central obesity are stronger predictors of cardiovascular disease. Both general and abdominal obesity are associated with atherosclerotic changes and risk of death (3, 31).

Several lifestyle factors known to influence arterial stiffness were not considered, including salt intake, daily coffee consumption and alcohol consumption. Anyway, arterial stiffness reflects the cumulative effect of both known and non-identified cardiovascular risk factors (8, 9).

Further longitudinal studies are needed in this area, to confirm the causative relationship between obesity and arteriography variables, to enable pathophysiological speculations and to explain the mechanisms.

Our results were obtained in middle and aged, apparently healthy participants, and therefore, may not be extended to younger subjects or to patients with clinically manifest cardiovascular disease.

PWV determination with Arteriograph has been questioned in a computer model (2). However, aortic PWV measurement provided by this device has been validated against invasive measures (2).

Conclusion

Overweight and obesity predict endothelial dysfunction, arterial stiffness, impaired coronary perfusion and early arterial aging. Elevated BMI and blood pressure have less than additive effects on endothelial function, pulse wave velocity, vascular age and coronary perfusion.

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Hydroxyurea therapy and parameters of health in sickle cell patients

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Abstract

Background: We tried to understand possible effects of hydroxyurea therapy on health parameters in sickle cell diseases (SCDs).

Methods: All patients with SCDs were enrolled into the study. A hydroxyurea therapy was initiated to all patients.

Results: The study included 337 patients. Hydroxyurea was used and well-tolerated with a high majority of cases (80.1%). Mean number of painful crises per year was significantly decreased with the therapy (10.3 versus 1.7 crises per year, $p<0.000$). Mean severity of painful crises was decreased, too (7.8 versus 2.2, $p<0.001$). Although the body weight, mean hematocrit (Hct) value, and mean corpuscular volume (MCV) increased, the white blood cell (WBC) and platelet (PLT) counts and the total and direct bilirubin and lactate dehydrogenase (LDH) levels of serum decreased with the therapy, significantly ($p<0.000$ for all). We detected avascular necrosis of bones in 18.9% (90.6% at the hip joints), leg ulcers in 12.7%, pulmonary hypertension in 11.5%, chronic renal disease in 8.3%, coronary heart disease in 7.7%, digital clubbing in 6.5%, stroke in 6.5%, exitus in 5.3%, chronic obstructive pulmonary disease in 4.7%, and cirrhosis in 3.2% of the SCDs patients.

Conclusion: SCDs are chronic inflammatory disorders with a high morbidity and mortality, and hydroxyurea therapy is a well-tolerated and highly effective regimen for them. Hydroxyurea decreases frequency and severity of painful crises, WBC and PLT counts, and total and direct bilirubin and LDH levels, whereas it increases body weight, Hct value, and MCV, all of which may result with a prolonged survival in such cases.

Key words: Hydroxyurea, sickle cell diseases, atherosclerosis, metabolic syndrome

Introduction

Aging is the major health problem of the human being, and systemic atherosclerosis may be the major underlying cause of it. Atherosclerosis is an irreversible process mainly keeping larger, high blood pressure (BP) carrying vessels. Accelerating factors of atherosclerosis are collected under the heading of metabolic syndrome including overweight, dyslipidemia, elevated BP, and insulin resistance for the development of terminal diseases such as obesity, hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), peripheric artery disease, and stroke (1-6). On the other hand, sickle cell diseases (SCDs) are systemic microangiopathic processes that are characterized by sickle-shaped red blood cells (RBCs) caused by homozygous inheritance of the hemoglobin S (Hb S) (7,8). Glutamic acid is replaced with a less polar amino acid, valine, in the sixth position of the beta chain of the Hb S. Presence of valine promotes polymerisation of the Hb S. So Hb S causes RBCs to change their normal elastic and biconcave disc shaped structures to hard bodies. The decreased elasticity of RBCs instead of their shapes may be the central pathology of the diseases. The sickling process is probably present in whole life, but it is exaggerated during various stressful conditions of the body. The RBCs can take their normal elastic shapes after normalization of the stressful conditions, but after repeated cycles of sickling and unsickling, they become hard bodies, permanently. The hard cells induced chronic endothelial damage together with tissue ischemia and infactions, even in the absence of obvious vascular occlusions, are the final consequences of the diseases, so life expectancy of such patients is decreased by

25 to 30 years (9). We tried to understand whether or not there are some changes of clinical severity, body weight, and laboratory parameters with hydroxyurea therapy in the SCDs cases.

Material and methods

The study was performed in the Hematology Service of the Mustafa Kemal University between March 2007 and September 2013. All patients with SCDs were enrolled into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography. Their medical histories including smoking habit, regular alcohol consumption, and leg ulcers were learnt. Frequency of painful crises was detected as a mean number of crises per year, and severity of them as a mean degree between 0 to 10 according to patient's self-explanation. Cases with a history of three pack-year were accepted as smokers, and cases with a history of one drink a day for three years were accepted as drinkers. A check up procedure including body weight, serum creatinine value on three occasions, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, an electrocardiography, a Doppler echocardiography, an abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging of hips was performed. Other bone areas for avascular necrosis were scanned according to the patients' complaints. Cases with acute painful crisis or any other inflammatory event were treated at first, and then the spirometric pulmonary function tests to diagnose COPD, the Doppler echocardiography to measure the systolic BP of pulmonary artery, and renal and hepatic function tests were performed on the silent phase. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (10). Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent phase is accepted as pulmonary hypertension (11). CRD is diagnosed with a permanently elevated serum creatinine level of 1.3 mg/dL or higher on the silent phase. Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, ascites, and liver biopsy in case of requirement. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of greater than 1.0 and with the presence of Swamroth sign (12,13). A stress electrocardiography was performed in cases with an abnormal electrocardiography and/or angina pectoris. A coronary angiography was obtained just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of the cardiac walls. Then, a hydroxyurea therapy was initiated to all patients with an initial dose of 15 mg/kg/day, and then the dose was increased up to the final dose of 35 mg/kg/day according to patients' requirement and compliance. Finally, the mean number and severity of painful crises, body weight, white blood cell (WBC) and platelet (PLT) counts, hematocrit (Hct) value, mean corpuscular volume (MCV), and the total and direct bilirubin and lactate dehydrogenase (LDH) levels of the serum were compared before and after the hydroxyurea therapy. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 337 patients with the SCDs (169 females and 168 males). The mean ages of them were 28.4 ± 9.3 (8-59) versus 29.8 ± 9.3 (6-58) years in females and males, respectively ($p>0.05$). The hydroxyurea treatment was used and well-tolerated with a high majority of cases (80.1%), and the remaining cases could not been followed up. We have not observed any major side effect of the therapy during the follow-up period. The final dose of 35 mg/kg/day was just achieved in 25 cases (7.4%), and the usual dose was 500 mg twice daily during the 7-year follow-up period. During the period, the mean number of painful crises per year was significantly decreased with the treatment (10.3 versus 1.7 crises per year, $p<0.000$). The mean severity of painful crises was decreased, too (7.8 versus 2.2, $p<0.001$). Although the body weight, mean Hct value, and MCV increased, the WBC and PLT counts and the total and direct bilirubin and LDH levels of the serum decreased with the therapy, significantly ($p<0.000$ for all) (Table 1). On the other hand, we detected

Table 1. Characteristic features of sickle cell patients before and after hydroxyurea therapy

Variables	Before hydroxyurea therapy	*p*-value	After hydroxyurea therapy
Mean number of painful crises per year	10.3 ± 10.6 (0-48)	<0.000	1.7 ± 1.1 (0-6)
Mean severity of painful crises	7.8 ± 2.2 (0-10)	<0.000	2.2 ± 1.7 (0-10)
Weight (kg)	59.1 ± 11.4 (37-95)	<0.000	65.2 ± 13.0 (46-107)
White blood cell (μL)	15.050 ± 6.148 (4.890-38.800)	<0.000	11.349 ± 5.029 (5.010-31.850)
Hematocrit value (%)	23.2 ± 4.0 (16-35)	<0.000	27.8 ± 3.4 (20-36)
Mean corpuscular volume (fL)	88.7 ± 9.6 (57-112)	<0.000	105.2 ± 13.6 (66-129)
Platelet (μL)	449.840 ± 217.370 (169.000-1.561.000)	<0.000	430.840 ± 142.681 (219.000-936.000)
Total bilirubin (mg/dL)	5.3 ± 5.6 (0.6-38.2)	<0.000	3.1 ± 2.2 (0.7-11.0)
Direct bilirubin (mg/dL)	2.0 ± 3.4 (0.2-15.0)	<0.000	0.9 ± 0.9 (0.2-6.0)
Lactate dehydrogenase (IU/L)	647.5 ± 265.8 (196-1.552)	<0.000	509.9 ± 315.4 (235-2.218)

autosplenectomy in 46.8%, avascular necrosis of bones in 18.9% (90.6% at the hip joints), leg ulcers in 12.7%, pulmonary hypertension in 11.5%, CRD in 8.3%, CHD in 7.7%, digital clubbing in 6.5%, stroke in 6.5%, exitus in 5.3%, COPD in 4.7%, and cirrhosis in 3.2% of the patients (Table 2).

Table 2. Sickle cell patients with associated disorders

Variables	Prevalence
Autosplenectomy	46.8% (158)
Avascular necrosis of bones	18.9% (64)
Leg ulcers	12.7% (43)
Pulmonary hypertension	11.5% (39)
Chronic renal disease	8.3% (28)
Coronary heart disease	7.7% (26)
Digital clubbing	6.5% (22)
Stroke	6.5% (22)
Exitus	5.3% (18)
Chronic obstructive pulmonary disease	4.7% (16)
Cirrhosis	3.2% (11)

Although smoking was observed in 6.5% (22) of the patients, there was only one case (0.2%) of regular alcohol consumption, who was not cirrhotic at the moment. Although antiHCV was positive in two of the cirrhotics, HCV RNA was detected as negative by polymerase chain reaction in both. Prevalences of mortality were similar in both genders (4.7% versus 5.9% in females and males, respectively, $p>0.05$), and mean ages of such cases were 32.1 versus 29.1 years in females and males, respectively ($p>0.05$).

Discussion

SCDs particularly affect microvascular systems of the body (14,15), since the capillary systems are the main distributors of the hard bodies to tissues, so they are destroyed much more than larger vessels. Because of the microvascular nature of the disease, we can observe healing of leg ulcers with hydroxyurea therapy in early years of life, but later in life the healing process is difficult due to the excessive fibrosis around the capillaries. Eventually, the mean survival was 42 years for males and 48 years for females in the literature (9), whereas it was 29.1 and 32.1 years, respectively, in the present study ($p>0.05$). The great differences between the survival should be searched with further studies, but it may be secondary to the initiation of hydroxyurea treatment in early years of life. On the other hand, the prolonged survival of females with SCDs should also be searched, effectively. As a result of such a great variety of clinical presentation, it is not surprising to see that the mean body weight and body mass index (BMI) were significantly retarded in the SCDs cases (16). Probably parallel to the significantly lower mean body weight and BMI, mean values of the low density lipoprotein cholesterol, alanine aminotransferase, and systolic and diastolic BPs were also significantly lower in the SCDs (16), which can be explained by definition of the metabolic syndrome (17,18).

Painful crises are the most disabling symptoms of the SCDs. Although some authors reported that

painful crises themselves may not be life threatening directly (19), increased basal metabolic rate with any underlying cause including infections, tissue damage, operations, and depression usually terminate with painful crises and an increased risk of mortality. Probably pain is the result of a generalized inflammatory process on the endothelium, and the increased WBC and PLT counts and the decreased Hct values show presence of a chronic inflammatory process during whole their lives in such patients. For example, leukocytosis even in the absence of an infection was an independent predictor of the disease severity (20), and it was associated with an increased risk of stroke probably by releasing cytotoxic enzymes and causing endothelial damage in another study (21). Because of the severity of pain, narcotic analgesics are usually required to control them (22), but according to our practice, simple and recurrent RBC transfusions are highly effective during the severe crises both to relieve pain and to prevent sudden death that may develop secondary to the multiorgan failures on chronic inflammatory background of the SCDs.

Hydroxyurea is an effective therapeutic option for the treatment of chronic myeloproliferative disorders and SCDs. It interferes with cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyper-proliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F) (23,24), we think that its main action way is the suppression of leukocytosis and thrombocytosis via blocking the DNA synthesis in the SCDs. By this way, the continuous inflammatory process of the SCDs that initiated at birth on the vascular endothelium is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyper-proliferating skin cells. As in viral hepatitis cases, although presence of a continuous damage of sickled cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' immune system particularly by the actions of WBCs and PLTs. So suppression of excessive proliferation of WBCs and PLTs probably limits the endothelial damage-induced tissue ischemia and infarctions all over the body. Similarly, it was reported that lower neutrophil counts were associated with lower crises rates, and if a tissue infarction occurs, lower neutrophil counts may limit severity of pain and extent of tissue damage (25). On the other hand, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels, significantly (25).

Physicians at the National Institutes of Health Consensus Conference agreed that hydroxyurea is underused both in children and adults due to some reasons. Hydroxyurea is a chemotherapeutic agent, thus it is not taken by women planning to become pregnant in near future. Additionally, there is fear of potentially increased risk of cancers in people (26). However, the cancer risk has not been substantiated by more than a decade of using hydroxyurea for adults (27). Although investigational and post-marketing data show risk to fetus (28), potential benefits may outweigh potential risk in pregnancy. According to our experiences, there are several female patients with infertility, abortus, or stillbirth in the absence of hydroxyurea therapy, and the decreased number and severity of painful crises, increased body weight, decreased WBC and PLT counts, and increased Hct value will probably result with resolution of the above problems with some extent. It is clear that there is a need for more effective treatment regimens in SCDs, but until they become available, hydroxyurea should be used in all cases, and its dose should be kept as higher in the moderate and severe patients.

Hydroxyurea probably has a life-saving role in the SCDs. As similar results to our study, the Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with sickle cell anemia (Hb SS), and compared the results of patients treated with hydroxyurea or placebo (29). The study particularly searched effect of hydroxyurea on painful crises, acute chest syndrome, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated in all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (29). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (29). But this study was performed just in severe Hb SS cases alone, and the rate of pa-

inful crises was decreased from 4.5 to 2.5 per year (29). Whereas in our study, we used all subtypes of the SCDs with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year (p<0.000) with an additional decreased severity of them (7.8 versus 2.2, p<0.000). Parallel to our results, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (30). The underlying disease severity remains critical to determine prognosis, but hydroxyurea may decrease severity of disease (30). Probably the chronic endothelial damage of the SCDs is initiated at birth, and complications may start to be seen even in infancy. For instance, infants with lower hemoglobin levels were more likely to have a higher incidence of clinical events such as acute chest syndrome, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidence of them (31). Hydroxyurea in early life may also protect splenic function, improve growth, and prevent multiorgan dysfunctions by reversing early capillary damage. Transfusion programmes also reduce all of the complications of SCDs, however transfusions carry many risks including potential infection transmission, development of allo-antibodies causing subsequent transfusions more difficult, and iron overload.

As a conclusion, SCDs are chronic inflammatory disorders with a high morbidity and mortality, and hydroxyurea therapy is a well-tolerated and highly effective regimen for them. Hydroxyurea decreases frequency and severity of painful crises, WBC and PLT counts, and the total and direct bilirubin and LDH levels of the serum, whereas it increases body weight, Hct value, and MCV, all of which may terminate with a prolonged survival in such cases.

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Frequency of endocrine dysfunction with Patients of psoriatic arthritis and other rheumatic diseases

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Abstract

Introduction: Psoriatic arthritis (PsA) is a sub acute or chronic, oligo-or polyarthritis with patients with psoriasis. It is considered that the impact of endocrine glands, not directly, but go through the vegetative nervous system. Ovarian hypo function causes hyper function of antagonistic endocrine glands, (bark of suprarenal glands hypertrophied), thyroid function and increases your muscle tone increases the vegetative nervous system (so for example. Reduced tolerance for carbohydrates as it is perceived in rheumatoid, arthritis). Increased sympathetic tone leads to local spasm of the arteries feeding the worse in the periphery (joints, muscles, skin) and create conditions for the development of this disease. This factor is taken into account in rheumatoid and psoriatic arthritis.

Goal: Aim of the study was to determine whether patients with psoriatic arthritis have the same incidence of endocrine dysfunction, as well as people with other rheumatic diseases.

Method: The study included 174 patients. Patients were predetermined set into two groups, of which 38 patients had a diagnosis of psoriatic arthritis, they constituted the study group. Control group (136) consisted of patients with other rheumatic diseases and endocrine dysfunction, who had no psoriatic arthritis.

Results: Among all X-ray search most frequent positive finding in both groups, is a X-ray of the hand (57.89% in the study, and 57.35% in the control group). No one, in the study and control Group has not reduced triglycerides values. Elevated values are recorded in 57.89% of participants of the study and 31,34% of participants of the control group. Therefore, statistical is more respondents of study group with elevated values triglycerides in compared on control group (χ^2=7, 83, p=0, 0051<0, 01). All participants of both groups where is determined LDL cholesterol having values in limit reference. Statistically significant difference is at respondents with elevated glycemia in study (44.74%) in control group (24.64%) g.

Conclusion: Considering that many of the endocrine glands inter-relate, we cannot always determine which of these glands could be related to arthritis and created psoriatic changes.

Key words: Psoriatic arthritis, endocrine gland dysfunction,

Introduction

Psoriatic arthritis (PsA) is a sub acute or chronic, oligo-or polyarthritis with patients with psoriasis (1). Association of psoriasis and arthritis existed from time. Psoriatic skin lesions all to 1860. Were considered as leprosy, when Herb found that leprosy and psoriasis are two different diseases. The real relationship between disease psoriasis and arthritis understood Devergre and Bazin in 1860, when the first time, the term "arthritic psoriasis" was used (2).

In addition to the peripheral joints, inflammation process gets affected sacroiliac joints (sakroiliitis), spine (spondylitis) and insertions of tendons and ligaments (enthesitis) (3).

According to the classification and Espinoza Cuellar, a PsA has three subspecies: the dominance of peripheral arthritis, spondylitis with dominance and dominance extra-articular events, including Sapho Syndrome (sinovit with, acne, palmoplantar pustuloza, hiperostoza, and osteitis), (4).

The results of many studies indicating that a significant number of patients develop progressive destructive arthropathy, refuses the notion that early psoriatic arthritis was considered a benign form of arthritis compared to rheumatoid arthri-

tis (RA). As with other rheumatic diseases, the etiology and pathogenesis are unknown. Multi factorial inheritance of disease (genetic, immune factors, trauma, and physical agents) is generally accepted. The frequency of B antigens in 27 patients with arthritis indicates that genetic factors play a role in the occurrence of psoriatic arthritis. Numerous studies have shown that specific HLA antigens predispose to rapid progression of PsA and require early aggressive treatment. It was found that HLA B 27 positive patients with findings of DR 7, as well as those with B 39, have a worse prognosis. On the other hand carriers of HLA B 22 or W3 DQ DR 7 with a slower flow and require less aggressive treatment (3). There is no laboratory results characteristic for psoriatic arthritis (5).

Primary place of inflammation in PsA synovial tissue from which cytokines are released into the systemic circulation and affect numerous functions in the peripheral tissues such as the liver, skeletal muscle, adipose tissue and endothelium. In this way generate a proatherogenic changes including insulin resistance, a characteristic dyslipidemia, prothrombotic effects and endothelial dysfunction and (6).

Given that biological agents are hormones that are synthesized and released from a tissue, and then transmitted via blood and act on distant target organs and other tissues, target also loco motor system, as well as to patients with psoriatic arthritis. (7, 8, 9, 10).

The pathogenesis osteoartrosis (spondilosis) takes into account certain functional disorders of some endocrine glands. In particular, hypo function or, a function of ovary, as this disease often occurs in post menopausal women or when artificial castration is done. Described in hysterectomized women is common and known as osteoarthritis: osteoarthropathia ovaripriva.

Question of way to manifest affection of endocrine gland dysfunction, there are different interpretations, but generally it is considered that the impact of endocrine glands, not directly, but go through the vegetative nervous system. Ovarian hypo function causes hyper function antagonistic endocrine glands, namely suprarenal (bark suprarenal glands hypertrophied), thyroid function and increases your muscle tone increases the vegetative nervous system (so for example. Reduced tolerance for carbohydrates as it is perceived in rheumatoid, arthritis). Elevated sympathetic tone leading local arterial spasms aggravate food in the periphery (joints, muscles, skin) and create conditions for the development of this disease. This factor is taken into account in rheumatoid and psoriatic arthritis and correlated is recommended for both these diseases giving acetylcholine to remove the spasm of blood vessels.

Under normal circumstances, prevents spasm through counter regulation, which is absent in pathological circumstances.

Pathology of the endocrine imbalance in psoriatic arthritis can be divided into the following chapters:

- Endocrine dis balance as an integral element of the rheumatoid inflammatory process (term psoriasis arthritis).
- Endocrine dis balance as a result of rheumatic diseases attached as part of mixed connective tissue disease in a broad sense (particularly rheumatoid arthritis and other systemic diseases of the connective tissue, seronegative arthropathy).
- Endocrine imbalance psoriatic arthritis as a result of disease attached outside the previously defined mixed disease, most other no inflammatory, but also a number of male and internist and no internist diseases.
- Endocrine imbalance psoriatic arthritis as a consequence of a complication of psoriatic arthritis.
- Iatrogenic endocrine imbalance caused by primary, basic and complementary therapies.
- Endocrine imbalance as a result of coincidences.

Goal

Taking into account the above data, the goal of this study was to determine whether patients with psoriatic arthritis have the same incidence of endocrine dysfunction, as well as people with other rheumatic diseases.

Materials and Methods

In study included 174 patients. Patients were divided into two groups, the study group (38 subjects

a) consisted of patients with psoriatic arthritis and endocrine dysfunction included, and the control group (136) consisted of patients with other rheumatic diseases and endocrine dysfunction, however, who had psoriatic arthritis. Patients included in the study after the consent the data collected were written into separate, pre defined forms.

The reference laboratory was biochemical laboratory of Health Center of the city of Kosovska Mitrovica.

Prospective research area that lasted three years include Attila 174 sufferers from rheumatic disorders and diagnosed according to the criteria osteoar troze American College of Rheumatology - ACR who had their first symptoms disease at least 6 months before the beginning of the beginning of the study.

According to the pre defined protocol all subjects had been submitted to physical examination, and standard biochemical tests were performed (on a multichannel biochemical analyzer Olympus AV400). With control reside biochemical parameters, which included determining the value of blood glucose, triglycerides (TR), total cholesterol (UH), the concentration of low density lipoprotein, LDL-cholesterol (low density lipoprotein cholesterol, LDL-C), high density lipoprotein, HDL-cholesterol (high density lipoproteins, HDL). During the study we administered according to the latest recommendations of the National Cholesterol educational programs (Cholesterol National Education Program Adult Treatment Panel III; NCEP ATP III) (11).

The gold standard for the diagnosis of diabetes is hyperglycemia in plasma glucose> 7.0 mmol / L in at least two reached the age ata (11), and criteria for the diagnosis of diabetes values of fasting glucose> 7 mmol/L, or glucose in any random sample of blood> 11 mmol/L (12, 13).

The main indication in the application of musculoskeletal ultrasound (MSUZ) in the diagnosis of psoriasis term arthritis is enteritis diagnosis, including ultrasound: calcification or bone erosion at the site of the unit I thickening (increase in size) tendon or plantar fascia. MSUZ examination is more sensitive diagnostic method of clinical examination in the detection of these changes. With Karnela and associates showed that the superior and magnet nuclear resonance (NMR) in detecting enteritis (14). MSUZ joint inspection was conducted on the SDU-1200 apparatus using a linear probe of 10 MHz

To the patients with psoriatic arthritis by using instrument of PASI (15) psoriasis condition is registered. PASI instrument includes four body regions: head, upper limbs, trunk and lower extremities, the surface of which is respectively 10%, 20%, 30%, and 40% of the total body surface. The surface of the skin affected by psoriasis at each of the four regions of the body is assigned a numerical value from 0 to 6, which corresponds to the percentage of psoriatic involvement of the body of 0-100% of the body surface. For each region in the erythematic, in duration and desquamation assessed according to a scale of 0 to 4 Each of these regions was scored separately, and then the four scores tended in total PASI score, which can range from 0.0 to 72.0 (higher scores indicate a higher degree of severity of psoriasis.

Statistical data processing

All tests were conducted using a computer software package SPSS 8.0 for Windows Microsoft. Standard description methods are applied in this paper. Analytical statistical method for comparison of mean values of parametric features used Student's t-test, and to assess the significance of the difference X 2 test. Differences at $p < 0.05$, $p < 0.01$ were taken as statistically significant.

The results

The study included 58 male patients (33.33%) and 116 females (66.67%). The age of the respondents of the study group was 56.87 - + 13.32 years, while the control group 56.15 - + 12.65 years.

Of all radiographic (X-ray) findings (Table 1), the most common positive finding in both Groups the X-ray hand (57.89% in study, and 57.35% in the control group). RTG Foot is second frequent but percent of respondents with positive findings is considerably larger in study (52.63%) compared on control group (33.82%), close level statistical significant differences 0.05 ($c\ 2 = 3.70$, $p = 0.0544$). Percent of respondents of study Group with (SI) patients statistical is significantly larger in study (26.32%) in compared on Control nu group (8.09%) - ($p < 0.01$).

Table 1. Fortified radiographic (X-ray) and sonographic findings in study and control group

RTG findings	Study group		Control group		p
0 RTG is not done	4	10.53%	1	0.74%	**
First RTG hands	22	57.89%	78	57.35%	
Second RTG feet	20	52.63%	46	33.82%	
3rd RTG SI joints	10	26.32%	11	8.09%	**
4th Sonography Knee +	6	15.79%	24	17.65%	
5th Sonography Pop-up joints	0	0.00%	7	5.15%	
6th Sonography Foot	1	2.63%	4	2.94%	
7 Sonography SI joints	0	0.00%	29	21.32%	**

p<0, 05, ** - p<0, 01

Table 2. Average value lipid status in investigated groups

Tested parameter	Study Group			The control group			t-test	p
	N	X ±	SD	N	X ±	SD		
Serum cholesterol	37	6.15 ±	1.69	134	5.54 ±	1.29	2.02	0.0198 *
LDL cholesterol	10	4.23 ±	0.17	15	3.85 ±	0.44	2.56	0.0174 *
HDL cholesterol	5	1.36 ±	0.21	20	1.29 ±	0.33	0.46	0.6503
Triglycerides	38	1.98 ±	1.32	134	1.63 ±	0.81	2.00	0.0467 *

**-P<0.05*

Table 3. The structure of studied group as compared to reference values lipid parameters

Parameter	Value	Reference value	Study group		Control group		In total	
Cholesterol	Reduced	<3.88 mmol / l	1	2.70%	3	2.24%	4	2.34%
	Normal	3.88 to 5.20 mmol / l	13	35.14%	61	45.52%	74	43.27%
	Raised	> 5.20 mmol / l	23	62.16%	70	52.24%	93	54.39%
	In total		37	100.00%	134	100.00%	171	100.00%
LDL	Reduced	<1.55 mmol / l (m / f)	0	0.00%	0	0.00%	0	0.00%
	Normal	1.55 to 4.53 (4.14) mmol / l (m / f)	10	100.00%	15	100.00%	25	95.39%
	Raised	> 4.53 / 4.14 mmol / l (m / f)	0	0.00%	0	0.00%	0	0.00%
	In total		10	100.00%	15	100.00%	25	95.39%
HDL	Normal	to 1.07 (1.17) mmol / l (m / f)	1	20.00%	8	40.00%	9	36.00%
	Raised	> 1.07 (1.17) mmol / l (m / f)	4	80.00%	12	60.00%	16	64.00%
	In total		5	100.00%	20	100.00%	25	100.00%
Trig - glycerides	Reduced	<0.40 / 0.45 mmol / l m / f)	0	0.00%	0	0.00%	0	0.00%
	Normal	0.40 to 1.50 / 0.45 to 1.80 mmol / l (m / f)	16	42.11%	92	68.66%	108	62.79%
	Raised	> 1.50 / 1.80 mmol / l (m / f)	22	57.89% **	42	31.34%	64	37.21%
	In total		38	100.00%	46	100.00%	84	100.00%

Table 4. The structure of the study subjects and the control group compared to the reference values of glycemic

Blood glucose value	Study Group		The control group		In total	
Reduced	3	7.89%	11	7.97%	14	7.95%
Normal	18	47.37%	91	65.94%	109	61.93%
Raised	17	44.74%	34	24.64%	51	28.98%
In total	38	100.00%	138	98.55%	176	98.86%

Lipid status respondents were determining on serum cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. Average value all investigated parameters lipid status council are in study in relations are on control group, with statistical considerably more worth of serum cholesterol, LDL cholesterol and triglycerides ($p < 0.05$).

In Table 2. Are shown reference value parameters of lipid status and structure of respondents in compared on value quiet parameters?

The increased value HDL was observed in 80% of the study group, but no significant differences in compared on control group, in whom 60% of respondents with elevated value these parameters (Table 3).

In study group in compared on control, larger is percent respondents with values who not in field reference and for serum cholesterol (80%: 60%), but without statistical significant differences.

No respondent, the study and control Group no reduced value triglycerides. His elevated value recorded are 57.89% of respondents study and 3 1, 34% of respondents control group. Accordingly Therefore, statistical is more respondents study Group with elevated values triglycerides in compared on control group ($c\ 2 = 7, 83$, $p = 0.00\ 51 < 0.01$). All respondents both Group which is determined LDL cholesterol have value in limits reference.

In both groups very is low percent of respondents (slightly below 8%) with values of glycemia below reference minimal (Table 4), so that is statistical significant difference contributed considerably larger number respondents with elevated glycemia in study (44.74%) in compared on control (24.64%) group.

Discussion

According to the CASPAR criteria (Classification Criteria for Psoriatic Arthritis):

- Patient has to have arthritis,
- Psoriasis in relatives of first or second degree
- Typical psoriatic lesions on the nails
- negative rheumatoid factor (latex test is not accepted)
- Daktilitis, current or previous (confirmed by a rheumatologist)
- Radiological signs of new bone creation, the hand or foot radiographs.

There are the differences that are more or less typical for some types of arthritis, especially PsA, particularly in relation to RA n, from which it first, and should be distinguished. Destructive changes inter phalangeal joints of hands and / or feet with abnormally wide joint space and clearly limited are as adjacent bone, the veil of matter characteristic of PsA, especially if these changes are also noticeable in the hands and feet, which can be seen on the sloping foot footage .

Destructive changes with widening of the joint space, tapered proximal and distal joint ends often leads to large destruction of the descriptive displayed as "cup-mug", " mushroom ", "sharpened pencil", "pen in the inkwell BLIK" " z and w and laziness, "depending on the degree of deformation of the shape and the maximum of the manifest form, leading to mutating arthritis.

Absorption peaks of the distal phalanges of the hand, foot, or more frequently (ankylosis) in characteristic form occurs only in the dog and is readily distinguished from the ANC and lineage in systemic sclerosis. For psoriatic arthritis is almost patognomonic findings consisting of a combination of these radiological changes.

Results of this study shows that of the 38 patients who were diagnosed with psoriatic arthritis, 22 of them (57.89%) and l is their destructive changes of the hands, feet positive radiological changes were in 20 (52.63%) of the respondents, a positive radiological finding SI joints was found in 10 (26.32%) patients with para spinal ossification and wide rough no marginal sindesmofitima. In the control group of whole number of respondents, 78 (57.35%) had radiological changes on the hands, the feet of 46 (33.82%), and the sacroiliac joint changes were present in only 11 (8.09 %) of the respondents.

Although currently well-principles postulated that the appearance of the PsA, its progression, intensity, sequels and outcomes depend not only on the level of total hole with terrorism, but the whole range of his fractions. In our study, the study group was significantly high percentage of patients with elevated HDL cholesterol (80%), but no statistically significant differences compared to the control group (60%). None of the subjects of the study and control group does not value women triglycerides setback. Raise the value of women registered with 57.89% of the study and 31.34%

in the control group. All subjects in order to determine LDL cholesterol are within normal values.

Their studies Seishi et al. (16) but the demo of lipid and lipoprotein cut proved results in 50 patients with PsA, including 20 patients with active joint disease. HDL was significantly reduced cholesterol in patients with PsA, and there is a difference to patients with HDL3, among a group of 50 and those with active disease, the apparent difference patients in the study group than in the control group. Decreased levels of total cholesterol was more pronounced in 20 patients with active synovitis, which are analyzed.

Some research findings indicate that a large percentage of skin changes with patients with diabetes mellitus should be linked to the suppression of immunity that is found in patients with poor metabolic control of the underlying disease, and where there are functional and organic disorders of circulation and neuropathy, as well as arthropathy, associated with underlying disease (17). Examining the role of the skin as a protective SITEMA breakthrough infection in the body patients with diabetes mellitus, and Nakai al. (18), found that the basis of skin infection whose changes are in keratinocytes of skin that has a great impact hyperglycemia. Oh no, on the basis of the obtained results and the exposure NaCaT (immortal human keratinocytes) cell line with high levels of glucose (ten days) observed decreased production of nitric oxide (NO). Such findings led the authors to highlight the participation of NO in the reduced skin resistance against infections and slow healing of wounds.

Our study, on d total number of patients studied groups; most patients had normal blood glucose value. Decreased blood glucose value in the study group had only 3 respondents or 7.89% in the control group, 7.97%, respectively, 11 patients. Unlike reduced, hyperglycemia was found in a larger number of respondents in both groups. Increased in the study group had a value of 44.74% of patients (17/38), 24.64% in the control group (34/136).

Clinical, biochemical and epidemiological studies have shown that patients with poor regulated diabetes are more subjected to of psoriatic and joint manifestations , however, is still not clear whether poor metabolic control cause or consequence of the coexistence of skin and joint changes. (19).

Diagnosis of PsA is usually not easy. Disease expresses in different clinical forms, variable and unpredictable clinical course, and no typical clinical and laboratory findings, which confirm or exclude the disease. Early detection of early PsA and appropriate treatment is necessary to prevent disability disease. New criteria for the classification of RA and PsA developed by the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) represent a new approach with special emphasis on the detection of patients with relatively short symptoms that may benefit from early treatment, especially non-biological and biological drugs (20, 21).

Conclusion

Among the endogenous factors that may impact the pathogenesis osteoarthritis (and spondilatrosis) deformances and psoriatic arthritis, and it takes a certain innate, inherited, the tendency of some people to fall ill with osteoarthritis deformances, especially when they later join other exogenous and endogenous factors predispose to the development of this disease. In this connection it may be noted that psoriatic arthritis and endocrine dysfunction sometimes occur in several members of the same family.

Bearing in mind that many of the endocrine glands inter-relate, we cannot always determine which of these glands could be related to arthritis and created psoriatic changes.

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Effect of health reforms on antibiotic consumption

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Abstract

Aim: Irrational use of antibiotics is an important problem that contributes to increasing antibacterial drug resistance. Some important legal regulations concerning antibiotic consumption were put in place in Turkey in 2003 and 2005. In this study, we aimed to investigate the effect of legal regulations on antibiotic consumption after national health reform.

Methods: Data concerning restricted antibiotics were taken from the Intercontinental Medical Statistics office in Turkey. Health expenditure data for Turkey were taken from web sites of institutions, and other health data were taken from the website of the Ministry of Health.

Results: Health investment and expenditure increased significantly between 2006 and 2010 in Turkey. Box-based consumption of restricted antibiotics increased in these years. The box-based consumption between 2006 and 2010 increased 1.8, 2.8, 2.1, and 4.9 fold for carbapenems, piperacillin/tazobactam, cefoperazone/sulbactam and linezolid, respectively. The consumption of cefepime and teicoplanin decreased 0.4 and 0.8 fold.

Conclusion: Easily accessible health service with the reform increased the consumption of antibiotics even restricted. The necessity of Infectious Diseases specialist approval lonely is not enough to decrease consumption. New, additional policies are needed to ensure rational consumption of broad spectrum antibiotics.

Key words: Anti-bacterial agents, Restriction, Infectious Diseases, Specialist.

Introduction

Antibiotics are one of the most important discoveries of the last century. However, irrational use of antibiotics causes economic loss and the spread of resistant microorganisms, which threaten the health of the population [1]. Because of resistance, many antibiotics can today no longer be used [2]. The infections caused by resistant microorganisms (methicillin resistant staphylococci, multi-drug resistant gram negative bacilli, azole resistant candida) that are seen especially in intensive care units (ICU) are difficult to treat, lead to higher cost and produce a high mortality rate. To combat resistant microorganisms many strategies have been developed. Microbiological sampling, surveillance, and rational antibiotic use policies are some of these strategies. In many countries, to support rational antibiotic use, some antibiotics can only be prescribed by Infectious Diseases Specialists (IDS) [3].

Turkey has a population of over 70 million. In our country, some measures were taken to prevent antibiotic resistance and irrational use of antibiotics. Since 2003, antibiotic prescriptions have been restricted by legal regulations. Some broad spectrum antibiotics such as carbapenems, vancomycin, teicoplanin, daptomycinand anti-fungals can be prescribed only by IDS [4].

An effective social insurance reform (SIR), including remarkable changes in drug reimbursement, was implemented by Turkish Government in 2005. Before SIR, there were different restrictions and limitations for drug reimbursements in the healthcare refund system. Almost 70% of population was affected by the restrictions before the implementation of SIR. Especially Workers Insurance Organization (SSK), a semi-governmental insurance organization, did not provide sufficient drugs. The low incomers, who are called Green Card holders and make 14% of total population, were not reimbursed for outpatient prescribes. All reimbursement foundations joined together to form the Social Security Board (SSB) in Turkey in 2005. The uniform and larger SIR made the prescription and consumption of drugs easier for the governmental and semi-governmental insurance holders. The SSB started to reimburse the health costs of patients in

private hospitals in addition to state and university hospitals. In this way, it became easy for patients to receive health care from private hospitals. After the reform, all people insured including green card holders were provided with full insurance and had a right to buy their medicine from any pharmacy [5]. The increase in expenditures on health caused an increase in applications of patients to the hospitals and the increase in the number of patients caused an increase in the consumption of antibiotics. Moreover after 2005, both hospital bed capacity and ICU bed capacity were increased in Turkey [6].

In brief, the restrictive policies after 2003 slowed the increase in consumption of broad spectrum antibiotics, and even a decrease was achieved for some antibiotics. After 2005, the union of all insurance foundations as the SSB caused an increase in the consumption of restricted broad spectrum antibiotics according to the Intercontinental Medical Statistics (IMS) data. The aim of this study was to investigate the factors that affected the consumption of restricted broad spectrum antibiotics that are only prescribed by IDS.

Material and Methods

The broad spectrum antibiotics that can be prescribed only by IDS are listed. The sales data of these antibiotics were obtained from the Intercontinental Medical Statistics (IMS) office in Turkey [7]. All data were recorded in MS Excell file. The data on antibiotic consumption per year is given in the table. The health expenditure data for Turkey were taken from web sites of institutions and the bed capacity of hospitals and intensive care units were obtained from the website of the Ministry of Health [8,9].

By law since 2003, broad-spectrum antibiotics and some antifungals can be used only when required by an infectious disease specialist. These drugs were; Piperacillin-tazobactam, Cephoperazone-sulbactam, Cefepime, Ceftazidime Meropenem, Imipenem, Vancomycin, Teicoplanin, Linezolid, intravenous forms of quinolones, caspofungin, and voriconazole. Liposomal amphotericin B and Piperacillin-tazobactam had not been provided in 2009.

This work considered aggregated data and not individual ones. Thus, no ethic statement or patient consent was involved.

Results

Based on the results, most restricted antibiotic consumption is increasing year by year. We detected almost 4-fold increase in the use of linezolid and voriconazole. The increase in the piperacillin-tazobactam and caspofungin was % 176 and % 172, respectively. Another notable increase in the consumption was observed in cefoperazon-sulbactam.

Table 1. Box-based consumption of restricted antibiotics by year

Drugs (Box/Year)	Year 2006	Year 2007	Year 2008	Year 2009	Year 2010	% Change	
Linezolid	41.024	72.931	128.522	144.341	204.728	↑	399
Voriconazole	19.980	35.088	58.314	97.185	97.341	↑	387
Piperacillin/TazobactAm	531.996	935.327	1.139.986	1.024.275 a	1.469.910	↑	176
Caspofungin	24.341	32.071	31.261	54.562	66.149	↑	172
Cefoperazon Sulbactam	779.399	1.184.163	1.465.077	1.489.883	1.669.888	↑	114
Carbapenems	1.727.792	2.118.156	2.511.210	2.531.625	3.091.000	↑	79
Vancomycin	566.465	623.624	625.789	572.401	760.895	↑	34
Ceftazidim	316.888	347.873	310.687	263.261	413.047	↑	30
Ampbd*	34.060	40.819	23.455	37.994	33.426	↓	-2
Lampb**	121.708	130.665	130.581	55.890	118.580	↓	-3
Teicoplanin	478.567	510.996	589.224	417.385	377.860	↓	-21
Cefepime	415.281	134.015	275.164	170.160	185.533	↓	-55
Ampb- Lc ***	19.466	10.570	1.995	271	0	↓	-99
Total	**5.076.967**	**6.176.298**	**7.291.265**	**6.859.233**	**8.488.357**	↑	**67**

** AMPBD: Amphoterisin B deoxycholate, **LAMPB Lipozomal Amphoterisin B: ***AMPB-LC: Amphoterisin B lipid complex a: Piperacillin/Tazobactam was sold to another manufacturer so the product was withdrawn from the market 3-4 months in 2009.*

It's consumption was increased more than two fold. The consumption of carbapenems increased 1.8 fold between 2006 and 2010 and became the most consumed restricted antibiotic (Table 1, Figure 1).

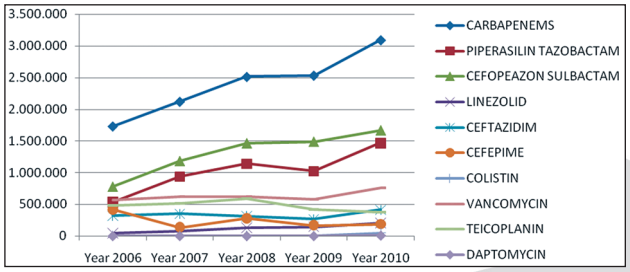

Figure 1. Antibacterial consumption between 2006-2010 in Turkey

The more pronounced increase was for promotion antibiotics. For example, consumption of piperacillin-tazobactam increased 2.8-fold in these years, but there was a decrease after 2009. There was a 2.1-fold increase in consumption of cephoperazone-sulbactam in these years. After equivalents of cefepime came onto the market, its consumption decreased 0.4-fold. Between 2006 and 2010 the most consumed antibiotic was linezolid. The consumption of linezolid increased 4.9-fold, whereas the consumption of teicoplanin decreased 0.7-fold in these years. Vancomycin and ceftazidime consumption increased 1.3-fold (Table 1).

When we investigated antifungal drugs, there was 2 % reduction in consumption of amphotericin B, but the consumption of voriconazol and caspofungin increased 4.8-fold and 2.7-fold, respectively (Table 1, Figure 2). Because of the change of the company that manufactures liposomal amphotericin B, the drug could not be found on the market. Amphotericin B lipid complex consumption vanished because of the change of the manufacturer company in Turkey.

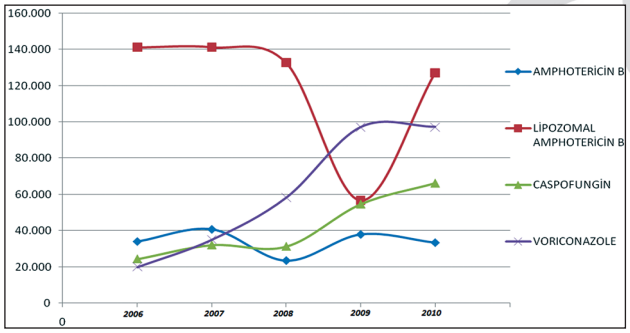

Figure 2. Antifungal consumption between 2006-2010 in Turkey.

Discussion

According to our results, box based consumption of restricted antibiotics has increased yearly. In total, the consumption of restricted antibiotics was about 5 million boxes in 2006 and increased to 8.5 million boxes 5 years later. The increase was significant for linezolide, voriconazole, piperacillin-tazobactam, cephoerazone-sulbactam, carbapenems, and vancomycin. The restricted antibiotics that had a decrease in consumption were amphotericin B formulations (amphotericin B deoxycholate, liposomal amphotericin B, amphotericin B lipid complex), teicoplanin and cefepime.

Even though very-broad-spectrum antibiotics can be prescribed by Infectious Diseases specialists with the reforms undertaken in 2003, consumption of them has increased. There were various reasons for this increase. First of all, it became easier for patients to reach the doctors and drugs, and the opportunities to obtain healthcare were increased. Due to these legal regulations and the increase in the health budget, health expenditure per capita increased from 310 dollars in 2004 to 624 dollars in 2008 [10]. Over the same period, drug expenditure per person increased from 87 dollars to 157 dollars. Total drug expenditure increased from 6.24 billion dollars to 11.17 billion dollars in the same period [11]. Between 2006 and 2010, public health care expenditures and drug expenditures increased 1.7-fold and 1.5-fold, respectively. Within the last 10 years, drug expenditure and total health care expenditure increased 5.6 and 7.1-fold, respectively. (Figure 3) [8,9]. In general, the 3-fold increase in surgical interventions could explain the 3-fold increase in hospital acquired infections. This naturally caused an increase in consumption of antibiotics. The increase in intensive care unit bed capacity caused an increase in care of severely ill patients, and multidrug resistant organisms like *Acinetobacter spp*., *Pseudomonas spp* and MRSA. As a result, the consumption of antibiotics that could be prescribed only with IDS approval increased. Together with the increase in intensive care unit bed capacity there was an increase in pneumonia and bacteremia due to methicillin resistant *S. aureus* and vancomycin resistant enterococci.

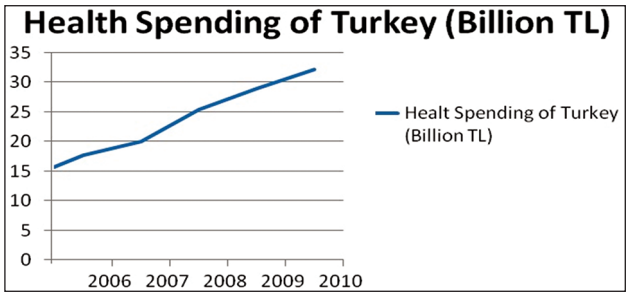

Figure 3. Health care expenditure in Turkey by year

Interestingly in this period decreased only a few antibiotics. One of them is teicoplanin. When we analyse the data in order to find the answer of the question; "why teicoplanin decrease in this period?". It was seen that new groups were used instead of teicoplanin. About 10 years ago, only vancomycin and teicoplanin were used for these infections, but today linezolid and daptomycin are preferred. In intensive care units, since it is more effective, IDS use linezolid instead of teicoplanin for pneumonia [12]. Similarly, the use of amphotericin B and liposomal amphotericin B formulations decreased and the consumption of voriconazole, a newer molecule, increased. The efficacy against aspergillus and candida spp. and the less adverse effect potential of voriconazole has influenced this change [13].

Pharmaceutical industry has an important role in the consumption of antibiotics. The promotional activity of the drug industry may also influence these changes. The increase in promotions and ignorance of empirical treatment principles may cause an increase in consumption of some new antibiotics [14,15]. We think that the decrease in the utilization rate of teicoplanin and increase in the consumption of linezolid which is a new group is depend on the lack in promotional activity of teicoplanin.

Due to legal regulations introduced in 2003, broad spectrum antibiotics can be prescribed only with IDS approval in Turkey. In our country, various studies have been conducted to measure the effectiveness of this practice. Hosoglu et al. [16] indicated a significant decrease in antibiotic consumption in hospitals due to these regulations. In other studies by Ozkurt et al. [3] and Arda et al. [17] the consumption and cost of restricted antibiotics decreased significantly as well. However, Tunger et al. [4] showed a decrease in unnecessary use of antibiotics but an increase in rational use of antibiotics. Moreover Karabay et al. found an increase in antibiotic consumption in Turkey [6].

In a study that included 56 intensive care units in Turkey, the most frequently isolated bacteria were *Pseudomonas aeruginosa* (20.8%), *Acinetobacter spp*. (18.2%) and *Staphylococcus aureus* (18.2%) [18]. In another multicenter study from Turkey, 52.2% of *Acinetobacter* isolates were resistant to carbapenems [19]. After 2005, intensive care unit bed capacity increased in Turkey. The increase in intensive care unit bed capacity was 8.6-fold between 2002 and 2010. This increase caused an increase in severely ill patients. In addition, the number of large and mid-level operations increased in hospitals. According to a regulation made by the Ministry of Health in 2006, due to the performance of health care workers, additional funds had been given from the revolving fund. As a result of this regulation, interventional procedures increased in hospitals. The number of large operations was increased to 34.0 per 1000 people in 2008 from 11.0 per 1000 people in 2002. Also, the number of mid-level operations was increased approximately 3-fold (from8.1 to 24.6 per 1000 people) in this period [14]. According to population census data, Turkey's population is 65,299,000 in 2000 and is estimated to be 74,559,000 with a 1.14-fold increase in 2010. Therefore, there is no relation between the increased rate of surgical operations and the increased population. The increase in surgical operations could be due to the increase in number of patients as well as the additional funds that were given to health care workers due to performance [20].

The use of box-based data is a limitation of this study. In several similar studies, defined daily doses (DDD) were used. DDD is not used in this study because data obtained from this study, when compared with the population of 75 million, represents extremely small values and the real trend cannot be estimated. However, the antibiotics that are investigated in this study are broad spectrum antibiotics and are used in severely ill patients that are treated in intensive care units. To compare them with Turkey's population may cause a misinterpretation of results. Therefore, instead of making this comparison we used box-based data. Thus, the results can be interpreted more clearly.

In conclusion, only limitation of antibiotic use by IDS approval is not enough to restrict the con-

sumption of antibiotics. IDS consultation as well as a multidisciplinary draft of national antibiotic use guidelines, rational use of antibiotics, and use according to World Health Organization suggestions would be most useful. Novel finding of our study is that only antibiotic restriction is not enough strategy for rational antibiotic use. More comprehensive approachs needed for rational antibiotic usage in hospitals.

Acknowledgements

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Effects of cell phone radiation on the levels of T_3, T_4 and TSH, and histological changes in thyroid gland in rats treated with hydroalcholic *Allium sativum* extract

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Abstract

Context: Thyroid is one of the organs most likely to be exposed to radiation whereas garlic is known as reducing risk factors for various diseases.

Objective: To assess the adverse effects of radiation along with the protective effects of garlic on thyroid gland.

Materials and methods: 5groups of rats were used: control, sham (900MHz wavelength), experimental1 (400ml/kg extract), experimental2 (200mg/kg extract and microwaves) and 3 (400mg/kg extract and microwaves). Groups receiving radiation, were exposed 12times a day, each time 10Min. After the first round of irradiation, experimental groups2 and 3 received the extract followed by 11rounds of daily exposure. After a month, levels of hormones were measured. Thyroid glands were also removed then processed and analyzed.

Results: The mean body weight in the sham (217.7±17.67) showed a significant decrease compared to the control (243.7±30.44), whereas, an increase was seen in the experimental3 compared with sham. The concentrations of T_4 and T_3 were lowered while TSH increased significantly in all groups compared to control (P<0/05). Also reduction in the number of cubic cells, a reduction in the amount of follicular fluid and follicular diameter in groups exposed to radiation and received extract were seen.

Conclusion: Microwaves cause weight lost and presence of allicin, vitamins A and B in garlic can compensate some of this weight lost. Both microwaves and garlic extract have effect, on secretion and morphology of thyroid gland. These changes might be attributed to induction of heat and non-specific stresses, production of ROS and activities of various enzymes.

Key words: Electromagnetic; garlic; thyroid hormones.

Introduction

Electromagnetic (EM) spectrum has a broad frequency range including very low frequencies, radio frequencies (radio waves), radar waves, microwaves, infrared radiation, visible light, ultraviolet radiation, X-rays and gamma rays. These waves are intentionally or unintentionally produce by various common devices such as refrigerators, freezers, television, radio, microwave, photocopiers, computer monitors, halogen lamps, printers and diathermic machines (Baharara et al., 2004). Microwave radiation, as a part of electromagnetic spectrum, has a frequency ranging from 300 MHz to 300 GHz (Banik et al., 2003; Baharara et al., 2004; Hemayatkhah Jahromi et al., 2012). This area of electromagnetic spectrum is used in cell phones, and the frequency of waves emitted from cell phones is between 900 MHz to 1GHz (Baharara et al., 2004).

According to some studies ,EM waves emitted from a cell phone even with the power density (Pd) lower than the permitted limit ("1 mw/cm^2") could lead to a wide range of disorders, such as headache, heat sensation in ears, memory loss and fatigue (Hocking, 1998; Sandstrom et al., 2001;). In order to explain the interaction between EMF and living organisms, two different mechanisms have been proposed -thermal and non-thermal mechanisms (Ferreri et al., 2006).

Exposure to magnetic fields generated by cell phones influences different organs and organ systems by either thermal or non-thermal mechanisms. EMF 900 MHz and its effects on the nervous and endocrine systems have been studied extensively. It has been reported that exposure to magnetic fields increases fat breakdown and glycogenolysis; it also elevates the levels of some hormones such as glucagon, cortisol and thyroxin in mice (Aghdam shahryar et al., 2009).

It appears that hormones and their receptors are the first line of health to be adversely affected in cell phone (both present types an next generation) users (Sultan et al., 2010). Since cell phones are usually placed near the thyroid gland during their use, it is one of the organs most likely to be exposed to cell phone irradiation (Lauer et al, 2013; Mortavazi et al., 2009). In an investigation of changes in thyroid hormones and TSH following cell phone use, higher than normal levels of TSH, decreased T4 concentration and normal level of T3 were observed (Mortavazi et al., 2009). Investigated the effect of 900 MHz electromagnetic radiation on TSH and thyroid Hormones in rats showed a reduction in the serum levels of TSH, T4 and T3 (Koyu et al, 2005).

On the other hand, recent scientific studies have been focusing on the use of plant products as therapeutic agents (Sarkar et al., 2006; Mahmoodi et al., 2011). Garlic is one of these plant products, traditionally used for its cytotoxic, antitumor, antifungal, antibacterial, antiviral and anti protozoal properties. Furthermore, in the ancient Indian medicine (Sanhita Sushruta), garlic is recommended for the treatment of hemorrhoids, rheumatism, dermatitis, abdominal pain, cough, leprosy, etc (Sarkar et al., 2006).

As a member of the *Liliaceae* family, *Allium sativum* (Ulbricht et al., 2010), contains various substances including minerals, carbohydrates, proteins, fats and vitamins (Haciseferogullari et al., 2005; Cobas et al., 2010; Kemper, 2000). Vitamins found in garlic include vitamin A, various kinds of vitamin B, such as riboflavin, thiamine, nicotinic acid, and vitamins C and E.

Among many different compounds found in garlic, studies suggest that biological and pharmacological effects of this plant is mainly due to its sulfur compounds (Kemper, 2000; Khlid & Gordon, 2006; Lanzotti, 2006; Cobas et al., 2010). Some of these organo-sulfur compounds are aliin, allicin, ajoene, allylpropyl disulfide, diallyl trisulfide, sallylcysteine, vinyldithiines, S-allylmercaptocystein, and others (Kemper, 2000; Sarkar et al., 2006).

In recent years, there has been a tendency among researchers in attempting to treat disorders by replacing chemical drugs with some natural plant components, because of their high costs, their potential side effects, as well as restrictions of their use, (Mahmoodi et al., 2011). Although, cell phone use is wide spread and some of their inevitable deleterious effects on the body have been documented, there hasn't been any attempt to reduce these effects through diet or use of herbs. Since garlic has some health benefits and microwaves have some adverse effects on the same area of human health, in this study we tried to investigate the effects of cell phone radiation along with the consumption of hydro alcoholic extract of garlic on the thyroid gland. The position of this vital organ in the body and the ubiquity of cell phones are sufficient enough to urge the performance of such studies and make the mobile phone use safer.

Materials and methods

Soaking method (Maceration) was used to prepare garlic extract (Tatara et al., 2005). 40 Wistar rats with mean body weight of 200 ±١٠ g and 80 to 90 days old were used in this study. In order to adapt to new environmental condition all animals were kept in the Animal House of Kazeroon Islamic Azad University for one week before entering into the trial. They were placed in special cages under standard conditions of 23-25C and 12 hours of light and 12 hours of dark cycle. They had unlimited access to food and water, and all moral principles on using and treating animals were taken into consideration.

Animals were randomly divided into 5 groups of 8 including control (left untreated), sham group (exposed to wavelength of 900 MHz), the experimental group 1 (receiving 400mg/kg garlic extract), Experimental group 2 (receiving 200mg/kg extract plus 900 MHz waves), and experimental group 3(receiving 400mg/kg extract plus 900 MHz waves). Groups receiving radiation, were exposed 12 times a day, each time 10 minutes. Nokia 1200 cell phone was used to make electromagnetic field (EMF) and cages were surrounded by aluminum foil to focus waves and limit the EMF to the interior of the cages (figure1). During wave exposure, the cell phone was sat in different modes, including call, missed call and turn on mode (without real talk). After the first round of irradiation, animals of experimental groups 2 and 3 received the extract followed by 11 rounds of daily exposure.

At the end of the experiment (lasting a month), animals were weighed, blood samples were collected and serum levels of TSH, T4 and T3 were measured using ELISA kits (Made by Biosouece

Europe). Thyroid glands were also removed, prepared using classical method of *hematoxylin* and *eosin* staining and studied by light microscope. The results were examined by SPSS software, one-way ANOVA and Tukey's test and the significant difference was sat at ($P<0.05$).

Results

Results of body weight are shown in table 1 which indicates a significant decrease in the mean body weight of sham group in respect to the control, and an increase in the experimental group 3 in respect to the sham group (figure 2 and table.1). Mean serum levels of T3 in the sham group and experimental groups 1, 2 and 3 showed a significant decrease compared to control (figure 3 and table 1). Similarly, a significant decrease was observed in the mean serum levels of T4 in these groups (figure4 and table1). In contrast, mean serum levels of TSH in the sham group and experimental groups 1, 2 and 3 were significantly increased (figure 5 and table 1).

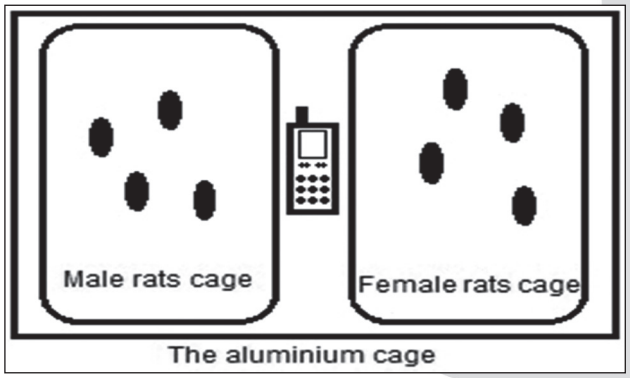

Figure 1. Schema of cellular phone EMFs exposure condition. The mobile set was placed in the middle of the cage containing for male and female rats

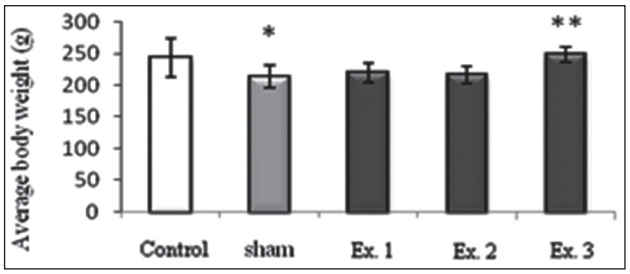

Figure 2. Mean body weight differences among various groups exposed to cell phone radiation and/or received garlic extract
** indicates a significant difference.*

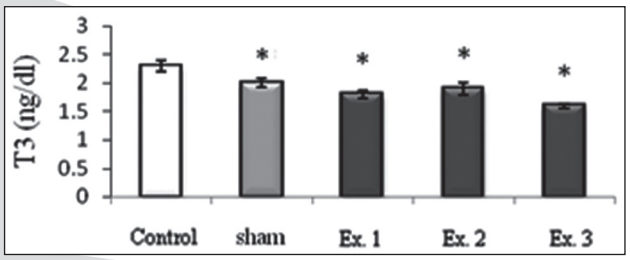

Figure 3. Mean serum levels of T3 hormone among various groups exposed to cell phone radiation and/or received garlic extract
** indicates a significant difference.*

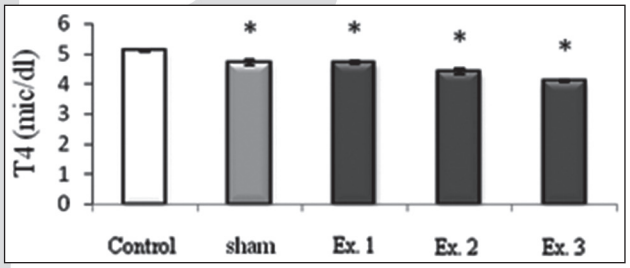

Figure 4. Mean serum levels of T4 hormone among various groups exposed to cell phone radiation and/or received garlic extract
** indicates a significant difference.*

Table 1. Mean body weight and serum levels of T3, T4 and TSH in different groups
** indicates a significant difference*

Groups	Weight (g)			T3 (ng/dl)			T4 (mic/dl)			TSH (micIU/dl)		
	Mean±SE	P*	P**	Mean±SE	P*	P**	Mean±SE	P*	P**	Mean±SE	P*	P**
Control	243.7 ± 30.44			2.3 ± 0.10			5.1 ± 0.05			3.7± 0.06		
Sham	217.7 ± 17.67	*		2.0 ± 0.07	*		4.7 ± 0.10	*		4.0± 0.09	*	
Ex. 1	220.5 ± 15.13			1.8 ± 0.07	*		4.7 ± 0.05	*		4.0± 0.09	*	
Ex. 2	216.5 ± 14.07			1.9 ± 0.11	*		4.4 ± 0.10	*	**	4.2± 0.07	*	**
Ex. 3	248.7 ± 12.17		**	1.6 ± 0.04	*	**	4.1 ± 0.04	*	**	4.7± 0.03	*	**

** compared to control*
*** compared to sham*

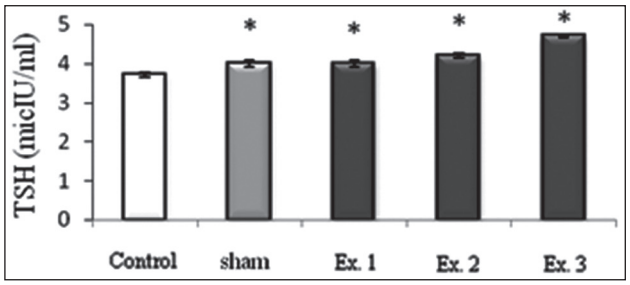

Figure 5. Mean serum levels of TSH hormone among various groups exposed to cell phone radiation and/or received garlic extract
** indicates a significant difference.*

Figure 6 show morphological changes in thyroid gland in different groups. As seen, there is a disordering among cubic cells, a reduction in the number of cubic cells and follicles, and a decrease in the amount of follicular fluid and diameter compared to control.

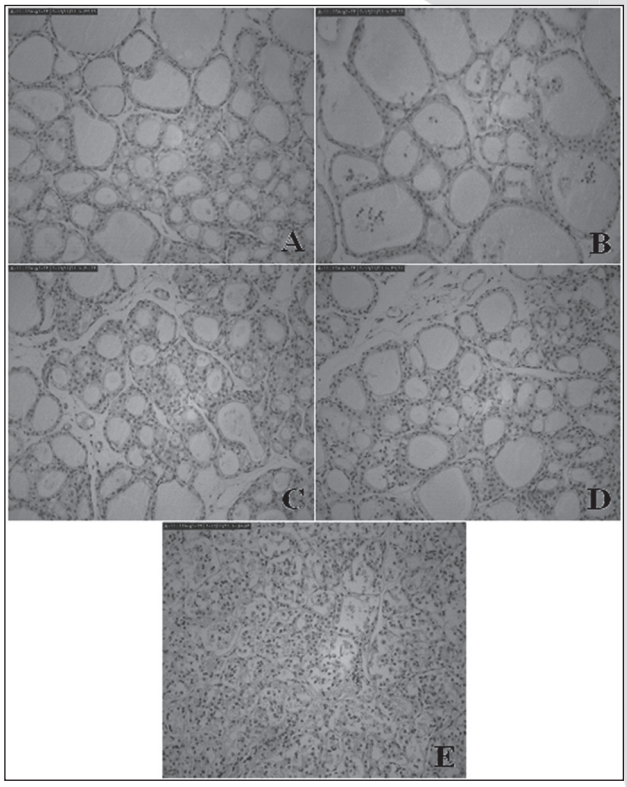

Figure 6. Profile layout of thyroid tissues in different groups exposed to cell phone radiation and/or received garlic extract
A: control,
B: sham,
C: experimental 1,
D: experimental 2 and
E: experimental 3. (Magnification=70X)

Discussion

Since mobile phones are generally held and used close to the body, they are considered as the **main source of E**M radiation that an average person is exposed to. In fact, the whole body could act as an efficient antenna for absorption of EM radiation. Thus, the signals transmitted by a cell phone can reach all parts of the body and penetrate into the living tissues, and influence the body at the cellular level (Sarookhani et al., 2011). It is possible to say that the deleterious effects of electromagnetic microwaves are generally exerted through elevation of body temperature (Thalau et al., 2003; Bagher et al., 2009) and creation of free radicals (Rollwitz et al., 2004; Bagher et al., 2009).

Our study showed that EM waves can cause weight loss and that administration of garlic extract, especially high dose, can prevent weight loss caused by radiation (table 1 and figure 2). Exposure of rats to microwave frequencies at 900 MHz (used in cell phones) can cause oxidative stress on these animals and decrease their antioxidant activities, leading to weight loss (Atilla Ilhan et al, 2004). In contrast, it has been reported that consumption of garlic juice can inhibit body weight reduction in diabetic rats (Musabayane et al., 2006) and can impose anti mutagenic effects against gamma radiation, possibly through inhibition of free radicals (Singh et al., 1996). Garlic contains a significant amount of *thiosulfanat*s or allicin (Jessica et al, 2011) and pharmacological studies have shown that allicin can trap free radicals, and cause an inhibition of lipid oxidation, inhibition of platelet aggregation and stimulation of fibrinolysis resulting in blood lipid reduction (Shahrani et al., 2007).

Have been indicated that, plasma cholesterol and triglyceride levels decline in rodents following exposure to 900 MHz radiation emitted from cell phones leading to weight lost (Aghdam Shahriar & Lotfi, 2009). However, it deviates from the results of some previous study that in there, no significant changes were observed in the body weight of mice at the end of experiment (Jin sang lee et al, 2004). Nevertheless, many studies have shown that MF And EMF can reduce total cholesterol and triglyceride levels in human and laboratory animals, and that these effects were more significant in long-term exposure to radiation and

can be related to an increase in body lipid metabolism. Moreover, these changes may due to the reversible accumulation of triglycerides in the liver or its precursors after acute exposure to 900 MHz microwaves, because Magnetic fields can enhance fat breakdown and glycogenesis (Aghdam shahryar et al., 2009). It also increases body metabolism, body temperature and activity of the sweat glands (Russel & Reiter, 2007).

Although, it has been suggested that garlic influences body weight through lowering of cholesterol and lipids, consumption of this plant does not necessarily lead to weight loss (Saba et al., 2011). Presence of vitamin B family (especially thiamine) in garlic can stimulate the appetite (Newall et al., 1996; Khalid rahman & Gordon, 2006) and Vitamin B6 helps the body to convert carbohydrates and fat into energy (Newall et al., 1996). It makes digestion easier and activates stomach acid secretion.

On the other hand, garlic contains vitamin A (Corzo, 2007) which is considered an important growth factor in animals, and its absence in mice can lead to stunted growth and weight loss. This vitamin can be converted to retinoid that can induce fat storage in the form of triglycerides and cause weight gain (Bakkali, 2008). Thus, one can conclude that presence of allicin and vitamins A and B in garlic can compensate some of the weight lost caused by exposure to radiation.

The results of this study also showed a considerable effects of both microwaves and garlic extract on thyroid gland, reflected both in its secretion and in its morphology. Interference in thyroid functions may occur through an increase in the level of TSH following excessive use of cell phones, leading **to a decline in** the levels of T4 and T3 (table 1 and figures 3-5). Apparently, hypothalamus or pituitary gland play no direct roles in this interference, because if there was any adverse effects on these organs, TSH levels would have been lower than normal (Mortavazi et al., 2009). The strongest and most consistent effects of such irradiation on the endocrine systems would be the induction of heat in tissues and elevation of temperature, or it could be attributed to some non-specific stresses associated with irradiation (Naduvil Narayanan et al., 2010).

Study of other biological effects of EM waves includes the increase level of ornithine carboxylase enzyme that plays some roles in tumor enhancement, changes in thyroid hormone levels and behavior. Other studies are indicative of the induction of reactive oxygen species (ROS) by EM waves which play an important role in damaging cells (Sinha, 2008). In addition, EM waves can cause stress and increase serum cortisol level. Stress can alter thyroid functions through an increase in endogenic cortisol production, because elevation of glucocorticoid secretion constitutes an obstacle to the conversion of T4 into T3 (Aghdam shahryar et al., 2009). Our findings are in agreement with the results of Mortavazi et al. (2009), but they are inconsistent with Sinha (2008) survey. These differences may due to the differences in the dose and duration of exposure to radiation.

Likewise, the effects of garlic extract on observed hormonal changes is well justified. This plant contains flavonoids (Eteng & Aletan, 2012), which inhibit the activities of enzymes antithyroperoxidase (TPO) and liver deiodinase as the key enzyme in the biosynthesis of thyroid hormones and bring about some changes in thyroid functions (Ferreira et al., 2006). Another compound present in garlic is coumarin cis (Abebe, 2002) that influences thyroid functions via blocking the conversion of T_4 to T_3 (Patton et al., 1989).

Garlic can affect TSH level in different ways. It can mediate TSH production through calcium - phosphatidyl inositol as secondary messenger (Ulianich et al., 2004), since it contains calcium and magnesium (Khalid rahman & Gordon, 2006). Garlic is also known as an inhibitory factor in the production of cortisol, and this could be considered another reason for the observed changes in the serum level of TSH, because reduced cortisol level has an elevating effect on the secretion of TSH.

The observed alterations in the levels of T_3 T_4 and TSH are accompanied by the histological changes in thyroid gland. Our histological study indicates a reduction in the number of cubic cells, an irregularity in the arrangement of these cells, and a decline in the number of follicles, amount of follicular fluid and their diameters in the groups exposed to EM waves and received garlic extract (fig 6B & 6C). When both factors were administered simultaneously, tissue degradation rate and destruction of follicles increased (fig 6D & 6E), and at the same time, led to a significant reduction in the rate of thyroid hormone production (table 1 and figures

3 and 4). These signs of thyroid malfunction may be the results of increased caspase-dependent apoptosis pathways (Esmekaya et al., 2010).

In short, it appears that, body exposure to microwave radiation emitted by mobile phones can cause pathological changes in the thyroid gland leading to changes in its secretion and its structural alteration. Moreover, some of these changes are in the same area where garlic components can influence. However, some of these overlaps are synergistic and others are antagonistic, and thus, garlic consumption are not always beneficial in reducing deleterious effects of cell phone use.

Conclusion

This study highlights some adverse effects of microwaves and benefits of garlic in making cell phone use safer. Although, microwaves can cause weight lost by enhancing fat breakdown and glycogenesis, presence of allicin and vitamins A and B in garlic can compensate some of this weight lost through an increase in appetite, digestive processes and body's metabolism. In addition, both microwaves and garlic extract has a considerable effects on thyroid gland, reflected both in its secretion and in its morphology. These effects could be attributed to induction of heat in tissues and non-specific stresses associated with irradiation, changes in the levels of cortisol, reactive oxygen species, calcium - phosphatidyl inositol and various enzymes, such as ornithine carboxylase, anti thyroperoxidase and liver deiodinase. In spite of these, consumption of Garlic is not recommended to prevent the deleterious effects of cell phone radiation on thyroid gland.

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Platelet and white blood cell counts in severity of sickle cell diseases

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Abstract

Background: We tried to understand whether or not there is an association between platelet (PLT) and white blood cell (WBC) counts of peripheric blood and severity of sickle cell diseases (SCDs).

Methods: The SCDs patients with red blood cell transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups.

Results: The study included 316 cases. There were 224 cases (70.8%) in the first and 92 cases (29.1%) in the second groups ($p<0.001$). Male ratio was significantly higher in the second group (45.5% versus 64.1%, respectively, $p<0.001$). Although both the WBC and PLT counts were higher in the second group, the difference was only significant for the PLT counts ($p= 0.005$) probably due to the small sample sizes. Although prevalences of smoking, avascular necrosis of bones, cirrhosis, and exitus were similar in the groups, mean number of painful crises per year, digital clubbing, chronic obstructive pulmonary disease, leg ulcers, stroke, chronic renal disease, and coronary heart disease were significantly higher in the second group ($p<0.05$ for all).

Conclusion: Although the difference was statistically nonsignificant between the WBC count and severity of SCDs probably due to the small sample sizes of the study, there was a highly significant association between the PLT count and disease severity. So the higher PLT and WBC counts of the second group may indicate the significant roles of the cells for the chronic endothelial damage of the SCDs all over the body.

Key words: Platelet, white blood cell, sickle cell diseases, chronic endothelial damage

Introduction

Atherosclerosis may be the major cause of aging by inducing end-organ failures. Although it mainly keeps high blood pressure (BP) carrying arteries, the arterioles and even capillaries are probably affected with some extent. Some of the triggering factors of the systemic process are overweight, elevated BP, dyslipidemia, and insulin resistance for the appearance of final pathologies including obesity, hypertension, diabetes mellitus (DM), peripheric artery disease, chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), cirrhosis, coronary heart disease (CHD), stroke, and aging, all of which are collected under the title of metabolic syndrome (1-6). On the other hand, sickle cell diseases (SCDs) are microangiopathic processes affecting whole body which are caused by homozygous inheritance of hemoglobin S (Hb S) (7,8). Glutamic acid is replaced with valine in the sixth position of the beta chain of the Hb S. Presence of valine promotes polymerisation of the Hb S. So Hb S causes red blood cells (RBCs) to loss their normal elastic and biconcave disc shaped structures. Probably the loss elasticity of RBCs instead of their shapes is the main pathology of SCDs, since sickling is rarely observed in the peripheric blood smears of the patients associated with thalassemias. Loss of elasticity is probably present with some extent in whole life, but it is exaggerated with stressful conditions. The hard RBCs can take their normal elastic natures after normalization of the stressful events, but they become permanent hard bodies in time. The hard bodies induced chronic endothelial damage at the capillary systems are the final consequences that developed secondary to the edematous endothelium. On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport but not distribution functions of them. We tried to

understand whether or not there is an association between platelet (PLT) and white blood cell (WBC) counts of peripheric blood and severity of SCDs.

Material and methods

The study was performed in the Hematology Service of the Mustafa Kemal University between March 2007 and January 2014. All patients with SCDs were enrolled into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Their medical histories including numbers of painful crises per year, units of transfused RBC in their lives, smoking habit, regular alcohol consumption, leg ulcers, and stroke were learnt. Cases with a history of one pack-year were accepted as smokers, and cases with a history of one drink a day for one year were accepted as drinkers. A check up procedure including serum iron, total iron binding capacity, serum ferritin, serum creatinine value on three occasions, hepatic function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, an electrocardiography, a Doppler echocardiography, an abdominal ultrasonography, a Doppler ultrasonography to evaluate the portal blood flow in required cases, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bone areas for avascular necrosis were scanned according to the patients' complaints. Cases with acute painful crises or any other inflammatory event were treated at first, and then the spirometric pulmonary function tests to diagnose COPD, renal and hepatic function tests, and measurement of serum ferritin were performed on the silent phase. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (9). Avascular necrosis of bones was detected via MRI (10). CRD is diagnosed with a permanently elevated serum creatinine level which is 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females on the silent phase. Cases with renal transplantation were put into the CRD group. Cirrhosis is diagnosed with hepatic function tests, ultrasonographic findings, and ascites without any histologic procedure in the absence of indication. Digital clubbing is diagnosed by determining of the ratio of distal phalangeal diameter to interphalangeal diameter which is required to be higher than 1.0, and with the presence of Swamroth sign (11,12). Associated thalassemias are detected by serum iron, total iron binding capacity, serum ferritin, and the hemoglobin electrophoresis performed via HPLC. A stress electrocardiography was performed in cases with an abnormal electrocardiography and/or angina pectoris. A coronary angiography was obtained just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of the cardiac walls. Eventually, cases with RBC transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups, and the groups were compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 316 patients with SCDs (155 females and 161 males). There were 224 cases (70.8%) in the first and 92 cases (29.1%) in the second groups ($p<0.001$). There was not a significant difference according to the prevalence of associated thalassemias between the groups (Table 1). Mean ages of the groups were similar, too (28.9 and 30.0 years, respectively, $p>0.05$). The mean units of transfused RBCs were 12.9 and 99.0, respectively ($p<0.000$). Interestingly, the male ratio was significantly higher in the second group (45.5% versus 64.1%, respectively, $p<0.001$). Although both the WBC and PLT counts of the peripheric blood were higher in the second group, the difference was only significant for the PLT counts ($p= 0.005$), probably due to the small sample sizes of the study (Table 2). Hematocrit values were similar in the groups (23.8% versus 23.7%, $p>0.05$). Although the prevalences of smoking, avascular necrosis of bones, cirrhosis, and exitus were similar in the two groups ($p>0.05$ for all), the mean number of painful crises per year, digital clubbing, COPD, leg ulcers, stroke, CRD, and CHD were significantly higher in the second group ($p<0.05$ for all) (Table 3). Mean ages of the mortal cases were 29.5 ± 9.8 (19-50) and 34.6 ± 6.7 (26-44) years in the first and second groups, respectively ($p>0.05$). Mean ages of the

mortal cases were 29.7 ± 9.6 (19-50) and 33.3 ± 8.5 (21-44) years in males and females, respectively in both groups (p>0.05). On the other hand, there was not any patient with regular alcohol consumption among the study cases. Additionally, five of the CRD cases were on hemodialysis, and one with renal transplantation. Although antiHCV was positive in two of the cirrhotic cases, HCV RNA was detected as negative by polymerase chain reaction in both. Histological diagnosis of cirrhosis was required in none of the cases.

Discussion

The SCDs mainly affect microvascular endothelium (13), since the capillary system is the main distributor of the hard RBCs to tissues. Because of the microvascular nature of the SCDs as in microvascular complications of DM, we can observe healing of leg ulcers with hydroxyurea therapy in early years of life, but the healing process is difficult due to the excessive fibrosis around the capillaries later in life. Eventually, the mean survival was 42 years in males and 48 years in females in the literature (14), whereas it was 29 and 33 years in males and females in the present study, respectively (p>0.05). According to our practise, the differences between the survival are secondary to the initiation of hydroxyurea treatment in early years of life in developed countries. On the other hand, the prolonged survival of females with SCDs and the longer overall survival of females in the world

Table 1. Sickle cell patients with the units of red blood cell transfusions

Variables	Cases with RBC* transfusions of less than 50 units	*p*-value	Cases with RBC transfusions of 50 units or higher
Prevalence	70.8% (224)	<0.001	29.1% (92)
Thalassemia minors	62.0% (139)	ns†	58.6% (54)
Mean RBC units	12.9 ± 11.2 (0-48)	<0.000	99.0 ± 56.5 (50-362)
Mean age (year)	28.9 ± 9.9 (5-59)	ns	30.0 ± 9.2 (9-56)
Male ratio	45.5% (102)	<0.001	64.1% (59)

**Red blood cell †Nonsignificant (p>0.05)*

Table 2. Sickle cell patients with peripheric blood values

Variables	Cases with RBC* transfusions of less than 50 units	p-value	Cases with RBC transfusions of 50 units or higher
Mean WBC† counts (µL)	14.931 ± 6.791 (2.460-39.200)	ns‡	15.346 ± 5.640 (1.580-36.900)
Mean PLT§ counts (µL)	435.670±236.693 (48.000-1.827.000)	0.005	498.310±224.570 (53.000-1.370.000)
Mean hematocrit value (%)	23.8 ± 4.8 (11-42)	ns	23.7 ± 4.9 (13-39)

**Red blood cell †White blood cell ‡Nonsignificant (p>0.05) §Platelet*

Table 3. Sickle cell patients with associated disorders

Variables	Cases with RBC* transfusions of less than 50 units	*p*-value	Cases with RBC transfusions of 50 units or higher
Painful crises per year	3.8 ± 6.3 (0-52)	0.000	8.4 ± 10.9 (0-52)
Smoking	12.0% (27)	ns†	17.3% (16)
Digital clubbing	7.1% (16)	<0.01	15.2% (14)
COPD‡	6.6% (15)	<0.001	20.6% (19)
Leg ulcers	11.6% (26)	<0.01	21.7% (20)
Stroke	5.8% (13)	<0.05	11.9% (11)
CRD§	4.9% (11)	<0.001	14.1% (13)
Avascular necrosis of bones	20.5% (46)	ns	17.3% (16)
Cirrhosis	4.4% (10)	ns	4.3% (4)
CHD¶	4.0% (9)	<0.05	8.6% (8)
Exitus	4.4% (10)	ns	5.4% (5)

**Red blood cell †Nonsignificant (p>0.05) ‡Chronic obstructive pulmonary disease §Chronic renal disease ¶Coronary heart disease*

(15) could not be explained by the atherosclerotic effects of smoking alone, instead it may be explained by the dominant role of male sex in life (16). Similarly, the male ratio was significantly higher in the second group in the present study (45.5% versus 64.1%, respectively, $p<0.001$).

Severe painful crises are nearly the pathognomonic signs of the diseases, and they may be precipitated by infections, operations, depressions, and tissue damage. Although painful crises may not be life threatening directly (17), increased basal metabolic rate with the crises may terminate with multiorgan failures on the chronic inflammatory background of the SCDs (18). The severe pain may be secondary to the generalized inflammation of the capillary endothelium, and the increased WBC and PLT counts and decreased hematocrit values indicate presence of a chronic inflammatory process during whole their lives in such cases in the present study. Similar to our results, increased WBC counts even in the absence of a painful crisis was an independent predictor of the disease severity (19), and it was associated with an increased risk of stroke by causing endothelial damage in brain (20). Due to the severity of pain, narcotic analgesics are usually needed (21), but according to our experiences, repeated RBC transfusions according to the requirement are highly effective during the severe crises both to relieve pain and to prevent sudden death that may develop secondary to the multiorgan failures on the prolonged inflammatory background of the SCDs. Simplicity of preparation of RBC suspensions in a short period of time provides advantages to clinicians to use them even in small public hospitals without the requirement of specialized health workers and equipments as in RBC exchange. Additionally, preparation of one or two units of RBC suspension in each time provides times to us to prepare more units by preventing sudden death of the patients. By this way, we can prevent some of the deaths developed during the transport of severe cases to tertiary health centers.

Hydroxyurea is an effective therapeutic option in chronic myeloproliferative disorders and SCDs. It interferes with cell division by blocking the formation of deoxyribonucleotides that are building blocks of DNA. Hydroxyurea mainly acts on hyperproliferative cells. Although the action way of hydroxyurea is thought to be the increase of gamma globin synthesis for fetal hemoglobin (Hb F) (22,23), its main action may be suppression of hyperproliferative WBC and PLTs in the SCDs. By this way, the continuous inflammatory process of the SCDs that initiated at birth on the capillary endothelium is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferative skin cells. As in autoimmune diseases, although presence of a continuous damage of hard bodies on the capillary endothelium in the SCDs, the severity of destructive process is probably exaggerated by the patients' WBCs and PLTs. So suppression of excessive proliferation of them probably limits the capillary damage-induced tissue ischemia and infarcts all over the body. Similarly, lower neutrophil counts were associated with lower crises rates, and if a tissue infarction occurs, lower neutrophil counts may limit severity of pain and extent of tissue damage in another study (24). On the other hand, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels, significantly (24).

It was reported in the National Institutes of Health Consensus Conference that hydroxyurea is underused both in children and adults (25). First of all, due to the fear of some side effects, females and even males may not use the drug for a long period of time just to get a baby with additional inhibitory effects of the chronic inflammatory disease on fertility. Whereas we have not observed any significant side effect of the drug during the 7-year follow up period. Additionally, there is fear of cancers in people, since hydroxyurea is a chemotherapeutic agent (25). However, the cancer risk has not been substantiated by more than a decade of using hydroxyurea for adults (26). Although some data show risk to fetus (27), potential benefits may outweigh potential risk even in pregnancy. According to our experiences, there are several patients with infertility, abortus, and stillbirths in the absence of hydroxyurea therapy, and the decreased number and severity of painful crises, increased body weight, decreased WBC and PLT counts, and increased hematocrit value with the hydroxyurea therapy will probably result with resolution of the above problems with some extent. It is clear that there is a need for more effective treatment regimens in the SCDs, but until they become more

available, hydroxyurea should be used in all cases, and its dose should be kept as higher in the moderate and severe patients.

Hydroxyurea may have a critical role in the SCDs (13). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely involved adults with sickle cell anemia (Hb SS), and compared the results of patients treated with hydroxyurea or placebo (28). The study especially searched effects of the drug on painful crises, acute chest syndrome, and need of RBC transfusions. The results were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated to all patients. The patients treated with hydroxyurea had a 44% decrease of hospitalizations, and there was an independent association of lower neutrophil counts with the lower crisis rates (28). But this study was performed in severe Hb SS cases alone, and the frequency of painful crises was decreased from 4.5 to 2.5 per year (28). Whereas in one of our studies, we studied 337 patients with all subtypes and all severity of SCDs, and the frequency of painful crises was decreased from 10.3 to 1.7 per year (p<0.000) with an additional decreased severity of them (7.8 versus 2.2, p<0.000) (29). Parallel to the above, adult SCDs patients using hydroxyurea appear to have reduced mortality rate after a 9-year follow-up period (30). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may decrease severity of disease (30) and prolong survival (13). Chronic endothelial damage of the capillaries is initiated at birth, and complications start to be seen in infancy. For example, infants with lower hemoglobin levels were more likely to have higher incidences of acute chest syndrome, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (31). Hydroxyurea in early life may also protect splenic function, improve growth, and prevent multiorgan dysfunctions by preventing early capillary damage. Transfusion programmes can also reduce complications, but they carry some major risks including infections, development of allo-antibodies, and iron overload. Additionally using an oral drug at home is a much easier method than the regular blood transfusions for the patients, their families, and governments.

As a conclusion, although the difference was statistically nonsignificant between the WBC count and severity of SCDs probably due to the small sample sizes of the study, there was a highly significant association between the PLT count and disease severity. So the higher PLT and WBC counts of the second group may indicate the significant roles of the cells for the chronic endothelial damage of the SCDs all over the body.

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Evaluation of the relation between smoking frequency, smoking addiction and depression in university students

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Abstract

Objective: To determine the smoking frequency in university students, review some associated factors and evaluate the relation between smoking addiction and depression.

Material and method: The study is a cross-sectional research conducted on the students of the Sakarya University between 10 November 2012 and 10 January 2013. The study group included 1,010 students. Questionnaire forms prepared in line with the study objective were completed by the students under supervision. In this study, students who smoke at least one cigarette per day regularly were defined as smokers. The Fagerstrom Test for Nicotine Dependence was used to assess the nicotine dependence in our study. Depression level was evaluated with the Beck Depression Inventory. Chi-square test and Spearman's Correlation Analysis were used to analyze the data. Statistical significance level was accepted as $p < 0.05$.

Results: The study group consisted of 543 female (53.8%) and 467 male (46.2%) students. Their age ranged from 18 to 33 with an average of 21.1 ± 1.94 years. Smoking frequency was found to be 26.7% (n = 270) in our study. Smoking frequency was determined to be higher in the students of the Faculty of Fine Arts, those who have spent most of their life in the city centre, freshman students, male students, those aged 23 and above, those having divorced parents, those whose parents were graduated from the junior high school or higher, those with no social security ($p < 0.05$ for each) whereas it was determined to be lower in the students living with their parents and staying at private dormitories and those whose family income is average ($p < 0.05$ for each). Depression level was higher in the smokers ($p < 0.05$). There was no relation between the quantity of cigarette consumed and addiction level ($p > 0.05$). There was a positive relation between the addiction level and depression level ($p < 0.05$).

Conclusion and suggestions: Smoking is a negative health-related habit common among university students. The addiction level increases with higher consumption in pack years. The smokers were found to be more depressive. There was a positive relation between the addiction level and depression level. In addition to implementation of indoor smoking ban, organizing smoking cessation events, raising awareness on the harms of smoking among the university students and launching anti-smoking campaigns would be useful.

Key words: Smoking, addiction, depression, university students

Introduction

Smoking is an important public health problem because of great number of diseases and death associated with it (Ozcebe et al., 2013).

It is a well-known fact that tobacco is the most commonly used addictive substance in the world (American Cancer Society, 2013). The World Health Organization (WHO) defines smoking as "the fastest growing and most prolonged outbreak of the world" (Nakajima, 1996). As the cigarette can be easily obtained all around the world, its use has been spreading day by day. This spread is particularly fast among the young population in developing countries (Barut, 1992). At the present time, 30-50% of men and 10-20% of women in developed countries as well as 40-60% of men and 2-10% of women in developing countries smoke (Ogel et al., 2003; Jairath et al., 2003).

Based on the WHO data, 84% of 1.3 billion of smokers currently live in developing countries such as Turkey (Warren, 2008). Smoking frequency is 33.4% in Turkey and 6.9% among young people (WHO, 2009). Rigotti et al. reported that smoking habit has increased dramatically among young people aged 18 to 24 in the United States (Rigotti et al, 2000). Unless the smoking frequency changes around the world, 8.4 million people are expected to die by 2020 because of smoking (Global Youth Tobacco Survey Collaborating Group Differences in worldwide tobacco use by gender: findings from the Global Youth Tobacco Survey, 2003).

Young adults constitute the highest risk group in terms of using addictive cigarette, alcohol and drugs (Drobes, 2002). More than 80% of smokers are known to start smoking before the age of 18 (US Department of Health and Human Services, 1994). Family members and close friends are determinant in this period (Tanrikulu et al, 2009). Smoking may have an earlier onset because of reasons such as adolescence psychology, being away from home and family and orientation to a new environment (Drobes, 2002). Some recent studies showed that the reasons for starting smoking are different in young men and women. Reason to start smoking was reported to be associated with variables such as negative stress management and social effect of parents and social circle. For young men, curiosity and problems in relationships with parents and friends were emphasized to effective in starting smoking (Charlton and Blair, 1989; Flay et al, 1998; Van den Bree et al, 2004).

Depression is a bio-psychosocial illness along with its reasons and results and suggests low mood, feeling sad and reduction of functional and vital activity. Depression is observed in all periods of life. Various life events and environmental stress factors may reveal depression (Paarlberg et al., 1996; WHO, 1999). Smoking frequency in adolescence is 15-20% whereas frequency of depression may be up to 35% in smoking adolescents (Gulec et al., 2003). Smoking is a common behavior observed in depressive persons (Hall et al., 1994; Cosar et al., 1996; Allgöwer et al., 2001). This habit may also be observed with some mood disorders other than depression (Dallack et al.,, 1995). Individuals may incline to smoking for dealing with such negative mood disorders (Campo-Arias et al., 2006). Depressive individuals consider smoking as a stimulating and calming habit. This conception is related to expectations from smoking (Acierno et al., 1996).

This study is intended to determine the smoking frequency among students of Sakarya University, review some associated factors and evaluate the relation between smoking addiction and depression.

Material and method

This study is a cross-sectional research conducted on the students of the Sakarya University between 10 November 2012 and 10 February 2013.

28,453 students are educated within 10 Faculties and 3 Institutes of the Sakarya University. In this study, the sample size was calculated as 853 students by using the sample size formula that is used when the number of universe is known (incidence of the condition is 33%, margin of error 0.04, confidence level 95.0%). After these departments were selected by casting lots, 1,010 students who were randomly selected from each class constituted the study group.

Questionnaire form which was prepared based on the literature (Charlton and Blair, 1989; Shafey et al., 2003; Fernander et al., 2006; Warren et al., 2008) in line with the objective of the study included questions on some socio-demographic characteristics (settlement where they have spent most of their lives, where they stay, school, grade, sex, age, family type, family income, social security status, educational background and employment status of parents), some smoking related characteristics (smoking status, age to start smoking, number of cigarettes smoked daily, number of smoking years), questions related to Fagerström Tolerance Questionnaire and questions related Beck Depression Inventory.

Before starting the study, required approvals were obtained from the Sakarya University management and Faculty managers. The students were gathered in the classes, informed about the subject and objective of the study, and their verbal consents were taken. Previously prepared questionnaire forms were completed by the students under supervision. This procedure lasted for approximately 20-25 minutes. The rules stated in the Helsinki Declaration were complied in the stage of data collection.

Table 1. Some socio-demographic characteristics of smokers and non-smokers in the study group

Socio-demographic characteristics	Smoking			Statistical Analysis X^2; p
	No n (%)*	Yes n (%)*	Total n (%)**	
Settlement where they spent most of their lives				
District and village	346 (80.5)	84 (19.5)	430 (42.6)	**19.806; 0.000**
City centre	394 (67.9)	186 (32.1)	580 (57.4)	
Where they stay				
State dormitory	78 (72.9)	29 (27.1)	107 (10.6)	**9.602; 0.048**
Private dormitory	236 (79.29	62 (20.8)	298 (29.5)	
With their family	129 (74.1)	45 (25.9)	174 (17.2)	
At house with friend	212 (68.8)	96 (31.2)	308 (30.5)	
At house alone	85 (69.1)	38 (30.9)	123 (12.2)	
School				
School of Health	126 (84.6)	23 (15.4)	149 (14.8)	**18.536; 0.002**
Faculty of Engineering	169 (73.8)	60 (26.2)	229 (22.7)	
Faculty of Arts and Sciences	162 (70.1)	69 (29.9)	231 (22.9)	
Faculty of Economics and Administrative Sciences	198 (74.2)	69 (25.8)	267 (26.4)	
School of Physical Education and Sports	50 (66.7)	25 (33.3)	75 (7.4)	
Faculty of Fine Arts	35 (59.3)	24 (40.7)	59 (5.8)	
Grade				
1	143 (68.8)	65 (31.2)	208 (20.6)	**4.325; 0.228**
2	287 (75.5)	93 (24.5)	380 (37.6)	
3	123 (70.7)	51 (29.3)	174 (17.2)	
4	187 (75.4)	61 (24.6)	248 (24.6)	
Sex				
Female	442 (81.4)	101 (18.6)	543 (53.8)	**39.653; 0.000**
Male	298 (63.8)	169 (36.2)	467 (46.2)	
Age group				
≤19	148 (74.4)	51 (25.6)	199 (19.7)	**11.520; 0.021**
20	157 (74.1)	55 (25.9)	212 (21.0)	
21	171 (74.3)	59 (25.7)	230 (22.8)	
22	134 (79.8)	34 (20.2)	168 (16.6)	
≥23	130 (64.7)	71 (35.3)	201 (19.9)	
Family type				
Nuclear	607 (74.3)	210 (25.7)	817 (80.9)	**15.632; 0.000**
Extended	109 (75.7)	35 (24.3)	144 (14.3)	
Divorced	24 (49.0)	25 (51.0)	49 (4.9)	
Family income				
Poor	35 (68.6)	16 (31.4)	51 (5.0)	**15.458; 0.000**
Moderate	458 (77.9)	130 (22.1)	588 (58.2)	
Good	247 (66.6)	124 (33.4)	371 (36.7)	
Social security status				
Not available	62 (53.4)	54 (46.6)	116 (11.5)	**26.282; 0.000**
Available	678 (75.8)	216 (24.2)	894 (88.5)	
Total	740 (73.3)	270 (26.7)	1010 (100.0)	

**: Percentages were calculated based on the line total*

***: Percentages were calculated based on the column total.*

Students who smoked at least one cigarette per day were defined as smokers, whereas nonsmokers were defined as students who had never smoked or who had not smoked in the past 6 months (Tolonen et al., 2002).

In this study Fagerstrom Tolerance Questionnaire (FTQ) was used to assess Nicotine Dependency. This test was developed by Fagerstrom et al. (Fagerstrom et al., 1990) in 1990 and its reliability and validity study in Turkey was conducted in 2006 (Aksakal and Khorshid, 2006). The test consists of 6 items and items 1 and 2 were scored 0-1-2-3 and items 3 to 6 were scored 0-1. The scores to be obtained from this test ranged between 0 and 10. In this test, a score of 0-2 corresponded to very low, 3-4 to low, 5 to moderate, 6-7 to high and 8-10 to very high nicotine dependency.

Depression was measured with a Turkish version of the Beck Depression Inventory (BDI), which consists of 21 items. The BDI was developed by Beck et al. in 1961 (Beck et al, 1961) and later modified by Hisli in 1999 to suit the Turkish culture and norms (Hisli, 1998). The answer for each item was evaluated as 0, 1, 2, and 3 points. The lowest number of points was accepted as '0' and the highest '63', with a cut-off point of 17.

The data obtained was evaluated in IBM SPSS (version 20.0) Statistical Package Program in computer. Chi-square test and Spearman's Correlation Analysis were used for analyses. Statistical significance was accepted as $p < 0.05$.

Results

The study group consisted of 543 female (53.8%) and 467 male (46.2%) students. Age of students ranged from 18 to 33 with an average of 21.1 ± 1.94 years. Smoking frequency was found to be 26.7% (n = 270) in our study. Distribution of smoker and non-smoker students by some sociodemographic characteristics is given in Table 1.

While 435 students (43.1%) had a mother who graduated from junior high school or higher, 690 students (68.3%) had a father who graduated from junior high school or higher. 202 students (20.0%) had a working mother and 852 students (84.4%) had a working father. The distribution of smokers and non-smokers in the study group by some parental characteristics is given in Table 2.

Number of cigarettes smoked daily ranged 1 to 40 among the smokers in the study group and age to start smoking was between 7 and 25. Number of cigarettes smoked in pack year was determined to range 0.5 to 19.5 among the smokers. The scores obtained by the smokers from Fagerström Tolerance Questionnaire were between 1 and 10 with a mean score of 4.75 ± 1.94. No association was determined between the number of cigarettes

Table 2. Some parental characteristics of smokers and non-smokers in the study group

Some parental characteristics	Smoking			Statistical Analysis X^2; p
	No n (%)*	Yes n (%)*	Total n (%)**	
Education status of mother				
Primary school and lower	442 (76.9)	133 (23.1)	575 (56.9)	**8.845; 0.003**
Junior high school and higher	298 (68.5)	137 (31.59	435 (43.1)	
Education status of father				
Primary school and lower	273 (85.3)	47 (14.7)	320 (31.7)	**34.697; 0.000**
Junior high school and higher	467 (67.7)	223 (32.3)	690 (68.3)	
Employment status of mother				
Unemployed	599 (74.1)	209 (25.9)	808 (80.0)	1.548; 0.213
Employed	141 (69.8)	61 (30.2)	202 (20.0)	
Employment status of father				
Unemployed	117 (74.1)	41 (25.9)	158 (15.6)	0.059; 0.809
Employed	623 (73.1)	229 (26.9)	852 (84.4)	
Total	740 (73.3)	270 (26.7)	1010 (100.0)	

**: Percentages were calculated based on the line total*

***: Percentages were calculated based on the column total.*

smoked in pack year and the scores obtained from Fagerström Tolerance Questionnaire (r_s=0.099; p=0.105). Distribution of number of cigarettes smoked in pack year and the scores obtained from Fagerström Tolerance Questionnaire among the smokers is given in Figure 1.

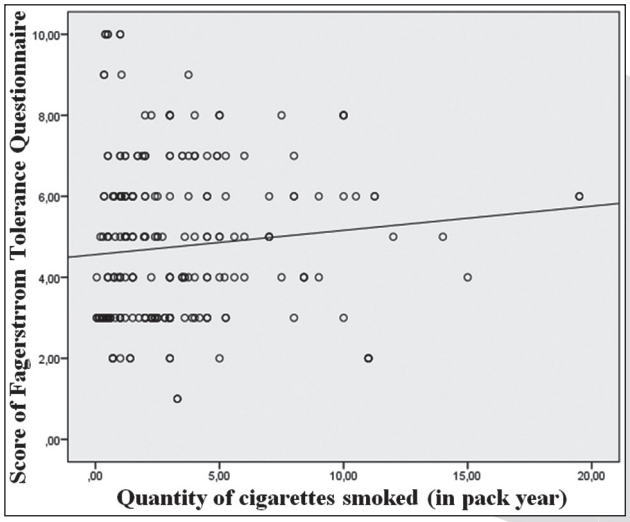

Figure 1. Distribution of number of cigarettes smoked in pack year and the scores obtained from Fagerström Tolerance Questionnaire among the smokers in the study group

Frequency of suspected depression was determined to be 19.0% (n=192) in our study. Distribution of those with and without suspected depression by smoking in the study group is given in Table 3.

The frequency of suspected depression among the smokers was 4.4% (n=66). Based on the scores obtained from Fagerström Tolerance Questionnaire, very low dependency was established in 16 smokers (5.9%), low dependency in 125 smokers (46.3%), moderate dependency in 38 smokers (14.1%), high dependency in 64 smokers (23.7%) and very high dependency in 27 smokers (10.0%). Distribution of those with and without suspected depression by the degrees of Nicotine Dependency among the smokers in the study group is given in Table 4.

The scores obtained by the smoker students from Beck Depression Inventory ranged 0 to 60 with a mean score of 12.67. A positive relation was determined between the scores obtained from Beck Depression Inventory and Fagerström Tolerance Questionnaire (r_s=0.147; p=0.015). The distribution of scores obtained by the smokers in the study group from Fagerström Tolerance Questionnaire and Beck Depression Inventory is given in Figure 2.

Table 3. Distribution of those with and without suspected depression by smoking in the study group

Smoking	Suspected depression		
	No n (%)*	Yes n (%)*	Total n (%)**
Non-smoker	614 (83.0)	126 (17.0)	740 (73.3)
Smoker	204 (75.6)	66 (24.4)	270 (26.7)
Total	818 (81.0)	192 (19.0)	1010 (100.0)

**: Percentages were calculated based on the line total X^2=7.069; p=0.008*
***: Percentages were calculated based on the column total.*

Table 4. Distribution of those with and without suspected depression by the degrees of Nicotine Dependency among the smokers

Nicotine Dependency Degree	Suspected depression		
	No n (%)*	Yes n (%)*	Total n (%)**
Very low	13 (81.2)	3 818.8)	16 (5.9)
Low	98 (78.4)	27 (21.6)	125 (46.3)
Moderate	26 (68.4)	12 (31.6)	38 (14.1)
High	50 (78.1)	14 (21.9)	64 (23.7)
Very high	17 (63.0)	10 (37.0)	27 (10.0)
Total	204 (75.6)	66 (24.4)	270 (100.0)

**: Percentages were calculated based on the line total X^2=4.423; p=0.352*
***: Percentages were calculated based on the column total.*

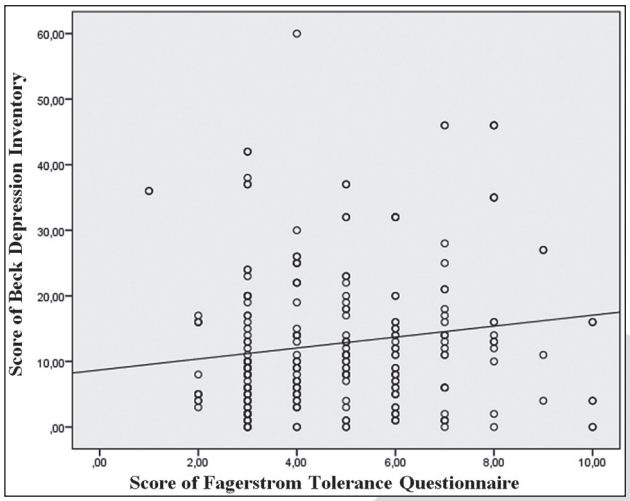

Figure 2. The distribution of scores obtained by the smokers in the study group from Fagerström Tolerance Questionnaire and Beck Depression Inventory

Discussion

While frequency of smoking tends to reduce in developed countries, there is an increase in developing countries. Frequency of smoking in the United States was reported to be 25% (United States Department of Health and Human Services, 1998). Whereas frequency of smoking ranges between 20% and 48% among university students in Turkey (Akdur, 2010). Smoking frequency was found to be 26.7% in this study. As for the reason of reducing smoking ratio, extension of the scope of statutory provision regarding smoking in 2008 is believed to have an impact on reducing the smoking habit among university students.

Onder (2002) demonstrated that smoking possibility is higher in people living in urban areas compared to those living in rural areas (Onder, 2002). The results of our study were consistent with this conclusion and indicated that frequency of smoking is higher among students who have spent most of their lives in city centre ($p < 0.05$). One of the reasons for higher frequency of smoking among those living in urban areas may be the fact that individuals are exposed to more stimulants for smoking.

In this study, frequency of smoking was determined to be lower among students who live with their families and stay in private dormitories ($p < 0.05$). Similar results were reported in various studies (Boyaci et al., 2003; Kartal et al., 2012; Cilingir et al., 2012; Durmaz and Ustun, 2006). However, there are studies indicating that the students who live alone in house and stay in dormitories smoke more cigarettes (Zahran et al., 2007; Mayda et al., 2007). Environment and friends may be determinants for smoking as with all matters. Friends of young people and how they spend their time may have impacts on smoking.

In their study in the UK, Vries et al. determined that the students being educated on arts, social sciences and biology smoke more cigarettes (Vries et al., 2003). In our study, the highest frequency of smoking was observed in the students of the Faculty of Fine Arts and the lowest frequency of smoking was observed in the students of the School of Health ($p < 0.05$). One of the reasons of this situation may be the fact that students of social sciences are more easygoing compared to other students.

Frequency of smoking was expected to be higher because of the reasons such as being away from family, stress caused by the classes and transition to young adulthood particularly in those who completed high school education and started university as well as liberation from family control and being in a free environment in freshman students (Parlar et al., 2006; Rudatsikira et al., 2007). A higher frequency of smoking was determined in freshman students in the study group ($p < 0.05$).

The studies conducted in Turkey and abroad reported a higher frequency of smoking in young men compared to young women (Ogel et al., 2003; Shafey et al., 2003; Dogan and Ulukol, 2010). WHO indicated that frequency of smoking in developing countries has reached to 48% in men and 7% in women (WHO, 2009). In our study, frequency of smoking in male students was higher than female students, similarly ($p < 0.05$). In Global Youth Survey (2008), ratio of smoking was found 10.2% in males and 5.3% in females (Ozcebe et al., 2013). Supporting the smoking behavior in young men by cultural characteristics of our society and embarrassment of young women caused by intolerance to smoking women may be among the reasons of higher frequency of smoking in our study.

Kaptanoglu et al. (2012) reported a positive correlation between the age and number of cigarettes smoked daily (Kaptanoglu et al., 2012). In our study, frequency of smoking was higher in the students aged 23 and above, consistently ($p <$

0.05). One of the reasons of higher frequency of smoking with advancing age may be working life, habits and problems at work.

In the study of John in 2006, higher consumption of smoking was reported in people with low income level (John, 2006). In Onder's study (2002), a positive relationship was found between the number of cigarettes and income level (Onder, 2002). However, this is contrary to the fact that those with poor economic situation would have difficulty in accessing cigarette. Prices of cigarette are particularly lower in our country compared to many countries, which facilitates access to cigarette. In our study, frequency of smoking was found to be lower in those with moderate family income level in the study group, consistently ($p < 0.05$).

Boredom, enjoyment and calming nerves were the top reasons triggering the desire for smoking in some studies (Dagci et al., 1998; Yanikkerem et al., 2003). Smoking individuals may sometimes have an insubordinate, reckless, conflict seeking and hostile character. However, individuals with a strong self-control are less inclined to smoking (Adalbjarnardottir and Rafnsson, 2001). Yazici (2012) reported that smoking attitudes increase in depressive individuals (Yazici et al., 2007). In Talay's study (2008) depression scores in smoker students were reported to be higher compared to non-smokers (Talay et al., 2008). There are investigators who reported a similar relationship between smoking and frequency of depression (Almeida and Pfaff, 2005; Fernander et al., 2006). In this study, a significantly higher frequency of suspected depression was determined in smoker students ($p < 0.05$). These results may be interpreted that individuals with depressive symptoms believe to have control on their behaviors by smoking. Some studies indicated that frequency of smoking and smoking addiction caused emergence of depression symptoms (Almeida and Pfaff, 2005).

Nicotine acts as a basic receptor stimulating the release of other neurotransmitters by dopamine in reward and motivation center of brain. As with all addictions, brain accommodates addiction of the substance eventually and cannot function normally without the substance in question. Nicotine addiction is generally higher in anxious, quick-tempered and lonely people with sudden changes in states of mood. These features may create an environment fit for smoking behavior in the face of challenging or exciting life (Karanci et al., 2007). In our study, a positive relationship was determined between nicotine addiction and depression level ($p < 0.05$).

Limitations

The limitations of the study may include the facts that it is a cross-sectional study, it was conducted on the students of only one university and it is not possible to establish definitive diagnosis with used scales.

Conclusion and recommendations

Smoking is a negative health-related habit common among university students. The addiction level increases with higher consumption in pack years. The smokers were found to be more depressive. There was a positive relation between the addiction level and depression level. In addition to implementation of indoor smoking ban, organizing smoking cessation events, raising awareness on the harms of smoking among the university students and launching anti-smoking campaigns would be useful.

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Evaluation of views of the university hospital nurses on euthanasia

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Abstract

Objektive: The study was conducted to examine and evaluate the views of the university hospital nurses about euthanasia.

Materials and Method: This descriptive study included 325 nurses working at Fırat University Hospital. The research data was collected using a questionnaire form.

Results: The mean age of nurses included in the study was 27.49±5.67, and 93.2% stated that they had information about euthanasia. 54.2% of the nurses reported that they would want the right to euthanasia for themselves, while 76.3% stated that they might ask for euthanasia for a relative or family member. 69.5% of the participants reported that they did not want euthanasia to be legalized, and 78.5% believed that it would be mainly (64.0%) abused by relatives for their inheritance if euthanasia were ever legalized, whereas 16.3% stated that euthanasia should be applied to the patients requesting euthanasia. It was also found that religious beliefs played a significant role on the views of 85.5% of the nurses.

Conclusion: As a result of this study, we concluded that nurses generally have adequate information about euthanasia, while more than half of them did not want euthanasia to be implemented and legalized as they thought legalization would lead to a significant amount of abuse.

Key words: Hospital, nurses, euthanasia.

Introduction

Euthanasia is the medical practice of ending the life of a patient, on patient's request, suffering from an incurable disease or excruciating condition that inspires a sense of mercy (1). Euthanasia is separated into two categories according to the way it is implemented: passive euthanasia and active euthanasia. Active euthanasia is the intentional shortening of life whether by oneself or through direct assistance, with or without the help of medical professionals, while passive euthanasia is the practice of allowing a terminally ill or injured person to die by either withholding or withdrawing life-extending treatment or support (2,3). Euthanasia has become a highly controversial issue as a result of rapid changes in human life (4). In his oath, Hippocrates declared: "*I will neither give a deadly drug to anybody if asked for it, nor will I make a suggestion to this effect*" (5). However, famous philosophers of Antiquity, such as Plato and Aristotle, suggested that mercy-killing the adult patients with incurable diseases, who kept consuming the resources of the city, or allowing them to die without receiving any kind of treatment for the prolongation of life would be an appropriate practice even if they were involuntary to do so (6). Since the mid-1960s, the debate has intensified, and even the most dogmatic religious circles have at least begun supporting passive euthanasia. On the other hand, while human rights are heavily defended, the right to die was concluded to be a fundamental human right (7). With rapid advances in medical knowledge and technology, the nature of how people die has changed. In many countries, average life expectancy has increased to advanced ages. However, this also brought about the prolongation of suffering and other difficulties (8).

The immediate witnesses of this thin line between life and death are health care professionals (7). Some studies reported that about half of the physicians received demands of active or passive euthanasia from patients (9). Euthanasia still continues to raise many heated ethical and political debates both in the world and in our country, and it continues to pose dilemmas for the healthcare professionals, which arise from ethical considerations such as treatment, protecting and sustaining the individual's life as well as the prin-

ciple of respect for autonomy (10). In addition, with every new incident, euthanasia debate sparks up again, dividing the medical world. On one side, opponents of euthanasia argue that it is intentional homicide and acting against the will of God, thus should never be carried out on any grounds, nor should it be legalized. On the other side, the proponents support euthanasia because they believe that it is a medical practice and they should respect their patients' right to be treated as autonomous human beings, thus necessary legal arrangements should be made to allow euthanasia (11,12,13).

The most appropriate approach towards euthanasia should be determined based on the conditions of each country. In this regard, investigating these conditions to obtain adequate data will lead to the most beneficial solution for the issue in our country (4). For this reason, further studies are needed to obtain and evaluate the opinions of healthcare professionals regarding euthanasia in our country. This study was conducted to evaluate the understanding and attitudes of nurses working at Fırat University Hospital towards euthanasia.

Materials and Methods

The target population of this descriptive study was 370 nurses working at Fırat University Hospital. Without selecting a sample, all nurses in the target population were included in the study. We were able to reach 325 of these nurses, thus determining the response rate as 87.8% (325 persons). Data collection was conducted through a questionnaire developed by the researchers in accordance with the literature, which consisted of 32 items covering socio-demographic characteristics and views of nurses on euthanasia. After the nurses were informed about the purpose of the study and they were told that the data obtained would not be used outside of the scientific purposes, the voluntary participants were delivered the questionnaire forms and the forms were collected after they were completed. After obtaining permission from the Ethics Committee and relevant authorities, the study was completed in one-month period, between 1 and 30 April 2012.

The research data were analyzed by a statistical software package, and all error checks, tables and statistical analyses were made using this program. For the statistical analyses, percentages, averages and chi-square tests were used depending on the nature of the variables. Averages were given with standard deviation, and P values less than 0.05 ($p<0.05$) were considered significant.

Results

The mean age of the nurses included in the study (n = 325) was 27.49±5.67 (min: 18, max: 47), and their mean duration of work in the field was 73.04±67.53 months (min: 3 months, max: 336 months). It was found that 87.7% of the participants were female, 51.1% single, 64.6% had Bachelor's degree, and 37.5% worked in internal clinics (Table 1).

Table 1. Distribution of Demographic Characteristics of Nurses

Demographic Characteristics (n = 325)	Number	%
Gender		
Female	285	87.7
Male	40	12.3
Marital status		
Married	155	47.7
Single	166	51.1
Widowed	2	0.6
Divorced	2	0.6
Age Groups		
24 years and under	105	32.3
Between the ages of 25-29	119	36.6
Between the ages of 30-34	60	18.5
35 years and over	41	12.6
Education		
Medical Vocational High School	69	21.2
Associate's Degree	36	11.1
Bachelor's Degree	210	64.6
Master's Degree	10	3.1
Work Unit		
Surgical Clinics	75	23.1
Internal Clinics	122	37.5
Emergency Services	26	8.0
Intensive Care Units	57	17.5
Polyclinics	24	7.4
Operating Rooms	21	6.5
Total Work Experience		
1 year or less	68	20.9
2-8 years	77	54.5
9-15 years	54	16.6
16 years and over	26	8.0

Table 2 shows the knowledge and views of the nurses included in the study about euthanasia.

38.2% of the participants thought that euthanasia was secretly practiced in our country although it was strictly prohibited. Table 3 demonstrates the participant nurses' attitudes towards euthanasia.

69.5% of the nurses included in the study thought that euthanasia should never be legalized in our country as they believed only God could decide life and death (26.8%), while 58.2% stated that euthanasia, if ever legalized, should only be applied to patients suffering total brain death (54.8%) by a dedicated euthanasia team. 78.5% of the participants reported believing that euthanasia, if legalized, would be mainly abused by relatives for inheritance purposes (%64.0). 7.1% of the nu-

Table 2. Nurses' Knowledge and Views about Euthanasia

Characteristics	Number	%
Do you have a relative with chronic disease?		
Yes	172	52.9
No	153	47.1
Do you have a relative that is bedridden?		
Yes	39	12.0
No	286	88.0
Have you encountered with a patient in the terminal stage?		
Yes	257	79.1
No	68	20.9
Do you think a person has the right to end his/her own life?		
Yes	126	38.8
No	199	61.2
Do you think a patient with a terminal disease who knows he/she is about to die is able to make a healthy decision?		
He/she can make a healthy decision	19	5.8
He/she cannot make a healthy decision	258	79.4
Undecided	48	14.8
Do you know anything about euthanasia?		
Yes	303	93.2
No	22	6.8
In your opinion, which of the following describes the practice of euthanasia?*		
It is a patient/human right	100	30.8
It is a medical practice	78	24.0
It is against the will of God/nature/universe	170	52.3
It is murder/intentional manslaughter	134	41.2
Definition of euthanasia is "*Painless killing of a person who has a painful incurable disease or incapacitating disorder*". **Which of the following should be added to this definition?**		
The patient's request in this regard	134	41.2
Doctor's involvement in the practice	36	11.2
The demand of the relatives of patients	41	12.6
The patient's mental capacity	108	33.2
All	6	1.8
Do you think euthanasia should be applied to patients who have fatal diseases with no possibility of recovery and no legal capacity?		
Yes	34	10.4
No	215	66.2
Undecided	76	23.4

**More than one answer. Percentages were taken based on the number n.*

Table 3. Nurses' Attitudes towards Euthanasia

Characteristics	Number	%
If you were confined to bed, would you ask for euthanasia?		
Yes	45	13.8
No	176	54.2
Undecided	104	32.0
Would you demand euthanasia for a relative that is unconscious?		
Yes	25	7.7
No	248	76.3
Undecided	52	16.0
Do religious beliefs prohibit euthanasia?		
Yes	278	85.6
No	18	5.5
Undecided	29	8.9
Do you think a doctor should be punished for applying euthanasia to a person with legal capacity through his/her consent?		
Yes	107	32.9
No	142	43.7
Undecided	76	23.4
If a legal regulation allowed euthanasia, would you participate in a euthanasia team?		
Yes	20	6.2
No	272	83.7
Undecided	33	10.1

rses stated that euthanasia should be legal in our country (20.0%), because they believed "*patient's wishes should be respected*", whereas those opposing the legalization of euthanasia (69.5%) expressed that "*only God has the right to take a person's life away*" (Table 4).

It was also found that nurses with higher education levels were more knowledgeable about euthanasia ($p < 0.05$).

When we evaluated the opinions of nurses about euthanasia based on the units they worked at, we found that 61.9% of the nurses stating euthanasia was a fundamental patient/human right were operating room nurses ($p<0.05$) (Table 5).

The study also revealed that 71.2% of the female participants thought euthanasia should not be legalized in our country ($p<0.05$) (Table 6).

Only 21.5% of the nurses supporting the legalization of euthanasia in our country stated that they would be willing to participate in a dedicated euthanasia team if legal regulations allowed such implementations. However, we also determined that 50.8% of the nurses who wanted legalization of euthanasia would not be willing to participate in a euthanasia team even if it were legalized ($p<0.05$) (Table 7).

Discussion

Euthanasia concerns individuals, families and communities only when they are faced with an incurable disease or an untreatable severe injury after an accident or disaster, whereas it is an inevitable and non-negligible issue for nurses, which they are exposed once or multiple times during their nursing education and professional careers (12,14).

The current study revealed that 93.2% of the nurses had information about euthanasia and they thought practice of euthanasia was against the laws of God, nature and universe (Table 2). However, the results of a study by Kumaş demonstrated that half of the participant nurses did not have adequate knowledge about euthanasia. In the same study, contrary to the current research findings, the majority of the nurses reported that they thought euthanasia was a fundamental human/patient right (12). Another study by Çelik et al found that only half of the intensive care nurses had sufficient information

Table 4. Nurses' Views on Legalization of Euthanasia

Characteristics	Number	%
Do you think euthanasia should be legalized in our country?		
Yes	65	20.0
No	226	69.5
Undecided	34	10.5
If euthanasia is legalized, who do you think should carry it out?		
Doctor	100	30.8
Nurse	3	0.9
A special team formed to carry out euthanasia	189	58.2
Nobody	32	9.8
The person himself/herself	1	0.3
If euthanasia is legalized, who do you think it should be applied to?		
To patients suffering total brain death	178	54.8
To patients with poor prognosis and malignant disease suffering excruciating pains	77	23.7
To patients surviving only on life-support system	72	2.22
To patients that are in the terminal stage	52	16.0
To bedridden patients with no ability to meet own needs	20	6.2
Nobody	63	19.4
Do you think euthanasia will be abused if legalized?		
Yes	255	78.5
No	21	6.5
Undecided	49	15.0
(If yes) For which of the following reasons do you think euthanasia will be abused?		
Family's desire to avoid further treatment costs	164	50.5
Inheritance	208	64.0
İt hindering medical research and advances	55	16.9
It causing inequalities between people	73	22.5
It encouraging laziness of healthcare professionals	110	33.8

**More than one answer. Percentages were taken based on the number n.*

Table 5. Distribution of nurses' beliefs about euthanasia based on the units they work

Work units	Euthanasia is a patient / human right			
	Yes		No	
	Number	%	Number	%
Surgical clinics	22	29.3	53	70.7
Internal clinics	40	32.8	82	67.2
Emergency Service	8	30.8	18	69.2
Polyclinics	5	20.8	19	79.2
Operating Room	13	61.9	8	31.8
Intensive Care Units	12	21.1	45	78.9
Total	100	30.8	225	69.2

X^2=13.501 Sd=5 p=0.019

Table 6. Distribution of Nurses' Views on the Legalization of Euthanasia by Gender

Gender	Do you think euthanasia should be legal in our country?					
	Yes		No		Undecided	
	Number	%	Number	%	Number	%
Female	51	17.9	203	71.2	31	10.9
Male	14	35.0	23	57.5	3	7.5
Total	**65**	**20.0**	**226**	**69.5**	**34**	**10.5**

X^2= 6.465 Sd= 2 p=0.039

Table 7. Distribution of Nurses Based on Their Views on the Legalization of Euthanasia and Willingness to Participate in a Euthanasia Team

	Do you think euthanasia should be legal in our country? If a legal regulation allowed euthanasia, would you participate in a euthanasia team?					
	Yes		No		Undecided	
	Number	%	Number	%	Number	%
Yes	14	21.5	33	50.8	18	27.7
No	4	1.8	211	93.4	11	4.9
Undecided	2	5.9	28	82.4	4	11.8
Total	**20**	**6.2**	**272**	**83.7**	**33**	**10.2**

X^2= 69.012 Sd= 4 p=0.000

about euthanasia, and they were of the opinion that the practice of euthanasia was against the will of God, nature and universe (15). The results of our study were consistent with the findings of the study by Çelik. While 38.8% of the nurses supported the idea that "a person should have the right to end his/her own life", 16.3% of the participants said "yes" to the question "Do you think euthanasia should be applied to patients requesting euthanasia?" (Table 2). In a study conducted with physicians by Özkara et al, 74% of the physicians supported the individual's right to end his/her own life, while in another study by the same group of authors, this rate was found as 77% (4). In their study conducted with students, Nehir et al found the rate of proponents of this view was 32% (16). The results of our study were found to be consistent with the findings of Nehir et al, whereas they differed significantly from the other studies covering this topic.

The sociological structure of the society, beliefs, level of education, even the economic status appear to affect the attitudes towards euthanasia (16). In their study, Nehir et al reported that 68.0% of the nursing students thought religious beliefs could prohibit euthanasia (17). In our study, we determined that religious beliefs played a significant role (by 85.6%) on the perspectives of nurses on euthanasia (Table 3). While 13.8% of the nurses reported that they would ask for euthanasia for themselves, only 7.7% stated that they would demand euthanasia for a relative or family member (Table 3). Similar findings were obtained in the study by Doğan et al, where 32.5% of the nurses reported positive view on euthanasia for themselves, but this rate declined to 15.6% for the euthanasia of a family member or relative (18). In their study carried out with nursing students, Kaya and Akçin found that the reasons for not approving euthanasia for a family member or relative included answers such as "they could not take such a responsibility", "it was against their religious beliefs" and "it should be decided by the patient himself/herself" (13). These results might be explained by the fact that nurses do not want to be in a direct decision-making position for someone else's life.

It was reported that nurses supported euthanasia, but they were not willing to carry out or assist euthanasia (19). Similarly, our study revealed that 83.7% of the nurses would not like to participate in a euthanasia team even if a legal regulation allowed euthanasia (Table 3), and 58.2% stated that euthanasia should be carried out by a dedicated team formed for such practice (Table 4). Several studies on euthanasia have produced similar results supporting our findings in this regard (18,20,21). In our study, we found that only 20.0% of the participants supported the legalization of euthanasia in our country (Table 4), which was similar to the results of other studies conducted with nurses (16,22). This rate was found as 29.1% among the nurses in the study by Doğan et al (18), and 47% among the physicians in the study conducted by Özkara et al (4). In another study by Kumaş, it was reported that 39.8% of the intensive care nurses opposed the legalization of euthanasia in Turkey, while 33.9% argued that euthanasia should be legalized (12).

Our study also revealed that the opinion that euthanasia was a patient/human right was more common among nurses working in operating rooms (%61.9) than those working at other sections (Table 5). This finding may be explained by the

fact that admission of aggravated patients in terminal stage is higher among the research institutions such as university hospitals.

The current research determined that the number of nurses opposing the legalization of euthanasia in our country was higher among women (Table 6), which suggests that women approach this subject in a more emotional way. We also found that 50.8% of the nurses who supported legalization of euthanasia were not willing to participate in a euthanasia team even if it were legalized (Table 7). It is considered that this might arise from the perception of euthanasia as murder/voluntary manslaughter by almost half of the nurses (41.2%).

Conclusion and Recommendations

As a result of the current study carried out with the aim of examining and evaluating the views and attitudes of nurses towards euthanasia, we determined that the majority of the participants had sufficient information about euthanasia, and more than half of them opposed the application and legalization of euthanasia.

Based on the data obtained from this research, we might suggest that nurses should be encouraged to attend conferences, training, case discussions and research on euthanasia and they should be educated about the most appropriate course of action to possible euthanasia demands and institutional policies through on-the-job training sessions. In addition, we think that the amount of current research on euthanasia is inadequate in our country and further studies on this widely debated issue, which should also include healthcare professionals, will help illuminate the topic in all aspects.

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Life quality of caregivers to cancer patients

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Abstract

The present study is done because of examining the life quality of caregivers to cancer patients and the factors that affect their reactions about helping to family members.

The sample of the present study that is carried out as the definitive type includes the 124 caregivers who get a treatment of cancer at Denizli State Hospital Radiation Oncology unit on July 18th, 2011-February 15th, 2012 and accept to participate the study. Before the data acquisition process, essential permissions are got from the care takers and the institution that the study is done.

Data is collected with the data acquisition form which includes the demographic information, "Scale of The Life Quality of Family Members Who Give Care to Cancer Patients" (its validity and reliability is done by Okçin in 2007) and "Scale of The Reactions about Helping to Family Member" (done by Uğur in 2006). For assessing the data, Percentage, Mann Whitney U and Kruskal Wallis tests.

%69.4 of participants are female and %51.6 of them are 38 age and above. %80.6 of care takers' social security is Social Security Institution (SSI), %66.1 don't work and %61.3 live with the patient in the same house. %30.6 of the patients who get cancer treatment have lung cancer and %56.5 of them had operation because of the cancer. The difference between the gender of care givers, social security types, the condition of having a job, the condition of living together with the patient, the condition of getting an operation because of the cancer and life quality subscale dimension and scale total score is statistically significant ($p<0.05$). Life quality of the participants who are female care givers, have SGK social security, have a patient who get an operation because of the cancer is found as high, whereas the life quality of participants who have a job and live together with the patient in the same house is found as lower. It is found that the care givers who do not get an operation because of the cancer have more helping reactions to family member ($p<0.05$). It was found that there is a strong and significant, negative relationship between the "Scale of The Life Quality of Family Members Who Give Care to Cancer Patients" and the "Scale of The Reactions about Helping to Family Member" ($p<0.05$).

In the direction of the results, it is suggested that in the process of giving care to cancer patients, family members should be informed about care giving, psychoeducation programs can be arranged for reducing the psychosocial problems which might be experienced during the process of patient care and it should be informed about carrying out consultancy services and prompting the social support systems (family, friend, work).

Key words: life quality, cancer, care giver.

Introduction

The most important factor which determines the importance of a disease in the aspect of human health is the incidence of the disease and the number of deaths it causes. Cancer is one of the most important life-threatening problems in the world and also in our country and it is in the second place after coronary-arterty diseases among the causes of deaths in many countries and Turkey as well (Kutluk and Kars, 1998; Ugur 2006; Karabulut and Uslu; 2006). In Western societies each one of every 250-300 people get cancer in each year. In our country, despite uncertain statistics, it is estimated that the incidence of cancer is half of these figures. The incidence of cancer is increasing in the 60 and over age group, and it rises to four-five people in every 300 people (Kutluk and Kars, 1998; Berkarda, 2002).

Cancer is affecting the diagnosed individuals and their families in a negative way in the physical, psychological and social aspects, and it creates a heavy burden on both the family and the society.

The diagnosis of cancer is a traumatic experience for the individual and the family. Cancer disrupts the daily life balance of the individual more compared to other diseases because it may affect the individual and the family in many aspects such as the physical, psychological and social aspects. Cancer may carry different meanings for the individual such as having an effect on the adaption mechanisms, disruption of the future plans or loss of strength for the individual (Hinds, 1985). The changes created by cancer gradually increases over time and these changes affect the individual and the family in a negative way; in short, these changes threathen the life quality of the individual and the family (Ugur, 2006; Okcin, 2007).

Miller and Keane (1992) described the caregivers as "people who accept responsibility for the care of an individual who is not able to care for themselves in the emotional and physical aspects". Caregiving is a complex, important and a stressful occupation (Scherbirng, 2002). A cancer patient may be affected from social norms, values and the disease environment. Caregiving for a cancer patient may create a positive effect body and spiritual health of the caregiver. Caregivers may lose their ongoing relationships and social interactions in this process. In addition, family caregivers give care without having any official information of the importance of their roles in this process. These factors may create a feeling of isolation and abandonment, so it is quite important to assess, approve and support caregivers in their roles. Many of them can not continue their lives at their homes without this caregiving. For this reason, supporting the caregivers is extremely important in the proctection of the quality of life of the individual and the family (Stetz and Brown; 1997).

Işikhan et al. (2001) made a study about the quality of life of the cancer patients and determined that the treatment, early diagnosis, acceptance process have an important effect on the pain, spiritual burden and the quality of life of the caregivers (Işikhan et al., 2001). In a study made by McMillan et al. (2005), it was determined that the family members of the cancer patient who are caregivers have increased levels of stress, depression and risk for other health problems (McMillan et al., 2005).

In a study made by Ferrell et al. (2005), it was determined that the physical and psychological burden on the caregivers and the changes in their quality of lives affect the quality of care for their patients (Ferrel et al., 1995).

This study was made to determine the factors which affect the quality of lives of the caregivers for the cancer patients and the their reaction towards helping the member of the family.

Material and method

The sample of this descriptive study was formed by 124 caregivers who were in the Denizli Government Hospital Radiation Oncology unit between the dates of July 18th, 2011-February 15th, 2012. Necessary permissions and consent were granted before the beginning of the study.

Data were obtained by the usage of data collection survey which includes demographic features, "Quality of Life Family Version Scale" which was tested by Okcin (2007) in the aspects of validity and reliability for our country and the "Reactions Towards Family Help Scale" which was adapted by Ugur (2006).

Quality of Life Family Version Scale developed for cancer patients consists of 37 points. This was developed by Ferrell and Grant to assess the quality of life of the cancer patients and its validity and reliability was tested and adapted by Okcin to measure the quality of lives of the family members.

Scale has 37 points; it has four sub-dimensions called Physical Condition, Psychological Condition, Social Concerns and Spiritual Well Being. Scores are between 0 and 10 for each answer with "10" being the best and "0" being the worst. Scale is interpreted from the total score and sub-dimensions scores; the higher the score, the higher the life quality.

"Reactions Towards Family Help Scale" was developed in 1983 by Archbold & Steward and it was adapted by Ugur (2006). Type of the scale is 5-likert and it has 15 points with no sub-dimensions. Participants score the points on the scale with 0-Never, 1-Very little, 2-A little, 3-A lot, 4-Very much. The higher the score, the higher the number of reactions (Ugur, 2006).

In the evaluation of the data, Percentile, Mann Whitney U and Kruskal Wallis tests were used.

Findings

Table 1. Descriptive features of the caregivers (n:124)

Variables	N	%
Age groups		
37 and under	60	48.4
38 and over	64	51.6
Gender		
Female	86	69.4
Male	38	30.6
Marital Status		
Married	96	77.4
Single	28	22.6
Educational Status		
Elementary	74	59.7
High School	20	16.1
University	30	24.2
Type of social security		
None	14	11.3
SGK	100	80.6
Greencard	10	8.1
Occupational status		
Employed	42	33.9
Unemployed	82	66.1
Chronical Disease Status		
Has one	30	24.2
Does not have one	94	75.8
Total	124	100.0

Table 2. Descriptive features of the cancer patients undergoing treatment

Variables	N	%
Cancer type		
Lung cancer	30	30.6
Breast cancer	20	16.1
Pancreas cancer	18	14.5
Stomach cancer	16	12.9
Other (Liver, colon, larenx, bone, brain, lymph, uterus)	32	25.9
Treatment period from the beginning		
Less than 6 months	42	33.9
7-12 months	28	22.6
13 months and over	54	43.5
Surgical status due to cancer		
Had a surgery	70	56.5
Did not have surgery	54	43.5
Accomadation status considering the caregiver		
Lives at the same house	76	61.3
Does not live at the same house	48	38.7
Total	**124**	**100.0**

Descriptive features of the caregivers are given in Table 1. %51.6 of them are 38 and over, %69.4 of them are female and %77.4 of them are married. It was determined that %59.7 of them are elementary school graduates, %80.6 of them have Social Security Institution (SSI) as social security, %66.1 of them are unemployed and %24.2 of them have a chronical disease. Descriptive features of the cancer patients undergoing treatment are given in Table 2. %30.6 of them have lung cancer and %33.9 of them are undergoing treatment for less than 6 months. %56.5 of them had surgery and %61.3 of them live at the same house with their caregivers.

The comparison of the gender, social security types and employment status of the caregivers and the mean quality of life scores is given in Table 3. A statistically significant difference was found between gender, social security types and employment status of the caregivers and the mean quality of life scores ($p<0.05$). While the quality of life of the caregivers who are female and have social security was found to be higher, the quality of life of the unemployed caregivers was found to be lower.

The comparison of the surgery status due to cancer and accomadation status considering the caregiver of the patients undergoing cancer treatment and the mean quality of life scores is given in Table 4. A statistically significant relationship was found between the surgery status due to cancer and accomadation status considering the caregiver of the patients undergoing cancer treatment and the mean quality of life scores ($p<0.05$). While the quality of life of the caregivers who were caring for a patient who had a surgery due to cancer was found to be higher, the quality of life of the caregivers living at the same house with their patients was found to be lower. The comparison of the social security types of the caregivers and the surgery status due to cancer of the patients and the mean scores of the reactions towards family help scale is given in Table 5. A statistically significant difference was found between the social security types of the caregivers and the surgery status due to cancer of the patients and the mean scores of the reactions towards family help scale ($p<0.05$). While it was determined that the caregivers with SGK social security were found to have less reactions, it was found that the caregivers with a patient who did not have surgery due to cance have more reactions.

Table 3. The comparison of the gender, social security types and employment status of the caregivers and the mean quality of life scores

Variables	N	X ± sd	Statistical test *p*
Gender			
Female	86	231.81±25.32	**MU:** 229.000
Male	38	206.26±34.19	**p**:0.006
Type of social security			
None	14	219.71±28.32	
Social Security Institution	100	228.36±29.61	**KW:** 9.159
Greencard	10	186.20±2003	**p**:0.010
Employment status			
Employed	42	214.52±34.18	**MU:** 217.500
Unemployed	82	228.82±28.01	**p**:0.002
Total	**124**	**223.98±30.73**	

Table 4. The comparison of the surgery status due to cancer and accomadation status considering the caregiver of the patients undergoing cancer treatment and the mean quality of life scores

Variables	n	X ± sd	Statistical test *p*
Surgical status due to cancer			
Had a surgery	70	225.08±33.30	**MU:** 300.500
Did not have surgery	54	222.55±27.59	**p**:0.015
Accomadation status considering the caregiver			
Lives at the same house	76	223.57±27.65	**MU:** 307.00
Does not live at the same house	48	224.62±35.68	**p**:0.031
Total	**124**	**223.98±30.73**	

Table 5. The comparison of the social security types of the caregivers and the surgery status due to cancer of the patients and the mean scores of the reactions towards family help scale

Variables	N	X ± sd	Statistical test p
Type of social security			
None	14	46.00±7.65	
Social Security Institution	100	40.48±10.49	**KW:** 11.749
Greencard	10	60.60±11.10	**p**:0.003
Surgical status due to cancer			
Had a surgery	70	39.60±11.07	**MU:** 300.500
Did not have surgery	54	46.77±11.10	**p**:0.015
Total	**124**	**42.72±11.56**	

Table 6. The correlation between the "Quality of Life Family Version Scale" and the "Reactions Towards Family Help Scale"

	"Reactions Towards Family Help Scale"	
	R	**p**
"Quality of Life Family Version Scale"	-.304	0.016

The correlation between the "Quality of Life Family Version Scale" and the "Reactions Towards Family Help Scale" is given in Table 6. A statistically significant strong and negative relationship was found between the "Quality of Life Family Version Scale" and the "Reactions Towards Family Help Scale" ($p<0.05$). As the quality of life of the family member caregiver decreases, these caregivers tend to give more reactions towards helping the individual.

Discussion

In this descriptive study which was made to determine the factors which affect the quality of lives of the caregivers for the cancer patients and the their reaction towards helping the member of the family, these findings were obtained: %51.6 of the caregivers are 38 and over, %69.4 of them are female and %77.4 of them are married (Table 1). In a study made by Ugur (2006), %72 of the caregivers giving care for oncology patients were found to be female and %92 of them were found to be married (Ugur, 2006). In a study made by Okcin (2007) most of the family member caregivers for cancer patients were found to be 35 or over years old (Okcin, 2007). In a study made by Sahin et al. (2009), %55.7 of the caregivers were found to be 38 and over, %53.3 of them were found to be female and %63.1 of them were found to be married (Sahin et al., 2009). In a study made by Bodur and Cingil (2003) and another study made by Babaoglu and Oz (2003), it was found that most of the caregivers for cancer patients were female (Abaoglu and Oz, 2003; Bodur and Cingil, 2006). In a study made by Edward et al. (2002) in USA, it was found that %84 of the caregivers were female (Edward et al., 2002). Similiar findings in the world and also in our country show that caregiving is mainly made by women. The reason behind this may be general role for women in the society which suggests that they should be responsible for the organization of the house of the family (Akun and Demirel 2003). Moreover, women have different personality traits such as being more compassionate and being more resistant towards the difficulties of caregiving and it is stated that these findings support this situation as well (Sahin et al., 2009). These findings are similiar with the findings of this study.

It was determined that %59.7 of the cancer patient care givers are elementary school graduates, %80.6 of them have SSI as social security, %66.1 of them are unemployed (Table 1). In a study made by Ferrell et al. (2002), it was found that family member caregivers for ovary cancer patients had to quit their jobs to give this care (Ferrell et al., 2002). In a study made by Babaoglu and Oz (2003), it was found that %56.3 of the caregiver spouses were elementary school graduates, %61.2 of them were unemployed (Babaoglu and Oz, 2003). In a study made Ugur (2006), it was found that %88 of the caregivers were unemployed, %44 of them were middle school graduates and %94 of them had SSI social security. In a study made Okcin (2007), it was determined that %93.6 of the caregivers had SSI social security and %54.6 of them were found to be unemployed. In a study made by Sahin et al. (2009), it was found that %50 of the caregivers were elementary school graduates and %57.4 of them were unemployed (Sahin et al., 2009). These results support the findings of this study.

%30.6 of the patients have lung cancer and %33.9 of them are undergoing treatment for less than 6 months. %56.5 of them had surgery and %61.3 of them live at the same house with their caregivers (Table 2). %36 of the patients included in Ugur's study were being treated for less than 6 months (Ugur, 2006). In the study made by Okcin (2007), it was found that %42.2 of the patients were being treated for cancer less than 6 months and %81.2 of them stated that they were living in the same house with their caregiverts (Okcin, 2007). In the study made by Beydag (2012), it was determined that %48.1 of the patients undergoing cancer treatment were being treated for less than 6 months (Beydag, 2012). These results are similiar with the findings of this study.

A statistically significant difference was found between gender, social security types and employment status of the caregivers and the mean quality of life scores ($p<0.05$) (Table 3). While the quality of life of the caregivers who are female and have social security was found to be higher, the quality of life of the unemployed caregivers was found to be lower. Caregiving is mainly a female responsibility (Aranda and Hayan 2001). It is traditionally seen as a female responsibility and women may be forced to have this role more than man (Pa-

sacreta et al., 2000). If the caregivers have social security, they can get health services for free. Cancer treatment is very expensive and corrosive. For this reason, people with lower socioeconomical status feel this burden even more (Ugur, 2006). Educated people may have more financial resources; this may help them deal with stress in an easier way. Uneducated people have a higher risk of developing stress symptoms so they should be more careful about this risk (Carmen and Chang 1999; Ugur, 2006). In a study made by Baer (1993), it was determined that family member caregivers are being disrupted from doing their original occupations (Baer, 1993). In the study made by Kim and Gaven (2008), it was stated that the unemployed caregivers for cancer patients have a lower quality of life (Kim and Given, 2008). Moreover, in other studies it was determined that these caregivers have problems in carrying out their other responsibilities in the occupational lives, at home and child care (Babaoglu and Oz, 2003).

A statistically significant relationship was found between the surgery status due to cancer and accomadation status considering the caregiver of the patients undergoing cancer treatment and the mean quality of life scores ($p<0.05$). While the quality of life of the caregivers who were caring for a patient who had a surgery due to cancer was found to be higher, the quality of life of the caregivers living at the same house with their patients was found to be lower.

Cancer is a disease which can be treated more successfully if it is diagnosed early and patients may have better surgical opportunities this way. Patients undergoing surgery is interpreted as a good sign by the caregivers and create a belief that the treatment will be successful, life period of the patient will get longer and increases the hope of a complete recovery. For this reason, this increases their hope during the treatment process and this make them percieve their quality of lives in a more positive way. Caregiver living in the same house with the patient may disrupt the caregiver from joining valuable activites (occupation, recreation, social trips etc.) and this may create a spiritual burden. Caregivers are isolated due to the nature of their position and they may get socially detached from their previous relationships. They gave up from their time which they could have spent socially, recreationally, doing their hobies or meeting with friends otherwise. This caregiving role generally create an extra burden on the caregiver because home becomes a prison for him/her and he/she may spent only limited time for the activities outside the house. All of these situations create an effect on the quality of lives of the individuals (Harrington et al, 1996; Stetz and Brown, 1997; Cameron et al, 2002; Silver and Wellman, 2002).

A statistically significant difference was found between the social security types of the caregivers and the surgery status due to cancer of the patients and the mean scores of the reactions towards family help scale ($p<0.05$). While it was determined that the caregivers with SGK social security were found to have less reactions, it was found that the caregivers with a patient who did not have surgery due to cance have more reactions (Table 5). The lack of social security means people have to pay for the treatment expenses. This situations creates an emotional, social, physical and financial stress on the caregiver. Present health care system support of the family, financial constraints and the perception of the present options are all affecting the reactions shown by the caregiver (Stetz and Brown, 1997; Ugur, 2006). People having social security is important in the aspect that they would not have deal with the treatment expenses in this process which is already a very difficult and stressful one

It was found that the caregivers who were caring for a patient who did not have a surgery reacted more towards helping the family member (Table 5). Cancer creates concern due to its uncertain clinical course and with no existing guarantee treatment. Uncertainity issues about cancer are mainly recurrence, loss of control and the existence of life and death. Cancer is a disease which creates a serious burden and disrupt all balances and adaptations of the patient and the caregivers from its onset till the terminal period. Family is mainly affected during diagnosis, the treatment period, recurrence and death (Sneeuw, 1997; Ugur, 2006). Patients undergoing surgery is interpreted as a good sign by the caregivers and create a belief that the treatment will be successful, life period of the patient will get longer and increases the hope of a complete recovery. This decreases their spiritual burden and make them support the individual more during this process.

A statistically significant strong and negative relationship was found between the "Quality of Life Family Version Scale" and the "Reactions Towards

Family Help Scale" ($p<0.05$) (Table 6). As the quality of life of the family member caregiver decreases, these caregivers tend to give more reactions towards helping the individual. Cancer is affecting the diagnosed individuals and their families in a negative way in the physical, psychological and social aspects, and it creates a heavy burden on both the family and the society. The changes created by cancer gradually increases over time and these changes affect the individual and the family in a negative way; in short, these changes threathen the life quality of the individual and the family. Cancer is not just a crysis, it is a constant psycho-social process. The reactions given by the family member caregiver change according to their perceptions, not their characteristics (Okcin, 2007). In a study made by McMillan et al. (2005),), it was determined that the family members of the cancer patient who are caregivers have increased levels of stress, depression and risk for other health problems and higher mortality rates (McMillan et al., 2005). In a study made by Myaskovsky et al. (2005), it was shown that the usage of coping methods against stress by the family members has an effect on the relationship between the family member and the patient (Myaskovsky et al., 2005).

Suggestions

In the light of these results, we advise the following:

- A fund should be created to fund the treatment expenses of the cancer patients who have no social security and under heavy emotional and financial burden during this process.
- Caregiving family members for the cancer patients who are under heavy burden in the caregiving process should be informed about the treatment and caregiving processes for the disease.
- Legal planning and regulative acts should be put into play for the health insurance to be used for covering the expenses of the caregivers for cancer patients or caregivers who may not work due to focusing on caregiving should be supported financially in another way.
- In order to decrease the number of psychosocial problems which may occur during the caregiving process, psychological educational programs should be developed towards this group and the caregivers should be informed about being consultants and the activation of the social support systems (such as family, friend, occupation).

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Burnout levels of teachers working in special educational institutions and relevant factors

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Abstract

Introduction: This descriptive research was carried out with the aim of determining the burnout levels of teachers working in special educational institutions and the relevant factors.

Materials and Method: The universe of the research consisted of 252 teachers employed in special educational institutions located in the central districts of Elazig and Malatya. A sample was not selected, that is, the entire universe was included in the scope of the research, and in the end the study was completed with 225 (89.3%) teachers. The data were collected in 2012 using the questionnaire form which investigated respondents' socio-demographic characteristics and the Maslach Burnout Inventory (MBI). Teachers were informed about the importance of the research and then they filled out the questionnaire under supervision.

Results: Of the participant teachers; 58.7% are aged 25-36 and 47.1% are women. Their emotional exhaustion mean score was found to be 11.12±6.39, depersonalization 2.61±2.65 and personal accomplishment 7.58±4.18. In the research, it was found that the burnout level is affected by factors such as age, type of students' disability, efficiency level in the profession, ability to put into practice the professional knowledge and experience, having chosen the profession willingly, finding the profession suitable for the self, satisfaction with the working environment, finding the number of materials in the school, finding the system of punishment and reward fair, receiving support from managers, and receiving social support from the environment ($p<0.05$).

Conclusion: It is recommended that a good counselling service should be provided before choosing a profession, the working environments of special education teachers should be improved in compliance with the characteristics of the types of disability that their students have, and school managers should support and motivate teachers.

Key words: Special education, teacher, burnout

Introduction

The concept of burnout entered the psychology literature with Freudenberger's article published in 1974 in "Journal of Social Issues". According to Freudenberger, burnout is "failure, frazzle, loss of energy and power or a matter of exhaustion which is the result of the unfulfilled desires of human internal resources" (1,2). Burnout is considered by Freudenberger and Richelson as a type of professional stress (3).

Various professional groups suffer from stress due to their organizational structures and working conditions. The profession of teaching is shown as one of the high-risk professions in terms of risking health and making it difficult to cope with everyday life problems (4). Sources of stress such as students' disciplinary problems, overpopulated classes, extensive bureaucratic works, low wages, difficulties in promotion, lack of support from managers, and the society's criticisms cause burnout in teachers. It is thought that student behaviours, parent-teacher relationships and self-doubt about professional competence might also trigger burnout (5).

It is noted in the literature that special education teachers are more prone to experience burnout than other teachers due to more intense direct contact with students. In special education practices; characteristics of students, difficulties experienced by teachers in controlling students, difficulties in teaching subjects and teachers' lower satisfaction with the teaching process are prevalent (5,6).

Working with children with disabilities requires a variety of methods and a special and one-to-one care; yet developments are observed very slowly in children. Therefore, the care and edu-

cation of handicapped children necessitates much more patience and devotion. Special education teachers are therefore considered to be at greater risk for experiencing burnout (5,7). Besides, teachers can also experience burnout when they lack the required knowledge and skills that would respond to their students' needs and characteristics, when they have not been trained as special education teachers, and when they have unrealistic expectations from their students (8).

In order to be able to ensure parallelism between the school and the home, teachers should be in effective cooperation with parents. However, it is not possible for teachers who are not well-educated and experienced in special education and who experience various problems in the teaching process to meet these requirements. In return, they feel further stressed (7).

Students' academic achievements and mental developments would be positively influenced when teachers work in a comfortable and secure environment with confidence, satisfaction and health. Teamwork is needed for ensuring the effectiveness of school health services which are given with the aim of monitoring and improving health of both students and teachers, and attaining and maintaining a healthy school life. The nurse has a central role in this team. In teacher burnout which should be addressed as part of school health services; school health nurses shoulder important responsibilities such as determining relevant risks early; planning appropriate endeavours; working in coordination with the school management in taking necessary measures; planning, executing and supervising counselling and health training programs (9,10).

This study was planned and carried out in order to determine burnout levels of special education teachers as well as the affecting factors; on the assumption that special education teachers are more prone to burnout due to special practices and professional responsibilities necessitated by the characteristics and needs of handicapped students.

Material and method

The research was carried out in 31 special education schools and rehabilitation centers (11 in Elazığ and 20 in Malatya) that serve mentally-challenged, hearing-impaired, visually-impaired and autistic children. The fieldwork was completed within one month between January and February 2012. After being informed about the importance of the research, teachers who agreed to participate filled out the questionnaire under supervision.

A total of 252 teachers who were employed in special education and rehabilitation centers located in the central districts of Elazığ and Malatya constituted the universe of the research. A sample was not selected as the aim was to reach the entire universe. In the end, with the exception of teachers who did not agree to participate, who were on leave in the time of the research, or who left question(s) unanswered in the questionnaire form; the study was completed with 225 (89.3%) teachers.

The personal information form that had been developed by the researchers and the Maslach Burnout Inventory (MBI) were used as data collection instruments. This inventory, which consists of 22 items, measures the burnout level under the subscales of emotional exhaustion, depersonalization and personal accomplishment.

Emotional exhaustion (EE) is defined as the escalation of employees' emotions such as feeling over-exhausted due to fatigue. The items 1, 2, 3, 6, 8, 13, 14, 16 and 20 are aimed at measuring this subscale. Depersonalization (DP) refers to an unfeeling or impersonal response towards recipients of one's service or care treatment, without considering that they are unique individuals. The items 5, 10, 11, 15 and 22 are aimed at measuring this subscale. The subscale of personal accomplishment (PA) consists of the items 4, 7, 9, 12, 17,18, 19 and 21; and aims to measure how individuals evaluate their competence at work (1,8,11,12).

The validity and reliability study of the inventory in Turkish was carried out in 1992 by Ergin. In this research carried out with special education teachers, the questionnaire form consisted of five-choice questions. The expression "people I meet as part of my job" was replaced with "my students" (5,8,11).

In the Maslach Burnout Inventory, responses are assessed and then a total score and subscale scores are obtained. The items that constitute the subscales are scored between 0 and 4 and then these points are added for each subscale in order to calculate the score of the respondent in that subscale. A person can get a score within the

following ranges from the subscales: 0-36 in EE, 0-20 in DP and 0-32 in PA. The first two subscales consist of negative responses. Similar to what Ergin did in the study to adapt the inventory into Turkish, the subscale of personal accomplishment which consists of positive expressions was scored reversely, and thus interpreted as "personal inefficacy". Therefore, high scores from all the three subscales point to higher burnout levels (11,13).

Percentage ratios and means were used in the analysis of data. The test of significance of differences between two percentages was used in order to compare the groups in terms of percentages, whereas one-way variance analysis was performed to compare the groups in terms of means, and Tukey test was used to determine the source of the difference. The significance level of $p<0.05$ was used to interpret results.

Results

It was determined in the research that 58.6% of the participant teachers were aged between 25 and 36, whereas 47.1% of them were females and 68.9% of them were married. While 24.4% of them had graduated from a special education program, 70.2% was working with children with mental disabilities, and 84.4% of them had been working for 0-5 years.

Table 1 shows the distribution of teachers with respect to their other professional characteristics.

Of the participant teachers; 86.2% stated that they had chosen this job willingly, 85.3% reported that they are satisfied with the working environment, and 41.3% expressed that they do not consider the reward and punishment system in the institution to be fair. While 37.3% of them see their professional productivity levels as highly productive, 52.0% believe that they can practice their professional knowledge and skills, and 58.1% want continue working in the field of special education in the future. 38.2% of the participant teachers consider their relations with managers to be very good, whereas 45.3% feel the same with other teachers and 54.2% with students. 58.7% of them reported that they find adequate the social support they receive from their environments when they encounter a problem.

Their emotional exhaustion mean score was found to be 11.12±6.39, depersonalization to be 2.61±2.65 and personal accomplishment (inefficacy) to be 7.58±4.18.

While their EE and DP scores do not differ with respect to their ages; the personal inefficacy mean

Table 1. Distribution of Teachers by Professional Characteristics

Teachers' Professional Characteristics (n=225)	Number	Percentage
Graduated Program		
Special Education	55	24.4
Classroom Teacher	85	37.8
Branch Teacher	62	27.6
Pre-School Teacher	23	10.2
Field of Special Education		
Mentally-Challenged	158	70.2
Hearing-Impaired	54	24.0
All Disabilities	13	5.8
Total Duration of Professional Service		
0-5 years	94	41.8
6-10 years	60	26.7
11-15 years	21	9.3
16-20 years	7	3.1
21 years and more	43	19.1
Duration of Professional Service in the Current Institution		
0-5 years	190	84.4
6-10 years	25	11.2
11-15 years	10	4.4

Table 2. Distribution of Teachers' Subscale Mean Scores by Several Variables

Variables	Subscales		
	EE	DP	PA
Teachers' Age Groups	**Mean±SD**	**Mean±SD**	**Mean±SD**
30 years and below	11.01±6.56	2.95±2.85	8.45±4.61*
31-42 years	12.20±6.69	2.38±2.41	7.27±3.91
43 years and above	9.85±5.56	2.42±2.68	6.73±3.68
P	0.097	0.310	0.035
Disabilities of Children They Work With			
Mentally-challenged	11.46±6.70	2.70±2.75	7.45±4.04
Hearing-impaired	9.80±5.43	2.37±2.40	7.22±4.16
All sorts of disabilities	12.46±5.94	2.46±2.70	10.62±5.12*
P	0.189	0.716	0.024
Perception of Professional Productivity			
Highly productive	7.96±5.32*	2.05±2.24	5.14±3.07*
Somewhat productive	12.84±6.08*	2.86±2.73	8.93±4.01*
Unproductive	24.0±11.31*	9.0±4.24*	16.0±4.24*
p	0.000	0.000	0.000
Ability to Practice Professional Knowledge and Skills			
I can	9.11±5.89*	1.97±2.29*	6.56±4.33*
I somewhat can	12.80±6.06	3.01±2.69*	8.46±3.35
I cannot	15.78±6.65	4.78±3.25*	9.83±5.22
p	0.000	0.000	0.000

Table 3. Comparison of MBI Subscale Mean Scores based on Teachers' Opinions on the Profession and on their Working Environments

Variables	Subscales		
	EE	DP	PA
Having Chosen the Profession Willingly	**Mean±SD**	**Mean±SD**	**Mean±SD**
Yes	10.41±6.32	2.42±2.53	7.41±4.18
No	15.58±4.97	3.81±3.12	8.65±4.09
P	0.000	0.007	0.126
Finding the Profession Suitable for the Self			
Suitable	10.15±6.04	2.33±2.47	7.05±3.87
Not suitable	17.43±4.93	4.43±3.10	11.0±4.56
P	0.000	0.000	0.000
Satisfaction with the Working Environment			
Satisfied	10.29±6.12	2.48±2.50	7.35±4.09
Not satisfied	15.97±5.87	3.36±3.39	8.91±4.54
P	0.000	0.077	0.047
Receiving Adequate Support from Managers			
Yes	10.11±6.01	2.32±2.42	7.45±4.02
No	14.85±6.44	3.69±3.18	8.04±4.76
P	0.000	0.001	0.387
Finding the Reward and Punishment System Fair			
Fair	9.71±5.80	2.28±2.49	7.02±3.80
Unfair	13.12±6.70	3.08±2.82	8.37±4.58
p	0.000	0.027	0.017
Experiencing Problems with Parents			
Yes	12.59±7.05	3.19±2.95	7.54±4.36
No	10.40±5.94	2.32±2.46	7.60±4.11
P	0.015	0.021	0.926
Social Support received from the Environment			
Adequate	9.61±5.66	2.12±2.31	7.52±4.16
Inadequate	13.27±6.78	3.30±2.96	7.66±4.23
p	0.000	0.001	0.815

score of those teachers at the age group of 30 years and below was found to be significantly higher than those of teachers aged 31-42 years and 42 years and above ($p<0.05$). The personal inefficacy mean score of teachers who work with children with all sorts of disabilities was found 10.62±5.12 ($p<0.05$, Table 2).

It was determined that the EE and DP mean scores of those teachers, who did not choose the profession willingly, who think that they do not receive sufficient support from managers, who experience problems with students' parents, and who considers the social support they receive from their environments to be inadequate, are significantly higher; and the EE, DP and PA mean scores of those teachers who do not find themselves suitable for the profession and those who think that the reward and punishment systems in their institutions are unfair are also significantly higher ($p<0.05$, Table 3).

Discussion

While the participant teachers' EE mean score is at a medium level, their mean scores in the subscales of DP and PA are at low levels. This finding supports the findings of the researches conducted by Girgin and Baysal, and Ulutaşdemir (13,14).

While their EE and DP scores do not differ with respect to their ages; the personal inefficacy mean score of those teachers at the age group of 30 years and below was found to be significantly higher than those of teachers aged 31-42 years and 42 years and above ($p<0.05$, Table 2). The feeling of personal accomplishment increases as age rises. Given that professional experience and maturity are expected to increase with age, this finding can be regarded as probable. In similar studies, a positive correlation was found between age and personal accomplishment (8,15,16,17,18,19).

In the research, the personal inefficacy mean score of those teachers who work with all groups of disabled students was found to be higher than those of teachers who work only with mentally-challenged and hearing-impaired students ($p<0.05$, Table 2). On the other hand, EE and DP mean scores did not differ with respect to types of disabilities. This finding can be explained with the ideas that children with different disabilities have different characteristics, that teachers are not fully prepared for such an education, that the subjects are difficult to teach, and as a result, the teacher cannot derive satisfaction in terms of personal accomplishment from this process. This finding is in parallel with the findings of Sucuoğlu and Kuloğlu (5). However, different findings are also found in the literature. Karahan found that the EE mean score of teachers who work with teachable students are significantly higher than that of teachers who work with autistic children (15). In the studies of Aksoy and Yiğit, on the other hand, no differences were found between the subscales of burnout and the disabilities that teachers work with (20,21).

In the research, the EE, DP and PA mean scores of those teachers who consider themselves to be professionally unproductive were found to be higher ($p<0.05$, Table 2). It could be suggested that higher burnout levels negatively influence professional productivity, or that those teachers who feel professionally productive experience lower levels of burnout due to reasons such as satisfaction derived from productivity and the fulfilment of their expectations. It could also be argued that teachers who consider themselves to be professionally unproductive tend to experience higher burnout since they feel more stressful. This finding is in parallel with what Baysal found in the study with high school teachers and what Girgin found in the study with primary school teachers (22,23). The study of Egyed and Short demonstrated that there exists a negative correlation between teachers' professional efficacy beliefs and burnout levels (24), whereas the studies of Cemaloğlu and Şahin, Dolunay and Piyal, and Şahin showed that whether one considers himself to be professionally productive or not is a factor that influences burnout at the subscales of Personal Accomplishment, Emotional Exhaustion and Depersonalization (16,25,26). Teachers who feel incompetent in their professions experience burnout at the subscales of EE, PA and DP.

In the research, the mean scores of teachers, who think that they can put into practice their professional knowledge and skills, were found to be lower in all the three subscales ($p<0.05$, Table 2). Individuals want to use their professional knowledge for the benefit of themselves and of their institutions. When people do not have the chance of using this knowledge; they most probably forget it, and they might get unhappy as they consider themselves to

be useless. Barutçu and Serinkan found, in their study with nurses, that those who think that they are unable to put into practice their knowledge and skills experience high levels of burnout in terms of personal accomplishment (19), whereas Şahin et al. determined that those who stated that they can put into practice their knowledge and skills have lower levels of emotional exhaustion. These results are in parallel with our findings (27).

In the research, the EE and DP mean scores of those teachers who had chosen the profession willingly were found to be lower than those who had not ($p<0.05$, Table 3). The difference between PA mean scores was not significant. Making free choice of a profession will enable the individual to do his/her job happily and derive more satisfaction, and thus have a lower burnout level. In the studies of Oruç and Gürbüz; teachers who had not chosen the profession of teaching willingly scored significantly higher in the subscales of EE and DP (8,28).

The EE, DP and PA mean scores of teachers who consider the profession to be suitable for themselves were found to be higher than the scores of those who do not ($p<0.05$, Table 3). Individuals who communed with their professions tend to adapt to certain professional circumstances better, to derive more satisfaction from doing their jobs, and to feel more competent professionally. This finding is in parallel with the findings of Oruç, Aksoy, Ulutaşdemir, Girgin, Dolunay, Dolunay and Piyal, and Sinat (8,13,16,17,21,23,29). In contrast with this finding, Taycan et al. determined that the burnout levels of teachers who do not consider the profession suitable for themselves are lower (18).

In the research, The EE and PA mean scores of teachers who are not happy with their working environments were found to be higher than the scores of those who are ($p<0.05$, Table 3). This finding can be explained with the idea that the fulfilment of teachers' professional needs and expectations increases their satisfaction with their jobs, and this in return affects burnout reversely. Other studies have also examined the relationship between satisfaction with the working environment and burnout, and they demonstrated that it is a factor influencing burnout levels. Oğuzberk, Yavuzyılmaz et al., and Demir found that those who are happy with their working environments have lower burnout scores (30,31,32). As Tuğrul and Çelik quote, Maslach and Jackson indicated that the working environment is linked with burnout (33). These findings support those of this study.

In the research, the EE and DP mean scores of teachers who do not receive sufficient professional support from their managers were found to be higher than the scores of those who do ($p<0.05$, Table 3). This might have stemmed from the facts that their efforts go unnoticed and they are not rewarded, and as a result they become dispirited. This finding is in parallel with the findings of Aksoy (21). In the studies conducted by Oruç and Aksoy, the EE mean scores of teachers who do not receive sufficient professional support from their superiors were found to be significantly higher (8,29). Brouwers et al. determined that the burnout levels of teachers, who see the support they receive from their colleagues and superiors as insufficient, are negatively affected (34).

Teachers who consider the reward and punishment system in their institutions to be unfair scored higher in all the three subscales ($p<0.05$, Table 3). Aksoy determined that teachers who think that the reward and punishment systems in their institutions do not operate fairly experience more emotional exhaustion (21). Similarly, Karahüseyin found that nurses who think that their institutions lack proper reward and punishment mechanisms have higher depersonalization scores (35). These results support our findings.

In the research, the EE and DP mean scores of teachers who reported that they experience problems with students' parents were found to be higher ($p<0.05$, Table 3). Similarly, Aksoy found that special education teachers who experience problems with parents have significantly higher burnout levels at the subscales of emotional exhaustion and depersonalization (21). It could be argued that teachers' burnout levels are affected by parents' insufficient support and care, low level of cooperation with teachers, and their unrealistic expectations.

In the research, the EE and DP mean scores of teachers who consider the social support they receive from their environments to be insufficient were found to be higher ($p<0.05$, Table 3). Karataş and Altay found similar results in their studies (36,37). Gündüz determined that teachers who receive social support experience lower burnout and have higher personal accomplishment levels (38). Kahn et al.,

similarly, found that teachers who receive positive social support experience lower levels of emotional exhaustion and have higher levels of professional productivity (39). Brouwers et al. determined that social support is an influential factor especially on emotional exhaustion (34). These results suggest that teachers who receive social support experience lower burnout and be more successful in their jobs compared to other teachers.

Conclusion and suggestions

It is concluded in this study that;

- The participant teachers' EE mean score is at a medium level, whereas their mean scores in the subscales of DP and PA are at low levels,
- Teachers who do not consider their profession to be suitable for themselves, who think that they are unproductive in their jobs, and who do not see the reward and punishment system in their institutions as fair experience higher levels of emotional exhaustion, depersonalization and personal inefficacy,
- Teachers who are not happy with their working environments experience higher levels of emotional exhaustion and personal inefficacy,
- Teachers who did not choose the profession willingly, who do not receive sufficient professional support from their superiors, and who see the social support that they receive from the environment as inadequate experience higher levels of emotional exhaustion and depersonalization.

In line with these results, it could be suggested that;

- A good counselling service should be provided before choosing a profession, and thus it should be ensured that teachers choose the profession willingly,
- The working environments of special education teachers should be improved in compliance with the characteristics of the types of disability that their students have,
- School managers should support and motivate teachers,
- As part of public health services, school health nurses should introduce burnout to school managers and teachers by planning relevant trainings related to the causes and symptoms of burnout syndrome as well as methods of coping with it,
- School health nurses should work in coordination with school managements in taking necessary early measures for burnout as well as planning, executing and supervising counselling and health training programs.

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The comparison of some blood parameters of elite athletes and sedentary people

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Abstract

This research aims to compare some blood parameters of elite wrestling athletes, judo athletes, and sedentary people.

60 athletes (30 judo, 30 wrestling) and 45 sedentary people whose training ages are 10.5 years have participated in the study. Levels of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), high density lipoprotein - cholesterol (LDL-C), and glucose and insulin in the serums, which are obtained from 5 ml venous blood samples taken from athletes and sedentary people were measured. The difference between the groups is analyzed with computerized package program and using one-way ANOVA test and post hoc Scheffe (multiple comparisons) test.

According to our findings, sedentary people have higher body weights and higher rates of fats, but lower systolic and diastolic blood pressures compared to wrestling and judo athletes, and this difference is significant ($p<0.01$). Also, it is found that while athletes have lower glucose levels ($p<0.05$), sedentary people have a lower level of insulin ($p<0.01$). While wrestlers' total cholesterol and amount of LDL-C values are significantly higher than the values of the control group and sedentary people ($p<0.01$), wrestlers have a lower level of triglyceride ($p<0.01$). No significant difference between groups in terms of HDL-C levels is found.

In sum, it is found that while judo and wrestling athletes have lower values of fat ratio and glucose level compared to the control group, their systolic blood pressure is significantly higher. Findings indicating that LDL-C and total cholesterol levels of wrestlers are higher than others and that there is no difference between HDL-C values might be due to trainings of athletes. It is found that type of training exercised might also affect blood parameters.

Key words: Athletes, sedentary people, lipid.

Introduction

It is noticed that there are numerous researches conducted for identifying athletes' capacities by looking at their physical and physiologic traits in various sports branches. These studies concentrate on determining athletes' critical requirements for success.

Although, studies cover positive changes in athletes' lipid profiles, which lipid parameters undergo change is controversial. Cholesterol and triglyceride are two mutual fat components and risk factors for heart attack. These fats do not circulate freely inside blood plasmas, but they circulate by binding to a carrier protein that has the shape of lipoprotein. According to researches, having more than 200mg of cholesterol, more than 100mg of triglyceride, and more than 20% body fat inside blood lipids brings forth risk factors (1).

It is known that negative effects of having a sedentary lifestyle, especially the risk of atherosclerosis, are reduced with people having inactive lifestyles and that the duration of time they live healthy increases. It is also suggested that regular exercise has positive effects on lipid profile. However, researchers report contradictory findings regarding the time and the exercise type that produce alterations in the lipid metabolism(2).

Low Density Lipoproteins (LDL): This lipoprotein transports cholesterol to the cells in arterial regions that suffer from fat storage and to other cells. Thus, LDL-cholesterol is often called "bad cholesterol", because it covers inside of the venous vessels thoroughly.

High Density Lipoproteins (HDL): They transport cholesterol to the liver for elimination. HDL cholesterol is also referred to as "good cholesterol", because it does not produce accumulation inside vessels. Instead, it has the ability to clear inflammation from arteries. As HDL rate increases, the risk for cardiovascular diseases reduces. Findings indi-

cating the dominance of HDL levels in endurance sports (aerobic) and with inactive people who are driven to various aerobic trainings may change the perspective on training to be operative(1).

Materials And Methods

Characteristics of the subjects participating in the research

105 male athlete and sedentary people (the control group) have voluntarily participated in the study. Some blood parameters of 30 elite wrestlers, 30 elite judokas, and 45 health sedentary individuals, of whom all are university students, have been analyzed. After interviews, it is concluded that they do not use any kind of drugs.

Measurements and tests performed in the research

Measurements related to body compositions were held at Ondokuz Mayıs University Physical Education and Sports Facilities; blood biochemical tests have taken place at internal medicine polyclinics and the medical laboratories of Ondokuz Mayıs University Health Application and Research Center.

Measurement of height and body weight

Subjects' body weights were measured with electronic bascule (premier) in kilograms. They wore t-shirts and leggings and no shoes during the measurement. Their heights, on the other hand, were measured with Rodi Super Quality in cm while subjects were standing upright and barefooted.

Measuring body composition

Systolic and diastolic blood pressures were measured in mmHg with the sphygmomanometer. Body fat ratio: Calculated with Green formula after performing skin fold (triceps, biceps, scapula, abdominal, iliac, quadriceps femoris) measurements with Skinfold Caliper.

Body Fat Ratio (B.F.R.) = 3.64 + Total Skin Fold X 0.097(3).

Measurement of blood biochemical values

Without changing the diets of athletes and sedentary people, their 5ml blood samples were taken on an empty stomach in morning (after 12 hours) with yellow-lidded tubes from the front arm antecubital region. Levels of total cholesterol (TC), triglyceride (TG), high density lipoprotein - cholesterol (HDL-C), high density lipoprotein - cholesterol (LDL-C), and glucose and insulin in the serums, which were obtained from venous blood samples, were immediately analyzed with Hitachi 717 auto analyzer, by using spectrophotometry. Participants' blood parameters were analyzed at the Medical Laboratories of Ondokuz Mayıs University Health Application and Research Centre, and their statistics and reference intervals were specified.

Statistical analysis

Arithmetic means ($\overline{X}$) and standard deviance (σ) of all data were calculated. The difference between the groups is analyzed with computerized package program and using one-way ANOVA test and post hoc Scheffe (multiple comparisons) test. Results were checked to see whether or not they were in the significance level of 0.05.

Discussion

Wrestlers have an average age of 23.43 years, an average height of 173.29 cm, and an average body weight of 73.63 kg. On the other hand, judokas have an average age of 22.48 years, an average height of 173.67 cm, and an average body weight of 73.96 kg. In the control group, average age is 22.84 years, average height is 172.33 cm, and average body weight is 82.67 kg. It is found that while the control group's age and height averages are similar to athletes' values, they have more body weight and fat ratio compared to wrestlers and judokas and that this difference is significant ($p<0.01$).

In our study, judokas' average systolic blood pressure is found to be 115.95 mmHg and their diastolic blood pressure to be 76.60 mmHg. It is seen that wrestlers' average systolic blood pressure is 116.92 mmHg and their average diastolic blood pressure is 76.55 mmHg. In the control group, the average systolic blood pressure is 114.10 mmHg and their average diastolic blood pressure is 75.40 mmHg. It is found that among the wrestlers, who represented Turkey at 1996 Atlanta Olympics, freestyle wrestlers have an average systolic blood pressure of 115.83 mmHg and an average diastolic blood pressure of 76.66, while Greco-Roman wrestlers have an average systolic blood pressure of 117.85 mmHg and an average diastolic blood pressure of

Results

Table 1. Some anthropometric and physiologic characteristics of national athletes and sedentary people (control)

Variables		n	$\overline{X}$	Σ	F / Scheffe
Age (year)	*Judo (1)*	30	22,48	0,29	1,71
	Wrestling (2)	30	23,43	0,32	
	Control (3)	45	22,84	0,23	
Height (cm)	*Judo (1)*	30	173,67	1,50	0,53
	Wrestling (2)	30	173,29	1,31	
	Control (3)	45	172,33	0,73	
Body Weight (kg)	*Judo (1)*	30	73,96	2,31	9,28** 3>1,2
	Wrestling (2)	30	73,63	1,93	
	Control (3)	45	82,67	1,34	
Fat (%)	*Judo (1)*	30	10,66	1,71	23,26** 3>1,2
	Wrestling (2)	30	9,85	1,30	
	Control (3)	45	13,50	3,50	
Systolic blood pressure (mm/hg)	*Judo (1)*	30	115,95	1,93	12,94** 3<1,2
	Wrestling (2)	30	116,92	1,92	
	Control (3)	45	114,10	1,89	
Diastolic blood pressure (mm/hg)	*Judo (1)*	30	76,60	1,36	7,57** 3<1,2
	Wrestling (2)	30	76,55	1,37	
	Control (3)	45	75,40	2,50	

p<0.05 p<0.01***

Table 2. Comparison between insulin and glucose levels of national athletes and sedentary people (control).

Variables		n	Min	Max	$\overline{X}$	σ	F / Scheffe
Glucose (mg/dL)	*Judo (1)*	30	73,00	94,00	82,89	1,03	4,81* 3>2
	Wrestling (2)	30	53,00	97,00	80,23	2,02	
	Control (3)	45	80,00	89,00	85,18	0,34	
Insulin mIU/mL	*Judo (1)*	30	4,00	8,90	6,21	0,26	37,41** 3<1,2
	Wrestling (2)	30	4,00	8,70	5,97	0,25	
	Control (3)	45	2,09	6,80	4,06	0,14	

p<0.05 p<0.01***

Table 3. Comparison of serum lipid levels of national athletes and sedentary people (control).

Variables		n	Min	Max	$\overline{X}$	Σ	F / Scheffe
Total cholesterol (mg/dL)	*Judo (1)*	30	132,00	187,00	157,00	2,83	11,60** 2>1,3
	Wrestling (2)	30	138,00	237,00	180,20	4,88	
	Control (3)	45	125,00	195,00	158,20	3,13	
Triglyceride (mg/dL)	*Judo (1)*	30	100,00	186,00	132,38	5,35	40,26** 2<1,3
	Wrestling (2)	30	46,00	158,00	84,67	6,41	
	Control (3)	45	110,00	174,00	129,88	2,18	
LDL-C (mg/dL)	*Judo (1)*	30	46,40	110,60	92,37	2,95	30,33** 2>1,3
	Wrestling (2)	30	69,00	175,00	110,03	4,67	
	Control (3)	45	67,00	168,00	101,42	1,52	
HDL-C (mg/dL)	*Judo (1)*	30	38,00	71,00	49,66	1,69	2,46
	Wrestling (2)	30	40,10	66,50	51,14	1,25	
	Control (3)	45	40,00	51,00	54,53	1,86	

p<0.05 p<0.01***

73.57(4). founded wrestlers' systolic blood pressure to be 114.95 mmHg and their diastolic blood pressure to be 76.63 mmHg in one of their studies(5). The systolic blood pressure of judokas and wrestlers is significant higher compared to the control group ($p<0.05$). One of the reasons for this is that athletes are not able to rest fully because of their trainings. In another source, delay in the diminution of systolic blood pressure after training is considered as abnormal answer(6). More effective resting methods can be suggested for wrestlers and judokas.

While body fat ratio is found to be 10.66% with judokas, 9.85% with wrestlers, and 13.50% with the control group in our study, in his study on body composition of elite wrestlers, found fat ratio to be 9.88 % according to Brozek formula(7). in a comparison of physical fitness and somatotype particularities of young wrestlers who are in the wrestling national teams of two different countries, showed that Turkish national wrestlers have a fat ratio of 9.8%, while Kazak national wrestlers have a fat ratio of 10.9 % (8). Found wrestlers' fat ratios to be 5% and 15.3% in a study on similar age groups (9). demonstrated that wrestlers in the NCAA III league have a body fat ratio of 12.0% in his study(10). Similarly, Yoon showed that wrestlers qualified for national teams usually have low fat ratios (10%) (11).

Participants' blood parameters were analyzed at the Medical Laboratories of Ondokuz Mayıs University Health Application and Research Centre, and their statistics and reference intervals were specified.

HDL-C amount is found to be 49.66 mg/dL with judokas, 51.14 mg/dL with wrestlers, and 54.53 mg/dL in the control group, while the amount of LDL-**C** is found to be 92.37 mg/dL with judokas, 110.03 mg/dL with wrestlers, and 101.42 mg/dL in the control group. Laboratory reference interval is 25-75mg/dL for HDL-C, and 0-160 mg/dL for LDL-C. showed that LDL-C level is high with sedentary people ($p<0.01$) and HDL-C level is high ($p<0.01$) with athletes(12). showed that athletes have higher serum HDL levels ($p<0.05$) compared to sedentary people and that there is no significant difference between the two groups in terms of LDL levels(13). found that serum HDL-C level measured right after the cycle ergometer exercise increases in a statistically significant way(14). and in a study on wrestlers and sedentary people, showed that HDL-C level is significantly higher with wrestlers, but LDL-C level is lower(15). found that HDL-C levels of 15 sedentary males increase after 5 weeks of submaximal running, but their LDL-C levels stay the same(2). have come to the conclusion that the decrease in LDL and HDL cholesterol levels of male students after eight weeks of endurance training is insignificant(16). found LDL cholesterol to be statistically insignificant and the increase in HDL cholesterol to be significant(17). In our study, wrestlers' values are found to be significantly higher than the values of judokas and the control group in terms of LDL-C amounts ($p<0.01$). No significant difference in HDL-C is found between the groups.

The type of trainings might also be causing wrestlers' LDL-C levels to be higher than others, although they fall into normal limits. Male wrestlers usually perform non-aerobic exercises such as strengthening exercises. This type of exercises does not increase HDL-C levels significantly. All studies on this subject propose that aerobic exercises are necessary for increasing HDL-C levels instead of non-aerobic exercises. In other words, aerobic exercises are emphasized to be vital due to their impact on blood parameters for athletes who carry on their strengthening exercises (18).

Total cholesterol values are found to be 157.00 mg/dL, 180.20 mg/dL, and 158.20 mg/dL in judo, wrestling, and the control groups respectively. Laboratory reference interval is 0-200 mg/dL. While argued that it is higher ($p<0.001$) with sedentary people(12). showed that there is no difference in total cholesterol levels with sedentary people(2). showed that athletes do not have a significant difference from sedentary people in terms of serum TK levels(13). demonstrated that there is a significant decrease after 4 weeks of exercise period (19). and showed the statistical significance of the decrease after 4 weeks of walking exercises for 60 minutes each (20). found that the decrease in cholesterol is insignificant(16). In our study, we have observed that wrestlers' cholesterol level values are significantly higher than both the values of judokas and the values of the control group ($p<0.01$). Their trainings and diets might be causing wrestlers' total cholesterol values to be higher than the values of judokas and the control group, although these values fall into normal limits.

Triglyceride values are found to be 132.38 mg/dL with judokas, 84,67 mg/dL with wrestlers, and 124,88 mg/dL in the control group. Laboratory reference interval is 0-200 mg/dL. While identified triglyceride values to be higher ($p<0.001$) with sedentary people(12). showed that these values significantly decrease with sedentary people(2). found that athletes' serum TG levels are significantly ($p<0.01$) lower than the levels of sedentary people(13). argued that the decrease in triglyceride level is significant(16). showed that 80% max VO_2 level does not decrease with regular exercises carried on for 3 days in a week(21). identified that there is no statistical difference between sedentary middle age women and sedentary young women after 12 weeks of aerobic (running, walking) exercise(22). showed that it is significantly higher with wrestlers(15). found the changes in triglyceride level to be insignificant(17). In our study, wrestlers' triglyceride level is found to be lower than the level of judokas and the control group ($p<0.01$).

Amount of glucose is found to be 82.89 mg/dL with judokas, 80.23 mg/dL with wrestlers, and 85.18 mg/dL in the control group. Laboratory reference interval is 70 - 110 mg/dL. A significant increase in blood glucose levels after an acute exercise(23). In treadmill is identified by, and an increase after an acute aerobic exercise is identified by(24). Showed that there is no difference between athletes' levels and sedentary people's levels(25). In our study, glucose levels of judokas and wrestlers are lower than the level of the control group ($p<0.05$).

Amount of insulin is found to be 6.21 mIU/mL with judokas, 5.97 mIU/mL with wrestlers, and 4.06 mIU/mL in the control group. Laboratory reference interval is 6-27 mIU/mL, in their study on 45 Turkish national team wrestlers and 43 sedentary university students who were in the preparation process before 2008 Beijing Olympic Games, showed that sedentary people have significantly higher fasting insulin values (15). In a study on 67 women between 18 and 69 ages of whom 53 are athletes and 14 are sedentary people, it is found that sporting people have higher blood glucose levels and better insulin sensitivities(26). In our study, insulin level of the control group is found to be lower than the levels of wrestlers and judokas ($p<0.01$).

In conclusion, it is found that fat ratio and glucose level of judokas and wrestlers are lower than those of the control group, while their systolic blood pressure is significantly higher. Findings indicating that wrestlers have higher LDL-C and total cholesterol levels compared to other participants and that there is no difference between HDL-C values of the groups might be due to differences in the types of exercises performed. It is thought that judokas' high triglyceride levels might be due to obtaining 50% of energy from fats (from free fatty acid molecules) and performing aerobic exercises. It is concluded that the types of trainings performed might be effective on blood parameters.

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Hepatitis A virus exposure among HIV/AIDS patients in Istanbul, Turkey

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Abstract

Introduction: Although the Hepatitis A virus (HAV) does not cause chronic hepatitis, the morbidity in HIV-infected patients is substantial. We aimed to determine the seroprevalence and related risk factors of HAV infection among HIV/AIDS patients in Istanbul, Turkey, which is classified intermediate HAV, low HIV endemic region.

Methodology: A total of 242 HIV/AIDS patients that were admitted to our outpatient clinic between 2006 and 2011 were included in this study. Demographic information such as age, sex, transmission routes, socio-economic and educational status, CD4 counts, HAV-IgG test results were collected retrospectively from medical records. All analysis was performed by using SPSS version 16.0 software.

Results: Mean age was 38±11.21 years (range: 20-79) and 83% were male. Most frequent route of transmission was heterosexual (69.4%) followed by homosexual (30.1%) intercourse. The percentage of patients with low educational levels was 58.6% and the mean CD4 count of patients was 393.6 cells/mm^3 (range 4–1270). Out of 242 patients, 221 (91%) were diagnosed with HAV IgG positive. HAV IgG seroprevalence was found in 123 (95.3%) of 129 heterosexual, and 61 (83.5%) of 73 homosexual men (p=0.005). Noticeable higher education levels of homosexual patients compared to heterosexual males deserve attention (p<0.001).

Conclusions: As the main way of getting infected is different between HAV and HIV, it is postulated that its prevalence among HIV/AIDS patients is similar to our general population. Despite being in a major risk group, high educated MSM patients' HAV seroprevalence is evaluated remarkably less than that of heterosexuals.

Key words: HIV/AIDS, Anti-HAV IgG, Turkey

Introduction

Hepatitis A virus (HAV) is one of the most common causes of acute, usually self-limiting disease that doesn't lead to chronic hepatitis and the main route of transmission is faecal-oral. Transmission also via blood and blood products has been reported rarely [1, 2]. Hence, faecal-oral transmission by unprotected oral or anal sex is probably the major mode of transmission among men who have sex with men (MSM) [3].

Seroprevalence of HAV infection shows differences between countries and this may be attributed to geographical location, hygienic standards, as well as social, economic and cultural factors. Turkey is an endemic country for hepatitis A where most people have asymptomatic infections during childhood [4]. According to a study conducted by Tosun et al. with the contribution of 10 different centres in 2012, Anti-HAV positivity was determined at the rate of 91.1% in Turkey. This research showed HAV seropositivity increases after 20 years of age and HAV exposure skips to adulthood [5]. At the time of this study being conducted, in our country Hepatitis A vaccination was not obligatory neither for children nor for adults. Hepatitis A vaccination has been recently included in the National Immunization Programme.

Although the HAV seroprevalence has been reported in various HIV negative groups, there is no such data for HIV-infected adults in our country. Therefore, the purpose of this study is to investigate the HAV seroprevalence and realted risk factors among HIV/AIDS patients in Istanbul, Turkey, which is classified intermediate HAV, low HIV endemic region.

Methods

A total of 242 HIV/AIDS patients that were admitted to Haseki Training and Research Hospital Infectious Diseases and Clinical Microbiology Outpatient Clinic between May 2006-December 2011 were included in this study. Nevertheless, patients with known hepatitis A vaccination before were excluded. Demographic information such as age, sex, transmission routes, socio-economic and educational status, CD4 counts, HAV IgG test results by ELISA (General Biologicals Corp, Taiwan) were collected retrospectively from medical records. CD4 count was done by flow cytometry (FACScalibur, Becton Dickinson, New Jersey, US). All analyses were performed by using SPSS version 16.0 software. Data were described using mean ± standard deviation (SD). Data were analyzed, using the chi-square test and t-tests. A *p*-value less than 0.05 was considered to be significant. As it is retrospective study, we do not need ethical approval because all laboratory tests carried out were part of the routine management of HIV-infected patients.

Results

Out of 242 cases, 202 (83%) were men and the mean age was 38±11.21 years (range: 20-79). Most frequent route of transmission was heterosexual intercourse (69.4%), followed by MSM (30.1%). Intravenous drug abuse was present just in one case. Homosexual transmission was in 73 (36%) male patients. More than half of the patients 142 (58.6%) had low educational levels. The majority of women, 26 (65%), were housewives and had inadequate education. Largest employment categories among men were labourers (n=54), unemployed (n=19) and drivers (n=14), in total 87 (43%).

Mean CD4 count of the patients was 393.64 cells/mm^3 (range 4–1270 cells/mm^3). Among men 184 (91%) and women 37 (92.5%), in total 221 (91%) patients were diagnosed HAV IgG positive. Analyzes of HAV IgG seropositivity, age and education levels according to sexual preferences in men is shown in Table 1. As clearly seen in the table HAV IgG seropositivity is statistically higher in heterosexual men.

Fifteen out of 21 HAV IgG negative cases were vaccinated against Hepatitis A (Havrix 1440 ELU, GSK) within the months 0 and 6, and immune response of over 20 mIU/ml was received in 13 (86.6%) cases.

Discussion

All patients in our study were also over 20 years of age and the results indicate that a high percent (91%) of HIV infected patients have subsequent immunity to HAV. This correlates well with the endemicity of the Turkish population. HAV seroprevalence was smiliar both in male and female patients in our study. Nevertheless, homosexual intercourse was evaluated as the transmission route of HIV infection in 36% of male HIV/AIDS cases. MSM are at the risk of HAV infection as a result of outbreaks occuring in MSM communities [6-8].

The correlation of HAV antibodies is the function of the age in endemic countries. In this study the HAV IgG seroprevalence of homosexual males is observed remarkably less than heterosexuals despite their similar age groups. However, noticeable higher education levels of MSM patients compared to heterosexual males deserve attention. Subsequently, this case is interpreted as an indication of the ability to decrease the prevalence of

Table 1. Characteristics of HAV IgG seropositivity according to sexual preferences in men

	Heterosexual n=129 n (%)	**Homosexual n=73 n (%)**	**p**
HAV IgG positivity	123 (%95.3)	61 (%83.5)	**=0.005**
Mean age in HAV IgG (+) patients	40.19 ±13.54	37.43±10.37	**=0.42**
Education level - Primary school - Secondary school - College/University	 85 (%65.9) 36 (%27.9) 8 (%6.2)	 27 (%37) 21 (%28.8) 25 (%34.2)	**<0.001**

HAV infection within the risk group of individuals as their education levels rise.

Higher HAV seronegative rate of our MSM patients than heterosexual cases indicates the need to protect these cases in the risk group through vaccination. Many reports show that the load and the duration of HAV viremia are significantly higher and longer in HIV/AIDS patients than in non-HIV-infected patients. Thus, the prolonged HAV viremia might cause a long outbreak of HAV infection in MSM [9, 10]. Therefore, HAV vaccination may prevent the outbreak of HAV infection in this population. According to international guidelines, HIV-infected patients should be tested for HAV IgG at HIV diagnosis and they should be vaccinated irrespective of age and CD4 lymphocyte count if proved susceptible [11]. Decision on vaccination in endemic areas like in our country, is better to be based on seroepidemiologic studies [12]. According to high seroprevalence of HAV in HIV-infected patients, routine vaccination seems to be unnecessary in our country.

In conclusion, as the main way of getting infected is different between HAV and HIV, its prevalence among HIV/AIDS patients is similar to our general population. Despite being in a major risk group, high educated MSM patients' HAV seroprevalence evaluated remarkably less than that of heterosexuals. However, we underline the need for hepatitis A screening and vaccination for MSM and high educated groups in our country.

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Giant hepatic hydatid cyst in an adult farmer from western Romania

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Abstract

Cystic hydatid disease is an important zoonotic disease with frequent hepatic involvement. We present a 30-year-old man with a giant hepatic hydatid cyst and discuss the management of this case. The diagnosis was made based on epidemiologic elements, clinical symptoms, abdominal ultrasonography and computed tomography (CT). The diagnosis was confirmed by the histopathological examination of a biopsied fragment of the parasite. The surgical intervention consisted of apartial pericystectomy (Lagrot surgery). The post-operative recovery was successful. Abdominal ultrasonography allows for an early detection of hydatid cysts in patients, and this way an appropriate therapy can be initiated in order to avoid further complications.

Key words: hydatid cyst, abdominal ultrasonography, computed tomography, echinococcosis

Introduction

Cystic hydatid disease (echinococcosis) is an important zoonotic disease caused in humans by *Echinococcus granulosus*, a cestode that usually inhabits the intestine of dogs and other canines as a definitive host. Humans are accidental intermediate hosts due to ingestion of the parasitic eggs (1).

Hydatid disease can involve any organ. The liver is the most common organ involved and, together with the lungs, accounts for 90% of the cases. Other sites of involvement are the muscles (5%), bones (3%), kidneys (2%), brain (1%) and spleen (1%) (2).

Echinococcosis is highly endemic in the Mediterranean countries (the southern parts of Spain, France and Italy; Greece, Bulgaria, Romania, Turkey, Israel, Lebanon, Syria, Jordan, Tunisia and Morocco), as well as Iran, India, China, Chile and Argentina (3). Hydatid disease is common in agricultural and pastoral communities, and the disease continues to be a serious public health threat in many countries including Romania (4).

We report a patient with a giant hepatic hydatid cyst from western Romania who was treated successfully by surgical cure.

Case report

We present the case of a 30-year-old Roma male patient from a rural region in Timis County. To support his family, the patient previously worked as temporary farmer. His work included the loading, transporting and unloading of melons and the use of a horse's cart.

For almost a year the patient has had pyrosis, belching and abdominal distress. He has also experienced a feeling of tightness in the epigastric region, the left upper abdomen and peri-umbilically. The symptoms had worsened progressively, and in the last weeks he had felt that 'his belly is bigger'; furthermore, in the last few days he threw up immediately after eating.

The doctor from his village prescribed the following medications in the last 12 months: omeprazolum, analgesics and anti-spasmodics. However, the symptoms worsened,the patient no longer feed himself, became asthenic and lost 12 kg of weight in the last 3 months.

The physical examination indicated normochromic skin, afebrile and a distended abdomen that was painful upon deep palpation in the epigastric region and in the right upper abdomen. Also, the left hepatic lobe increased in size and contained a 6–7-cm sized tumour that was orientated in the epigastric area.

Abdominal ultrasonography revealed the following: the left hepatic lobe presented with a giant, multiseptated hypoechogenic mass with scratchy content that extends to the spleen and the hypogastrium, measuring 140 mm in diameter. The gallbladder is not visible, and a giant hepatic hydatid cyst was suspected.

In this context (clinical and echographical), the physician decided to taken a computed tomography (CT) scan with contrast that indicated a dimorphic liver due to an extensive intra-abdominal hepatic tumour located in the left hepatic and caudate lobes, measuring 15 cm × 10 cm × 12 cm, poly-lobated and poly-septated, well delimited and containing fluid. Considering the anamnestic data, the diagnosis pleads for a hepatic hydatid cyst. The tumour exerted a mass effect on the hepatic hilum, inferior vena cava (IVC) and pancreas. The gallbladder has no gallstones, and the intrahepatic and extrahepatic bile ducts have normal calibres. The hepatic portal vein has no calibre modifications. The spleen is homogenous and has normal dimensions. The pancreas has normal morphology and dimensions, and homogenous contrast intake. Both kidneys were in a normal position, with no morphological modifications. The adrenal glands were normal as well. The patient did not have abdominal ascitic collections (Figures 1, 2). When the diagnosis was clinically confirmed, the infectious disease doctor decided to urgently admit the patient to a surgery clinic, where laboratory tests were performed and the patient was prepared for surgical intervention.

Routine laboratory tests revealed the following: 7440 leucocytes/μL, haemoglobin = 14.3 g/dL, haematocrit = 45.5%, 294000 platelets/μL, 72% neutrophils, 1% eosinophil, erythrocyte sedimentation rate was 15 mm/h, total cholesterol =178 mg/dL, triglycerides=75 mg/dL, ALT=21 U/L, AST=15 U/L, negative AgHBs, negative AbHCV, negative IgG Ac *Helicobacter Pylori*, positive IgG Ac *Echinoccocus granulosus*. Creatinine= 1.1 mg/dl, total bilirubin = 0.7 mg/dL, direct bilirubin = 0.23 mg/dL, serum amylase = 51 U/L, urea = 36 mg/dL, glycemia = 102 mg/dL. The urine exam was normal.

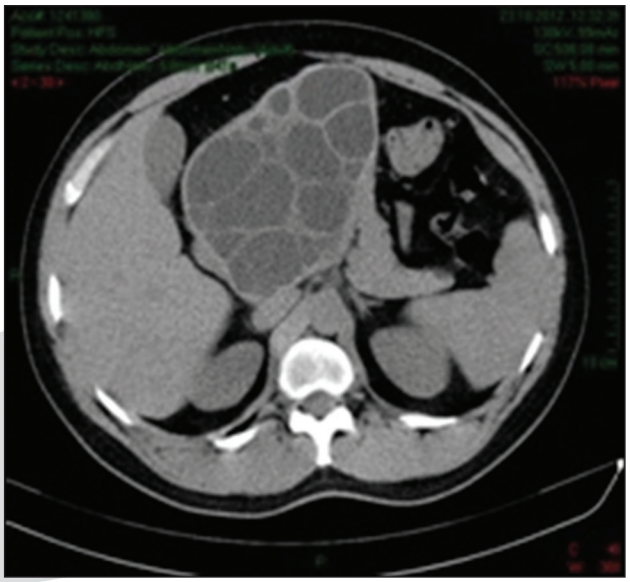

Figure 1. Transverse CT showing large hydatid cysts of the liver

Figure 2. Parasagittal CT revealed the giant hydatid cysts of the liver compressing the inferior vena cava and pancreas

During surgery, the surgeon observed a giant hydatid cyst with measuring 25 cm in diameter that exerted a mass effect on the pancreas, small gastric curvature, hepatic hilum, IVC and aorta. The surgical intervention comprised a partial pericystectomy Lagrot and the covering of the remaining cavity using the omentum.

The post-operatory recovery with antibiotics, analgesics, anti-coagulants, gastric anti-secretory drugs and intravenous solutions was favourable,

with resumption of the intestinal transit on the second post-operative day and abdominal drainage suppression on the fourth day after the surgery. The patient was discharged. After surgery, albendazole (10 mg/kg) administration was started for 6 weeks.

The macroscopic examination of the cystic fragment revealed that the cystic wall was deformed, with a smooth surface,whitish-grey, shiny, measuring 12/5 cm and the wall thickness was between 0.2 and 0.6 cm. The histopathological examination of the fragment showed a stratified, laminated cystic wall, without any scolexes (infertile); the internal layer presented a polymorphic inflammatory infiltrate with multiple eosinophiles, a laminated and avascular membrane and an adventitial layer with dense fibro-vascular conjunctive tissue and dystrophic micro-calcifications (Figures 3, 4).

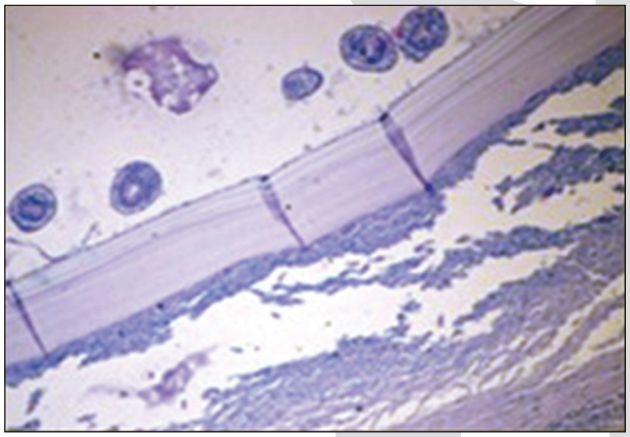

Figure 3. Histological view (H&E X 100 stained) of the hydatid cyst showing hyaline membrane, hydatid liquid and free scolexes

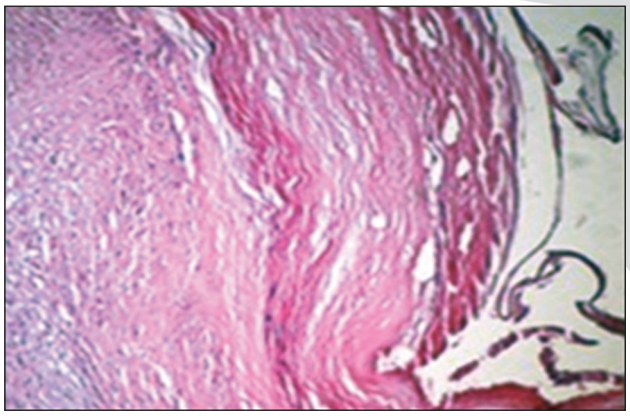

Figure 4. Histopathologic findings (H&E X 100 stained) of the cyst showing the cystic wall and adjacent parenchyma infiltrated with multiple inflammatory cells

A 30-day treatment with albendazol (Zentel), 400 mg/day (2 tablets/day) and clinical control after 7 days is recommended for patients with this condition. The patient made an unevent ful recovery with return to a normal appetite. The patient was kept under regular follow-up and to date has had no recurrence of the hydatid cyst.

Discussion

Echinococcosis is a zoonotic endemic infection caused by larval forms of *Echinococcus* (*E. granulosus*, *E. multiloculares*, *E. oligarthrus* and *E. vogeli*). The life cycles of these parasites involve two mammalian hosts. The adult cestode inhabits the small intestine of a carnivore (definitive host) and produces eggs containing infective oncospheres. Either cestode segments (proglottids) containing eggs or free eggs are released from the intestinal tract of the carnivore into the environment (5).

Humans become infected by the accidental ingestion of *E. granulosus* eggs shed in the faeces of infected canids, resulting in cystic echinococcosis (CE). CE is characterized by cystic lesions, most commonly in the liver and lungs, which can be fatal if not treated with surgery and/or chemotherapy (6).

Dogs are the usual definitive hosts, which contaminate both the environment and intermediate hosts. Human beings are accidentally infected by ingestion of contaminated food or water, or through close contact with domesticated dogs. Parasite embryos gain portal circulation by mesenteric veins and are distributed to the liver and other sites. New larvae give origin to the cysts, with an external membrane and an inner layer where daughter cysts are found. The liver and lungs are the most frequently involved organs. Liver cysts often grow unsuspected for decades, being casually seen during imaging studies, but can cause abdominal pain, bile duct compression and palpable masses (7).

This reported case gathers all the epidemiological elements in sustaining of the final diagnosis, hydatid cyst. The patient came from a rural region, where he was in permanent contact with his horses and dogs. He belongs to the Roma community, went to elementary school only for the first 3 years, and has a reduced intellectual and medical education level, proven by his ignoring concern for individual and alimentary hygiene rules. The

onset of the cystic disease was insidious with digestive symptoms, and in the last 3 months were added weight loss (11 kg), vomiting and increasing volume of the abdomen.

Hydatid cysts are usually asymptomatic until diagnosed incidentally or various complications occur. Complications of hepatic hydatid disease occur in 5%–40% of patients and include the formation of small cysto-biliary fistulas, cyst rupture into the biliary tree, biliary compression, adjacent organ compression, cyst infection, spontaneous or traumatic intraperitoneal rupture and, rarely, hepatic and perihepatic vascular tree compression.

The signs and symptoms of Budd-Chiari syndrome (BCS) may develop as a result of compression of the IVC, hepatic vein and portal venous system by hydatid disease, portal hypertension and thrombosis (8). In our case, the location and the giant dimensions of the hydatid cyst could lead anytime to symptoms of BCS. Furthermore, the patient had demanding physical work (uploading and unloading melons), an aspect that could lead to anaphylactic shock (produced by the rupture of the cyst). This kind of event could be fatal because the patient was working every day on the agriculture field far away from any first aid point, where he could not receive any medical help.

Ultrasonography and CT are both excellent imaging modalities for the detection of hydatid cysts. Ultrasonography is cost-effective in endemic areas and when the diagnosis of a hydatid cyst is certain. However, ultrasonography is less accurate in localising and delineating the extent of the cyst. The sensitivity of CT is 90%–100%, provides a three-dimensional view and delineates the cyst, which is useful when diagnosis is uncertain, or when rupture or infection has occurred (8).

In this reported case, the ultrasonography had an important role in the identification and the suspicion of hydatid cyst. The CT confirmed the diagnosis of hepatic hydatid cyst, offering important anatomical details for the surgical intervention. The histopathologic examination of the biopsied fragment also confirmed the diagnosis of hydatid cyst.

Although rare in the Western world, hydatid disease should be considered in the differential diagnosis of BCS in endemic areas such as in Mediterranean countries. Decompression of cyst pressure is adequate treatment for early-stage cases (4).

We have to appreciate the professionalism of the infectious disease doctors and of the surgeons that managed this case correctly, optimally and efficiently, avoiding any imminent complication during the diagnostic and therapeutic algorithm.

In Mediterranean countries, despite the decline observed in the incidence of echinococcosis during the last decades, it still remains a common disease. The amelioration of the situation was attributed to the adoption of safer procedures, which in turn were supported by the economic flourishing of these countries. Despite some progress in the control of echinococcosis, this zoonosis continues to be a major public health problem in several countries, and in several others it constitutes an emerging and re-emerging disease (9).

Conclusions

In our patient, the abdominal ultrasound examination was decisive in guiding the diagnosis, and we recommend performing this non-invasive exam regularly (every 4–6 months) to all rural people with risk factors for cystic echinococcosis.

It requires also the implementation of programmes to increase the level of medical education, with minimum compliance for the alimentary and individual hygiene rules, among the Roma communities and the patients living in rural areas.

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The burden of family caregivers of elderly in Turkey and Affecting Factors

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Abstract

Objective: This study was conducted with the aim of investigating the burden of family caregivers of the elderly and to identify affecting factors.

Methods: This is a cross-sectional descriptive study. The sample consisted of 250 caregivers of the elderly. A demographic questionnaire and the Burden interview were used as data-gathering tools.

Results: The burden interview mean score for caregivers was 31.34±9.41. The most of caregivers were female. The caregiver burden was found to be higher for women, people with a low educational level, people who are married with children, people without a regular income, people who are not working, daughters-in-law and people who were not asked for their opinion regarding caring for the elderly.

Conclusion: Nurses must be knowledgeable about the factors that predict caregiver burden for the sake of the target group. Early recognition of risks factors of caregiver burden and of health problems in caregivers can provide early support and prevention of caregiver burden.

Key words: Elderly, caregiver/caregiving, burden, affecting factors

Introduction

Aging of the population is one of the most important demographic dynamics that affects families and societies throughout the world. The increase in the population aged 65 and above and the effort necessary to meet the needs of these aging individuals are challenging issues for policy makers, families, businesses, and healthcare providers.[1]

According to 2010 data, 7.23% of the Turkish population is 65 years old and above.[2] This ratio is 6% in urban areas and 10% in rural areas.[3] According to the Turkish Family Structure Survey, 5.3% of the residences in Turkey include an elderly person who is cared for.[4] Despite the changing social structure, supportive family relationships continue to exist in Turkey and in developing countries.[5]

One of the most important social problems related to old age is caring for the elderly. [6] Most of the old people in Turkey prefer to live at home with their families (sons, daughters, etc) instead of living in a nursing home or taking institutional care.[7] Family members play important and essential roles in providing elder care.[8] Elderly people in Turkey are predominantly cared for at home, probably due to Turkey's socio-economic structure. Despite the social processes of modernization and urbanization and the increase in facilities, such as nursing homes, that care for elderly people, it is a common perspective among both the elderly and their adult children that elderly people should be cared for at home. [6] The responsibility for taking care of the elderly is rarely shared equally by all family members. Studies show a predominance of women in caregiver roles. Due to social norms, 75-80% of the responsibility for taking care of the elderly is assumed by women. [5,9] Wives, daughters and daughters-in-law are primarily responsible for caring for elderly people. Consequently, women must take on this new role in addition to their other roles. [9,10]

Although caregiving is not characterized by a specific type of assistance, emotional support, rather than physical or financial support is the most common and the most important type of assistance provided by family caregivers.[11] Other frequently provided types of assistance include transportation, shopping, household chores, coordinating assistance from social services and healthcare providers, routine healthcare (such as administering and monitoring medications), personal care (such as bathing, feeding, toileting, and dressing), supervision, financial management, financial assistance, and the sharing of a common household.[8,11] Caregiving is an experience that is perceived multidimensionally by the caregiver. In

addition to the positive characteristics attributable to caregiving, such as an increase in intimacy and emotional bonding, finding meaning in life due to the caregiving experience, personal development, receiving support from other individuals, and feelings of self-respect and self-satisfaction, it can also create hardships. [11] Although caring for elderly people at home solves the caretaking problem, to some extent, the caregiving adult may experience other problems.

Studies show that caregiving is generally experienced as a stressful process with potentially negative physical and psychological outcomes. [11,12,13,14] It has been reported that when the life quality and health status of caregivers of elderly people and their families are evaluated, caregivers are often found to experience physical, psychological, social and economic difficulties and burdens, such as fatigue, exhaustion, loneliness, deterioration of family relationships, and financial problems.[11,14,15]

Caregiver burden has been defined as a multidimensional response to the negative appraisal and perceived stressresulting from taking care of an elderly. Caregiver burden threatens the physical, psychological, emotional and functional health of caregivers.[16,17,18] Caregiver burden affects the health of both caregivers and their carerecipents. The latest studies of family caregivers have emphasized the importance of understanding the factors that influence a caregiver's ability to care for an elderly adult and informing makers, clinicians and nurses to help reduce caregiver burden and improve care for the elderly in the future. [19,20] Early recognition of risks factors of caregiver burden and of health problems in caregivers can provide early support and prevention of caregiver burden. [21] For this reason, this study was conducted with the aim of investigating the burden of caregivers of the elderly and affecting factors of the burden of caregivers.

The following research questions were posed:

- What is the level of the burden of family caregivers
- What are the relationships between caregiver socio-demographical factors and the burden of caregivers.
- What are the relationships between care recipient socio-demographical factors and the burden of caregivers.

Materials and Method

Design: This is a cross-sectional descriptive study.

Sample and setting

The research was conducted in the Denizli region in the west of Turkey. To define the research population, the 21 public health centers affiliated with the Denizli Province Health Ministry were divided into three groups according to socioeconomic level: high, medium and low. One public health center from each socioeconomic group was chosen using a simple random sampling method. We identified 832 residences in the three health center regions in which individuals 60 years old and above lived with their children. A population-based study reported a 36% prevalence of caregivers living with the elderly. [22] To establish the case numbers for the sample, we used a prevalence value of 0.36 and a standart error value of 0.05. [22] The number of people included in the sample for this study was set at 250. Caregivers were selected randomly with probabilities proportional to the number of caregivers at each public health center. The study group was subsequently chosen by random sampling from 250 caregivers from these centers who were eligible according to the study criteria.

The criteria for inclusion in the study were being over 18 years old, being the person primarily responsible for caretaking, and sharing a house with an elderly person for at least 6 months.

Data collection tools

Two data collection tools were used. First, a questionnaire examined the demographic data of the caregiver and the elderly person who required care. Then, the "Burden Interview" was administered.

Demographic questionnaire

This questionnaire included a total of 19 questions. Questions addressed to the caregiver requested information on gender, age, educational level, marital status, status of having child, regular income, employment status, relationship between elderly and caregiver, participation in decision of caregiving and caregiver's perception about together with elderly. Questions regarding the elderly person who required care requested information on gender, educational level, marital

status, regular income, whether the elderly person had a bedroom of their own, chronic illness.

The Burden interview (BI)

Caregiver burden was assessed using the Zarit scale which has 22 questions about the impact of the disorders of elderly on the quality of life of their caregivers. The scale was developed by Zarit, Reever ve Bach-Peterson. The items of the BI are evaluated using a 4-point Likert scale from 0 (never) to 4 (always). The BI was scored by adding the numbered responses from individual items.Total score ranged from 0 to 88, with higher scores indicating greater caregiver distress. Norms for the ZBI have not been computed, but estimates of the degree of burden can be divided into four categories: 0 to 20 (little or no burden), 21 to 40 (mild to moderate burden), 41 to 60 (moderate to severe burden), and 61 to 88 (severe burden). [16]

A validity and reliability study for the Turkish population was conducted in 2008 by Inci and Erdem. The Cronbach alpha coefficient was calculated to determine the internal consistency reliability of the interview; The Cronbach alpha coefficient was 0.95 for the BI. [23]

Data collection method

Before beginning the study, a pilot study was conducted with 10 elderly people who were not included in the main study but who had characteristics similar to the sample group. Corrections were made to the questions that were unclear. Data were collected using in face-to-face interviews during home visits in which the researchers read the questions from the questionnaire and recorded the caregivers' answers. First, the interviewers went to the homes of the participants, showed their identity card for this study and introduced themselves. Next, the participants were given information about the purpose of the research and written consent was received from all participants. Each interview lasted approximately 30 min.

Ethical considerations

Permission was obtained from the Denizli Province Health Ministry. Written informed consent was obtained from all of the caregivers who participated in the research. The caregivers' identities were kept confidential to protect their anonymity, and they were ensured that the information they provided would not be used for any purpose other than scientific research. The participants were assured that they could withdraw from the study at any time.

Data analysis

All statistical analyses were performed using the SPSS 15.0 software package. P values of <0.05 were considered statistically significant. Frequencies and percentages were used to describe the descriptive data and the characteristics of the caregivers and the elderly. The data were analyzed using independent samples t-test, Kruskal Wallis and Mann Whitney U test and bonferroni analysis.

Results

The mean age of the caregivers who participated in this research was 35.18±11.26 years (18–65 years). Overall, 72.0% of the caregivers were female, 37.2% of the participants had a primary school education, 46.8% were married, 55.2% had children, 87.6% had a regular income, and 62.4% indicated that they did not work (Table 1).

Table 1. Descriptive characteristics of caregivers

Variables	N	%
Age mean	35.18±11.26	Min.18 max.65
Gender		
Female	180	72.0
Male	70	28.0
Education status		
No formal education	22	8.8
Primary school	93	37.2
Middle school	23	9.2
High school	60	24.0
University	52	20.8
Married Status		
Married	117	46.8
Single	133	53.2
Having children		
Yes	138	55.2
No	112	44.8
Regularly income status		
Yes	219	87.6
No	30	12.4
Employment status		
Working	94	37.6
Not Working	156	62.4
Total	250	100.0

The mean age of the care recipients was 71.68±6.41 years (60–96 years). Of the elderly, 75.2% were female, 54.4% had no formal education, 42.8% were married, 74.0% had a regular income, and 64.0% indicated that they had their own bedrooms. Furthermore, 66.4% had a chronic illness diagnosed by a doctor (Table 2). There was a statistically significant difference in the scores for the Burden interview when they were evaluated according to the caregiver's gender, educational level, marital status, having of children, regular income, employment status, degree of relationship, participation in decision of caregiving and the caregiver's perception that his or her life had changed due to living with the elderly person (Table 3). There was a statistically significant difference in the mean scores for the burden caregiving when they were evaluated according to the care recipient's gender, educational level, presence of a room of his or her own, and regular income (Table 4).

Table 2. Descriptive characteristics of elderly

Variables	N	%
Mean age	71.68 ± 6.41	Min. 60 max. 96
Gender		
Female	188	75,2
Male	62	24,8
Education *status*		
No formal education	186	74.4
Primary and middle school	51	20.4
High school and university	13	5.2
Marital status		
Married	107	42.8
Not married	143	57.2
Regularly income status		
Yes	185	74.0
No	65	26.0
Having their own bedroom		
Yes	160	64,0
No	90	36,0
Chronic diseases status		
Yes	83	33.2
No	167	66.8
Total		

Discussion

It is common for married children to live with their parents in Turkey, a country with a traditional family structure. Although children in western countries do not tend to live with their families and are focused on their own marriages, in countries with traditional and strong family bonds, it is common for children to offer social support to parents when needed. This study was conducted cross-sectional descriptive with the aim of investigating the burden of family caregivers of the elderly and to identify affecting factors.

The mean BI score was found 32.9[24], 33.02 [25] in the literature. According to the findings of this study, the mean BI score for caregivers was 31.34±9.41. The mean score BI of the study was mild to moderate burden. Despite the high burden of caregiving identified in many studies, a study conducted in China found that countries with traditional values, such as Turkey, had a lower burden of caregiving [26]. The mean score BI of the study was lower than expected which might result from the fact that individuals have difficulty in sharing their real thoughts about parents with other people, they believe that they have to caregiving parents in cultural sense and adopt this as a role, they think they would be condemned. It was thought that even if they have burden caregiving, people who give care cannot express themselves because of the respect towards elder or because of social reasons.

The effect of caregivers' demographic characteristics on the burden of family caregivers

Researchers have found that the degree of burden experienced by caregivers depend on several contextual factors; caregiving related factors and primary stressors including the socio-demographical factors of caregivers and care recipient. [17,18] It is important to consider caregiver characteristics such as age, gender, educational level, ethnicity, and cultural values. [27]

The results of this study suggest that some demographic characteristics of caregivers are significantly associated with the burden caregiving. The mean scores for the burden caregiving were higher for female caregivers, caregivers without a formal education, people who were married with

Table 3. Burden of living together scale mean scores according to descriptive characteristics of caregiver

Variables	N	Mean ±	S.D	Statistical significant
Gender				
Female	180	32.27	10.03	t=2.958
Male	70	28.93	7.09	p=0.004
Education status				
No formal education	22	36.72	13.00	
Primary school	93	31.42	9.19	K-W=11.566
Middle school	23	32.43	8.61	p=0.021
High school	60	31.58	8.89	
University	52	28.14	7.97	
Married status				
Married	117	33.39	10.59	t=3.230
Single	133	33.39	7.85	p=0.001
Having children				
Yes	138	32.49	10.41	t=2.238
No	112	29.91	7.82	p=0.026
Regularly income status				
Yes	220	30.57	8.77	t=-2.676
No	29	36.83	12.18	p=0.012
Employment status				
Working	94	29.65	7.85	t=-2.363
Not working	156	32.36	10.13	p=0.019
Relationship between elderly and caregiver				
Child of elderly	184	29.65	8.00	t=-4.194
Daughter-in-law	66	36.01	11.35	p=0.001
Participation in decision of caregiving				
Yes	220	30.38	8.69	t=3.623
No	30	38.32	11.56	p=0.001
Perception by the caregiver that their lives had changed due to living with the elderly				
Not changed	125	28.86	7.61	K-W=56.727
Negative changed	96	35.97	9.57	p=0.001
Positive changed	29	26.69	9.88	
Total	**250**	**31.34**	**9.41**	

Table 4. Burden of living together scale mean scores according to descriptive characteristics of elderly

Variables	Frequency	Mean ±	S.Deviation	Statistical significant
Maried status				
Married	107	30.15	9.47	t==1.72
Single	143	32.22	9.31	p=0.086
Educational Status				
No formal education	186	31.88	9.21	K-W =10.191
Primary and middle school	51	30.93	10.56	p= 0.006
High school and university	13	25.22	4.57	
Having a room of their own				
Yes	160	30.13	8.71	t=-2.62
No	90	33.49	10.26	p=0.010
Regularly income status				
Yes	185	30.24	8.92	t=-2.96
No	65	34.44	10.11	p=0.004
Total	**250**	31.34	9.41	

children, people without a regular income, and people who were not working.

Gender differences, particularly as they apply to husbands and wives, have been a focus of interest in caregiver research. Our study found that female caregivers experienced a greater burden caregiving compared to men caregivers. Many studies have found that female caregivers experience more hardships compared to male caregivers. [13,28,29] When caring for elderly people is added to the responsibilities female already have, female may be physically, psychologically, and socially affected in a negative way. [30] As a developing country, Turkey has encouraged nuclear families. As increasing numbers of women have begun to work outside the home, women who are both spouses and mothers must accomplish many tasks simultaneously. Therefore, women caregivers experience more hardships because they must balance their personal needs and wishes with their responsibility for family members and elderly care recipients.[10]

On the other hand, the results of this analysis suggest that recommended level of education is associated with burden caregiving. It was determined that those who have no formal education experience more burden caregiving. Lai (2007) found that a higher level of caregiving burden is significantly associated with caregivers with lower education. In the literature it was also stated that one of the factors which influences the burden of caregiver is the educational status. [14,31,32,33] Hence our findings are in line with the findings of earlier studies. Considering this group as a risk group, practices should be done in order to decrease negative effects burden caregiving.

We also found a statistically significant difference in the mean scores for the burden caregiving according to marital status, with a higher burden caregiving for married caregivers compared to single caregivers. Married women have many roles; they are wives and mothers, and they manage the housework and take care of their families. As the number of people living in a house increases, women's physical burdens also increase. If a woman is in indirectly in charge of caregiving, she has the additional burden of a crowded house and different generations living together. If she is directly in charge of caregiving, her social activities and opportunities for entertainment diminish, and she may have less time to rest. These factors can affect an individual's health status. [34,35]

When the scores were evaluated based on whether the caregivers had children, the burden caregiving scores for caregivers with children was found to be higher than the scores for those without children. This result may be due to the increased responsibility and the hardship of having insufficient space at home for every individual. It is difficult for women to take care of both children and elderly people. [36]

Financial status is a significant predictor of caregiving burden. This study found that caregivers without a regular income experienced a greater burden caregiving compared to those with a regular income. This finding is supported by research on the financial consequences of caregiving. [26]

The majority of the family caregivers for the elderly are daughters-in-law. In our study, we found that caregiving daughters-in-law experience a greater burden caregiving compared to the child (daughter or son) of the elderly care recipient. There is no consanguinity between a bride and the parent of a spouse, and close, lifelong relationships may not be established. Furthermore, the family cultures of the bride and her spouse's parent may differ. When an elderly person lives with a married child, discussions and difficulties may arise between the parent and the bride/groom regarding the children's education and other issues. [37] According to the results of a study by Arpacı and Ersoy (2001), the most important social problem found among caregiving brides is that they cannot participate in social activities because there is an elderly person at home, and caregiving is a time-consuming job that does not allow them to pursue their hobbies. The same study found that the brides' activities were prevented by the care recipient and that the care recipient attempted to control them and found it odd that the caregivers wanted to do something for themselves (34.8%). [30] The results indicate that taking care of elderly people at home creates hardships, and this is especially true for caregiving brides. Our study results were similr to those in the literature.

Our study also evaluated the burden caregiving according to the caregiver's contribution to the decision. We found that caregivers who did not agree about living with the elderly person had a higher

burden caregiving compared to those who agreed to live together (Table 3). People who think that living with an elderly person has a negative effect upon their lives experience a higher level of hardship.

The effect of the demographic characteristics of the elderly care recipient on the burden caregiving

We evaluated the effect of some of the demographic characteristics of the elderly on the burden caregiving for the caregiver. We found that the following characteristics of the elderly affected the burden caregiving: gender, educational level, the presence a room of their own, and the contribution of the elderly to the family.

Caregivers who cared for elderly people who had low educational levels (no formal education) and those who cared for elderly people who did not have a private room experienced a greater burden caregiving. This may be because the room the elderly person used had been used for other purposes that were subsequently changed, creating a greater hardship.

People who care for elderly individuals who do not contribute to the family have a greater burden caregiving. In situations in which the elderly person has a pension and/or owns the house, the caregiver's economic burden diminishes, thereby decreasing some of the problems.

Study limitations

The main limitation of this study is the small sample size, which may have prevented sufficient scope for detecting potential relationships. A further limitation of this study is related to its cross-sectional descriptive research design, which makes it difficult to generalize the results.

Conclusions and Suggestion

Certain types of caregivers may experience greater hardship, including caregivers who are female, have no education, are married, have children, lack regular income or work, are the daughters-in-law of the care recipient, have not contributed to the caregiving decision, and those who believe that living with an elderly person has a negative effect on their lives.

Reresearchers, studies that aim to decrease the burden caregiving must be conducted. Furthermore, qualitative investigations should be planned with the aim of establishing correct information and sound experience. Thus early recognition of caregivers at risk of caregiving burden and the associated health problems and early support may prevent or alleviate caregiver burden. By assessing and understanding the problems involved in family caregiving, nurses can provide interventions that will be proactive and may prevent further stress in the lives of caregivers, clients and families. Caregiving services offered to the elderly at home should be enhanced with the aim of decreasing the burden of the caregiver in the family.

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Seroepidemiology of toxoplasma gondii in pregnant women: An empirical investigation

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Abstract

Toxoplasma is an intracellular protozoan which exists common in both humans and animals. Toxoplasma gondii infection in individuals with healthy immune systems is asymptomatic or with minor symptoms causing permanent immunity against infection. However, it can be transmitted to the fetus through the placenta during pregnancy and cause serious problems. It may dramatically affect the embryo development. Early detection of this disease is of great importance for prognosis and treatment. For this reason, it is necessary to develop a comprehensive knowledge of the parasite in different parts of the country in order to control the disease during pregnancy. This descriptive study was conducted on 835 14-49 year-old pregnant women. For these women, some questionnaires were administered and completed by practitioner. Venous blood samples were taken from all patients and were tested for the presence of T. Gondii IgG and IgM by ELISA. After testing blood samples of 835 pregnant women admitted to Ayatollah Mousavi hospital, there were IgG antibodies to Toxoplasma gondii in 173 patients (7/20%) and IgM antibodies in 57 patients (8/6%). 20 (3/2 %) were also positive for IgG and IgM. There was a significant relationship between levels of IgG and IgM and age ($P < 0.001$). The relatively high prevalence of T. Gondii shows that woman are susceptible to infection with Toxoplasma and fetal complications. In addition, given that 75 % of people have no immunity against Toxoplasma, some protective decisions are required.

Key words: Toxoplasma gondii, IgM and IgG, ELISA, pregnancy

Introduction

Toxoplasma is an intracellular obligate parasite found throughout the world even developed countries. Contact with cat droppings, contaminated undercooked meat, contaminated fruits and vegetables, unpasteurized dairy, raw eggs and untreated water may increase the risk of this disease. Toxoplasma gondii (T-gondii) is an optionally single-host protozoan that can complete its evolution in both one host and two hosts; however, its final host is cat. There are two stages in its evolution: 1) extra-intestinal evolutionary path, 2) intestine evolutionary path. Extra-intestinal cycle can be done in both nucleated cells of cats and intermediate host. Intermediate hosts such as humans are infected by eating tissue cysts containing bradyzoites and Oocysts containing Sprozoite. Intestinal phase is done only in the intestines of cats. In this phase, there is both schizogony and game to gonyproliferation [1]. Through life cycle of this protozoan, Oocysts come into the stools of cats and sporulate in the environment within 1-5 days; then, they can cause infection. Intermediate hosts are infected after eating food contaminated with cat stool. Oocysts promptly convert to tachyzoite) and evolve to bradyzoites in muscle and nervous tissues. Cats are infected after eating these hosts. Humans also can be infected with this parasite by low-heated foods, foods contaminated with cat stool, blood transfusion from an infected person and from mother to fetus [2] (Figure 1).

T-gondii infection is asymptomatic or with minimal symptoms in 80% of individuals with healthy immune systems [3]. The rest of the population may experience fever or neck lymphadenopathy and myalgia as well as fever, fatigue, sore throat, retinitis (retinal inflammation) [4], and rash [5]. T-gondii infection is important in people with weak immune system and pregnant women. In people with weakened immune system, it can always be life threatening. In the case of pregnant women, a study conducted in America indicates that 48 percent of mothers with children infected

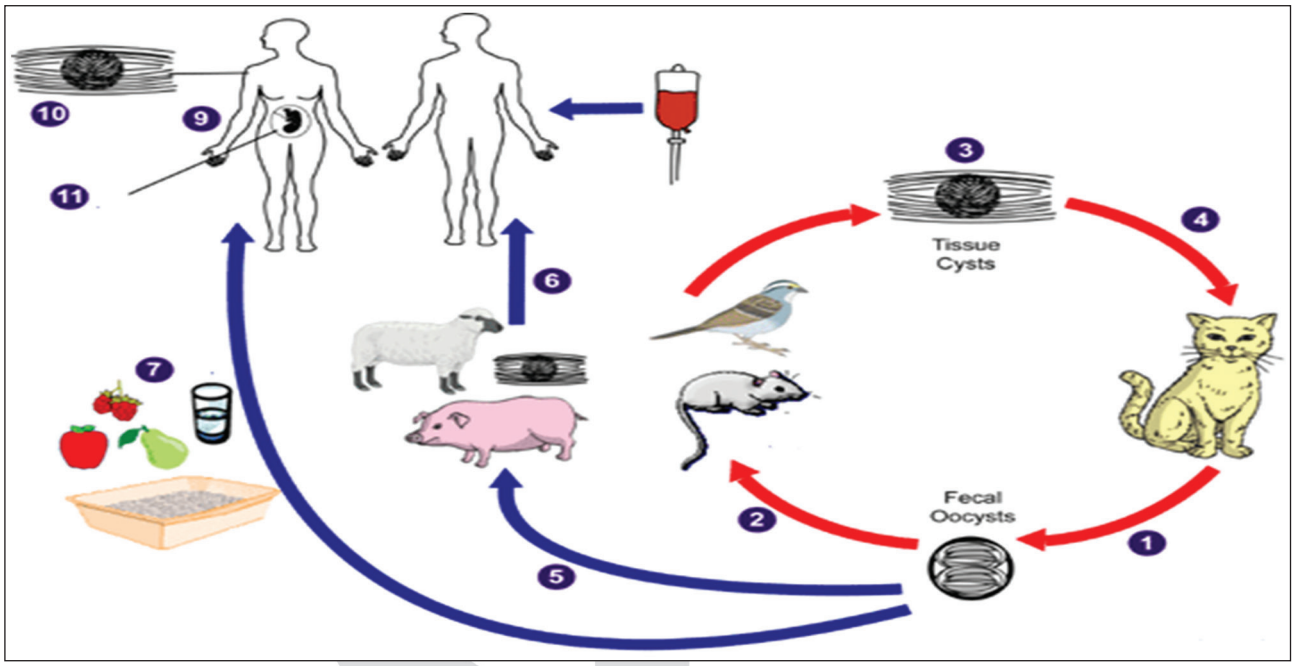

Figure 1. Toxopasma gondii life cycle

to toxoplasmosis at birth showed symptoms of T-gondii infection [6]. Primary infection during pregnancy can cause abortion, neurological damage to the fetus, hydrocephalus, microcephlus, infection and symptomatic disease in the new born considering the age of the fetus. The rare individuals may experience visual problems and chorioretinitis [7,8]. Congenital toxoplasmosis has various clinical signs. Many factors can contribute to the diagnosis of neonatal disease; some of them include diagnosed disease in pregnant women and babies, type of congenital encephalomyelitis and experimental findings in infants [2,9]. Serologic tests and antibodies are used for its diagnosis in pregnant mothers. 50-80% of the infants are asymptomatic; the type of disease must be diagnosed by serological tests [10] and be treated, because 30% of asymptomatic untreated cases develop chorioretinitis in childhood particularly during puberty. A few experience delayed growth. Symptomatic neonatal type is in the form of gastrointestinal disorders like diarrhea and vomiting, seizures, thrombocytopenia and bleeding in less than 20% of cases and usually hyperthermia or sometimes hypothermia. There are also jaundice, hepatosplenomegaly and lymphadenopathy, interstitial pneumonia, skin maculopapular rashes, sometimes oliguria, edema and as cites and heart involvement. Eye fond us may be observed in examination of the eye. In laboratory findings, anemia, and sometimes eosinophilia are often simultaneous symptoms of thrombocytopenia and occasionally disseminated intravascular coagulation (DIC). 10% of cases of congenital encephalomyelitis include drowsiness, seizures, irregular breathing, difficult swallowing, and temperature, early hydrocephalus, microcephaly, one- or two-sided microphthalmia, cataract, hypotonia, hypertonia and paralysis. Above symptoms may also be associated with additional symptoms such as hepatosplenomegaly. The children with serious forms of the disease who have survived experience developmental delay in about 80 % of cases [11], severe eye infection in 30 % of the generalized forms and in 60 % of neurologic cases and finally hearing loss in 20 % of cases.

Detection of toxoplasma occurs in different ways the most important of which can be toxoplasmin skin test, complement fixation test, indirect hemagglutinin test and ELISA [2,12,13].

ELISA stands for Enzyme-Linked Immunosorbent Assay as a simple biochemical test with high sensitivity which allows the simultaneous analysis of large numbers of samples. The results were analyzed by variance analysis.

Materials and Methods

This descriptive study was conducted on 835 pregnant women referred to Ayatollah Mousavi Hospital, Zanjan for prenatal care. A questionnaire was developed and completed by the practitioner for these women. This questionnaire forms included information such as age, education level, use of raw vegetables, raw or low-cooked meat and direct contact with cats. Diagnosis is usually based on detection of related antibodies in the blood. IgG and IgM levels increase in one to two weeks of the acute infection. Increased IgG levels indicates infection; however, it cannot differentiate recent infection and the infection has previously occurred. Detection of IgM indicates recent infection. Meanwhile, 5ml blood samples were taken from all patients by sterile syringes under sterile conditions to measure Toxoplasma antibodies. All samples were centrifuged at a speed of 3000 rpm for 5 min; the plasma was separated and held at -20°. To measure IgG and IgM antibodies, ELISA was used. Detection kit for Toxoplasma IgG and IgM was obtained from Genesis Co. Microplate wells were coated with purified Toxoplasma gondii antigens. The serum samples were added to the wells; after washing, they were added to above antibody collection labeled with peroxidase. Finally, test result was observed after adding substrate chromogen. The colour changed if specific antibody existed. Colour intensity is in proportion to the amount of serum antibody. Colour photometric measurements were conducted by a 450nm filter within 30 minutes and by adding finishing solutions. Positive results indicated IgG and IgM antibodies against Toxoplasma.

Results

After testing blood samples from 835 pregnant women referred to Ayatollah Mousavi Hospital, Zanjan, there were IgG antibodies to Toxoplasma gondii in 173 patients (7/20%) and IgM antibodies in 57 patients (8/6%). 20 (3/2%) were also positive for IgG and IgM (Table 1).

Most of those who were positive for anti-Toxoplasma antibodies were 21-25 years old including 96 patients (71/45%). There was a significant relationship between IgG and IgM levels and age ($p < 0.001$). 24 patients were 16-20 years old (42/11%). 63 cases with positive for Toxoplasma antibodies were 26-30 years old (30%). 20 cases who were positive were 31-35 years old (52/9%). Finally, 4 positive patients were 36 to 40 years old (9/1%) and3 patients were positive in 41-45 age group (42/1%) (Table 2).

Table 1. Seropositivity for IgG and IgM

Toxoplasma Gondii	Number (percent)
IgG positive	173 patients (7/20 %)
IgM positive	57 patients (8/6%)
IgG and IgM positive	20 (3/2%)

Toxoplasma antibodies in people who had contact with cats were positive in 89 cases (42%); number of people with positive IgG was higher than the number of people with positive IgM. The 96 people had contact with soil (45 %); in this population, the number of positive IgG was higher than positive IgM individuals. Raw materials were used by 124(59%) among whom patients with positive IgG were higher than positive IgM individuals. IgG positive rate was higher in patients with moderate economic level (n = 112). There was a significant relationship between IgM and IgG and socioeconomic levels ($p < 0.001$) (Table 3).

Overall, 835 patients entered the study among whom 210 (15/25%) had IgG and IgM antibodies in their serum, indicating previous infection or current infection. According to the above, among 173 people (7/20 %) with positive and IgG, 153 were only positive IgG with previous infection and 57 subjects (8/6%) with positive IgM had new infections (Figure 2).

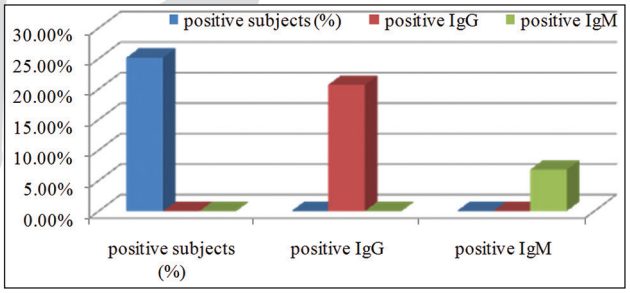

Figure 2. Percent of seropositivity in all cases and for IgG and IgM

Table 2. Seropositivity for IgG and IgM on basis of age

Age group	Number of people with positive IgG (%)	Number of people with positive IgM (%)	Total number (%)
16-20	23	4	24 (11.42%)
21-25	81	25	96 (45.71%)
26-30	53	16	63 (30%)
31-35	12	9	20 (9.52%)
36-40	3	1	4 (1.9%)
41-45	1	2	3 (1.42%)

Table 3. Seropositivity for IgG and IgM on basis of risk factors

	Number of people (%)	Number of positive IgG patients (%)	Number of positive IgM patients (%)
Contact with cat	89	53	36
Contact with soil	96	64	32
Raw vegetables	124	98	26
Socioeconomic Condition			
Low	75	43	32
Average	112	87	35
High	23	15	8

Discussion

Evidence suggests that Toxoplasma infection can cause fetal loss during pregnancy. This organism tends to infect cells such as intestinal epithelium, placenta and muscle. This organism can be transmitted through the placenta to fetus; developed active disease in the mother can cause miscarriage, stillbirth and congenital anomalies [14]. This protozoan contamination can be identified by measuring IgG and IgM antibodies in human serum which may be associated with active infection or previous infection.

After testing blood samples of 835 pregnant women, there were IgG antibodies to Toxoplasma gondii in 173 patients (7/20%) and IgManti bodies in 57 patients (8/6%). 20 (3/2 %) were also positive for IgG and IgM. Therefore, 20 people who were positive for IgG and IgM probably were infected with T. gondii during the past 12 months. 37 cases were positive for IgMalone which indicates acute infection with Toxoplasma. 153 individuals were positive for IgG alone indicating previous infection.

Most of antibody positivity was observed in 21-25 years old patients including 96 cases (71/45%) followed by 26-30 years old group including 63 patients (30%).

There are risk factors that increase the likelihood of positive anti-Toxoplasma antibodies. In our study, the impact of these risk factors were measured. Contact with cat was observed in 89 (38/42 %)patients which support the role of this animal in transmission of this organism. Contact with soil was observed in 96 (71/45 %) patients with positive Toxoplasma antibodies, which confirms the role of soil in the transmission of disease. Unwashed raw vegetables had the greatest impact on the transmission; so that 124 (59 %) patients had such history. The higher positive rate of the test was observed in subjects with moderate socioeconomic level including 112 (3/53 %) subjects.

Uysal et al. [15] found that 9/39% of pregnant women were positive for T. gondii antibodies; of this number, 5/2% were positive IgM. Lopes-Mori et al. [16] reported that 7/51 % of pregnant women were positive for IgG antibodies to Toxoplasma gondii and 3/1 % were also positive for IgM. In a study conducted in China by Hua et al. [17], was a positive IgM was zero and positive IgG was 98/3%. In this study, there was a significant relationship between antibody levels and age and socioeconomic class ($P < 0.001$). Hashemi and Saraei [18] studied the incidence of positive antibody among unmarried women; they found that the overall prevalence of antibody was posi-

tive in 34% of patients Saeedi et al. [19] reported that positive IgG was 3/48% and positive IgM was 7/11%.They found no relationship between age, education, job and living place. Fallah et al. [20] found that 5/33% of subjects were positive for Toxoplasma antibodies. In this study, age and eating raw vegetables were significantly associated with a positive test.

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Risk factors for early and late postpartum depression: A prospective study from Turkey

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Abstract

Objective: This study aimed to identify the prevelance of postpartum depression and risk factors for postpartum depression the 6th week and 6th month after the delivery.

Methods: A cohort study a random survey method were used. 96 women were included in sample group for the 6th week after the delivery, 74 women were included for the 6th month after the delivery.

Results: The occurrence of postpartum depression was determined to be 31.3% in the 6th week, and 18.9% in the 6th month. Strong predictors of depression at 6th week were as follows: Economical difficulties, to graduate from primary school, unintended pregnancy, to strain of caring for the baby, the baby's sleep problem, lack of husband's support during pregnancy. Strong predictors of depression at 6th month were as follows: Physical problems in postpartum, being married for five years or less, the baby crying for long periods, the baby who underwent treatment for any reason, and the presence of depression at 6th week.

Conclusion: The findings of this research suggested that every woman who gives birth should be scanned for depression during the first 6 months postpartum and that especially women who have the predetermined risk factors should be more closely monitored.

Key words: Postpartum depression, Risk factors, Edinburgh Postnatal Depression Scale, Turkey

Introduction

Postpartum depression (PPD) is an important public health problem that may surface anytime within a year postpartum (PP), which may last for months or even years [1]. During the first postpartum year, the incidence of postpartum depression is 13.8 % of the mothers in Japan [2], 10.9 % of the mothers in Hungary [3], 7.6 % in Pakistani mothers who living in Norway [4], 12.7 % - 13% in Switzerland [5,6] and 12.7% in Canada [7]. PPD affects 11.4%- 51.3% of mothers within the first year after the delivery in Turkey [8,9,10].

Various studies have reported that the factors leading to PPD. The risk factors for postpartum depression are as follows: the stress of baby care, general life stress, the lack of social support, anxiety during pregnancy, maternal sadness, dysfunctional marriage, story of depression [11], working women [12], the presence of psychiatric disorders in the family [13], low socio-economical status [10] and factors related to the baby [4].

PPD affects the mother, the baby, the father and other family members negatively. In cases of late diagnosis and treatment, the risks of the mother becoming insufficient in caring for the baby and the baby experiencing a delay in physical and cognitive development become more pronounced, and the depression may become chronic [14]. Thus, identifying and treating the problem early is very important. In order to be able to make an early diagnosis, the patients in the risk groups should be assessed and followed by medical personnel [13,15,16]. Many studies have been made regarding PPD and the factors related to it. However, the number of studies where the same group of women was followed up and the risk factors for the 6th month were evaluated is insufficient. This study aimed to identify the prevelance of postpartum depression and risk factors for postpartum depression on the 6th week and 6th month after the delivery.

Methods

Study Desing

This descriptive cohort study has been carried out was carried out between March 2009 and Semptember 2011, in Istanbul, Turkey.

Participants and data collection

Written permission was provided by the Marmara University Ethic Committee and the director of the hospital to conduct the study.

The universe of the study was consisted of women gave birth in the hospital during the study period and 127 women (Women willing to participate in the study that can speak Turkish, has a phone number where she can be reached, lives within the Istanbul metropolitan area, doesn't use antidepressants, and whose baby is alive postpartum) took place in the sampling. Before the data collection, participants were informed about the purpose and duration of the study and that participation was voluntary. Informed consent was obtained and it was made clear that withdrawal from the study could take place at any time. 127 women who volunteered to participate were included. During the interviews of the 6th week, 31 women couldn't be interviewed for various reasons (Refusing to be interviewed, moving, being on vacation, changing their phone number, etc.), and 22 more couldn't be interviewed in the 6th month. Thus, 96 women were included in sample group for the 6th week after the delivery, whereas 74 were included for the 6th month after the delivery.

Data-collection tools

The data was collected with Risk Factor Assessment Questionnaire (RFAQ) prepared by researchers and Edinburgh Postnatal Depression Scale.

Risk Factor Assessment Questionnaire (RFAQ)

RFAQ consist of 30 items identifying the risk factors (Demografic and socio-economic factors, reproductive factors and history, psychiatric history story about the care of the baby economics, difficulties) for postpartum depression after delivery.

The Edinburg Postpartum Depression Scale (EPDS)

The scale has been used as a mood assesment tool to obtain women's self reports of depressive symptomatology experienced in the past seven days [9,15,17]. Based on this ten item scale, a score from 0 to 30 is given to each respondent, the higher scores impliying greater psychological distress. Engindeniz, Kuey, and Kultur (2000) have conducted linguistic and pilot studies in order to be able to apply EPDS to Turkish women. The authors used an EPDS score of 12 as a cut-off point and detected a major depression with a sensitivity of 0.84 and a specificity of 0.88. In our study, the internal consistency of EPDS assessed by Croncbach's Alpha was 6th week 0.83, 6th month 0.82. Scoring on the EPDS was rated as follows: 1-11 indicated no evidence of depression; 12-30 symptoms of depression [18].

Procedure

Data was collected in three stages via face to face or telephone interviews through the self-report technique. *In the first stage,* the women filled out the first section of the RFAQ in the hospital twenty four hours after the delivery. *In the second stage*, the women were contacted via phone by the researchers in the 6th week PP, and filled out the second section of the RFAQ and the EPDS. *In the third stage*, the same women contacted in the 6th week PP were contacted via phone by the researchers in the 6th month PP, and filled out the RFAQ and the EPDS again.

Data analyses

Data analyses were carried out using the Statistical Software Package for the Social Science (SPSS), version 14.0 (SPSS Inc., Chicago, IL). Descriptive statistics, such as frequency, means and standard deviations were used to describe the sample and main variables. Reliability was assessed using Cronbach's alpha coefficients. The relationship between RFAQ and postpartum depression was evaluated using the Logistic Regression analyses. Values of p less than 0.05 were considered statistically significant.

Results

The mean age of the women was 26.5 ± 5.1 years, the mean age of getting married was 20.9 ± 4 years, the duration for which they had been married was 66.9 ± 58 months, 87.5% (n=84) had graduated from primary school (5 years), and only 6.3% (n=6) were employed.

It was found that 30.2% (n=29) of the participants had unintended their pregnancy, 38.5% (n=37) had pregnancy related problems, 55.2% (n=53) gave

birth through intervention [Sectio Cesarean (S/C), Instrumental delivery (vacuum, perineal episiyotomy)]. The mean of gestational week were found to be 38.8±2.6 weeks (n=96), and the mean of the birth weights of the babies were found to be 3145.4 ± 606 (n=96) grams. It was determined that 76% (n=73) of the women had PP physical problems [breast problems, back pain, bowel problems etc.], and that only 24.7% (n=18) received treatment for those problems. Of the participants, 78.1% (n= 75) stated that they only breastfed their babies, 52.1% (n=50) stated that others supported them in caring for the baby, and 47.9% (n=46) stated that they had difficulties caused by economical problems within the last year.

In this study, depression incidence at 6th week PP and at 6th month PP after delivery, measured by the EPDS, the cutoff point was determined to be 12 and above. The incidence of PPD was found to be 31.3% (30 / 96) in the 6th week PP, and 18.9% (14 / 74) at 6th PP month after the delivery.

Risk factors associated with PPD

Risk factors associated with PPD at 6th postpartum week (Table 1).

Twelve risk factors were determined as predictive factors. Postpartum depression at the 6th week PP was higher in those who had been married for five years or less (Odds ratio (OR): 2.6), had graduated from primary school (OR: 16.8), unintended pregnancies (OR: 12), lack of social support in postpartum (OR: 1.1), lack of husband' support in pregnancy (OR: 3.2), primipar mothers (OR: 1.5). There were statistically meaningful relationships between PPD and graduated from primary school, as well as PPD and cases of unintended pregnancy (p=0.20 and p=0.005, respectively). PPD was seen 1.2 times more in those who had physical problems during in pregnancy. When whether factors related to the baby caused depression or not was examined; PPD was found to be higher by a multiplier of 1.2 in cases where the baby who underwent treatment for any reason, 3.7 when there were strain of caring for the baby, and 3.1 when the baby had sleep problem. Evaluated whether PPD is caused by physical in PP or economical difficulties within the last year the mother; was found to be higher by a multiplier of 1.4 in those who had PP physical problems, and economical problems with in the last year (OR=17.6; p=0.002) was the major significant correlate for postpartum depression.

Risk factors for depression in the 6th month PP (Table 2)

Six risk factors were determined as predictive factors for depression in the 6th month PP. Depression in the 6th month PP was higher by a multiplier of 5.3 in those who had been married for five years or less, and 1.3 in those who didn't receive support from their husband in pregnancy.

Depression in the 6th month PP was higher by a multiplier of 3.1 in those whose babies cried

Table 1. Logistic Regression Analysis For Risk Factors Associated With Postpartum Depression at 6th Postpartum Week. (n=96)

Variables	OR[a]	95 % CL	p-value
Economical Difficulties	17.6	2.87 - 108.7	**p=.002**
To Graduate From Primary School	16.8	1.57 - 8.3	**p =.020**
Unintended Pregnancy	12	2.14 - 67.3	**p = .005**
To Strain of Caring For The Baby	3.7	.81- 17.2	p = .089
Lack of Husband' Support In Pregnancy	3.2	.26 - 39.7	p = .356
The Bayb's Sleep Problem	3.1	.68 - 14.7	p = .140
Being Married For 5 Years ≤	2.6	.46 - 14.7	p =.273
Primipar	1.5	.31 - 7.5	p = .599
Physical Problems In Postpartum	1.4	.22 – 8.99	p = .699
Physical Problems In Pregnancy	1.2	.25- 6.5	p = .762
The Baby Who Underwent Treatment For Any Reason	1.2	.19 – 7.4	p = .833
Lack Of Social Support In Postpartum	1.1	.03 – 42	p = .937

[a] *An odds ratio greater then 1.0 indicates the variable is higher among depressed women who gives birth.*
OR*: Odds Ratio,* **CI:** *Confidence Interval*

Table 2. Logistic Regression Analysis For Risk Factors Associated With PPD at 6th Postpartum Month (n=74)

Variables	OR	95 % CL	p-value
Physical Problems In Postpartum	11.8	1.17-119.8	**p = .036**
Being Married For 5 Years ≤	5.3	.71-39.9	p = .103
The Baby Crying For Long Periods	3.1	.47- 20.4	p = .235
The Baby Who Underwent Treatment For Any Reason	2.3	.27- 20.2	p = .434
Lack of Husband' Support In Pregnancy	1.3	.13- 12.7	p = .814
Presence of Depression at 6th Week Postpartum	1.1	.14- 9.8	p = .876

[a] *An odds ratio greater then 1.0 indicates the variable is higher among depressed women who gives birth.*
OR: *Odds Ratio,* **CI:** *Confidence Interval*

frequently, and by 2.3 in those whose babies received treatment PP. Additionally the risk for PPD was 11.8 times higher in those who had PP physical problems. There was a statistically meaningful relationship between PPD and having physical problems PP (p=0.03). The risk for PPD in the 6th month was 1.1 times higher in those who suffered depression in the 6th week PP.

Discussion

This study aims at evaluating the incidence of PPD in the 6th week and 6th month PP as well as the risk factors on the occurrence of depression. The strong point of our study is that it evaluates the same group of women with regard to the risk factors that may cause PPD in a multidimensional manner as well as evaluating the risk factor for the 6th month.

PPD is a psychological condition that may lead to various problems in the baby, the mother or the family if left untreated [11,14,15,19-22]. Literature states that PPD is especially prevalent in the first year postpartum [14]. Studies in different countries have found that the incidence of PPD in the PP 6th-8th week between 9.1% and 66.5% [1,5,23,24], whereas its incidence in the PP 3rd-6th month between 8.1% and 23% [2,3,5,6,7,23,24,25]. While the PPD rate in our study in the 6th week PP (30%) was found to be lower than the 66.5% that Stowe et al. reported, the incidence of PPD in the 6th month PP (18.9%) is similar to the findings of studies made in several countries [23]. The differences in these rates are thought to be caused by cultural characteristics, sample size, and methodological differences. Goodman found higher incidence of PPD in the 6th - 8 th week PP [14]. While the 6th week and 6th month PPD rates of our study group are similar to the findings of some studies made in different regions of Turkey [1,8,9], they are different from Dindar and Erdoğan [10]. This difference may be caused by the differences methods used in the studies. For example, Dindar and Erdoğan evaluated depression in women in any time within a year PP, have reported 45.5% rate of PPD in the 2nd-6th months and 48.5% PPD rate in the 7th-12th months [10]. Similarly, Yıldırım et al. also found PPD in 51.3% of the mothers within one year PP. These rates, which are different from findings of this study, may be related to the time when PPD was evaluated [25].

An important part of the women in Turkey (48%) are primary school graduates [26]. Similarly, it was determined that the majority of the women in this study were primary school graduates. In many studies, the PPD rates were found to be higher in women with lower levels of education. Similarly, this case arises as an important risk factor in our study [3,14,27].

Women in our country receive an important amount of support from both their husbands and their social environment during their pregnancy. A pregnant woman is considered to have two lives, and her needs and problems are cared for [28]. A woman who expects support during her pregnancy may become disappointed [29], unhappy and depressed if she doesn't receive such support. Like many studies conducted recently, this study shows that the lack of social support in postpartum [10, 15, 19, 24, 30] and partner's support in pregnancy [2, 9] are risk factors for PPD. Leahy- Warren et al. have reported that women who receive low emotional support in postpartum are diagnosed with depression 7.16 times and 7.8 times more in the 6th and 12th week PP, respectively [24]. Dindar and Erdoğan

reported that the incidence of PPD in women who had problems with their partners was 3.4 times higher. The fact that the lack of husband's support in pregnancy is a risk factor for PPD in both the 6th week and 6th month, over time, the woman may be associated with more isolated [10].

In our study, being married for 5 years or less was found to increase the risk of PPD in both the 6th week and the 6th month. This finding, which can't be found in other studies, may indicate that the subjects have a hard time coping with their situation because of their low age and education levels. The lack of knowledge of primipar women on baby care and the baby' normal characteristics, baby' behavior and illnesses of a baby is a cause for anxiety in mothers, and it may reduce the satisfaction with the role of a mother, affect parent-baby health and life changes negatively, and cause anxiety in women [31]. When the literature is evaluated, it can be seen that some studies find being primipara as a risk factor [4], while others find being multipara as such [3,6,9,15]. In this study, it was found that being primipara is a risk factor for PPD only in the 6th week. This finding may be interpreted as the woman adapting and coping with the role of a mother in time.

Unintended pregnancies are unexpected for a woman and may negatively affect a woman's life. It has been found that 30% of the women in our country have unintended pregnancies, which is similar to our findings. Unintended pregnancy was found to be a strong risk factor for PPD in both our findings and the findings of other studies [3,30,32]. While in Nagy et al. [3], Mercier et al. [32] and Bener et al. [30] study the risk for PPD in women having unintended pregnancies was found to be 3.5, 2.1, 1.9 times higher, respectively, in this study it was found to be 12 times higher in the 6th week PP.

Many women experience pregnancy related problems during pregnancy. In a similar to other studies [5,33], the risk for PPD in the 6th week PP was found to be higher in women who experience pregnancy related problems in this study. Postpartum physical problems also make it difficult for a woman to adapt to the PP period. Additionally, PP physical problems are encountered by many women, and most of them don't receive medical help for them [28]. Similarly, a significant part of the women in our study group were found to experience various PP physical problems, and that very few of them received treatment by contacting a doctor. Yet, the rate of women receiving PP care in the first 6 weeks is 82% in our country [26]. Findings of this study may indicate the insufficiency of PP care provided in our country. The PP period encompasses not just the first 6 weeks but the first 6 months, and for these months, the mother must be evaluated physically and psychologically [20]. Similar findings indicating that having PP physical problems increases the risk of PPD have been found in the literature [14, 29].

In the PP period, psychological problems affect the mothers negatively as much as physical problems. For this reason, health professionals should assess the mother as psychologically in the PP period and should recommend treatment to the patient if there is a problem. PPD may develop into chronic depression and present clinical or subclinical symptoms if untreated [14]. Chronic depression the woman, her family life and the members of her family negatively affects [34].In accordance with this finding, among the women in this study group, the risk of developing PPD in the 6th month was found to be higher in women who were diagnosed with PPD in the 6th week. Similar findings was found in the literature.

The presence of a problem in the baby or medical treatment of baby after delivery are very serious stress factors for the mother [31]. This study shows that the baby undergoing a medical treatment increases the risk of PPD in the mother, as well. Similar findings were encountered in other studies.

As it has been reported in other studies [29,35] the risk of PPD was found to be higher in our study in those who have strained of caring for the baby, those whose baby has sleep problem, and those whose baby cries often.

In addition to the strain of caring for the baby, not being economically able to meet the baby's needs may cause PPD. In this study, having economical problems was found to be a strong risk factor for PPD. In various studies conducted in our country and around the world [10,15,25,27,28,29,30] having low economical status was found to be a risk factor for the development of PPD.

Conclusion

As a result of our study, the incidence of PPD was found to be significantly high in both the 6th week PP and the 6th month PP. Most of the risk factors that we identified for PPD were found to be similar to those in studies conducted in both our country and around the world. This, in turn, has reconfirmed that PPD is a universal phenomenon.

In our study, two new risk factors for PPD in both the 6th week and the 6th month PP (Being married for five years or less and the baby who underwent treatment for any reason) were identified, which we think would contribute to the literature. Additionally, it has been found that having PPD in the 6th week PP increases the risk of PPD in the 6th month PP and this finding which we think is an important contribution to the Turkish literature. In the light of our findings, it can be suggested that every woman who gives birth should be scanned for depression during the 6 months PP and that especially women who have the predetermined risk factors should be more closely monitored. An early diagnosis would enable an early treatment. Health professionals, especially nurses, should inform women who give birth on baby care, possible postpartum problems they may encounter and possible psychological changes before they are discharged, and instruct them to contact a health institution in case of encountering a problem. Every institution that provides postpartum care for women (e.g.,child polyclinics, family health centers) should also provide PPD evaluation for women.

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Effect of Polymorphism and Human Papilomavirus on Esophageal Cancer in Compare with other Cancers – A Systematic Review

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Abstract

The p53 gene is one of the most extensively studied human genes because of its role as a tumor suppressor. A common polymorphism of the p53 gene at codon 72 has been associated with human cancer susceptibility and prognosis. Human papilloma virus (HPV) has also been suggested to be involved in the pathogenesis of different cancers. In this study,we have reviewed codon 72 polymorphism and human papilomavirus on different cancer cases. The present review summarizes case-control studies on genetic polymorphisms and different cancer risks. It is observed that the most commonly studied genes included members of phase I and phase II metabolic enzymes. Other than these genes, genetic polymorphisms for cell cycle and apoptosis-related factors, DNA repair enzymes, immune response elements, growth factors, folate metabolizing enzymes, vitamin/hormone receptors, etc., were investigated. In conclusion, this result can be considered as a probable reason in observing difference in frequency of different genotypes codon 72 in geographical regions.

Key words: P53 Codon 72 , HPV , Esophageal Cancer

Introduction

The p53 gene is one of the most extensively studied human genes because of its role as a tumor suppressor. A common polymorphism of the p53 gene at codon 72 has been associated with human cancer susceptibility and prognosis. Human papilloma virus (HPV) has also been suggested to be involved in the pathogenesis of different cancers. p53 (also known as protein 53 or tumor protein 53), is a tumor suppressor protein that in humans is encoded by the *TP53* gene. p53 is crucial in multicellular organisms, where it regulates the cell cycle and, thus, functions as a tumor suppressor that is involved in preventing cancer. As such, p53 has been described as "the guardian of the genome" because of its role in conserving stability by preventing genome mutation. The name p53 is in reference to its apparent molecular mass: It runs as a 53-kilodalton (kDa) protein on SDS-PAGE. But, based on calculations from its amino acid residues, p53's mass is actually only 43.7 kDa. This difference is due to the high number of proline residues in the protein, which slows its migration on SDS-PAGE, thus making it appear heavier than it actually is[16] This effect is observed with p53 from a variety of species, including humans, rodents, frogs, and fish. In humans, p53 is encoded by the *TP53* gene located on the short arm of chromosome 17 (17p13.1). The gene spans 20 kb, with a non-coding exon 1 and a very long first intron of 10 kb.The coding sequence contains five regions showing a high degree of conservation in vertebrates, predominantly in exons 2, 5, 6, 7 and 8, but the sequences found in invertebrates show only distant resemblance to mammalian TP53. *TP53* orthologs, have been identified in most mammals for which complete genome data are available. In humans, a common polymorphism involves the substitution of an arginine for a proline at codon position 72. Many studies have investigated a genetic link between this variation and cancer susceptibility; however, the results have been controversial. For instance, a meta-analysis from 2009, failed to show a link for cervical cancer. A 2011 study found that the *TP53* proline mutation did have a profound effect on pancreatic cancer risk among males. A study of Arab women found that proline homozygosity at *TP53* codon 72 is associated with a decreased risk for breast cancer [63]. One study suggested that

TP53 codon 72 polymorphisms, MDM2 SNP309, and A2164G may collectively be associated with non-oropharyngeal cancer susceptibility and that MDM2 SNP309 in combination with *TP53* codon 72 may accelerate the development of non-oropharyngeal cancer in women. A 2011 study found that *TP53* codon 72 polymorphism was associated with an increased risk of lung cancer. There are wide evidences which express genetic polymorphism role in increasing the danger of affecting cancer in different people. P53 gene also has been considered a lot, because of its importance in cell cycle control, DNA reparation, apoptosis and so on. It plays main role in many cancers. This gene has 10 known polymorphism. One of these polymorphism that has been studied a lot, exists in codon 72. This polymorphism causes producing two forms of p53 molecule which are in 72 codon have Arg or pro. frequency of allele gene p53 in codon 72 in different population and in different geographical areas is variable. (table 1-3) Yet in many of cancers one of alleles in patients show higher frequency for example studying the role of codon 72 in china in patients affected to liver cancer showed that allele pro in patients has higher frequency.

HPV is a virus from the papillomavirus family that is capable of infecting humans. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. While the majority of the known types of HPV cause no symptoms in most people, some types can cause warts (verrucae), while others can – in a minority of cases – lead to cancers of the cervix, vulva, vagina, penis, oropharynx and anus. Recently, HPV has been linked with an increased risk of cardiovascular disease [128]. In addition, HPV 16 and 18 infections are strongly associated with an increased odds ratio of developing oropharyngeal (throat) cancer. Human papillomavirus (HPV) plays an important role in the development of malignant disease at various body sites, including the anogenital area, the upper respiratory tract, the digestive tract, and the breast.1,2 However, not all HPV-containing lesions proceed to the full malignant phenotype. It has been shown that HPV infection alone may not be sufficient for the malignant transformation of a host cell and requires additional genetic lesions. Germline polymorphisms of some genes involved in multiple steps of carcinogenesis may account for the genetic susceptibility to HPV-associated carcinoma. The high-risk HPV types, such as HPV type 16 (HPV-16) and HPV-18, encode two viral oncoproteins, E6 and E7, that are expressed in HPV-associated malignancies.1,2 It has been shown that E7 protein is capable of binding and inactivating the cellular tumor suppressor protein Rb, whereas the E6 protein interacts with and degrades p53 through the ubiquitin pathway. These Interactions are responsible for the transforming activity of HPV.3–5 A common polymorphic site in the wild type p53 gene at codon 72 of exon 4 results in translation to either an arginine residue (CGC) or a proline residue (CCC). The frequency of two alleles varies among ethnic groups that dwell at different latitudes.6 The p53 codon 72 polymorphism (C/G) was one of the first susceptible factors of HPV-associated carcinoma that was found in 1998 by Storey et al., 7 who reported that the p53 arginine (p53Arg) isoform increased the susceptibility of p53 to HPV-16 and HPV-18, E6-mediated degradation either in vitro or in vivo. Moreover, there is a significant over-representation of the p53 Arg/Arg genotype in patients with cervical carcinoma compared with the normal population. Individuals homozygous for p53Arg were about seven times more susceptible to HPV-associated carcinogenesis compared with heterozygotes.7 However, many subsequent studies in different populations have failed to prove the results.8–13 the correlation between the p53 codon 72 polymorphism (C/G) and HPV-associated carcinoma remains controversial. We showed previously that HPV-16 plays a significant role in the pathogenesis of esophageal carcinoma in Anyang, which is recognized as a high-incidence area for esophageal carcinoma in China. Retaining of viral DNA fragments E6/E7 and stable expression of viral genes may be associated with the malignant progression of esophageal epithelial cells.14 our recent investigation also showed a correlation between HPV and breast and ovarian carcinoma15 (and unpublished results). It was found that the HPV-16 infection rate was significantly higher in samples of epithelial ovarian malignancy (26 of 50 samples; 52%) compared with the rate in normal ovarian tissues (2 of 30 samples; 6.7%), and

HPV-16 E6 mRNA was found in 17 of 34 breast carcinoma samples (50%). Based on our previous studies, investigation of genetic cancer susceptibility in the p53 gene, which may be involved in the steps of carcinogenesis, is important for the identification of high-risk individuals in an HPVinfected population. More than 30 to 40 types of HPV are typically transmitted through sexual contact and infect the anogenital region. Some sexually transmitted HPV types may cause genital warts. Persistent infection with "high-risk" HPV types — different from the ones that cause skin warts — may progress to precancerous lesions and invasive cancer. HPV infection is a cause of nearly all cases of cervical cancer. However, most infections with these types do not cause disease. Most HPV infections in young females are temporary and have little long-term significance. Seventy percent of infections are gone in 1 year and ninety percent in 2 years. However, when the infection persists — in 5% to 10% of infected women — there is high risk of developing precancerous lesions of the cervix, which can progress to invasive cervical cancer. This process usually takes 10–15 years, providing many opportunities for detection and treatment of the pre-cancerous lesion. Progression to invasive cancer can be almost always prevented when standard prevention strategies are applied, but the lesions still cause considerable burden necessitating preventive surgeries, which do in many cases involve loss of fertility. In more developed countries, cervical screening using a Papanicolaou (Pap) test or liquid-based cytology is used to detect abnormal cells that may develop into cancer. If abnormal cells are found, women are invited to have a colposcopy. During a colposcopic inspection, biopsies can be taken and abnormal areas can be removed with a simple procedure, typically with a cauterizing loop or, more commonly in the developing world — by freezing (cryotherapy). Treating abnormal cells in this way can prevent them from developing into cervical cancer. Pap smears have reduced the incidence and fatalities of cervical cancer in the developed world, but even so there were 11,000 cases and 3,900 deaths in the U.S. in 2008. Cervical cancer has substantial mortality in resource-poor areas; worldwide, there are an estimated 490,000 cases and 270,000 deaths each year.

Materials and methods

This was a case control study conducted in north Iran. The total of 40 tumor biopsies and 40 other samples of the control group have been analysed. Biopsy specimens were collected from operation theatre of gastro endoscopies in the internal department of Shahid Rajai Tonekabon hospital. These samples were collected from 2008 to 2011. Tissue samples were stored in -20 -70 Degree centigrade (-20 -70°C). Filtering DNA from Samples(by Fermentase Kit): Prior to

DNA extraction, the sample should be digested for a night with digestion buffer 100ml and 2.5ml proteinase k. Mixing binding solution with tissue samples has been carried out with the ratio 1 to 3 (100ml to 300ml) and then 5ml of silica was added. Incubation was carried out for 5 minutes in the temperature of 55°C. Washing buffer was added to the settle and then vortex was performed. The quick centrifusion 3 times, for 5-10 seconds was performed and then DNA was extracted during this process and the result was analysed in Agarose gel 0.8 %. p53 Polymorphism Analysis: Exon 4 of the p53 Gene containing the poly morphic sequence variant at codon 72 was analysed using direct genomic sequencing. The following primers have been used:

C Arg- primer F: 5' – TCCCCCTTGCCGTCCCAA-3' (25 Pmol).
C Arg- primer R: 5' – CTGGTGCAGGGGCCACGC-3' (25 Pmol).
C Pro- Primer F: 5' – GCCAGAGGCTGCTCCCCC- 3' (25-Pmol).
C Pro- Primer R: 5' – GCCAGAGGCTGCTCCCCC- 3' (25 Pmol.

Primer Name PCR Temperature Profile
Arg- Primer F 94°C (5') 94°C (30") 60°C (30") 72°C (30") 72°C (5')
Arg- Primer R
Pro- Primer F 94°C (5') 94°C (30") 54°C (30") 72°C (30") 72°C (5')
Pro- Primer R

HPV Detection and Identification: This step was also done the same as previous treatment with this difference that GP5+/GP6+Primers were used. The following primers have been used:

Gp5+: 5'TTGGA
TCCTTTGTTTACTGTGGTAGATACTAC_3',
GP6+: 5'_T
TGGATCCGAAAAATAAACTGTAAATCA-TATTC_3'.

Primer Name PCR Temperature Profile
GP5 94°C (5') 94°C (30") 40°C (30") 72°C (30") 72°C (5')
GP6

Results and discussion

Esophageal cancer is common in several areas of central Asia, including Xinjiang Uygur Autonomous Region, China. The incidence of Kazakh's EC is the highest among population in Xinjiang and its age-adjusted mortality rate up to 91/100 000 has been reported in Kazakh's population[1]. The population size of Kazakh was estimated to be 13 million around the world and 10 million Kazakh distributed in Kazakhstan and 2 million in Xinjiang, China. The genetic homogeneity and geography stability of the population, along with shared exposure to common environmental variables, provide an excellent opportunity for the study of genetic influence on EC. These cancers are mostly SCC , and show a high frequency of mutation in the p53 tumor suppressor. Epidemiological studies have suggested that a number of risk factors are involved in the carcinogenesis of Kazakh's SCC, including deficiencies in vitamins and minerals, consumption of pickled foods and environmental exposure to specific nitrosamines, etc. Viral infections, in particular HPV infection, have been reported in esophageal cancers from China, and HPV DNA has been detected in 0-60.0% of cancer tissues by polymerase chain reaction analysis. HPV is implicated in the pathogenesis of squamous cell carcinoma of the cervix and esophagus. HPV-16 encodes E6 protein, which binds to cellular tumor-suppresser protein p53 and directs degradation through the ubiquitin pathway. This event is mediated by another cellular protein termed E6-AP, a component of the ubiquitin pathway. The arginine allele at codon 72 of p53 was found to be more susceptible to degradation by HPV E6 protein than the proline allele in vivo, thus resulting in a high frequency of esophageal SCC in individuals homozygous for arginine at the codon. On the basis of these experiments, it has been widely assumed that p53 is functionally inactivated by the viral E6 protein in HPV-associated cancer cells and that infection with high-risk HPV types leads to the same phenotype as a loss of p53 function because of p53 gene mutations or direct degradation. The association of p53 codon 72 polymorphism with HPV-16-associated esophagus SCC risk has been studied by several groups but with inconsistent results. Kawaguchi et al. reported that the form of p53 protein carrying an Arg residue at this position in HPV-16/18 positive samples was found to be significantly more susceptible to degradation by E6 protein than that in HPV-16/18 negative samples. There are controversial results from several clinical studies of esophagus SCC. A part of Kazakh's esophageal SCC correlated with the presence of HPV-16/18. To our knowledge, p53 polymorphism in Kazakh's esophageal SCC has apparently not been documented. The data we obtained seemed to be the first regarding the association of this polymorphism with HPV-associated risk for cancer of the esophagus.

To investigate p53 alterations in esophageal squamous-cell carcinomas of patients in the high-risk area of southern Thailand, 72 paraffin-embedded samples were analyzed immunohistochemically for p53 protein expression and 16 frozen samples for p53 mutational status by Suwiwat S and his colleagues . Forty-two of the 72 tumors (58.3%) showed p53 protein accumulation in the nuclei of tumor cells. Analysis of the p53 gene in a sub-set of 16 tumors showed mis-sense mutations in 7 out of 11 p53-positive and 1 out of 5 p53-negative tumors. A meta-analysis which studies nine case-control involving 5545 subjects was done in this study. Significantly reduced risk of EC was associated with *TP53* genotypes for Arg/Arg + Arg/Pro *vs* Pro/Pro (OR = 0.73, 95% CI: 0.57-0.94, $P = 0.014$). Subgroup analyses according to the source of controls and the specimens used for determining *TP53* Arg72Pro genotypes or sample size showed that significantly reduced risk was observed only in studies which have population-based controls (Arg/Arg *vs* Pro/Pro: OR = 0.56, 95% CI: 0.47-0.66, $P < 0.001$), and use white blood cells or normal tissue to assess *TP53*

genotypes of cases (Arg/Arg *vs* Pro/Pro: OR = 0.56, 95% CI: 0.47-0.65, $P < 0.001$) or include at least 200 subjects (Arg/Arg *vs* Pro/Pro: OR = 0.56, 95% CI: 0.47-0.65, $P < 0.001$). Analysis restricted to well-designed studies also supported the significantly decreased risk of EC (Arg/Arg *vs* Pro/Pro: OR = 0.54, 95% CI: 0.46-0.64, $P < 0.001$).

Tao Li[1] and his colleagues used an allele specific polymerase chain reaction (PCR) method to analyze correlation between the p53 codon 72 (C/G) polymorphism and HPV-associated, noncancerous esophageal epithelium as well as esophageal, ovarian, and breast carcinoma in the Chinese population. Esophageal balloon cytology examination samples were obtained from high-incidence and low-incidence populations for esophageal carcinoma in Anyang (Henan Province). Thirty-six of 48 esophageal balloon samples from the high-incidence population were HPV positive, and 13 of 33 esophageal balloon samples from the low-incidence population were HPV positive. Thirty-nine of 62 esophageal carcinoma samples from Anyang Tumor Hospital were HPV positive. It is noteworthy that the distribution of the p53 codon 72 Arg homozygous genotype in HPV positive samples of esophageal epithelium was significantly higher compared with HPV negative tumor samples. ($P < 0.05$). The distribution of p53 codon 72 genotypes in samples from high-incidence and low-incidence populations for esophageal carcinoma as well as samples of esophageal, ovarian, and breast carcinoma is summarized in Table 1. The distribution of the p53 codon 72 polymorphism (C/G) showed no significant differences between the Beijing population and the Anyang population (chi-square test, 0.685; degrees of freedom [DF] = 2; $P = 0.710$). However, there were significant differences in the frequency of the Arg genotype between HPV positive and HPV negative carcinoma samples and between HPV positive carcinoma samples and the control samples. The $p53_{Arg}$ homozygotes were significantly higher in HPV positive carcinoma samples.These results of Tao Li 's study suggest that p53 polymorphism may not be related to an increased HPV infection rate or to the progression of cytopathologic grade in esophageal epithelium, implying that p53 polymorphism may have less importance in the susceptibility to carcinoma until the *last step* in carcinogenesis. In other words, the p53 codon 72 polymorphism (C/G) may be a factor for susceptibility only in the very late stage of carcinogenesis.

The aim of Piao's study in 2011 was to assess whether p53 codon 72 polymorphism is associated with an increased risk of esophageal cancer (EC) in South Korea. They conducted a case-control study including 340 patients with EC, and 1700 controls. P53 codon 72 polymorphism was determined by real-time polymerase chain reaction. The frequencies of p53 codon 72 polymorphisms (*Arg/Arg*, *Arg/Pro*, and *Pro/Pro*) in EC were 39.4%, 45.6%, and 15.0%, respectively; frequencies in the controls were 43.2%, 45.6%, and 11.2%, respectively. Compared with the *Arg*/*Arg* genotype, the OR of the *Arg*/*Pro* genotype was 1.09 (95% CI = 0.85–1.41) and that of the *Pro*/*Pro* genotype was 1.47 (95% CI = 1.02–2.11) for EC overall. He observed that the p53 codon 72 polymorphism was associated with an increased risk of EC in this Korean case-control study, and smoking status modified the association between the p53 codon 72 polymorphism and the risk of EC.

The aim of a report done by Eltahir HA in 2010 was to determine frequencies and associations of p53 codon 72 arg/pro polymorphism with different types of cancer in Sudan. p53 codon72 arg/pro polymorphism distribution and allele frequencies in 264 samples of different types of cancers were investigated using PCR. The results were compared to 235 normal controls. The results indicated significant differences in frequency and genotype association between different types of cancers. Breast carcinoma patients most prominently showed excess of homozygous arg genotype as compared to controls with an Odd ratio (OR) of 19.44, 95 %CI: 6.6-78.3, $P < 0.0001$. Less prominently cervical cancer showed genotype effect of 2.4 OR, 95 %CI: 1.12-5.33, $P = 0.015$, while esophageal cancer had an OR of 0.57, 95 %CI: 0.23-1.42, $P = 0.1$. He concluded that p53 arg/pro polymorphism has different pattern of frequency in different types of cancer among Sudanese patients, indicating perhaps different etiology and biology of these tumours.

According to recent reports, some cancer types exhibit nonrandom allele loss at codon 72 in exon 4 of the p53 gene [coding for proline (72Pro) or arginine (72Arg)]. To clarify this phenomenon for

colorectal cancer and to find out if this preferential loss might have any functional significance, p53 loss of heterozygosity (LOH) and p53 mutations were investigated in a group of 61 colorectal cancers and 28 liver metastases, and were correlated with clinicopathologic factors (Regine Schneider-Stock et al, 2004). A comparison of a patient's blood codon 72 status with a healthy control group did not reveal an enhanced risk of developing colorectal tumors for one of the two isoforms. P53-LOH and p53 mutations were found in 62.2% and 39.4% of primary tumors, respectively, and in 57.9% and 25% of hepatic metastases, respectively. In 14 heterozygous cases showing exon 4-LOH, only the 72Pro allele was lost and the retained 72Arg was preferentially mutated. In general, p53 mutations were significantly associated with the 72Arg tumor status (P < .001). Distal tumors showed allelic losses of the p53 gene more commonly than proximal tumors (P = .054). The prevalence of 72Arg increased in frequency with higher Dukes stage (P = .056). We suggest that either the preferential loss of 72Pro or the mutation of the 72Arg in colorectal cancer and hepatic metastases is associated with malignant potential and might reflect carcinogenic exposure, particularly in the distal part of the large intestines.

Worldwide, carcinoma of the uterine cervix is one of the most common malignancies among women. Incidence rates of this disease vary from about 5 cases per 100 000 women per year in many industrialized countries to more than 50 per 100 000 in some developing nations. Approximately 80% of all cases occur in less-developed countries, because prevention programs are either non-existent or poorly conducted (WHO, 2009). Furthermore, in the less developed areas of the world, cervical cancer begins to strike significantly among women as young as 25-30 years of age, clearly identifying this disease as the cancer priority in women. Clinical epidemiology have clearly identified that the association between infection with high-risk types of human papillomavirus (HPV) and high-grade cervical cancer precursors as well as cervical cancer is very strong (Wright Jr., 2006). However, even highrisk HPV infection are widespread in the world, the majority of HPV-associated lesions such as cervical intraepithelial neoplasia (CIN) will remain stable or spontaneously regress over time (zur Hausen, 2000; Ferenczy, 2001; Holowaty, 1999; Syrjanen, 1996), suggesting that other genetic and epigenetic events are likely to be involved in cervical carcinogenesis. Indeed, genomic alterations leading to tumor suppressor gene inactivation and/or oncogene activation are the critical pathways in the development and progression of cervical cancer as well as the other types of cancer. In this field, p53, p16 and Ecadherin are important proteins that play critical role in the development and the progression of cervical cancer.

The polymorphism of p53 codon 72, a transversion of G to C (Arg to Pro), has been demonstrated to be associated with the risk for lung cancer (Siyang Wang, et al). However, individual studies conducted in Asians have provided conflicting and inconclusive findings. Thus, they performed a meta-analysis by pooling all currently available case–control studies to estimate the effect of p53 codon 72 Arg/Pro polymorphism on the development of lung cancer. The pooled odds ratios (ORs) with the corresponding 95 % confidence intervals (95 %CIs) were calculated to assess this effect. A total of 14 individual studies involving 7,929 cases and 5,924 controls were included intothis meta-analysis according to the inclusion criteria. The overall OR for the dominant genetic model indicated that the p53 codon 72 Arg/Pro variant was positively correlated with lung cancer risk (ORArg/Pro + Pro/Pro vs. Arg/Arg=1.14, 95 %CI 1.07–1.23, POR<0.001). Similar results were found in the stratified analysis of population-based studies. The histological types of lung cancer and smoking status seemed to exert no effect on the lung cancer risk. Sensitivity analysis confirmed the stability of the above findings. The updated meta-analysis suggests that the p53 codon 72 Arg/Pro polymorphism is a risk factor for lung cancer in the Asian population. However, the potential role of gene–environment interaction in lung cancer susceptibility needs further investigation in future studies with high quality.

The polymorphisms of the tumor suppressor gene p53 have been extensively investigated in numerous malignant tumors, particularly carcinomas associated with human papillomavirus (HPV) infection (Wenjun Yang, et al). However, the results remain controversial. To address a potential

correlation between the p53 genotypes and the risk of esophageal squamous cell carcinoma (ESCC), they investigated the p53 codon 72 polymorphism in 435 patients with ESCC and 550 cancer-free subjects from the same geographical region. p53 Arg/Arg genotype was significantly increased in ESCC cases compared with control subjects (85.7 vs. 49.6%, $P < 0.001$), resulting in an elevated ESCC risk (OR = 6.48, 95% CI = 4.65–9.03). In addition, among p53 Arg/Arg carriers, HPV infection, smoking, and drinking might further increase the risk of ESCC development.

Studies investigating the association between p53 codon 72 polymorphism and gastric cancer risk report conflicting results (Yong Zhou, et al). their recent meta-analysis suggests that the p53 codon 72 polymorphism may be associated with gastric cancer among Asians. The objective of this study was to investigate the association between p53 codon 72 polymorphism and gastric cancer risk in Chinese Han patients. they extracted the peripheral blood samples from 150 patients with gastric cancer and 150 control subjects. Polymerase chain reaction-restriction fragment length polymorphism analysis was performed to detect p53 codon 72 polymorphism in these patients. Patients with gastric cancer had a significantly lower frequency of Arg/Arg (odds ratio [OR] =0.48, 95% confidence interval [95% CI] =0.28, 0.80; p=0.005) than control subjects. Patients with cardia gastric cancer had a significantly higher frequency of Pro/Pro (OR=2.26, 95% CI=1.12, 4.55; p=0.02) than those with noncardia gastric cancer. Patients with advanced gastric cancer had a significantly higher frequency of Arg/Arg (OR=2.66, 95% CI=1.06, 6.65; p=0.03) than those with early gastric cancer. When stratified by the Lauren's classification, histological differentiation of gastric cancer, no statistically significant result was observed. This study suggests that the p53 codon 72 polymorphism may be associated with gastric cancer in Chinese Han patients, and that difference in genotype distribution may be associated with the location and stage of gastric cancer.

Mutations in the codon 72 of exon 4 in the p53 gene have been associated with higher risk in the development of several types of cancer. This polymorphism occurs with two alleles encoding either arginine (CGC) or proline (CCC). The aim of Guillermo Ignacio Pérez-pérez, et al´s study was to assess the role of the codon 72 polymorphism of p53 in the risk for the development of distal gastric cancer (GC) in a Mexican population. Material and methods We studied 247 patients who were enrolled at the Servicio de Gastroenterología, Hospital Universitario "Dr. José Eleuterio González" Universidad Autónoma de Nuevo León. The study group included 65 distal GC cases [mean age, 58.2 (22–84), median=60, F: M=0.6] and 182 patients without evidence of GC [mean age 53.9 (18–89), median=53, F: M=1.07) as the control group. The polymorphism in the codon 72 of the p53 gene was determined by PCR-RFLP in all the patients. Results As expected, the majority of GC patients were old male. We found a previously unknown association of the Arg/Arg genotype and distal GC (OR: 1.96, 95% confidence interval [CI] =1.06–3.61, p=0.03). Because of age and gender differences, cases and controls were matched in those two variables and the association of Arg/Arg genotype with distal GC persisted (OR: 2.29, 95% CI=1.22–4.32, p=0.01). When cases and controls were matched by age, gender, H. pylori positivity and excluding patients with atrophic gastritis and/or intestinal metaplasia (n=97) the association was stronger (OR: 2.37, 95% CI=1.18–4.77, p=0.01). The results of this study suggest that the carriage of the Arg/Arg genotype could be associated with the development of distal GC in this Mexican population.

Gastric cancer is one of the most common cancers of the gastrointestinal system, and its overall five-year survival rate is still 15 % to 20 %, as it can mostly be diagnosed at an advanced stage (ayse basak engine et al). On the other hand, although colorectal cancer has a rather good prognosis, mortality is one half that of the incidence. As carcinogenesis is believed to involve reactive radicals that cause DNA adducts formation, impaired repair activity, and weakened tumour suppression, it would help to understand the role of the polymorphisms of nucleotide excision repair enzyme XRCC1 and of tumour suppressor gene p53 in gastric and colorectal cancers. Our study included 94 gastric cancer patients, 96 colorectal cancer patients, and 108 cancer-free individuals as control with the aim to see if there was an association between XRCC1 Arg399Gln and p53 Arg72Pro polymorphisms and

cancer susceptibility. DNA was extracted from peripheral blood cells and genotypes were determined using the polymerase chain reaction-restriction fragment length polymorphism. Polymorphism p53 Arg72Pro was not associated with either gastric or colorectal carcinoma, while XRCC1 Arg399Gln was not associated with the increased risk of colorectal cancer. However, XRCC1 homozygous Gln allele at codon 399 was associated with 2.54 time's higher risk of gastric cancer.

The polymorphism of codon 72 in the p53 tumour suppressor gene has been associated in the last decade with the risk of developing various neoplasias (Agorastos T, et al). An influence of this polymorphism on ovarian and endometrial cancer has also been suggested. They examined the genotype frequency of this polymorphism in archival samples from 56 patients with endometrial neoplasias and 51 patients with ovarian neoplasias. Cervical smears from 30 healthy, human papillomavirus (HPV)-negative women with normal cytology and colposcopy, served as control sample. Women with ovarian neoplasias, especially adenocarcinomas, had Arg/Arg more often than healthy controls [odds ratio (OR) 4.16 at P=0.0058]. No statistically significant difference was found between women with endometrial cancer and controls. Differentiation of ovarian tumours did not appear to be associated in a statistically significant manner with the genotype, whereas a positive linear trend of Arg/Arg towards poor differentiation was noted in endometrial malignancies (mainly endometrioid adenocarcinomas). Our results suggest that homozygous arginine at codon 72 of p53 may represent a risk factor for developing ovarian malignancies and may affect the differentiation of endometrial cancer. Further studies need to be carried out in order to establish the clinical use of this polymorphism for risk assessment and possibly outcome prediction of ovarian and endometrial neoplasias.

Thyroid cancer is the most common endocrine malignancy. Molecular mechanisms underlying this disorder are heterogeneous and need to be clarified (Cenk Aral,et al). Different polymorphic variants of the *p53* gene have been demonstrated to be in association with several human malignancies. Of those, codon 72 polymorphism is the most extensively studied variant; however, so far only two studies have investigated the association of this polymorphism with thyroid cancer. Thus, they aimed to investigate the association of p53 codon 72 polymorphism with thyroid cancer in a group of Turkish patients. 58 thyroid cancer patients and 115 healthy individuals were genotyped by PCR based RFLP analysis. Polymorphic proline allele frequency was higher in patients than in the controls. Pro/pro genotype was found to be a risk factor for thyroid cancer development. Arginine/proline genotype frequencies in patients and controls did not show any significant differences. There was no statistical difference between follicular adenoma and papillary carcinoma patients or TNM stages of papillary carcinoma patients for codon 72 genotypes. Further studies involving codon 72 polymorphism of the p53 gene along with other susceptibility factors in different populations may be useful to clarify the molecular mechanisms underlying thyroid cancer development.

The tumor suppressor gene p53 play general role in cell cycle control, the initiation of apoptosis, and in deoxyribonucleic acid (DNA) repair (Abbas Doosti, et al). The human p53 gene is mutated and accumulated in more than 50% of cancers. Codon 72 exon 4 polymorphism (Arg72Pro) of the p53 gene has been implicated in cancer risk. The objective was to investigate the possible association between p53 Arg72Pro polymorphism and susceptibility to breast cancer among Iranian population. The p53 Arg72Pro genotypes were determined by polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) analysis in 135 breast cancer cases and 140 controls. The PCR products were digested with BstUI restriction enzyme and the DNA fragments were then resolved by electrophoresis in 2% agarose gel. Out of the 135 breast cancer samples, 70 (51.85%) samples were heterozygous (Arg/Pro), 52 (38.52%) samples homozygous for arginine (Arg/Arg) and 13 (9.63%) samples homozygous for proline (Pro/Pro). The frequencies of the three p53 genotypes; Arg/Pro, Arg/Arg and Pro/Pro in controls were 58.57, 25.72 and 15.71%, respectively. Hemozygosity for Arg/Arg of p53 codon 72 is potentially one of the genetic risk factors for breast cancer. The p53 codon 72 Arg/Arg polymorphism may be used as a stratification marker in screening individuals at a high risk of breast cancer.

TP53 is the most common mutated gene in human cancers. Approximately half of all human malignancies exhibit TP53 mutations (Hung-Yu Lin, et al). The TP53 codon 72 polymorphism is a single-nucleotide polymorphism (SNP) in exon 4, resulting in the expression of either arginine (CGC) or proline (CCC) residues. The Arg72 variant has been shown to be more likely to induce apoptosis than the Pro72 variant, due to its ability to localize itself to mitochondria and trigger the release of cytochrome c into the cytosol. However, the influence of the TP53 codon 72 polymorphism on the risk of developing various cancers, and their progression remains inconclusive because there has been no sustained evidence supporting a crucial role for the codon 72 variant in cancer therapy till now. It has been shown that TP53 gene might not only be involved in cell cycle control and the apoptosis induction response to DNA damage, but may also modulate individual cancer risk, and that this may correlate with the biofunctions of the two codon 72 variants. Additionally, latent factors might function synergistically with codon 72 variants to confer susceptibility to cancer development, progression, prognosis, and therapeutic responsiveness. Further etiological investigations are essential to reveal the association of and interaction between genetic and environmental factors in relation to carcinogenesis.

Our recent study demonstrated the increased risk of renal cell carcinoma (RCC) associated with high urinary total arsenic levels among people living in a low arsenic exposure area (Chao-Yuan Huang, et al). Genomic instability is important in arsenic carcinogenesis. This study evaluated the relationship between the polymorphisms of p53, p21, and MDM2, which plays a role in gene stability, and the arsenic-related RCC risk. Here, we found that p53 Pro/Pro genotype and MDM2 SNP309 GG genotype significantly increased RCC risk compared to the p53 Arg/ Arg genotype and MDM2 SNP309 TT genotype. RCC patients with the p53 Arg/Arg genotype had a signicantly low percentage of inorganic arsenic, a low percentage of monomethylarsonic acid (MMA), and a high percentage of dimethylarsinic acid (DMA), which indicates efcient arsenic methylation capacity. Subjects with the p53 Arg/Pro + Pro/Pro genotype or MDM2 SNP309 TG+GG genotype, in conjunction with high urinary total arsenic (≥14.02 μg/L), had a signicantly higher RCC risk than those with the p53 Arg/Arg or MDM2 SNP309 TT genotypes and low urinary total arsenic. Taken together, this is the first study to show that a variant genotype of p53 Arg72Pro or MDM2 SNP309 may modify the arsenic-related RCC risk even in a non-obvious arsenic exposure area.

The codon 72 polymorphism of the p53 tumor suppressor gene has been investigated extensively for its association with various cancers around the world (Suparp Kietthubthew, et al). However, its influence has not been elucidated in the Thai population. Therefore, a case-control study with 97 patients and 97 matched controls was conducted to elucidate the association between the polymorphic p53 and oral cancer risk in a Southern Thai population. The frequencies of the Arg/Arg, Arg/Pro, and Pro/Pro genotypes were 36%, 35%, and 29%, respectively in the controls and 33%, 45% and 22%, respectively in the patients. This study shows that there was no significant association between the p53 codon 72 polymorphism and oral cancer risk. There was also no link with respect to smoking or drinking habits. However, our data suggest that for individuals who were younger than 65 years old, the Pro/Pro genotype may offer some protection against oral cancer (OR = 0.13, 95%CI 0.04-1.10). This is the first report on p53 polymorphism and oral cancer in Thailand.

Human papillomaviruses (HPV) are thought to be involved in penile squamous cell carcinomas (SCC) (O. Humbey, et al). A common polymorphism at codon 72 of exon 4 encoding either arginine (Arg) or proline (Pro) has been shown to affect HPV-mediated degradation of p53 in vitro, and may represent a risk factor for HPV-induced carcinogenesis. The presence of HPV DNA as well as the TP53 polymorphism at codon 72 of exon 4 were investigated in a series of 45 penile SCC. HPV detection and typing were carried out by polymerase chain reaction (PCR) with generic primers (MY09-MY11 and FAP59-FAP64), and type-specific DNA probes. TP53 polymorphism was further investigated using Denaturing Gradient Gel Electrophoresis (DGGE). HPV DNA was detected in 67% of penile SCC and 32% of benign lesions (BL) ($P<0.05$). Among the TP53 amplified samples, the rate of Arg homozygosity in penile

SCC was 61% compared with 68% in BL (non-significant (NS)). Their results demonstrate a strong association between penile SCC and the presence of HPV DNA. The TP53 Arg/Arg genotype does not appear to represent a risk factor for the development of genital SCC in men, and no correlation was found between the TP53 polymorphism at codon 72 and the presence of HPV DNA.

Intact p73 function is shown to be an important determinant of cellular sensitivity to anticancer agents (Daniele Bergamaschi,et al). Inhibition of p73 function by dominant-negative proteins or by mutant p53 abrogates apoptosis and cytotoxicity induced by these agents. A polymorphism encoding either arginine (72R) or proline (72P) at codon 72 of p53 influences inhibition of p73 by a range of p53 mutants identified in squamous cancers. Clinical response following cisplatin-based chemo-radiotherapy for advanced head and neck cancer is influenced by this polymorphism, cancers expressing 72R mutants having lower response rates than those expressing 72P mutants. Polymorphism in p53 may influence individual responsiveness to cancer therapy.

Dreilich and his colleagues compared both the presence and the viral load of high-risk HPV types 16, 18, 31, 33, 39, 45, 52, 58, and 67 in relation to clinical data from patients with esophageal carcinoma. Survival data and tumor samples were retrieved from 100 patients receiving treatment at the Department of Oncology, Uppsala Hospital, and Uppsala, Sweden. The tumor samples were investigated for HPV viral load using real-time PCR. Results showed that HPV 16 was detected in 16% of the patients; no other HPV type was detected. HPV 16 infection had no significant effect on survival (p = 0.72). Also, HPV 16 did not improve survival after treatment (radiotherapy or chemotherapy).

In the year 2006 Farin Kamangar and his colleagues selected 29,584 participants in the Linxian General Population Trial. Prediagnostic serum samples from 99 cases of ESCC, 100 cases of GCA, 70 cases of GNCA, and 381 age- and sex-matched controls were selected for this study. The presence of antibodies to HPV virus-like particles was determined by type-specific enzyme-linked immunosorbent assays. Fewer than 15% of ESCC, GCA, or GNCA cases were positive for each HPV type, and no significant associations were found. The adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for HPV 16 seropositivity and ESCC, GCA, and GNCA risk were 1.6 (0.8–3.3), 1.3 (0.6–2.8) and 0.4 (0.1–1.6), respectively. The comparable ORs (95% CIs) for HPV 18 were 1.0 (0.4–2.2), 0.9 (0.4–2.1) and 1.5 (0.6–3.4). For HPV 73, these figures were 1.3 (0.6–2.5), 1.2 (0.6–2.3) and 0.9 (0.4–2.1). The results of this study do not support a major role for HPV 16, HPV 18 and HPV 73 in the etiology of esophageal and gastric cancers in Linxian, China.

Results in the study of Li T (2001) Showed that HPV-16 plays a significant role in the pathogenesis of esophageal carcinoma in Anyang, which is recognized as a high-incidence area for esophageal carcinoma in China. Retaining of viral DNA fragments E6/E7 and stable expression of viral genes may be associated with the malignant progression of esophageal epithelial cells.

Differences in p53 polymorphism in the corresponding normal mucosa were nil between HPV-positive and -negative tissues (P = 0.64; odds ratio, 1.32; 95% confidence interval, 0.42–4.13). In the HPV-positive group, six of eight cases displayed LOH in the eight patients in whom the Pro/Arg type was detected using the corresponding normal mucosa. Interestingly, all of the six LOH cases had lost the Pro allele, yet the Arg allele was never lost Certain HPV types such as HPV-16/18 found in the SCC of cervix and esophagus suggest a model by which E6 degrades cell growth control by elimination of the p53 tumor suppresser protein and leads to HPV-associated cervix and esophageal SCC. this study revealed the potential role of the loss of the Pro allele in HPV-associated carcinogenesis of the esophagus.

HPV L1 DNA and HPV genotypes were evaluated in 435 esophageal carcinoma specimens collected from four geographic regions with different ethnicities including Anyang in north China, Shantou in south China, Xinjiang in west China, and the United States in Xueqian Wang study (2010) .The HPV L1 fragment was detected using SPF1/GP6+ primers. HPV genotyping was performed using genotype specific PCR. RESULTS: Two hundred and forty four of 435 samples (56.1%) tested positive for HPV L1. Significant differences in detection rate were observed neither among the three areas of China nor between China

and the US. HPV6, 16, 18, 26, 45, 56, 57, and 58 were identified in L1 positive samples. HPV16 and 57 were the most common types in all regions, followed by HPV26 and HPV18. In conclusion HPV infection is common in esophageal carcinoma independent of region and ethnic group of origin. Findings in this study raise the possibility that HPV is involved in esophageal carcinogenesis. Further investigation with a larger sample size over broader geographic areas may be warranted.

Jill Koshiol et.al. agues attempted to evaluate HPV and ESCC more definitively using extreme care to prevent DNA contamination. they collected tissue and serum in China from 272 histopathologically-confirmed ESCC cases with rigorous attention to good molecular biology technique. They tested for HPV DNA in fresh-frozen tumor tissue using PCR with PGMY L1 consensus primers and HPV16 and 18 type-specific E6and E7 primers, and in formalin-fixed paraffin-embedded tumor tissue using SPF(10) L1 primers. In HPV-positive cases, They evaluated p16(INK4a) overexpression and HPV E6/E7 seropositivity as evidence of carcinogenic HPV activity. beta-globin, and thus DNA, was adequate in 98% of the frozen tumor tissues (267/272). Of these, 99.6%(95% confidence interval (CI)= 97.9%-100%) were negative for HPV DNA by PGMY, and 100%(95% CI = 98.6%-100%) were negative by HPV16/18 E6/E7 PCR. In the corresponding formalin-fixed paraffin-embedded tumor specimens, 99.3 %(95% CI = 97.3%-99.9%) were HPV negative by SPF(10). By PGMY, one case tested weakly positive for HPV89, a non-cancer causing HPV type. By SPF (10), two cases tested weakly positive: one for HPV16 and one for HPV31. No HPV DNA-positive case had evidence of HPV oncogene activity as measured by p16 (INK4a) overexpression or E6/E7 seropositivity. This study provides the most definitive evidence to date that HPV is not involved in ESCC carcinogenesis in China. HPV DNA contamination cannot be ruled out as an explanation for high HPV prevalence in ESCC tissue studies with less stringent tissue procurement and processing protocols.

The development of cervical cancer is preceded by precursor lesions (cervical intraepithelial neoplasia) (Alex Ferenczy and Eduardo Franco). Evidence-based epidemiological and molecular data suggest that persistent infections with human papillomavirus (HPV) types that carry a high oncogenic risk are the intermediate endpoints, leading to both intraepithelial and invasive cervical neoplasia. Integration of highly oncogenic HPVs into host-cell chromosomes is followed by binding of HPV E6 and E7 oncoproteins to tumour-suppressor genes p53 and RB, respectively. This process results in impaired tumour-suppressor-gene function, involving DNA repair, decreased apoptosis, and eventual cell immortalisation. Mutations causing chromosomal alterations, loss of heterozygosity, and proto-oncogene and telomerase activation in immunopermissive individuals have important roles in virus-induced cervical carcinogenesis. The so-called non-European variants of HPV 16 and 18 may increase the degradation potential of p53. HPV 16 is polymorphic and, although the evidence is controversial, the Arg/Arg genotype of p53 could have greater susceptibility to HPV-E6 degradation than the other genotypes. The coincident interplay between the non- European genomic variants of HPV 16/18 and p53 Arg/Arg may explain, at least in part, the persistence of HPV infection and tumour progression in women with cervical neoplasia. Further epidemiological and molecular research is needed, to gain insight into HPVmediated cervical carcinogenesis. The evidence highlights the need to develop appropriate prophylactic HPV vaccines and diagnostic and screening tests.

Non-melanoma skin cancers frequently harbour multiple human papillomavirus (HPV) types. A recent report suggests that a polymorphism of the p53 tumour suppressor gene that results in the substitution of a proline residue with an arginine residue at position 72 of the p53 protein might act as a risk factor in HPV associated malignancies. This study aimed to determine the following: (1) the relation between HPV infection and the development of cutaneous squamous cell carcinoma (SCC), and (2) whether there is a correlation between p53 codon 72 polymorphism and the development of SCC. Blood samples were taken from 55 patients with skin cancer (both renal transplant recipients and immunocompetent patients with skin cancer) and 115 ethnically matched volunteers. A polymerase chain reaction based assay was used to determine p53 codon 72 genotypes. In addition, 49 benign and malignant lesions from

34 of the patients with skin cancer and 20 normal human skin samples from 20 of the control volunteers were examined for HPV. The proportions of p53 codon 72 genotypes found were 78% arginine homozygous, 2% proline homozygous, and 20% heterozygous among patients with skin cancer and 79% arginine homozygous, 3.5% proline homozygous, and 17.5% heterozygous among the control population. Statistical analysis showed no significant differences in the distribution of the two p53 isoforms between the patients with skin cancer and the control population. The predominant viral types detected in both the patients and the control group were EV associated HPVs, although the incidence was lower in normal skin samples than in malignant lesions or viral warts. These results suggest that in a Celtic population there is no correlation between the presence of HPV, the p53 codon 72 arginine polymorphism, and the development of skin cancer.

Conclusion

Several studies have revealed that in fifferent types of cancer, one of the alleles show higher frequency, for example studing the role of codon 72 in patients affected to liver cancer showed that allele pro has higher frequency. In this regard there are also some studies about the role of codon 72 p53 in lung cancer, stomach canver, breast cancer and so on. It is similar to the present findings that among the examined population of patients, Allele pro codon 72 had more frequency that represents its likely role in induction cancers.furthermore codon 72 has different frequency in ethnic populations and geographical situations and in this regard different studies have shown completely various results regarding the frequency of this codon. In another word, the frequency in allele p53 even in a case of esophageal cancer is extremely an important variable in different ethnics and geographical populations. Genetic influences on cancer development have been extensively investigated during the last decade following publication of human genome sequence. Genetic changes cause increasing sensitivity to some environmental factors. Among the genes, P53 having the main role in induction cancer. Generally each factor that cause changes in DNA can activate P53 and cell cycle arrest and reparation of damage or apoptosis. Destroying the activity of P53 is very current in carcinogen process and seems that it is regarded as a prerequisite for this stage.Making mutation in p53 is observed in more than %50 of all human cancers [14]. Moreover P53 mutations are seem in all kinds of histological cancers like colon cancer (%60),stomach cancer (%60)lung cancer (%20),brain cancer (%48) esophagus cancer (%60) [16]. One of these polymorphism that has been studied a lot, exists in codon 72. This polymorphism causes producing two forms of p53 molecule which are in 72 codon have Arg or pro [17]. frequency of allele gene p53 in codon 72 in different population and in different geographical areas is variable. It appears that much more experiments involving larger sample size, cross-tabulating genetic polymorphisms and environmental factors are required in order to identify genetic markers for different cancers.

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Nasal myiasis caused by *Lucilia sericata* (Diptera: Calliphoridae) in a hospital from Kermanshah, Iran: A case report

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Abstract

Myiasis has been defined as the invasion of human or animal tissues by the fly larvae (maggots) causing either facultative or obligatory miyasis. This disease can be classified based on the area of the body infested, including cutanious, ophthalmic, auricular, oral, nasal and urogenital myiasis. Among different types of miyasis, nasal miyasis is rare, so there are a few reports of occurrence of nasal miyasis in the world. In this report, another case of nasal miyasis caused by *Lucilia sericata* was diagnosed in a patient admitted to ward of psychiatry, Farabi hospital in Kermanshah, west province of Iran.

Introduction

The order Diptera are holometabolous and contain four life stages including egg, larva, pupa and adult. This order contains many species of medical importance insects including blood sucking mosquitoes, horse and deer flies and flies which transmit some pathogens to man. However, in this order, there are some flies that cause a disease commonly named myiasis. Myiasis has been defined as the invasion of human or animal tissues by the fly larvae (maggots) causing either facultative or obligatory miyasis.[1] Clinically miyasis has a wide range of impacts on human host, as well as, on a variety animal hosts including sheep, goats and cows.

Generally, Myiasis has been classified based on the area of the body infested, including cutanious, ophthalmic, auricular, oral, nasal and urogenital myiasis.[2]

Among different types of miyasis, nasal miyasis is rare, so there are a few reports of occurrence of nasal miyasis in the world. Kim et al., 2009, reported nasal myiasis in a patient in Korea due to *Lucilia sericata*.[3] Recently, Wu et al., 2012, reported a case of nasal form of myiasis in a patient from Taiwan, without species identification.[4] Although, Salimi et al., 2010, have previously reported this type of myiasis caused by *Eristalis tenax* from Iran[5],however, for the first time a nasal form of myiasis due to *Lucilia sericata* from Iran was reported in a 74 years old patient in a hospital from Mazandaran, north province of Iran.[6]

In this report, another case of nasal miyasis caused by *Lucilia sericata* was diagnosed in a patient admitted to ward of psychiatry, Farabi hospital in Kermanshah, west province of Iran.

Case report

The patient was a 50 years old female who was admitted to ward of psychiatry, Farabi hospital in Kermanshah in June 2012. She presented with mild nasal discharge and coughing without any wound or bleeding. Two emerged larvae from her left nostril with viscose mucorrhea were preserved in 70% Ethanol and sent to the Entomology laboratory of department of Public Health. The nasal cavity irrigation with saline solution was done after emerging of the larvae. The patient was treated by antihistamine and also antibiotic to prevent secondary infections. Then, after several days, no more larvae were obtained from her nostrils.

The photography of the relevant specimen was carried out (Figure 1). Definite identification was performed according to some characters including Preitreme ring, Cephalopharyngeal skeleton, so the maggots were definitely identified as *Lucilia sericata* (Figures 2 & 3).

Figure 1. Larvae of Lucilia sericata

Figure 2. Perithremal ring is closed

Figure 3. Cephalopharyngeal skeleton without pigmented area in lower part

The patient was living in a rural area with livestock and pets, thus being in contact with some flies which are agent of myiasis.

Discussion

Different types of myiasis usually occur in tropical and subtropical areas in the world. It is also expected to observe these infections in rural area which individuals live near animal husbandry, thus being in contact with the flies which causing myiasis in human and animals. In the nasal form of the myiasis, the nostrils are infested by the maggots of flies.The maggots of different fly species have been involved in nasal myiasis in the world. For instance, *Eristalis tenax*[5, 7], *Lucilia sericata*[3, 6, 8, 9], *Chrysomya bezziana* [10]and *Drosophila melanogaster* [11]have been reported causing nasal myiasis in different areas of the world. Family caliphoridae contains several myiasis causing fly species which widespread in all over of Iran, especially in rural area where individuals are in contact to flies and so are vulnerable to myiasis. Kermanshah the west province of the country is surrounded by animal husbandry and farms. In this report the microscopic examined specimen was identified as *Lucilia sericata.* Although this species of maggot usually causes wound myiasis however, nasal myiasis has been previously reported[6,12]. As the emerged maggots from the nostril of our patient at the second day of admission to ward of psychiatry were at the third instar larvae, she was likely infested before admission. She lived in countryside in the vicinity of farms and animal husbandry.

Environmental sanitation and health education about the roles of the flies in causing myiasis are essential for preventing of this kind of disease.

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Mean Platelet Volume of Child Patients with Chronic Otitis Media

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Abstract

Aim: Chronic otitis media is a disease involving persistent inflammation in the middle ear. Although various factors are involved in its development, the exact pathogenesis is unknown. Mean platelet volume is an inflammation marker. The aim of this study was to analyze mean platelet volume and other hematological parameters in chronic otitis media.

Method: Mean platelet volume, PDW, PCT, platelet numbers, hemoglobin and white blood cell counts from venous blood specimens collected from patients with chronic otitis media and an age- and gender-matched control group were recorded.

Results: Sixty-nine children were included, 33 with chronic otitis media and 36 controls. There was no significant difference between the groups in terms of age or gender (P>0.05). Mean platelet values were significantly higher in the chronic otitis media group compared to the control group (8.78 ± 0.1 fL, 7.28 ± 0.13 fL, P<0.0001).

Conclusion: Thrombocytes are involved in inflammation developing in chronic otitis media. Elevated mean platelet value may be a marker of inflammation in chronic otitis media.

Key words: Chronic otitis media, platelet, mean platelet volume

Introduction

Chronic otitis media (COM) is an inflammatory process of more than 3 months' duration involving chronic changes in the middle ear mucosa. Persistent inflammation is present in COM. Cytokines may be an agent in the development of inflammation. Thrombocytes are involved in cytokine production. No previous studies have examined thrombocyte functions in COM and other middle ear pathologies involving intense inflammation [1, 2].

Mean platelet volume (MPV) is a parameter produced by an automatic blood count device during routine blood count and that is generally overlooked by clinicians. MPV is a good indicator of thrombocyte size and thrombocyte-specific activities [3]. Changes in MPV have been shown in diabetes mellitus, myocardial infarction, obesity, and various inflammatory diseases such as familial mediterranean fever, ankylosing spondylitis and Crohn's disease [4-9].

The aim of this study was to investigate the levels of MPV and other hematological parameters in patients with COM, with its widespread inflammation.

Materials and methods

Study group

The study was performed at the Ministry of Heath Erzurum Teaching and Research Hospital pediatric clinic, Turkey. Ours is the largest tertiary hospital in the East Anatolian region of Turkey. Local ethical committee approval was obtained before the study began. Families of children to be enrolled in the study were given detailed information about the shape and purpose of the study at face-to-face interviews, and written consent forms were obtained. Children aged 2-10 and diagnosed with COM and healthy children matched with these patients in terms of age and gender such as to constitute a control group were enrolled. COM was defined as persistent otitis media with effusion lasting longer than 3 months. Diagnosis was made by an otolaryngologist on the basis of audiometry findings including symptoms, otomicroscopy and tympanometry.

Exclusion criteria were 1) congenital neck and facial deformity, 2) disease affecting the liver, kidney, respiratory and immune systems, 3) a history of malignity, 4) present or previous drug use such as to compromise thrombocyte function, 5) cholesteatoma, 6) Down syndrome, cystic fibrosis or primary ciliar dyskonesia.

MPV, PDW, PCT, platelet numbers and hemoglobin and white cell count values in venous blood specimens taken from the study group consisting of children with COM (COMG) and the control group (CG) were recorded.

Biochemical Analysis

Two milliliters of blood were drawn into a vacutainer tube containing 0.04 ml of the 7.5% K3 salt of ethylenediaminetetraacetic acid from each individual. Complete blood cell counts were performed on the same day within 6 h using a Beckman Coulter LH 750 Analyzer; Beckman Coulter Inc. Miami, Florida, USA. Blood sampling was performed in the early morning (all patients being asked to fast) between 09:30 and 10:30 h, and the samples were analyzed at 16:00 h.

Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Sciences version 18.0 (SPSS for Windows 18.0, Inc., Chicago, IL, USA). Categorical variables were provided as numbers and percentages, and numerical variables as mean ± standard error mean. Gender comparisons between groups were made using the Chi-square test. Initial comparisons of laboratory parameters between the two groups were made depending on normality of distribution, followed by two-way comparisons using the t-test for independent samples.

Results

Sixty-nine children were enrolled; 33 in the COMG and 36 in the CG. The COMG consisted of 17 males (51.5%) and 16 females (48.5%), compared to 20 males (55.6%) and 16 females (44.4%) in the CG. Mean ages in the COMG and CG were 5.39 ± 0.31, 4.85 ± 0.33 years, respectively. There was no significant difference between the groups in terms of sex or age (P>0.05).

Mean MPV values in the COMG were significantly higher compared to those in the CG (8.78 ± 0.1 fL and 7.28 ± 0.13 fL, respectively. P<0.0001) (Figure 1).

PDW, PLT, HB and WBC values in the groups are shown in the Table.

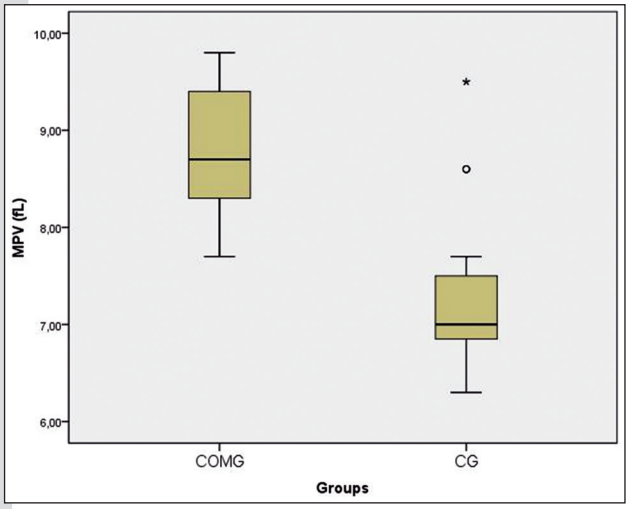

Figure 1. Comparison of groups' mean MPV values

Discussion

Several factors are involved in the development of COM, although the exact pathogenesis is unknown. The pathological tissues in COM are ulcerated mucosa, polypoidal mucosa with granulation, cholesteatoma and osteitic tissues. Although pat-

Table 1. Comparison of groups' hemogram parameters

	COMG N:33	CG N:36	P
PDW	16.1 ± 0.08	16.5 ± 0.13	<0.05
PCT (%)	0.28 ± 0	0.21 ± 0	<0.05
PLT (10^3/µL)	299848 ± 12856	312416 ± 12698	>0.05
Hb (g/dL)	13.5 ± 0.18	14.2 ± 0.93	<0.05
WBC (10^3/µL)	8748 ± 433	7516 ± 252	<0.05

hological agents have been described, some cases are still regarded as idiopathic. Infectious agents and structural and genetic factors all play a role in the development of COM. Underlying anatomical defects and immune deficiency may lead to inflammation in some cases [1, 2]. Cytokines such as IL-1α, IL-1β, IL-6, IL-8, TNF and interferon-α may be agents in the development of inflammation and edema [10, 11]. Our study, an examination of thrombocyte functions in COM with severe inflammation, determined higher MPV compared to the CG. This is also an indication that thrombocytes are involved in inflammation in COM.

Thrombocytes have long been known to be involved in hemostasis. Studies have reported that some cytokines produced by thrombocytes play important roles in inflammation, increased vascular permeability, chemotaxis of polymorphonuclear leukocytes and phagocytosis. Changes occur in their shape and dimensions when thrombocytes are activated [12]. MPV is a marker of thrombocyte activity. High MPV values show that thrombocytes are metabolically and enzymatically active [3]. Calcium, ATP, thromboglobulin, thromboxane A2, serotonin and thrombocyte factor 4 secretory mediators released from thrombocytes may also contribute to inflammation [12, 13].

Cytokines released from thrombocytes may cause thrombosis and ischemic events and large thrombocyte production by stimulating bone marrow[12-14]. Elevated MPV has been shown in pathologies in which thrombolytic events such as myocardial infarction, angina, obesity and diabetes are frequently seen [5, 6, 9]. Increased thrombocyte activity may also play a role in the development of lateral sinus thrombophlebitis, one of the complications of COM.

Elevated MPV levels have been reported to be associated with Crohn's disease, ulcerative colitis, familial mediterranean fever, rheumatoid arthritis and acute pancreatitis [4, 7, 8]. It has recently been suggested that MPV may be a simple inflammation marker in inflammatory diseases. Can MPV be used to evaluate severity of inflammation in chronic inflammations requiring long-term monitoring, such as COM? The fact that MPV is a simple and inexpensive technique may make it important for clinicians in the monitoring of chronic inflammations. However, randomized, control studies comparing MPV levels in COM patients when the disease is active and in remission are needed in order to confirm this.

In conclusion, elevated MPV values may be an inflammation marker in COM patients. Further studies must establish whether it is a parameter that can be used in monitoring.

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Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

Key words: Camera ready paper, Journal.

Introduction

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Table 1. Page layout description

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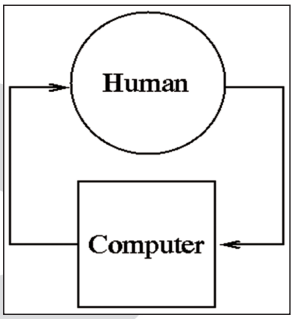

Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

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