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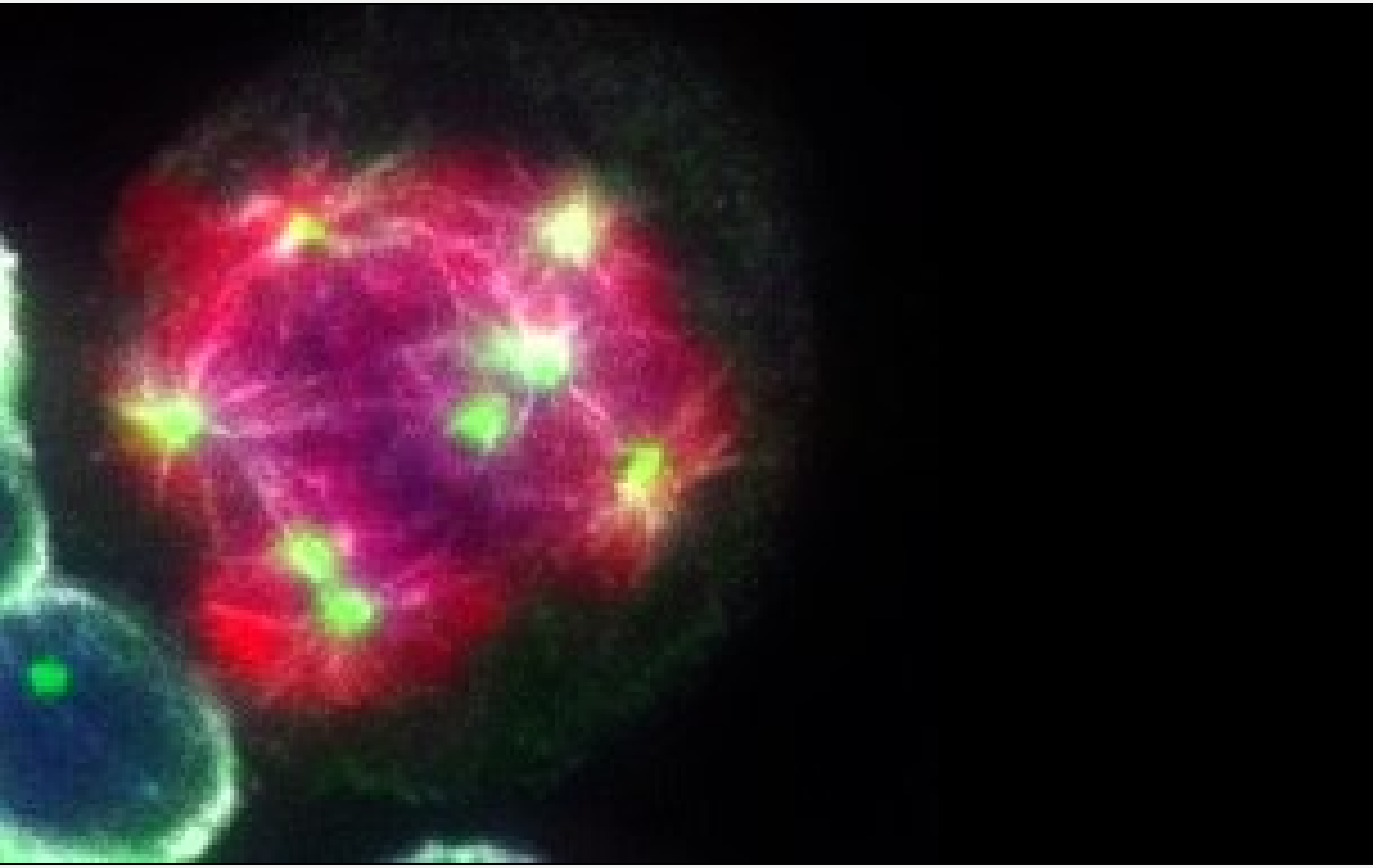

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Letter to Editor Doi: 10.17546/msd.71668

Urinary tract infections in newborns

Gokmen Bilgili[1], Mehmet Bilgehan Yuksel[2]

The incidence of neonatal urinary tract infection (UTI) varies from 0.1 to 1% of all infants, and its frequency is inversely proportional to birth weight [1]. Neonatal UTI presents different features than those observed in other age groups for several reasons, including higher prevalence, male sex predominance, and most importantly higher risk of urosepsis [2]. As the symptoms of a UTI in a neonate, such as irritability, poor feeding and vomiting are generalized, the clinician should have a high index of suspicion. The best correlates of infection in infants with UTI were found to be a body temperature greater than 38° C and uncircumcised males [3]. *Escherichia coli* is the most likely pathogen, but *Klebsiella pneumoniae, Enterobacter* spp., *Enterococcus* spp., *Pseudomonas* spp., *Candida* spp. and coagulase-negative staphylococci have to be considered in nosocomial UTI as well [1-3]. A positive blood culture is reported in 12.4% of cases, and nosocomial UTI is nearly twice likely to result in urosepsis compared with community-acquired UTI [2]. Bladder puncture or transurethral catheter is recommended for urine sampling in neonates to avoid urinary contamination. Parenteral antibiotic regimen, including a combination of a third-generation cephalosporin or aminoglycoside with ampicillin for a total of 7-14 days should be commenced urgently in the suspicion of pyelonephritis following urine sampling for culture. Vancomycin and an aminoglycoside should be considered for nosocomial UTI. In the light of the results of sensitivity testing, a single-antibiotic coverage, if possible, should be considered [1-3]. The presence of high-grade reflux, severe urinary obstruction, and recurrent pyelonephritis mandates antibacterial prophylaxis, however its efficiency has not yet been proven [2]. Radiological studies have to be undertaken once a diagnosis of UTI has been made. An abnormal renal ultrasound is reported in around one third of cases, and vesicoureteral reflux is observed in nearly one fourth during voiding cystourethrogram (VCUG). The urine should be sterile while performing a VCUG [2, 3].

Gram-negative antibiotic resistance is emerging worldwide and outbreaks have occurred in neonatal units due to multi-resistant gram-negative bacteria [4]. To overcome this problem in the case of a UTI, urine cultures should be appropriately obtained, and the treatment should be tailored based on sensitivity results; antibiotic prophylaxis should be spared to aforementioned high-risk groups, while emphasizing the importance of compliance; and pediatric-specific antibiograms should be used [5].

Finally, evidence-based guidelines for the diagnosis and management of UTI in febrile infants aged less than 2 months are lacking, and urgently required [2].

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Effects of oleic acid

Kayihan Karacor[1], Meryem Cam[1]

Abstract

Content of fatty diet plays a significant role in the development and progression of chronic diseases. Generally, it is accepted that unsaturated fatty acids are beneficial. According to literature review, oleic acid (C18:1n-9) has positive impacts on various tissues in general and has negative impacts rarely. Olive oil composition includes high amount oleic acid. Considering of the effects of oleic acid on the cardiovascular system, it was determined that decreasing of the myocardial infarction rate, platelet aggregation and secretion of TXA2, plus reduce of the systolic blood pressure. LDL cholesterol was decreased. In terms of effects on the liver, while some studies suggest that oleic acid has beneficial effects, unlike other studies proved that exposed to oleic acid of hepatocytes induce ER (endoplasmic reticulum) stress in long - term period. The several studies which were investigating the efficacy of the oleic acid on the tumor tissue proved that OA increased to hepato-tumorigenesis in vivo as a potential. On te other hand, another research showed that oleic acid blocked the action of HER-2 / neu oncogene that led to breast cancer. Although some researchers reported that OA develop neutrophil phagocytic capacity and candidacidal activity, other researchers point out that these fatty acids didn't cause any changes on bactericidal activity and fatty acids caused moderate decreases on phagocytosis and chemotaxis only in extremely high concentrations, and they suppressed to T lymphocytes. Although, most of studies have indicated to beneficial effects of oleic acids, also the adverse effects of oleic acid have been reported in a few studies. This situation requires further researches for detail information about oleic acid

Keywords: Oleic acid, Cancer, Liver, Immune system, Cardiovascular system disease

Introduction

Lipids, in addition to being an important component within the structure of the cell membrane, they also act for storage and transmission of energy. So, they constitute significant part of our diet. Fats obtained from natural sources by diet are composed of a mixture of fatty acids. Most of these fatty acids are included within the structure of triglycerides. (1) Fatty acids are categorized in two groups as saturated fatty acids and unsaturated fatty acids. Both solid and liquid fats contain a mixture of saturated and unsaturated fatty acids. In general, fats obtained from animal products are more saturated while vegetable oils contain unsaturated fatty acids.

Contents of dietary fat play an important role in the development and progression of chronic diseases such as obesity. In general, saturated fatty acids (SFAs) and trans- fatty acids are considered to be harmful while unsaturated fatty acids are considered as beneficial for cardiovascular health in diets. Conventionally unsaturated fatty acids are classified according to their chemical structures as either monounsaturated fatty acids with one double bond (MUFAs) or polyunsaturated fatty acids with more than one double bond (PUFAs). If the first double bond is three carbons from the methyl end, the fatty acid is classified as n-3 fatty acid and if the first double bond is six carbons from the methyl end, the fatty acid is classified as n-6 fatty acid. Most dietary fats contain a part or all of the 18-carbon fatty acids sequence -having both saturated and unsaturated fatty acids- such as stearic acid (C18: 0; SFA), oleic acid (C18: 1n-9; MUFA), linoleic acid (C18: 2n-6, n-6 PUFA) and α-linolenic acid (C18: 3n-3 ; n-3 PUFA). Oleic acid has one double bond in N-9 position, linoleic acid has two double bonds in n-6 and n-9 positions and α-linolenic acid has three double bonds in n-3, n-6 and n-9 positions and these double bonds have cis configuration. Oleic acid, in general, is found in animal oils such as tallow and lard as well as in vegetable oils such as olive oil and sunflower oil and canola oil which have high oleic acids (2). Studies conducted on oleic acid have revealed the fact that oleic acid has positive or negative effects on various tissues.

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Cardiovascular Effects of Oleic Acid

Cardiovascular diseases such as hypertension, aneurysm, thrombosis and MI are responsible for 30% of deaths according to 2005 data of the World Health Organization. Cigarette consumption, low physical activity, obesity and malnutrition constitute the risk factors for cardiovascular diseases. Myocardial infarction rate in Mediterranean countries is lower compared to Northern Europe, USA or Australia (3, 4, 5). Olive oil is major component of the Mediterranean diet and has high oleic acid ratio (3, 6). Hence, US Food and Drug Administration have recommended 23 grams of olive oil per day in 2004 against the risk of coronary heart disease due to MUFAs content (7).

Numerous studies state that oleic acid is effective in prevention of ischemic heart diseases (3,8). It has been shown that oleic acid inhibits platelet aggregation induced by platelet aggregation factor (PAF) as well as the secretion of serotonin. It has been discovered, as a result of the studies which were carried out for understanding of the molecular mechanism of this effect, oleic acid inhibits the aggregation of platelets induced by PAF by reducing the phosphatidylinositide (PIP) and PIP2 levels (3-9). It has been shown in several studies that oleic acid inhibits platelet function, reduces the aggregation of platelets, reduces the secretion of TXA_2, increases thrombocyte membrane oleic acid content significantly and decreases levels of arachidonic acid. The inhibiting effect of oleic acid on platelet function in various ways may be associated with its lowering of the risk of heart diseases as well as the protective role (3, 10).

The beneficial effects of olive oil are related to the high level of oleic acid in the composition of its own (%70-80). This composition of olive oil helps the regulation of lipids in the membrane structure by increasing the oleic acid level in the cell membrane. In this way it leads to signal-dependent G protein control and reduces the blood pressure (3-11). Cardiovascular tissues which are applied to 2-OHOA (hydroxyl oleic acid) in rat's shows the cAMP activation as a response to activation of the Gs-α protein which is thought to increase the expression of Gs-α proteins. Consequently, there is a significant fall in systolic blood pressure. (3).

In 1985, Mattson and Grundy are found that olive oil increases HDL cholesterol which has antiatherogenic function, supports the elimination of LDL cholesterol, and plays a protective rol. Sirtori et al. have suggested in 1986 that olive oil plays a protective role against thrombosis and platelet aggregation in addition to the effects thereof on cholesterol and atherosclerosis. Accordingly, consumption of olive oil in high levels is not harmful since it reduces only LDL cholesterol but not HDL levels (3).

Effects of cardiovascular, hepatic and metabolic parameters of macadamia oil (63% oleic acid, 17% palmitoleic acid) rich in MUFAs(monounsaturated fatty acids), safflower oil rich in n-6 PUFAs (polyunsaturated fatty acids) and flaxseed oil rich in n-3 PUFAs (polyunsaturated fatty acids) have been compared in the study conducted by Poudyal et al. in 2013 (2).

They have determined that the groups which are rich in both oleic acid and alpha linolenic acid reduce weight gain unlike linoleic acid when compared with the control groups. There was reduction in plasma total cholesterol in COA (corn starch + Macadamia oil rich in oleic acid) and HOA (high carbohydrate, high fat + Macadamia oil rich in oleic acid) groups compared to the control groups (2).

Eccentric hypertrophy has been found characterized with preload defined by increase in inner diameter of left ventricle in diastole without change in wall thickness was identified in H group rats fed by a high-carbohydrate and high-fat diet compared to the control group rats (C). Deterioration in systolic function as decreased fractional shortening, increased wall stress, increase in diastolic resistance and decrease both in pressure increase and dP/dt were also observed in H group rats. Furthermore, high diastolic, systolic and stroke volume, and cardiac output were found in H group rats compared to C group rats (2).

There was increase in inner diameter of left ventricle in diastole in COA (corn starch + Macadamia oil rich in oleic acid) and CLA (high corn starch+ rich in linoleic acid) groups with oleic and linoleic acid supplementation. There was increase in inner diameter of left ventricle in systole in all groups except HLA (high carbohydrate, high fat, rich in linoleic acid) group and decreasing left ventricular internal diameter in systole in HLA was compensated by left ventricular posterior wall dimension, left ventricular internal diameter of which has increased. These effects were accompanied by low fractional shortening in the COA and CLA groups in contrast to HLA. Furthermore, diastolic, systolic and stroke volume and cardiac output were significantly higher in CO and CLA group compared to C rats. Diastolic volume, stroke volume and cardiac output remained unchanged in the HOA and HLA groups compared to H group rats while systolic volume increased in the HOA group and decreased in the HLA group. The addition of alpha-linolenic acid has normalized systolic and diastolic left ventricular internal diameter and all the volumes. In addition, systolic blood pressure has been normalized in HOA and HALA (flax seed oil with high volume of oil + rich in α-linolenic acid) groups in contrast to the HLA group (2).

However, oleic acid supplementation has increased the systolic wall stress in COA, compared to the C (corn starch) and H (high carbohydrate,

high fat) group rats and maintained the high wall stress in HOA (2). Wall stress did not change in the CLA group while it decreased in CALA (corn starch + flax seed oil rich in α-linolenic acid), HLA, and HALA groups (2).

Oleic acid has decreased the total plasma cholesterol, however it has not changed plasma triglycerides and non-esterified fatty acids. Oleic or linoleic acid supplementation did not change the left ventricle structure induced by H diet, however both of the fatty acids have caused left ventricular enlargement and subsequently led to impaired function in rats fed with low-fat (C) diet. However, oleic acid supplementation has normalized the systolic blood pressure (2).

It was observed that inflammatory cell infiltration as well as collagen deposition increased in H group rats compared to C group rats after 16 weeks in the histological evaluation of the left ventricle. It was observed that inflammatory situation induced by H diet did not change in oleic acid supplemented HOA group but collagen deposition decreased (2). Inflammatory situation normalized in linoleic acid and alpha-linolenic acid supplemented HLA and HALA groups and collagen growth decreased. Tissue histology was found normal in COA, CLA and CALA rats (2).

Effects on Liver

Decrease was observed in plasma ALT, AST aminotransferase, alkaline phosphatase and creatine kinase activity in the HOA group compared to H group rats in the study of Poudyal et al. in terms of liver structure, functionality and fatty acid composition. There was increase in the hepatic lipid accumulation and inflammatory cell infiltration in H group rats compared to C group rats, and oleic acid supplementation has decreased significantly portal inflammation and macrovesicular steatosis in HALA and HOA rats. Plasma bilirubin concentrations have decreased in both COA and HOA groups (2).

It was revealed in the study of Fuchs et al. conducted in 2011 that OA (oleic acid) has protective features against PA (palmitic acid) which induces toxicity. Both WT (wild type) rats and ATGL KO (adipose triglyceride lipase knock out) rats were stimulated by TM (tunicamisin) to induce ER (endoplasmic reticulum) stress. It was found that by the adjustment of PIK3IP1 (phosphoinositide 3-kinase - inhibitor-1), OA (oleic acid) inhibited PA (palmitic acid) which induces the ER (endoplasmic reticulum) stress. It was seen in ATGL KO rats that OA amount may have a protective function against PA resulting from ER stress. In summary, it can be said that these data has revealed the fact that WT rats exposed to ER stress rats cannot create TG form as a result of the high PA levels and reduced hepatic OA and additionally due to increase of PIK3IP1 (phosphoinositide-3-kinase-inhibitor-1) expression and increase of ER stress in relation with it. On the contrary, it was determined that TM inducing hepatic ER stress in ATGL KO rats inhibited the growth of OA in hepatic TG pool (12).

In the study made by Caviglia et al. (13) it was found that although short-term incubation of hepatocytes with oleic acid stimulated APOB100 (apolipoprotein B100) secretion (13,14,15), long-term and high doses of oleic acid application induced ER (endoplasmic reticulum) and as a result of this it reduced the secretion of APOB100 (apolipoprotein B100) (13,16) and although palmitic acid (PA) triggered the ER stress its effects on apoB100 secretion was uncertain(13,16) and although it was shown that docosahexaenoic acid (DHA) inhibited apoB100 secretion, they made comparison as to apoB100 secretion in McArdle RH7777 (MCA) cells and the effects of OA and PA and DHA on ER stress because effects on the ER stress was not studied (13). OA and PA induced ER stress in high doses and inhibited apoB100 secretion and PA was found to be more because its effect increased synthesis of ceramides. It has been shown that DHA did not stimulate ER stress however it was the strongest inhibitor of apoB100 secretion by stimulating autophagy. These specific effects of each fatty acid have been confirmed by infusing C57BL6J rats. These results have shown that both VLDL and apoB100's increase of liver secretion accompanied hepatic steatosis, however ER stress was reduced and hepatic steatosis was alleviated at the expense of VLDL secretion. In contrast, it was determined that increased autophagy could reduce the secretion of VLDL without causing steatosis. They have concluded that different fatty acids has suppressed APOB100 (apolipoprotein B100) secretion in different ways such as ER stress, ceramide synthesis and autophagy (13). Other studies have shown that apoB100 may undergo degeneration through autophagy which is one of the nonproteosomal ways (13, 17, 18)

In the study carried out by Wu et al. steatosis was induced by incubating the HepG2 cells with oleic acid and it was found that oleic acid caused a significant increase in PPAR gamma expression in a calcium-dependent way. It was also understood that oleic acid regulated the sensitivity of insulin because PTEN (phosphatase and tensin homolog) increasing insulin resistance in hepatic steatosis is regulated by PPAR gamma (19).

Over expression of liver PPAR gamma has increased the liver steatosisin diabetic db/db rats. Finally, it has been proven that OA increases the PPAR gamma expression by the way of GPR40-PLC-calcium and in steatotic situation PPAR gamma increase has proven to have higher role in the regulation of lipid metabolism of and insulin sensitivity (19).

In a study made in 2011, the effects of the high-fat diet rich in oleic acid on rat liver and the role in weight gain were examined (20). When body weight, liver weight and epydidimal fat weight of rat groups was compared with each order, there was no significance difference found among groups. As a result of the biochemical analysis LDH was found to be significantly higher in the 16-week high carbohydrate group while ALT was found to be significantly higher in the 20-week high carbohydrate group. Although fibrosis, inflammation and steatosis findings were observed in all groups in the portal area in the histological examination, a statistically significant difference was not determined (20).

The effect of oleic acid on tumor tissue

Kudo et al. focused on fatty acids as additional pro-tumorigenic factors that contribute to in vivo hepato-tumorigenesis in Tg (transgenic) rats. OA or PA was applied to BNL-CL2 cells to investigate the potential of OA (oleic acid) or PE (palmitic acid) which downregulated the expression of the tumor suppressors containing PTEN (phosphatase and tensin homolog deleted on chromosome 10). It was found that OA suppressed the expression of PTEN, AridB5, Xpo4 (exporting 4 gen) and Dlc1 (deleted in liver cancer-1) while PA did not create such an effect. Moreover, BNL-CL2 cells exposed to OA became significantly more colonized in soft agar. These findings have revealed the fact that OA increases the in vivo tumorigenesis potentially (21).

A study carried out by Mendez has revealed that oleic acid blocked the action of HER-2/neu an oncogene causing cancer which % 30 of patients have breast cancer and 1 or 2 tablespoons of olive oil per day has been recommended to adults (22,23).

The role of oleic acid in the immune system

Effects of oleic acid on neutrophil functions

Numerous studies have evaluated the effect of OA on adhesion of leukocytes. According to some authors, in vitro studies have revealed the fact that micromolar quantities of oleate inhibit expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin and intercellular adhesion molecule-1 (ICAM-1) in endothelial cells (24, 25-29). Other authors have expressed that OA does not have any effect on endothelial cells or human leukocyte adhesion molecule (24, 30). In any case, it has been reported that OA does not have pro-inflammatory effect.

Furthermore, it was has been determined that OA is capable of reducing the inflammatory effects of long chain saturated fatty acids in human aortic endothelial cells, OA caused this situation by inhibiting both of stearic acid-induced ICAM-1 expression and nuclear factor kappa B (NF-KB) phosphorylation which is transcriptional regulator of ICAM-1 (24,31).

In contrast, it has been reported that OA increases the cell surface expression of CD11b and this leads to high affinity state of the integrin. It has been reported that oleic acid causes neutrophil accumulation and neutrophil-endothelial cell adhesion by virtue of a CD11b mediated mechanism (24, 32).

The effect of OA on leukocyte migration has been found only in a few studies. Ferrante et al. have shown that it is possible to inhibit the leukocyte migration, however, this effect has been reported to be far from the effect shown by PUFAs (24, 33).

Contradictory results can be found also in relation with other leukocyte functions. Although some researchers have reported that OA improves the neutrophils' phagocytic capacity and candidacidal activity (24,34,35) other researchers have shown that these fatty acids did not cause any change in the bactericidal activity and only led to a moderate decrease in phagocytosis and chemotaxis in very high concentrations (24,36).

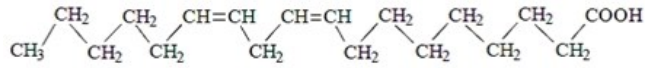
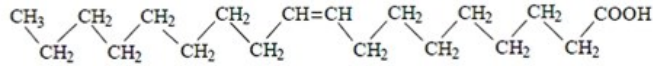
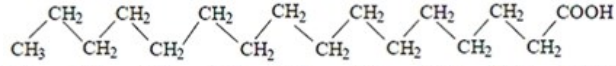
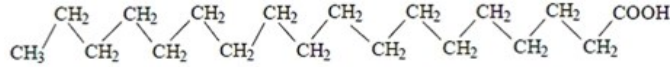
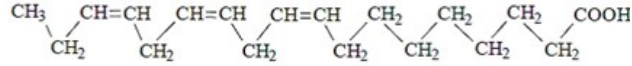
Production of reactive oxygen species (ROS)

Several studies have reported that unsaturated fatty acid effects the ROS production in neutrophils (24,34, 37-46). Nevertheless, fatty acids can develop or inhibit the development of neutrophil activation depending on the experimental conditions. For example, some studies have reported that of C18 fatty acids inhibit ROS production (24, 45). In contrast, it has shown a significant interaction between other fatty acids, and cytokines and it has been shown that superoxide have increased in neutrophils pretreated with TNF remarkably which is generated in response to fatty acids (24, 42). In any case, most of the studies in literature have reported increased ROS production in neutrophils stimulated by unsaturated fatty acids (24).

Some studies have reported that OA changes the Ca^{+2} homeostasis in different immune system cells (24, 47-52).

However, the relationship between OA-induced ROS production and Ca^{+2} mobilizations is complex and its mechanism of action is still not known clearly. Some authors have reported a Ca^{+2} independent mechanism in the background of ROS production (24, 43). In contrast, other studies have shown the connection between these two ways (24, 39, 53).

Table 1: Common Oleic Acid and Formulas.

Linoleic Acid $C_{18}H_{32}O_2$	
Oleic Acid $C_{18}H_{34}O_2$	
Palmitic Acid $C_{16}H_{32}O_2$	
Stearic Acid $C_{18}H_{36}O_2$	
Linolenic Acid $C_{18}H_{30}O_2$	

The effect of oleic acid on T cell proliferation

Verlengia et al. has reported that OA leads to reduction in production of IL-2 and IFN-gama and has in vitro inhibitory effect on proliferation of JurkatT cells (24, 54). It has been confirmed by these findings that minerval which is a synthetic analog of OA inhibits the proliferation of Jurkat cells (24, 55).

Animal studies have reported the inhibition of lymphocyte proliferation in response to T-cell mitogen. It has been shown that lymphocyte proliferation was inhibited in the spleen and the lymph nodes of rats fed on olive oil diet during the weeks inhibited (24, 56, 57). Similarly, it has been found that splenic lymphocyte proliferation was inhibited in rats fed with cashew kernel oil rich in OA compared to rats fed with coconut oil rich diet (24, 58). It has been shown that this effect is due to oleic acid more than the other components in olive oil (24,59). Another study showed that when the dietary levels of OA are increased, proliferation of spleen lymphocytes decrease (24, 60).

Inhibitory effects on NK (Natural Killer) cell proliferation of diet with olive oil have been caused by virtue of oleic acid (24, 61).

Jeffery et al. concluded that inhibitory effects on NK (Natural Killer) cell proliferation of olive oil diet has been arised from OA rather than other components of olive oil (24, 59). Human lymphocytes, jurkat (T lymphocytes) and raji (B lymphocytes) cells show morphological features of apoptosis after being exposed to OA (24, 61, 62). In addition to this Llado et al. have stated for the first time that minerval which is a synthetic OA analogue also induced apoptosis in jurkat T cells (24, 55).

Conclusion

Studies conducted revealed the fact that oleic acid which is present in large amounts in olive oil compositions, have positive effects on human health especially by reducing the systolic blood pressure on the cardiovascular system, inhibiting platelet aggregation, reducing TXA_2 secretion and decreasing serum LDL cholesterol, while some experimental studies reported the fact that some negative effects could also emerge due to increase in the ER stress depending on the dose. Further studies are needed to be carry out because of different results of oleic acid studies such as increased of tumorigenesis in some cancers, inhibited oncogene causing cancer in some cancer types; made anti-inflammatory effect on T cells by affecting the immune system by different ways, and didn't make any change in this activity and even led to decrease of high doses of phagocytosis function.

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Preliminary test of the radiopharmaceutical potential of PDI-Pyr radiolabeled with ^{131}I

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Abstract

Objective: Cancer is a fatal disease that arises as a result of unregulated growth and spread of malignant cells. According to the reports of World Health Organization (WHO), cancer related deaths are projected to increase in the future with the value of about 13.1 million deaths by the year 2030. In order to control this danger and growing burden, new technologies and therapeutic methods for improving the life quality of cancer patients are being developed. The overall aim of this work was to design of a new anti-cancer drug.

Methods: Radiolabeling and quality control studies of PDI-Pyr were carried out by using thin layer radiochromatography. Scintigrams were obtained using a gamma camera (Infinia, GE), which was adjusted to detect γ radiations of ^{131}I.

Results: Radiolabeling yield of ^{131}I-PDI-Pyr was obtained to be about 97%. Also, the highest uptakes of ^{131}I-PDI-Pyr were observed in the stomach, the liver, the lung and the bladder.

Conclusion: The novel PDI-Pyr compound was successfully radiolabeled with ^{131}I using iodogen method for the first time. The preliminary results obtained in this study have indicated that in the case of verification of selective accumulation in some stomach liver, lung and bladder cancer cells, perylene chromophore derivatives promise to be used as new anticancer agents.

Keywords: Radiolabelling, Thin Layer Radiochromatography, Scintigraphy, PDI Dyes

Introduction

Cancer remains the second leading cause of death all over the world [1]. Cancer chemotherapy is generally accompanied by side effects. If an anticancer drug could be delivered only to the right site in the right concentration at the right time, cancer could be cured without any side effects [2-3]. Thus, anticancer and antitumor properties of products have great importance.

Perylene diimide derivatives have been widely studied as G-quadruplex interactive compounds and telomerase inhibitors.[4-13]. G-quadruplexes are unusual DNA secondary structures based on planes of four guanines (G-tetrads) stabilized by Hoogsteen G-G pairings and monovalent cations. The central aromatic core of the perylene diimides is suitable for π-π stacking interactions with the terminal G-tetrad of DNA Gquadruplex, while the hydrophilic side chains interact with the DNA grooves. By means of these two kinds of interactions, these molecules are able to induce and stabilize G-quadruplex structures in G-rich singlestranded Oligonucleotides.

This is of great pharmaceutical interest, since the terminal ends of eukaryotic chromosomes (telomeres) are characterized by the presence of a single-stranded G-rich overhang that represents the substrate of a reverse transcriptase enzyme, the ribonucleoprotein telomerase, which is involved in the maintenance of telomere length. This enzyme is not active in most somatic cells but is active in most human tumors, and is, therefore, considered as being of high potential as a selective target for different anti-tumor strategies [4]. Several investigators have experimentally observed that if an ^{125}I radionuclide is incorporated into the nucleus of a cell, it results in a high radiotoxic effectiveness when its decay occurs [14-15]. The same authors have also demonstrated that this radiotoxicity of ^{125}I becomes more effective when ^{125}I decay occurs in the structure of DNA or very close to it. This extreme radiotoxicity is at least 10 times greater than that of other radionuclides such as ^{131}I, ^{14}C, or ^{3}H [16]. In the case of the combination of radiolabeled perylene diimide with the high radiotoxicity of an appropriate radionuclide such as ^{125}I, Auger and/or α-emitting radionuclides, it is expected that a very effective radiolabeled anti-cancer drug can be designed, which will have large potential applications in cancer therapy. In addition, in the case of labeling this drug with an appropriate radionuclide, this may similarly be used for early diagnosis of some kinds of tumors.

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One of the more novel and beneficial application of singlet oxygen in medicine is the cure of tumors. Today, photodynamic therapy (PDT) has become a potential candidate for the major utilization in the modern operation of cancer. Targeted photodynamic therapy is a new strategy that aims to direct the photosensitizers specifically towards the tumor tissues to enhance the efficiency and specificity of PDT [17].

Starting from this consideration, PDI-Pyr (N-(2,6-diisopropylphenyl)-N′-(3-carboxy-2-pyridyl)-1,7-bis{4-[(4-pyrene-1-ylbutanoyl)oxy]phenoxy}perylene-3,4,9,10-tetracarboxylicdiimide) which was considered as an anti-cancer drug was synthesized and subjected to radioiodination, and its biological activities in the metabolism of rats were examined for preliminary testing of the anti-cancer potential of PDI-Pyr (Fig. 1).

As a result, it is hoped that PDI-Pyr will be able to be used as an appropriate carrier for selective incorporation of radioactive iodine atoms into the nucleus of tumor cells, and in addition, the radiotoxicity, for example, of ^{125}I can be realized on the same agent, which will be used as an effective anti-cancer drug for cancer types. Thus, the overall aim of this work was to design of a new anti-cancer drug.

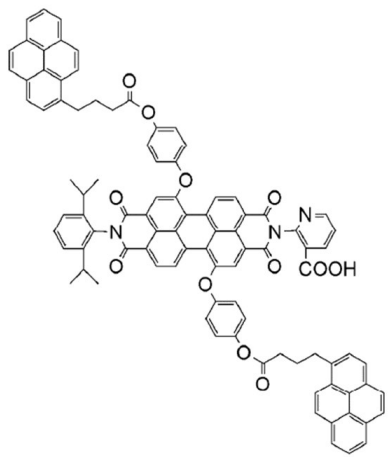


Figure 1. Chemical structure of PDI-Pyr

Material and Methods

Preparing the iodogen coated tubes

1 mg amount of iodogen was dissolved in CH_2CI_2 and transferred to closed tubes. CH_2CI_2 was evaporated by air flow and iodogen was deposited on the walls of glass tubes as a thin film. These tubes were stored at +4 °C until use.

Radioiodination procedure

PDI-Pyr was radioiodinated with ^{131}I using the iodogen method under the same conditions as earlier described by Avcıbaşı et al [18-21]. In order to label PDI-Pyr with ^{131}I, 100 µg of PDI-Pyr was added into the iodogen coated tube and then 1mCi (37 MBq) of $Na^{131}I$ was added. This reaction mixture was kept at room temperature without stirring for 15 min. At the end of this time, the mixture was transferred to another tube by a syringe, and then quality control was performed.

TLRC Studies

For TLRC studies, TLC Aluminum sheets (Merck, 20×20 cm code: 5552) were used, and citric acid monohydrate (100%, pH:6) was used as the mobile phase. The TLRC technique was used to determine the R_f values of the radioiodinated products. Each TLRC sheet was covered by an adhesive band after its development and was cut into 0.5 cm width. Those pieces of TLRC were then counted by using a Cd(Te) detector equipped with a RAD 501 single-channel analyzer. The R_f values were determined and given in Tables 1.

Scintigraphic Studies

The imaging studies were performed on healthy male Albino Wistar rats using a gamma camera (Infinia, GE, Tirat Hacermel, Israel) at Department of Nuclear Medicine of Celal Bayar University. ^{131}I- PDI-Pyr and $Na^{131}I$ were intravenously injected into male Albino Wistar rats via the tail vein after anesthetizing by the mixture of ksilazin and ketamin to determine the dynamic and static situations in the metabolism. Dynamic and static scintigrams were obtained using a gamma camera (Infinia, GE), which was adjusted to detect γ radiations of ^{131}I. Dynamic scintigrams were obtained over the first half hour with frames of 1 minute following the administration of the labelled compound. Static images were obtained from posterior projection after different time intervals up to about 2 hours following the administration of the ^{131}I-PDI-Pyr and $Na^{131}I$. Dynamic and static scintigrams of ^{131}I-PDI-Pyr and $Na^{131}I$ were given in Fig. 3,5 and Fig. 4,6 respectively.

Table 1. R_f values for radiolabeled compound and $Na^{131}I$.

Comounds	Rf
^{131}I-PDI-Pyr	0.88
$Na^{131}I$	0.81

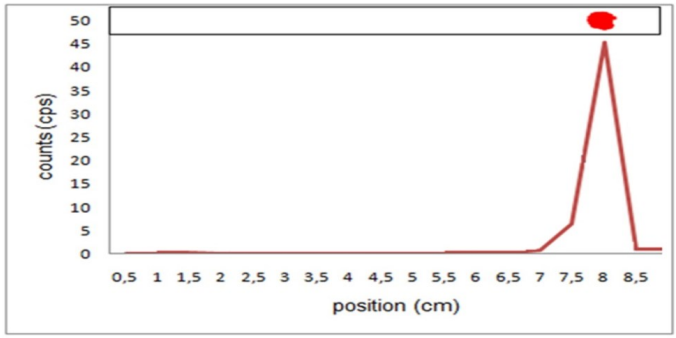


Figure 2. The radiochromatogram of ^{131}I-PDI-Pyr developed with citrate buffer (citric acid mono hydrate) 100% (10 mM) pH:6

Results

Results of TLRC Studies

The results of TLRC studies showed that citric acid mono hydrate, 100%, was the most suitable developing solvent to establish their R_f values given in Table 1. The best labeling yield was obtained at about 97% when the pH value was set to 6. Radiochromatograms of ^{131}I-PDI-Pyr was given in Fig. 2.

Results of Scintigraphy Studies

After administration of ^{131}I-PDI-Pyr and Na^{131}I to rats, static and dynamic scintigrams were obtained. Fig. 3 and 5 show the dynamic images of ^{131}I-PDI-Pyr and Na^{131}I, respectively. Fig. 4 and 6 show the static images corresponding to 30, 60 and 120 min after the administrations of these compounds. Table 1 and 2 also showed organ/background (BG) ratios of ^{131}I-PDI-Pyr and Na^{131}I.

As seen dynamic scintigrams of ^{131}I-PDI-Pyr, it was clearly observed that there were an important accumulation in the abdominal and the chest zone. ^{131}I-PDI-Pyr was significantly localized in the stomach within 30 min. Another result of dynamic images of related compound was the presence of high uptake in the heart, the lung and the liver. As seen dynamic scintigrams of Na^{131}I, it was clearly seen that metabolism of Na^{131}I was completely different from that of ^{131}I-PDI-Pyr. Na^{131}I was highly accumulated in the stomach and the bladder after the administration within 1-2 min. There was a high accumulation in the bladder in the 30 min.

In the static images of the ^{131}I-PDI-Pyr, activities mentioned above were seemed to be increased at 120 min. Accumulation in these zones could probably be caused by the increased specificities of the drug into the liver, the lung, the stomach and the bladder.

Similar results were obtained from a pyridine substituted PDI derivative which was radioiodinated with ^{131}I, and this product was accumulated in the stomach of a male Albino Wistar rats over about 30 minutes [22]. Organ/background (BG) ratios of ^{131}I-PDI-Pyr and Na^{131}I were given in Table 2 and 3, respectively. If the regions of interest values of radiolabeled ^{131}I-PDI-Pyr are evaluated with time, the highest uptake of radioiodinated PDI-Pyr is evidently seen in the stomach within 120 min.

Conclusion

^{131}I-PDI-Pyr which has diagnostic and therapeutic applications potential in nuclear medicine was synthesized and firstly radioiodinated in this study. Radiolabeling of PDI-Pyr with ^{131}I means that it can also be radioiodinated with other radioiodine isotopes such as ^{123}I, ^{124}I, ^{125}I under the similar conditions. The principal aim of this study was to progress the synthesis of an effective radioiodinated anticancer drug. The preliminary results obtained in this study have indicated that in the case of verification of selective accumulation in some cancer cells, perylene chromophore derivatives promise to be used as new anti-cancer agents.

At the next step of this study, the selective incorporation of ^{125}I- PDI-Pyr into some cancer cells should be examined using tumor bearing laboratory animals or cultured cancer cell lines.

Table 2. Organ/BG (background) ratios of ^{131}I-PDI-Pyr and Na^{131}I in 30, 60 and 120 min

Organs	^{131}I-PDI-Pyr			Na^{131}I		
	30 min.	60 min.	120 min.	30 min.	60 min.	120 min.
Head	2.80	2.40	2.03	4.78	2.61	2.59
Thyroid	2.42	2.30	2.90	3.43	4.05	4.63
Right Lung	2.75	2.65	3.20	2.85	3.06	3.19
Left Lung	2.69	2.50	3.20	2.93	2.83	3.08
Heart	3.64	4.00	4.00	3.65	3.40	3.52
Liver	4.39	3.90	4.00	3.14	3.60	3.73
Stomach	4.73	4.70	5.04	4.32	4.40	4.48

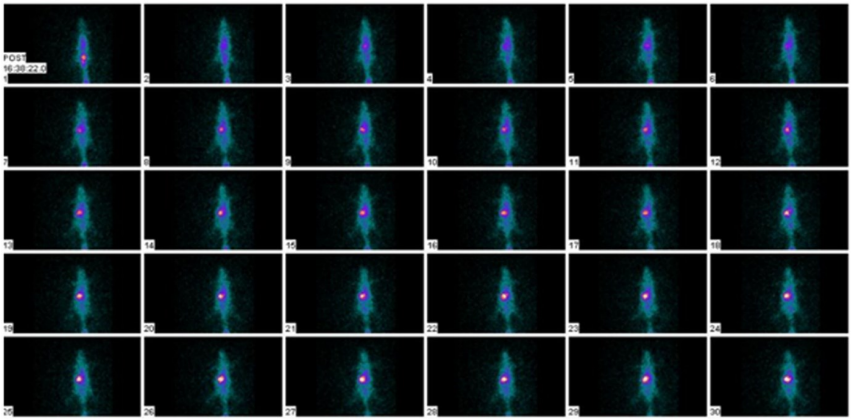


Figure 3. Dynamic scintigrams of ^{131}I-PDI-Pyr which was administered to a male Albino Wistar rats via the tail vein in 30 min. (The mixture of ksilazin and ketamin anesthesia was used in the scintigraphy studies. Dynamic scintigrams were obtained over the first half hour with frames of 1 min following the administration of the labeled compound)

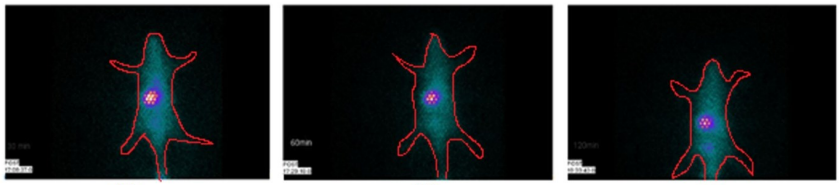


Figure 4. Static scintigrams of ^{131}I-PDI-Pyr which was administered to a male Albino Wistar rats via the tail vein in 30 min (a), 60 min (b), and 120 min (c)

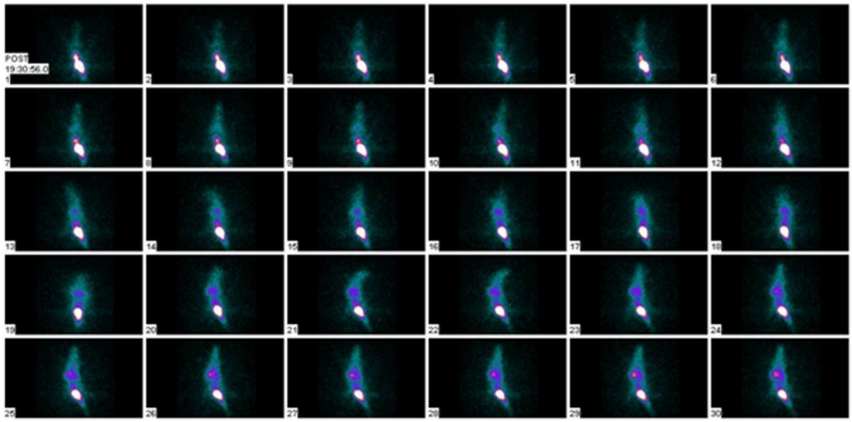
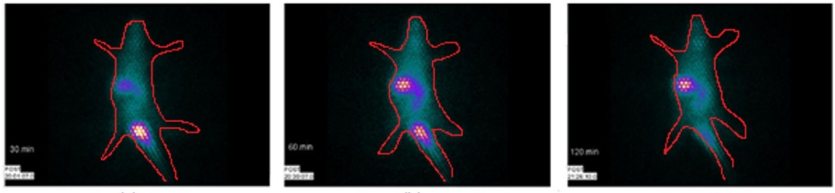


Figure 5. Dynamic scintigrams of $Na^{131}I$ which was administered to a male Albino Wistar rats via the tail vein in 30 min. (The mixture of ksilazin and ketamin anesthesia was used in the scintigraphy studies. Dynamic scintigrams were obtained over the first half hour with frames of 1 min following the administration of the labeled compound)



(a) (b) (c)

Figure 6. Static scintigrams of $Na^{131}I$ which was administered to a male Albino Wistar rats via the tail vein in 30 min (a), 60 min (b), and 120 min (c)

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Conflict of Interest: The authors declared that they had no conflicts of interest.

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Examination of preoperative and postoperative levels of rare earth elements (Zn, Cu, Mg, Pb, Mn, Cd, Co and Fe in the blood of ovarian cancer patients

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Abstract

Objective: In this study, serum material drawn preoperatively and postoperatively from totally 33 patients who applied to Department of Gynaecology of Yüzüncü Yıl University Faculty of Medicine and Van Training and Research Hospital due to suffering from ovarian cancer was used.

Material and Methods: The serum levels (Zn, Cu, Mg, Pb, Mn, Cd, Co and Fe) were determined by the method of Atomic Absorption Spectrophotometry at Spectrometer in Yüzüncü Yıl University Central Research Laboratory. The levels of rare-earth, trace and heavy elements were determined from the serum samples which were drawn from healthy and volunteer 30 women who were close to the same age group.

Results: This study found out a significant difference ($p<0.001$) between the preoperative and postoperative levels of lead, manganese and iron in ovarian cancer patients. While a significant difference ($p>0.005$) wasn't discovered between the preoperative and postoperative levels of zinc, copper, cadmium and cobalt in ovarian cancer patients, a statistically significant difference was found between the preoperative and postoperative levels of magnesium ($p=0.07$) in those patients.

Conclusion: Consequently, Zn is important in the prognosis of the disease because it is a strong antioxidant element. The elements Mg, Mn and Fe can be significant markers for ovarian cancer and especially low level of Mn may increase the risk of ovarian cancer. Also, such elements as Zn, Cu, Mg, Pb, Mn, Cd, Co and Fe may play an important role in pathogenesis of ovarian cancer.

Keywords: Ovarian Cancer, Blood, Serum, Rare-earth Element, Heavy metals

Introduction

According to World Health Organization (WHO), there are three reasons behind such an increase in cancer cases as follows: smoking, increasing elderly population and obesity. Considering the data obtained from their studies, WHO put forwards that cancer cases will be the first and the most important reason of death across the world after the year 2015 [1,2] According to the data of Ministry of Health, approximately 175,000 people are diagnosed with cancer every year in Turkey. There isn't a statistically significant difference among regions in terms of cancer incidence. The number of deaths arising from cancer is increasingly growing in Turkey. For the last decade, the death rate has increased by 80%. Basing on the research conducted by the Turkish Statistical Institute [3,4,5,6], the rate of cancer-related deaths reached to 21% in 2012 whereas that rate was 12% in 2002. The incidence of cancer-related deaths and cancer cases in Turkey increases by the rates similar and parallel to those seen across the world. Apart from those reasons, the fact that the previously-unknown cancer cases have been found out and cancer recording has been improved is another reason behind the increase in cancer statistics. Considering the data obtained by World Health Organization [1,2], the cancer incidence in Turkey is lower than those seen in the countries of America and Europe. Ovarian cancer is increasingly posing a hazard for people lately. Ovarian cancer is highly seen among elderly women and most of the studies deal with aetiology of ovarian cancer because the primary goal should be finding out the different reasons of ovarian cancer.

It is essential to take rare-earth elements at certain rates to enable human organism to maintain its normal functions. These elements join the various structural and functional activities of organism and get involved especially in different enzyme systems and hence they play important roles for occurrence of living phenomena and survival [7]. It has been discovered by the studies on different types of cancer within literature that the levels of Zn, Mn, Cu, Mg and Fe sometimes increase and decrease [8,9,10,11]. There are a

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considerably limited number of researches regarding rare-earth elements on ovarian cancer.

In this study, the preoperative and postoperative levels of rare-earth elements (Zn, Cu, Mg, Pb, Mn, Cd, Co, Fe) in blood in ovarian cancer patients were examined.

Materials and Methods

Materials

Totally 33 patients who applied to Yüzüncü Yıl University Dursun Odabaşı Medical Center Gynaecology Unit and Van Training and Research Hospital Gynaecology Unit and were diagnosed with ovarian cancer were determined preoperatively and postoperatively between June 2013 and February 2014. Before collecting the blood samples in this research, the approval of Clinic and Laboratory Researches Local Ethics Committee of Van Training and Research Hospital was obtained. A control group consisting of 30 healthy and volunteer people was used in order to compare the results gained from the patient group in the study.

In our research, 3 ml blood was drawn from brachial vein of 33 patients, who were diagnosed with ovarian cancer, before operation and after one month following the operation. The drawn blood was centrifuged in venous biochemistry tube at Nüve NF 800 centrifuge at 5000 rpm for ten minutes and its serum was extracted. The serum was kept at -80^0C until it was treated. When the adequate number of samples was obtained, the rare-earth elements in serum (Zn, Cu, Mg, Pb, Mn, Cd, Co and Fe) were determined by the method of Atomic Absorption Spectrophotometry at Spectrometer: M Series V1,23 in Yüzüncü Yıl University Central Research Laboratory.

Analysis Methods

Determining heavy metal, rare-earth elements and trace elements

Trace elements, mineral substances and metals (Zn, Cu, Mg, Pb, Mn, Cd, Co and Fe) were determined from serum samples by the method of Atomic Absorption Spectrophotometry.

Statistical Comments

Regarding the focused properties, the descriptive statistics were expressed as average, standard deviation, minimum and maximum value. In terms of these properties, one-way analysis of variance was performed in order to compare the group averages. Following the analysis of variance, Duncan Multiple Comparison - test was used to determine the different groups. For identifying the relation between these variables, Pearson correlation coefficients were calculated separately for each group. Statistical significance level was taken as 5% ($p<0.05$) in the calculations for which SPSS statistics package program was used.

Results

This study found out a significant difference ($p<0.001$) between the preoperative and postoperative levels of lead, manganese and iron in ovarian cancer patients. While a significant difference ($p>0.005$) wasn't discovered between the preoperative and postoperative levels of zinc, copper, cadmium and cobalt in ovarian cancer patients, a statistically significant difference was found between the preoperative and postoperative levels of magnesium ($p=0.07$) in those patients.

Discussion

Ovarian cancer ranks the fourth among the cancer-related deaths after breast, lung and colon cancer [12]. Ovarian cancer leads to more deaths than the total number of all gynaecological malignance in the United States. 204,000 women are diagnosed with ovarian cancer and 125,000 of these women die because of it across the world every year (WHO). Except several particular early symptoms, there isn't an efficient screening test for ovarian cancer. Consequently, ¾ of the patients are at advanced stage of cancer when they are diagnosed. In a research conducted on the patients undergoing chemotherapy in Finland, it was discovered that the patients taking selenium and vitamin E supplement respond to treatment better [13]. A study which compared the serum Cu/Zn levels in healthy and gynaecological tumour cases found out that the serum Cu/Zn levels help following up the course of disease [14]. There are several studies which put forwards that there is a relation between trace element level and progress of hepatocellular carcinoma. In those studies, the levels of serum, copper, iron and zinc were been found low in liver cancer patients [15].

A research conducted in China revealed that the activity of superoxide dismutase enzyme was low in the patients with hepatocellular carcinoma. The fact that Zn and Cu levels were found low in the same patient group was associated to low enzyme activity. In a study on colon cancer in the literature, Zn level was found higher compared to those of healthy people [10]. A research discovered that Zn level in lung cancer patients was significantly lower than those of healthy control group [8]. Likewise, a study revealed that Zn level in prostate cancer patients was significantly lower than those of healthy control group [11]. This study found out that Zn level in ovarian cancer patients was found higher in preoperative group compared to those of control and postoperative group; but there was no statistically significance ($p=0.160$).

Table 1. The findings regarding ovarian cancer patients, postoperative and healthy control group

Parameter	Control n=30 X±Sx	Preoperative Ovarian Cancer n=33 X±Sx	Postoperative Ovarian cancer n=33 X±Sx	p Value
Zn (mg/L)	0.863±0.277	0.875±0.307	0.745±0.288	0.160
Cu (mg/L)	1.200±0.299	1.185±0.363	1.085±0.343	0.322
Mg (mg/L)	28.435±2.952	29.866±4.976	25.760±6.537	0.007
Pb (mg/L)	0.157±0.113 [a]	0.206±0.118*	0.352±0.201 [b]	0.001
Mn (mg/L)	0.107±0.023 [a]	0.064±0.025*	0.093±0.023 [b]	0.001
Cd (mg/L)	0.030±0.249	0.069±0.115	0.060±0.043	0.095
Co (mg/L)	0.268±0.082	0.254±0.120	0.316±0.168	0.146
Fe (mg/L)	1.812±0.438 [a]	0.491±0.136*	1.050±0.571 [b]	0.001

1: difference between a and b is significant. ($p<0.05$)
2: difference between a and * is significant. ($p<0.05$)
3: difference between b and * is significant. ($p<0.05$)

Table 2. Correlation coefficients for control group

	Zn	Cu	Mg	Pb	Mn	Cd	Co	Fe
Zn	1							
Cu	0.195	1						
Mg	0.427*	0.439*	1					
Pb	0.076	0.279	0.341	1				
Mn	-0.080	-0.105	0.140	-0.109	1			
Cd	0.212	0.345	0.403*	0.778**	-0.202	1		
Co	0.052	0.139	0.181	0.616**	-0.232	0.585**	1	
Fe	-0.345	-0.248	0.004	-0.036	0.272	-0.242	-0.126	1

* $p<0.05$; ** $p<0.01$
Mg level: There is positive correlation with Zn and Cu.
Cd level: There is a positive correlation with Mg and Pb.
Co level: There is positive correlation with Pb and Cd.

Table 3. Preoperative correlation coefficients for patient group

	Zn	Cu	Mg	Pb	Mn	Cd	Co	Fe
Zn	1							
Cu	0.103	1						
Mg	0.549**	0.201	1					
Pb	0.239	0.120	0.270	1				
Mn	0.117	0.346*	0.429*	0.184	1			
Cd	0.028	-0.076	0.195	0.410*	0.210	1		
Co	0.246	-0.085	0.555**	0.335	0.539**	0.460**	1	
Fe	0.085	0.302	0.125	0.335	0.389*	-0.047	0.147	1

Mg level: There is positive correlation with Zn.
Mn level: There is positive correlation with Cu and Mg.
Cd level: There is positive correlation with Pb.
Co level: There is positive correlation with Mg, Mn and Cd.
Fe level: There is positive correlation with Mn.

Table 4. Correlation coefficients for postoperative group

	Zn	Cu	Mg	Pb	Mn	Cd	Co	Fe
Zn	1							
Cu	0.268	1						
Mg	0.491**	0.702**	1					
Pb	-0.218	0.244	0.439*	1				
Mn	0.072	0.297	0.398*	0.464**	1			
Cd	-0.104	0.207	0.421*	0.906**	0.482**	1		
Co	-0.179	0.240	0.505**	0.805**	0.442*	0.871**	1	
Fe	0.436*	-0.216	-0.177	-0.538**	-0.165	-0.514**	-0.551**	1

$p<0.05$; ** $p<0.01$
Mg level: There is positive correlation with Zn and Cu.
Pb level: There is positive correlation with Mg.
Mn level: There is positive correlation with Pb and Mg.
Cd level: There is positive correlation with Pb, Mg and Mn.
Co level: There is positive correlation with Mg, Pb, Mn and Cd.
Fe level: There is positive correlation with Zn and negative correlation with Pb, Cd and Co.

In a study, Cu level in colon cancer patients was found significantly higher compared to those of healthy control group [10]. A research on lung cancer discovered that Cu level was lower than those of healthy people [8]. This study revealed that Cu level in ovarian cancer patients was lower in preoperative group compared to control group and higher than those of postoperative group; but there was no statistically significance.

A research on colon cancer discovered that Mg level was higher than those of healthy people [10]. Mg level in lung cancer patients was found significantly lower than those of healthy control group in a study [8]. This study found out that Mg level in ovarian cancer patients was higher in the preoperative group than those of control and postoperative group and was statistically significant.

It was revealed by a study that Pb level in lung cancer patients was significantly higher than those of healthy control group [8]. Likewise, a research discovered that Pb level in kidney cancer patients was higher than those of healthy people [9]. It was presented by a study in Turkey that Pb level in renal cell carcinoma increased significantly compared to healthy people [16]. A literature on colon cancer found out that Pb level was higher than those of healthy people [10]. In this study, Pb level in ovarian cancer patients was found higher in the preoperative group compared to control group but lower than those of postoperative group and statistically significant.

Mn level was found higher than those of healthy people in a research regarding colon cancer [10]. A study discovered that Mn level in lung cancer patients was significantly higher than those of healthy control group [8]. Likewise, it was revealed by a research that Mn level in prostate cancer patients was significantly higher than those of healthy control group [11]. This study revealed that Mn level in ovarian cancer patients was lower in the preoperative group than those of control and postoperative group and statistically significant.

A study found out that Cd level in lung cancer patients was significantly higher compared to those of healthy control group [8]. It was discovered by a literature on kidney cancer patients that Cd level was higher than those of healthy people [9]. A study on colon cancer revealed that Cd level was higher than those of healthy people [10] It was presented by a study in Turkey that Cd level in renal cell carcinoma increased significantly compared to healthy people [16]. A study compared Cd levels of glioma cancer patients and healthy people and presented that CD level in glioma patients was significantly higher [17]. This study found out that Cd level in ovarian cancer patients was higher in the preoperative group compared to those of control and postoperative group and a result close to statistically significance was obtained.

Co level in lung cancer patients was found significantly higher than those of healthy control group in a research [8]. In this study, it was discovered that Co level in ovarian cancer patients was lower in the preoperative group compared to those of control and postoperative group and there was no statistically significance.

A study revealed that Fe level in lung cancer patients was significantly higher than those of healthy control group [8]. In a research, Fe level decreased in prostate cancers [11]. This study presented that Fe level in ovarian cancer patients was found lower in preoperative group compared to those of control and postoperative group and there was statistically significant difference.

This study discovered that Mg level in control group had a positive correlation with Zn and Cu values while Cd level had a positive correlation with Mg and Pb. Also it was revealed that Co level had positive correlation with Pb and Cd. In preoperative group, Mg level was found to have positive correlation with Zn. A positive correlation was seen between Mn level and Cu and Mg. Also Cd level had a positive correlation with Pb. While Co level had positive correlation with Mg, Mn and Cd, Fe level had positive correlation with Mn. In postoperative group, Mg level had positive correlation with Zn and Cu. Pb level had positive correlation with Mg; Mn level with Pb and Mg; Cd level with Mg, Pb and Mn; Co level with Mg, Pb, Mn and Cd and Fe level with Zn. Fe level had negative correlation with Pb, Cd and Co.

Conclusion

In conclusion, Zn is important in the prognosis of the disease because it is a strong antioxidant element. Zn level was found high in some studies in literature while it was low in some of them. In our study, Zn level in ovarian cancer patients was found higher in preoperative group compared to control and postoperative group; but a statistically significance wasn't obtained. However, it can be stated that this result is compatible with the literature studies [8,10,11]. Likewise, the variations in the levels of Mg, Mn and Fe can be important markers for diagnosis and follow-up of ovarian cancer. Low serum Mn level can be related to ovarian cancer risk. According to these conclusions, such elements as Zn, Cu, Mg, Pb, Mn, Cd, Co and Fe can play an important role in pathogenesis of ovarian cancer. Due to low number of patients and local service of the hospital in our study, we consider it beneficial to conduct studies on wider areas and more patients. We are of the opinion that this study will provide an insight for the further studies to be performed in this field.

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Documentation of the Salivary Gland Tumors: An institutional data from Turkey

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Abstract

Objective: World-wide series show some differences in the incidence and clinicopathologic features of salivary gland tumors.

Methods: A total of 248 cases of SGTs diagnosed in our hospital between 1998 and2013 were reviewed with respect to their clinicopathologic features.

Results: There were 128 male and 116 female patients with a mean age of 49.2. Of these 248 tumors 214 were benign and 34 were malignant. The mean age of the patients with benign tumors was 48.6 years and with malignancies was 55.3 years. The most common site was the parotid gland (83.5%) followed by submandibular and minor ones. Pleomorphic adenoma (50.4%) was the most common benign tumor and affected female patients more frequently. It is followed by Warthin's tumor that favored parotid gland. Adenoid cystic carcinoma was the most frequent malignant tumor followed by mucoepidemid carcinoma and carcinoma ex pleomorphic adenoma and the majorities were located in the submandibular gland.

Conclusion: In the present study, epidemiological data was compared with other worldwide series. Our retrospective study revealed that; benign tumors were more frequent, major salivary glands were more affected by both benign and malignant tumors than minor salivary glands and the parotid gland was the most affected site. Epidemiological data in the various parts of the world can be helpful for a better understanding of SGT's biology and characteristics.

Key words: Salivary gland, benign, malignant, tumors, epidemiology

Introduction

Salivary gland tumors (SGTs) consist of a group of heterogeneous lesions with complex clinicopathologic characteristics and distinct biological behavior that correspond to approximately 3% to 10% of the neoplasms of the head and neck region [1-5]. Epidemiological studies have shown geographical differences in the incidence and frequency of histological subtypes of SGTs [1]. In this retrospective study, hospital records of 244 patients with salivary gland tumors were documented with demographic features and histological diagnosis.

Material and Methods

Files of the Department of Pathology, from 1998 to 2014 were retrieved and 244 cases of salivary gland tumors were analyzed according to age, gender, location, size and histopathology of the tumor. In 4 cases bilateral tumors were present, hence 248 tumors were documented. Microscopic slides were reevaluated by 2 expert pathologists. All the tumors were classified according to the criteria suggested by 2005 WHO histological classification.

Results

Of 244 patients with salivary gland tumors, 128 were male (52.5%), and 116 were female (47.5%) and the mean age of the patients was 49.2 (min:5-max:86). The distributions of age, gender, tumor location, size, and histopathological diagnosis are summarized in table 1. Of these 248 tumors 197 (86.3%) were benign and 34 (%13.7) were malignant. The mean age of the patients with benign tumors was 48.6 years (min:5-max:86), and that of those with malignancies was 55.3 years (min:21-max:81). The average size of benign tumors was 2.90 cm (min:0.70 cm-max:7 cm), while that of the malignant tumors was 3.77 cm (min:0.8 cm-max:8 cm).

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Most of the salivary gland tumors (232/248, 93.5%) originated from major salivary glands. The rest (16/248, 6.5%) originated from minor glands. The most common site was the parotid gland (207 cases, 83.5%) followed by the submandibular (25 cases, 10.1%) and minor ones (16 cases, 6.4%).

Average size of PA cases were 2.83 (min:1 cm-max:7 cm), WT were 3.07 cm (min:0.70 cm-max:7 cm), ACC were 3.33 cm (min:0.8 cm-max:5.20 cm), MEC were 3.08 cm (min:1 cm-max:5 cm) and CaexPA cases were 3.41 cm (min:1.5 cm-max:6 cm).

Table 1. Subtypes of SGTs up to topography, gender and tumor size . (PG: parotid gland, SMG: Submandibular gland, MSG: Minor salivary gland, PA: Pleomorphic adenoma, WT: Warthin's tumor, MEC: Mucoepidermoid carcinoma, CaexPS: Carcinoma ex pleomorphic adenoma)

Tumors	PG n (%)	SMGn(%)	MSGn (%)	Gender n F/M (%)	Average tumor size (cm) (min-max)
PA	100(48.3)	16 (64)	9 (56.3)	82/43(70.7/32.6)	2.83 (1-7)
WT	75 (36.2)	2 (8.0)	0	11/66 (9.5/50)	3.07 (0.7-7)
Basal cell adenoma	5 (2.4)	0	1 (6.3)	3/3 (2.6/2.3)	1.86 (0.8-3)
Oncocytoma	2 (1)	1 (4)	0	1/2 (0.9/1.5)	3.3 (3-4)
Myoepithelioma	1 (0.5)	0	1 (6.3)	2/0 (1.7/-)	1.95 (1.4-2.5)
ACC	0	5 (20)	3 (18.8)	4/4 (3.4/3.0)	3.33 (0.8-5.2)
MEC	6 (2.9)	0	0	3/3 (2.6/2.3)	3.08 (1-5)
CaexPA	4 (1.9)	0	2 (12.5)	3/3 (2.6/2.3)	3.41 (1.5-6)
Adenocarcinoma, NOS	3 (1.4)	1 (4)	0	1/3 (0.9/2.3)	4.37 (3-7.5)
Asinic cell carcinoma	3 (1.4)	0	0	3/0 (2.6/-)	5.16 (3.5-8)
Squamous cell carcinoma	3 (1.4)	0	0	2/1 (1.7/0.8)	4.2 (2-6.5)
Malignant oncocytoma	2 (1)	0	0	0/2 (-/1.5)	4.5 (3-6)
Epithelial-myoepithelial carcinoma	1 (0.5)	0	0	0/1 (-/0.8)	-
Ductal carcinoma	1 (0.5)	0	0	0/1 (-/0.8)	4.5
Giant cell tumor	1 (0.5)	0	0	1/0 (0.9/-)	3.5

In the parotid gland there were 184 benign (88.9%) and 23 malignant (11.1%) tumors. In the submandibular gland 19 (76%) cases were benign and 6 (24%) were malignant. In the minor salivary glands 11 (68.8%) cases were benign and 5 (31.3%) were malignant.

Among the 248 salivary gland tumors 125 cases were pleomorphic adenoma (PA) (50.4%) and 77 cases were Warthin's tumor (WT) (31%). Among malignant tumors 8 cases were adenoid cystic carcinoma (ACC) (3.2%), 6 cases were mucoepidermoid carcinoma (MEC) (2.4%) and 6 cases were carcinoma ex pleomorphic adenoma (CaexPA) (2.4%).

The frequency of PA and WT among the benign tumors were 58.4% and 36% while the frequency of ACC, MEC and CaexPA were 23.5%, 17.6% and 17.6%. The frequency of PA, WT, ACC, MEC, CaexPA in female patients were 70.7%, 9.5%, 3.4%, 2.6%, 2.6% while in male patients 32.6%, 50%, 3%, 2.3%, 2.3%.

According to the location, 100 (80%) cases of PA were located in the parotid gland, 16 (12.8%) in the submandibular gland and 9 (7,2%) in the minor salivary glands. WT were also common in the parotid gland (75 cases, 97.4%) followed by the submandibular gland (2 cases, 2,6%). On the other hand, the majority of ACC were located in the submandibular gland (5 cases, %62.5) followed by the minor salivary glands (3 cases, 37.5%). All cases of MEC (6 cases) occured in the parotid gland. 4 cases (66.7%) of CaexPA were located in the parotid gland and 2 (33.3%) in the minor salivary glands.

Discussion

SGT are a group of heterogeneous lesions with complex clinicopathological characteristics. Reports from several parts of the world have shown differences in epidemiology and incidence [1-11]. According to the World Health Organization and some previous studies, SGTs affect female patients more than males [2, 3, 6]. In a study with 3461 cases, Long-Jiang et al. reported the male:female ratio of 1.11/1 [7]. A study from Nigeria reported predominance for men with a male:female ratio of 1.4/1 [12]. In the present study males (52.5%) were also more frequently affected than females (47.5%).

In the current study the mean age of patients was 49.2 and the mean age of patients with malignant neoplasia's was about 7 years higher than benign tumors (55.3/48.6). In the study of Fonseca et al. with 493 cases, the mean age of patients with benign tumors was 46.3 and malignant tumors was 54.0 [1]. Long-Jiang et al. reported that the peak incidence age of benign tumor was third and fourth decades and of the malignant tumor was fourth and the fifth [7]. In the present study average size of benign tumors was slightly smaller than malignant tumors (2.90 cm/3.77cm). The average size of PA was 2.83 cm, WT was 3.07 cm, ACC 3.33 cm, MEC was 3.08 cm and CaexPA was 3.41 cm. In the series of Vargas et al. the average tumor size of PA was 3.12 cm, WT was 4.15 cm, ACC was 4.10 cm, MEC 3.06 cm and CaexPA 3.30 cm [3].

The majority of salivary gland tumors in this study were located in the parotid gland (83.5%) followed by the submandibular gland (10.1%) and

the minor salivary glands (6.4%). In most of studies the parotid gland was the most frequent location (64-80%) nevertheless frequency of tumor locations vary in different series [1, 2, 7]. Some authors reported less involvement of the parotid gland in salivary gland tumors, showing only 36.6 % and 45.6% of the cases [12, 13].

In the present study 86.3% of the cases were benign and 13.7% were malignant, confirming the predominance of benign SGTs. In the literature it is reported that benign SGTs are more frequent than malignant tumors. In the study by Satko et al. with 1021 cases, benign SGT ratio was reported 74% and in another study by Tian et al. with 6982 cases that ratio was 68% [9]. All epidemiologic studies clearly show that PA is the most common benign salivary gland neoplasia. The frequency of PA among all salivary gland tumors published in the literature ranges from 40% to 72% [2]. In the series of 493 cases by Fonseca et al. the frequency of PA was 63. 6% and in the series of 124 cases by Vargas et al. the frequency of PA was 59% [1, 3]. Likewise in the series of 496 cases by Ito et al. PA was determined the most frequent tumor comprising 54.2% of all SGTs and 80.3% of the benign tumors [2]. In our study the frequency of PA was detected 50.4% with 125 tumors among all SGTS and 58.4% among benign tumors. Considering the gender of the patients PA was more frequent in females (82 females/43 males). On the contrary WT was more frequent in male (11females/66 males). A similar result was observed by Vargas et. al. According to their study PA was more frequent in females (55 females/29 males), WT was more frequent in males (10 males/3 females) [3].

In the present study, the most common malignant tumor was ACC and the majority of ACC were located in the submandibular gland followed by the minor salivary glands. This is in agreement with findings reported by some investigators [5, 12-15]. According to World Health Organization and some previous studies MEC is the most frequent malignant tumor and ACC is the second [1,3,4,6].

Conclusion

In the present study, epidemiological data was compared with other worldwide series. Our retrospective study revealed that; benign tumors were more frequent in the salivary glands, major salivary glands were more affected by both benign and malignant tumors than minor salivary glands and the parotid gland was the most affected site. Pleomorphic adenoma was the most common benign tumor and affected female patients more frequently. The second most common benign tumor was Warthin's tumor which affected male patients more than females. Adenoid cystic carcinoma was the most frequent malignant tumor followed by mucoepidemid carcinoma and carcinoma ex pleomorphic adenoma. World-wide series show some differences in the incidence and clinicopathologic features of salivary gland tumors. Epidemiological data in the various parts of the world can be helpful for a better understanding of its biology and characteristics.

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The contribution to studies of the effect of β-glucan on plasma viscosity in a rat sepsis model

Meltem Ercan[1], Semra Ozdemir[1]

Abstract

Objective: Sepsis is a complex pathophysiological process that involves both alterations in the microcirculation and changes in the biochemical and physiological characteristics of the blood constituents and hyperdynamic syndrome characterized by maldistribution of blood flow. Plasma viscosity is a major determinant of capillary blood flow through the microcirculation. β-glucan is accepted to be one of the most powerful immune response modifiers. The aim of this study was to investigate the possible protective effect of β-glucan on the levels of plasma viscosity and malondialdehyde (MDA), after rats was exposed to sepsis.

Methods: Sepsis was induced by cecal ligation and perforation (CLP) in 14 male Wistar albino rat. To evaluate this, rats were divided into four groups as sham operated, β-glucan treated sham operated, CLP and β-glucan treated CLP. Sixteen hours after operation, rats were decapitated and MDA, plasma viscosity levels were measured.

Results: Plasma viscosity represented, 1.30±0.12 mPa.s in CLP group and 1.35±0.09 mPa.s in CLP+β-glucan group. In the CLP group, MDA levels were found to be higher than in control group. When CLP group compared with CLP+β-glucan group, no significant statistical differences were observed in the levels of plasma viscosity and MDA.

Conclusion: Our results seem that the given dose of β-glucan was probably insufficient to prevent sepsis induced plasma viscosity.

Keywords: Sepsis, plasma viscosity, β-glucan, MDA, Rat

Introduction

Severe sepsis and septic shock are the most common causes of death in intensive care units (ICUs), with associated mortality rates of 30–50%. Sepsis is a heterogenous group of syndromes caused by a systemic inflammatory response and is associated with the development of progressive damage in multiple organs. Disturbances in microvascular flow appear to play a crucial role in the impairment of tissue oxygenation that can contribute to multiple organ failure and death. Rheological changes in patients with severe sepsis and septic shock include slowing of capillary blood flow as a result of decreased perfusion pressure and local arteriolar constriction , viscosity alterations , and disturbances of red (RBC) and white (WBC) blood cell rheology [1, 2, 3, 4]. Plasma viscosity is a major determinant of capillary blood flow through the microcirculation. Elevated plasma viscosity leads to an increase in blood viscosity, thereby decreasing blood flow in microcirculation. In this way, ‘’elevated plasma viscosity ‘’ may contribute to tissue damage by impairing microcirculatory flow [5].

Microvascular dysfunction is one of the key contributors to organ failure and death in sepsis; however the mechanisms linking sepsis with vascular dysfunction is not understood. Sepsis is associated with heightened oxidative stress [6]. Oxidative stress is described as impairment of balance between prooxidant and antioxidant systems. Under physiological conditions, there is equilibrium between oxidants and antioxidants. These oxidants and antioxidants that are produced by organism in order to avoid and protect from the toxic byproducts that are produced as a result aerobic mechanism [7].

Through the sepsis, overproduction of oxygen free radicals leads to weakening of natural scavenging mechanisms, causing implication in endothelial cell damage and multi organ failure [8]. The oxygen free radicals, which include malondialdehyde (MDA), hydrogen peroxide, and hydroxyl radicals, cause “oxidative stress.

Glucans are natural produced as a result of biological response modifiers that are composed of (1-3)-β-D-linked polymers of glucose. In animal studies glucans have been shown to be effective in

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preventing experimental peritonitis. Clinical studies suggest that intake of glucans in trauma surgical patients will increase the chance of survival via decreasing the frequencies of septic complications that will stimulate conversion of energy.

The mechanism(s) by which glucans alter the septic state is unknown [9]. Several mechanisms were proposed for the protective effect of β-glucan, one of them is related to antioxidant capacity of the molecule [10]. There are several studies in which the relationships between sepsis and rheological changes have been investigated [4, 11, 12]. However, the β-glucan's effect over plasma viscosity or its alterations have not been studied.

The aim of this study was to understand the effect of β-glucan application over the possible changes in plasma viscosity, in sepsis model created on rats by CLP method

Material and Methods

All experimental protocols were performed in accordance with the National Institutes of Health guidelines and the approval of the Istanbul University, Cerrahpasa Medical Faculty Animal Care and Use Ethics Committee.

Animals and experimental design

Male Wistar albino rats, weighing 200-250 g were kept in individual wire-bottom cages, in a room at a constant temperature (22±2^{o}C) with 12-h light and dark cycles, and fed standard rat chow. The rats were divided into the following four groups of seven rats each: sham operated control (C), sham operated+ β-glucan treated group (Glucan), cecal ligation and perforation (CLP) group, and cecal ligation and perforation+β-glucan treated (β-glucan+CLP) group. Sepsis was induced by CLP (cecal ligation and perforation) technique [13,14]. (Figure 1). General anesthesia was induced by injection of intraperitoneal ketamine hydrochloride (Ketalar, Parke-Davis, USA). All procedures were performed under sterile conditions. The antimesentric surface of the cecum was perforated with an 22 gauge needle at two locations 1 cm apart and the cecum was gently compressed until fecal matter was extruded and then returned to the abdominal cavity and the laparotomy was closed with 4.0 silk sutures. The sham procedure consisted of identification, exteriorization, and then replacement of the cecum within the peritoneal cavity. The incision in both cases was closed in two layers. At the end of the surgical procedure, the rats were allowed to recover from anesthesia with free access to rat chow and water. After operation, all rats were resuscitated with saline, 3 ml/100g body weight given subcutaneously. Postoperatively, the rats were then returned to their cages with free access to food and water. After the CLP or sham procedure was performed (2 h), animals were reviewed for clinical signs of the development of sepsis. All CLP animals were lethargic; showed lack of interest in their environment, food, and hygiene; displayed piloerection; and had crusty exudates around their eyes. In contrast, the sham animals were healthy, moving freely, and eating.

β-glucan treatment

The β-glucan (Mustafa Nevzat Company, Turkey) we used in this study is 1, 3-1, 6 β –D glucan in the microparticulate form which is prepared from Saccharomyces cerevisiae yeast. β-glucan was suspended in saline. β-glucan 50 mg/kg per oral (po) was given by intragastric gavage once a day for 10 days and 30 min before and also 6 h after the operation [14,15]. The rats were decapitated 16 h after the CLP procedure, bloods were taken and samples were stored at -70^{o}C.

Measurement of thiobarbituric acid reactive species (TBARS)

Thiobarbituric acid (TBA) test was applied for MDA level measurement that is the final product of lipid peroxidation. Measurements were done according to Uchiyama and Mihara method [16]. Absorbance's were read at 532 nm. 1, 1, 3, 3-Tetra-ethoxypropane was used as the standard. Results were calculated as nmol MDA/ml in plasma.

Measurement of plasma viscosity (PV)

Blood samples for plasma viscosity measurements were drawn into vacutainers with potassium EDTA as anticoagulant and were posed in two hours following collection in accordance with the committee of hemorheology standardization (1986). The viscosity of a liquid depends on its temperature, and for most fluids viscosity decreases as temperature increases. The viscosity of a liquid can be measured by a viscometer, which is a device built for studying stress strain relations. Capillary viscometers are the most widely used devices for measuring viscosity of Newtonian liquids. The working principle of a capillary viscometer is based on the measurement of flow rate of the liquid through a well-defined capillary tube under a certain pressure difference; at constant temperature and pressure difference; the flow rate decreases as viscosity increases. Plasma viscosity was measured from plasma isolated from each subject after the subject's blood was centrifuged for 10 min at 3.000 rpm and the plasma and buffy coat were separated. Plasma viscosity was measured by Harkness capillary viscometer (Coulter Electronics LTD Serial Number 6083, England) at 37^{o} C [17]. For the measurement of blood plasma, a specialized Harkness capillary viscometer has been recommended by Baskurt O.K. [18] which allows measurement of sizes as low as 0.5 ml within 1 min. The flow rate, measured in seconds (s), of each plasma sample (Tp) was compared with that of distilled water (Tw) to obtain

the relative plasma viscosity (coefficient of variation, 1.00 %). For quality control measurements were compared with daily water. Plasma viscosity measurements were carried out in triplicate. The plasma viscosity was expressed as in milliPascal × seconds (mPa.s) which is numerically equal to centipoise (cP);

$$P_v = \eta_w \frac{T_p(s)}{T_w(s)}$$

η_w = 0.693 mPa.s (Constant value for water viscosity at 37°C)

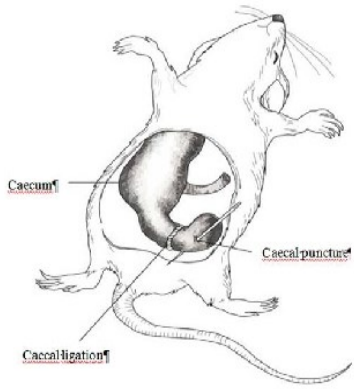

Figure 1. CLP (cecal ligation and perforation) technique

Statistical Analysis

All data are expressed as mean ± standard deviation (SD). Statistical analyses were performed with Statistical Products and Service Solution package (SPSS, for Windows, 10.0.1 version, Chicago, III., USA). Significance of the differences was tested by analysis of variance (one-way ANOVA), followed by Tukey's test to determine statistical differences between groups. Differences were considered statistically significant when the p value was < 0.05.

Results

The levels of plasma viscosity represented, 1.58 ± 0.17 mPa.s in control group, 1.53±0.15 mPa.s in β-glucan group, 1.30±0.12 mPa.s in CLP group and 1.35±0.09 mPa.s in CLP+β-glucan group. In the CLP group, the levels of plasma viscosity were found to be significantly lower than in control group ($p < 0.001$). In the CLP+β-glucan group, plasma viscosity ($p < 0.01$), were found to be significantly lower than those of controls. When CLP group compared with CLP+β-glucan group, no significant statistical differences were observed in the levels of the plasma viscosity ($p > 0.05$), (Table 1). In the CLP group, plasma MDA levels were found to be significantly higher than in control group ($p < 0.001$). In the CLP+β-glucan group, MDA levels of plasma ($p < 0.001$), were found to be significantly higher than those of controls. When CLP group compared with CLP+β-glucan group, no significant statistical differences were observed in MDA levels of the plasma ($p > 0.05$) (Table 1).

Discussion

Sepsis is associated with abnormalities in systemic and microcirculatory blood flow, decreased red blood cell (RBC) deformability and impaired oxygen delivery leading to tissue hypoperfusion and tissue dysfunction with subsequent cardiovascular changes [19]. Sepsis is characterized by a number of circulatory disorders, including decreased systemic vascular resistance, hypotension, impaired oxygen utilization, lactic acidosis, and maldistribution of blood flow in the microcirculation [6]. Alterations in microvascular blood flow and oxygenation have been demonstrated in various models of sepsis. In a normodynamic septic model using cecal ligation and puncture (CLP) in rats, reduced perfused capillary density and increased heterogeneity have been observed in striated muscles and intestinal mucosa [20].

The impairment leads to tissue hypoxia due to increased diffusion distance for oxygen. It has been proposed that hypoxia is the initial and important step towards organ failure. Maldistribution of blood flow within the capillary bed is one of the hallmarks of sepsis. This dysfunction is associated with oxygen transport impairment within tissues and may precipitate organ failure [21]. Because the microcirculation is essentially adaptive, it is important to understand whether the sepsis-associated alterations are the primary event leading to cellular dysfunction or the changes in perfusion reflect directly altered cellular metabolism (adaptive theory). In addition, oxygen saturation at the capillary end of well-perfused capillaries is low, suggesting that the tissues are using the delivered oxygen [22].

Distribution of blood flow through the many parallel, small vessels of the microcirculation is of vital importance for organ function. For a given vascular architecture, flow resistance is determined by the rheological behavior of the blood flowing through microvessels. The mechanisms by which this blood flow is regulated include myogenic factors (i.e., strain and stress forces, via blood and plasma viscosity), metabolic factors such as pH, pCO_2 and potassium, O_2, and nitric oxide (NO) and neurohormonal control [23].

Table 1. The levels of plasma MDA and viscosity in control, β-glucan, cecal ligation and perforation (CLP) and CLP+β-glucan groups

	Control (n=7)	β-Glucan (n=7)	CLP (n=7)	CLP+ β-Glucan (n=7)
MDA(nmol/ml)	3.45±0.31	3.27±0.34	7.30±0.54***	7.26±0.30***
PV(mPa.s)	1.58±0.17	1.53±0.15	1.30±0.12***	1.35±0.09**

PV: plasma viscosity, MDA: malondialdehyde
Results were calculated as nmol MDA/ml in plasma.
Values are expressed as Means ±SD. ** $p < 0.01$, *** $p < 0.001$ *versus* control group

Hemorheology is the study of deformation and flow of blood and blood cells. The prime function of blood is transport by flow, and the most important rheological property of blood is its resistance to flow, or viscosity. Since the viscosity of blood is a major determinant of normal blood flow throughout the circulation, any increase in viscosity will cause an impairment of the normal flow. Whole blood viscosity is affected by four parameters: hematocrit levels, erythrocyte aggregability, erythrocyte deformability and plasma viscosity[4].

Plasma is the suspending phase for the cellular elements in blood, and thus a change in its viscosity directly affects blood viscosity regardless of the hematocrit and the properties of the cellular elements. Plasma is a Newtonian fluid (i.e., viscosity independent of shear rate), yet technical artifacts have led some to report non-Newtonian behavior of plasma. If the value of plasma viscosity is normal, it is not a specific parameter that reflects the disease process. In physiological situations that are related to acute phase reactions and/or, value of plasma viscosity may differ due to a change of proteins in size and in number. Under these conditions plasma viscosity can be used as a parameter. Plasma proteins influence both whole blood viscosity and red cell aggregation. Plasma proteins exert their effects either directly or through their influence on red cell aggregation [24].

Changes in fibrinogen and immunoglobulins, under both physiologic and pathologic conditions can increase whole blood viscosity. Blood flow through the microvasculature is impaired when viscosity increases, leading to tissue ischemia. Abnormalities of fibrinogen greatly increase its ability to cause red cell aggregation, and are a contributory pathogenic factor in ischemic heart disease and stroke. Immunoglobulins may affect blood viscosity directly, or by increasing the red cell aggregation [4, 25].

Sepsis induces profound changes in the microcirculation with loss of capillary density, maldistribution of blood flow, increased flow heterogeneity, changes in microvascular reactivity, and WBC-endothelial cell adhesion and vascular leakage. [1, 11, 22, 26].

In our previous study in which showed that sepsis may occur with histopathological methods, we benefited from CLP method for creating a sepsis. Thereby it is shown that it is possibility of creating sepsis with CLP method was shown in histopathologically [27]. In this study, the values of plasma viscosity represented 1.58 ± 0.17 mPa.s in the control group. These results are consistent with Windberger U. et al. [28]. A statistically significance was seen in values of the plasma viscosity of control group and CLP group. As far as we could reach, there has been no study measuring plasma viscosity in experimental sepsis by inducing CLP technique.

During the course of severe sepsis, several biochemical abnormalities develop, causing a change in metabolic pathways of various organs that result in secondary damage. MDA is the breakdown product of the major chain reactions leading to oxidation of polyunsaturated fatty acids, and thus serves as a reliable marker of oxidative stress-mediated lipid peroxidation. An increased concentration of MDA reflects the level of lipid peroxidation in tissues and plasma [29].

Sepsis is associated with heightened oxidative stress. There is evidence that oxidative stress has an important role in the development of sepsis-induced multiorgan failure. Diminished antioxidative defences, superoxide dismutase, catalase and glutathione, also contribute to oxidative stress. Recent studies have reported increased levels of lipid peroxides and decreased antioxidant enzyme activity in experimental sepsis, indicating an exhaustion of the antioxidant system [30, 31, 32]. Bateman et al. [32] reported that there was no significant difference in TBARS levels of normal and CLP exposed animals.

Ritter et al. [33] showed that MDA and plasma superoxide dismutase levels are markers of early mortality in septic rats. Batra et al. [34] found that MDA levels were also increased in neonates with sepsis suggesting that the elevations of these antioxidant enzymes were not so effective as to prevent cellular damage Enhancement of antioxidant status in animal models of sepsis has demonstrated beneficial effect and administration of antioxidants to septic patients may be protective.

The beneficial effects on the immune system and the lack of toxic or adverse effect had focused the studies on β-glucan molecule. Some researchers have claimed that protective effect was due to the antioxidant capacity. Furthermore, it has been suggested that β-glucan binds to scavenger receptors Brown and Gordon and Lazarová et al. [35,36] observed protective effects of

carboxymethyl chitin-glucan (dose approximately 200 mg/kg body weight for 21 days) supplementation in term of the decreased level of DNA damage measured by comet assay in different primary rat cells damaged after isolation either with genotoxic carcinogens requiring metabolic activation or oxidative stress induced by visible light-excited methylene blue. Lazarová et al. [37] also, showed immunopotentiating activity of β-D-glucans, efficiently inhibiting the genotoxicity of carcinogens requiring metabolic activation. Sener et al. [10] showed that treatment with β-glucan significantly reversed the elevations in MDA levels in the liver, kidney, heart, lung, diaphragm and brain tissues. However, the relationship between the plasma viscosity and plasma MDA levels effects of β-glucan administration in sepsis has not been defined.

We examined the effects of β-glucan therapy on the plasma viscosity and MDA levels in experimental sepsis. The results of the present study demonstrate that sepsis causes a decrease in the levels of plasma viscosity and an increase in the levels of plasma MDA._In our previous study, we observed that kidney and liver tissues of control and β-glucan groups show similarity in histological changes. β-glucan treatment was not effective in correcting histological changes seen in the subjects of the sepsis group [27].

Our results indicated that β-glucan administration did not return the levels of plasma viscosity and MDA to the control group level. It seems likely that the given dose of β-glucan was insufficient to prevent sepsis induced the level of plasma viscosity and MDA. In order to determine the effect of β-glucan, the study should be carried out with different doses and lengths.

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Lead analysis of air pollution in Istanbul utilizing by the vehicle cabin air filters

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Abstract

Objective: Lead that are common in nature and widely consumed through industry and transportation are leading metals that cause toxicity in humans and other living organisms. The cabin air filters are made out of paper with many layers having the ability to capture particles with nearly one micron size or higher. Aim of this study is to search the trace element pollution in the air, in different regions by analyzing lead concentration in cabin filters of 10 different vehicle marks, obtained from various auto services in the city of Istanbul-Turkey.

Methods: All collected filters were initially resolved in the HCl and HNO_3 mixture. Lead levels that had been adsorbed in filters were measured by Atomic Absorption Spectrophotometer (AAS). Results of the study were further analyzed by region where the sample air filters were originally collected.

Results: According to our findings, it has been observed that lead levels in 5th region are maximum compared to the other regions of Istanbul-Turkey.

Conclusion: This fact concludes that the used vehicle cabin air filters are one of the best sources to get information about air quality and pollution levels. The results of this research exemplifies and concludes that utilizing replaced cabin filters is an efficient and effective method to measure heavy metals pollution in big cities such as Istanbul, Turkey.

Keywords: Heavy Metals, cabin air filters, Lead (Pb), air pollution Istanbul-Turkey

Introduction

Nearly 70 metals including lead, aluminium, chromium, tin, cadmium, titanium and strontium, called as heavy metals because of their high densities, are taken into body through air, water and food. Lead (Pb) and cadmium (Cd) that are common in nature and widely consumed through industry and transportation are leading metals that cause in toxicity in humans and other living organisms. Pb exposure is by means of respiratory and digestive systems and skin. Pb is mostly cumulated in bone tissue, liver and kidneys. It is a toxic element that gets through blood-brain barrier [1, 2, 3]. Pb is found in solid (dust and usually PbO_2 particles) and gas (Alkyl Pb, released from exhaust gases) phases in atmosphere [4]. Dust that is formed during industrial grinding and leaded fuels are the most important resources of Pb in air. It's very small particular structure enables it to reach alveolar surface without being attached to barriers in nasal and respiratory tracts. Nearly 90% of Pb in atmosphere is emitted by lungs, and more than 90% of emitted Pb is collected in erythrocytes. By time, since alveolar surfaces are as much permeable to toxic materials as it is to oxygen; this causes a risk of toxication. It is stated that there is linear relation between Pb concentration in air and Pb concentration in blood [5]. Goodman and Gilman [6] studied that consumption of 2.5 mg Pb per day will in 4 years, and 3.5 mg Pb per day will in months result in Pb toxication. Usually when Pb concentration in air is about 0,001 mg/m^3, Pb level in blood will increase to 0,01-0,02 µg/ml [7]. Pb, even in a very small amount is absorbed from gastrointestinal system and transmitted to tissues by blood. Inorganic Pb compounds are absorbed from adult gastrointestinal system by 10% or less. There are a lot of factors effecting Pb absorption in gastrointestinal system, such as existence of calcium, phosphorus, iron, zinc and copper; age and the physical condition of the person [8]. On the other hand, it is reported that deficiency of iron, zinc and calcium redoubles Pb absorption in gastrointestinal system [9; 10]. Matousek and Brodie [11] have analyzed the Pb amount that is absorbed both from the respiratory tract and the gastrointestinal system, and they observed that lead taken through respiratory system is 5 times more than the amount absorbed from the gastrointestinal system. Pb is also stored in soft tissues and its half-life is approximately 2 months.

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Brain is an exception; Pb gets through blood-brain barrier slowly, and its biological half-life is more than one year. Besides, it results in astrocyte accumulation and affects the glutamate balance [10, 12]. Some of the lead is disposed by the gastrointestinal system via faeces but main excretion is from the urinary system (76%). Also it is excreted from the organism by hair, nails and perspiration in small amounts [7].

According to World Health Organization (WHO)'s classification, Pb is a 2nd class carcinogenic [13]. Contagion through soil and dust carries an important role in toxication, too. Because tetraethyl and tetra methyl compounds of Pb are used as fuel additives, they have importance in air and environmental pollution. Pb compounds that are formed with the burning down of fuel are diffused in atmosphere, turning into oxide, chloride, sulphate and phosphate compounds of Pb [11, 14, 15]. It is stated that Pb pollution in air varies depending on the number of motor vehicles in different countries. In our country, allowed Pb amount in fuel was 0.80 g/l in 1988, decreased to 0.21 g/l in 1998 and 0.13 g/l in 2009; and was decided to be Pb -free in 2012 [16]. Though Pb concentration in air has a downward trend since Pb free fuel consumption is improving, still Pb pollution is a serious environmental risk factor for especially children and pregnant women [1, 17]. Determination of Pb amount in blood and tissue is the most valid method in Pb toxicity analysis [12, 18]. Decrease in blood Pb concentration (B-Pb) is observed with the start of Pb free fuel consumption [9, 15, 19].

Number of vehicles per person in our country is increasing rapidly especially in big cities like Istanbul, Ankara, Izmir, Adana etc. It is reported that there are 200 vehicles per 1000 people in Istanbul-Turkiye. In USA, this rate is 700 vehicles/1000 people and 600 vehicles/1000 people in West Europe. Accretion in emission of air pollutants such as carbon monoxide, particles, hydrocarbon and nitrogen resulting from increase in fuel consumption and traffic density is observed connected in parallel with the number of vehicles [20]. Vehicles that are not being examined, repaired and controlled for their exhausts periodically, cause more air pollution; especially high amount of sulphur in diesel fuels corrodes the engine, cast of more pollutants from the exhaust and increase of sulphate particles in atmosphere. It is reported that pollutants from vehicles result in health and environmental problems as well as global warming. It is known that the air we breathe is being polluted by the increasing number of vehicles and the use of fossil fuels. Pb that has a part in this pollution is important hazards for human health and different clinical symptoms occur in living organisms that are exposed to these elements [21].

Vehicle cabin air filters are filters that work as regulators of air conditioning systems in our cars. These changeable filters are made of many layers of papers are able to capture particles of nearly one micron size. Since filter materials and their media are very dense, they may create serious resistance in air flow. As the air flow resistance increases, the performance of the filter starts decreasing. . It is stated that paper fibres in vehicle cabin air filters are produced with pores that are big enough to let air ventilation and small enough to capture the dust particles that are not welcome in order to enable effective filtration.. Vehicle cabin air filters have an important design restriction. Moisture and vapour will result in filter element to swell and dilate thus large dust particles will settle in pores, blocking air ventilation. It is again confirmed that blockage of filters increase in dusty places, too. Paper used in the production of vehicle cabin air filters is generally named non-woven; and is produced as a homogenous mixture of materials such as resin, fibre and polyester either woven straight or across. This paper is used in production of vehicle cabin air filters and each different type has specific characteristics such as air permeability, number of pores, tear point, resistance etc. These characteristics play the main role in the lifetime of vehicle cabin filters. The most important thing is the quality of the materials used in the filter. The role of vehicle cabin filters is to filter dust, soot, bacteria and pollens as well as to hinder the entrance of trace elements with the air that gets in [22, 23, 24, 25, 26].

There are two different cabin air filters. One of them is standard the other is active carbon air filter. Active carbon air filters have active carbon layer that absorb particles in gas form like ozone, benzol and toluel and thus disabling these harmful elements to reach inside the cabin. It is observed that the particles adsorbed by active carbon cabin filters are in micron (µ) size (Figure 1) [23, 25].

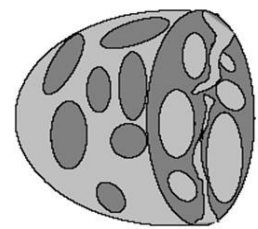

Figure 1. Schematic representation of the pore structure of active carbon particles [27]

Activated carbon is one of the best tools which can be used to reduce risks to human health. Activated carbon adsorption proceeds through 3 basic steps;

Substances

1. Adsorb to the exterior of the carbon granules
2. Move into the carbon pores
3. Adsorb to the interior walls of the carbon

The most important difference of active carbon cabin filter from the standard filter is that it can adsorb the unwanted scent without letting the poisonous gases (ozone, benzol and toluel) leak inside the cabin. Paper characteristics of the active carbon cabin filter is; one layer with the same features with the standard filter paper that has double filter effect and the other layer absorbing coal dust (Figure 2) [20, 28].

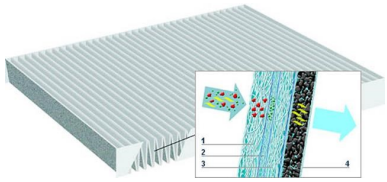

Figure 2: Schematic illustration of active carbon cabin filter [20]

The reason that activated carbon is such an effective adsorbent material is due to its large number of cavernous pores. These provide a large surface area relative to the size of the actual carbon particle and its visible exterior surface. An approximate ratio is 1 gram = 100 m^2 of surface area [22, 24].

Material and Methods

Materials

In our study, vehicle cabin air filters of various standard vehicle marks that had been obtained from different car services from several regions of Istanbul had been used. Air pollution was analyzed in 7 different regions by the help of cabin air filters taken from different car services (Figure 3).

Regions Specifications

It is reported that Istanbul takes the first place in all cities of Turkey according to the licensed vehicles traffic density with 34% among other cities according to the data dated in November, 2010 (Table 1) [30]. In European part of Istanbul-Turkiye, other regions considered as blind spots because of their heavy traffic are as follows in decreasing order: Avcılar (6^{th} region), Bagcılar (5^{th} region), Bahcelievler, Bakırkoy (4^{th} region), Besiktas (7^{th} region), Eyup (1^{st} region), Gaziosmanpasa (2^{nd} region), Gungoren (5^{th} region) and Zeytinburnu (4^{th} region) (Figure 3) [26].

Experimental Design

Vehicle cabin air filters of cars at 12.000-15.000 km had been collected from different regions of Istanbul-Turkiye with the allowance of car owners. All filters' weights had been measured on sensitive scales.

Figure 3. Location of seven different regions in Istanbul-Turkey in map scale (795x701 pixel)
Region 1: Eyup- Alibeykoy
Region 2: Bayrampasa-Gaziosmanpasa
Region 3: Zeytinburnu-Eminonu-Yenikapi
Region 4: Bacelievler-Bakirkoy-Atakoy
Region 5: Bagcilar- Gungoren-Mahmutbey
Region 6: Sefakoy- Avcilar- Kucukcekmece- Esenyurt
Region 7: Besiktas- Mecidiyekoy

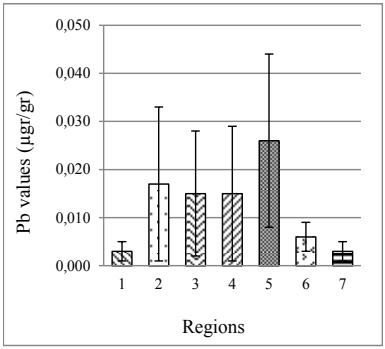

Figure 4. Average values of lead concentrations in cabin air filters of seven regions. Mean±SD, n=8

Materials that had been prepared were grouped in five. Solutions of 3HCL (Rhiedel) + 1HNO_3 (Merck) (gold bath-aquaregia) mixtures of 100 ml were prepared in 200 ml measures, and they were added to filters providing full submerge of filters in solutions. Vehicle cabin air filters were left to dissolve in room temperature, shivering and engaging to solutions with polypropylene bonds in shape of small thread balls. In order to maintain enough diffusion, all experimental filters were left in room temperature for 48 hours; and then different sized particles formed from adsorption of filters dissolving in beakers, were transferred to experimental tubes with lids. After filtration, used and control group cabin air filters were eliminated from the dust particles that have dissolved in solutions by centrifugation [27, 28, 29, 30].

Determination of Lead

Since Atomic Absorption Spectrophotometer (AAS - Shimadzu-AA680) measurement system is a rapid measurement tool for the analysis of air originated particle materials.

Thus samples were completed to 5 ml total volumes with automated pipettes; and the lead levels in dust particles that are adsorbed in cabin filters were measured in AAS device located in I.U. Cerrahpasa Medical Faculty, Biophysics Department [31, 32].

Statistical Methods

Statistical comparison and evaluation to determine the trace element levels belonging to different cabin air filters from 7 specific regions of İstanbul, SPSS (version 17.0) package program have been used. Results were declared as average and standard deviation (M±SD). Data were tested at significance levels of $p < 0.05$ using Mann-Whitney U Test.

Results

Vehicle cabin air filters of several vehicle marks that had been collected from different car services in Istanbul's various regions were separated according to seven different regions and their Pb values were measured. Pb measurements were compared; averages and standard deviations are shown in Table 2.

When the values of Pb in cabin air filter solutions in all regions were compared, Pb values of Region 1 versus Region 5 (0.003 ± 0.002 µgr/gr; 0.026 ± 0.018 µgr/gr) showed a statistical significance ($p<0.001$). Region 5 (0.003 ± 0.002 µgr/gr) versus Region 6 (0.006 ± 0.003 µgr/gr), Pb values also showed a statistical significance ($p<0.001$). The Pb values of Region 5 were measured higher than the other Regions. The values of Pb in cabin air filter solutions, Pb were significantly higher in Region 7 (0.014 ± 0.010 µgr/gr) than Region 1 and Region 6 (0.003 ± 0.002 µgr/gr; 0.006 ± 0.003 µgr/gr) ($p<0.05$, $p<0.01$). Significance was also demonstrated between Region 7 (0.014 ± 0.010 µgr/gr) and Region 5 (0.026 ± 0.018 µgr/gr) at Pb values ($p<0.05$). Furthermore, there was not a difference among Regions 1, 2, 3, 4 in cabin air filter solutions Pb values (Figure 4).

Table 1. The regional effects of population, traffic and industry on trace elements in air pollution

Regions	Population	Traffic	Industry
Region 1	increasing	heavy traffic in weekdays	decreasing
Region 2	crowded	heavy traffic in all days	spare parts, metalwork, moulding, electric-electronics parts production, plastic foundry, cold iron embroidery, machining, hardware production,textile
Region 3	varies during the day	heavy traffic in all days	Leather and weaving industry
Region 4	crowded	heavy traffic in all days	Textile and weaving industry
Region 5	irregular increasing	heavy traffic in all days	Automotive, textile, industrial electronics and metal products industries and factories; as well as all turnery, automat and welding, rubber production (rubber, shoes, steelwork etc)
Region 6	crowded	heavy traffic in all days	Construction sector
Region 7	crowded	heavy traffic in all days	Shopping malls, company head offices, banks, plazas, international hotels and some pharmaceutical companies

Table 2. Values of Lead (Pb) concentrations in cabin air filters of seven regions

Regions (n:8)	Pb values (µgr/gr)
Region 1	0.003 ± 0.002
Region 2	0.017 ± 0.016
Region 3	0.015 ± 0.013
Region 4	0.015 ± 0.014
Region 5	0.026 ± 0.018 ^{a***}
Region 6	0.006 ± 0.003 ^{e***}
Region 7	0.003 ± 0.002 $^{e*, f**}$

Data are Show as the mean ± SD, **a** Statistical comparison Region 1, **b** Statistical comparison Region 2, **c** Statistical comparison Region 3, **d** Statistical comparison Region 4, **e** Statistical comparison Region 6, **g** Statistical comparison Region 7 with other Regions* p<0,05, **p<0,01, ^{b***}p<0,001.

Discussion

Every year, approximately 3 million people die because of air pollution. This rate is 5% of all deaths (nearly 55 million) in the world in one year. 90% of deaths resulting from air pollution is observed in developing countries. As a consequence of unwanted effects of air pollution to health; it is observed that there is an increase in lung cancer, chronic asthma chrisis, asthma, frequency in cough/sputum, acute disorder of upper respiratory system, eye/nose/throath damage and health costs; and decrease in business efficiency and production. Particles in air are composed of solid and liquid drops. Some particles are thrown away from chimneys. Some are formed in atmosphere**.** Particles that are smaller than 10 µm are important and they may be transferred to kilometres away with the wind effect. Small particles as (PM_{10} and $PM_{2.5}$) reach to lungs with the respiratory tract and they cause serious health problems. PM_{10} has 5 times and $PM_{2.5}$ has 20 times smaller diameter than human hair and they may only be detected by electron microscope [33].

The main aim of vehicle cabin air filters is to block the entrance of pollens and dust inside the cabin in order to increase the quality of air that is being breathed by driver and passengers. It was observed that the first cabin filters produced were nearly incapable of capturing the particles entering inside the cabin. With different type and structures of filter production, decrease in irritation (eye/nose/throat damage) and in symptoms of allergy to pollens and dust, originating from exposure to heavy metals in air has been observed in drivers and passengers [23]. In the study of Rudell et al [34], it is reported that number and concentration of particles with the size of 0.4 µm or smaller entering inside the cabin varies with the usage of different structured filters. Kalman et al. [35] demonstrated that in order to increase the quality of air inside the cabin, active carbon cabin filters are being used as new technology. Active carbons with developed pores are the most important of adsorbents that are used as industrial adsorbents at the time, to avoid environmental pollution [25]. In our study, active carbon filters belonging to 10 different cars were used. Our aim in this study was to determine trace element pollution in air, by measuring lead concentration in 7 different regions of Istanbul.

The highest levels of Pb measured were in 5th and 2nd regions (Figure 4). Pb levels in these 2 regions being meaningfully high leads to think that lead release to air might be the maximum because of these two regions being industrial zones. Another reason effecting lead level in 5th region might be the increase in construction sector. We confirmed that lead concentration in 7th region is higher than the 6th region. This might be because the traffic density was higher, and the main highway to the Bosphorus Bridge is in 7th region.

WHO (1996) declared that Pb concentration that effects air pollution in big cities worldwide is 0.002-0.004 mg/m^3. It is also known that air pollution varies with the countries' number of vehicles. Kismet et all [16] analyzed in their study that with the start of unleaded fuel, Pb concentration in air has decreased. Considering Pb levels found in our study (Figure 4), the maximum values found in filters were from the 5th region (0.026 ± 0.018 µgr/gr) and the 2nd region (0.017±0.016 µgr/gr). These areas being industrial and having heavy traffic supported the results' accuracy. On the other hand, Sezgin et al. [36] have found out that Pb levels measured in dust samples taken from 22 different points in E-5 highway-routes of regions 4 and 6 in our study- were 9-11 times higher than the normal Pb level in soil. Sezgin et al. [36] demonstrated Pb levels in dust coming from these areas as 211.88 mg/kg (dry soil normal lead level is 20 mg/kg). In our country, it is reported that air pollution in big cities are 40% traffic originating and this problem keeps going on especially in Istanbul-Turkiye. Lead, zinc, copper and iron levels are especially high in areas with huge traffic density and this is being supported by the study, too [37].

Overall, data presented in this study suggest that using vehicle cabin air filters to determine the trace element pollution in air is a very effective and suitable method. According to our findings; most pollution was reported in the fifth region. Bagcilar - Gungoren- Mahmutbey having not only automotive, textiles, electronics and other metal industries but also non-stop traffic through the day contribution to the pollution. In drivers and passengers of regions that have high lead concentrations in air, increase in symptoms of toxication effect (irregularities in respiratory system, eye/nose/throat irritation, crisis of asthma) may be expected.

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Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Tumor mimicking bladder endometriosis

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Abstract
Endometriosis is described as the presence of endometrial tissue outside the uterine corpus. Though urinary tract endometriosis is uncommon, the bladder is the most common localization amongst them. Here we present three cases admitted to our hospital with similar complaints such as dysuria and abdominal pain. All of the patients had previous cesarean section history. And radiological examination of the bladder revealed solid masses located on the bladder wall. One of the cases additionally had a protruding, polipoid luminal mass. Two of the cases were treated with transurethral resection and one with partial cystectomy. We noted similar histological findings such as endometrial stroma and glands within the smooth muscle fibers. The stromal components were positive with CD10, epithelial components were positive with both estrogen and progesterone receptor immunohistochemically. As a result bladder endometriosis should be kept in mind in the differential diagnosis of mass forming urinary tract lesions.

Key Words: Endometriosis, Urinary System, Bladder, Treatment

Introduction

Endometriosis is the most common gynecologic disorder amongst women [1]. It is defined as the presence of endometrial tissue (glands and/or stroma) outside the uterine corpus [2]. Approximately 1% of women with pelvic endometriosis have urinary tract endometriosis (UTE) [3]. In urinary tract, the disease is mostly seen in bladder (80-84), ureter (15%), kidney (4%), urethra (2%) [4]. Here we present three urinary bladder endometriosis cases in terms of clinical, radiological and morphological features.

Case-1: 41-years old woman was admitted to our hospital with weight loss, grumble, dysuria and hematuria. She had a previous cesarean section history. Abdominal ultrasonography (USG) revealed 3.6 x 2.4 cm mass at the posterior wall of the urinary bladder. On computed tomography (CT) 8 x 5 cm sized, solid hyperdense mass was noticed at the superior midline of the bladder. The mass had lobulated, well-circumscribed contours and homogenous texture with no distinct peripheral invasion (Figure 1A). Hemorrhagic curetted material (3 cc) was obtained by transurethral resection of bladder (TURB).

Case-2: 43-years old woman was admitted to our hospital with long-term dysuria and abdominal pain. She also had cesarean section history. Pelvic magnetic resonance imaging (MRI) revealed a protruding mass (3,5 cm) at the left side of the posterior wall. The lobular solid mass had same intensity with myometrium (Figure 1B). Hemorrhagic curetted material (6 cc) was obtained by TUR-B.

Case-3: 31-years old woman with three months old new pregnancy complained of dysuria and pelvic pain. She also had previous cesarean section in history. Pelvic USG of the case revealed 3.8 x 3.3 x 2.5 cm sized hyperchogenic lobular solid mass with irregular borders. The case following in obstetric clinic was consulted to urology clinic. On MRI, 3.5 cm sized solid mass was observed at the superior wall of the bladder. TUR-B was planned after delivery. During cesarean section urologist consulted the case again and decided partial cystectomy. The operation specimen was 4.5 x 4 x 3.5 cm sized nodular mass. One side of the lesion was papillary and the other side was solid. The cut surface was gray-white and partially hemorrhagic.
All three cases had similar histological findings with endometrial stroma and glandular structures within the smooth muscle fibers. Case 3 showed decidualization in the endometrial stroma due to the pregnancy (Figure 2A, Figure 2B). The stromal components were positive with CD10, epithelial components were positive with both estrogen and progesterone receptor immunohistochemically (Figure 2C, Figure 2D).

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Figure 1: (A) Solid hyperdens mass with minimally lobulated contours and homogenous texture in the midline superior of the bladder on CT. (B) The mass protruding into the lumen in the left side posterior of the bladder on pelvic MRI.

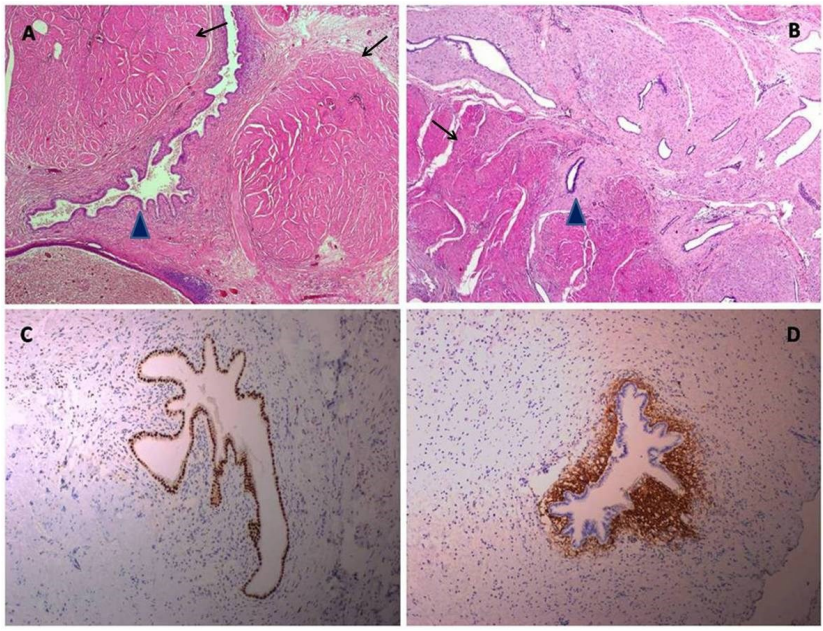

Figure 2: (A) Endometrial stroma and gland structures amongst the smooth muscle fibers (HEX40). (B) Desidualization of the endometrial stroma and gland structures amongst the smooth muscle fibers in the pregnant case (HEX40). (C) Epithelial components positive with progesterone receptor DAPX100, (D) Stromal components positive with CD10 immunohistochemically (DABX100). (Δ: endometrial stroma and gland structures, →**:** smooth muscle fibers)

Discussion

Pelvic endometriosis is mostly detected in ovary (54%), broad ligament (35%), Douglas sac (35%) and uterosacral ligament (8%) respectively [2]. Approximately 1% of the women with pelvic endometriosis presents with UTE [2]. Endometriosis is most common in 2-5th decades but postmenopausal women who had exogenous estrogen therapy can be affected [5].

In English literature, more than 300 reports have been published about urinary bladder endometriosis. The most common involvement sites are urinary bladder (80-84%), ureter (15%), kidney (4%), urethra (2%) respectively [4].

Endometriosis is a chronic, multifactorial systemic disease [6]. Etiopathogenesis is not known exactly. There are many different theories in the etiopathogenesis of urinary tract endometriosis. The most widely accepted theory is implantation of endometrial tissue after menstrual reflux. The discussion point is that although nearly all women have retrograd menstruation, the prevalence of urinary tract endometriosis is rare. So additional factors such as genetic, environmental, endocrinological, immunological might also play a role in the pathogenesis [6].

Embryogenic theory suggests that endometriosis develops from the metaplasia of Wolfian, Mullerian and peritoneal structures. Immunological theory suggests that there is an incomplete immunological response to prevent ectopic implantation of endometrial tissue [7].

Cesarean section is a risk factor for endometrioma at the operation site. Andolf et al found a relationship between C/S and pelvic endometriosis [8]. But the relation between C/S and endometriosis should be analyzed with different comprehensive studies. All of our cases also had previous C/S in history.

Patients with UTE have no specific clinical symptoms. Nearly half of the cases are asymptomatic [9]. Urgency, suprapubic pain and hematuria are the most common complaints [5]. Our cases had dysuria, abdominal pain, hematuria, weight loss and grumble.

Urinary tract endometriosis may be detected with palpation or by endoscopic examination [5]. It may be seen within the wall of urinary bladder, deeply or superficially and perivesical soft tissue. So the diagnosis can be missed by TURB.

Clinical and laparoscopic findings are not always diagnostic because of nonspecific endoscopic findings [3]. Imaging techniques can be useful to determine diagnosis. The initial radiologic technique should be USG which aids distinction of solid and cystic components. But endometriosis may have many different radiologic findings and none of them is specific. The most specific technique seems MRI, since the depth and the size of the lesion can be determined clearly [2].

The disease is locally aggressive with low recurrence risk. Definitive treatment is surgery and hormonotherapy [10]. Two of our cases were treated with TUR-B and one case was treated with partial cystectomy. As the symptoms restored, the cases were started to follow up yearly with urine cytology. The control cystoscopy of the patient treated with partial cystectomy was normal. Patient 2 was out of follow up during five years but the bladder mucosa was observed normally at a recent cytoscopic examination. All of the cases are still following with routine urine cytology without any symptoms.

The bladder is an uncommon localization for endometriosis. It may mimic bladder tumors both clinically and radiologically. Endometriosis should be kept in mind in the differential diagnosis of tumoral lesions of the urinary tract in women.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Transient ischemic attack after *Mesobuthus gibbosus* envenomation

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Abstract
Mesobuthus gibbosus is a medically important venomous scorpion in western of Turkey which causes significant morbidity. Envenoming of this species scorpion results with varying degrees of local symptoms and clinically important systemic effects. This case describes an authenticated first case of transient ischemic attack in a 68 year-old-woman following envenoming by *M. gibbosus* in Turkey.

Keywords: Scorpion, Envenomation, Emergency department

Introduction

Scorpion envenomation and their consequences represent an important cause of emergency in certain regions of the world [1]. *Mesobuthus gibbosus* (also called Anatolian yellow scorpion or Mediterranean scorpion) is a member of the Buthidae family which is one of the most widely distributed and important scorpion in western of Turkey (eg Manisa, Aydın, Izmir)[2]. Scorpion envenomation can cause life – threatening complications such as respiratory, neurologic, and cardiovascular compromise [3]. We report here the first case of transient ischemic attack (TIA) following *M. gibbosus* envenoming.

Case

A 68-year-old woman with a past medical history of peptic ulcer disease was stung by a large yellow scorpion on her first finger of the right foot. She was admitted to our emergency department (ED) an hour later due to severe sharp pain, paresthesia and burning at the sting site. The scorpion was killed and brought to the ED and later identified as *M. gibbosus*. On initial examination, the patient was conscious and well oriented, and her vital signs were as follows: a blood pressure of 148/68 mmHg, a pulse rate of 84 beats per minute, a respiratory rate of 16 breaths per minute, a body temperature of 36.4°C, and an oxygen saturation of 98% on room air. There was a red spot on her first digit of the right foot. Otherwise, her physical examination was unremarkable. An initial laboratory values were within the normal limits. During the ED course, the patient received intravenously 50 µg fentanyl for pain relief and admitted to observation unit for any complication.

Approximately over 5 hours after envenomation, her blood pressure was progressively elevated (max level of 218/115 mmHg) despite the 50 mg captopril orally administration (prazosin was not administered, because it is not available in our hospital) and the patient developed new-onset and progressive neurologic deterioration.

In neurological examination, she had moderate dysarthria, left-sided hemiparesis with muscle power of 3/5 in upper and lower extremities. The deep tendon reflexes were brisk and a left Babinski sign could be easily elicited. An urgent non-contrast computed tomography scan of the brain detected no acute hemorrhage, mass effect, or sign of acute ischemic lesion.

A single vial (dissolved in 100 mL of crystalloid) polyvalent scorpion antivenom (Refik Saydam Hygiene Center, Ankara, Turkey) was administered intravenously over approximately 30 minutes. Subsequent diffusion-weighted magnetic resonance imaging revealed no diffusion restriction with normal apparent diffusion coefficient values.

Following the antivenom administration, her neurologic symptoms resolved completely within 2 hours. After treatment with antivenom, bedside transthoracic echocardiography revealed mild mitral regurgitation, severe pulmonary hypertension and normal left ventricular wall motion with an ejection fraction of 60%. Color Doppler of the carotid arteries examination showed a 20% right-sided internal carotid artery stenosis. She was discharged from the ED after 2 days in good clinical condition and without any neurologic sequelae.

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Discussion

Venom of *M. gibbosus* generally consists of several toxins and other compounds. The most important components of the venom are neurotoxins that primarily target voltage-gated ion channels. The NaScTx toxins bind to the resting state of Na^+ -channels and inhibit fast inactivation, and they induce a reduction of the peak sodium current amplitude and shift the voltage dependence of Na^+ -channel activation towards a more hyperpolarized membrane potential. The MegKTx toxins, recently described K^+ -channel specific toxins of *M. gibbosus*, bind with high affinity to the K^+ -channels and block the potassium permeability. Combine effect of this neurotoxins causes stabilization of voltage-gated ion channels in the open position, leading to continuous, prolonged, repetitive firing of the somatic, sympathetic, and parasympathetic neurons. As a consequence, neurotoxins result in release of excessive neurotransmitters such as epinephrine, norepinephrine, acetylcholine, glutamate, and aspartate at synapses and the neuromuscular junction [4].

Neurological complications after scorpion envenomations typically include cranial nerve dysfunctions (eg, ptosis, nystagmus, blurred vision, tongue fasciculations, slurred speech, and hypersalivation), somatic skeletal neuromuscular dysfunction (eg, restlessness, fasciculations), ischaemic or haemorrhagic strokes, and acute hypertensive encephalopathy. On the other hand, TIA is a rare complication after scorpion envenomation [2]. To the best of our knowledge, this is the first report of TIA due to *M. gibbosus* envenomation.

The exact pathogenesis of TIA due to *M. gibbosus* envenomation is not fully understood, but some possible mechanisms have been postulated. First of all, scorpion toxins and other venom components induce inflammation because of neutrophil infiltration occurs in different tissue, causing vasculitis, arteritis, fibrin deposition, and intravascular thrombosis [5]. Although serum catecholamine levels were not measured in our case, second possible mechanism of TIA combined with significant hypertension and tachycardia was postulated from the catecholamine-induced vasospasm that may play a role in arterial occlusion [4]. Moreover, it is also possible that, in our patient pre-existing carotid artery stenosis might act as a predisposing factor in the mechanism of *M. gibbosus* venom induced thrombotic occlusion.

In conclusion, all patients with scorpion envenomation should be closely monitored in anticipation of possible neurological complications due to direct toxic effects of the venom, vasospasm, and hypertension especially in patient with known carotid artery disease. In this case, antivenom holds a pivotal place in treating severe envenomation.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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