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Thymoquinone exhibits anti-inflammatory, antioxidant, and immunomodulatory effects on allergic airway inflammation

Timokinon allerjik solunum yolu inflamasyonu üzerine anti-inflamatuar, antioksidan ve immünomodülatör etkiler gösterir

Ali Parlar [1], Seyfullah Oktay Arslan [2]

Abstract

Aim: Asthma is an allergic disease causing mucus secretion, release various pro-inflammatory mediators such as tumor necrosis factor- α (TNF-α) and interleukins. The aim of this study was to evaluate the effect of thymoquinone (TQ) on allergic airway inflammation in rats.

Methods: Allergic airway inflammation induced by ovalbumin (OVA) challenge in sensitized-rats and effect of TQ were studied. Inflammatory cells, interleukin (IL)-6 and TNF-α in bronchoalveolar lavage (BAL) fluid, and lipid peroxidation (LPO) in lung tissue were measured. Microvascular leakage was detected by Evans blue dye leakage in airway tissues.

Results: Tidal volume was significantly lower in OVA group (1.4± 0.07 ml) than control group (1.9±0.04 ml) (p = 0.002), while breathing frequency was significantly higher in OVA group (135.3±12.9 min-1) than control group (p=0.017). In terms of tidal volume, statistical significance between TQ30 and OVA groups was found (1.8±0.07 ml) (p=0.008), while in terms of breathing frequency, no significance was found between both of them (126.7±7.3). Total white blood cell count was significantly higher in OVA group (1,376.8±136.4 x103/ml) than control group (545.0±106.7 x103/ml) (p<0.001). Statistical significance was found in TQ10 (824.7±4.5 x103/ml) group when compared OVA group (p=0.036), while statistical significance was not found in TQ1 group (1,282.2±137.7 x103/ml). When compared OVA group (60.3±4.9 pg/ml) with control group in terms of the TNF-α level, statistical significance was found (36.7± 4.7 pg/ml) (p=0.011). The Evans blue dye level was significantly higher in OVA group (31.8±3.6 ng/mg of tissue) than control (12.5±1.1 ng/mg of tissue) group (p<0.001), and TQ10 group (16.3±6.7 ng/mg of tissue) (p=0.002), and TQ30 (13.5±1.0 ng/mg of tissue) group (p<0.001).

Conclusion: These findings reveal that TQ could be beneficial in asthma pathophysiology due to its immunomodulatory, anti-inflammatory, and antioxidant effects.

Keywords: allergic airway inflammation, TNF-α, microvascular leakage, ovalbumin, thymoquinone.

Öz

Amaç: Astım, mukus sekresyonuna neden olan, TNF-α, IL'ler gibi çeşitli proinflamatuar mediatörleri salgılayan alerjik bir hastalıktır. Timokinon'un (TQ) sıçanlarda alerjik solunum yolu inflamasyonu üzerindeki etkisini değerlendirmektir.

Yöntemler: Duyarlılaştırılmış sıçanlarda ovalbumin (OVA) ile indüklen alerjik solunum yolu enflamasyonu ve TQ etkisi çalışıldı. Bronkoalveoler lavaj (BAL) sıvısında enflamatuar hücre sayıları, interlökin (IL)-6 ve tümör nekroz faktör alfa (TNF-α) düzeyleri ve akciğer dokusunda lipit peroksidasyonu (LPO) seviyeleri ölçüldü. Mikrovasküler sızıntı, solunum yolu dokusunda Evans mavisi ile tespit edildi.

Bulgular: Bu çalışmada, OVA grubunda tidal hacim (1,4±0,07 ml), kontrol grubuna göre önemli ölçüde düşük bulunmuştur (1,9±0,04 ml) (p = 0,002). OVA grubunda (135,3±12,9 dk-1) solunum sıklığı kontrol grubuna (p=0,017) göre anlamlı bulunmuştur. Tidal hacim açısından TQ30 (1,8±0,07 ml) grubu ile OVA grubu karşılaştırıldığında istatistiksel anlamlılık bulunurken (p=0,008), solunum frekansı açısından gruplar arasında istatistiksel anlamlılık bulunamamıştır (126,7±7,3 dk-1). OVA grubunda (1.376,8±136,4 x103/ml) toplam beyaz küre sayısı, kontrol grubuna göre anlamlıydı (545,0±106,7 x103/ml) (p<0,001). TQ10 (824,7±4,5 x103/ml) grubu ile OVA grubu arasında istatistiksel anlamlılık bulunurken (p=0,036), TQ1 (1.282,2±137,7 x103/ml) ile OVA grubu arasında istatistiksel anlamlılık yoktu. TNF-α yönünden OVA grubu (60,3±4,9 pg/ml) ile kontrol grubu (36,7±4,7 pg/ml) karşılaştırıldığında, aralarında istatistiksel anlamlılık bulundu (p=0,011). OVA grubunda Evans mavi düzeyi (31,8±3,6 ng/mg doku), kontrol (12,5±1,1 ng/mg doku) (p<0,001), TQ10 (16,3±6,7 ng/mg doku) (p=0,002) ve TQ30 (13,5±1,0 ng/mg doku) (p<0,001) gruplarına göre önemli derecede yüksekti.

Sonuç: Bu bulgular, timokinonun immünomodülatör, antienflamatuar ve antioksidan etkileri nedeniyle astım patofizyolojisinde yararlı olabileceğini ortaya koymaktadır.

Anahtar kelimeler: alerjik solunum yolu enflamasyonu, TNF-α, mikrovasküler sızıntı, ovalbumin, timokinon.

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Introduction

Allergic airway inflammation, asthma, is still a common problem in clinic, for especially children health. Inflammatory cells, mast cells, macrophages, eosinophils, lymphocytes, basophiles, neutrophils, and platelets, are recruited to allergic airway tissues. These are capable of synthesizing and releasing pro-inflammatory mediators, mainly interleukin (IL) and tumor necrosis factor alpha (TNF-α) that produce many effects in the airways, including bronchospasm, plasma extravasations, mucus secretion, neural effects, and activation of inflammatory cells [1]. Studies from the past decade have confirmed that eosinophilic infiltration causes mild asthma, but infiltration of neutrophils and increased interleukins occur in severe asthma [2, 3].

Thymoquinone (TQ, C10H12O2) is the main bioactive component of the volatile oil of the black seed (Nigella sativa, Ranunculaceae family). Nigella sativa is known for its medical use as an antispasmodic, anti-inflammatory and anti-oxidant especially against gastrointestinal disorders, respiratory ailments, and antineoplastic medicines [4–6]. There is evidence of relaxant effects of volatile oil from this plant on isolated tracheal muscles of guinea pigs [4]. El-Tahir et al. [6] reported that the volatile oil from Nigella sativa protected guinea pigs against histamine-induced bronchospasm. Recent research papers have shown that the potential immunomodulatory and immunotherapeutic potential of TQ is linked to its antioxidant, antihistaminic and anti-inflammatory properties [7, 8]. TQ improves both oxygenation and compliance in human gastric acid induced acute lung injury, in rat, by bronchodilation and preventing heavy inflammatory response [9]. Houghton et al. [10] reported that TQ have an anti-inflammatory action through inhibition of eicosanoid generation and membrane LPO. TQ attenuates acetic acid induced colitis as evidenced by its ability to inhibit the release of the mediators, platelet activating factor (PAF) and histamine, also the prevention of glutathione (GSH) depletion and LPO points to antioxidant property [7], and attenuates ethanol induced gastric damage via inhibition of LPO and reversed GSH depletion in rats [11]. Moreover, newer paper indicates that intraperitoneal injection of TQ before the ovalbumin (OVA) challenge attenuated airway inflammation as demonstrated by the significant decrease in levels of leukotriene (LT)-B4 and LTC4, Th2 cytokines, lung eosinophilia, and goblet cell hyperplasia, all of which are characteristics of airway inflammation. This attenuation of airway inflammation was concomitant to the inhibition of cyclooxygenase (COX)-2 protein expression and prostaglandin (PG)-D2 production [12]. TQ also showed a significant effect in inhibiting IL-4, IL-5 and IL-13 in the bronchoalveolar lavage (BAL) fluid, it did show a slight effect on in vitro production of IL-4 by cultured lung cells stimulated with OVA antigen [13].

OVA sensitization and aerosol challenge elicits inflammatory cell infiltration, reactive oxygen species production, antioxidant enzymes, LPO, cytokines release into BAL fluid or lung tissue, microvascular plasma leakage in airway tissues, and respiratory abnormalities, in rats or other experimental animals [1, 14–19]. Therefore, in the present study we used an animal model of allergic airway inflammation, as asthma like reaction, to elucidate the mechanisms of possible therapeutic effect of TQ.

Material and methods

Chemicals

In this study, the following drugs and chemicals were used: Ovalbumin (grade V), thiobarbituric acid (TBA), trichloroacetic acid (TCA) thymoquinone and formamide (Sigma, St. Lous, M.O., USA); Evans blue dye (Fluka Chemie GmbH, Buchs, Switzerland); thiopental sodium (Pentothal sodium, Abbott Lab. Ltd. Sti, Turkiye); aluminum hydroxide. Ovalbumin was dissolved in 0.9% sodium chloride. TQ was dissolved in 10% ethanol in 0.9% saline.

Animals and Treatments

After ethics committee approved for the animals ((DÜ-HADYEK) 2011/006), male Wistar rats weighing 180-200 g were obtained from the Experimental Animal Unite of Duzce University and housed at 22±1 °C under 12:12 h light-dark cycle. Animals were allowed free access to standard laboratory chow and water. All procedures complied with the standards for the care and use of animals as stated in Guide for the Care and Use of Laboratory Animals.

Groups were subdivided as series A for inflammatory cells infiltration, cytokines, LPO, lung function tests and series B for microvascular leakage detection (n=7, for each subgroup).

1. Unsensitized control group (Control): Rats were injected with only saline (1 ml, ip.) and treated with an aerosol of saline.

2. Sensitized and challenged group (OVA): Rats were sensitized and challenged with OVA. Vehicle group as subgroup was TQ's vehicle (10% ethanol in 0.9% saline)

3. TQ administrated group (TQ): Sensitized rats were treated with TQ, three times as 30 min, one and two days before the OVA provocation. The three doses of TQ, as 1, 10, and 30 mg/kg, were treated for the studies of inflammatory cell counts, the analysis of lipid peroxidation (LPO), and IL-6 and TNF-α levels. Median effective inhibition dose of TQ (10 mg/kg, intraperitoneal) on inflammatory cells infiltration to BAL fluid was chosen for the other studies, microvascular leakages.

Sensitization and antigen challenge and evaluation of respiratory activity

Rats were sensitized and challenged with ovalbumin antigen [20]. Rats were sensitized on days 0, 14, and 21 with ovalbumin (at 100 µg administered with aluminum hydroxide adjuvant at 100 mg, by intraperitoneal). Aluminum hydroxide is used as an adjuvant with ovalbumin to boost the immune response to produce more antibodies and longer-lasting immunity [21]. The sensitized rats were used for microvascular leakage studies or OVA challenge studies on days 28-30. Assessment of pulmonary function test by a noninvasive method was used to determine the severity of lung failure. Therefore, at days 28-30 to challenge with OVA and to record the respiratory abnormality, the animals, one by one, were placed in whole body respiratory chamber [22]. After stabilization of the breath pattern (within 30 sec), rats were challenged with an aerosol of ovalbumin (1% in distillated water) with an ultrasonic nebulizer device for 20 minute. The rats were withdrawn from OVA antigen exposure at the first sign of respiratory abnormality. The changes in the respiratory activity of the animals were recorded for 5 min after the aerosol administration, with whole body plethysmograph (Emka, Paris, France). Before experiments, animals were handled and familiarized with the apparatus to reduce stress (Figure 1).

BAL fluid collection and cell counting and analysis

To evaluate airway inflammation, all inflammatory cells in the BAL fluid were counted and classified. Hence, BAL was performed in deep sodiun thiopental (70 mg/kg, ip.) anesthetized rats. For this purpose, a total volume of 30 ml (3 times, 10 ml) of PBS was injected into the lungs by the tracheal route. The BAL fluid was collected and centrifuged (170 g, 10 min); the cellular pellet was re-suspended in 1 ml PBS. Aliquots of cells suspensions (90 µl) were stained with 10 µl of 0.2% crystal violet to quantify total cells. Differential cell counting

(neutrophils, eosinophils, and mononuclear cells) were carried out using standard morphological criteria after cytospin processing and staining with Rosenfeld's dye.

IL-6 and TNF-α assay in BAL fluid

IL-6 and TNF-α levels in BAL fluids were measured by ELISA method according to the manufacturer's kits using guideline for users (Abcam, ab100772, ab100785, respectively). The lower limits of detection of IL-6 and TNF-α were measured as 8 pg/ml and 4 pg/ml, respectively.

Lipid peroxidation determination in lung tissue

After performing BAL fluid, lung lobes were excised, thawed and homogenized in isotonic saline with a polytron. The products of LPO, as MDA concentrations, according to the method of Ohkawa et al. [23]. Briefly the tissue samples were homogenized in an ice bath, ice-cold TCA by adding 10 ml of 10% TCA per g of tissue, with an ultrasonic tissue homogenizer. After two consecutive centrifugations at 3,000 g for 15 min, 500 µl supernatant was mixed with equal volume of 0.67% TBA and heated to 100°C for 15 min. The absorbance of the samples was then measured by using spectrophotometry at 535 nm. Each assay was performed in duplicate.

Microvascular leakage

Microvascular leakage was measured as described by previous study [24]. Briefly, sensitized rats were anaesthetized with Na thiopental (50 mg/kg) and given Evans blue dye (25 mg/kg as 25 mg/ml in saline, intravenously). Two minute later, they were given ovalbumin (2 mg/kg, intravenous) or saline. Cervical jugular vein was used for intravenous injections. Animals were killed by Na thiopental overdose (100 mg/kg, intraperitoneal), 15 minutes after allergen administration.

The chest was opened and an incision made in the left ventricle, then a cannula was inserted through the left ventricle and into the ascending aorta and, approximately 150 ml of sterile saline (0.9 %) was perfused at a pressure of 100 mmHg. The heart and lungs were removed en bloc. The pulmonary airways were each placed in 2 ml of formamide for 18 h at 40 °C to facilitate the extraction of Evans blue dye. The absorbencies of the resulting extracts were determined against standard concentrations of Evans blue at a 620 nm wavelength. The measurements were duplicated. The results are expressed as concentration of Evans blue dye (ng/mg of wet tissue).

The experimental protocol for the effect of TQ was put on ovalbumin-induced microvascular leakage in the airways and plasma leakage was assessed as described above. Sensitized rats were received TQ (10 mg/kg, intraperitoneal) 20 min before ovalbumin injected. The animals were killed 15 min after ovalbumin and the tissues were removed for Evans blue dye extraction.

Asthma was induced by intraperitoneal administration of 100 µg OVA/100 mg aluminum hydroxide (Al(OH)3) suspended in 1 ml saline for 0, 14 and 21th days then inhalation of 1% OVA with all body nebulizer at day 28th.

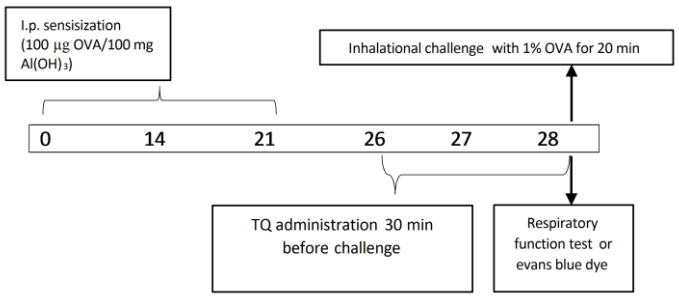

Figure 1: Schematic diagram of experimental design.

Statistical evaluation

Results are presented as means S.E.M. Statistical comparisons means were carried using one-way ANOVA followed by the Bonferroni's multiple comparison test, using Graph Pad Prism, version 3.0. A value of $P<0.05$ was considered as significant.

Results

Effect of TQ on respiratory abnormality caused by ovalbumin challenge in sensitized rats

As seen in Table 1, there was a significant decrease ($p=0.002$) in the tidal volume, whereas there was a significant increase ($p=0.017$) in the frequency of breathing of OVA group as compared to the control group. Treatment with TQ (10, and 30 mg/kg) significantly increased ($p=0.046$, $p=0.008$) in Tidal volume, whereas the frequency of breathing was not affected significantly by TQ in treatment group as compared to OVA rats (Figure 2).

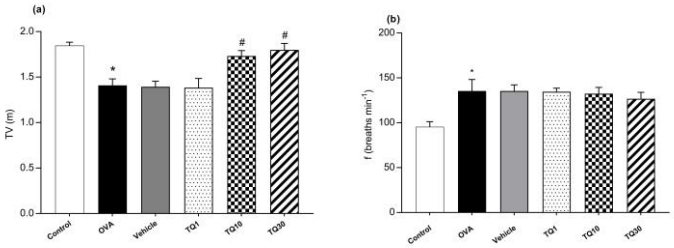

Figure 2: Effect of TQ on OVA-induced asthma in lung functions of rats.Data are expressed as mean ± S.E.M. (n= 7) and one-way ANOVA followed by Bonferroni's multiple range test. *p< 0.05 as compared to control group, #p < 0.05 as compared to OVA group.

Effects of TQ on inflammatory cell infiltration in BAL fluid caused by ovalbumin challenge in sensitized rats

As shown in Figure 3, total inflammatory cells were significantly elevated in the OVA group compared with control group, clearly eosinophils and neutrophils. TQ treatment resulted in significantly reduced numbers of total inflammatory cells in the BALF from rat with OVA-induced allergic asthma, especially eosinophils and neutrophils.

Table 1: Comparison of parameters measurements between the groups.

(n=7)	Control	OVA	Vehicle	TQ1	TQ10	TQ30	P1	P2	P3	P4
TV (ml)	1.9±0.04	1.4±0.07*	1.4±0.06	1.38±0.1	1.73±0.06$^{\#}$	1.80±0.07$^{\#}$	0.002	1	0.047	0.008
f (breaths min^{-1})	95.3±5.9	135.3±12.9*	135.3±8.9	134.50±4.0	132.33±0.06	126.67±3.3	0.017	1	1	1
Total WBC in BALF (x10^3/ml)	545.0±106.7	1,376.8±136.4*	1,373.2±10.0	1,282.17±137.7	824.67±4.5$^{\#}$	621.33±5.5$^{\#}$	<0.001	1	0.036	0.001
Lymphocyte (x10^3/ml)	146.2±25.3	410.2±38.8*	395.7±5.5	380.17±49.9	213.33±5.5$^{\#}$	166.17±2.2$^{\#}$	0.002	1	0.036	0.004
Eosinophil (x10^3/ml)	95.1±19.8	287.3±21.3**	282.5±4.4	242.17±20.8	140.06±1.1$^{\#\#}$	121.83±8.9$^{\#\#}$	<0.001	1	0.001	<0.001
Monocyte (x10^3/ml)	57.0±13.8	125.0±12.0*	131.1±2.2	118.01±9.6	69.33±5.6$^{\#}$	67.02±0.02$^{\#}$	0.002	1	0.019	0.013
Neutrophil (x10^3/ml)	214.5±40.0	749.2±79.4**	765.8±4.4	593.83±81.3	382.67±1.1$^{\#}$	346.33±8.9$^{\#}$	<0.001	1	0.006	0.002
IL-6 in BALF (pg/mL)	23.7±1.8	26.8±1.5	26.8±1.9	21.67±1.8	20.67±2.3	20.67±2.3	0.657	1	0.205	0.091
TNF-a in BALF (pg/mL)	36.7±4.7	60.3±4.9*	63.7±5.7	59.02±4.9	40.33±2.5$^{\#}$	39.83±3.2$^{\#}$	0.011	1	0.050	0.040
MDA in lung tissue (nmol/g)	8.3±1.1	15.9±1.2*	15.3±8.8	14.67±1.7	9.67±6.7$^{\#}$	9.32±5.5$^{\#}$	0.003	1	0.026	0.016
Evans blue dye (ng/mg of tissue)	12.5±1.1	31.8±3.6**	31.1±7.8	24.98±2.9	16.33±6.7$^{\#}$	13.50±1.0$^{\#}$	0.001	0.992	0.002	0.001

Effects of TQ on IL-6 and TNF-α levels in BAL fluid caused by ovalbumin challenge in sensitized rats

As demonstrated in Figure 4, IL-6 level in BAL fluid was not significantly changed both in OVA and TQ groups as compared to control group (a). However, TNF-α level in BAL fluid was significantly elevated in the OVA group as compared to the control group (p=0.011), while TNF-α level in BAL fluid was lower in the TQ group than those in the OVA group (p=0.040) (b).

Effect of TQ on MDA level in lung tissue caused by ovalbumin challenge in sensitized rats

Malondialdehyde (MDA) level was increased in lung tissue of the OVA group as compared to the control group (p=0.003). As shown in Figure 5, TQ treatment decreased MDA level when compared to OVA group (p=0.016).

Effect of TQ on ovalbumin induced microvascular protein leakage in sensitized rats

The 30 mg/kg dose of TQ significantly increased microvascular leakage in airway tissue (p<0.001). TQ (10 mg/kg, intraperitoneal) given 20 min prior to OVA challenge decreased the high microvascular leakage response in airway tissues (p=0.002) (Figure 6)

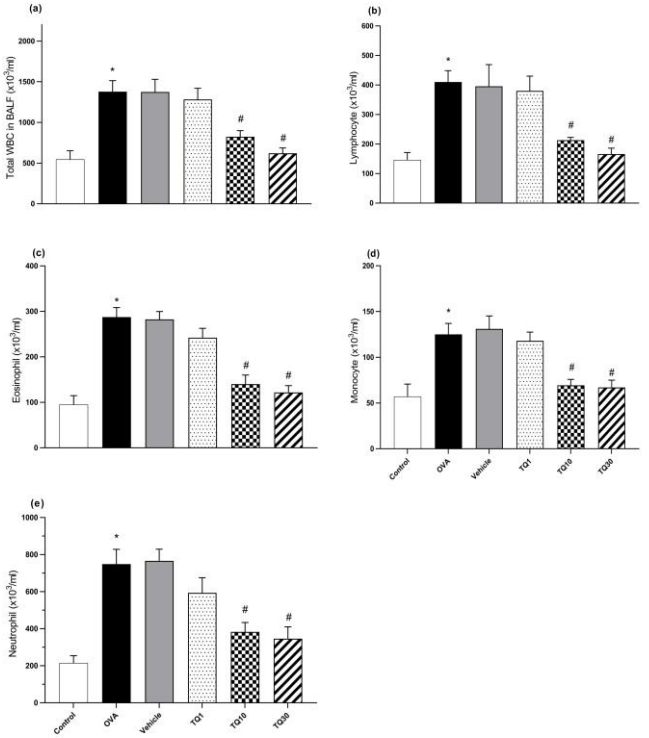

Figure 3: Effect of TQ on OVA-induced asthma in count of total WBC (a), lymphocyte (b), eosinophil (c), monocyte (d), and neutrophil (e) in BALF. Data are expressed as mean ± S.E.M. (n= 7) and one-way ANOVA followed by Bonferroni's multiple range test. *p< 0.001 as compared to control group, #p < 0.05 as compared to OVA group.

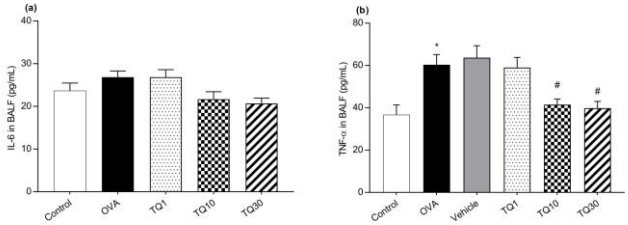

Figure 4: Effect of TQ on OVA-induced asthma in IL-6 (a) and TNF-α level (b) in BALF of rats. Data are expressed as mean ± S.E.M. (n= 7) and one-way ANOVA followed by Bonferroni's multiple range test. *p< 0.05 as compared to control group, #p < 0.05 as compared to OVA group.

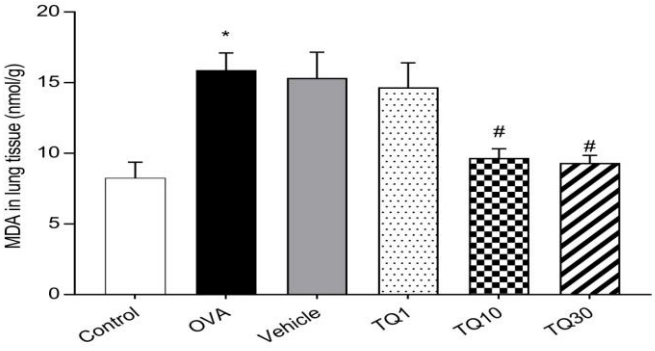

Figure 5: Effect of TQ on OVA-induced asthma in MDA content in BALF of rats. Data are expressed as mean ± S.E.M. (n= 7) and one-way ANOVA followed by Bonferroni's multiple range test. *p< 0.05 as compared to control group, #p < 0.05 as compared to OVA group.

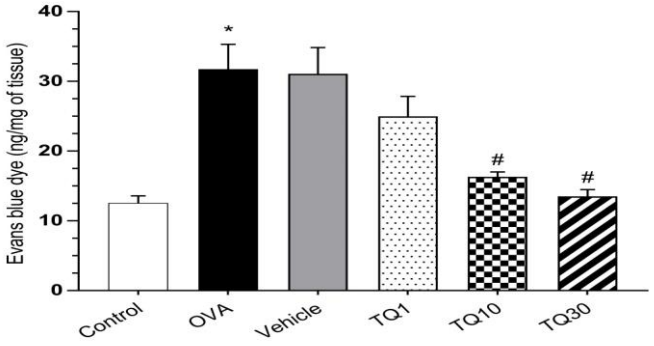

Figure 6: Effect of TQ on OVA-induced asthma in microvascular leakage in lung of rats. Data are expressed as mean ± S.E.M. (n= 7) and one-way ANOVA followed by Bonferroni's multiple range test. *p< 0.05 as compared to control group, #p < 0.05 as compared to OVA group.

Discussion

The efficacy of anti-asthmatic drugs depends on the asthma pathophysiology: cell recruitment, edema, mediators release, interleukins release, oxidative stress, bronchospasm and respiratory abnormality. The anti-asthmatic effects seen for TQ might be produced due to several different mechanisms.

In this study, we investigated the effect of TQ on the allergic airway inflammation provoked by ovalbumin challenge in the pulmonary tissue of actively sensitized rats. Our results demonstrated that TQ administration effectively inhibit the respiratory abnormality, microvascular leakage, leukocyte influx, including eosinophils, LPO, and pro-inflammatory cytokine release such as TNF-α, in allergic airway inflammation.

Papers have showed that inflammatory insult to the lungs resulted in an alteration in respiration. Thus, determination of respiratory function test is used for diagnosis of the nature and degree of lung sensitivity. The results of the present research are in accordance with the findings of the previous study where OVA-induced rats showed altered lung functions [25]. However, administration of TQ (10-30 mg/kg) showed significant restoration of these effected parameters.

Intensity of inflammatory immune responses is controlled by recruitment of inflammatory cells into inflammatory area. Inflammatory cells, as leukocytes, especially eosinophils release inflammatory mediators give a major contribution to the pathogenesis of allergic airway inflammation. Inflammatory cells elevated in BAL fluid are also source of leukotrienes that are formed by the breakdown of a membrane constituent, arachidonic acid, via the 5-lipoxygenase enzyme pathway. Leukotrienes may a play an important role in attracting neutrophils and eosinophils into airways, and produce

bronchoconstriction, mucus secretion, microvascular leakage, airway edema, and neuronal interactions [14, 17, 26–28]. Therefore, the reduction of leukocyte infiltration may be a mechanism for the beneficial effect of TQ. The results of this study showed that pretreatment of sensitized animals with TQ suppressed the eosinophilic and neutrophilic inflammation.

This is the report to comprehensively demonstrate that TQ inhibits microvascular protein leakage induced by OVA. The enhanced microvascular leakage associated edema in the airway wall and lumen that were observed in our animal model of allergic airway inflammation may play a role in its pathogenesis by contributing to narrowing of airways, and respiratory abnormality. The leakage of plasma proteins from the microvasculature into airway tissue is an important consequence of asthmatic airway inflammation. The leakage of plasma proteins was evaluated by measuring the tissue accumulation of Evans blue dye, which binds to proteins. The present experimental model was undertaken on ovalbumin-sensitized rats that were evoked with intravenously administration of ovalbumin. Our results show that ovalbumin can cause microvascular leakage into the airway tissue. The increase in airway microvascular leakage induced by ovalbumin could be inhibited by pretreatment with TQ (10, and 30 mg/kg). The inhibitory mechanism of plasma leakage and eosinophil enrichment seems to be closely associated with inhibition of histamine release from mast cells. Previous studies show that microvascular airway leakage is increased in sensitized rats, mice, and guinea pigs by ovalbumin [17, 25, 29–32], and capsaicin [33, 34].

The increased airway microvascular leakage induced by intravenous application of ovalbumin to ovalbumin-sensitized rats could be a result of several factors. Ovalbumin antigen may elicit the release of inflammatory mediators from inflammatory and structural cells in airways [16, 20]. These mediators can lead to the typical pathophysiological changes of asthma, including microvascular plasma leakage. Many mediators are released in asthma, and it is clear that these mediators interact with each other in some way. Mediators may act synergistically to enhance each other's effects, or one mediator may modify the release or action of another mediator [22]. The effect of TQ on airway microvascular leakage in sensitized rats might be explained by its inhibitory action on histamine [35, 36]. So it seems that it is logical to focus on the further studies to understand the interaction of opioid and histamine on microvascular leakage in airway of sensitized animals. As another mechanism, neurogenic inflammation may be stimulated by ovalbumin antigen [34, 37]. This effect may be relevant by release of tachykinins from sensory nerves. Among the tachykinins, substance P is the most potent to cause leakage. It can induce microvascular leakage in guinea pig airways when it is administered alone [38, 39]. It is known that cytokines as TNF-α can alter the sensitivity of the sensory nerves for neurogenic stimulants [40]. TQ can reduce the inflammation mediated by sensory nerves in the airways; this effect may be associated with the direct or indirect inhibition of tachykinin and neuropeptide release. This hypothesis should be supported by more detail further studies demonstrated that TQ inhibits neurogenic inflammation in sensitized animals.

There is increasing evidence that oxidative stress and reactive oxygen species are involved in allergic airway inflammation. Inflammatory cells activated in allergic airway inflammation produce reactive oxygen species. ROS may damage airway wall, resulting in increased bronchoconstriction, plasma leakage, mucus secretion, and induce LPO, resulting in the formation of additional mediators. Superoxide and hydrogen peroxide may interact in the presence of free iron to form the highly reactive hydroxyl radicals. Oxidative stress describes an imbalance between ROS and antioxidant. In this study the MDA, LPO products of oxidation were studied in lung tissue. We observed an increase in LPO in lung tissue of allergic airway inflammation model of rats. Therefore, it is possible that beneficial effect of TQ may be related to its anti-peroxide properties. Previous studies have shown the same effect in other disease models [10, 24].

Based on our present results, we conclude that TQ effectively inhibits TNF-α that it is considered important mediators of inflammation and is considered to be a main of inflammatory cytokine production [12]. Pro-inflammatory cytokines are involved in allergic airway inflammatory. In the present study IL-6 and TNF-α levels in BAL fluid were determined after OVA challenge in sensitized rats. TNF-α potently stimulates airway epithelial cells to produce other cytokines, and increases the expression of intracellular adhesion molecules that are the adhesion of inflammatory cells, such as neutrophils and eosinophils at the airway surface. Previous studies shown that TNF- α is present in the BAL fluid from asthmatic patients [41], and also released in the BAL fluid from allergen challenged animals [42]. TNF-α target different cells such as endothelial cells, macrophages and neutrophils. TNF-α leads to the increased production of macrophages and stimulates their differentiation and activation. TNF-α augment inflammatory cascades by triggering macrophages to release other pro-inflammatory cytokines such as IL-6, reactive oxygen/nitrogen species and lipid mediators, which are important in ovalbumin-induced asthma like reaction. The current results showed that TQ can modulate the marked increase in TNF-α levels during ovalbumin sensitization and provocation, which may explain, at least in part, its beneficial effect during allergic reaction of lung tissues. However, it was not observed IL-6 levels in BAL fluids of ovalbumin sensitized and provoked rats.

For all that, limitation of this study is that asthma like reaction was examined in rats and the results cannot be fully extrapolated or adapted to clinical pathophysiological conditions. Thus the present data need to support by the results of various clinical circumstances of asthma.

Taken together, these findings suggest a potential therapeutic effect of TQ against allergic airway inflammation that would be translated to clinical setting in humans for management of allergic diseases, particularly asthma-like disease manner. In conclusion, we demonstrate that administration of TQ attenuates allergen-evoked eosinophilic inflammation in the rat.

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Comparison of fasting and postprandial levels of commonly used biochemical and hematological parameters

Sık kullanılan biyokimyasal ve hematolojik parametrelerin açlık ve postprandiyal düzeylerinin karşılaştırılması

Elif Turan [1], Recep Tunç [2], Yaşar Turan [3]

Abstract

Aim: Physicians and patients may have varying preferences for optimal blood analysis time. We aimed to determine the tendency for the optimal blood analysis time of the physicians and patients and also to determine the difference in some commonly used biochemical and hematological parameters, between fasting and food intake.

Methods: Questionnaire and cross-sectional designs were used. The doctors and patients were conducted to a survey about the appropriate time for blood tests before the study. 112 patients were included in study. Blood samples were collected after 8-10 hours of fasting and 2 hours after 600-700 calories lunch. Blood creatinine, alanine aminotransferase, sodium, glucose, calcium, albumin, total cholesterol, triglyceride, HDL, LDL, alkaline phosphatase, total bilirubin, lactate dehydrogenase, complete blood count, erythrocyte sedimentation rate, prothrombin time and TSH were studied and the values were compared.

Results: In our survey, 75% of patients (54 patients in the outpatient clinic and 98 patients in the blood collection unit, a total of 152) and 77% of doctors were thinking that fasting was the appropriate time for blood tests. There were significant increase in glucose ($p<0.01$), triglyceride ($p<0.01$) and platelets ($p=0.035$) and significant decrease in sodium ($p=0.01$) after the food intake. There was no statistically significant difference in the other parameters.

Conclusion: The majority of physicians and patients had the opinion that blood tests should be given in fasting. Although there were significant differences in glucose, triglyceride, thrombocyte and sodium levels in our study, thrombocyte and sodium differences may not exhibit any clinical importance. Notwithstanding, high postprandial levels of glucose and triglyceride are valuable indicators for cardiovascular disease and diabetes risk.

Keywords: fasting, food intake, glucose, triglyceride.

Öz

Amaç: Hekimler ve hastaların kan tahlili verme zamanı tercihleri değişiklik gösterebilmektedir. Çalışmamızda anketler ile hekim ve hastaların eğilimlerini belirlemeyi ve günümüzde sık kullanılan bazı biyokimyasal ve hematolojik tetkiklerde açlık ve tokluk arasında farklılık olup olmadığını tespit etmeyi amaçladık.

Materyal-metod: Anket ve kesitsel dizayn birlikte kullanıldı. Çalışmaya başlamadan önce doktorlara ve hastalara kan tahlilleri için uygun kan verme zamanı konusunda anket yapıldı. Çalışmaya toplam 112 hasta alındı. Bu hastalarda 8-10 saatlik açlık sonrası ve 600-700 kalorilik öğle yemeğinden 2 saat sonra kan alındı. Alınan kanlardan kreatinin, alanin aminotransferaz, sodyum, glukoz, kalsiyum, albumin, total kolesterol, trigliserid, HDL, LDL, alkalen fosfataz, total bilirubin, laktat dehidrogenaz, hemogram, sedimentasyon, protrombiz zamanı ve TSH çalışıldı ve değerleri karşılaştırıldı.

Bulgular: Çalışmamızın anket evresinde; hastaların %75'i (54 poliklinik hastası ve 98 kan alma birimine gelen hasta olmak üzere toplam 152), doktorların % 77'si tetkiklerin aç karna yapılması gerektiğini düşünmekteydiler. Çalışılan kanların sonucunda glukoz ($p<0.01$), trigliserid ($p<0.01$) ve trombositlerde ($p=0.035$) toklukta istatistiksel olarak anlamlı artış, sodyumda ($p=0.01$) ise toklukta anlamlı azalma tespit edildi. Diğer parametrelerde açlık ve tokluk arasında istatistiksel olarak anlamlı farklılık bulunmadı.

Sonuç: Doktor ve hastaların büyük çoğunluğu kan tetkiklerinin açlıkta verilmesi gerektiği görüşündedir. Çalışmamızda glukoz, trigliserid, trombosit ve sodyumda anlamlı farklılık tespit edilse de, trombosit ve sodyum düzeyindeki farklılık klinik önem arzetmeyecek seviyelerdeydi. Toklukta tespit edilen yüksek glukoz ve trigliserid düzeyleri kardiovasküler hastalık ve diyabet riski için kıymetli göstergelerdir.

Anahtar kelimeler: açlık, gıda alımı, glukoz, trigliserid.

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Introduction

Laboratory test results can be affected by various controllable factors such as alcohol use, smoking, physical activity, and diet as well as fasting state before blood collection. Patients must be informed about how to prepare before a laboratory test [1]. The Clinical and Laboratory Standards Institute (CLSI) recommends verification of dietary restrictions, as certain tests may require fasting [2]. In the Mayo Clinic website, it is stated that fasting is not required, only if complete blood count test is to be performed [3].

In addition, there is no consensus among physicians and patients as to whether dietary restriction is required before blood collection. A debate still exists regarding some particular tests. Although recent studies have made suggestions regarding the testing conditions of lipids, it is still unclear for other tests [4-7]. On the other hand, patients with a chronic condition such as hypertension and diabetes mellitus (DM) skip their medications or face such risks as hypoglycemia for the sake of having their fasting blood tests done.

In the present study, we aimed to determine the tendency of the physicians and patients for the optimal blood analysis time, with simple questionnaires. We also aimed to evaluate whether commonly used biochemical and hematological parameters were affected by dietary restrictions.

Material and methods

The study protocol was approved as a thesis by the Ethics Committee of Necmettin Erbakan University, Faculty of Medicine, Konya, Turkey (No. 2008/207). A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki [9], as revised in 1975 and 1983.

The study included five stages as shown in Figure 1.

ALGORITHM OF THE STUDY

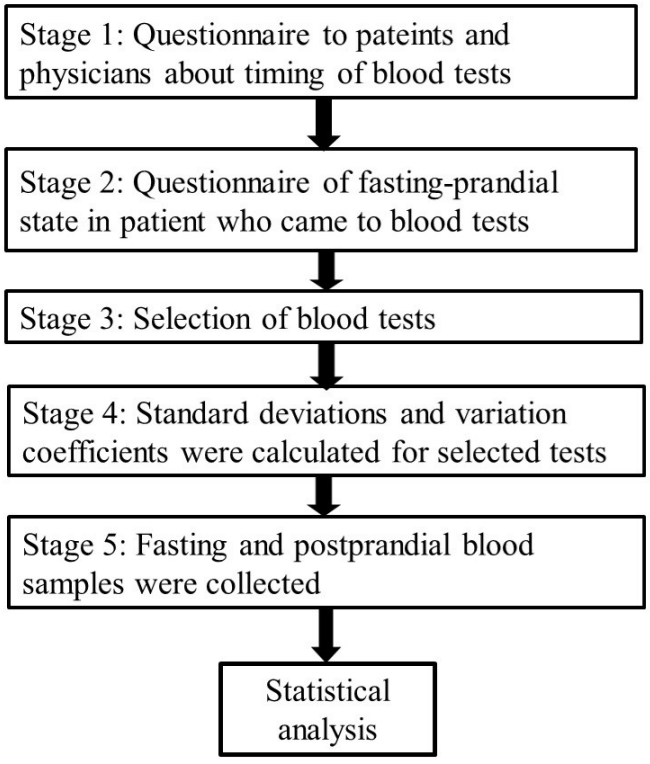

Figure 1: Algorithm of the study

First stage: In the first stage, a questionnaire was administered to patients and physicians to evaluate their attitudes toward the timing of blood tests. The questionnaire administered to 54 patients attending to the internal medicine outpatient clinics contained two options as fasting and postprandial. Forty (74%) of them thought that fasting was appropriate for blood testing. and the questionnaire administered to 57 physicians consisted of attending physicians, residents, and intern physicians with three options as fasting, postprandial, and at any time of the day and 44 (77%) of them preferred their patients to have their tests done in the fasting (Table 1) .

Table 1: Results of the surveys.

The patient group comprised of 54 patients (attended outpatient clinics)		
	At what time of the day would it be appropriate to have blood tests?	
	Morning fasting	40 (74%)
	Morning postprandial	14 (26%)
A total of 98 patients attending for blood collection were asked:		
	Are you in fasting state?	
	Yes	75 (76%)
	No	23 (24%)
	Do you have Diabetes Mellitus?	
	Yes	19 (19.3%)
	No	79 (80.7%)
	Do you have regular medications?	
	Yes	61 (62%)
	No	37 (38%)
	If yes, have you taken your medication?	
	Yes	16 (26%)
	No	45 (74%)
Of physicians including residents, interns, and attending physicians 57 responded to this question:		
	In what state do you prefer your patients to have their tests done?	
	Morning fasting	44 (77%)
	Postprandial	2 (4%)
	At any time of the day	11 (19%)

Second stage: A questionnaire was administered to 98 patients who were admitted to the blood collection unit of Necmettin Erbakan University, Faculty of Medicine. This questionnaire inquired dietary restrictions, presence of chronic diseases, and medications used (Table 1). Seventy-five (76%) of 98 patients who were admitted to the blood collection unit were in a fasting state. Although 61 of them were using regular medications, 45 patients (74%) attended the unit without taking their medicines.

Third stage: This stage involves the selection of blood tests to be performed for the study. For this purpose, the number of tests performed in the biochemistry and hematology laboratories within the last month was examined. A total of 22 frequently performed tests were selected all of which have clinical importance and performed more than 1,000 within the last month.

Fourth stage: We questioned the reliability of our laboratory by working the same blood sample repetitively. For this purpose, blood samples were collected from a healthy volunteer. Blood samples of this volunteer were divided into 10 tubes. The test tubes were sent to the laboratory for the repetitive analysis. Coefficient variation (CV) is one of the methods used for the validity of the method [8]. Method validity is a process

that is performed to obtain the same result every time. In order to evaluate the safety of our blood test results, we calculated the CV and standard deviation (Table 2).

Table 2: Standard deviation and coefficient variation of the study parameters calculated from the blood samples of a healthy volunteer.

	Mean	SD	CV%
Glucose (mg/dL)	85.60	3.534	4.12
Creatinine (mg/dL)	0.883	0.04448	5
Sodium (mEq/L)	144.5	2.068	1.43
Calcium (mg/dL)	9.90	0.2025	0.204
Uric acid (mg/dl)	3.54	0.0972	0.27
ALT (U/L)	41.40	0.51	1.23
Albumin (mg/dL)	4.590	0.0568	1.23
Total bilirubin (mg/dL)	0.720	0.0422	5.8
Alkaline phosphatase (U/L)	86.3	1.889	2.18
Lactate dehydrogenase (U/L)	204	5.793	2.83
Total cholesterol (mg/dL)	248	3.859	1.55
Triglyceride (mg/dL)	171.90	1.792	1.04
HDL (mg/dL)	51.20	1.317	2.5
LDL (mg/dL)	162.5	4.062	2.4
TSH (mIU/L)	2.9306	0.0556	1.89
Prothrombin time (sec)	1.05	0.0867	8.25
ESR (mm/h)	31	5.292	17
Leukocyte (x10^9/L)	5.620	0.0789	1.48
Hemoglobin (g/dL)	16	0.05	1.01
MCV (fL)	86.80	0.422	0.4
MCH (fL)	18.78	3.129	16.66
Platelet (x10^9/L)	285.20	6.233	2.1

CV: coefficient of variation, SD: standard deviation, ALT: alanine aminotransferase, HDL: High-density lipoprotein, LDL: low-density lipoprotein, TSH: thyroid stimulating hormone, ESR: erythrocyte sedimentation rate, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin.

Fifth stage: A total of 128 patients who were hospitalized in the nephrology, gastroenterology, endocrinology and rheumatology clinics of the Department of Internal Medicine of Necmettin Erbakan University, Faculty of Medicine and who agreed to participate in the study. Hospitalized patients were preferred to minimize the difference of the calorie intake between the patients. During this period, the patients were consecutively enrolled in the study. Patients with poor oral intake and poor general condition and significant anemia were excluded. In total, 112 patients were included in the study. Among the patients, 37 had hypertension, 29 had diabetes, 17 had chronic renal failure (CRF), and 11 had liver failure. Blood samples from patients with CRF were collected on days off from dialysis.

Fasting blood samples in the morning (after an 8 to 10-h fasting) and postprandial blood samples at two hours with a 600-700 calorie diet were collected from a total of 112 patients for hematological and biochemical tests [glucose (mg/dL), creatinine (mg/dL), sodium (mEq/L), calcium (mg/dL), uric acid (mg/dL), alanine aminotransferase (ALT) (U/L), albumin (mg/dL), total bilirubin (mg/dL), alkaline phosphatase (U/L), lactate dehydrogenase (U/L), total cholesterol (mg/dL), triglyceride (mg/dL), high-density lipoprotein (HDL) (mg/dL), low-density lipoprotein (LDL) (mg/dL), thyroid-stimulating hormone (TSH) (mIU/L), prothrombin time (PT) (sec), erythrocyte sedimentation rate (ESR) (mm/h), leucocyte count (x109/L), hemoglobin (g/dL), mean corpuscular volume (MCV) (fL), mean corpuscular hemoglobin (MCH) (fL), platelet count (x109/L)]. The tests were performed on fresh blood samples without storage using standard methods.

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows version 18.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed in mean, standard deviation (SD), and number and percentage. The paired sample test was used to analyze significant differences between the two groups. The questionnaires administered to the physicians and patients were analyzed using the chi-square test. A p value of <0.05 was considered statistically significant.

CVs were calculated for 22 parameters examined in the study. When we calculated the CV for these 22 parameters, the CV of the parameters except total bilirubin, sedimentation rate, MCH, and PT were found to be $\leq$5%. This situation was regarded as the sufficient reliability and repeatability of these 18 parameters.

Results

Forty of 54 patients (74%) attending to the general internal medicine outpatient clinics preferred fasting blood collection, whereas 44 of 57 physicians (77%) including attending physicians, residents, and intern physicians found fasting blood collection to be appropriate for blood tests. There was no significant difference in the preferences of dietary restriction between the physicians and patients (p=0.157). Seventy-five (76%) of 98 patients who were admitted to the blood collection unit were in a fasting state. Although 61 of them were using regular medications, 45 patients (74%) attended the unit without taking their medicines (Table 1). There was no significant difference in the ratio of fasting-postprandial state between patients who were on regular follow-up due to a chronic disease and those who did not have a chronic disease and presented to the clinic for the first time (p=0.157). Furthermore, there was no significant difference in the patient and physician survey results and the practices of the patients for blood collection (p=0.199).

Of a total of 112 participants, 67 were females and 45 were males with a mean age of 56.34±14.55 years. The questionnaires administered to the patients and physicians and their results are presented in Table 1.

The CV was $\leq$5% for 18 parameters other than total bilirubin, ESR, MCH, and PT (Table 2).

Fasting and postprandial test results of 112 patients included in the final stage of the study are presented in Table 3. Compared to the results in the fasting state, postprandial glucose mg/dL (107.68±28.70 vs. 144.81±36.20, p<0.01), triglycerides mg/dL (149.49±21.78 vs. 165.83± 25.75, p=0.006), and platelet count g/dL (251.55±32.5 vs. 262.25±33.7, p=0.035) were

significantly higher, while sodium level mEq/L (136.32±2.06 vs. 135.25±1.94, p=0.01) was significantly lower. The corrected sodium level was calculated in the patients with a glucose level above 125 mg/dL and the difference in the sodium levels remained statistically significant (p=0.02). However, there was no statistically significant difference between the fasting and postprandial levels of other parameters (p>0.05).

Table 3: Fasting and postprandial test results of 112 patients.

Parameter	Fasting value	Postprandial value	P
Age (year) [μ]	56.34±14.55		
Gender (male/female)	45/67		
Glucose (mg/dL) [μ]	107.68±28.70	144.81±36.20	<0.01
Creatinine (mg/dL) [μ]	1.17±1.10	1.32±1.09	0.146
Sodium (mEq/L) [μ]	136.32±2.06	135.25±1.94	0.010
Calcium (mg/dL) [μ]	8.74±0.22	8.67±0.24	0.251
Uric acid (mg/dL) [μ]	5.43±0.89	5.47±0.82	0.706
ALT (U/L) [μ]	40.56±1.77	41.75±1.58	0.589
Albumin (mg/dL) [μ]	3.531±0.1	3.74±0.09	0.081
Total bilirubin (mg/dL) [μ]	1.32±0.05	1.23±0.05	0.560
Alkaline phosphatase (U/L) [μ]	88.56±1.78	92.34±2.65	0.121
Lactate dehydrogenase (U/L) [μ]	261.29± 6.74	248.92±5.93	0.082
Total cholesterol (mg/dL) [μ]	166.29±34.26	172.75±35.88	0.512
Triglyceride (mg/dL) [μ]	149.49±21.78	165.83± 25.75	0.006
HDL (mg/dL) [μ]	32.24±8.28	32.41±8.32	0.809
LDL (mg/dL) [μ]	101.10±30.3	98.68±33.3	0.328
TSH (mIU/L) [μ]	2.69±0.4	2.41±0.39	0.174
Prothrombin time (sec) [μ]	1.145±0.02	1.140±0.02	0.726
ESR (mm/h) [μ]	34.42±11.21	36.61±12.1	0.082
Leukocyte ($x10^9$/L) [μ]	9.71±0.92	9.58±0.95	0.105
Hemoglobin (g/dL) [μ]	12.39±0.53	12.40±0.57	0.621
MCV (fL) [μ]	82.71± 3.15	82.60±4.01	0.902
MCH (fL) [μ]	29.16± 1.17	29.34±1.22	0.220
Platelet ($x10^9$/L) [μ]	251.55±32.5	262.25±33.7	0.035

[μ]: mean ± standard deviation.

ALT: alanine aminotransferase, HDL: High-density lipoprotein, LDL: low-density lipoprotein, TSH: thyroid stimulating hormone, ESR: erythrocyte sedimentation rate, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin.

Discussion

In the survey stage of the study, the opinions of patients presenting to the outpatient clinics and of the physicians about dietary restrictions before blood tests were similar and fasting state of patients presenting to the blood collection unit was also similar. The CV were ≤5% for the majority of the parameters examined in the study. This finding suggests high reproducibility (accuracy) of these tests [10]. In the laboratory analysis stage of the study, postprandial glucose (p<0.01), triglyceride (p<0.01), and platelet (p=0.035) values were higher, whereas postprandial sodium (p=0.01) was found to be lower. These four parameters had a CV below 5%. No statistically significant difference was found between the fasting and postprandial levels of other parameters.

Postprandial blood samples were collected two hours after meal. The reason for the selection of this time interval is that the American Association of Diabetes recommends blood collection two hours after a meal for oral glucose challenge test and postprandial glucose testing [11]. In addition, insulin secretion which increases after meal and affects carbohydrate and lipid metabolism [12] and intestinal incretins [13] return to baseline values two hours after meal.

Hyperglycemia is associated with two defects in type 2 DM; the first defect is insulin resistance in the liver and muscle tissue and the second defect is the progressive decline in the pancreatic insulin production. Glucose taken in a normal diet is largely (70%) used by the muscle tissues. Insulin resistance in the muscle tissues causes postprandial hyperglycemia and impaired glucose tolerance. In the natural course of type 2 DM, an individual with insulin resistance and normal glucose tolerance adopts this condition by excessive insulin secretion. Due to increased compensatory insulin secretion initially, insulin resistance is not able to disrupt the glucose uptake by the muscle tissues and to increase hepatic glucose production. Glucose uptake by the muscle tissues is impaired with increasing insulin resistance and the increase in postprandial plasma glucose concentration, then, becomes remarkable. The increase in baseline insulin secretion during this period is sufficient to maintain fasting plasma glucose and hepatic glucose production in normal ranges. However, there is a substantial increase in the postprandial plasma glucose concentration and duration required for elevated glucose levels return to normal. Thus, insulin resistance is further impaired and a compensatory increase in the insulin secretion fails to maintain fasting plasma glucose concentration within normal ranges. This series of pathophysiological disturbances explains why postprandial hyperglycemia occurs many years before fasting hyperglycemia becomes evident [14].

It is well-known that the prevalence of type 2 DM is 12 times higher than that of type 1 diabetes [15]. If type 2 DM is more prevalent in a particular population and if postprandial glucose is first impaired in type 2 DM [16], testing of postprandial glucose concentrations is more important to early diagnose DM.

In addition, triglyceride levels substantially increase after meal. Lipoproteins follow a complex metabolic pathway after meal, as triglycerides found in the structure of very-low density lipoproteins and chylomicrons are processed through the same catabolic pathway. It is, therefore, recommended that

triglycerides be tested after an overnight fasting to obtain comparable results [17]. In their study, Ferreira et al. [18] administered 900 isocaloric diet to two groups: one group receiving poor-fat content diet and the other receiving high-fat content diet. They found a significant increase in the triglyceride levels at one and three hours in the high-fat group, but no significant increase in the low-fat group. In our study, we also found a significant increase in triglycerides at two hours after meal (p=0.06). Similarly, Plumelle et al. [19] reported significant increases in both glucose and triglyceride levels.

Several studies have shown that increased fasting triglyceride levels are associated with an increased risk of cardiovascular disease [20, 21]. Of note, atherosclerosis has been suggested to be a postprandial phenomenon [22]. A recent prospective cohort studies have demonstrated a close relationship between postprandial hypertriglyceridemia and coronary heart disease and stroke [23, 24]. The Women's Health Study found that postprandial triglyceride levels were associated with cardiovascular events independent from other risk factors, lipids, and insulin resistance, whereas fasting triglyceride levels showed a weaker association [23]. In particular, triglyceride levels measured in blood samples collected two to four hours after meal exhibited a stronger correlation. Similarly, in a population study, which published 23-year follow-up results of a total of 103,860 individuals in 2018, postprandial triglyceride levels were found to be associated with the development of heart failure [25].

In the present study, we found no significant difference between fasting and postprandial total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels. The study by Ferreira et al. [18] showed no significant difference between the fasting and postprandial HDL and non-HDL measurements at one and three hours after meal. In a free-diet study conducted by Ginsberg et al. [26] in young and non-obese patients, serial measurements showed no significant difference between the fasting and postprandial total cholesterol levels, whereas there was a slight decline in the LDL and HDL levels between two and four hours after meal. Another study demonstrated that both postprandial LDL and fasting LDL levels had a similar prognostic value [27].

The guidelines published until 2009 emphasized only the importance of fasting lipid profile. As of 2009, however, the Danish Society of Clinical Biochemistry recommended that postprandial lipid measurement would be of benefit in predicting cardiovascular risks [4]. This was followed by the report of the American Heart Association (AHA) on triglycerides and cardiovascular diseases in 2011, stating that postprandial triglyceride measurement could be of use [5]. In 2016, the consensus report by the European Society of Cardiology and European Federation of Clinical Chemistry and Laboratory Medicine emphasized the importance of postprandial lipid profile [7]. Finally, in 2017, the joint declaration of the American Association of Clinical Endocrinologists and the American College of Endocrinology stated that postprandial lipid profile was useful in cardiovascular risk prediction [28]. Despite current recommendations, the majority of physicians (77%) preferred fasting blood tests in the survey stage of the present study.

Furthermore, we found a statistically significant decrease in the postprandial sodium levels in the present study. A statistically significant difference remained even after the correction of sodium levels in patients with blood glucose levels above 125 mg/dL. Sothern et al. [29] investigated the circadian rhythm of sodium in 14 healthy volunteers and found a significant increase in the sodium levels measured in the afternoon. Their results are not consistent with our findings. The CV for sodium in our laboratory was 1.43%, indicating the reliability of our laboratory. Thus, we need further studies to confirm or rule out whether postprandial hyponatremia occurs.

On the other hand, we found no significant difference between the fasting and postprandial leukocyte, hemoglobin, MCV, MCH, erythrocyte sedimentation rate, and PT. In a study of 77 patients, Plumelle et al. [19] similarly found no significant difference between fasting and postprandial values of hematological parameters. However, some studies showed a significant increase in the postprandial neutrophil count and a decrease in the lymphocyte and eosinophil count, hemoglobin, and hematocrit levels [30, 31]. Lippi et al. [30] suggested that a decline in hemoglobin and hematocrit levels could be related with postprandial hemodilution.

Moreover, we found a significant increase in the postprandial platelet count than fasting platelet count (p<0.035). The CV for platelets in our laboratory was 2.1%. This suggests that platelet count in our laboratory has a high reproducibility (accuracy). A study by Wiens et al. [32] reported significantly higher platelet counts at three hours after a high-fat diet. Bremner et al. [33] observed an increase in the platelet count measured in the morning than the platelet count measured in the afternoon. Lippi et al. [30] found a significant decrease in platelet count and attributed this finding to hemodilution. The increase in the platelet count in the present study may be associated with the circadian rhythm, as postprandial blood samples were collected two hours after lunch.

In their study, Plumelle et al. [19] evaluated hormonal parameters in fasting and postprandial blood samples and reported no significant difference in vitamin D, free T3, free T4, dehydroepiandrosterone sulfate, follicle-stimulating hormone, luteinizing hormone, and insulin-like growth factor, but a significant difference in the prolactin, adrenocorticotropic hormone, C-peptide, insulin, thyroid-stimulating hormone (TSH), and parathyroid hormone levels. It was found that serum TSH levels showed diurnal variation with postprandial decrease particularly after breakfast. In our study, we were able to analyze only TSH levels and found no significant difference between the fasting and postprandial measurements.

Nonetheless, our study has some limitations. The first limitation is that current results deriving from 22 parameters cannot be generalized to all biochemical and hematological parameters. Second, four of 22 parameters had a CV of higher than 5%; however, these parameters were eventually included in the statistical analysis. On the other hand, parameters with a CV of higher than 5% did not show significant difference between the fasting and postprandial measurements.

In conclusion, our study results suggest that postprandial blood collection is convenient for patients, as it allows blood collection at any time of the day. It also reduces the risk of hypoglycemia in patients with DM receiving glucose-reducing medications. In addition, the postprandial blood collection allows early diagnosis of diabetes, if the test is performed to screen the patient for diabetes, as postprandial glucose is the first to be impaired in diabetes cases. Also, it avoids dose interruptions in such patients as those with hypertension. Finally, it eases the workload of the laboratory by distributing patients to different hours of the day. With accumulating data, clinicians may be more positive in blood tests in postprandial.

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Evaluation of atherogenic index of plasma levels at hypertensive patients

Hipertansif hastalarda plazma aterojenik indeks düzeylerinin incelenmesi

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Abstract

Aim: Hypertension is a major risk factor for cardiovascular system. Recent studies showed that atherogenic index of plasma (AIP) has a strong association with cardiovascular morbidity, all-cause mortality, atherosclerosis and severity of coronary artery disease. It also has a relationship with endothelial damage in hypertensive patients. With this study we aim to investigate the association between AIP and hypertension.

Methods: A total of 213 patients were enrolled for the study. Patients with previous hypertension, nephrotic syndrome, diabetes mellitus, hypotiroidism diagnosis, patients under statin treatment and patients under 18 years of age were excluded. Diagnosis of hypertension and blood pressure (BP) results were obtained with 24-hour ambulatory blood pressure monitoring (ABPM). AIP was defined as the logarithmic transformation of the triglyceride to high-density lipoprotein-cholesterol ratio.

Results: Mean age of the population was 49.2 ± 14.6 years and 41.8% (n=89) was male. According to 24-hour ABPM results, AIP was positively correlated with day-time systolic blood pressure (SBP) (r=0.244, p<0.001), day-time diastolic blood pressure (DBP) (r=0.276, p<0.001), night-time SBP (r=0.259, p<0.001), night-time DBP (r=0.299, p<0.001), average SBP (r=0.213, p=0.002) and average DBP (r=0.296, p<0.001). AIP was also increased in hypertensive patients compared to normotensive subjects (p=0.001).

Conclusion: Results of our study showed that AIP was positively correlated with blood pressure and statistically higher in patients with hypertension.

Keywords: atherogenic index of plasma, hypertension, blood pressure, 24-hour ambulatory blood pressure monitoring.

Öz

Amaç: Hipertansiyon, kardiyovasküler sistem için önemli risk faktörlerinden biridir. Son dönemde yapılan araştırmalar, plazma aterojenik indeksinin (PAİ) kardiyovasküler morbidite, tüm nedenlere bağlı ölüm, ateroskleroz ve koroner arter hastalığının ciddiyeti ile güçlü bir ilişkisi olduğu gösterilmiştir. Ayrıca hipertansif hastalarda endotel hasarı ile ilişkisi vardır. Biz bu çalışma ile PAİ ile hipertansiyon arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Çalışmaya toplam 213 hasta alındı. Daha önce hipertansiyon, nefrotik sendrom, diyabetes mellitus, hipotiroidizm tanısı olan, statin tedavisi alan ve 18 yaşın altındaki hastalar çalışmadan dışlandı. 24 saatlik ambulatuvar kan basıncı ölçümü ile hipertansiyon tanısı ve kan basıncı (KB) sonuçları alındı. PAİ, trigliseritin yüksek yoğunluklu lipoprotein kolesterol oranının logaritmik dönüşümü olarak tanımlandı.

Bulgular: Çalışmaya katılan hastaların yaş ortalaması 49,2 ± 14,6 yıl idi ve % 41,8'ü (n = 89) erkekti. 24 saatlik ambulatuar kan basıncı ölçümü sonuçlarına göre, PAİ, gündüz sistolik kan basıncı (SKB) (r=0,244, p<0,001), gündüz diyastolik kan basıncı (DKB) (r=0,276, p<0,001), gece SBP (r=0,259, p<0,001), gece DKB (r=0,299, p<0,001), ortalama SKB (r=0.213, p=0,002) ve ortalama DKB (r=0,296, p<0,001) ile pozitif olarak korele idi. Hipertansif hastalarda PAİ normotansif hastalara göre istatistiksel olarak anlamlı düzeyde yüksekti (p=0,001).

Sonuç: Çalışmamızın sonucunda PAİ'nin kan basıncıyla pozitif olarak korele olduğu ve PAİ değerlerinin hipertansif hastalarda istatistiksel açıdan anlamlı şekilde yüksek olduğunu saptamıştır.

Anahtar kelimeler: Plazma aterojenik indeksi, hipertansiyon, kan basıncı, 24 saatlik ambulatuar kan basıncı ölçümü.

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Introduction

Hyperlipidemia is a major risk factor for development of vascular diseases and atherosclerosis [1]. Especially low levels of high-density lipoprotein cholesterol (HDL-C) and high levels of triglyceride and low-density lipoprotein cholesterol (LDL-C) are considered as mediators and markers for cardiovascular diseases [2]. Recent studies suggested atherogenic index of plasma (AIP) which is the logarithmic transformation of triglyceride to HDL-C ratio, can be used as a new marker for atherosclerosis and cardiovascular diseases [3-5]. AIP is associated with low LDL-C particle size and is suggested to be a surrogate for small dense LDL-C particles [5]. Dobiasova et al. reported that AIP can be used as an indicator for cardiovascular risk [6]. AIP also predicts type 2 diabetes mellitus development risk [7].

It is also important to determine the effects of the newly identified risk factors such as AIP to other major diseases such as hypertension. It was found that AIP was correlated with microalbuminurea in hypertensive patients [8]. Onat et al. [9] found out that AIP was increased with higher blood pressure. But the literature research revealed no direct study comparing AIP levels with hypertensive and normal population. With this study we aim the determine the relationship between AIP and blood pressure and to find out if there was a difference in AIP levels between newly diagnosed hypertensive patients and normal population via 24-h ambulatory blood pressure monitoring (ABPM) results.

Material and methods

A total of 213 patients whom 24-hour ABPM was applied between September 2017 and September 2018 were evaluated retrospectively. The study was approved by the local ethics committee (Çanakkale Onsekiz Mart University Ethics Committee, 17.10.2018-011-KAEK-27/2018-1800139853). The study was performed in accordance with Declaration of Helsinki. Due to the retrospective design of the study, written consent from the patients could not be taken.

Consecutive patients who admitted to cardiology outpatient clinic with medical indication for 24-hour ABPM were included for the study. Patients with previous hypertension, nephrotic syndrome, diabetes mellitus, hypotiroidism diagnosis, patients under statin treatment and patients under 18 years of age were excluded.

Demographic (age and sex), clinical and echocardiographic data were obtained from hospital medical records retrospectively. Modified Simpson's method was used for the calculation of left ventricular ejection fraction. Fasting blood glucose (mg/dl), blood urea nitrogen (mg/dl), creatinine (mg/dl), HDL-C (mg/dl), LDL-C (mg/dl), triglyceride (mg/dl), hemoglobin (g/dl), leukocyte ($x10^3/mm^3$) and platelet ($x10^3/mm^3$) values were obtained from the laboratory records of the hospital. The fasting results of triglyceride and HDL-C levels were used for calculation of AIP. The AIP was defined as the base 10 logarithm of the triglyceride to HDL-C ratio.

Patients with high ABPM results (waking ambulatory SBP/DBP >135/85 mmHg and/or sleeping SBP/DBP >120/70 mmHg) were categorized as hypertensive.

Statistical Analysis

Data were analyzed using SPSS 20.0 (IBM SPSS Ver. 20.0, IBM Corp, Armonk NY, USA). Data are presented as mean ± standard deviation (SD) and as proportions for categorical variables. The t-test or Chi-square test was used for comparisons of continuous and categorical variables, respectively. Distribution of data for normality was tested by the Shapiro–Wilk test and homogeneity of group variances were tested by the Levene test. For the parameters which are not normally distributed, Mann Whithey U test is used. Pearson correlation test was used for correlation analysis. Binary logistic regression analysis was performed to identify associations of hypertension with clinical and laboratory parameters of the patients. P values <0.05 were considered statistically significant.

Results

A total of 213 patients were enrolled for the study. Mean age of the population was 49.2 ± 14.6 years and 41.8% (n=89) was male. Hypertensive and normotensive study groups were formed according to 24-hour ABPM results. Hypertensive patients constituted 54.0% (n=115) of the study group and 46.0% of the study group was normotensive (n=98). The groups were statistically similar in terms of age (p=0.060), gender (p=0.792) and left ventricular ejection fraction (p=0.605) (Table 1).

Table 1: Comparison of the baseline characteristics and laboratory results of the study groups.

Variables	Hypertensive Patients (n=115)	Normotensive Group (n=98)	p
Sex/Male[µ]	49 (42.6)	40 (40.8)	0.792
Age (years)[¥]	50.9±13.8	47.1±15.2	0.060
LVEF (%)[¥]	57.9±2.2	58.0±2.6	0.605
FBG (mg/dL)[¥]	93.7±11.0	91.9±10.4	0.233
BUN (mg/dL)[¥]	14.3±4.3	13.1±4.4	0.068
Creatinine (mg/dL)[¥]	0.8±0.1	0.7±0.1	0.184
HDL-C (mg/dL)[¥]	50.9±13.3	53.6±11.3	0.125
LDL-C (mg/dL)[¥]	129.6±36.8	121.9±39.3	0.147
Triglyceride (mg/dL)[¥]	161.8±97.7	126.6±65.8	0.002
Hb (g/dL)[¥]	14.5±1.6	13.9±1.9	0.021
Leukocyte ($x10^3/mm^3$)[¥]	7.8±1.9	7.4±1.9	0.165
Platelets ($x10^3/mm^3$)[¥]	275.1±64.6	268.6±64.6	0.473
AIP [¥]	0.45±0.30	0.33±0.26	0.001

[µ]: n (%), [¥]:mean±standard deviation.
BUN, blood urea nitrogen; FBG, fasting plasma glucose; Hb, hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; AIP: Atherogenic index of plasma.

There were no significant difference in fasting blood glucose, blood urea nitrogen, creatinine, HDL-C, LDL-C, leukocyte and platelet values between the groups (p>0.05). Hemoglobin (p=0.021) and triglyceride (p=0.002) values were higher in hypertensive patients compared to normal population. AIP was also increased in hypertensive patients (p=0.001) (Table 1).

According to Pearson correlation analysis, AIP was positively correlated with day-time SBP (r=0.244, p<0.001), day-time DBP (r=0.276, p<0.001), night-time SBP (r=0.259, p<0.001), night-time DBP (r=0.299, p<0.001), average SBP (r=0.213, p=0.002), average DBP (r=0.296, p<0.001) (Table 2).

Table 2: Pearson correlation analysis of AIP and 24-hour ABPM values.

	AIP	
Variables	r	p
Day SBP	0.244	<0.001
Day DBP	0.276	<0.001
Night SBP	0.259	<0.001
Night DBP	0.299	<0.001
Average SBP	0.213	0.002
Average DBP	0.296	<0.001

AIP: Atherogenic index of plasma, ABPM: ambulatory blood pressure monitoring, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Based on the sex distribution, in male subjects; AIP was positively correlated with day-time SBP (r=0.230, p=0.032), day-time DBP (r=0.296, p=0.005), night-time DBP (r=0.285, p=0.007) and average DBP (r=0.319, p=0.003). There was no correlation with AIP and night-time SBP (r=0.193, p=0.074) and average SBP (r=0.159, p=0.142). For female subjects, AIP was positively correlated with day-time SBP (r=0.237, p=0.008), day-time DBP (r=0.228, p=0.011), night-time SBP (r=0.309, p=0.001), night-time DBP (r=0.297, p=0.001), average SBP (r=0.261, p=0.004) and average DBP (r=0.252, p=0.005).

Binary logistic regression analysis to investigate which variables have a significant effect on hypertension showed that AIP (odds ratio, 4.108; 95% confidence interval, 1.436–11.754, p = 0.008), hemoglobin (odds ratio, 1.206; 95% confidence interval, 1.013-1.434, p=0.035) and age (odds ratio, 1.023; 95% confidence interval, 1.003-1.045, p=0.027) had explanatory power on hypertension diagnosis (Table 3).

Table 2: Binary logistic regression analysis results.

Variables	Beta	Std. Error	p	Exp. (Beta)	95% CI	
					Lower	Upper
Age	0.023	0.010	0.027	1.023	1.003	1.045
AIP	1.413	0.536	0.008	4.108	1.436	11.754
Hemoglobin	0.187	0.089	0.035	1.206	1.013	1.434
Constant	-4.224	1.445	0.003	0.015		

AIP: Atherogenic index of plasma, CI: confidence interval, Std; standard.

Discussion

In our study we found out that AIP is significantly higher in hypertensive patients compared to normotensive subjects. Also AIP is positively correlated with day-time systolic and diastolic BP, night-time systolic and diastolic BP, all-day systolic and diastolic BP. Binary logistic regression analysis revealed that AIP was associated with incidence of hypertension diagnosis.

Traditionally atherogenic lipid profile consists of increased triglyceride, LDL-C, total cholesterol and decreased HDL-C. At 1999, Connelly et al. [10] found out that smoking, diabetes, and hypertension were more common at high triglyceride and low HDL-C patients. Studies like this one showed the importance of combined effect of triglyceride and HDL-C values. Combining two lipid profile measurements and taking ratio of triglyceride to HDL-C has been shown to be higher in patients with myocardial infarction [11]. But this ratio lacks the normative distribution. The logarithm of this ratio corrects the lack of normative distribution and demonstrates a correlation with smaller LDL particles and increased fractional esterification rate which is an index for lecithin cholesterol acyl-transferase activity [5]. Increased triglyceride and decreased HDL-C values shows oxidative stress and low grade inflammation and because of these effects, AIP has been shown to be associated with metabolic syndrome [9, 12].

Dobiasova et al. [5] showed the correlation between AIP and LDL-C particle size and since then studies have been performed to investigate the relationship between AIP and cardiovascular diseases. Later on AIP has been proven to be an indicator for cardiovascular risk [6]. It has a strong association with cardiovascular morbidity, all-cause mortality, atherosclerosis and severity of coronary artery disease [4, 9, 13-15] AIP also associated with major risk factors of cardiovascular diseases. For example AIP was also found to be associated with the risk of diabetes mellitus [7]. Moura Rdo et al. [8] showed that AIP is also associated with microalbuminuria in hypertensive patients which may suggest that AIP also associated with endothelial damage. Onat et al. [9] showed the relationship of AIP with high blood pressure and diabetes. In this study blood pressure was measured in the clinic and data was obtained by the mean of two recordings at least 3 minutes apart. In our study we evaluated patients with 24-h ABPM. Patients with previous hypertension diagnosis or under hypertensive medication treatment were excluded and we found that all parameters of 24-h ABPM results were correlated with AIP values. Ours and previous studies show that AIP is associated with blood pressure and hypertension diagnosis.

It is known that prevalance of hypertension increases with age [16]. We also found out that age along with AIP and hemoglobin had explanatory power on hypertension. Previously Shimizu et al. reported positive association between hemoglobin levels and hypertension risk [17]. Krishnamoorthy et al. [18] stated that hypertension is more prevalent in polycythemia patients. Also during pregnancy, hemoglobin concentrations are significantly increased at pregnancy induced hypertension patients [19]. When previous studies are examined, it was expected to found the association between hemoglobin levels, age and hypertension and our study supports these results.

Major limitation for this study was the small number of the patients. Further studies with large sample size must be performed to evaluate the effects of AIP on both hypertension and its complications to improve our knowledge on these issues. Also, this study was conducted at one center and the study population represented a limited population. Similar multicenter studies must be conducted to confirm our results.

In conclusion, AIP is higher in patients with hypertension and correlated with day-time, night time and all day systolic and diastolic blood pressure values.

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C-reactive protein and red cell distribution width as indicators of complications in patients with acute appendicitis

Akut apandisit tanısı konmuş hastalarda komplikasyon belirteçleri olarak C-reaktif protein ve kırmızı küre dağılım indisinin yeri ve önemi

Okan Murat Aktürk [1], Mikail Çakır [1], Doğan Yıldırım [1], Muzaffer Akıncı [1]

Abstract

Aim: Acute appendicitis is one of the most common operations in general surgery. When complicated, mortality and morbidity increases. We aimed to find out whether use of C-reactive protein (CRP) and red cell distribution width (RDW) may help to find out development of complications with acute appendicitis at initial evaluation in an emergency department.

Methods: Files of the patients who underwent operations for acute appendicitis between January 2017 and August 2017 were reviewed. Development of complications was recorded and the patients were grouped as with and without complications and were compared about age, sex RDW, CRP, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Diagnostic efficiency of CRP and RDW on the development of complications in acute appendicitis was investigated with regression analysis and by receiver operator characteristic curve analysis.

Results: Age, CRP and RDW were found to be significantly related to perforation ($p<0.001$ for all) (Bonferoni correction), while white blood cell (WBC), AST and ALT were found to be insignificant ($p=0.052$, $p=0.806$ and $p=0.804$, respectively. There was a significant correlation between RDW and CRP in the Spearman non-parametric correlation analysis (correlation coefficient $r=0.244$ and $p<0.001$). There was no significant correlation of WBC to CRP and RDW.

Conclusion: CRP and RDW are biochemical parameters that help us to identify the development of complications in acute appencitis. CRP may be elevated in acute appendicitis; however, it must be kept in mind to be cautious about a potentially complicated acute appendicitis after a certain level, RDW in our study has been found to be elevated in complicated appendicitis cases; but, it may not helpful to detect for perforated or gangrenous appendicitis.

Keywords: acute appendicitis, hematologic tests, laboratory analysis, complications.

Öz

Amaç: Akut apandisit genel cerrahide en sık karşılaşılan operasyon sebeplerinden biridir. Komplike olduğu zaman mortalite ve morbidite artmaktadır. C-reaktif protein (CRP) ve kırmızı küre genişlik dağılım indisi (RDW) değerlerinin kullanılmasının komplike olan akut apandisit vakalarını acil servisteki ilk muayenede ayırt etmemizde faydalı olup olmadığını incelemeyi amaçladık.

Yöntemler: Ocak 2017 ve Ağustos 2017 tarihleri arasında akut apandisit nedeniyle opere edilmiş olan hastaların dosyaları tarandı. Hastalar yaş, cinsiyet, CRP, RDW, alanin aminotransferaz, aspartat aminotransferaz değerleri açısından komplike olan ve olmayan akut apandisit vakalarında karşılaştırıldı. Artmış serum CRP ve RDW değerlerinin komplike apandisit tanısı koymada ne kadar etkin olduğu regresyon analizi ve alıcı işlemci nitelikleri eğrisi analizi ile değerlendirildi.

Bulgular: Yaş, RDW ve CRP, perforasyon ve gangrenöz apandisit ile belirgin olarak ilişkili olarak bulundu, $p<0,001$, beyaz küre, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT) düzeyleri ise P değerleri açısından anlamsız olarak bulundu (sırasıyla $p=0,052$, $p=0,806$ ve $p=0,804$). RDW ile CRP arasında korelasyon olmakla birlikte (korelasyon katsayısı $r=0,244$ ve $p<0,001$), beyaz küre ile RDW ve CRP arasında anlamlı bir ilişki yoktu.

Sonuç: CRP ve RDW komplike apandisit tanısını koymamızda biyokimyasal parametreler olarak değerlendirilmelidir. CRP akut apandisit vakalarında artmış olarak tespit edilebilir ancak belli bir seviyeden sonra komplike olmuş bir apandisite işaret edebilir. RDW bizim çalışmamızda komplike apandisitlerde artmış olarak bulundu. Ancak bu yükseklik için bir eşik değer tespit edilemedi.

Anahtar kelimeler: akut apendisit, hematolojik testler, laboratuar analiz, komplikasyonlar.

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Ethics Committee Approval: The study was approved by the local ethical authority (29.11.2018/270).
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Introduction

In the emergency surgery, acute appendicitis (AA) is one of the most common operations [1]. The lifetime risk of developing an AA is 7% [2]. Even though it is such a common situation in the emergency department, the diagnosis may not be so easy at all the times causing challenges [3]. In addition to non-classical clinical presentation, what makes the diagnosis uneasy is that symptoms may sometimes overlap with other medical situations [4]. The condition may progress to perforation during almost 48 hours following the occurrence of AA and the delay is mostly responsible for most of perforated appendices [5].

C-reactive protein (CRP) is an acute inflammatory protein that rises up to a thousand times at sites of infection or inflammation [6]. IL-6 is the main promoter of the protein with IL-1 enhancing its effect [7]. CRP is elevated in inflammatory conditions such as rheumatoid arthritis, some cardiovascular diseases, and infection [8]. CRP has also been used as a diagnostic tool in appendicitis [9].

Red cell distribution width (RDW) is a well-known erythrocyte parameter that shows the variation and heterogeneity in the diameter of red blood cells. This old erythrocyte indice is now regarded as an inflammation related bio-marker. RDW and CRP values were shown to be correlated and an elevated RDW may be associated to elevation in erythrocyte sedimentation rate and interleukin-6 levels as well [10]. Elevated RDW has been found to be predictive or prognostic in various health conditions such as acute myocardial infarction and pulmonary hypertension [11, 12]. RDW has been also used diagnostic tool in appendicitis [13].

There is a great difference between the complications of a perforated appendicitis and a non-perforated case, thus, in order to use the sources in an efficient way and to help the accurate assessment of the patient at the initial evaluation in the emergency room, we hypothesized that we could identify predictive factors for an appendicitis case which has been complicated. To achieve this goal we studied efficiency of blood parameters of CRP, RDW and white blood cell count (WBC).

Material and methods

The study was designed as a retrospective cohort study in the Department of General Surgery, Haseki Training and Research Hospital. The files of the patients who underwent operation for AA between January 2017 and August 2017 were reviewed. The permission was obtained from the local ethics committee (29.11.2018/270). The preoperative diagnosis is carried out by a combination of physical examination, laboratory tests and radiological findings. The laboratory tests comprise of complete blood count and liver function tests. All patients had an ultrasound or a computerized tomography scan.

All the patients who underwent appendectomy (both open appendectomy and laparoscopic appendectomy) were taken in the study; then, the patients who had an appendectomy for purposes other than appendicitis (histologically normal appendix vermiformis, parasitic appendicitis, intra-operative diagnosis of Crohn's disease, accompanying gynecological operations, appendiceal mucocele and plastrone formation) were excluded. Then, the patients were checked for the availability of the blood parameter tests within the specified time and they were included in the study (Figure 1).

The complicated and simple appendicitis (SA) were verified by the pathology report and perforated or gangrenous appendicitis (PGA) is given as a cardinal output. The blood samples were obtained six to eight hours prior the operation.

The complicated and non-complicated appendicitis were verified by the pathology reports and perforated or gangrenous appendicitis is given as a cardinal output. The blood samples were obtained at the six to eight hours prior the operation.

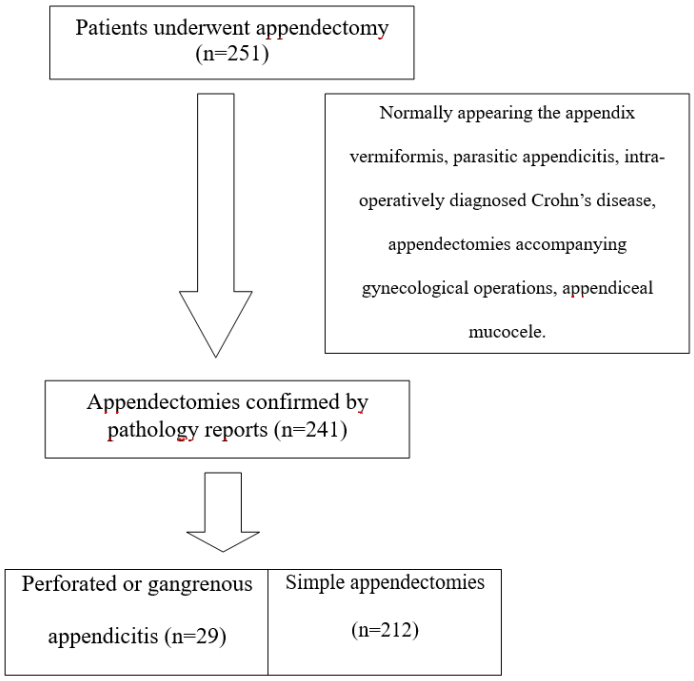

Figure 1: Flow chart of the study.

Surgical technique

Single dose antibiotic was administered pre-operatively (2nd generation cephalosporins or metronidazole and gentamycin) to all patients. Foley′s catheter was selectively employed In LA group Veress needle was used to induce pneumo-peritoneum under general anesthesia. A 3-trocar technique using 5- and 10-mm cannulas was the preferred way under general anesthesia. Electrocautery or other energy devices were used to dissect the mesoappendix and the stump was closed with endoclips. The appendix was placed inside a disposable bag to avoid contamination while taking out. Peritoneal cavity was irrigated with warm saline until the drainage fluid became clear and then pelvic drains were placed. Open appendectomy was carried out through a traditional McBurney operation and in rare cases by lower midline incision either by general or spinal anesthesia. Post-operative intravenous antibiotics (3rd generation cephalosporins combined with metronidazole) were given. Non-steroidal anti-inflammatory drugs were given either as intramuscular injection or via intravenous route to all patients during their hospital stay. Oral intake was started with return of bowel function in both groups. Patients were discharged when proper oral intake and mobilization are achieved save for those with post-operative complications. Oral antibiotics (ciprofloxacin and metronidazole) were given for one week after discharge. The follow up in the outpatient clinic was at the first and seconds weeks, and the first month. Patients were instructed to report back immediately for any complaints after the discharge. Complications recorded were wound infections (purulent discharge from wounds), intra-abdominal abscess (symptomatic post- operative collections in the peritoneal cavity), ileus (absence of peristaltic activity beyond 48 h) and fecal fistula. Clavien-Dindo grading system for the classification of surgical complications was used for evaluation of complications following appendectomy. These were graded into overall

complications (Grade I–V), severe complications (Grade III–IV) and mortality (Grade V) [14].

Statistical Analysis

The variables age, white blood cell count (WBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), RDW and CRP values were tested for normality with Shapiro-Wilk test. The variables WBC, RDW, CRP, AST, age and hospital stay were tested for normality and all were found to be non-normally distributed except for the hospital stay. Accordingly, the non-normally distributed data was represented in median and percentiles and normally distributed parameters as mean±standard deviation (SD). Mann-Whitney U test, Student's t test and $\chi 2$ test were used to assess differences where appropriate. Binary logistic regression analysis (with Bonferoni correction) was carried out to identify factors significantly associated to PGA.

We measured the prognostic performance of the RDW using receiver operating characteristic curves and calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (−LR) for different cutoff values We also made a correlation analysis to see if serum CRP levels correlated with RDW and WBC. All statistical tests were rendered with SPSS 22 (SPSS Inc, Chicago, Illinois). A value of P<0.05 was considered significant.

Results

The average age of 241 patients was 32.21±12.62 years. Twenty-nine (12%) patients were found to have a perforated or gangrenous appendicitis confirmed in the pathology report.

The values of the whole study group parameters were as follows: hospital stay was 2±0.13 (1-18) days, WBC 13.85 10^3uL (interquartile range (IQR)10.99-16.32), AST 20 U/L (IQR 16-25), ALT 18 (IQR 13-27) U/L, CRP 19.80 mg/L (IQR 5.55-80.60), RDW 13% (IQR 12.60-13.60).

Table 1: The general characteristics of the study groups.

	PGA (n=29)	SA (n=212)	p
Age (year)[¥]	46 (29.5-51.5)	28 (22-36)	0.005
Stay (day)[µ]	3.42±4.01	1.79±1.45	0.008
Gender[β]			0.045
Female	11 (4.6)	45 (18.6)	
Male	18 (7.4)	167 (69.4)	

[¥]: median (interquartile range), [µ]: mean±standard deviation, [β]: n (%). SA: Simple acute appendicitis group, PGA: perforated or gangrenous appendicitis group.

Table 2: The main outcomes of the study groups.

	PGA (n=29)	SA (n=212)	P
WBC (10 ^3uL) [¥]	14.35 (11.84-17.16)	13.62 (10.94-16.19)	0.202
CRP (mg/L) [¥]	82.9 (19.48-171.30)	16.95 (4.00-65.40)	<0.001
RDW (%) [¥]	13.5 (12.90-14.70)	12.90 (12.60-13.50)	0.005
AST (U/L) [¥]	24.47 (15-25.50)	23.00 (17.00-24.00)	0.980
ALT (U/L) [¥]	23 (12.75-24.25)	23.14 (14.00-26.00	0.562

[¥]: median (interquartile range), SA: simple acute appendicitis group, PGA: perforated or gangrenous appendicitis group, WBC: white blood cell, CRP: C-reactive protein, RDW: red cell distribution width, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

In the nonparametric analysis the PGA group was found to be significantly older than the SA group, 46 (IQR 29.5-51.5) years vs 28 (IQR 22-36), (p=0.002). The mean hospital stay for the PGA group was 3.42±4.01 days vs 1.79±1.45 days in the SA group, (p=0.008, Table 1). The median CRP was 82.9 mg/L (IQR 19.48-171.30) vs 16.95 mg/L (IQR 4.00-65.40) in the PGA and SA groups respectively, (p<0.001). Median RDW was 13.5% (IQR 12.90-14.70) in the PGA group vs 12.90% (IQR 12.60-13.50) in the SA group (p=0.005) (Table 2).

In the binary logistic regression analysis, age, CRP and RDW were found to be significantly related to perforation, (p<0.001), while WBC, AST and ALT were found to be insignificant (p=0.052, p=0.806 and p=0.804, respectively. To identify perforated or gangrenous cases, receiver operating characteristics (ROC) curves were plotted for CRP with a statistically significant area under the curve (AUC) of 0.716 (95% confidence interval, 0.615–0.818) (Figure 2). ROC curves were also plotted for WBC and RDW, as well, yielding AUCs as 0.604 and 0.671 respectively (Figure 3), It was only significant for RDW (p=0.005). However, it did not give a specific threshold for discrimination (Table 3).

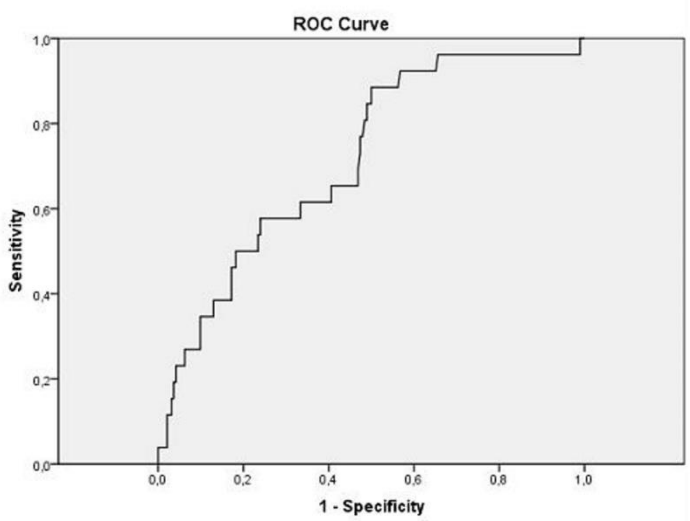

Figure 2: The area under the curve (AUC) for CRP was 0.716 (95% confidence interval, 0.615–0.818, p<0.001).

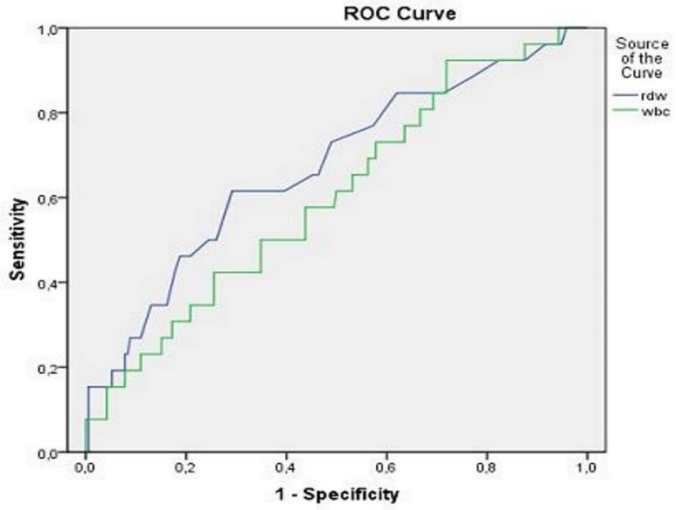

Figure 3. Receiver operator characteristics for WBC and RDW.

Table 3: Area Under Curve (AUC) for WBC and RDW.

	AUC	P	95% Confidence Interval	
RDW	0.671	0.005	0.556	0.787
WBC	0.604	0.086	0.490	0.718

WBC: white blood cell, CRP: C-reactive protein.

Around a level of 4.95 for CRP, the sensitivity in this study was 96.15% with a specificity of 32.29 % and with a positive predictive value of 16.13%. By the ROC curve analysis, a cut-off level was defined and with that level of 16.7 mg/dL,

these values were 88.46%, 49.48 % and 19.17%, respectively (Table 4).

Table 4: The predictivity of CRP at different cut-off values.

Cutoff for CRP	Sensitivity	Specificity	PPV	NPV
5 mg/L	96.15	32.29	16.13	98.41
16.7 mg/L	88.46	49.48	19.17	96.94

CRP: C reactive protein, PPV: positive predictive value, NPV: negative predictive value.

There was a significant correlation between RDW and CRP (correlation coefficient r=0.244 and p<0.001). But no significant correlation of WBC to CRP and RDW was observed (p>0.05 for all).

Overall, there were 13 wound infections, 10 intra-abdominal fluid collections, one fecal fistula encountered in the follow up. There were nine simple wound infections that required bed-side opening or drug therapy (grade 1); three abscess and hematoma in the wound that required recurrent draining (grade 3a). One case that underwent multiple debridement and resturing of the wound was classified as grade 3b.

Of 10 intra-abdominal fluid collections, four resolved by drug therapy alone (grade 2). Six cases were sent to ultrasound guided drainage (grade 3a). Ultrasound guided drainage was effective in treatment of intra-abdominal fluid collections combined with antibiotherapy.

One fecal fistula following appendectomy occurred in a patient who discontinued medication after a removal of appendicitis with pericecal abscess (grade 3b). Six cases of postoperative ileus resolved by medical therapy (grade 1).

Discussion

Appendicitis is still the most common non-elective surgical operation carried out by the general surgeons [15]. Traditionally, appendectomies are carried out as soon as possible after the diagnosis to avoid the progression of the inflammation and potential complications of of the disease[16]. However, there are also other factors which effect the timing of the operation like the availability of the surgery room, or delays in the diagnostic procedure [17]. Giraudo et al. [18] in a retrospective study report that a delayed appendectomy more than 24 hours after the initial admission increase rate of the postoperative complications. Earley et al. [19] report that the decrease in the time elapsed between the admission to hospital and the intervention reduces the perforation and postoperative complication rate. Dtillo et al. [20] classified the appendicitis cases with regard to the pathological state. They figured out that the pathological condition, defined as a higher pathology grade, progressed with the total time taken to intervene. There are also other studies which advocate a traditional prompt operation [21]. However, some recent studies report about a somewhat delayed appendectomy (until the working hours) does not increase the postoperative complications [22,23]. There are also other reports about treatment of appendicitis with antibiotics. In 1995, in a randomized prospective study they treated patients with antibiotics with the criterion that the symptoms had an onset less than 72 hours [24]. In another prospective study they report that non-perforated appendicitis can be treated successfully with antibiotics with a risk of recurrence of 14% in the following year [25].

For a more efficient utilization of available sources, identification of complicated cases is crucial. The importance of CRP in diagnosing appendicitis is well-known, and our study is no exception, either. In harmony with our study, Ortega-Deballon et al. [26] report that CRP has more accuracy in diagnosing appendicitis than the WBC and granulocytes counts. Sack et al. [27] found that WBCs count was clearly elevated in children with phlegmonous and perforated appendicitis. In a study by Xharra et al. [28] they reported that the elevated level of the CRP directly correlated to the severity of inflammation, as they classified the appendicitis in three stages, normal, simple (catarrhal and phlegmonous), complicated (gangrenous and perforated) (p-value <0.05). Yokoyama et al. [29] designed a study to display the importance of C-reactive protein (CRP) as a surgical indication marker for appendicitis to discriminate between the simple cases to be cured medically and complicated appendicitis which necessitate surgery . The AUC for CRP to identify necrotic appendi-citis in their study was 0.862. This value is 07.16 in our study and is significant, p<0.001. Around a level of 4.95 for CRP, they reached a sensitivity of 84.3%, specificity of 75.8%, positive predictive value of 64.2%, and a negative predictive value of 90.4%. Around this cut-off the sensitivity in this study is 96.15% with a specificity of 32.29 %, a positive predictive value of 16.13% and a negative predictive value of 98,41%. In our study with a cut-off level of 16.7 mg/dL, these values are 88.46%, 49.48 %, 19.17%, 96.94, respectively (Table 4). Our threshold seems to be higher than their estimation and this gives us more space to start medication for a presumably uncomplicated appendicitis case.

In a study Boshnak et al. [30] observed a conclusion that RDW level was significantly elevated in the complicated AA cases, (13.30±0.58 vs13.02±0.40, p=0.006). Our study confirms that RDW is elevated in the complicated AA cases (14.28±2.12 vs 13.25±1.11, p=0.005). However, these elevated values are within the normal range of the laboratory test; even though, in our study the median RDW for a complicated appendicitis is close to the upper limit of normal (11.5%-14.5%). In a study by Bozlu et al. [31] they found out that RDW was elevated in children with AA but they did not find a significant difference in complicated cases, unlike our study. In the same study they confirmed that CRP levels were significantly different between complicated and SA cases, in agreement with our findings.

Our study has some shortcomings. Due to the retrospective nature of the research, selection bias may be possible. All consecutive patients were included in the study, besides all the information was readily available in the database.

In conclusion, an elevated level of CRP in an acute appendicitis is an expected finding; however, the volume of this elevation may be related to a complicated appendicitis. Beyond a certain threshold prediction capability of CRP for a potentially complicated AA increases. We compared our suggested threshold with the findings of a previous study and found similar predictivity but for a much higher threshold. For a decisive threshold the number of total observations must be increased and supported by meta-analysisses. RDW in our study has been found to be elevated in complicated appendicitis cases; however, this finding is not conclusive for a potentially perforated or gangrenous appendicitis.

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Vertical banded gastroplasty combined with Roux-en-Y gastrojejunostomy to enable effective weight loss without compromising access to stomach, duodenum and biliary tract for selected patients

Mide, duodenum ve safra yollarına erişimden ödün vermeden, seçilmiş hastalarda etkili kilo kaybını sağlayan bir yöntem: Vertikal bantlı gastroplasti – Roux-en-Y gastrojejunostomi

Tuğba Han Yılmaz [1], Hüseyin Gülay [1]

Abstract

Aim: To evaluate the feasibility of vertical banded gastroplasty combined with Roux-en-Y gastric bypass as an operational gastro-gastric outlet technique with the potential to allow appropriate management of whole biliary and upper gastrointestinal tract after bariatric surgery without compromising weight loss.

Methods: This study included 24 patients (mean age: 36.8 years, range 18 to 58 years, 62.5% female) who had undergone vertical banded gastroplasty combined with Roux-en-Y gastric bypass between 2003 and 2016 in our clinic and had completed a 7-year postoperative follow up. Data on operative characteristics, length of hospital stay and follow up data on postoperative complications and weight loss were recorded for each patient.

Results: Mean operative time was 180±45 minutes while length of hospital stay was 6.0±1.0 days. There was no mortality, and only one patient (4.2%) was reoperated for hemorrhage on the first postoperative day. The most common patient complaints were early nausea and vomiting in 11 patients (45.83%), which disappeared in the second postoperative month, while 7 patients (29.2%) had dysphagia in the early postoperative period. No marginal ulcers or ulcers on anastomosis were found. Mean percentage of excess weight loss values recorded at the end of the first, second, third, fifth and seventh year following vertical banded gastroplasty combined with Roux-en-Y gastric bypass were 68.1±13.8 71.3±8.8 70.8±14.6, 68.2±11.3 and 61.4±13.3, respectively.

Conclusions: Our findings indicate the feasibility of vertical banded gastroplasty combined with Roux-en-Y gastric bypass as a bariatric surgical procedure providing better postoperative evaluation and management of the whole upper gastrointestinal system through the stomach window created with the band along with acceptable weight loss in selected patients.

Keywords: Obesity surgery; vertical banded gastroplasty; gastric bypass; endoscopic interventions

Öz

Amaç: Bu çalışmada, oluşturulan gastro-gastrik yol ile bariatrik cerrahi sonrası mide duodenum ve safra yollarının değerlendirilmesine olanak sağlayan vertikal bantlı gastroplasti ve Roux-en-Y gastrojejunostomi tekniğinin kilo kaybı üzerine etkilerinin değerlendirilmesi amaçlandı.

Yöntemler: Kliniğimizde 2003-2016 yılları arasında vertikal bantlı gastroplasti-Roux-en-Y gastrojejunostomi yapılmış ve 7 yıllık takiplerini tamamlayan toplam 24 hasta (ortalama yaş: 36.8 yıl (18 - 58 yıl), % 62.5 kadın) çalışmaya dahil edildi. Yapılan ameliyatın özellikleri, hastaların hastanede kalış süreleri, ameliyat sonrası komplikasyonlar ve kilo kaybı ile ilgili veriler kaydedildi.

Bulgular: Ortalama ameliyat süresi 180±45 dakika ve hastanede kalış süresi 6.0±1.0 gündü. Mortalite olmadı, sadece bir hasta (% 4,2) ameliyat sonrası birinci günde kanama nedeniyle tekrar ameliyat edildi. Hastaların en sık görülen şikayetleri, ameliyat sonrası ikinci ayda kaybolan erken bulantı ve kusma idi, 11 hastada (%45,83) görülmüştür. 24 hastanın 7'sinde (%29,2) operasyonun erken döneminde disfaji şikayeti vardı. Hastalarımızın takibinde gelişmiş marjinal ülser veya anastomoz ülseri tespit edilmedi. Vertikal bantlı gastroplasti-Roux En Y Gastroenterostomi yapılan hastalarımızın birinci, ikinci, üçüncü, beşinci ve yedinci yıllarının sonunda kaydedilen ortalama fazla kiloların kaybı yüzdesi sırası ile 68,1 ± 13,8, 71,3 ± 8,8, 70,8 ± 14,6, 68,2 ± 11,3 ve 61,4 ± 13,3'dür.

Sonuç: Bulgularımız üst gastrointestinal sistemin değerlendirilmesine, oluşturulan gastro-gastrik yol ile olanak sağlayan vertikal bantlı gastroplasti- Roux-en-Y gastrojejunostomi'nin kabul edilebilir düzeyde kilo kaybı sağlayarak, seçilmiş bazı hastalarda uygulanabilir bir cerrahi yöntem olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Obezite cerrahisi, vertikal bantlı gastroplasti, gastrik by-pass, endoskopik girişimler

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Ethics Committee Approval: The study wass approved by the local ethical authority (94603339-604.01.02/15832/24.04.2019).

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Introduction

Bariatric surgery is considered the only effective, sustainable treatment for obesity and obesity related co-morbidities, which have become an epidemic in western populations [1, 2]. The number of bariatric operations has increased rapidly during the last few decades [1-3]. According to the International Federation for Surgical Obesity and other associations for obesity treatment, a body mass index (BMI) of ≥40 kg/m2 or ≥35 kg/m2 in combination with other serious medical problems is considered an absolute prerequisite for bariatric surgery candidacy [4, 5]. Although laparoscopic sleeve gastrectomy has become a more popular procedure lately, Roux-en-Y gastric bypass (RYGB) still remains one of the most effective surgeries for severe morbid obesity as it is associated with better long-term weight loss than vertical banded gastroplasty (VBG) [6].

Given the difficulties in accessing and evaluating the bypassed portion of the stomach and duodenum after RYGB, the postoperative utility of endoscopic procedures, such as sphincterotomy and gastroduodenoscopy, is limited for patients following bariatric surgery. This seems important given the expected increase in cholelithiasis and complications after bariatric surgery as well as the increasing prevalence of gastric cancer.

Therefore, a technical modification enabling access to the stomach and duodenum via X-ray or endoscopy after RYGB while not interfering with weight loss seems to offer earlier diagnosis and better management of any gastroduodenal pathologies that emerge following bariatric surgery.

In this regard, the adaption of the gastric bypass by connecting the Roux-en-Y limb to the VBG pouch, which was originally developed to improve long-term weight loss [6], could also enable endoscopic assessment of the bypassed portion of the stomach and duodenum after RYGB.

The present study was therefore designed to evaluate the feasibility of VBG combined with RYGB (VBG-RYGB) as an operational gastro-gastric outlet technique with the potential to allow appropriate management of the whole biliary and upper gastrointestinal tract after bariatric surgery without compromising weight loss.

Material and methods

Study population

Of 32 bariatric surgery patients who underwent VBG-RYGB at our tertiary care center between 2003 and 2016, 24 patients (mean age: 36.8 years, range, 18 to 58 years, 62.5% female) with 7-year follow up data were included in this study. All patients were informed about the operation, relative risks, benefits and complications.

This study was approved by the ethics committee of our institution (94603339-604.01.02/15832 and 24.04.2019). Informed consent documents were taken from all the patients. The study was performed following the Helsinki Declaration.

Study parameters

Data were recorded on patient demographics (age, gender), operative characteristics, length of hospital stay (LOS), and 7-year follow up data on postoperative complications and excess weight loss (EWL).

Surgery

All patients received antibiotic and antithrombotic prophylaxis. Subcostal incisions were used for all operations. The VBG technique was later adapted using an alimentary small bowel limb which was anastomosed to the jejunum with a Roux limb of 80-100 cm. CEEA 25 staplers, TA 90 were used for creating the gastric pouch (Figure 1). We prepared a 5-cm-length, 1.5-cm-width band with polytetrafluoroethylene (PTFE) vascular Gore-tex graft for the gastric pouch outlet. From the 30th cm of the Treitz, the jejunum was divided and anastomosed to the anterior wall of the prepared stomach pouch with side-to-side anastomosis of 2 cm diameter (Figure 2). A hand-sewn side-to-side jejuno-jejunostomy with the biliopancreatic limb completed the RYGB and the mesenteric windows were closed afterwards.

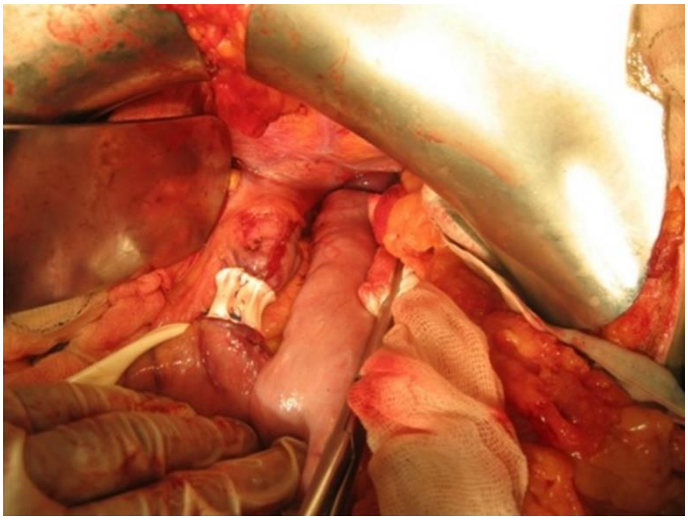

Figure 1. Vertical banded gastroplasty.

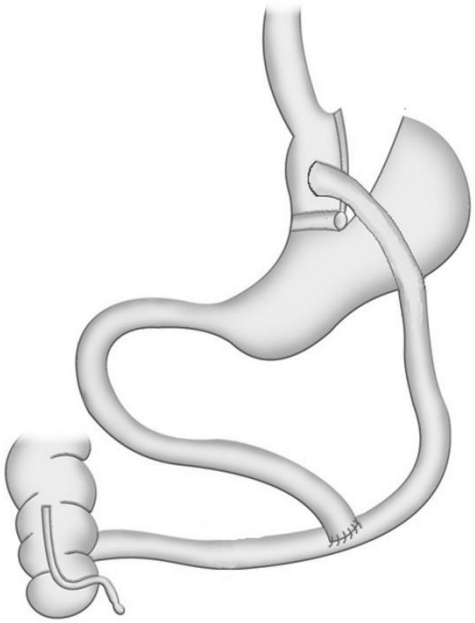

Figure 2. Vertical banded gastroplasty and Roux-en-Y gastrojejunostomy.

After VBG-RYGB, nearly all food was determined to follow the gastro-jejunostomy, with only a small amount crossing the gastro-gastric outlet restricted by the band (Figure 3).

Conversion to VBG-RYGB technique was also performed on three patients with VBG prior to study enrollment, who had dehiscenced stapler lines after operation. The omentum was placed between the divided gastric edges afterwards.

Liquid diet was started on the third day after the operation. This was gradually changed to solids over 6 weeks (clear diet: 3-4 days, semi-liquid diet: 5th day-3rd week, soft consistency solid foods: 3rd-6th week, solid foods: after 6

weeks). Follow up was programmed at 3, 6 and 12 months and then annually.

Results

Overall, the mean age of the patients was 36.8 (range 18 to 58) years while 62.5% were female patients. Preoperatively, mean body mass index (BMI) and body weight were 49.1±8.9 kg/m2 and 148.3 ±38.1 kg, respectively. Three patients had had VBG operation 2.5 years before study enrollment, who had dehiscenced vertical stapler lines.

Mean operative time was 180±45 minutes while LOS was 6.0±1.0 days. None of the patients needed blood transfusion. There was no mortality, while only one patient was reoperated for hemorrhage on the first postoperative day. The most common complaints of the patients were early nausea and vomiting in 11 patients (45.83%), which disappeared on the second postoperative month, while 7 of the 24 patients (29.2%) had dysphagia in the early postoperative period.

Three patients (12.5%) had fat necrosis at the wound site in the early postoperative period while 2 patients (8.3%) had incisional hernia in the second year.

Mean percentage of EWL values recorded at the end of first, second, third, fifth and seventh year of VBG-RYGB were 68.1±13.8, 71.3±8.8, 70.8±14.6, 68.2±11.3 and 61.4±13.3, respectively.

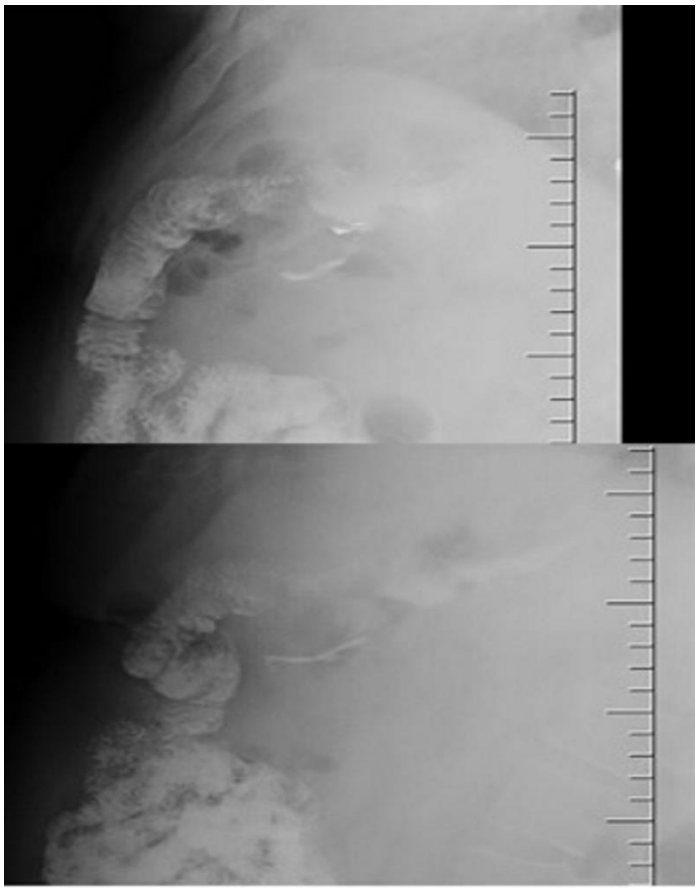

Figure 3. Contrast radiography. Only a very small amount of barium passes through the gastro-gastric outlet whereas nearly all passes through the gastro-jejunal anastomosis.

Cholecystectomy for cholelithiasis was performed in the second postoperative year in 2 patients and in the fourth postoperative year in 3 patients, while 3 patients received ursodeoxycholic acid following cholecystectomy for 5 months.

Barium x-ray assessment performed on all patients after the first year showed that only a small amount of barium in the late stage was able to pass through the gastro-gastric outlet (Figure 3), with nearly all the barium passing through the gastrojejunal anastomosis. This condition remained unchanged for the entire 5-year follow up. The passage film of 19 patients in the 5th year were similar to that shown in Figure 3.

Endoscopy was performed in 5 patients with gastrointestinal symptoms of nausea (Figure 4) in the first postoperative year, and in 16 patients in the third postoperative year. However, no marginal ulcers or ulcers on anastomosis were found in our series.

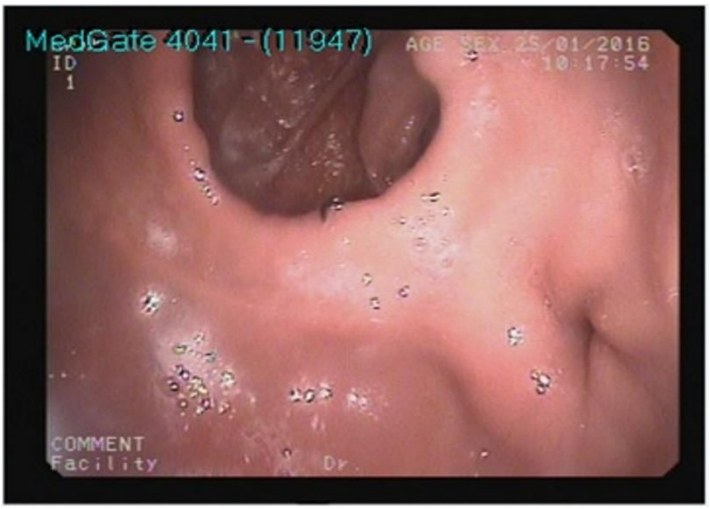

Figure 4. Endoscopy. Gastrojejunostomy (left), gastro-gastric outlet (right).

Discussion

Weight loss is the primary aim of bariatric interventions, and most studies have focused on reducing initial excess weight or lowering BMI to quantify the effects of the operation. A bariatric intervention is considered successful when a persistent weight loss of more than 50% body weight excess is achieved [7].

With 68.1% loss of the patients' initial excess weight on the first year, 71.3% in the second year and 70.8 % in the third year, the weight loss in our cohort of patients operated with VBG-RYGB, our findings seem consistent with the range for EWL (48.6 to 71.6%) reported from 54 studies involving 14,964 patients with current bariatric interventions [8, 9]. This seems also consistent with mean EWL reported specifically for 11 studies of 3,382 patients operated with VBG (58.3%) and 15 studies of 2,949 patients operated with RYGB (68.6%) [8, 9].

An earlier study assessing VBG-RGB for treating morbid obesity reported a complication rate of 0.5% and mortality rate of 0.3%, alongside mean weight loss of 58kg (range 14 to 143), percentage EWL of 77 (range 32 to 108) and mean BMI reduction to 29 kg/m2 (range 20 to 43) at 5-year follow up [6].

Another study of 289 patients who underwent RYGB-on-VBG as their primary procedure reported percentage EWL of 48.2±18.8 after 6 months, 59.0±17.7, 63.3±13.9, 66.9±17.5 and 70.0±17.7 after 1, 2, 3 and 4 years, respectively [10]. The authors noted that RYGB-on-VBG had a similar weight loss curve as standard RYGB while allowing for traditional radiography of the bypassed stomach and endoscopy of the distal stomach and biliary tract [10].

Patients with morbid obesity have a higher incidence of gallstones than the general population, with up to 50% rates reported in the literature [11, 12]. Formation of gallstones after rapid weight loss is also a well-recognized phenomenon, which RYGB patients are predisposed to during the first postoperative

year [13]. In our cohort, gallstones were managed individually by laparoscopic cholecystectomy in symptomatic patients.

The management of common bile duct (CBD) stones after RYGB is challenging given the difficulties in performing conventional endoscopic retrograde cholangiopancreatography (ERCP) for choledocholithiasis due to the exclusion of the duodenum from the gastrointestinal tract and the long anatomic route from mouth to the major papilla. The Roux limb is at least 100 cm in length. Several techniques have been proposed to treat bile duct stones in RYGB patients.

In 1998, Baron and Vickers described the creation of surgical gastrostomy to access the gastric remnant [14]. Later, a double balloon was introduced as a new endoscopic technique to allow examination of the entire small bowel [15]. In a recent report [16], percutaneous endoscopic gastrostomy with immediate self-expandable metal stent placement allowed antegrade transgastric ERCP during the same procedure. An antegrade biliary stenting following laparoscopic CBD exploration for CBD stones was also considered effective [17]. Percutaneous transhepatic cholangioscopic lithotomy has also been suggested as an alternative technique. However, these procedures require advanced technologies in large centers with considerable experience. The technique used in this study (VBG-RYGB) therefore seems significant in this regard as traditional endoscopic and x-ray study of the distal stomach remain possible along with a favorable weight loss outcome.

Hence, our findings support the data from a past study of 128 patients who underwent RYGB on VBG via an open approach, which indicated that the weight loss curve following RYGB on VBG was as effective as that for standard RYGBP, while allowing traditional x-ray and endoscopy of the bypassed stomach, and thus the biliary tract [18].

The successful outcome after VBG-RYGB in our 3 patients with prior failed VBG operation also seems consistent with consideration of RYGB on VBG having a lower rate of complications and better quality of life than VBG reoperation in patients with complicated or failed VBG [19].

Neoplasias are rather infrequent after surgery for morbid obesity. The constitutional symptoms in these patients may go unnoticed due to the association between weight loss and prior bariatric procedure.

A meta-analysis found that overweight and obesity are associated with an increased risk of gastric cancer [20], while a higher prevalence of helicobacter pylori infection is associated with an increased risk of developing gastric cancer [21]. A greater risk of developing adenocarcinomas of the esophagus and stomach was reported in obese patients with BMI ≥35 kg/m² than in those with BMI of 18.5 to 25 kg/m² alongside an increase in the strength of the association with increasing BMI [21, 22]. The risk for adenocarsinoma of the gastric cardia has also been associated with obesity, with relative risks in the range of 1.5-2.0 [23]. Hence, it seems important that VBG-RYGB allows easier detection of neoplastic lesions in patients who undergo surgery for morbid obesity.

The likelihood of late complications, such as hemorrhage from the excluded gastric segment or duodenum after gastric bypass, poses both diagnostic and therapeutic difficulties [24]. Diagnosis and treatment of these patients are also possible in patients who undergo VBG-RYGB, which makes it easier to perform endoscopy.

Indeed, a study of 40 patients treated with VBG-RYGB for morbid obesity reported that the use of double-balloon enteroscopy was an effective and safe means to evaluate the bypassed stomach after VBG-RYGBP. It enabled successful examination of the bypassed stomach in 87.5% of patients, with a mean time of 24.9 minutes (range 5-75 minutes) to reach the bypassed stomach [25]. The authors suggested that long-term endoscopic surveillance is necessary after this type of surgery, based on endoscopic findings that only 25.7% of patients were normal compared to considerable rates of abnormalities, specifically erythematous/erosive gastritis (28.6%), atrophic gastritis (17.1%) and suspicious areas of intestinal metaplasia (11.4%) [25].

Our findings revealed no mortality and effective weight loss after the 7-year follow-up in patients with morbid obesity operated on with VBG-RYGB, although there were two routes from the gastric pouch: one towards the jejunum and the other towards the stomach. Hence, based on our long-term experience, we consider VBG-RYGB to be an effective operation that allows postsurgical management of the whole biliary and upper gastrointestinal tract alongside adequate control of severe obesity. This confirms data from obesity surgery centers that have adopted this technique, which reported favorable outcomes, and superior weight loss in morbid and superobese patients with a low mortality and morbidity [6, 18].

In the last 5 years, 27 laparoscopic gastric bypasses and 390 laparoscopic sleeve gastrectomies have been performed in our center. The number of VBG-RY gastroenterostomy cases is limited due to the ease and rapid applicability and good results of laparoscopic sleeve gastrectomy. However, in this period when laparoscopic surgery was preferred by both surgeons and patients, laparoscopic VBG-RY gastroenterostomy can be planned for selected patients. Our study has some limitations, it is a retrospective study, its findings should be reinforced by prospective studies designed laparoscopically and with more patients.

In conclusion, based on 7-year follow-up data, our findings indicate the efficacy and safety of VBG-RYGB in bariatric surgery for weight loss combined with low mortality and morbidity rates. In addition, this technique enables postoperative diagnostic and therapeutic endoscopic and x-ray imaging of the distal stomach, duodenum and biliary tract. Hence, our study suggests that VBG-RYGB provides a feasible bariatric surgical procedure with better postoperative evaluation and management of the whole upper gastrointestinal system through the stomach window created with the band while also enabling acceptable weight loss.

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Is there a relationship between the lengths of the ipsilateral clavicle and the ulna? An anthropometric and statistical study

Klavikula ve ulna boyları arasında anlamlı bir oran varmı? Antropometrik ve istatistiksel bir çalışma

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Abstract

Aim: Mathematical relationships between bones in close proximity are useful for determining the proper length of comminuted or severely displaced bones during surgical reconstruction. This study examined the relationship between the lengths of the clavicle and ulna to develop a length propotion formula that can facilitate obtaining the proper length of the clavicle during surgery for displaced and comminuted fractures.

Methods: The study enrolled 130 individuals (76 males, 54 females) who were healty for their upper extremities and was seen in our orthopedics outpatient clinic during April 2019 to June 2019. The right and left clavicles and ulnas of each individual were measured. All measurements were peformed by two of the authors in an blinded fashion.

Results. Mean overall age was 32.2 years. There were significant correlations between the clavicle and ipsilateral ulnar lengths (p=0.001). However, there was a length difference between the right and left clavicles. The left clavicle was 9.00 ± 2.16 mm longer than the right in males and 7.13 ± 2.03 mm longer in females (p=0.001). There was no significant length difference between the right and left ulnas in either sex (0.84 ± 1.033 mm in males and 0.52 ± 0.818 mm in females).

Conclusion. There is a significant ratio between the clavicle and ulna lengths on both the right and left sides in both sexes, but it isn't the same for males and females. We propose that these length proportion formula can be used for determining the clavicle length for the surgical treatment of comminuted fractures with plates and particularly with nails.

Key words: Comminuted fracture, clavicle, ulna, length ratio.

Öz

Amaç: Parçalı ve deplase kırıkların cerrahi rekonstrüksiyonu sırasında opere edilen kemiğin uygun boyunun tahmin edilebilmesi için bu kemik boyu ile komşu diğer bir kemiğin matematiksel olarak boy oranının kullanılması oldukça kullanışlıdır. Bu çalışmada parçalı klavikula kırıkları cerrahi tedavisi sırasında kullanılmak üzere, klavikula ve ulna kemikleri arasında matematiksel olarak anlamlı bir boy oranı olup olmadığının araştırılması amaçlanmıştır.

Yöntemler: Nisan-Haziran 2019 dönemi içerisinde, ortopedi ve travmatoloji polikliniğimizde görülen üst ekstremiteleri sağlıklı 130 hasta (76 erkek, 54 kadın) çalışmaya dahil edildi. Bütün hastaların sağ ve sol ulna ve klavikulaları birbirinin ölçümlerine kör 2 yazar tarafından, aynı yöntemler kullanılarak ölçüldü.

Bulgular: Toplamda ortalama yaş 32.2 yıl idi. Aynı taraf ulna ve klavikula boyları arasında anlamlı bir oran olduğu saptandı (p=0.001). Aynı zamanda sağ ve sol klavikula boyları arasında anlamlı uzunluk farkı bulunduğu görüldü. Sol klavikula, erkeklerde 9.00 ± 2.16 mm ve kadınlarda 7.13 ± 2.03 mm sağ klavikuladan daha uzun idi (p=0.001). Ancak her iki grupta da sağ ve sol ulna boyları arasında anlamlı bir fark saptanmadı (0.84 ± 1.033 mm erkeklerde ve 0.52 ± 0.818 mm kadınlarda).

Sonuçlar: Hem kadın, hem de erkeklerde her iki tarafta klavikula ve ulna kemikleri arasında matematiksel olarak anlamlı bir oran var olduğu ortaya kondu. Ancak bu oran her iki cinsiyet için farklı idi. Biz bu çalışmanın sonucuna dayanarak, parçalı klavikula kırıklarının plak ve özellikle çivi ile cerrahi tedavisi sırasında, ortaya konan bu orantısal formüllerin uygun kemik boyunun hesaplanarak sağlanması için kullanılabileceğini düşünmekteyiz.

Anahtar kelimeler: Parçalı kırık, klavikula, ulna, boy oranı.

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Introduction

Mathematical relationships between bones lengths and volumes have been evaluated to improve our understanding of normal and disordered growth, stature estimation, and biomechanics [1]. This approach known as "process structualism" advocates exploring regularities in biology as, this regularities may be very important [1, 2]. Dogan and Aydınlioglu et al. [3, 4] had found evidence of fixed proportions between the length and width of metacarpals and phalanges in the foot. Besides authors defined proportions between the length and width of metatarcarpals and phalanges of hand as well. Although this philosophical perspective is a known issue among anatomists and mathematicians, its clinical application in to surgeons' daily practice is very limited.

Reconstruction of the length of a broken bone is at the utmost importance as inappropriate reconstruction will eventually result in further deterioration of the biomechanics of the extremity [5]. Particularly bones with irregular structures like the clavicle are the most challenging bones that allows exact estimation of its lengths during surgery [6].

Intramedullary nailing of clavicle fractures is an alternative to plate fixation, but it is difficult to estimate the proper length when using intramedullary devices because the clavicle has a double curvature and lies horizontally [6, 7], especially in comminuted fractures.

From this point of view, this study examined whether there is a mathematical relationship between the clavicle and another bone that can facilitate surgery and which bone is the easiest to measure with less exposure to radiation. During surgical intervention for clavicle fractures, the upper extremities are the easiest to access. In addition, the anatomical prominences of the upper extremity bones facilitate their evaluation without need for an x-ray. However, the lack of anatomical prominences on the humerus and radius makes them unsuitable for exact measurements. Therefore, we hypothesised that; if a proportion between lengths of both clavicles and ulnas exists, this finding can be applied to the clinical practice to estimate the length of the clavicle during a fracture surgery of this bone.

Material and methods

Study was conducted in accordance with principles for human experimentation as defined in the Declaration of Helsinki and approval was obtained from the institutional ethics committee and informed consent was received from all individuals. (Istanbul Medeniyet University, Goztepe Training and Research Hospital, Clinical Researchs Ethics Committee, Approval number: 2013-KAEK-64-2019/0235).

Study was carried out in our institution between April 2019 and June 2019. Individuals were examined only one time and further evaluation of measurements were not performed. The study enrolled 130 individuals (76 males, 54 females; mean age 32.2 years overall, 34.0 years for males, and 29.7 years for females) who were seen in our orthopedics outpatient clinic.

To increase the homogenity of the study only individuals from Caucasian races were included. Also individuls that had reached skeletal maturity and were healty for their upper extremities were included to the study. Individuals from other races rather than Caucasians, with recent trauma, a history of surgery, or congenital deformity of the upper extremities were excluded from the study.

The right and left clavicles and ulnas of each individual were measured while the individuals were standing, with both arms at their sides and their palms facing forward. The anatomical measurement points for the clavicle were the distal (lateral)-most prominence of the acromioclavicular junction and the medial-most prominence of the sternoclavicular joint (from the medial side of the sternal head of the sternocleidomastoid muscle) (Figure 1a). The measurement points for the ulna were the proximal-most prominence on the olecranon and the distal-most prominence on the ulnar styloid (Figure 1b).

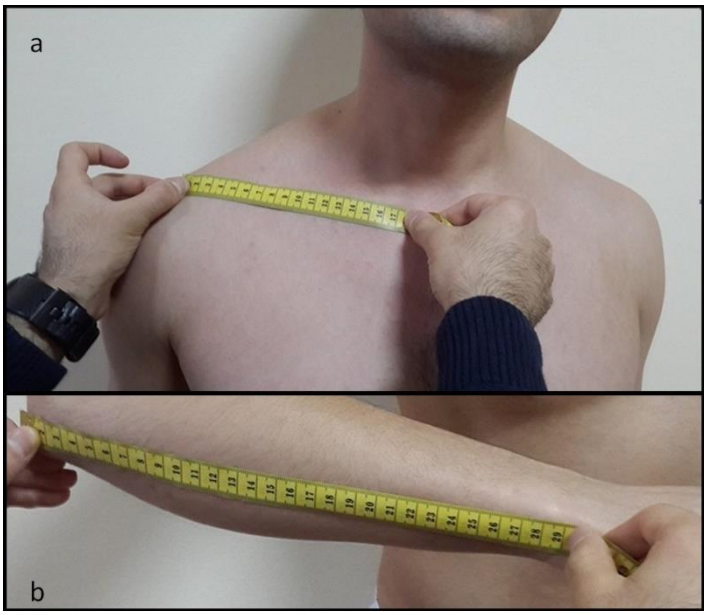


Figure 1. a) Measurement of clavicular length, b) measurement of ulnar length.

The measurements were made by two of the authors (M.D. and D.A.) in two different rooms. Each individual was evaluated by both surgeons, and each surgeon kept his records blind to the other. At the end of the study, all measurements were assessed by the senior author (K.O.) and the mean between the measurements was taken into account. After completion of clinical data collection, all measurements were analysed to find the mathematical relations between clavicula and ulna lengths and their difference among sexes.

Statistical analysis

Descriptive analysis was performed using SPSS® ver. 22.0 (IBM, Armonk, NY, USA). The Lilliefors-corrected Kolmogorov–Smirnov test was used to examine the normality of the distributions. The Levine test was used to examine the homogeneity of the variances. Independent samples t-tests with bootstrap results were used to compare two independent groups. A p value of <0.05 was considered to be statistically significant for all analyses.

Results

There were significant correlations between the lengths of each clavicle and the ipsilateral ulna ($p=0.001$). In addition, there was a length difference between the right and left clavicles, with the left clavicle being 9.00 ± 2.160 millimeters (mm) (range 12.00–5.00 mm) longer than the right clavicle in males and 7.13 ± 2.029 mm (range 10.00–4.00 mm) longer in females ($p = 0.001$). There was no significant length difference between the right and left ulnas in either sex (0.84 ± 1.033 mm in males and 0.52 ± 0.818 mm in females, respectively). The data analyses showed small differences between the various ratios for males and females and the results are shown in Table 1.

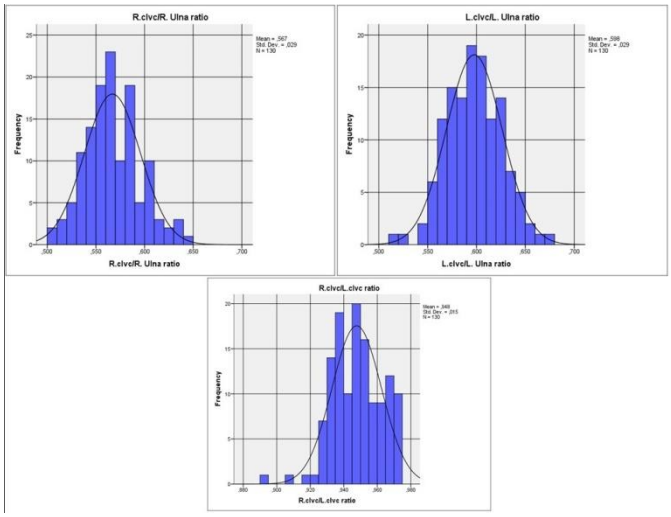
The difference between sexes for the left clavicle/left ulna ratio was significant ($p = 0.046$), while the differences for the clavicle/clavicle ratio ($p = 0.100$) and right clavicle/right ulna

(p = 0.121) were not significant. Therefore, although the left clavicle length can be determine in each sex with different ratio, the right clavicle length can be determined with the same ratio in both sexes (Figure 2).

Table 1: Ratios for males and females.

For Males	
Right clavicle length/ipsilateral ulna length	0.57 ± 0.029 mm
Left clavicle length/ipsilateral ulna length	0.60 ± 0.028 mm
Right clavicle length/left clavicle length	0.95 ± 0.015 mm
For Females	
Right clavicle length/ipsilateral ulna length	0.56 ± 0.029 mm
Left clavicle length/ipsilateral ulna length	0.59 ± 0.028 mm
Right clavicle length/left clavicle length	0.95 ± 0.015 mm

Figure 2. Data for right clavicle/right ulna, left clavicle/left ulna, and right clavicle/left clavicle ratios for both sexes.



Right clavicle length/ipsilateral ulna length = 0.57 for both sexes

Right clavicle length/left clavicle length = 0.95 for both sexes

Left clavicle length/ipsilateral ulna length = 0.60 for males

Left clavicle length/ipsilateral ulna length = 0.59 for females

The results of the other measurements are summarized in Table 2.

Table 2. Descriptive analyses of the data.

	Total (N=130)	Female (n=54)	Male (n=76)	P
Age (year) ¥	32.22±14.022	29.70±13.198	34.01±14.397	0.081
Right clavicle (mm) ¥	152.05±12.032	141.33±7.922	159.67±7.944	0.001
Left clavicle (mm) ¥	160.45±12.549	148.72±8.013	168.78±7.499	0.001
Length difference (mm) ¥	8.22±2.293	7.13±2.029	9.00±2.160	0.001
Right ulna (mm) ¥	268.38±19.601	251.54±11.955	280.36±14.500	0.001
Left ulna (mm) ¥	268.64±19.719	251.52±11.905	280.80±14.411	0.001
Length difference(mm) ¥	0.71±0.960	0.52±0.818	0.84±1.033 /	0.133
Right clavicle/right ulna	0.57±0.029	0.56±0.029	0.57±0.029	0.121
Left clavicle/left ulna	0.60±0.029	0.59±0.028	0.60±0.028	0.046
Right clavicle/left clavicle	0.95±0.015	0.95±0.015	0.95±0.015	0.100

¥: Mean±standard deviation.

Discussion

The anthropometric relations between the clavicle and the ulna is an unknown issue and there are very limited studies focusing on this issue [1, 2, 5]. Our study revealed that there are fixed proportions between ulna and the clavicle lengths. However these proportions are different among genders. These results can be applied to the clinical practice particularly during surgical intervention of comminuted the clavicle fractures.

The treatment of clavicle fractures remains controversial. Improvements in orthopedic surgery with new implant technologies have favored surgical intervention for midshaft clavicle fractures with improved clinical outcomes and earlier return to daily living activities. Surgery also reduces the nonunion and symptomatic malunion rates significantly compared with non-operative treatment, although the results still need to be improved [7, 8].

Osteosynthesis with plates for the treatment of midshaft clavicle fractures has been used extensively and is still the gold standard surgical treatment for these fractures [9]. Nevertheless, osteosynthesis with plates has disadvantages like cosmesis-related complaints due to the long incision scar, and delayed union or nonunion caused by excessive periosteal stripping in some cases [10]. Intramedullary nailing is being used successfully to treat fractures of this anatomically complex bone [11] because an intramedullary nail can be inserted with a minimally invasive technique. Closed reduction of the fracture preserves the fracture hematoma and the minimally invasive technique allows the surgeon to minimize soft-tissue dissection, thereby reducing surgical trauma, blood loss, infection, and wound complications [12]. Hill et al. [7] showed that the only parameter that affects fracture healing negatively in patients with a mid-shaft clavicle fracture is shortening exceeding 20 mm. Neither comminution of the fracture nor treatment method affects the development of nonunion when the pre-fracture bone length is achieved and maintained. Despite its superiority over plates, the disadvantage of intramedullary fixation of improper assessment of length caused by the complex anatomy of the clavicle is a major concern [13].

Intramedullary devices behave as internal splints that maintain alignment without rigid fixation [12]. In a study comparing conservative treatment and intramedullary fixation of displaced non-comminuted fractures, Smekal et al. [14] showed that clavicle shortening was significantly less with intramedullary fixation. However, 2 years later in a different study comparing plate and intramedullary fixation of clavicle fractures, the same authors recommended intramedullary fixation only for non-comminuted fractures because of shortening [15]. With rapid improvements in nail design, we will soon overcome this problem and intramedullary fixation can be used even in comminuted fractures. Then, only the intraoperative assessment of clavicle length will be a matter of concern. Using only fluoroscopic imaging will be problematic because the double curved anatomy of the clavicle cannot be assessed exactly in two-dimensional (2D) images.

Several studies have helped to increase our understanding of the restoration of clavicle fractures with plates and intramedullary nails. According to Cunningham et al. [16] Their trial showed only 28% clavicle have more than 5mm assymetry. Sehrawat et al. [17] found that left clavicle were longer length as our trial. Huang et al. [18] used a 3D digitizer to analyze the anatomy of the clavicle and applicability of pre-contoured clavicle plates. Bachoura et al. [19] found a positive correlation between the length of the clavicle, midpoint cortical diameter, and radius of the medial curvature of the clavicle. In a different study, the same authors tested the applicability of

intramedullary nails for midshaft fracture fixation using a similar method [6]. Daruwalla et al. [20,.21] determined the complex anatomy of the clavicle using 3D computed tomography (CT) and performed principal components analysis of the clavicle. They found some variation in the shapes and sizes of the left and right clavicles between genders. Although this information can be used to design new nails or plates for clavicle fracture treatment, its clinical application may be impossible since obtaining 3D CT images for every patient exposes patients to unnecessary radiation and its use in clinical practice may not be cost-effective. However, the ulna and contralateral clavicle lengths can be measured easily and the optimal clavicle length can be calculated with the use of our proposed ratio, even during surgery.

Preoperative measurement of the contralateral clavicle seems to be more valuable than intraoperative measurement of the ipsilateral ulna. Although the lengths of the right and left clavicles differed in both sexes, this did not change the ratio between the right and left clavicles in either sex, and it is easier to keep this length differences in mind. When preoperative measurements have not been made, intraoperative ulna measurements can provide the same results.

This study had some limitations. First, it would have been better if more individuals had been measured. Second, this study examined only Caucasians, and the measurements may vary with race. We recommend keeping this information in mind before employing the technique. It may also be useful to perform the same study in different races.

In conclusion, we found different right and left clavicle/ulna ratios. There was a significant relationship between the right and left clavicles in both sexes, and it was the same for males and females. We propose that the proportions between the clavicle and ulna lengths can be used to determine the appropriate length of the clavicle during surgical fixation of comminuted fractures with plates and particularly nails. This study may also form a basis for future studies.

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Which quality of life scale should be used to evaluate acne vulgaris patients? CADI or DLQI? A prospective study

Akne vulgaris hastalarının değerlendirilmesi için hangi yaşam kalite ölçeği kullanılmalıdır? CADI ya da DYKİ? Bir prospektif çalışma

Aslı Tatlıparmak [1], Berna Aksoy [1], Ayşe Serap Karadağ [2]

Abstract

Aim: Acne vulgaris is one of the most common diseases that affects quality of life. While the Dermatology Life Quality Index (DLQI) is the most frequently used life quality index for dermatologic disorders, the Cardiff Acne Disability Index (CADI) is an acne-spesific quality of life scale. The aim of this study was to determine which scale should be more appropriate and practical to evaluate the quality of life in acne patients and to compare the differences between two scales.

Methods: Acne scores of 273 patients who were admitted to the dermatology outpatient clinic between December 2015 and November 2016 were determined by the Global Acne Grading System (GAGS) (range 0 to 44). The DLQI (range 0 to 30) and CADI scores (range 0 to 20) were calculated to evaluate the effect of patients' quality of life.

Results: The mean GAGS score of the patients was 20.3, and the mean of CADI score was 6.1, while the mean of DLQI was 6.0. There was a significant positive correlation between total GAGS score and CADI and DLQI ($r=0.639$, $p<0.001$). When the relationship between the distribution of acne lesions and quality of life scales was evaluated; CADI score was significantly higher in the forehead localization group than in the non-forehead localization group ($p=0.012$), and the CADI and DLQI scores were higher in the upper back group than the group without back localization ($p=0.001$and $p= 0.017$ respectively).

Conclusion: In our study, it was observed that the DLQI and CADI scales were not superior to each other in evaluating the quality of life in patients with acne. Besides, we think that the effect of quality of life on facial acne cases can be determined more clearly with CADI scale.

Key Words: Acne, Cardiff Acne Disability Index, Dermatology Life Quality Index, quality of life.

Öz

Amaç: Akne vulgaris, sık görülen, kişinin yaşam kalitesini ve sosyal hayatını olumsuz yönde etkileyen dermatolojik bir hastalıktır. Klinik çalışmalarda, akne vulgarisin hastaların yaşam kalitesini olumsuz yönde etkileyen en sık hastalıklardan olduğu görülmektedir. Dermatolojik Yaşam Kalite İndeksi (DYKİ); dermatolojik hastalıklar için yaygın olarak kullanılan bir indeks iken, Cardiff Akne Kısıtlılık İndeksi (CADI) akneye özgü değerlendirme skalası olarak kullanılmaktadır. Bu çalışmanın amacı, akne hastalarında hangi ölçeğin daha uygun ve pratik olduğunu tespit etmek ve iki skala arasındaki farkları değerlendirmektir.

Yöntemler: Çalışmamızda Aralık 2015- Kasım 2016 tarihleri arasında Dermatoloji polikliniğine başvuran ve akne tanısı alan toplam 273 hastanın akne skorları Global Akne Skorlama Sistemi (GAGS) (aralık 0 ile 44 arası) ile belirlenip ardından DYKİ (aralık 0 ile 30 arası) ve CADI skorları (aralık 0 ile 20 arası) ile yaşam kalitesi belirlendi.

Sonuçlar: Hastaların GAGS skoru ortalaması 20,3, CADI skoru ortalaması 6,1 iken DYKİ ortalaması 6,0 idi. DYKİ ile CADI skorları arasında pozitif korelasyon mevcuttu ($r=0,639$, $p<0,001$). Akne lezyonlarının dağılımı ile yaşam kalite ölçekleri arasındaki ilişki değerlendirildiğinde; alın lokalizasyonu olan grupta CADI skoru, alın lokalizasyonu olmayan gruptan anlamlı olarak daha yüksekti ($p=0,012$). Sırt üst lokalizasyonu olan grupta CADI ve DYKİ skoru sırt lokalizasyonu olmayan gruptan anlamlı olarak daha yüksekti (sırasıyla $p=0,001$ve $p= 0,017$).

Tartışma: Çalışmamızda DYKİ ve CADI yaşam ölçeklerinin, akne tanılı olgularda yaşam kalitesini değerlendirmede birbirine üstünlükleri olmadığı ancak yüz yerleşimli akne vakalarında yaşam kalitesinin etkilenme düzeyinin CADI skoru ile daha net belirlenebileceği gözlemlendi.

Anahtar Kelimeler: Akne vulgaris, Cardiff Akne Kısıtlılık İndeksi, Dermatolojik Yaşam Kalite İndeksi, yaşam kalitesi.

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Introduction

Acne vulgaris is a skin disease that mainly affects adolescents. Although it is a benign condition, lesions have a significant negative impact on the patients' life [1]. Studies have shown that acne can be associated with a spectrum of psychosocial abnormalities including depression, suicidality, anxiety, psychosomatic symptoms and social inhibition [2].

The World Health Organization (WHO) defines quality of life as the individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns [3]. The measurement of life quality is important in the management, and determines the impact of the disease and treatment outcomes on the patients [1].

The Dermatology Life Quality Index (DLQI) is widely used quality of life measurement in dermatology [4]. Cardiff Acne Disability Index (CADI) is an acne-specific quality of life scale. Selection of which scale for acne vulgaris patients still remains controversial.

The objective of this study was to determine which quality of life scale is more practical and appropriate for acne patients.

Material and methods

Patients with acne vulgaris who attended the Dermatology Outpatient Clinic between December 2015 and November 2016 were enrolled in the study. Patients who are pregnant or under the age of 18 were excluded from the study. Prior to initiation of the study, written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Clinical Research Ethics Committee (Medeniyet University, 2016/0240).

Age, gender, occupation, concominant diseases of the patients and their duration, localization and symptoms of acne vulgaris were recorded. Clinical assessment of acne was evaluated by the Global Acne Grading System (GAGS) [7]. In this scoring system, a coefficient (the forehead, the right cheek and the left cheek as 2, the nose and the chin as 1, the chest and the upper back as 3) for each area is taken into consideration by dividing the face, the chest and upper back into six parts, considering the width of the region and the density and distribution of the pilosebaceous units in that area. Acne lesions were also graded between 0-4, depending on the severity (no lesions as 0, ≥1 comedones as 1, ≥1 papules as 2, ≥1 pustules as 3, ≥1 nodules as 4). After evaluating each area separately, multiplying the score obtained by the most severe lesion type in that area and multiplying the coefficient of that region, and determining a score for each area, the sum of the scores of the six regions and the GAGS scores were calculated. Total score ranges from 0 to 44, acne severity is determined according to GAGS score (0 for none, 1-18 points for mild, 19-30 for moderate, 31-38 for severe,> 39 for very severe) [7].

In order to assess the quality of life, the DLQI and the CADI scores were used both in each patient. The DLQI includes 10 questions with 4 possible answers that are designed to be based on the patient's symptoms, feelings, daily activity, leisure time, school/work life, personal relationships and treatment. In general, the severity of the disease affecting social and physical activations in the last week is determined. The score of DLQI varies between 0-30 [6]. CADI scale which consists of five questions, the questions are aimed to evaluate the psychological, emotional and social effects of acne in the last one month. Questions are given a score between1-4 and the score varies between 0-20. The higher the score, the more affected the quality of life [7].

Statistical analysis

Mean with standard deviation, median with minimum and maximum, frequency and ratio were used in descriptive statistics of data. The distribution of the variables was measured by the Kolmogorov Smirnov test. The Mann-Whitney U test was used for the analysis of quantitative independent data and Spearman correlation analysis was used for correlation analysis. SPSS 22.0 program was used.

Results

A total of 273 patients, 213 females (78%) and 60 males (22%) were included in the study. The mean duration of acne was 67.9±61.6 months. The most common localizations of the acne lesions were the cheek (97.4%), the forehead (93.4%), the perioral region (92.7%) and the upper back (71.1%) respectively (Table 1).

Table 1. Demographic and clinical characteristic of the patients.

Variable		Value
Age (year) ¥		23.4±6.4
Gender β	Female	213 (78)
	Male	60 (22)
Duration (month) ¥		67.9±61.6
Concominant diseases ¥		12 (4.4)
Lokalization		
Forehead β		255 (93.4)
Nose β		142 (52)
Cheek β		266 (97.4)
Perioral β		253 (92.7)
Submental β		61 (22.3)
Submandibular β		147 (53.8)
Chest β		157 (57.5)
Upper back β		194 (71.1)
Lower back β		57 (20.9)
GAGS score		
Forehead ¥		3.7±1.7
Right cheek ¥		4.2±1.8
Left cheek ¥		4.4±1.9
Nose ¥		0.9±1.1
Submental ¥		1.9±0.9
Chest ¥		5.3±3.3
Total ¥		20.3±6.3

¥:mean±standard deviation, β:n(%).

The total of GAGS scores were between 4 and 38 and mean GAG score of the patients was 20.3±6.3. The highest GAGS scores were found in the chest followed by the cheek and the forehead (Table 1).

Mean DLQI and CADI scores were 6.0±4.6 and 6.1±3.0, respectively.

There was no significant relationship between the quality of life, gender and the disease duration ($p > 0.05$ for all).However, a positive significant correlation was observed between the DLQI and the CADI scores ($r=0.639$ and $p<0.001$).

When the DLQI and the CADI scores were compared by age, there was a significant (r=-0.156, p=0,01 and r=-0.144, p=0.017, respectively) negative correlation between age and both scores.There was also a significant negative correlation between age of onset of the lesions and both scores (r=-0.141, p=0.02 and r=-0.159, p=0.008, respectively). There was a significant positive correlations between CADI scores and the GAGS scores of the forehead (r=0.165, p=0.06), and the left cheek (r=0.12, p=0.048). There was no significant relationship between CADI scores and the GAGS scores of the right cheek, the nose, the chin, the chest (p>0.05 for all) (Table 2).

Table 2: Relationship between the life quality scores and acne severity.

		Global Score						
		Forehead	Right cheek	Left cheek	Nose	Submental	Chest	Total
CADI	r	0.165	0.109	0.120	0.069	0.096	0.147	0.224
	p	0.006	0.071	0.048	0.258	0.113	0.015	0.000
DLQI	r	0.093	0.126	0.054	0.032	0.015	0.111	0.150
	p	0.123	0.037	0.373	0.603	0.811	0.067	0.013

There was a significant positive correlation between DLQI and GAGS score of right cheek (r=0.126, p=0.037). There was no significant correlation between DLQI and forehead, left cheek, nose, chin and chest GAG scores (p>0.05 for all) (Table 2).

The CADI scores of the patients with forehead and upper back acne were significantly higher than the patients without forehead (p=0.012) or upper back acne (p=0.001) (Table 3).

The DLQI scores of the patients with upper back acne, were significantly higher than the patients without upper back acne (p=0.017) (Table 3).

Table 3: Relationship between acne localization and life quality index scores.

		CADI¥	p	DLQI¥	p
Localization					
Forehead	Absent	4.4±2.9	0.012	5.2±4.4	0.405
	Present	6.2±3.0		6.0±4.6	
Nose	Absent	5.8±2.9	0.155	5.8±4.4	0.702
	Present	6.4±3.1		6.1±4.7	
Cheek	Absent	4.4±3.0	0.148	4.0±4.1	0.195
	Present	6.1±3.0		6.0±4.6	
Perioral	Absent	4.9±2.5	0.085	5.1±5.1	0.134
	Present	6.2±3.1		6.0±4.5	
Submental	Absent	5.9±3.0	0.239	5.8±4.3	0.773
	Present	6.5±3.3		6.4±5.4	
Submandibular	Absent	6.0±2.9	0.774	6.0±4.4	0.787
	Present	6.1±3.1		6.0±4.7	
Chest	Absent	5.8±3.0	0.086	5.4±4.2	0.063
	Present	6.3±3.0		6.4±4.8	
Upper back	Absent	5.2±3.0	0.001	5.0±4.2	0.017
	Present	6.4±3.0		6.4±4.7	
Lower back	Absent	6.1±3.0	0.924	6.1±4.4	0.245
	Present	6.1±3.3		5.6±5.3	

¥:mean±standard deviation.

Discussion

Acne vulgaris is a common skin disorder that mostly occurs in adolescence and located on the face. Therefore, it has important effects on psychosocial life of the patients [8]. Psychological involvements include depression, anxiety, social isolation and suicidal ideation or intent [9]. After understanding the psychosocial effects of acne vulgaris on patients, quality of life indexes are used to evaluate and follow up of treatment [10].

In recent years, the use of DLQI and CADI scales in the assessment of quality of life in patients with acne vulgaris have been increased. Both DLQI and CADI scales have been translated into various languages and validated [6, 11-13] and after that, quality of life studies in acne vulgaris accelerated.

The mean DLQI and CADI scores in our study were similar to previous studies [10, 14-18]. However, the studies performed on students at their school, reported lower DLQI and CADI scores [19, 20]. This may be related to the fact that the patients included in our study were those who referred to dermatology outpatient clinic and probably experienced more discomfort than others.

There was no significant difference in the quality of life based on gender that is similar to the results of Safizadeh and Yazıcı studies [18, 21].

While some authors found significant relationship between acne severity and quality of life; some of them did not report any significant relationship [10,16-18, 22-26]. The differences in the findings of various studies higlight the social, behavioral and cultural factors, differences in population characteristics and individual perception. In our study, both the CADI and the DLQI scores were in postive correlaiton with GAGS score as previous studies [14, 22, 27, 28]. Unlike the CADI score; the DLQI score was not corralated with GAGS score among patients who have acne lesions on forehead. Since majority of acne patients are consist of forehead localized acne lesions, CADI score might be a more appropriate scale for evaulating acne patinets' life quality rather than the DLQI score. Although the DLQI is widely used and eligible life quality scale for the dermaotlogic diseases, we believe disease-spesific scales should be developed and used for disease-based studies.

Limitation of our study was that the patients included in the study were not questioned for comorbid dermatologic diseases except acne vulgaris, and therefore the DLQI scale might be affected by these additional diseases.

As a conclusion, in patients with forehead localized acne (majority of patients in our study), unlike the DLQI, a positive correlation between the CADI and acne severity, suggested that the CADI might be more appropriate for assessing the quality of life in acne vulgaris. At the same time, the CADI scale has less questions than the DLQI and this might make it easier to perform.

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Evaluation of the autologous conditioned serum in the treatment of osteoarthritis

Osteoartrit tedavisinde otolog zenginleştirilmiş serumun değerlendirilmesi

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Abstract

Aim: The present study was a retrospective study aiming to determine the effect of the autologous conditioned serum (ACS) on osteoarthritis (OA); we made this analysis by injecting it to a symmetrically involved knee.

Methods: The present study comprised 33 patients (19 females, 14 males) with 66 knees and a mean age of 57.6±8.21 (range: 41-70). The patients included in the study had radiologically verified bilateral grade 2-3 OA of the knee according to Kellgren-Lawrence classification. Secondary arthritis, inflammatory joint diseases, clinically relevant hematologic or abnormal clinical chemistry values, joint instability, intra-articular corticosteroid injection within the previous 6 months, history of diabetes mellitus and body mass index greater than 30 kg/m2 were the exclusion criteria. Patients who had VAS difference more than 2 points between their knees were excluded from the study. ACS was injected twice a week for a total of 6 times in both knee joints for 3 weeks. The patients were analyzed with the Visual Analog Scale (VAS) (no pain was graded 0 and maximal pain was graded 10), the Knee Injury and Osteoarthritis Score (KOOS) (scoring ranges between 0 and 100. 0 indicates abnormally high level of knee problems, while 100 indicates a healthy knee with no problems) and the Knee Society Score (KSS) (Of the maximum 100 points, a possible 50 points are assigned to pain, 25 points to stability, and 25 points for range of motion) before the administration of the first injection and again 1 year after the last injection.

Results: The pre-treatment and 1-year follow-up VAS values of the patients were 7.36±0.93 (range: 5-9) and 3.27±1.23 (range: 1-6), respectively. ACS treatment showed a statistically significant decrease in VAS score ($p < 0.01$). Pre-treatment and 1-year follow-up KOOS values of the patients were 42.39±13.38 (range: 21-65) and 72.36±8.81 (range: 54-92), respectively. There was a statistically significant increase in the KOOS values of the patients ($p < 0.01$). The pre-treatment and 1-year follow-up KSS values of the patients were 42.79±10.26 (range: 14-61) and 70.61±9.32 (range: 49-84), respectively. There was a statistically significant increase in the KSS values of the patients ($p < 0.01$).

Conclusion: Use of intra-articular injection of ACS in patients with painful OA leads to significant improvements in pain severity, KOOS and KSS scores. In the light of these findings, ACS treatment may be considered as an effective and safe alternative treatment method in osteoarthritis.

Keywords: Intra-articular injection, autologous conditioned serum, knee osteoarthritis

Öz

Amaç: Çalışmamızda retrospektif olarak otolog zenginleştirilmiş serum (OZS) tedavisinin osteoartritteki etkisinin bilateral diz enjeksiyonu ile değerlendirilmesi amaçlanmıştır.

Yöntemler: Çalışmamıza yaş ortalaması 57.6 ± 8.21 yıl (41-70) olan 33 hasta (19 kadın, 14 erkek) 66 diz dahil edilmiştir. Çalışmamıza katılan hastaların diz osteoartritleri Kellgren-Lawrence sınıflamasına göre bilateral olarak evre 2-3 idi. Sekonder artrit, enflamatuar eklem hastalıkları, klinik olarak ilgili hematolojik veya anormal klinik kimya değerleri, eklem instabilitesi, son 6 ay içerisinde eklem içi kortikosteroid enjeksiyonu uygulanan, diabetes mellitus öyküsü, 30 kg/m2'dan büyük vücut kitle indeksi mevcut olan hastalar çalışmadan dışlandı. Her iki diz arasındaki VAS farklılığı 2 puandan fazla olan hastalar çalışmadan çıkarıldı. Üç hafta boyunca haftada iki kez toplamda 6 kez her iki diz eklem içine OZS enjekte edildi. Hastalar VAS ağrı skorlaması (hiç ağrı olmaması 0 olarak ve maksimum ağrı 10 olarak derecelendirildi), Diz Yaralanması ve Osteoartirit Skalası (DYOS) (puanlama 0 ile 100 arasında değişmektedir. 0 anormal derecede yüksek diz problemleri gösterirken, 100 problemsiz sağlıklı bir diz göstermektedir) ve Diz Cemiyeti Skorlaması (DCS) (Maksimum 100 puan olan skala ağrıya 50, stabiliteye 25 ve eklem hareket açıklığına 25 puan atanır) skalaları ile ilk enjeksiyon öncesi ve son enjeksiyondan 1 yıl sonra değerlendirildi.

Bulgular: Hastaların tedavi öncesi ve 1. yıl takip VAS değerleri sırası ile 7.36±0.93 (aralık: 5-9) ve 3.27±1.23 (aralık: 1-6) idi. OZS tedavisi VAS skorunda istatistiksel olarak anlamlı düşme göstermiştir ($p<0.01$). Hastaların tedavi öncesi ve 1. yıl takip DYOS toplam değerleri sırası ile 42.39±13.38 (aralık: 21-65) ve 72.36±8.81 (aralık: 54-92) idi. Hastaların DYOS total skorunda istatistiksel olarak anlamlı yükselme saptanmıştır ($p<0.01$). Hastaların tedavi öncesi ve 1. yıl takip DCS değerleri sırası ile 42.79±10.26 (aralık: 14-61) ve 70.61±9.32 (aralık: 49-84) idi. Hastaların DCS değerlerinde istatistiksel olarak anlamlı yükselme saptanmıştır ($p<0.01$).

Sonuç: Ağrılı diz osteoartriti olan hastalarda inra-artiküler OZS kullanımı ağrı şiddeti, DYOS ve DCS skorları açısından anlamlı iyileşmelere yol açmaktadır. Bu bulgular ışığında, OZS tedavisi osteoartritte etkili ve güvenli bir alternatif bir tedavi yöntemi olarak değerlendirilebilir.

Anahtar Kelimeler: intra-artiküler enjeksiyon, otolog zenginleştirilmiş serum, diz osteoartriti

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Introduction

Osteoarthritis (OA) is the most important cause of locomotor disability in Western societies and a major issue on their healthcare systems [1, 2]. It is a progressive and chronic condition leading to pain and loss of function that dramatically reduces patients' quality of life and ability to work. It is the most common type and encountered in 6% of adults, with a prevalence reaching up to 40% in advanced age cases (>70 years) [3]. The management of the knee OA begins with conservative treatment such as physical therapy, exercise, weight loss and medications. Pharmacologic treatment options for OA used to be restricted to the symptomatic use of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and the intra-articular injection of steroids or hyaluronan (HA) [4]. Intra-articular HA is commonly used as a safe, off-the shelf treatment for OA of the knee, but its efficacy is controversial. There is a pressing need for novel, improved, mechanism-based agents for treating OA. Surgical intervention can be indicated for patients with advanced OA [5].

In OA, the destruction of hyaline cartilage constitutes the central pathological mechanism causing various mechanical and biological dysfunctions within the joint. Of the cytokines identified in osteoarthritic joints, interleukin-1 (IL-1) appears to be of particular importance. Accordingly, the IL-1 receptor antagonist protein (IRAP), a naturally occurring inhibitor of IL-1, has been reported to limit the intra-articular damage associated with IL-1 [4, 5]. In animal models, many researchers have succeeded in positively modifying the osteoarthritic disease process by effectively antagonizing IL-1 [4-7]. Autologous conditioned serum (ACS) is an example of a presumably disease-modifying treatment for OA based on antagonizing the intra-articular effects of IL-1 [6, 7]. The resulting conditioned serum contains elevated levels of various anti-inflammatory cytokines, such as IRAP, IL-4 and IL-10 [4, 7, 8]. Several investigators have reported effectiveness of IL-1Ra in a pilot human study when delivered by intraarticular injection in a canine model of OA [9, 10]. After the initial skepticism, the positive outcome of an animal model and of recent prospective randomized controlled double-blind trials have provided the first evidence demonstrating that ACS is more effective in human samples than placebo and/or HA for the treatment of knee OA [4, 11-14].

The present study was a retrospective study aiming to determine the effect of ACS on OA; we made this analysis by injecting it to symmetrically involved knee.

Material and methods

With written informed patient consent, 33 (19 females, 14 males) patients not older than 70 years and with 66 knees were included in the study. Data collection and treatment took place at a single institution. The study was conducted in accordance with the Declaration of Helsinki. Approval for our study was obtained from the institutional review board. This study was based on a retrospective evaluation of one year follow-up findings of patients treated for osteoarthritis.

Patient selection

All patients presented to orthopedic outpatient clinic with bilateral knee pain score equal or more than 4 points of 0-10 Visual Analog Scale (VAS) on the day of the examination. Patients were included to the study to have radiological verified bilateral grade 2-3 OA of the knee according to Kellgren-Lawrence classification [15]. All patients in this study had dissatisfaction with previous attempts at conservative treatment including non-steroidal anti-inflammatory drugs.

No patient dropped out or underwent surgery while enrolled in the study. Secondary arthritis, grade IV OA, systemic or inflammatory joint diseases, a history of a crystalline arthropathy, clinically relevant hematologic or abnormal clinical chemistry values, bone cancer, and metastasis or tumor-like lesions in immediate proximity to the treated joint, joint instability, intra-articular corticosteroid injection within the previous 6 months, history of diabetes mellitus, recent history of trauma to the knee and BMI (kg/m2) greater than 30 were the exclusion criteria. Patients were also excluded if they had contraindication to injection, such as infection, anticoagulation therapy, allergy or hypersensitivity, to any of the study medications. Patients using systemic corticosteroids were also excluded. Patients who had a VAS difference of more than 2 points between their knees were excluded from the study.

Outcome Measurements

All patients were analyzed for pain with the visual analog scale (VAS), Knee Injury and Osteoarthritis Score (KOOS) and Knee Society Score (KSS) before the administration of the first injection (pre-treatment) and again 1 year after the last injection (post-treatment). VAS was used to measure knee pain during the last week at rest and during daily activities. No pain was graded 0 and maximal pain was graded 10 on a 100-mm scale. KOOS is a specific scale used in evaluating knee functions and knee-related quality of life. It is composed of five subscales as pain, patient's perception for other symptoms, daily life, sports and recreational activities. Scoring ranges between 0 and 100. 0 indicates abnormally high level of knee problems, while 100 indicates a healthy knee with no problems [16]. KSS includes three main constructs: pain, knee stability, and range of motion (ROM). Of the maximum 100 points, a possible 50 points are assigned to pain, 25 points to stability, and 25 points for ROM [17].

ACS preparation

To produce ACS, 50 mL of whole blood were taken from each patient using a special syringe with increased internal surface area; glass beads in the syringes increase the non-pyrogenic surface area and induce the dose-dependent production of IRAP (among others) by white blood cells in whole blood incubated at 37°C. After incubation, the blood-filled syringes were centrifuged, and the serum supernatant was filtered (0.22 mm; Millipore, Carrigtwohill, Co. Cork, Ireland) and aliquoted into 6-8.2 mL portions. The aliquots were stored at -20°C until use. A randomization procedure was followed to assign each compound to the right or the left knee.

Administration of injection

One orthopedic surgeon in one center applied all the injections. Patients were placed in sitting position with 90 degrees of knee flexion. Lateral approach to the knee was selected. The skin of the injection site was cleaned with povidone-iodine solution. No anesthetic was administered before injection. ACS was injected twice a week for a total of 6 times in both knee joints for 3 weeks. The patient was sent home after injection. Limited movement was allowed for 24 hours, and resting was recommended in case of pain. The patient was recommended not to receive NSAIDs nor to apply local ice for a week after injection in order not to reduce the efficacy of ACS. In addition, an exercise program was given to the patients, and performing normal daily activities when tolerable was recommended.

Another surgeon who was not aware of the study design performed the clinical evaluation. Clinical data were

retrospectively collected from the patients' files and reported on a case report form before analysis. Patients underwent clinical evaluation before the injection and at the 1st year follow-up. VAS, KOOS and KSS scores were compared before the treatment and at the 1-year follow-up. The possible complications and side effects were also evaluated in each visit.

Statistical Analysis

Statistical analysis was performed using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA). Descriptive statistics are expressed as number and percentage for categorical variables and as mean, standard deviation, median, minimum and maximum for numerical variables. . Paired Samples T-Test was used to compare KOSS and KSS scores before the treatment and at the 1-year follow-up. Non-parametric Wilcoxon Signed Ranks Test was used to compare VAS scores before the treatment and at the 1-year follow-up. $p<0.01$ was considered statistically significant.

Results

The present study comprised 33 patients (19 females, 14 males) with 66 knees and a mean age of 57.6±8.21 (range: 41-70); general characteristics of the patients are demonstrated in Table 1. Before the first admission, the mean VAS score was 7.36±0.93 (range: 5-9). After treatment at the 1-year follow-up time the mean VAS score was 3.27±1.23 (range: 1-6). The change in VAS scores before and after treatment was statistically significant. Treatment with ACS consistently showed significant decrease in VAS ($p<0.01$) (Figure 1, Table 2).

Table 1. Demographic changes of patients

		Range	Mean±SD
Age (year)		41-70	57.66±8.21
		n	%
Gender	Female	19	57.6
	Male	14	42.4

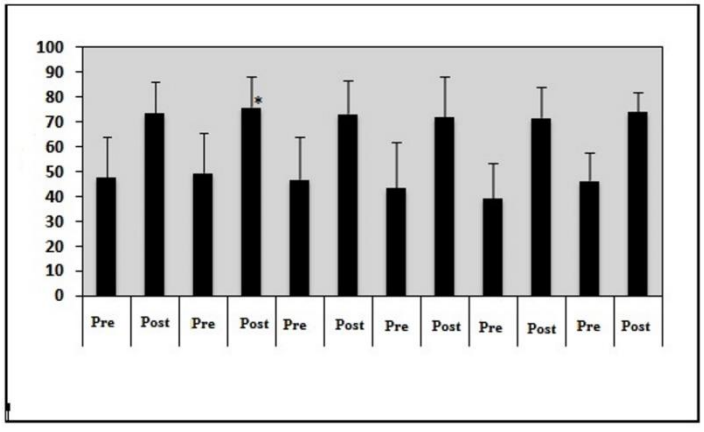

Figure 1. Before the treatment and at the 1-year follow-up of KOSS changes.

Pre-treatment and 1-year follow-up values of KOOS were 42.39±13.38 (range: 21-65) and 72.36±8.81 (range: 54-92), respectively. ACS resulted in significantly greater improvement over the 1-year period bilaterally. When asked to rate their health in retrospect using the test, the patients reported a significant improvement in KOOS (sub-scores and total) 1 year after ACS treatment ($p<0.01$). Patients rated their initial health (all outcomes of KOSS) as lower than how they had rated it before the actual ACS treatment (Figure 1, Table 2).

By the end of the study, there was a significant improvement in the KSS over time. Pre-treatment and 1-year follow-up values of KSS were 42.79±10.26 (range: 14-61) and 70.61±9.32 (range: 49-84), respectively. Increase in KSS score from baseline to post-treatment 1 year was significant ($p<0.01$) (Figure 1, Table 2).

Table 2. Before the treatment and at the 1-year follow-up scores of the patients.

		Min-Max	Mean±SD	p
KOOS stiffness	Before	18-78	44.67±18.09	0.001
	1 year	39-100	72.85±13.35	
KOOS pain	Before	17-75	45.30±14.90	0.001
	1 year	56-94	74.21±10.36	
KOOS function daily	Before	18-87	44.30±16.80	0.001
	1 year	53-95	72.82±10.20	
KOOS function activity	Before	10-65	31.82±14.94	0.001
	1 year	30-85	66.15±13.39	
KOOS life quality	Before	12-75	34.21±13.96	0.001
	1 year	56-92	72.85±10.17	
KOOS total	Before	21-65	42.39±13.38	0.001
	1 year	54-92	72.36±8.81	
VAS	Before	5-9	7.36±0.93	0.001
	1 year	1-6	3.27±1.23	
KSS	Before	14-61	42.79±10.26	0.001
	1 year	49-84	70.61±9.32	

KOOS: Knee Injury and Osteoarthritis Score, VAS: Visual Analog Scale, KSS:Knee Society Score.

No intraarticular injection-related major complications such as infection, deep venous thrombosis, muscular atrophy was detected in any of the patients over the course of the treatments. We had no complication after injections.

Discussion

OA is accompanied by a number of mechanical and biologic dysfunctions within the joint, the central pathologic feature being the destruction of hyaline cartilage. Of the catabolic cytokines identified in osteoarthritic joints, IL-1, the most potent known mediator of cartilage loss [16-18], appears pivotal. The naturally occurring inhibitor of IL-1, the IL-1 receptor antagonist (IL-1Ra), could potentially limit the intra-articular actions of IL-1 and thereby control the disease process [19, 20].

IL1b is a pivotal mediator of many inflammatory and regenerative diseases, including OA, rheumatoid arthritis (RA) and spinal disorders. Strategies for inhibiting the biological activities of IL-1b include the use of the recombinant IL-1 receptor agonist, soluble forms of IL-1 receptors and anti-inflammatory cytokines such as IL-4, IL-10 and IL-13, which inhibit the synthesis of IL-1 and/or increase the synthesis of IL-1Ra. A biologic therapeutic preparation known as ACS has been developed and used clinically in orthopedic patients suffering from OA, RA and spinal disorders. ACS is prepared from peripheral whole blood. Briefly, blood is drawn into a syringe containing treated glass beads with CrSO4 to initiate monocyte activation [21, 22].

ACS was developed in the mid-1990s in an attempt to generate an injectable material enriched in endogenous IL-1Ra as a novel therapeutic for OA. Meijer et al. noted that exposure of blood to glass beads elicits a vigorous and rapid increase in the synthesis of several anti-inflammatory cytokines, including IL-1Ra. This observation is the basis for producing ACS, which is injected into the affected joint in a series of six intra-articular injections given twice a week for 3 weeks. This therapy is currently available for humans in several countries, and its use is even more widespread for equine OA, where ACS considerably

improves clinical lameness in horses and may protect cartilage from degradation [23]. In our study, treatment with ACS produced a rapid decline in pain, accompanied by a large improvement in ROM. These results suggest that ACS is a valid option for the treatment of OA.

Injections of intra-articular therapies directly into the joint evade conservative obstacles to joint entry, rise bioavailability and minor systemic toxicity. Current progresses in osteoarthritis management have designed better diversity of treatment approaches. Based on novel opinions, an innovative therapy by ACS from the whole blood was settled. The inoculation of ACS into tissues has revealed clinical efficacy for the treatment of osteoarthritis and muscle injuries [6]. Our data show that ACS is safe and has a therapeutic effect on the major clinical parameters of painful knee OA. ACS resulted in significantly greater improvement over the 1-year period. Furthermore, patients treated with ACS consistently showed significantly higher improvements in terms of the pre-treatment parameters. Remarkably, the therapeutic effect persists for at least 1 year.

The ACS production process has been shown to reproducibly elevate IL-1Ra and other factors, although the mechanisms by which the effects are mediated are not fully understood [22, 24]. The multitude of synergistic and active therapeutic molecules may explain the observed clinical effect, but its long-term persistence is more difficult to explain. One possibility may be that the therapeutic molecules help re-establish a healthy joint homeostasis [25-29]. Given the favorable safety profile, reduction in pain and enhanced quality of life experienced by patients enrolled in this joint health program, ACS has the potential to offer an alternative, chondroprotective, natural, molecular approach to treating pain and functionality in patients with mild, moderate or severe knee osteoarthritis [29-31]. In terms of our experience, intra-articular injection of ACS in patients with painful knee OA has a safe profile and results in a strong clinical response. The data shows that ACS represents an effective and well-tolerated alternative to the currently predominant treatments of OA.

In summary, based on our clinical trial results, intra-articular ACS reduces pain and increases function and mobility for up to one year. It can be considered as clinically safe because of its autologous origin. No clinically serious side effects were observed in the ACS group during the observation period.

We have some limitations in our study. Firstly, the retrospective design of the study was the main limitation, and also we included patients with wide range of age distribution. However, we included similar grade of knee osteoarthritis and we treated our patients with same method. Our study may guide further studies when evaluating the effect of ACS in osteoarthritis treatment and relation the clinical outcomes.

In conclusion, the ACS is effective for the treatment of patients with low- to medium-grade painful knee OA. Although this study supports the use of ACS in mid-stage painful OA of the knee, we are aware of its shortcomings. We only treated patients with grade 2-3 OA of the knee according to Kellgren-Lawrence classification; so the results cannot necessarily be generalized to all OA patients.

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Effects of bacterial vaginosis and its treatment on sexual functions: A cross-sectional questionnaire study

Bakteriyel vajinoz ve tedavisinin cinsel fonksiyonlar üzerine etkileri: Bir kesitsel anket çalışması

Coşkun Şimşir [1], Bora Coşkun [1], Buğra Coşkun [1], Aynur Adeviye Erşahin [2], Tolga Ecemiş [3]

Abstract

Aim: To investigate the effects of bacterial vaginosis, which is the most frequent vaginal infection in women, and its treatment on sexual functions.

Methods: Patients who had applied to our gynecology outpatient clinic with bacterial vaginosis based on the culture results were included in this observational questionnaire study. Patients with an accompanying disease possibly resulting in sexual dysfunction and those with vaginitis etiology other than bacterial vaginosis were excluded from the study. Patients were asked to fill the Female Sexual Function Index (FSFI) during the diagnosis of bacterial vaginosis and 1 month later than the treatment.

Results: Seventy-two patients who had applied to our outpatient clinic between January 2018 and January 2019 and who met the study criteria were included in this study. Statistically significant improvement was found in post-treatment orgasm and pain scores and in total FSFI scores of the patients upon comparison of FSFI scores of patients before and after the treatment ($p<0.001$). However, no statistically significant differences were found in sexual desire, arousal, lubricity and general satisfaction scores before and after the treatment ($p>0.05$ for all).

Conclusion: It was found that sexual dysfunction was more common in patients with bacterial vaginosis and improvement was seen in some sexual functions with treatment.

Keywords: Bacterial vaginosis, sexual dysfunction, Female Sexual Function Index

Öz

Amaç: Kadınlarda en sık görülen vajinal enfeksiyon olan bakteriyel vajinozun ve tedavisinin cinsel fonksiyonlara olan etkilerini araştırmak.

Yöntemler: Ocak 2018-Ocak 2019 tarihleri arasında jinekoloji polikliniğimizde kültür sonuçlarına dayanarak bakteri vajinoz tanısı alan hastalar bu gözlemsel anket çalışmasına dahil edildi. Eşlik eden bir hastalığı olan ve muhtemelen cinsel işlev bozukluğu olan hastalar ile bakteriyel vajinoz dışındaki vajinit etiyolojisi olanlar çalışma dışı bırakıldı. Hastalara bakteri vajinoz teşhisi sırasında ve tedaviden 1 ay sonra Kadın Cinsel İşlev İndeksi (FSFI) anketi uygulandı.

Bulgular: Çalışma kriterlerini karşılayan 75 hasta çalışmaya dahil edildi. FSFI skorlarının karşılaştırılmasında tedavi sonrası orgasm, ağrı skorları ve toplam FSFI skorlarında istatistiksel olarak anlamlı düzelme saptandı ($p<0,001$). Ancak, tedavi öncesi ve sonrasında cinsel istek, uyarılma, kayganlık ve genel memnuniyet skorlarında istatistiksel olarak anlamlı bir fark bulunmadı (hepsi için $p>0,05$).

Sonuç: Bakteriyel vajinozlu hastalarda cinsel işlev bozukluğunun daha yaygın olduğu ve tedaviyle bazı cinsel işlevlerde düzelme olduğu tespit edildi.

Anahtar Sözcükler: Bakteriyel vajinoz, cinsel işlev bozukluğu, Kadın Cinsel İşlev İndeksi

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Ethics Committee Approval: The study wass approved by the local ethical authority (11.01.2018-2018/04).

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Introduction

The most frequent vaginal infection in the reproduction period is bacterial vaginosis [1]. The most common causative organism is Gardnerella vaginalis, which is found in the normal flora and causes vaginal infection in case of changes in the flora. The same picture can be seen with many other anaerobic bacteria with Bacteroides and M. hominis in the first place [2].

Almost half of patients with bacterial vaginosis are asymptomatic. While the most frequent complaints at presentation are vaginal discharge and bad odor that irritate the couple during sexual intercourse, complaints about the sense of disgust and lack of pleasure from the intercourse are mentioned more when the anamnesis is deepened somehow. This in turn affects the sexual lives of patients and can result in sexual dysfunction in patients [3].

Sexual dysfunction in women can be related to several factors including psychological, physiological and individual characteristics [4]. Conditions such as vaginal infection also result in sexual dysfunction leading to self-confidence problems and emotional stress, which in turn has negative effects on the quality of life [5]. Only half of these women apply to a doctor for a solution [6]. Sexual dysfunction in any member of the married couple will also impair the integrity of the marital union. Therefore, finding out the cause of sexual dysfunction in such individuals and its treatment is important.

In our study, we aimed at investigating if the sexual dysfunction related to bacterial vaginosis would improve with treatment.

Material and methods

Patients diagnosed with bacterial vaginosis among the patients who had applied to the Gynecology Outpatient Clinic of Ankara Liv Hospital were interrogated in our scaled and stratified survey. We have carried out after obtaining the approval of the Ethical Committee of Liv Hospital Ankara with the date of January/11/2018 and number of 2018/004.

Patients with accompanying diseases that could cause sexual dysfunction such as vaginal candidiasis, pelvic lesions, previous known psychological disorders, neuromuscular diseases, hormonal problems or vascular insufficiency were excluded from the study. Patients using antidepressants, antipsychotics, antihypertensive medicines, anticholinergic drugs, antacids or oral contraceptives were exclusives from the study.

Of the two hundred and eight patients diagnosed with bacterial vaginosis between the determined dates, 120 gave their consents and met the study conditions were included in the study and were required to fill the FSFI questionnaire. Following the bacterial vaginosis treatment, 72% of patients came back for control 1 month later and filled the FSFI questionnaire again (Figure 1).

Forty-two patients refusing to fill the questionnaire out of 162 meeting the study conditions were not included in the study. Helsinki Declaration Criteria were taken into consideration when implementing the study [7]. Patients included in the study were informed about the study as required, and their written consents were obtained.

Age, number of pregnancies, parity, abortion, body mass index (kg/m^2), level of education, profession, smoking and alcohol use of patients were interrogated. Patients were asked to fill the FSFI questionnaire including 19 items before and after the bacterial vaginosis treatment. Metronidazole 500 mg 2x1 oral preparations were administered for the treatment of patients.

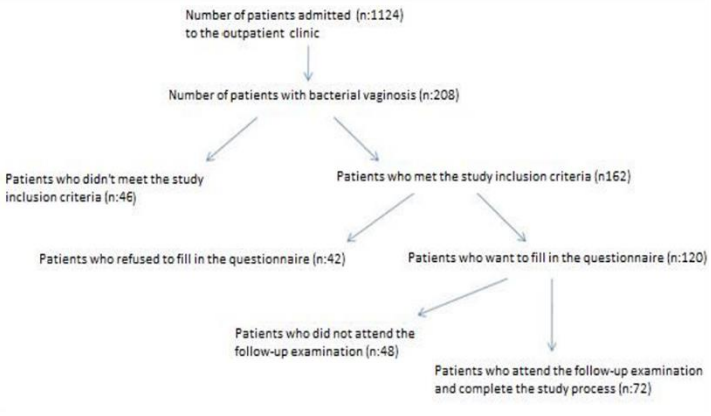

Figure 1. Study flow chart.

Female Sexual Function Index (FSFI)

FSFI questionnaire is a questionnaire with 19 items developed by Rosen and colleagues developed in 2000 to be used to evaluate the sexual functions [8]. It evaluates the sexual life within the last four weeks. The questionnaire interrogates the parameters related to sexual desire (items 1 and 2), arousal (items 3-6), lubrication (items 7-10), orgasm (items 11-13), satisfaction in general (items 14-16) and pain (items 17-19), respectively.

The first 2 items are scored between 1 and 5, while the remaining items are scored between 0 and 5. The greatest score can be 95, and the lowest score can be 2. Scores obtained in each domain are multiplied by coefficients homogenizing the effects (0.6 for items 1 and 2; 0.3 for items 3 to 10; and 0.2 for items 11 to 19). Total FSFI scores however, are calculated by summing each score in the homogenized domain. Total FSFI scores range between 1.2 and 36. Higher scores define better sexual lives. Total FSFI score ≤26.5 is defined as sexual dysfunction. This questionnaire was approved for the Turkish population also in 2005 [9].

Statistical Analysis

Data analyses were carried out by using the SPSS 23.0 program. Descriptive data and frequencies were calculated with the help of the computer. While the continuous variables were expressed as mean ± standard deviation and median (minimum-maximum), categorical variables were expressed as number and percentage. Kolmogorov-Smirnov test was used for the normality test. Whether or not there are any differences between the FSFI scores before and after the treatment was analyzed with t-test. P value<0.05 was accepted as the level of statistical significance.

Results

Bacterial vaginosis was detected in 208 (18.5%) of 1124 patients admitted to the outpatient clinic during the study period. The mean age of patients was 27.7 years, and the mean body mass index was 25.2 kg/m2. Majority of patients were graduates of high school (29.2%) and were working in some job (65.3%). Rate of smoking was 38.9% while alcohol consumption rate was 11.1% (Table 1).

Comparison of FSFI scores of patients before and after treatment showed statistically significant improvement in pain, orgasm, and total FSFI scores (p<0.001). However, no statistically significant differences were found in sexual desire, arousal, lubrication and general satisfaction scores (p>0.001 for all) (Table 2).

Table 1. Demographic findings.

Variable		n (N=72)
Age (years) [β]		27.7±6.3
Body mass index (kg/m^2) [β]		25.2±3.5
Gravida [¥]		2 (0-4)
Parity [¥]		1 (0-3)
Abortions [¥]		1 (0-2)
Occupation [µ]		
	Active	47 (65.3)
	Housewife	25 (34.7)
Level of education [µ]		
	No	8 (11.1)
	Primary education	19 (26.4)
	Secondary	14 (19.4)
	High school	21 (29.2)
	High education	10(13.9)
Smoking [µ]		
	Yes	28 (38.9)
	No	44 (61.1)
Alcohol [µ]		
	Yes	8 (11.1)
	No	64 (88.9)

[β]:mean±standard deviation, [¥]:median (range), [µ]:number (percentage).

Table 2. Comparison of pre- and post-treatment FSFI Scores.

Parameter	Before treatment	After treatment	p
Desire [β]	2.66±1.30	3.40±1.78	0.082
Excitement [β]	1.93±1.20	2.98±1.47	0.065
Lubrication [β]	1.87±1.13	3.30±1.15	0.058
Orgasm [β]	2.12±1.20	3.64±1.22	<0.001
Overall satisfaction [β]	1.93±1.23	2.88±1.16	0.062
Pain [β]	1.58±1.28	3.21±1.38	<0.001
FSFI total [β]	11.62±5.38	18.62±5.66	<0.001

[β]:mean±standard deviation.

Discussion

Sexual dysfunction is an important health problem that involves both females and males and affects feelings and attitudes of the couple against each other. However, too few couples verbalizes this problem and apply to a specialist for treatment. Even, they abstain to talk to each other with the idea that they could be misunderstood [10]. In particular, sexual dysfunction in women reduces their self-confidence, cause psychological burn-out and lower their quality of life [11, 12].

Sexual function can deteriorate in women together with advancing age, and almost half of women can face this problem in any period of their lives [13]. While there are no very comprehensive studies in our country, frequency of sexual dysfunction in women was found as 46.9% in a study conducted by Çayan and colleagues [14]. In another country carried out in our country on 518 female participants by Öksüz and colleagues, sexual dysfunction was found with a frequency of 48.3% [15]. With the reason that sexual dysfunction is common in the society, it is a health problem that should be addressed and attached importance to.

We conducted an FSFI questionnaire study at the baseline and in month 1 following the treatment in patients diagnosed with bacterial vaginosis and other causes of sexual dysfunction have been eliminated. We found the incidence of bacterial vaginosis as 18.5%. This rate was found between 10% and 20% in most of the studies [16]. We also found reduction in dyspareunia and increase in the frequency of orgasm. We also found marked improvement in total FSFI scores. In a question-answer study carried out by Bilardi and colleagues on 35 patients through face-to-face interviews or phone calls, it was found sexual life was affected in recurring bacterial vaginosis patients. It was concluded in this study that bacterial vaginosis affects the emotional, physical, social and sexual lives of patients in different levels. Patients have stated that they feel dirty and bad, were ashamed of their condition and avoided sexual intercourse [17]. In another study carried out Donders and colleagues, it was stated that abnormal vaginal microbiome caused vulvodynia, the most frequent cause was bacterial vaginosis, and this in turn caused sexual dysfunction in patients [18].

It has been shown that sexual dysfunction in women is much more complex than in men, and sexual dysfunction has many causes [19]. Both because the female sexual functions are more complex in structure and women avoid to discuss this subject, treatment of sexual dysfunction is difficult [20]. A portion of patients think that their condition is a part of their normal lives, and discharge is physiologic, because discharge is not always vexing. Sometimes discharge is seen only in small amounts that only smudges on the vaginal walls and labia, it can be in excessive amounts that will lead the patient to make a visit for examination and to accumulate in the posterior fornix [3].

In case of vaginal discharge, which is one of the reasons of visits of patients to gynecology outpatient clinics, dyspareunia and other sexual dysfunctions related to vaginal irritation are also seen commonly. In particular, the spoiled fish odor, which is unique for bacterial vaginosis, can cause sexual dysfunction in the spouse like in the female. In fact, bacterial vaginosis can be treated with a very simple antibiotic regime without even a necessity for the treatment of the spouse and the sexual life of the couple can return to normal. In case of neglected bacterial vaginosis however, this sexual dysfunction process will be elongated, drags the spouses even more apart, and affect their psychologica statuses in time. However, although delayed bacterial vaginosis treatment can eliminate the organic cause, spouses can need psychotherapy for their sexual dysfunctions.

Patients complain about bleeding and bad odor during the sexual intercourse, they are ashamed of this and create excuses to avoid intercourse. This leads to problems between the spouses. Therefore, level of awareness about the fact that bacterial vaginosis is a treatable disease, and efforts to increases their quality of life with treatment must be supported.

Although effectiveness of the FSFI questionnaire in displaying the sexual dysfunction is reliable, after all, it is based on the subjective answers of patients. Considering the conditions of the country we live in; women avoid to answer the questions related to their sexual lives. In our study also, number of women who meet the inclusion criteria and refused to participate is rather high. Our results seen support with studies based on larger patient populations.

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DOI: 10.25000/acem.530610 Olgu Sunumu / Case Report

Transconjunctival medial anterior orbitotomy for the removal of a wooden intraorbital foreign body extending to the optic nerve: A case report

Optik sinire uzanım gösteren tahta bir yabancı cismin transkonjonktival medial anterior orbitotomi ile çıkarılması: Bir olgu sunumu

Meryem Altın Ekin [1], Şeyda Karadeniz Uğurlu [1]

Abstract

Intraorbital foreign bodies can be classified into organic or inorganic according to their chemical composition. Wooden is inorganic in nature and is a rare, but serious form of intraorbital foreign body injuries. Evaluation and management of intraorbital wooden foreign bodies are highly challenging and can lead to severe orbital complications. In this paper, we report a case of a 33-year old man who presented with a penetrating wooden foreign body injury to the left orbit. Computed tomography revealed a linear shaped foreign body extending from left supraorbital ridge to the intraconal area. The tip of the foreign body was touching to the optic nerve without disrupting its integrity. The patient underwent transconjunctival medial anterior orbitotomy and the wooden foreign body was found to be located close proximity to the optic nerve in intraconal space. A 7cm wooden stick was removed completely with controlled traction. Postoperative recovery was uneventful with normal ophthalmic examination. Transconjunctival medial anterior orbitotomy is a useful and effective method for the removal of intraorbital wooden foreign bodies located in intraconal space.

Key words: wooden foreign body, intraconal, intraorbital, optic nerve, orbitotomy

Öz

İntraorbital yabancı cisimler kimyasal içeriklerine göre organik ve inorganik olarak sınıflandırılabilirler. Tahta inorganik yapıda ve intraorbital yabancı cisim yaralanmalarının nadir fakat şiddetli bir formudur. İntraorbital tahta yabancı cisim yaralanmalarının değerlendirilmesi ve yönetimi oldukça zordur ve ciddi orbital komplikasyonlara yol açabilir. Bu yazıda, otuz-üç yaşındaki erkek hastanın sol orbitasına tahta bir yabancı cisim ile olan penetran yaralanmasını sunuyoruz. Bilgisayarlı tomografi ile sol supraorbital bölgeden intrakonal bölgeye uzanım gösteren doğrusal bir yabancı cisim görüntülendi. Yabancı cismin ucu optik sinire yapısal bütünlüğünü bozmadan temas etmekteydi. Hastaya transkonjonktival medial anterior orbitotomi uygulandı ve tahta yabancı cisim intrakonal bölgede optik sinire çok yakın lokalize olarak bulundu. Kontrollü traksiyonla 7 cm'lik bir tahta parçası tamamen çıkartıldı. Postoperatif dönem normal oftalmik muayeneyle sorunsuzdu. Transkonjonktival medial anterior orbitotomi intrakonal bölgelerdeki tahta yabancı cisimlerin çıkartılması için kullanışlı ve etkili bir yöntemdir.

Anahtar Kelimeler: tahta yabancı cisim, intrakonal, intraorbital, optik sinir, orbitotomi

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Informed Consent: The written consent was received from the patient who was presented in this study.
Hasta Onamı: Çalışmada sunulan hastadan yazılı onam alınmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
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Introduction

Penetrating intraorbital foreign body injuries occur with one sixth of orbital traumas [1]. Intraorbital foreign bodies are most commonly caused by inorganic objects including metallic and non-metallic materials. Wooden is inorganic in nature and is a rare, but serious form of intraorbital foreign body injuries. It is very difficult to identify quantity and composition of wooden foreign bodies within the orbital tissue by radiological imaging techniques. Wooden foreign bodies have many pores on their surface which may serve as a nidus for bacteria. Compared with metallic ones, surgical removal of wooden foreign bodies in one piece is much more challenging due to the risk of fragmentation. Wooden foreign bodies may get retained in orbit and result in wide range of complications like abscess, cellulitis, fibrosis, functional and visual deficits [2]. Therefore, organic foreign bodies like wooden remain an important diagnostic and therapeutic problem. Due to the danger of functional and visual disorders, intraorbital wooden foreign bodies are to be removed as early as possible. Furthermore, lesions located in intraconal space are especially difficult to manage. Surgical complications of orbit are highest if the lesion is in the intraconal space [3]. However, the number of cases regarding management of intraconal wooden foreign bodies are limited [4-6].

In this unusual case, we described a successful surgical approach to an intraconal wooden foreign body extending to optic nerve.

Case report

A 33-year old man presented to the emergency department with an injury to his left orbit. Sixteen hours earlier, he had a head trauma in a motorcycle accident. On physical examination, a wooden stick was protruding out from the medial border of supraorbital ridge, appearing to be lodged deep within the orbit (Figure 1). There was no active bleeding from entry site and the patient was neurologically stable. Ophthalmic examination revealed lid edema and conjunctival hyperemia. His pupillary light reflex and color vision were normal. Ocular movements were free in all directions. Best corrected visual acuity of left eye was 10/10 with Snellen chart. Examination of the anterior and posterior segments was normal. Ophthalmic examination of his right eye was unremarkable.

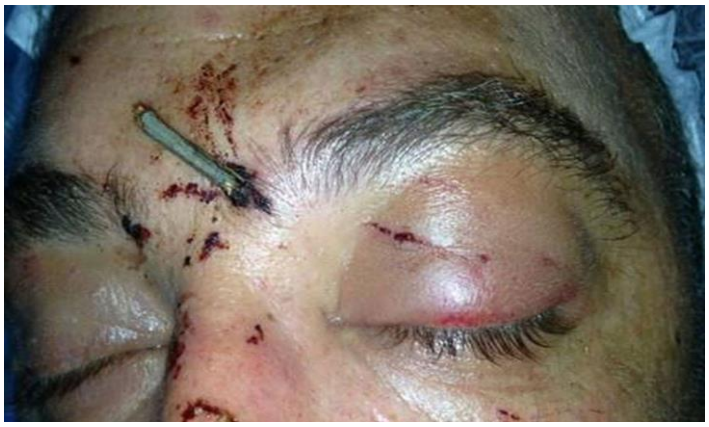

Figure 1.Wooden foreign body protruding from left medial supraorbital ridge.

Computed tomography (CT) that was performed upon admission revealed a linear shaped, well delineated foreign body as low density relative to surrounding orbital fat, which mimicked air bubbles (Figure 2).

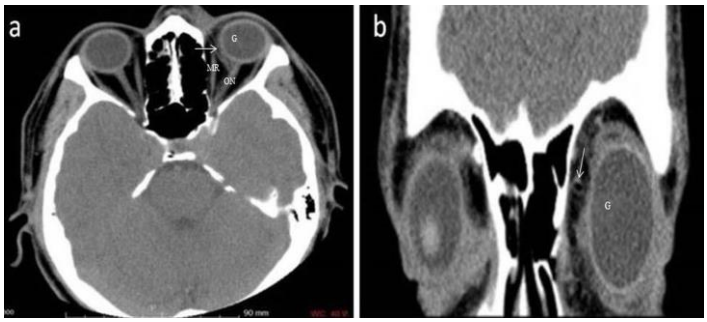

Figure 2. a, b: (a) Axial computed tomography scan showing linear shaped, air mimicked foreign body (white arrow) extending to the left intraconal space (G: globe, MR: the medial rectus muscle, ON: optic nerve). (b) Coronal computed tomography scan showing air density (white arrow) in the left retrobulbar area (G: globe).

The foreign body was measuring 7cm in length and breaking through medial side of the left orbit, proceeding along the left medial orbital wall and stopping at the left retrobulbar area. The tip of the structure was touching to the optic nerve without disrupting its integrity. The foreign body was not causing any deviation of the globe. There was no fracture in orbital bones and intracranial penetration was not observed.

A single 2 g dose of cefazoline was administered for prophylaxis. Transconjunctival medial anterior orbitotomy was considered the treatment of choice for removal of foreign body (Figure 3a). After spreading the eyelids apart under general anesthesia, a vertical incision line is marked on the upper eyelid at the junction of the medial one third and the lateral two thirds of the lid. The line was incised with a scalpel blade and extended full thickness along the eyelid with Stevens scissors. A 180 degree conjunctival peritomy was performed at the medial limbus. To improve exposure, radial relaxing incisions were made to the bulbar conjunctiva. Stevens scissors was used to bluntly separate the Tenon's capsule from sclera. Bleeding points sealed by diathermy coagulation. The conjunctiva was then retracted and a traction suture is then placed under the medial rectus muscle to guide the globe in the desired direction to reach the retrobulbar space. Medial rectus muscle was disinserted completely from its insertion. The intraconal space was entered through Tenon's capsule with Sewell and ¼ inch malleable retractors. The wooden foreign body was palpated just above the medial rectus muscle, lying next to the optic nerve. Optic nerve was found to be intact. The wooden stick was removed completely by grasping the tip with two fingers, and slowly pulling out with rotating movements (Figure 3b).

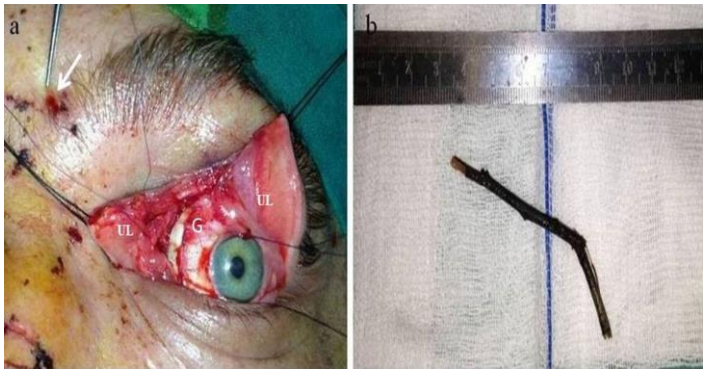

Figure 3. a, b : ((a) Intraoperative view of transconjunctival medial anterior orbitotomy. White arrow indicates entry site of foreign body (G: globe, UL: upper lid). (b) A wooden foreign body of 7 cm in length was removed from intraconal space.

Medial rectus muscle was sewn back on the globe and the conjunctiva was closed with absorbable sutures. Post-operatively, the patient was put on systemic broad spectrum antibiotics (clindamycin 4x600 mg and voriconazole 2x6 mg/kg). A microbiologic culture obtained from the wound revealed Staphylococcus epidermidis. Magnetic resonance imaging (MRI) after surgery showed postoperative changes along the tract of foreign body and did not reveal any hematoma, retained foreign body or abscess. The postoperative course was uneventful, and he was discharged without neurologi¬cal deficits. On postoperative day 7, the visual acuity measured 10/10. Incision was well healed with normal lid position. Eye movements were free to all directions (Figure 4).

Informed consent was obtained from the patient.

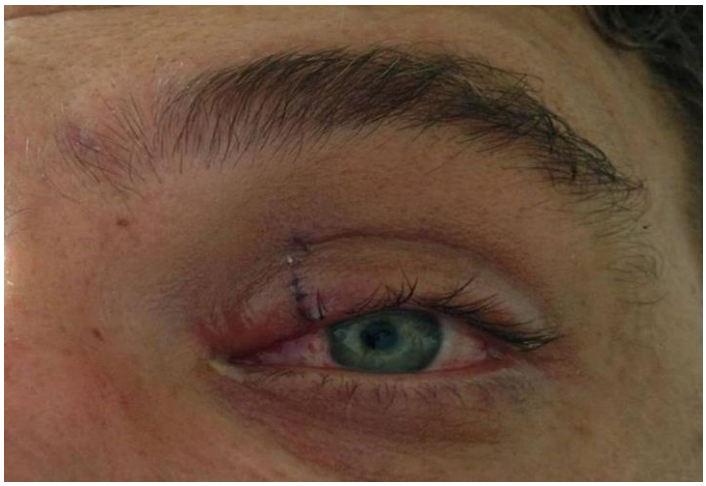

Figure 4. Early postoperative image of the patient.

Discussion

Orbital foreign bodies can cause a spectrum of presentations, from minimal symptoms to severe morbidity. Ocular manifestations of intraorbital foreign bodies mainly result from muscle impingement in fractured bones in the orbital walls or trauma to the trochlear, oculomotor or abducens nerve. Conical shape of the orbital cavity can cause penetrating injuries of ophthalmic vessels, cavernous sinus or optic nerve by directing foreign bodies toward the orbital apex. The orbital roof and apex have relatively thin bones that decrease resistance to cranial vault. Intraorbital foreign bodies can be classified into organic or inorganic according to their chemical composition. Most of the orbital foreign bodies are inorganic materials which are typically plastic, metallic or glass. Wooden is a type of organic foreign bodies.

Penetrating wooden orbital foreign bodies are difficult to evaluate clinically and mismanagement can lead to disastrous sequela for the orbital contents and even the brain. Management of intraorbital wooden foreign bodies are challenging for several reasons. Intraorbital wooden foreign bodies differ from inorganic foreign bodies, where retention of deep and small foreign bodies can be watched expectantly unless they cause functional impairment [7]. Unlike metal, plastic or glass, organic foreign bodies, such as wood carry high risk of infection and require removal as soon as possible. Even routine antibiotic use, infection rates of up to 64% with intraorbital wooden foreign bodies have been reported [8]. This is because infectious agents can easily attach to rough surface of wooden foreign bodies which acting as a potential nidus. Therefore, it is generally recommended to remove intraorbital wooden foreign bodies due to increased risk for infection and inflammation. In addition, infections due to retained intraorbital wooden foreign bodies may lead to abscess, panophthalmitis and fistula complications [5, 8].

Physical examination often underestimates the severity of injury and therefore, radiological investigations are mandatory. Radiological images assist in determining the integrity of the globe, proper localization of the foreign body, estimation of its shape, size and consistency and the relation to the adjacent orbital tissue. Nature of foreign body should be considered in the choice of imaging modality. Radiological imaging of intraorbital wooden foreign bodies can be performed using several different techniques. Standard radiography could not detect wooden foreign bodies in the orbit. Ultrasound has limited diagnostic value in some cases due to its availability and experience of the sonographer. Therefore, a CT scan is usually preformed in such cases. Numerous reports have demonstrated that CT is currently the imaging modality of choice for wooden intraorbital foreign bodies [2, 5, 8]. Serial imaging including axial, coronal and parasagittal views are required to maximally assess the superior orbital fissure and orbital roof. CT success in detection of intraorbital wood depends on extent of collateral inflammation, the location of the wood, incorporation of radiopaque substance and degree of wood hydration. The density of intraorbital wooden foreign bodies may change over time and the diagnosis is closely related to time of injury. In the subacute stage, it may be difficult to distinguish from surrounding orbital fat. In acute stages, wooden foreign bodies usually present as hypoattenuating on CT images; because of their low attenuation, they mimicked air bubbles, as revealed in our case. With the help of CT, we initially interpreted that proximal end of the foreign body extended to the level of optic nerve. MRI was shown to be superior to CT in detecting the smallest pieces of wood [9]. It is believed that MRI could detect intraorbital wooden foreign bodies, even when CT findings are negative [9]. In this case, we performed a CT scan instead of MRI because possibility of metal foreign bodies could not be excluded in open injuries.

Intraorbital wooden foreign bodies should be timely treated with the best surgical approach according to foreign body size, location and injured area. It should be noted that removal from intraorbital localizations, particularly from intraconal space is challenging. Because, surgery of foreign body in intraconal region carries an increased risk for motility disorders and optic neuropathy. Purgason and Hornblass pointed out that complication rate of orbital surgeries are highest when the lesion is in the intraconal region [10]. Therefore, blind intraorbital exploration should be discouraged. Surgical approach for intraorbital foreign body removal could be managed by exploring from entry site or through fistula pathway. Surgical access to intraconal region could be performed by multiple ways including transconjunctival, transmaxillary, transcranial and eyelid approaches. Presence of multiple splintered intraorbital wooden foreign bodies may further complicate the management. Multiple periorbital surgical exposures may be necessary for the control of foreign body tract. In this case, the wooden foreign body was safely removed by direct surgical exploration of the site using transconjunctival medial anterior orbitotomy. This approach allowed us to reach the deeper areas of intraconal spaces of the medial orbit. In our case, postoperative MRI confirmed complete removal of wooden foreign body. Extraocular muscle function of the patient was normal and no limitations have occurred in the movements of left eye. Wooden foreign bodies degrade easily; therefore, it may not be possible to remove as a single piece. Attention should be given to prevent fragmentation during withdrawal due to liable nature of wooden. In this case, the wooden foreign body was removed in a controlled manner with meticulous hemostasis. Vigorous attempts to remove cause loss

of hemostasis by disturbing tamponade effect and further damage the globe.

In the management of some orbital lesions, endoscopic orbital surgery instead of conventional orbitotomy techniques was also described. Endoscopic transnasal approach is a technique generally used for resection of orbital tumors located medially and/or inferiorly to the optic nerve. In recent years, several authors have reported successful removal of orbital foreign bodies using endoscopic surgery [10, 11]. Minimally invasive endoscopic surgery has the advantages of minimal surrounding tissue damage and avoiding any further facial scarring. However, the disadvantage of this technique is the risk of inadvertent optic nerve injury [10]. When small intraconal foreign bodies are embedded deep in the orbital fat, endoscopic visualization would be inadequate for accurate localization.

After removal of intraorbital wooden foreign bodies, cultures should be obtained for both bacterial, atypical mycobacterial and fungal pathogens. In this case, S. epidermidis was isolated from wound culture. However, other species such as streptecoccus, E. coli and anaerobes were also encountered from the cases with intraorbital wooden foreign bodies [8]. Therefore, empiric therapy is needed to cover multiple possible organisms. For wooden intraorbital foreign bodies with extension to intraconal area as in our case, it would be more efficient to recommend antibiotics with good blood-brain barrier penetration because of the proximity of the central nervous system and the possibility of infectious spread. It is sometimes impossible to complete initial removal of splintered intraorbital wooden foreign bodies. Even after years of surgery, delayed infectious presentation may occur [12]. To increase success of surgery, careful removal of all fragments, copious irrigation of wound with antibiotic solution and debridement of necrotic tissue are advised.

In conclusion, intraconal wooden foreign bodies require immediate attention and timely management due to severe complications. Furthermore, radiological localization should be ascertained to evaluate the status of surrounding structures and to plan the optimal surgical approach. Transconjunctival anterior orbitotomy can be used as an effective and safe approach for removal of wooden foreign bodies in intraconal orbital space.

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DOI: 10.25000/acem.505975 Olgu Sunumu / Case Report

3MC syndrome: A case report

3MC sendromu: Bir olgu sunumu

Seda Çakmaklı [1], Yaşar Kandur [2]

Abstract

3MC syndrome is a rare autosomal recessive disorder associated with distinctive facial features, cleft lip/palate, short stature, developmental delay, periumbilical defects, genitourinary and sacral anomalies. Mutations in the genes which encode proteins involved in the lectin complement pathway of innate immune system; MASP1, COLEC11 and COLEC10 have been identified in patients with 3MC syndrome.

We report a 2-year-old male patient with 3MC syndrome; in whom diagnosis was confirmed by mutation analysis of the MASP1 gene.

Key words: 3MC syndrome, MASP1, COLEC11, COLEC10, blepharophytosis, epicanthus inversus.

Öz

3MC sendromu tipik yüz bulguları, yarık dudak/damak, boy kısalığı, gelişme geriliği, umblikal defekt, genitoüriner ve sakral anomaliler ile seyreden, nadir görülen, otozomal resesif geçiş gösteren bir sendromdur. 3MC sendromlu hastalarda, doğal immun sistemin lektin kompleman yolağında görev alan proteinleri kodlayan MASP1, COLEC11 ve COLEC10 genlerinde mutasyonlar saptanmıştır.

Bu yazıda, MASP1 geni mutasyon analizi ile tanısı doğrulanan 3MC sendromlu 2 yaşındaki bir erkek hasta sunulmuştur.

Anahtar Kelimeler: 3MC sendromu, MASP1, COLEC11, COLEC10, blefaroptozis, epikantus inversus.

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Informed Consent: The written consent was received from the parents of the patient who was presented in this study.
Hasta Onamı: Çalışmada sunulan hastanın anne-babasından yazılı onam alınmıştır.

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Introduction

3MC syndrome is a rare autosomal recessive disorder that includes different entities with overlapping features. The Carnevale, Mingarelli, Malpuech and Michels syndromes were recently redefined to be a part of 3MC syndrome [1-4]. Malpuech syndrome is characterized by caudal appendage, cleft lip and palate, hypospadias, hypertelorism, intrauterine growth restriction, micropenis, and renal anomalies [3, 5]. Michels syndrome shows anterior chamber anomalies, blepharophimosis, cleft lip and palate, craniosynostosis, and epicanthus inversus [4]. Carnevale syndrome exhibits downslanting palpebral fissures, hypertelorism, large and fleshy ears, lozenge-shaped diastasis around the umbilicus, ptosis, strabismus, and synophrys [1]. Mingarelli syndrome, with similar features of Carnevale, exhibits also humeroradial synostoses and spinal anomalies as extra features [2].

3MC syndrome is caused by mutations in the genes regulating Mannose-binding lectin (MBL) associated serine proteases (MASP) which play a role in innate immune system and embryonic development [6, 7]. Mutations in two genes, MASP1 and COLEC11 (collectin 11) were found to be responsible for 3MC syndrome [7, 8]. In 2017, Munye et al. [9] identified a new gene that was also mutated in patients with 3MC syndrome: COLEC10.

The MASP1 gene encodes three proteins, MASP-1, MASP-3 and MAp44. The three isoforms share a common trunk but differ in their C-terminal serine protease domain [6].

Here, we report a male patient with suspected 3MC syndrome, diagnosis was confirmed through molecular analysis of MASP1 gene.

Case report

A two-year-old Syrian male patient, the fifth child of a consanguineous parents, was referred for genetic analysis due to developmental delay and dysmorphisms. Family history including siblings was unremarkable. There was no known drug exposure in the prenatal period. He was born on time with a weight of 3500 gr, a neonatal tooth was noted. He was operated for cleft lip at the 11 months of age. At physical examination, his height, weight and head circumference were 82 cm (3-10 percentile),11600 g (25 percentile) and 47.5 cm (10-25 percentile), respectively. He presented with facial dysmorphism including blepharophytosis, telecanthus, epicanthus inversus, mildly down-slanting palpebral fissures, blue sclera, high arched eyebrows, wide forehead, hypoplastic ala nasi, the left sided repaired cleft lip, dental crowding and retrognathia. The anterior fontanel was extremely large (3x3cm). He also showed a skin tag at the xiphisternum, peculiar supra-umbilical depression, mongol sign and sacral dimple (Figure 1).

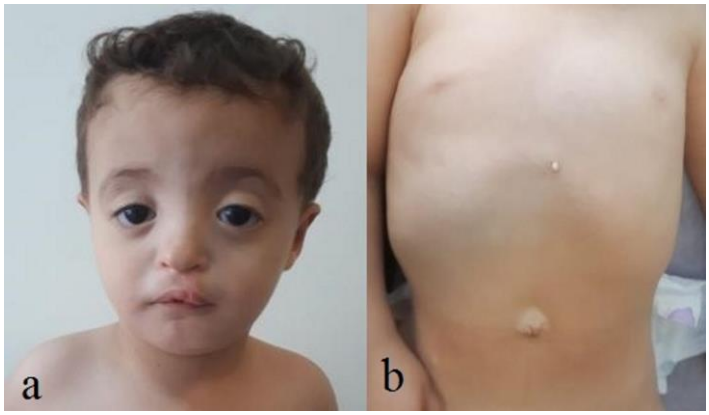

Figure 1. a ,b: Clinical pictures of the proband. (a) Photograph showing distinct craniofacial dysmorphism including a broad forehead, high arched eyebrows, blepharoptosis, hypertelorism, down-slanting palpebral fissures, blue sclera, hypoplastic ala nasi, a flat nasal tip, left sided repaired cleft lip scar. (b) Skin tag at xiphisternum and supra umbilical depression can be noted.

Routine laboratory investigations, transfontanelle ultrasonography, renal echography and bone X-ray were normal. Mild left ventricle dilation was detected on echocardiography; however, function of the left ventricle was normal. On the basis of suspected 3MC syndrome, next generation sequencing analysis (Miseq- Illumina Inc.) for all coding exons and exon-intron boundaries of the MASP1 gene was performed. Variants were named according to NM_139125. A homozygous c.1987G>T; p. Asp663Tyr mutation in the MASP1 gene was detected in the patient (Figure 2). Mutated exon was analyzed for cosegregation in unaffected parents; both parents were heterozygous carriers.

Written consent was taken from the parents of the patient.

Discussion

3MC syndrome (OMIM #257920;265050;248340) is associated with characteristic dysmorphic features (high-arched eyebrows, ptosis, blepharophimosis, hypertelorism and cleft lip/palate), short stature, developmental delay, hearing loss, umbilical hernias, urogenital and skeletal abnormalities such as craniosynostosis, radioulnar synostosis or caudal appendage [10]. We report on a two-year-old Syrian male patient with 3MC syndrome and describe his phenotype.

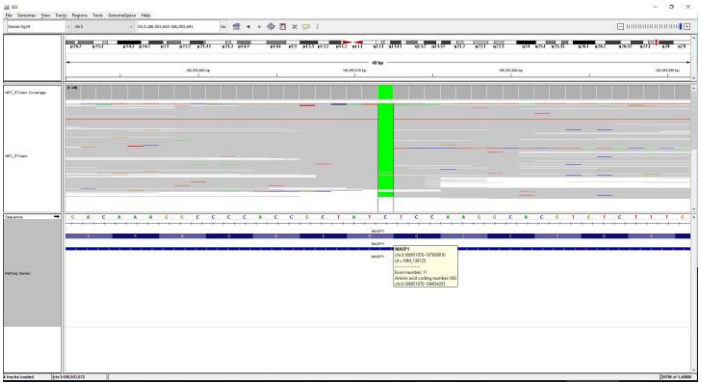

Figure 2. A screenshot from the Integrated Genomics Viewer (IGV) browser showing c.1987G>T mutation (according to NM_139125) in the MASP1 gene.

MASP1 and COLEC11 gene mutations have been held responsible for the clinical findings in 3MC syndrome. MASP1 and COLEC11 genes encode proteins related to the lectin complement pathway [7]. Mutations in another gene COLEC10, which is expressed in craniofacial tissues during development, have been identified later in 3MC patients [9]. MASP1 gene is located on chromosome 3q27-28 and encodes three protein isoforms: MASP-1, MASP-3, and MAp44, via alternative splicing [6,11]. All share the identical N-terminal amino acids. Serine protease domains in the C-terminals of MASP-1 and MASP-3 are different. MAp44 does not include a serine protease domain [8]. We identified a homozygous missense MASP1 mutation: c.1987G>T; p.D663Y (p.Asp663Tyr) (according to NM_139125) sufficient to cause 3MC syndrome in our patient. This change affects exon 11 and accordingly the C-terminal serine protease domain specific to MASP-3 [10,12]. The same domain is affected by missense mutations in previously reported patients, our findings further highlight the domain's essential role in the pathogenesis of 3MC syndrome [10,13].

Complements are an important part of innate immune defense. There are three complement activation pathways: Classical, alternative and lectin pathways. MASP1 gene is involved in lectin complement pathway [11]. We were unable to test complement function in our patient but on specific questioning, none is known to have an immunological phenotype.

We identified a homozygous missense MASP1 mutation: c.1987G>T; p.D663Y (p.Asp663Tyr) (according to NM_139125) sufficient to cause 3MC syndrome in our patient. The missense alteration, p. (Asp663Tyr), identified in the current study is the same as one reported by Atik et al. [10]. The authors reported a 6-month-old female patient presented with arched eyebrows, hypertelorism, blepharophytosis, bilateral cleft lip/palate, cliteromegaly, anterior ectopic anus, prominent coccyx with a sacral pit and a presacral capillary malformation. Echocardiography showed secundum ASD and wide PDA. Left renal agenesis and a hypoechoic solid lesion of the liver was revealed by abdominal ultrasound. The patient died 2 months after PDA ligation operation due to pneumonia [10]. Urquhart et al. [13] also described a female patient from Israel with c.1987G>T; p.D663Y mutation. The patient had typical facial features, cleft lip/palate, umbilical hernia, hearing loss, moderate intellectual disability, ventricular septal defect, hydrocephalus and tracheaesophageal fistula. Genitourinary anomaly and caudal appendage were also noted. The patient reported here was a 2-year- old Syrian male patient with a mild clinical course without any major malformations. The patient with the same mutation reported by Atik et al. [10] had poor prognosis, died 2 months after PDA ligation operation due to pneumonia. We can conclude

that expression of the phenotype in 3MC syndrome may be variable between patients even if they carry the same mutation.

Malpuech, Michels, Mingarelli and Carnevale syndromes are rare, autosomal recessively transmitted disorders. Although they are distinct entities, they share overlapping phenotypic features. Due to phenotypic similarities between Malpuech, Michels, Mingarelli and Carnevale syndromes, Titomanlio et al. [14] suggested to redefine the syndromes as the 3MC syndrome (for Malpuech-Michels-Mingarelli-Carnevale) [15]. Prevalence of 3MC syndrome is unknown; 32 affected individuals from 20 families were described in the literature until 2011 [7]. A small number of patients with mutations in COLEC11, MASP1 or COLEC10 genes have been reported until now. Sirmaci et al. [8] reported 3 Turkish patients from 2 families with MASP1 mutations. Rooryck et al. [7] reported 6 patients from 4 families with MASP1 mutations, 10 patients from 7 families with COLEC11 mutations. In 2015, Atik et al. [10] reported six patients with MASP1 mutations. More recently Urquhart et al. [13] described 2 patients with COLEC11 and 5 patients with MASP1 mutations. Gardner et al. [16] reported 2 sisters with exon 8 deletion in COLEC11. In 2017, Munye et al. [9] reported 3 patients with COLEC11, 1 patient with MASP1 and 3 patients with COLEC10 mutation. Therefore, in total, together with the isolated cases recently reported, 43 3MC patients with mutations in COLEC11, MASP1 or COLEC10 have been identified until now [17, 18]. Among 43 patients, 23 patients had mutations in MASP1 gene [9, 10, 13].

In this case report, we discussed the clinical and laboratory findings of a patient with 3MC syndrome. Diagnosis was confirmed by mutation analysis of the MASP1 gene. We found a homozygous missense mutation in MASP1. Limited number of 3MC patients have been reported in the literature, the number of patients with molecular evidence is even smaller. Thus, this report of the 3MC syndrome patient with homozygous mutation in MASP1, aims to expand the phenotype of this rare syndrome and provide insights into the genotype-phenotype correlation.

We report a 2-year-old male patient who was diagnosed with 3MC syndrome based on the phenotypic and molecular evidence. Combining empirical analysis of dysmorphology with current molecular analysis techniques can be a useful approach to understand the etiology of malformation syndromes. Further studies are required to explain the fundamental roles of lectin complement pathway genes in developmental disorders.

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DOI: 10.25000/acem.569181 Olgu Sunumu / Case Report

Coexistence of endolymphatic hydrops and benign paroxysmal positional vertigo treated with repositioning maneuver: A case report

Repozisyon manevrası ile tedavi edilen endolenfatik hidrops ve benign paroksismal pozisyonel vertigo birlikteliği: Bir olgu sunumu

Süha Ertuğrul [1], Emre Söylemez [2], Tuğçe Gürel [3]

Abstract

Benign paroxysmal positional vertigo (BPPV) is a peripheral vestibular disease that occurs by sudden head movements and is characterized by dizziness that lasts for seconds. Endolymphatic hydrops is a vestibular pathology that causes hearing loss, tinnitus, fullness in the ear and dizziness due to increased endolymphatic pressure in the inner ear. Although BPPV and endolymphatic hydrops are considered as two different entities, it has recently been reported that there may be a relationship between these two diseases. However, the pathophysiology of this relationship has not been clearly elucidated. In this paper, we discussed the relationship between these two diseases accompanied by a patient with a sudden onset of endolymphatic hydrops and BPPV which was treated with repositioning maneuver.

Key words: Benign paroxysmal positional vertigo, endolymphatic hydrops, hearing loss, repositioning maneuver.

Öz

Benign paroksismal pozisyonel vertigo (BPPV), ani baş hareketleriyle ortaya çıkan ve saniyeler süren baş dönmesiyle karakterize periferik vestibüler bir hastalıktır. Endolenfatik hidrops ise iç kulakta endolenfatik basıncın artmasına bağlı olarak işitme kaybına, kulak çınlamasına, kulakta dolgunluk hissine ve baş dönmesine neden olan vestibüler bir patolojidir. BPPV ve endolenfatik hidrops iki farklı antite olarak düşünülse de, son zamanlarda bu iki hastalık arasında bir ilişki olabileceği bildirilmiştir. Ancak bu ikilinin patofizyolojisi açık bir şekilde aydınlatılamamıştır. Biz bu yazıda, repozisyon manevrası ile düzelen ani gelişmiş endolenfatik hidrops ve BPPV birlikteliği olan bir olgu eşliğinde bu iki hastalık arasındaki ilişkiyi tartıştık.

Anahtar Kelimeler: Benign paroksismal posizyonel vertigo, endolenfatik hidrops, işitme kaybı, repozisyon manevrası.

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Introduction

Positional dizziness that occurs when otoconia particles in the utricle fall into the semicircular canals, or these crystals adhere to the cupula in the ampullas is defined as benign paroxysmal positional vertigo (BPPV). BPPV is the most common cause of vertigo caused by the peripheral vestibular system. The second most common cause of vertigo following BPPV is endolymphatic hydrops.

Although symptoms of these two diseases are quite different, recent studies on the relationship between BPPV and endolymphatic hydrops have been reported [1]. However, the relationship between the two diseases has not been fully explained. In our knowledge, there is no study in the literature on endolymphatic hydrops symptoms treated with repositioning maneuver.

In this paper, we discussed the relationship between these two diseases accompanied by a patient with a sudden onset of endolymphatic hydrops and BPPV which was treated with repositioning maneuver.

Case report

A 43-year-old male patient was admitted to the otorhinolaryngology outpatient clinic with a complaint of dizziness. In his anamnesis, he stated that he had a sudden vertigo attack while cutting wood three days earlier and that vertigo lasted for about 30 minutes. He stated that there was fullness, hearing loss and tinnitus in the right ear which started after vertigo attack and still persist. In the process following the first attack, he reported that his head was spinning during sudden movements when he was lying on the bed and getting out of bed. The otoscopic examination of the patient revealed no pathology. In the audiological examination, sensorineural hearing loss (SNHL) was present at the lower frequencies in the right ear in the pure tone audiometry test (Figure 1A). The mean pure tone average was bilateral normal (right ear: 7.5 dB, left ear: 3.5 dB). In the immitancemetric examination, the patient had bilateral type A tympanogram and 500, 1000, 2000 and 4000 Hz acoustic reflex thresholds were in the normal range. In the vestibular evaluation, the cervical vestibular evoked myogenic potential (c-VEMP) test, the Romberg test, the Fukuda test, tandem posture with eyes closed, tandem gait test with eyes open were performed. Oculomotor tests, Dix Hallpike test, supine roll test, and caloric test were performed under videonistagmography. Although the patient's history and symptoms indicated endolymphatic hydrops, the c-VEMP responses at 1000 Hz were within the normal limits (Figure 1B). The Fukuda test of the patient was lateralized to the right side. The Romberg and tandem gait with eyes open tests were normal. The tandem posture with eyes closed test was positive. Oculomotor tests were within the normal limits and the patient did not have spontaneous nystagmus. The Dix-Hallpike test performed on the right ear of the patient revealed horizontal-rotatory nystagmus with a vertical component lasting 20 seconds. When the patient was brought to the sitting position, a reverse phase of the nystagmus was observed (Fig. 1C). The Dix-Hallpike test performed in the left ear and supine roll tests were normal. In the caloric test, there was a 20% response asymmetry to the right side. After these tests, the patient was diagnosed with right posterior semicircular canal BPPV and endolymphatic hydrops in the right ear. Epley maneuver was performed for the right ear. After the maneuver, the patient stated that the dizziness had decreased and there was no nystagmus in the control Dix-Hallpike test. After 1 day, the patient was called back for the audiological evaluation. In the pure tone audiometry test, SNHL in the lower frequencies in the right ear was found to be improved (Figure 1D). The patient stated that the tinnitus and fullness in his right ear had improved. The patient was not given medical treatment. During the 1-year follow-up, the patient had no episodes of vertigo. A written consent form was taken from the patient.

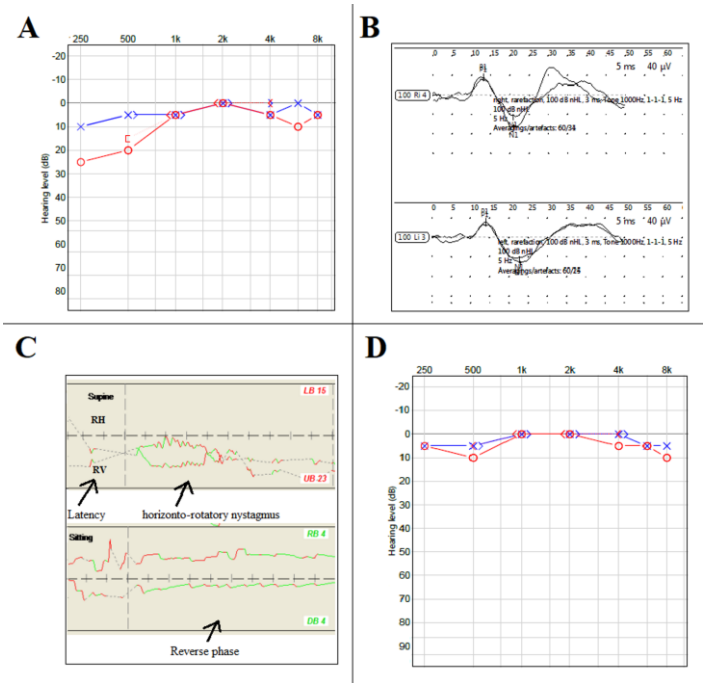

Figure 1. A, B, C, D: (A) Pure tone audiometry test shows sensorineural hearing loss in the right ear involving low frequencies. (B) Cervical vestibular evoked myogenic potential (c-VEMP) responses at 1000 Hz with 100 dB NHL intensity level (amplitude: right ear=47.2 µw, left ear=48.6 µw; latency: right ear: P1:13.9 ms, N1:22.9 ms, left ear: P1:13.2ms, N1:21.9 ms). (C) Nystagmus occurring during the Dix-Hallpike test recorded on videonystagmography. (D) Pure tone audiometry test performed 24 hours after the Epley maneuver shows that the sensorineural hearing loss involving low frequencies improved.

Discussion

BPPV causes vertigo which occurs suddenly with a change in the head's position and usually lasts for seconds. The direction and characteristics of nystagmus in BPPV differ according to the semicircular canal involved. In our case, the latency, direction, duration, and fatigue of the nystagmus encountered in the right ear in the Dix-Hallpike test performed on the patient had typical characteristics of the right posterior canal BPPV nystagmus. Head trauma, hormonal changes, aging and sleep position may be etiological factors in BPPV [2]. In our case, we think that the vibration of the patient's body during the wood crushing and the patient's continuous bending this process caused the dislocation of the otoconias.

In endolymphatic hydrops, episodic dizziness, tinnitus, and floating hearing loss occur with increased endolymphatic pressure. Endolymphatic hydrops may occur primarily in cases such as Mondini aplasia and Meniere's disease [3]. It may also occur secondary to head trauma and ear surgeries [3]. In the anamnesis, floating hearing loss during vertigo attacks, tinnitus, ear fullness and episodic vertigo attacks lasting for hours are the most important criteria in the diagnosis of endolymphatic hydrops. SNHL, which occurs in low frequencies in the pure tone audiometry test, is typical for endolymphatic hydrops. In our case, because of the typical endolymphatic hydrops findings in audiometry, otoacoustic emission test and Auditory Brainstem Response test were not performed. The c-VEMP test can also be used for diagnosis purposes. In the early stages of the disease, c-VEMP responses can be obtained normally. In the later period of the disease, c-VEMP responses are lost [4]. In our case, it was considered natural for c-VEMP responses to be normal because the patient experienced the first vertigo attack. Glycerol test is another diagnostic method used in the diagnosis of Meniere's disease. In a study, 77 Meniere patients had 70% gliseol test positivity, whereas non-Meniere sensorineural hearing loss patients had no positive glycerol test [5]. However, we did not perform the glycerol test in our case. Electrocochleography is an important diagnostic tool in Meniere's disease. In Meniere's disease, an increase in the summation potential / action potential ratio is observed on electrocochleography. However, there are some studies indicating that the role of electrocochleography in the diagnosis of Meniere cannot be very meaningful [6]. In our case, we could not do electrocochleography due to limited facilities. In recent years, magnetic resonance imaging after intratympanic gadolinium injection has gained value in radiological imaging of endolymphatic hydrops [7]. However, we could not have MRI with gadolinium in our case. The

diagnosis of endolymphatic hydrops was made with tinnitus, fullness in the ear and hearing loss involving low frequencies described by the patient.

As the endolymphatic pressure in the scala media increases, the pressure to Reissner's membrane and the basilar membrane is increased. This pressure affects hairy cells called cilia, which are responsible for hearing and balance, making the cilia more insensitive [8]. Thus, an episodic dizziness attack and floating hearing loss occur. The relationship between BPPV and endolymphatic hydrops was first investigated by Mizukoshi et al. [9]. They reported that there was an epidemiological relationship between BPPV and endolymphatic hydrops [9]. In a study conducted by Hughe et al. [10] on 151 BPPV patients, they reported that 45 BPPV patients had also Meniere's disease. Jahn [11] reported that every 100 non-diagnosed vertigo patients had both BPPV and endolymphatic hydrops. The high incidence of the coexistence of these two diseases can be explained in three ways. The first is the idea that both diseases may develop due to a common etiological factor. Studies have shown that both diseases may occur in head trauma and inflammatory conditions [2, 3]. In our case, a mechanism similar to the formation of BPPV during wood crushing may have caused endolymphatic hydrops to displace the otoconias that may be present in the saccule. The second possibility is the idea that endolymphatic hydrops may trigger BPPV. Karlberg et al. [1] suggested that diseases such as vestibular neuritis, labyrinthitis, and Meniere's disease may dislocate otoconia by damaging utricle and cause BPPV. In a recent review consisting of a series of 3 cases, it was stated that BPPV might trigger endolymphatic hydrops, as a third mechanism [11]. Walter and Reymond [12] found that the endolymph fluids of Meniere patients were more intense in terms of protein content. In another study, Johnsson et al. [13] reported that the content of endolymph fluids in patients who developed endolymphatic hydrops as a result of cochlear otosclerosis was more intense than normal. Otoconia are known to consist of calcium and protein [11]. In this case, displaced otoconia can change the density of the endolymph and increase osmotic pressure. The increased osmotic pressure may cause endolymphatic hydrops. The relationship between BPPV and endolymphatic hydrops can be also explained by this hypothesis in addition to other hypotheses.

In conclusion, in a patient with endolymphatic hydrops and BPPV, both diseases may develop secondary to a common etiologic factor, or endolymphatic hydrops may induce BPPV or, finally, dislocated crystalloids in BPPV may cause endolymphatic hydrops. Trauma may cause endolymphatic hydrops by displacing otoconias in the saccule as it causes BPPV by displacing the otoconias in the utricle. In patients with coexistence of BPPV and endolymphatic hydrops, endolymphatic hydrops findings may also improve after repositioning maneuver for BPPV treatment.

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