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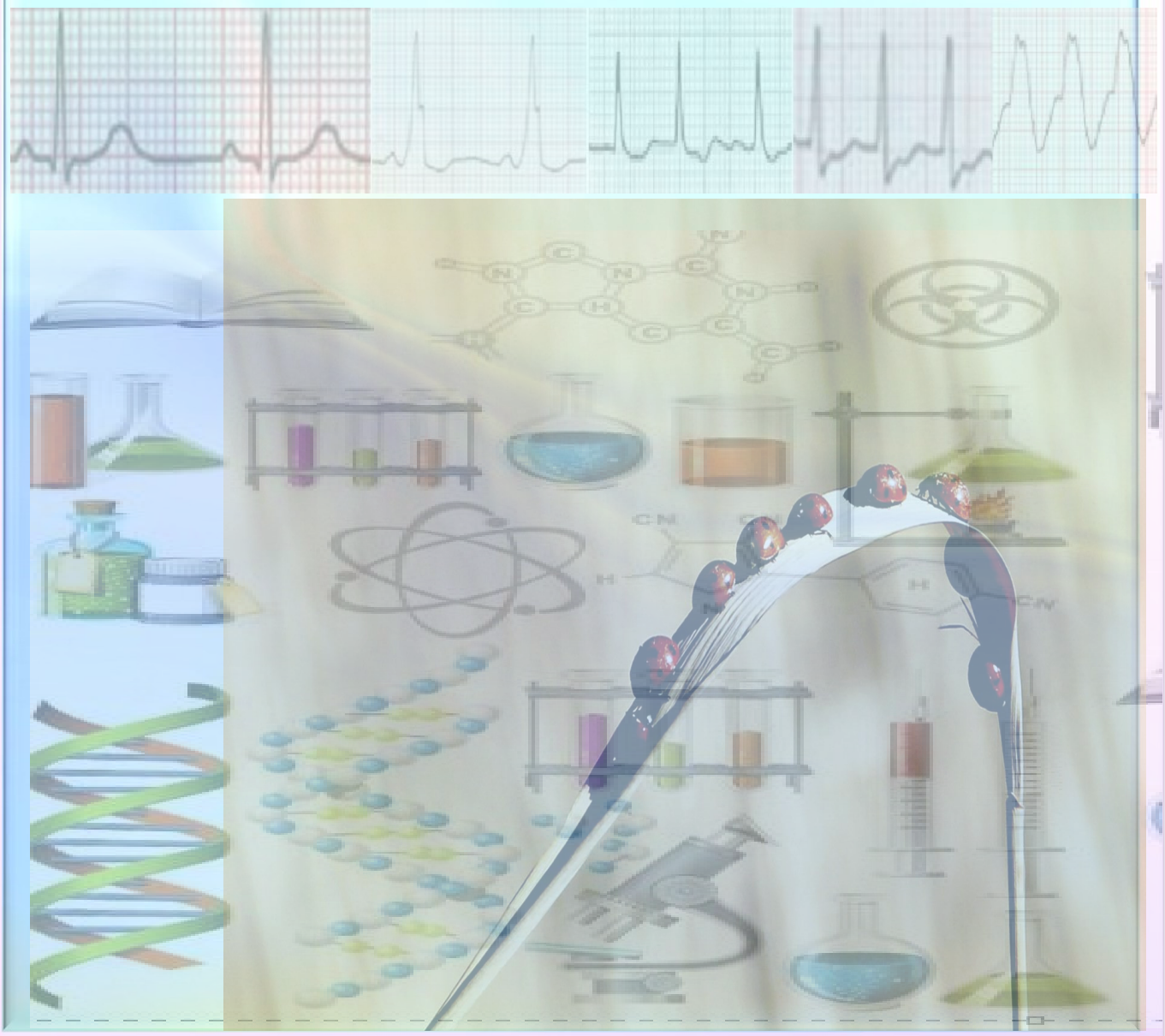

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All spellings must comply with Turkish spelling rules and must be in accordance with punctuation marks. Abbreviations should be avoided as much as possible. References, figures, tables and pictures should be numbered in the order they appear in the text.

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Books; 1. Wagner G. S. Marriott's Practical electrocardiography, Tenth ed. Lippincott Williams Publisher, 2000: 124-129

Web article: Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website; Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 July 2002]. Available from: www.cancer-pain.org

Thesis; Gezer R: Morphological Characteristics and Individual Differences of Rugae Palatines. Master Thesis, Şanlıurfa: Harran University Institute of Health Sciences, 2016.

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Contents /İçindekiler

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Orgınal Article

Evaluation of polypharmacy and adherence to the phosphorus binding treatment in hemodialysis patients

Hemodiyaliz hastalarında polifarmasi ve fosfor bağlama tedavisine uyumun değerlendirilmesi

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Highlights

- Polypharmacy will continue to be a more important problem in the future.
- To prevent this, studies should be conducted for effective combined treatment regimens

Abstract

Background: Polypharmacy and nonadherence to treatment regimens confront as an ever-mounting problem in hemodialysis patients. The aim of the present study was to emphasize the importance of polypharmacy and tablet load problem and to evaluate the adherence to phosphorus binding agent treatment and to examine the factors that cause to non-adherence. **Material and Method:** 361 patients who were in regular dialysis program in 4 different hemodialysis centers in Samsun city were included in the study. By meeting face to face, a questionnaire that was composed of 35 questions which investigated the factors that effect the polypharmacy and treatment adherence was filled to patients by a physician. Adherence to phosphorus binding treatment was measured according to both serum phosphorus level and Modified Morisky Adherence Scale. **Results**: In hemodialysis patients, the mean daily used drug groups were found as 5, the tablet count was found as 10. It was determined that the phosphorus levels of % 40.4 of patients who were using phosphorus binding agents were found above the target phosphorus level that was recommended in the guidelines. According to the adherence questionnaire that was performed to the patients, non-adherence rate to the phosphorus binding agents was found 77,3 %. In addition, age, educational background, smoking and tablet load are the factors that were not found effective on the adherence to the phosphorus binding agents treatment .**Conclusion:** Polypharmacy and non-adherence to the phosphorus binding treatment are serious and worth-stressing problems that should be solved in hemodialysis patients. We think that more, more advanced and quality research is needed to improve adherence on this subject

Keywords: Adherence ,hemodialysis, phosphorus binding treatment, polypharmacy

ÖZ

Amaç: Hemodiyaliz hastalarında polifarmasi ve tedavi rejimlerine uyumsuzluk giderek artan bir sorun olarak karşımıza çıkmaktadır. Bu çalışmanın amacı hemodiyaliz hastalarında polifarmasi ve tablet yükü sorununun önemini vurgulamak ve fosfor bağlayıcı ilaç tedavisine uyumu değerlendirmek ve uyumsuzluğa neden olan faktörleri incelemektir. **Materyal ve metod :** Samsun ilinde bulunan 4 ayrı hemodiyaliz merkezinde düzenli diyaliz programında olan 361 hasta çalışmaya alındı. Hastalarla yüz yüze görüşülerek, polifarmasi ve tedaviye uyumuna etki eden faktörleri araştıran 35 sorudan oluşan anket bir doktor tarafından doldurulduldu. Fosfor bağlayıcı tedaviye uyum hem serum fosfor düzeyine göre hemde Modifiye Morisky uyum skalasına göre ölçüldü. **Bulgular:** Hemodiyaliz hastalarında günlük kullanılan ilaç grubu ortalama 5, tablet sayısı ise 10 bulundu. Fosfor bağlayıcı ilaç kullanan hastaların %40.4' ünün fosfor düzeylerinin kılavuzlarda önerilen hedef fosfor düzeyinin üstünde olduğu saptandı. Hastalara uygulanan tedaviye uyum anketine göre ise fosfor bağlayıcılara uyumsuzluk oranı %77,3 bulundu. Ayrıca yaş, eğitim durumu, sigara kullanımı ve tablet yükü fosfor bağlayıcı ilaç tedavisine uyumda etkili bulunmamıştır. **Sonuç:** Hemodiyaliz hastalarında polifarmasi ve fosfor bağlayıcı tedaviye uyumsuzluk üzerinde durulması ve çözülmesi gereken ciddi bir sorundur. Bu konuda uyumu artırmak için daha fazla, daha gelişmiş ve kaliteli araştırmalara ihtiyaç olduğunu düşünüyoruz.

Anahtar kelimeler: Fosfor bağlayıcı tedaviye uyum, hemodiyaliz, polifarmasi

Introduction

Human lifespan is getting longer, so the elderly will use more drugs and polypharmacy will continue to be a more important problem in the future. Polypharmacy is associated with high morbidity and mortality as an increasing problem in patients with chronic diseases who have to take long-term drug therapy. In previous studies, polypharmacy has been investigated quite frequently in the elderly and in chronic diseases such as diabetes mellitus, hypertension, hyperlipidemia, AIDS, depression (1,2). However, few studies have investigated polypharmacy in chronic dialysis patients (3).

It has been determined that nonadherence to treatment regimens is common in patients with end-stage renal disease. Most of the studies were performed on hemodialysis patients. Non-adherence to treatment in dialysis patients; It is known to cause results such as increased blood pressure, hyperphosphatemia, hypocalcemia, renal osteodystrophy, anemia, increased risk in terms of drug side-effect reactions and increased drug load. For these reasons, we aimed to measure the extent of polypharmacy in chronic hemodialysis patients and to emphasize the importance of this problem. Another aim of the study is to measure the adherence of chronic hemodialysis patients to phosphorus-binding therapy and to determine the factors affecting adherence.

METHODS

361 patients who received regular hemodialysis treatment 1,2 or 3 times a week in 4 different hemodialysis centers in Samsun were included in the study. The inclusion criteria's of the study were to have hemodialysis for at least 3 months and to have the mental capacity to understand and answer the questionnaire. The questionnaire was completed by a single doctor by interviewing the patients face to face. The questionnaire was two-stage and included 35 questions. In the first stage, there were questions about the patients' socio-demographic characteristics and polypharmacy. Demographic characteristics of the patients (age, gender, education level, employment status, marital status, income status, who they live with at home), cigarette-alcohol use, chronic kidney disease (CKD) cause, comorbidities, duration of hemodialysis, and how many times a week they underwent dialysis were questioned. The patients were asked about the drug group, type of drug and the number of tablets they used daily, then the results were recorded by looking at the drug boxes they brought with them. The second phase of the questionnaire was conducted only on patients using phosphorus-binding drugs. The second-stage questionnaire included detailed questions related to the patient's understanding of the importance, effect, and side-effect of the phosphorus-binding drug. In addition, the patient was asked questions about which phosphorus binder drug he used at which dose, whether he knew the name, effect and side effects of the drug, from whom he received training about the drug, and the reasons for not taking the drug. The mean of three-month phosphorus measurements and Kt/V values of the patients were recorded. Then, the patients were asked six questions about the Morisky Medication Adherence Scale (MMAS) (4-6). Question 1,2 and 6 in the questionnaire; It measures forgetfulness and inattention. It is thought that it is the determinant of motivation and therefore it will affect motivation in terms of compliance. If the question is 3, 4 and 5; assesses whether patients discontinue medication and understand the long-term benefits of continued therapy. It was thought that these questions were the determinants of knowledge and would affect compliance in terms of knowledge. All questions in MMAS are answered as "yes" and "no". For the motivation domain, each "no" answer gets 1 point, while each "yes" answer gets 0 points. This provides a score in the range of 0-3 for the motivation domain. If the patient's total score is in the range of 0-1, the motivation area is scored as "low". In addition, the score is >1, the motivation area is scored as "high". In the knowledge area, for questions 3 and 4, the answer "no" gets 1 point, while the answer "yes" gets 0 points. In the 5th question, "no" answer gets 0 point and "yes" answer gets 1 point. As a result, a score between 0-3 is obtained for the knowledge domain. If a patient's total score is between 0-1, the information field is considered "low", and if >1, it is considered "high" **(Table 1)**. The study has been carried out according to the principles of the Declaration of Helsinki, and its protocol was approved by local ethical committee.

Table 1 Compliance Questionnaire for Phosphorus Binding Drug Treatment (Modified Medication Morisky Scale)

Question	Motivation	Knowledge
1-Have you ever forgotten to take your medicine?	Yes (0) , No(1)	
2- Are you careful about the times of taking medication?	Yes (0) , No(1)	
3-Do you sometimes stop taking your medicine when you feel better?		Yes (0) , No(1))
4-If you feel bad when you take medicine, Would you sometimes stop the medicine?		Yes (0) , No(1)
5-Do you know the long-term benefits of taking your medicine as told by your doctor or pharmacist?		Yes (1) , No(0)
6-Do you sometimes forget to prescribe your medicine on time?	Yes (0) , No(1)	

Statistical Analysis

Arithmetic Mean±Standard Deviation as the central distribution criterion of the data; As frequency criteria, numbers and percentages were used together. In the data analysis, using the SPSS (Version 12.0) computer program, Student t tests were performed in groups with normal distribution and Mann Whitney U tests were performed in groups that did not comply with normal distribution in pairwise group comparisons. Chi-square test was used to compare the percentages between groups. ANOVA test was used to compare more than two groups. In the study, $p<0.05$ was accepted as the level of significance.

Results

361 patients included in the study, 207 (57.3%) were male and 154 (42.7%) were female. The mean age of the patients was 57.5±13.9 years, and they were between 19-85 years old. Distribution of socio-demographical characteristics by gender of the study participants are listed in **Tables 2**. When the female and male patient groups are compared socio-demographically, it is seen that the rates of lack of education, divorce, not working in an income-generating job and living alone in women are quite high compared to men; however, smoking and alcohol use were found to be low. The most common cause of CKD was hypertension (35%), followed by Diabetes Mellitus (27%). Other causes of CKD are presented in **Table 3**. The mean duration of hemodialysis of the patients was 52.5±47.5 months, and the duration of dialysis of the patients ranged from 3 to 316 months. The mean number of drug groups used by all patients was 4.2 ± 1.5, and the number of drug groups used daily ranged from 1 to 8. The average number of tablets taken daily, varying between 2-25, was found to be 9.9 ± 3.7 **(Table 4-5).** Considering the drug group and number of tablets of the patients by gender; The mean group of drugs used by men was 4.1±1.4, women were 4.4±1.6, and there was no statistically significant difference between them ($p>0.05$). The average number of tablets used daily was 9.91±3.8 (Range:2-25) in men and 9.89±3.6 (Range:2-20) in women. There was no statistical difference between them ($p>0.05$) .

Of the patients using phosphorus-binding drugs, 90.9% (288 people) stated that they took the drug themselves, and 9.1% (29 people) stated that the drug was given to them by someone else. 83.9% of the patients stated that they took their medication with meals, 10.4% between meals, 5.7% on an empty stomach. While 45.7% (145 people) of 317 patients knew the name of the phosphorus-binding drug, 45.8% did not know the name of the drug, 8.5% (27 people) stated that they could not remember the name of the drug. Only 5.8% (16 people) of the patients stated that they knew about the side effects of phosphorus-binding drugs. 64.7% (205 people) of the patients knew the effect of the phosphorus-binding drug. It was determined that 5.7% (18 people) of the patients in the phosphorus binder group had a medication chart in their hands. Of the patients, 85.5% (271 people) stated that the effect and side effects of the drug were explained by the doctor.

Patients received information about drugs from doctors with 85.5%. Considering the education given to patients about phosphorus binder; 169 (53.3%) patients were informed about the dose/time/duration and purpose of use of the drug. Only education about dose/time/duration was given to 148 (46.6%) patients. The patients were never informed about the side effects and drug interactions of the drug. Of the patients using phosphorus binders, 84.8% (269 people) stated that they did not use the drug regularly, while 15.1% (48 people) stated that they used it regularly. The frequency of regular use of the drug was found to be 15.1% in men and 15.2% in women, and there was no statistically significant difference between them ($p>0.05$).

We found that the complaints about drug taste were 4 times more common in women than in men, and this difference was statistically highly significant ($p=0.002$). In addition we found that the complaints about the side effects of the drug were 1.5 times more common in women than in men, and this difference was statistically highly significant ($p=0.009$**).**

The reasons for getting tired of using the drug, forgetfulness and drug non-compliance related to tablet size did not different between the genders ($p>0.05$). There was no statistically significant difference between the Kt/V values of the patients who used phosphorus binders and those who did not ($p>0.05$). Only 59.6% of the patients using phosphorus-binding drugs have a phosphorus level below 5.5. Nonadherence to the use of phosphorus-binding drugs was found to be 40.4%. (When serum phosphorus level is taken as a measure of adherence) As seen in **figure 1 and 2** , only 22.7% of the patients scored 4 according to the MMAS. Accordingly, the rate of non-compliance with phosphorus binders was 77.3% according to the patients' self-report questionnaire. While the mean serum phosphorus level of 135 (42.6%) patients using phosphorus-binding drugs and having an MMAS compliance score below 4 was 5.7± 1.4 mg/dl, the mean phosphorus level of 182 patients (57.4%) with an MMAS score of 4 was 5.1±1.2 mg/dl and the difference between them was found to be statistically highly significant ($p=0.001$).

Figure 1. Modified-Morisky Adherence Scale (MMAS) distribution of patients using phosphorus-binding drugs

MMAS	Number	%
0	3	0,9
1	42	13,2
2	90	28,4
3	110	34,7
4	72	22,7
Total	317	100,0

Figure 2. Distribution of Modified-Morisky Adherence Scale (MMAS) in terms of motivation in patient using phosphorus-binding drugs

MMAS	Number	%
0	7	2,2
1	93	29,3
2	129	40,7
3	88	27,8
4	317	100

While the mean phosphorus level of 100 (31.5%) patients with low MMAS scores was 5.8±1.3 mg/dl, the mean phosphorus level of 217 (68.5%) patients with high scores was 5.1±1.2 mg/dl, and the difference between them was statistically highly significant (p=0.001)

Although the mean phosphorus level of 96 (20.5%) patients aged 65 and over using phosphorus-binding drugs was 4.9±1.2 mg/dl, the mean value was 5.5 ±1.3 mg/dl in 221 patients under 65 years of age, and the difference between them was statistically significant (p=0.002).

There was no statistically significant difference between the groups when the phosphorus level of the patients using phosphorus-binding drugs, in terms of gender, living alone or with a family, marital status monthly income, educational status, diabetes or not (p>0.05). While the mean serum phosphorus level of 37 (11.7%) smokers was 5.8±1.4 mg/dl, the mean phosphorus level of 280 (88.3%) non-smokers was 5.3±1.3 mg/dl, and the difference between them was statistically significant (p=0.03).

The mean serum phosphorus level of 139 (43.8%) patients with 9 or less daily tablets was 5.1±1.2, and the mean phosphorus level of 178 (56.2) patients who used 10 or more tablets was 5.5±1.3. The difference between the two groups was statistically significant (p=0.009). Among the patients using phosphorus-binding drugs, the mean serum phosphorus level of 141 (44.5%) patients using 5 or more drug types was 5.3±1.3 mg/dl, whereas the mean phosphorus level of 176 (55.5%) patients using less than 5 drug groups was 5.4±1.3 mg/dl. dl and the difference between them was not statistically significant (p>0.05).

Table 2 Distribution of Socio-Demographical Characteristics by Gender

Socio-Demographic Characteristics	Male		Female	
	Number	%	Number	%
Marital status				
Married	176	85.0	105	68.2
Single	20	9.7	10	6.5
Divorced	11	5.3	39	25.3
Who do you live with				
Alone	4	1.9	5	3.2
Family	203	98.1	149	96.8
Working in income generating job				
Yes	27	13.0	3	1.9
No	180	87.0	151	98.1
Educational status				
Illiterate	17	8.2	70	45.5
Primary education	147	71.0	72	46.8
High school	35	16.9	8	5.2
University	8	3.9	4	2.6
Smoking				
Yes	37	17.9	4	2.6
No	170	82.1	150	97.4
Alcohol use				
Yes	5	2.4	0	0.0
No	202	97.6	154	100.0

Table 3. Distribution of Causes of Chronic Kidney Failure in Patients

Cause	Patient Nubmer (%)
Hypertension	127(35)
Diabetes Mellitus	98(27)
Unknown	47(13)
Polycystic Kidney Disease	29(8)
Other	24(7)
Glomerulonephritis	23(6)
Amyloidosis	6(2)
Obstructive Nephropathy	7(2)
Total	**361 (100)**

Table 4. Distribution of patients according to the number of drug groups used daily

Number of drug groups per day	Number of patients (%)
1	3(0.8)
2	40(11.1)
3	81(22.4)
4	83(23.0)
5	82(22.7)
6	51(14.1)
7	16(4.4)
8	5(1.4)
Total	**361 (100)**

Table 5 Distribution of the patients according to the number of drug tablets used daily

Number of medication tablets per day	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	22	25	Total
Number of patients	4	7	14	12	25	28	52	34	36	30	35	35	12	8	10	5	9	2	1	1	1	**361**
%	1.1	1.9	3.9	3.3	6.9	7.8	14.4	9.4	10	8.3	9.7	9.7	3.3	2.2	2.8	1.4	2.5	0.6	0.3	0.3	0.3	**100**

Discussion

Polypharmacy is an increasing problem day by day because chronic diseases require long-term drug therapy and is associated with high morbidity and mortality (7). Polypharmacy complicates treatment, reduces adherence to treatment, increases costs and poses a problem for health-social security systems.

Polypharmacy is an increasing problem with the emergence of new supportive therapies in hemodialysis patients. Although polypharmacy is common in hemodialysis patients, the main problem in this patient group is the high tablet load. Considering the existence of drugs that need to be taken 6-9 tablets a day, especially phosphorus binders, the excess drug load of dialysis patients can be better understood.

Adherence with treatment regimens, as well as polypharmacy, remains a challenge for chronic dialysis patients and their medical caregivers. Poor adherence of the patient to the treatment may adversely affect the treatment results (5).

Chronic dialysis patients have to receive an average of 6-10 different treatments per day. These patients often receive a complex treatment regimen that includes phosphorus binders, vitamin D or calcimimetic preparations, statin agents, antihypertensive treatments, hypoglycemic agents, erythropoietin and iron supplements, and additional treatments for comorbidity (8). An important point in the non-adherence of hemodialysis patients is that ıts varies according to the drug class (9). The increase in serum phosphorus level is an independent risk factor for the development of bone mineral disease and mortality in patients with chronic renal failure or undergoing dialysis due to end-stage renal failure. There are several important methods in the treatment of hyperphosphatemia, which has such a negative effect on mortality. These; regulation of the diet, the use of phosphorus-binding drugs, and the application of effective and adequate dialysis (10).

In previous studies, they gave more importance to factors such as diet, fluid restriction and participation in dialysis in terms of determinants of adherence to treatment in hemodialysis patients. (11,12). Recently, however; Due to the large number of drugs required by hemodialysis patients on a daily basis, noncompliance due to not taking the drug directly or taking it irregularly is thought to be an important problem for this population. (13).

In 3 different studies, the average number of drugs taken by hemodialysis patients was found to be 11,10,13 tablets (8,14-15). The daily number of drugs of the patients in our study ranged from 1 to 8, and the average number of drug groups was found to be 5. The number of tablets taken daily was between 2-25, and the average number of tablets taken daily was 10. All these studies show that polypharmacy and especially tablet load pose a serious problem in chronic dialysis patients, which is supported by our study.

In studies, the compliance rate of hemodialysis patients to drug treatments has been reported in a wide range as 22-74% (mean 51%) (16). In studies evaluating the nonadherence of phosphorus-binding drug, the nonadherence rate was found to be 61% by Hartman et al. and 50% in the study by Bame et al (17-18). In our study, the limit of serum phosphorus level was taken as 5.5, and the nonadherence rate was found to be 40.4%.

In our study, the patient's marital status, gender, income level, diabetes or not, treatment compliance differed from other studies (18-20). Due to the difference in economic development, there may be relative differences between the classes of the countries. The middle class of a developed country may correspond to a standard of living close to the upper income level of a developing country. This may cause the results to be inconsistent. Similar results were seen in our study, where educated patient and elderly patients had better compliance with phosphate-binding drug therapy than younger patients, and smokers had worse compliance(8,21-23).

In all of the above studies, serum phosphorus level was taken as a measure of adherence to treatment. However, it may be insufficient to measure compliance with phosphorus binders by looking at the serum phosphorus level alone. Because phosphorus level is also affected by the patient's diet, dialysis adequacy, residual renal function, urine output, comorbid diseases, hormonal status, acid-base disorders, hypercatabolic states and dialysis type (24). Therefore, in this study, we used a self-reported compliance questionnaire in addition to serum phosphorus levels as a measure of adherence to treatment.

In the study of Tomasella et al. investigating compliance with phosphorus-binding therapy in 129 HD and 59 PD patients, they applied both the serum phosphorus level (>5.5) and the compliance questionnaire, which included the patients' self-reports. When the serum phosphorus level was taken as a measure of adherence to treatment, non-compliance was observed in 51% of the patients, and when the compliance questionnaire was taken as a criterion, non-compliance was observed in 38% of the patients (25). In our study, when the serum phosphorus level was taken as a measure of adherence, 40.4% of the patients found non-compliance, and when the compliance questionnaire was taken as a criterion, non-compliance was found in 77.3%. When the compliance questionnaire was taken as a criterion, the reason for the higher rate in our study may be that the questionnaire was conducted in the form of a question and answer interview with the patient, because in the other study, the compliance questionnaire was filled by the patient.

In another study, factors that disrupt compliance in phosphorus-binding therapy were investigated; Forgetfulness, neglect of the treatment, side effects and polypharmacy were found to be the most important causes (26). In our study, there was no difference in terms of non-compliance in those who used 5 or more drugs compared to those who did not. However, when the number of tablets per day was examined, it was seen that the compliance with the drug decreased with the increase in the number of tablets. When the causes of non-compliance were examined, similar results were obtained in our study. While forgetfulness was the most common cause of non-compliance, it was followed by drug side effects and boredom from using drugs.

In our study, according to the MMAS, the serum phosphorus level of the patients who were found to be high in compliance was significantly lower than those of the patients who were found to be inconsistent. This is proof that the MMAS is a good indicator to measure treatment compliance.

The results of the study show that; In order to increase adherence to treatment, all healthcare professionals, especially doctors, should provide more comprehensive education to patients, and patients with low understanding should be given a chart describing the use of the drug. There is no single strategy to increase medication adherence in hemodialysis patients, and studies suggest that behavioral and educational applied strategies should be combined to improve medication adherence pattern. Various strategies such as patient education, behavioral self-control, social and familial support, and effective patient-doctor communication can facilitate the increase in treatment compliance (27).

Study Limitation

Our study has some limitations . First, the sample size of the study was relatively small. Second, in this study, hemodialysis patients were relatively heterogeneous in disease duration.

Conclusion

In conclusion, polypharmacy and non-compliance with phosphorus-binding drugs are common in hemodialysis patients. And we think that more, more advanced and quality research is needed to improve adherence on this subject.

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Orgınal Article

Determination of dry tibia bone morphometry by photo analysis

Kuru Tibia Kemiği Morfometrisinin Foto Analiz ile Belirlenmesi

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Abstract

Background: This study was carried out to determine the morphometry of the dry tibia bones of the Turkish population using the photo analysis method.
Materials and Methods: 33 dry tibia bones were included in the study. The bones obtained were photographed with a professional camera. The photos were transferred to image processing program Image J (Version 1.53e) in jpeg format. From the images transferred, the parameters of articular surface width of medial condyle (MC-ASW), articular surface height of medial condyle (MC-ASH), articular surface width of lateral condyle (LC-ASW), articular surface height of lateral condyle (LC-ASH), distance between medial and lateral intercondylar tubercle (LMIT-D), medium width of body of tibia (BT-MW), length of total tibia (TT-L), height of medial malleolus (MM-H), angle of medial condyle- tibial tuberosity-lateral condyle (MCTTLG-A), angle of fibular notch - tibial tuberosity- medial malleolus (FNTTMM-A), height of inferior articular facet (IAS-H), width of inferior articular facet (IAS-W), distance between nutrient foramen- interosseous border (NFIB-D) were measured. **Results:** Morphometric analysis results were: MC-ASW 6.558±0.896 cm, MC-ASH 9.502±1.364 cm, LC-ASW 6.035±0.988 cm, LC-ASH 8.655±1.673 cm, LMIT-D 3.169±0.632 cm, BT-MW 2.382±0.312 cm, TT-L 36.784±2.734 cm, MM-H 1.296±0.209 cm, MCTTLG-A 97.14±11.63°, FNTTMM-A 7.313±0.514°, IAS-H 6.219±0.776 cm, IAS-W 6.540±1.011 cm, NFIB-D 0.958±0.326 cm. A statistically significant correlation was found between MC-ASW and MC-ASH, LC-ASW, LC-ASH parameters, between MC-ASH and LC-ASH, TT-L parameters, and between BT-MW and TT-L parameters ($p \leq 0.05$). **Conclusion:** As a result of our study, the morphometry of the parameters of the dry tibia bone in the Turkish population and the relationships between these parameters were revealed.
Keywords: Dry tibia bone, Morphometry, Photo analysis

ÖZ

Amaç: Bu çalışma, Türk popülasyonuna ait kuru tibia kemiklerinin foto analiz metodu kullanılarak morfometrilerinin belirlenmesi amacıyla yapıldı.
Materyal ve metod : Çalışmaya 33 adet kuru tibia kemiği dahil edildi. Elde edilen kemikler profesyonel fotoğraf makinesi ile fotoğraflandı. Fotoğraflarda jpeg formatında görüntü işleme programı olan Image J (Version 1.53e)'ye aktarıldı. Aktarılan görüntülerden her bir kuru tibia kemiğinin condylus medialis eklem yüzü genişliği (MC-ASW), condylus medialis eklem yüzü yüksekliği (MC-ASH), condylus lateralis eklem yüzü genişliği (LC-ASW), condylus lateralis eklem yüzü yüksekliği (LC-ASH), tuberculum intercondylare mediale – laterale arası uzaklık (LMIT-D), corpus tibia orta genişliği (BT-MW), tibia'nın total uzunluğu (TT-L), malleolus medialis yüksekliği (MM-H), condylus medialis – tuberositas tibiae – condylus lateralis açısı (MCTTLG-A), incisura fibularis – tuberositas tibiae – malleolus medialis açısı (FNTTMM-A), facies articularis inferior yüksekliği (IAS-H), facies articularis inferior genişliği (IAS-W), foramen nutricium – margo interosseus arası uzaklık (NFIB-D) parametrelerinin ölçümü yapıldı.
Bulgular: Morfometrik analiz ile MC-ASW 6.558±0.896 cm, MC-ASH 9.502±1.364 cm, LC-ASW 6.035±0.988 cm, LC-ASH 8.655±1.673 cm, LMIT-D 3.169±0.632 cm, BT-MW 2.382±0.312 cm, TT-L 36.784±2.734 cm, MM-H 1.296±0.209 cm, MCTTLG-A 97.14±11.63°, FNTTMM-A 7.313±0.514°, IAS-H 6.219±0.776 cm, IAS-W 6.540±1.011 cm, NFIB-D 0.958±0.326 cm olarak bulundu. MC-ASW ile MC-ASH, LC-ASW, LC-ASH parametreleri arasında, MC-ASH ile LC-ASH, TT-L parametreleri arasında, BT-MW ile TT-L parametresi arasında istatistiksel olarak yüksek anlamlı bir ilişki bulundu ($p \leq 0.05$).
Sonuç: Çalışmamız sonucunda kuru tibia kemiğine ait parametrelerinin Türk popülasyonuna ait morfometrisi ve bu parametrelerin aralarındaki ilişkiler ortaya konuldu.
Anahtar Kelimeler: Kuru tibia kemiği, Morfometri, Foto Analiz

Highlights

- Knowing the tibia morphometry of the Turkish population will make important contributions to medical science.
- Knowing the tibia morphometry will guide surgical interventions.

Introduction

Morphometry is a method that enables to show the distances between determined anatomical points and evaluates the relationship between these distances according to age, race and gender (1). Morphometry of the bones of the lower extremity is of greater importance than those of the upper extremity because the bones of the lower extremity take on the task of carrying the weight of the body and moving (2).

The exact determination of bone morphometry is critical in forensic identification, anthropology, anatomy and surgical sciences (1, 3). For example, for orthopaedists, the adaptation of proximal tibia end prosthesis to the bone tissue and thus a successful operation process is possible only when the bone morphometry is fully known (4). Lack of information in tibial morphometry may result in adverse scenarios such as incorrect positioning of the prosthesis, incompatibility and limitation of mobility (5, 6). In forensic medicine and anthropology, knowledge of bone morphometry is critical in cases with disintegrated body from which DNA and fingerprints cannot be obtained. Knowing about bone morphometry provides us important information about biological factors such as gender, age and race (7-9). At this point, tibial morphometry offers an accuracy of higher than 84% in terms of gender (7).

To the best of our knowledge, there is limited information in Middle East countries on tibial morphometry, especially on proximal end morphometry. On the contrary, there is more information in Asian-Pacific countries. Knowing about the tibia morphometry of individuals in Middle Eastern countries will greatly facilitate the selection of suitable prostheses (5). Bone morphometry can be revealed by dry bone or radiological imaging methods such as computed tomography, magnetic resonance imaging, peripheral quantitative computed tomography (1, 7, 8, 10, 11).

This study was conducted to find out dry tibia bone morphometry by using Image J measurement tool and to increase clinicians' level of knowledge on tibia morphometry.

Material and Method

Study Sample

The study was initiated with 2021/729 numbered approval of Karabük University Non-interventional Ethics Committee. 33 tibias of unknown gender taken from bone collections of anatomy laboratories in medical faculties at Karabük University, Bolu Abant İzzet Baysal University and Düzce University were used. Fractured bones, pathological bones and bones which were thought to belong to the pediatric group were excluded from the study. The bone side difference was ignored due to the insufficient number of bones in the bone collections.

Image protocol

Dry tibia bones in the collections were fixed at a height of 40 cm from the ground with a stabilizer. The Professional camera used during the shooting was fixed at a height of 60 cm from the ground with another stabilizer so that it would be stable during each shooting. These images in Jpeg format were transferred to Image J (Version 1.53e) image processing program and length and angle measurements were performed **(Figure1)**.

Determined length and angle measurements were;

- a) Medial condyle articular surface height (MC-ASH),
- b) Medial condyle articular surface width (MC-ASW),
- c) Lateral condyle articular surface height (LC-ASH),
- d) Lateral condyle articular surface width (LC-ASW),
- e) Distance between lateral-medial intercondylar tubercle (LMIT-D),
- f) Total length of the tibia (TT-L),
- g) Medium width of tibia body (BT-MW),
- h) Medial malleolus height (MM-H),
- k) Medial condyle – Tuberosity of tibiae – Lateral condyle angle (MCT-TLG-A),
- l) Fibular notch – Tuberosity of tibiae – Medial malleolus angle (FNT-TMM-A),
- m) Nutrient foramen – Interosseous border distance (NFIB-D).
- n) Inferior articular surface height (IAS-H),
- o) Inferior articular surface width (IAS-W),

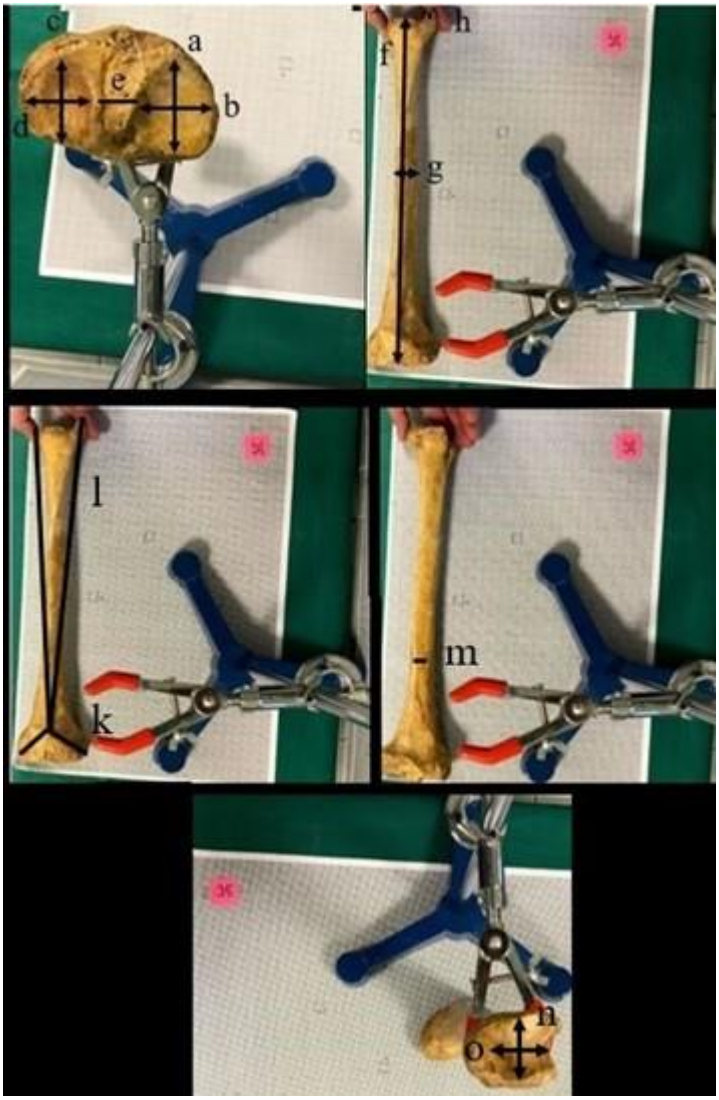

Figure 1. **Demonstration of parameters** (**a:** Medial condyle articular surface height (MC-ASH), **b**: Medial condyle articular surface width (MC-ASW), **c:** Lateral condyle articular surface height (LC-ASH), **d:** Lateral condyle articular surface width (LC-ASW), **e:** Distance between lateral-medial intercondylar tubercle (LMIT-D), **f**: Total length of the tibia (TT-L), **g:** Medium width of tibia body (BT-MW), **h**: Medial malleolus height (MM-H), **k**: Medial condyle – Tuberosity of tibiae – Lateral condyle angle (MCTTLG-A), **l**: Fibular notch – Tuberosity of tibiae – Medial malleolus angle (FNTTMM-A), **m**: Nutrient foramen – Interosseous border distance (NFIB-D), **n**: Inferior articular surface height (IAS-H), **o**: Inferior articular surface width (IAS-W)).

Statistical Analysis

Mean and standard deviation values were included in descriptive statistics. The Normality distribution of the parameters was tested with the Shapiro-Wilk test. Correlation between parameters and the degree of the correlation was tested with the Pearson Correlation test and $p \leq 0.05$ value was considered as statistically significant.

Results

Mean and standard deviation values of the parameters of 33 tibia were evaluated by using Image j are shown in **Table 1.**

Table 1. **Mean and standard deviations of parameters taken from Tibia**

Parameters	Mean	Standard Deviations
MC-ASW (cm)	3.018	0.494
MC-ASH (cm)	4.751	0.682
LC-ASW (cm)	3.279	0.448
LC-ASH (cm)	4.328	0.837

LMIT-D (cm)	1.584	0.316
BT-MW (cm)	2.383	0.312
TT-L (cm)	36.784	2.734
MM-H (cm)	1.296	0.209
MCTTLG-A (°)	97.14	11.63
FNTTMM-A (°)	7.313	0.514
IAS-H (cm)	6.219	0.776
IAS-W (cm)	6.540	1.011
NFIB-D (cm)	0.958	0.326

The correlation between parameters and the degree of correlation was tested with Pearson Correlation test and high significant correlation was found between the 6 parameters. High significant correlation was found between LC-ASW parameter and MC-ASW and MC-ASH parameters, between LC-ASH parameter and MC-ASH and LC-ASW parameters, between TT-L parameter and MC-ASH and BT-MW parameters ($p \leq 0.05$), (**Table 2).** These findings show that there is a high degree of relationship between condyle articular surfaces.

Table 2. **Pearson correlation table**

Parameters	**r/p**	**MC-ASW**	**MC-ASH**	**LC-ASW**	**LC-ASH**	**LMIT-D**	**BT-MW**	**TT-L**	**MM-H**	**MCTTLG-A**	**FNTTMM-A**	**IAS-H**	**IAS-W**
MCASH	r	0.548[c]	1.00										
	p	**0.001**	-										
LCASW	r	0.673[d]	0.642[d]	1.00									
	p	**0.000**	**0.000**	-									
LC-ASH	r	0.464[c]	0.639[d]	0.665[d]	1.00								
	p	**0.007**	**0.000**	**0.000**	-								
LMIT-D	r	0.218	0.354[b]	0.360[b]	0.243	1.00							
	p	0.223	**0.043**	**0.040**	0.173	-							
BT-MW	r	0.524[c]	0.436[c]	0.505[c]	0.382[b]	0.245	1.00						
	p	**0.002**	**0.011**	**0.003**	**0.028**	0.169	-						
TT-L	r	0.538[c]	0.618[d]	0.577[c]	0.453[c]	0.497[c]	0.669[d]	1.00					
	p	**0.001**	**0.000**	**0.000**	**0.008**	**0.003**	**0.000**	-					
MM-H	r	-0.153	0.093	0.110	0.251	-0.284	0.193	0.127	1.00				
	p	0.393	0.606	0.540	0.159	0.109	0.282	0.480	-				
MCTTLG-A	r	0.276	0.105	0.167	-0.251	-0.065	-0.039	-0.126	-0.147	1.00			
	p	0.120	0.560	0.354	0.158	0.719	0.831	0.484	0.414	-			

FNTTMM-AA	r	0.466[c]	0.402[c]	0.243	0.286	-0.079	0.257	0.194	-0.036	0.375[b]	1.00		
	p	**0.006**	**0.020**	0.173	0.107	0.663	0.149	0.279	0.843	**0.031**	-		
IAS-H	r	0.354[b]	0.514[c]	0.551[c]	0.585[c]	0.102	0.300	0.426[c]	0.380[b]	0.113	0.216	1.00	
	p	**0.043**	**0.002**	**0.001**	**0.000**	0.574	0.090	**0.013**	**0.029**	0.531	0.227	-	
IAS-W G	r	0.446 [c]	0.574[c]	0.414[c]	0.495[c]	0.165	0.281	0.399[b]	0.364[b]	-0.133	-0.028	0.594[c]	1.00
	p	**0.009**	**0.000**	**0.017**	**0.003**	0.358	0.113	**0.021**	**0.038**	0.462	0.876	**0.000**	-
NFIB-D	r	-0.077	-0.098	-0.237	-0.070	0.039	0.013	-0.022	-0.263	-0.159	-0.084	-0.450[c]	-0.182
	p	0.671	0.586	0.185	0.697	0.831	0.945	0.904	0.140	0.376	0.641	**0.009**	0.311

Aberrations: [a] very weak correlation, [b] weak correlation, [c] moderate correlation, [d] high correlation, (MC-ASH: Medial condyle articular surface height, MC-ASW: Medial condyle width, LC-ASH: Lateral condyle height, LC-ASW: Lateral condyle width, LMIT-D: Distance between lateral-medial intercondylar tubercle, TT-L: Total length of the tibia, BT-MW: Medium width of tibia body, MM-H: Medial malleolus height, MCTTLG-A: Medial condyle – Tuberosity of tibiae – Lateral condyle angle, FNTTMM-A: Fibular notch – Tuberosity of tibiae – Medial malleolus angle, NFIB-D: Nutrient foramen – Interosseous border distance, IAS-H: Inferior articular surface height, IAS-W: Inferior articular surface width)

Discussion

This study was conducted to determine the morphometry of dry tibia bone determined with photo analysis and to find out the correlation between parameters. The results found were MC-ASW 3.018±0.494 cm, MC-ASH 4.751±0.682 cm, LC-ASW 3.279±0.448 cm, LC-ASH 4.328±0.837 cm, LMIT-D 1.584±0.316 cm, BT-MW 2.382±0.312 cm, TT-L 36.784±2.374 cm, MM-H 1.296±0.209 cm, MCTTLG-A 97.14±11.63°, FNTTMM-A 7.313±0.514°, IAS-H 6.219±0.776 cm, IAS-W 6.540±1.011 cm, NFIB-D 0.958±0.326 cm. The correlation between parameters and the degree of correlation was tested with the Pearson Correlation test and high significant correlation was found between LC-ASW parameter and MC-ASW and MC-ASH parameters, between LC-ASH parameter and MC-ASH and LC-ASW parameters, between TT-L parameter and MC-ASH and BT-MW parameters ($p \leq 0.05$).

Knowing the exact tibial morphometry is critical for surgical interventions to this area and to find out pathologies. Knowing the morphometric information of this area will increase success in total knee prosthesis surgery, osteoarthritis treatment and anterior cruciate ligament ruptures. These morphometric data should be determined exactly since they will differ between races (4, 12-14). In total knee arthroplasty, morphometry of the proximal end of the tibia and morphometric relationships are of great importance (4, 15). In our study, it was determined that there was a high and positive correlation between the parameters of the proximal end of the tibia and the correlation result.

In their study they conducted on 60 dry tibia bones of Indian individuals, Ahmad et al. found the following results: LC-ASH 36.41±4.29 mm, MC-ASH 40.19±5.11 mm, LC-ASW 27.90±3.72 mm, MC-ASW 28.38±3.33 mm (16). In a study they conducted on 100 dry tibia bones of Korean individuals, Surendran et al. found LC-ASH as 42.2±3.7 and MC-ASH as 45.9±4.2 (4). In a study they conducted on 100 dry tibia bones of Indian individuals, Gandhi et al. found MC-ASH on the right side as 42.39±4.19 in women and as 48.45±4.14 in men, on the left side as 42.36±4.65 in women and as 47.73±4.37 in men; they found MC-ASW on the right side as 27.25±3.05 in women and as 30.18±2.83 in men, on the left side as 26.96±2.18 in women and as 29.38±3.14 in men; they found LC-ASH on the right side as 36.78±3.03 in women and as 40.86±3.79 in men, on the left side as 37.30±3.81 in women and as 40.69±4.13 in men; they found LC-ASW as 26.14±2.51 in women on the right side and as 28.82±3.12 on the left side in women and as 28.82±3.12 mm in men (2). In their study they conducted on 172 dry tibia bones of Chinese individuals, Cheng et al. found LC-ASH as 45.3±2.5 and MC-ASH as 50.7±2.4 mm (17). In their study they conducted on 120 dry tibia bones of Brazilian individuals, Santos et al. found LMIT-D as 1.054±0.262 in women and as 1.167±0.279 in men; they found MC-ASH as 4.334±0.317 in women and as 4.707±0.406 in men; they found LC-ASH as 3.549±0.382 in women and as 4.023±0.414 in men; they found MC-ASW as 2.702±0.298 in women and as 3.024±0.307 in men; they found LC-ASW as 2.991±0.281 in women

and as 3.405±0.323 cm in men (18). In a study conducted by Gardasevic on 664 individuals in the western part of Kosovo, TT-L was found as 37.60±2.52 (19). In the present study we conducted on dry tibia bones of 33 Turkish individuals, the results we found were: MC-ASW 3.018±0.494 cm, MC-ASH 4.751±0.682 cm, LC-ASW 3.279±0.448 cm, LC-ASH 4.328±0.837, TT-L 36.784±2.374 cm. Literature results support our results and shows that there is slight difference between populations. We believe that this difference is critical for surgical sciences.

Conclusion

As a result of our study, the range of values of tibial morphometry was determined in Turkish population. We believe that this range of values will guide both anthropological studies and specialist physicians who perform surgery in this region.

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Orgınal Article

Newly defined unbalanced distributions of paternal balanced chromosomal translocation and review of the literature

Paternal dengeli kromozomal translokasyonun yeni tanımlanan Dengesiz dağılımları ve literatürün gözden geçirilmesi

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Highlights

-It is common for individuals with balanced chromosomal translocations to show unbalanced chromosomal distribution in meiotic segregation.
- Coexistences of 5p partial trisomy with 7q partial monosomy and 5p partial monosomy with 7q partial trisomy in children due to balanced translocation of chromosomes 5 and 7 in their parent have not been reported before.
-It can be said that most of the deletion or duplication cases of 7q or 5p defined individually in the literature have milder clinic severity than our cases. This may indicate that by increase in the number and size of the affected chromosome regions, the clinic appearance would be severe.
-Copy Number Variation (CNV) analysis by microarray is important in the diagnosis of congenital anomalies, especially in motor-mental retardation and can identify new microdeletions or microduplications.

Abstract

Background: Balanced chromosomal re-arrangements (BCR) are re-arrangements with no loss or gain of genetic material and usually not associated with clinical abnormalities. However, BCR carriers may have children with a chromosomal anomaly as a result of an unbalanced transfer of chromosomes to the offsprings. The children with unbalanced chromosomal translocations may exhibit many congenital anomalies, especially motor-mental retardasyon. We report unbalanced translocation and multiple congenital anomalies in two siblings. Chromosomal microarray analysis was performed on the both siblings using Agilent Oligonucleotide Microarray 8×60K. Chromosomal microarray analysis showed partial deletion in 5p and partial duplication in 7q (arr[GRCh37] 5p15.33-p15.2x1, 7q36.1-q36.3x3) in one sibling, and partial duplication in 5p and partial deletion in 7q (arr[GRCh37] 5p15.33-p15.2x3, 7q36.1-q36.3x1) in the other sibling were detected. Subtelomeric Fluorescent In Situ Hybridization (FISH) analysis was performed on the entire family using Cytocell Telomark Probe. The father was found to have 46,XY.ish t(5;7)(p15-,q36+;q36-,p15+) balanced chromosomal translocation structure, while the mother was found to have 46,XX normal chromosome structure. To the best of our knowledge, 5p partial trisomy+7q partial monosomy and 5p partial monosomy+7q partial trisomy have not been previously reported. These findings provide us with the conclusion that Copy Number Variation (CNV) analysis with microarray is important in the diagnosis of congenital anomalies, especially motor-mental retardation.
Keywords: Chromosomal rearrangement, Congenital anomaly, Microarray, Unbalanced translocation

ÖZ

Dengeli kromozomal yeniden düzenlemeler (BCR), genetik materyal kaybı veya kazanımı olmayan ve genellikle klinik anormalliklerle ilişkili olmayan yeniden düzenlemelerdir. Bununla birlikte, BCR taşıyıcıları, kromozomların yavrulara dengesiz aktarımı sonucu olarak kromozom anomalili çocuklara sahip olabilir. Dengesiz kromozomal translokasyonlu çocuklar başta motor-mental retardasyon olmak üzere birçok konjenital anomali gösterebilirler. İki kardeşte dengesiz translokasyon ve çoklu konjenital anomalileri rapor ediyoruz. Agilent Oligonucleotide Microarray 8×60K kullanılarak her iki kardeş üzerinde kromozomal mikroarray analizi yapıldı. Kromozomal mikroarray analizinde çocukların birinde 5p de parsiyel delesyon ve 7q da parsiyel duplikasyon (arr[GRCh37] 5p15.33-p15.2x1, 7q36.1-q36.3x3) saptanırken diğer çocukta 5p de parsiyel duplikasyon ve 7q da parsiyel delesyon (arr[GRCh37] 5p15.33-p15.2x3, 7q36.1-q36.3x1) saptandı. Tüm aile üzerinde Cytocell Telomark Probe kullanılarak Subtelomeric Fluorescent In Situ Hybridization (FISH) analizi yapıldı. Babanın 46, XY.ish t(5;7) (p15-,q36+;q36-,p15+) dengeli kromozomal translokasyon yapısına sahip olduğu, annenin ise 46,XX normal kromozom yapısına sahip olduğu belirlendi. Mevcut bilgilerimize göre 5p parsiyel trizomizisi + 7q parsiyel monozomisi ve 5p parsiyel monozomisi + 7q parsiyel trizomisi daha önce raporlanmamıştır. Bu bulgular bize, motor-mental retardasyon başta olmak üzere konjenital anomalilerin tanısında mikroarray ile kopya sayısı varyasyon analizinin önemli olduğu sonucunu vermektedir.

Anahtar kelimeler: Kromozomal yeniden düzenleme, Konjenital anomali, Mikroarray, Dengesiz Translokasyon

Introduction

In humans, the incidence of balanced chromosomal translocation is approximately 1/500 (1, 2). Balanced chromosomal translocations are re-arrangements with no loss of genetic material or gain. Most balanced chromosomal re-arrangements (BCR) are not considered to be associated with clinical abnormalities or an abnormal phenotype (3). However, BCR carriers are alarming as they are riskier in terms of recurrent pregnancy losses and congenital anomalies in offsprings. It is estimated that 6.7% of de novo BCR carriers have a risk of phenotypic abnormality (4). Most of the hypotheses proposed to explain the relationship of BCRs with phenotypic abnormalities include monogenic disorders such as sickle cell anemia caused by modification or disruption of genes in the re-arrangement region at the molecular level, the mosaic structure containing unbalanced re-arrangement in different tissues, uniparental disomy of one of the chromosomes in the re-arrangement, and situations such as position effect variation phenomenon (1, 5).

Reciprocal translocations are structural chromosomal rearrangements in which two chromosomes break and mutual exchange of distal chromosomal segments occur, and two new derivative chromosomes are formed without loss or gain of genetic material. These balanced translocations typically do not produce a significant phenotypic effect unless one or both of the chromosomal breakpoints contain an important functional gene. However, 2:2 segregation may occur during the meiotic division, which leads to the formation of gametes, which are partially disomic for a chromosomal segment and partially nullisomic for the other. This results in a combination of partial trisomy and partial monosomy in the zygote (6).

In this article, two boys with unbalanced translocation and multiple congenital anomalies of a father with a balanced chromosomal translocation of 46,XY.ish t(5;7)(p15-,q36+;q36-,p15+)(5pter-,7qter+;7qter-,5pter+) and a mother with a 46,XX normal chromosome structure were presented. Partial deletion in 5p and partial duplication in 7q (arr[GRCh37] 5p15.33-p15.2x1, 7q36.1-q36.3x3) in one sibling, and partial duplication in 5p and partial deletion in 7q (arr[GRCh37] 5p15.33-p15.2x3, 7q36.1-q36.3x1) in the other sibling were detected.

Material and Methods:

Detailed anamnesis of the patients was obtained and physical examinations were performed according to the guidelines (7, 8). In all cases, chromosome analysis was performed in lymphocyte culture from peripheral blood samples. Following Trypsin-Giemsa (GTG) banding, twenty metaphases in each sample were routinely analyzed at 550 band level. Reporting was made according to the guidelines of the International Human Cytogenetic Nomenclature System (ISCN) 2016. The FISH analyses were performed using the Cytocell Telomark probe. Subtelomere multicolor DNA probe Mix 05 (5p Green, 5q Orange) and Mix 07 (7p Green, 7q Orange, 14q Orange and Green, TCARD (14q112) (blue) (Cytocell Ltd. Cambridge, UK) were used to identify subtelomeric rearrangements. About ten metaphases were captured under the Zeiss Axioscope.A1 microscope (Germany) and analyzed with Argenit Chromosome Analysis System (AKAS) (İstanbul, Turkey). The microarray analysis was performed using Agilent Oligonucleotide Microarray 8×60K microarrays platform and results were analyzed using CytoGenomics software, Edition 5.0.1.6. (Agilent Technologies, Santa Clara, CA).

The parents of children gave written consent for all genetic testing and for the academical use of patient photographs.

Results

Case 1

Proband was a 9-year-old boy born from a couple who was not related but from the same village and was directed to us for severe intellectual-motor disability. The patient was born with the C/S (due to fetal bradycardia) at 41 weeks of gestation from the first pregnancy of the 19-year-old mother. His birth weight was 3250 g. He was hypoactive at birth and had incubator care for 1 week postnatally. He achieved head control at the 9th month of age, sitting with support at the 7-8th month and sitting without support at the 10th month. He never walked and talked. At the age of 7, his scoliosis appeared. On physical examination, spelling was available, but the skill of forming words and sentences was not developed. He knew his mother but described his wishes in angrily. There were no involuntary movements, but autistic behaviors. He displayed behaviors of hitting/hurting himself. His height was 121 cm (<3 p.), weight 19 kg (<3 p.), and head circumference 48 cm (<3 p.). He could hold an object with his hand. There was one hypopigmented and one 2x2 cm hyperpigmented Cafe Au Lait. There were dysmorphic findings such as microcephaly, an outward shift in the left eye, long

palpebral fissures, dental anomalies, postaxial polydactyly of left foot, operated bilateral cryptorchidism (Figure 1). He had teeth grinding and stereotype. He could not receive simple commands. Deep tendon reflexes were alive. There was no pathological reflex. He was walking with support but could not speak. In cranial MRI, there was mildly dysmorphic cerebellar sulcus, bilateral slight pachygyria in temporal gyri, mild hypoplasia in inferior cerebellar vermis (Figure 2). No pathology was detected in echocardiography.

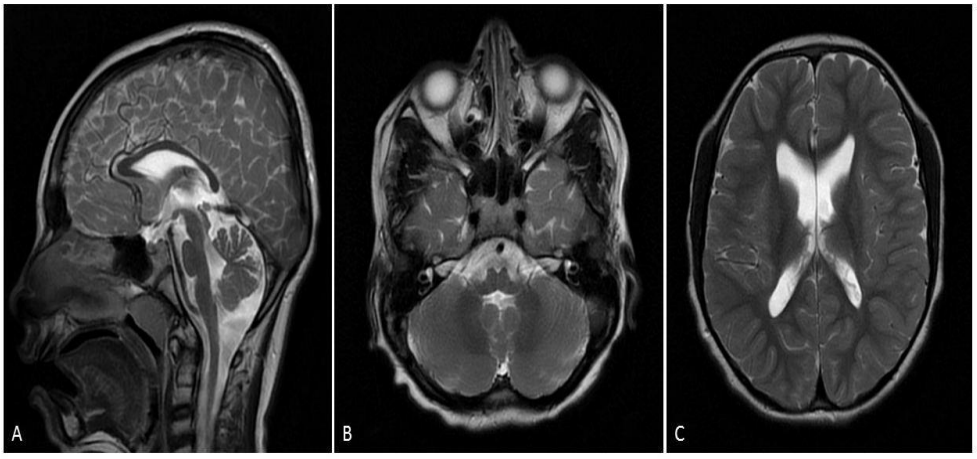

Figure 2. 9-year-old male. A) Hypoplasia of brain stem compartments and corpus callosum on the sagittal T2-weighted image. **B**) Normal cerebellum on the axial T2-weighted image. **C**) Slight dilatation of the lateral ventricles on the axial T2-weighted image.

In the chromosome analysis of the patient's peripheral blood by G-banding after short-term cell culture, the derivative structure of the short (p) arm of chromosome 5 was observed. After the chromosome analysis of the parents, the normal chromosome structure of 46, XX was observed in the mother, while a balanced reciprocal translocation was detected between the chromosome regions 5p15 and 7q36 (46,XY.ish t(5;7)(p15-,q36+;q36-,p15+)) in the father. As a result of the unbalanced transfer of this translocation to the child, it was observed that chromosome 5 had a deletion from the p15 region to the terminal, and the part of chromosome 7 from the q36 region to the terminal was translocated to this region. Accordingly, partial monosomy of chromosome 5 and partial trisomy of chromosome 7 were observed. These results were confirmed with the subtelomeric FISH analysis (46,XY.ish der(5)t(5;7)(p15-;q36+)(5pter-;7qter+)pat).
In the microarray analysis, 14.422.009 kb loss (number of markers: 294) covering the 5p15.33-p15.2 region (57 entries in OMIM Gene Map, 23 of which are phenotype related), and 8,645,736 kb gain (number of markers: 263) covering the 7q36.1-q36.3 region (61 entries in OMIM Gene Map, 27 of which are phenotype related) were detected (arr[GRCh37] 5p15.33-p15.2 (20,149-14,444,157)x1, 7q36.1-q36.3 (150,482,821-159,128,556)x3) (Figure 1).

Case 2

The second brother was an 8-year-old boy born from the second pregnancy of the 20-year-old mother by C/S at 41 weeks of gestation and weighing 2000 g. He had a history of intrauterine growth retardation, green vomiting at and after birth, and postnatal incubator care. When he was one year old, he had two generalized febrile convulsions. He had a history of short stature in his follow-ups. The first sibling who had similar complaints was in a more severe phenotype. He said his first word when he was 5 years old, but still could not make a sentence, started walking at age 2, and now he

can go down and up the stairs. On physical examination, his height was 100 cm (<3 p.), weight 12 kg (<3 p.), and head circumference 44.5 cm (<3 p.). he had moderate intellectual-motor disability, global developmental retardation, short stature, dysmorphic findings (microcephaly, triangular facial structure, strabismus, bilateral ptosis, hypertrophic palate, tooth anomaly (eruptive tooth structure)), pectus excavatum, behavioral problems, hyperactivity, mild stereotypical movements, mild drooling, repetition of words and movements but not neurocutaneous findings (Figure 1). There was no loss of strength. There were hypoplastic corpus callosum and brain stem compartments, and slightly dilated lateral ventricles in cranial MRI (Figure 3). No pathology was detected on echocardiography.

In the chromosome analysis, there was a derivative structure of the long (q) arm of chromosome 7. As a result of the unbalanced transfer of balanced translocation of the father to the child, there was a deletion from the q36 region to the terminal of chromosome 7, and the part of from p15 to the terminal of chromosome 5 was translocated to this region. Accordingly, partial monosomy of chromosome 7 and partial trisomy of chromosome 5 were observed. This result was confirmed with the subtelomeric FISH analysis (46,XY.ish der(7)t(5;7)(p15+;q36)(5pter+;7qter-)pat).

In the microarray analysis, 14.394.065 kb gain (number of markers: 293) covering the 5p15.33-p15.2 region (57 entries in OMIM Gene Map, 23 of which are phenotype related), and 8.702.559 kb loss (number of markers: 263) covering the 7q36.1-q36.3 region (62 entries in OMIM Gene Map, 27 of which are phenotype related) were detected (arr[GRCh37] 5p15.33-p15.2 (50,093-14,444,157)x3, 7q36.1-q36.3 (150,421,573-159,124,131)x1) (Figure 1).

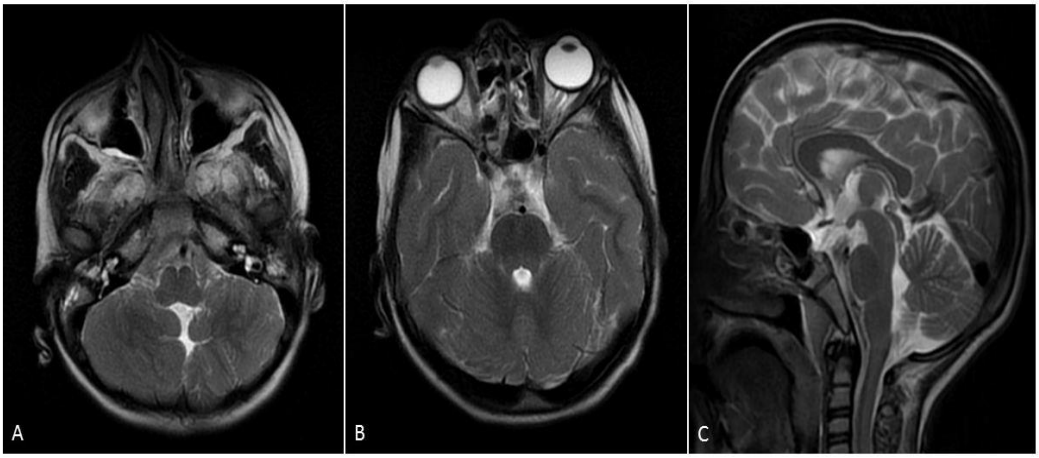

Figure 3. 8-year-old male. A) Mild dysmorphism in cerebellar sulcus at the level of cerebellum inferior on the axial T2-weighted image. B) Slight pachygyria in bilateral temporal gyri on the axial T2-weighted image. C) Sagittal T2-weighted image shows brain stem compartments and corpus callosum in a normal configuration, while mild hypoplasia is seen in the inferior cerebellar vermis.

Discussion

Reciprocal translocation is one of the most common structural anomalies in humans and generally harmless, however, it is associated with an increased risk of a fetus with malformations (9). In general, translocation carriers have a high-risk rate for pregnancy losses. Stern et al. reported that chromosomal translocations were present in 3.2% of couples with recurrent implantation failures (10). Spontaneous abortion risk of couples with balanced reciprocal translocation has been reported to be 50% and the risk of having children with an unbalanced karyotype as 20% (1, 11). In the family mentioned in this article, a father with a balanced translocation carrier and a mother with normal karyotype had no history of pregnancy loss, but two children had two different rare clinical pictures due to unbalanced translocation. Coexistences of 5p partial trisomy with 7q partial monosomy and 5p partial monosomy with 7q partial trisomy in children due to balanced translocation of chromosomes

5 and 7 in the parent have not been reported before, however, cases of t (5: 7), 5p monosomy (Cri du Chat syndrome) or trisomy, and 7q monosomy or trisomy have been reported separately (12-15).

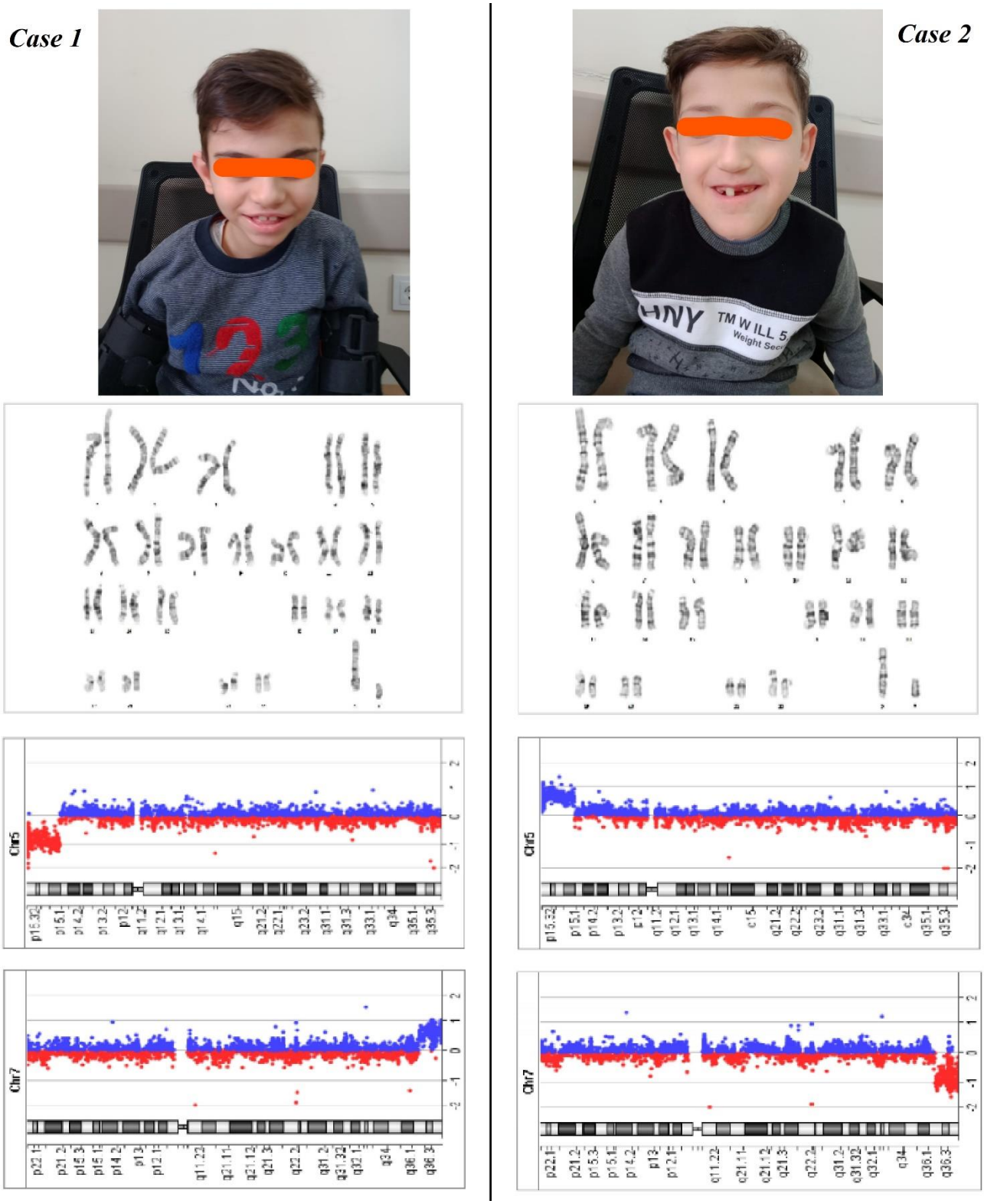

Figure 1. Photographs and images of karyotype and microarray analysis images of patients

In cases of chromosome 7q partial trisomy arising from translocations between chromosome 7 and another chromosome, the phenotype is linked to the chromosomal segment with increased copy number at 7q and the deleted segment of the other chromosome. However, the phenotypic effect of a large 7q duplication is more important than the smaller terminal deletion of the other chromosome (16). The phenotypic features reported

in partial trisomy 7q are not specific and also occur in other chromosomal rearrangements, so this makes phenotype-genotype correlation quite difficult. Some common but nonspecific features are macrocephaly, frontal protrusion, developmental retardation, psychomotor retardation, low ears, short neck, subsequent scoliosis, and genitourinary system abnormalities. It has been reported that a shortened lifespan is associated only with duplication of the entire arm (17).

5p deletion, also known as 5p monosomy, Cat Cry Syndrome or Cri du Chat Syndrome, is a spectrum disorder characterized by microcephaly, round face, hypertelorism, micrognathia, epicanthal folds, low ears, hypotonia, severe psychomotor and intellectual disability, high pitch crying at birth, low birth weight, weak muscle tone and some medical complications (12). The deletion can range in size from very small to large enough to cover the entire short arm. Although most deletions occur *de novo*, approximately 12% are caused by the unbalanced separation of translocations in one of the parents or recombination (18). Our first case had 7q duplication and 5p deletion. In addition to the non-specific features found in both chromosome anomalies such as intellectual disability, hypotonia, and developmental retardation, there were findings of only 7q duplication such as scoliosis and 5p deletion such as microcephaly. However, there were findings such as strabismus, cryptorchidism, hyperpigmented spots, and polydactyly of the foot, which were not reported previously in both chromosome anomalies.

In chromosome 7q deletion syndrome, the severity, signs, and symptoms of the disease depend on the size and location of the deletion, and which genes are involved. Among the features frequently seen in patients with 7q deletion syndrome, there are developmental retardation, hypotonia, short stature, speech and language impairment, speech apraxia, sometimes oral-motor dyspraxia, dysarthria, receptive and expressive language impairment, hearing loss, behavioral problems, and specific facial features. Individuals with great deletions in this region also showed intellectual disability and autism. Most cases are not inherited, but people can pass their deletions to their children (19). Since there are many genes in this region, it varies clinically according to the affected genes and it is difficult to talk about a uniform 7q deletion syndrome (20).

Common features in patients with chromosome 5p duplication include developmental retardation, intellectual disability, behavioral problems, and distinctive facial features. Most cases are not inherited, but people can pass duplication to their children. In general, when there is a chromosome material gain, associated symptoms can include a combination of physical problems, learning disabilities, and/or behavioral disorders. These symptoms largely depend on the location of duplication in the p-arm and the genes affected. Most people with any material loss or gain will have some degree of learning difficulties and developmental retardation because there are many genes in this chromosome that are important for the normal development and function of the brain (21, 22). In general, children with 5p duplication have hypotonia, macrocephaly, craniofacial anomalies, arachnodactyly, and intellectual-motor disability. Some affected people may have heart defects and seizures. The critical region for heart abnormalities and seizures is 5p13.3. Most physical properties are due to the repetition of 5p11 to 5p13.3 bands. The critical region for developmental retardation and intellectual disability is thought to be 5p14-5p15. While the 5p14-5p15 region is normal, it has been reported that there are normal development and mental state in patients with duplication at the terminal (22). Our second case had a moderate intellectual disability, global developmental retardation, dysmorphic facial findings, pectus excavatum, stereotypic movements, and behavioral disorders. The patient had duplication in the 5p15.33-p15.2 region, and as mentioned above, there was no developmental retardation and intellectual disability in anomalies covering areas outside the 5p14-5p15 region. Therefore, we think that global developmental retardation and intellectual disability in our patient are related to 7q deletion.

There are many genes in the affected chromosome regions in both patients, and most of them have been associated with a different phenotype in the OMIM database. Among the genes in the affected area on the chromosome 5p, especially the NSUN2 gene (Gene/Locus MIM number: 610916) and the TRIO gene (Gene/Locus MIM number: 601893) have been associated with intellectual disability (23, 24). The CCT5 gene (Gene/Locus MIM number: 610150) and MARCH6 gene (Gene/Locus MIM number: 613297) may be responsible for the seizures and neurological features in the patient (25, 26). Among the genes in the affected area on chromosome 7q, the KMT2C gene (Gene/Locus MIM number: 606833; Kleefstra syndrome 2, Phenotype MIM number: 617768) has been associated with neuromotor development retardation, many dysmorphic findings, and male genital system defects (27). The DHMN1 gene (Gene/Locus MIM number: 182960) may be responsible for neurological disorders, the SLI4 gene (Gene/Locus MIM number: 612514) for speech disorders, and the AUTS10 gene (Gene/Locus MIM number: 611016) for autistic/stereotypical behaviors (28-30). Mild brain anomalies detected in the cranial MRI may be related to the CDK5 gene (Gene/Locus MIM number: 123831) and SHH gene (Gene/Locus MIM number: 600725) (31, 32). The

LMBR1 (Gene/Locus MIM number: 605522) gene has been previously associated with polydactyly and other digital anomalies (33). Although there are many genes associated with dysmorphism and many more non-specific findings in both chromosome regions, the genes in the 7q region generally appear to be more dominant on the phenotype in both patients. As mentioned before, it has been stated in the literature that changes in the 7q region are more effective (16). In addition, this may be due to the affected part on chromosome 7 being larger than chromosome 5 in our patients.

Study Limitation

For the unbalanced chromosome distributions, meta-analyses with larger sample size will provide better clinical interpretations about the coexistence of these newly defined chromosomal disorders. In addition, the effect of these chromosomal associations would be revealed more clearly with further function test studies.

Conclusion

The coexistences of 5p partial trisomy with 7q partial monosomy and 5p partial monosomy with 7q partial trisomy in children as a result of balanced translocation of chromosomes 5 and 7 in the parent is firstly described in this study. On the other hand, most of the deletion or duplication cases of 7q or 5p defined individually in the literature had milder clinic severity than our cases. This indicates that the more number and size of the affected chromosome regions may refer to the more severe clinical manifestation.

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Orgınal Article

Breast glandular dose and effectiveness of in-plane bismuth breast shield in routine pediatric female chest CT examination

Kız çocuklarında rutin toraks bt çekimlerinde meme glandüler dozu ve bizmut koruyucunun etkinliği

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Highlights

- Breast tissue exposed to radiation from MSCT of the chest is an area of particular concern in pediatric female.
- In-plane bismuth breast shielding offers an additional method of decreasing dose to female pediatric patients undergoing MDCT.

Abstract

Background: The aim of our study is to determine the radiation dose to which the breast is exposed in pediatric female undergoing routine thoracic multislice computed tomography (MSCT) and to investigate the effectiveness of bismuth shielding in reducing this dose. **Materials and Methods:** Twenty patients who were referred to the radiology department for routine thorax MSCT between January 2012 and April 2012 were included in the study. A Thermolucent dosimeter (TLD) (3x3x1mm; Harshaw Lif TLD-100; Saint-Gobain Industrial Ceramics, Solon, Ohio) was placed on both breast skins of the patients to measure the radiation dose. An in-plane bismuth breast shield was placed on the right breast, and the left breast was chosen as the unshielded side. Radiation doses in the shielded and unshielded breast were calculated and compared using the Paired-t test. **Results:** The mean radiation doses were calculated as 7.0075 mSv and 9.0730 mSv for the shielded right breast and the unshielded left breast, respectively. It was found that in-plane bismuth breast shielding could lower the radiation dose to the right breast by 22.76 %. The difference between the radiation doses of the shielded side of the breast and the unshieldeded side was found to be significant ($p<0.001$). No deterioration was detected in the image quality of the lung parenchyma on the side where bismuth shield was placed.**Conclusions:** In-plane bismuth shielding significantly reduces the radiation dose of the breast in pediatric female undergoing routine thoracic MSCT examination without impairing the image quality.

Keywords: Bismuth shield, breast shield, pediatric female, multislice computed tomography

ÖZ

Amaç: Çalışmamızın amacı rutin toraks çok kesitli bilgisayarlı tomografi (ÇKBT) çekilen kız çocuklarında memenin maruz kaldığı radyasyon dozunu belirlemek ve bizmut koruyucunun bu dozu azaltmadaki etkinliğini araştırmaktır.**Materyal ve metod:** Çalışmaya Ocak 2012- Nisan 2012 tarihleri arasında radyoloji bölümüne rutin toraks ÇKBT çekimi için yönlendirilen 20 hasta dahil edildi. Hastaların her iki meme cildine radyasyon dozunu ölçmek amacıyla birer adet Termolusent dozimetre (TLD) (3x3x1mm; Harshaw Lif TLD-100;Saint-Gobain İndustrial Ceramics, Solon, Ohio) yerleştirildi. Sağ memenin üzerine bizmut koruyucu yerleştirilmiş olup, sol meme korunmamış taraf olarak seçildi. Bu teknikle yüzeyel meme radyasyon dozu hesaplandı. Korunan ve korunmayan memedeki radyasyon dozları hesaplandı ve Paired-t test kullanılarak karşılaştırıldı.

Bulgular: Ortalama radyasyon dozları korunan sağ meme ve korunmayan sol meme için sırasıyla 7.0075 mSv ve 9.0730 mSv olarak hesaplandı. Bizmut koruyucunun sağ memenin maruz kaldığı radyasyon dozunu %22.76 oranında azaltabileceği görüldü. Memenin korunan tarafı ile korunmayan tarafının maruz kaldığı radyasyon dozları arasındaki fark anlamlı bulundu ($p<0.001$). Bizmut koruyucu yerleştirilen tarafta akciğer parankiminin görüntü kalitesinde herhangi bir bozulma saptanmadı. **Sonuç:** Bizmut koruyucu rutin toraks ÇKBT incelemesi yapılan kız çocuklarında görüntü kalitesini bozmadan memenin maruz kaldığı radyasyon dozunu belirgin miktarda azaltmaktadır.

Anahtar Kelimeler: Bizmut koruyucu, meme koruyucu, kız çocuğu, çok kesitli bilgisayarlı tomografi

Introduction

Computed tomography (CT) has grown rapidly since its introduction as an imaging modality in the 1970s.Short acquisition times and high diagnostic accuracy have started to be attained with the development of multislice computed tomography (MSCT), and the daily number of scans has increased exponentially (1). In the United States, CT accounts for approximately 17% of all imaging modalities and is responsible for approximately 50% of medical radiation (2). Radiation exposure, especially to superficial organs, is the main drawback of CT.Due to children's and young adult's rapid cell division and relatively long life expectancies, it is assumed that the cytochastic and potential oncogenic effects of ionizing radiation contained in CT are greater than in adults(3). Studies on the prevalence of breast cancer, particularly in women who survived the atomic bomb, have revealed results that radiation affects breast tissue (4).Utilizing bismuth shielding during CT scans is one method used to decrease the radiation exposure to delicate organs like the breast, eye, thyroid, and testicles. (5).

In this study, we aimed to determine the radiation dose received by the superficial breast tissue and to determine the effectiveness of bismuth shielding in reducing the radiation dose in pediatric female who were referred to our department for routine thoracic MSCT examination.

Materials and Methods

Patient Selection

Our study was performed on a total of 20 pediatric female who were referred to our department for routine thoracic MSCT examination between January 2012 and April 2012. Patients with chest deformity and inability to stabilize the bismuth shield were excluded from the study. Demographic data of patients such as age, weight and height were obtained (Table 1). The patient's parents were informed about the study.Consent form was signed before CT examination. Approval was obtained from the local ethics committee for the study.

Table 1.Average Standard Deviations and Min-Max Values of Demographic Characteristics for Age, Weight and Height

Variables	Mean+SD	Min-max values
Age	10.0±4.2	2-16
Weight (kg)	34.2±15.6	10-62
Height (cm)	132.4±25.6	83-166

CT Examination

All CT scans were performed with a 128-channel MDCT device (Siemens Somatom Definition AS Siemens AG, Medical Solutions ,Computed Tomography, Forcheim, Germany).Scanning parameters were chosen as detector collimation 0.6 mm, gantry rotation time 0.5 sec, slice thickness 3 mm, average 280 mm field of view (FOV).Automatic tube current modulation was used during CT acquisition. The patients were placed in the gantry in the supine position. CT images were obtained from the thoracic inlet to the level of the adrenal gland.Two Thermolucent dosimeters (TLDs) (3x3x1mm; Harshaw Lif TLD-100; Saint-Gobain Industrial Ceramics, Solon, Ohio) were placed in the medial part of the nipple of 20 patients.All dosimeters were obtained from the same production center. The dosimeters were sensitive to radiation levels between 100 µGy and 1 Gy.Bismuth shields were obtained by placing bismuth coated latex sheets ((F & L Medical Products Co., USA) on a 1cm thick foam pad (Figure 1).The foam pad creates a distance between the bismuth latex and the chest wall, reducing the amount of radiation entering the body. In addition, image artifacts were prevented.TLD was placed on the right nipple and a bismuth shield was placed on it.Only TLD was placed on the left nipple.Bismuth shields were placed after scout images were taken.The superficial radiation dose of both breasts was calculated. The superficial radiation doses of the right breast with a bismuth shield and the left breast without a bismuth shield were compared.The relationship between the age, height and weight of the patients and the mean radiation doses was determined.

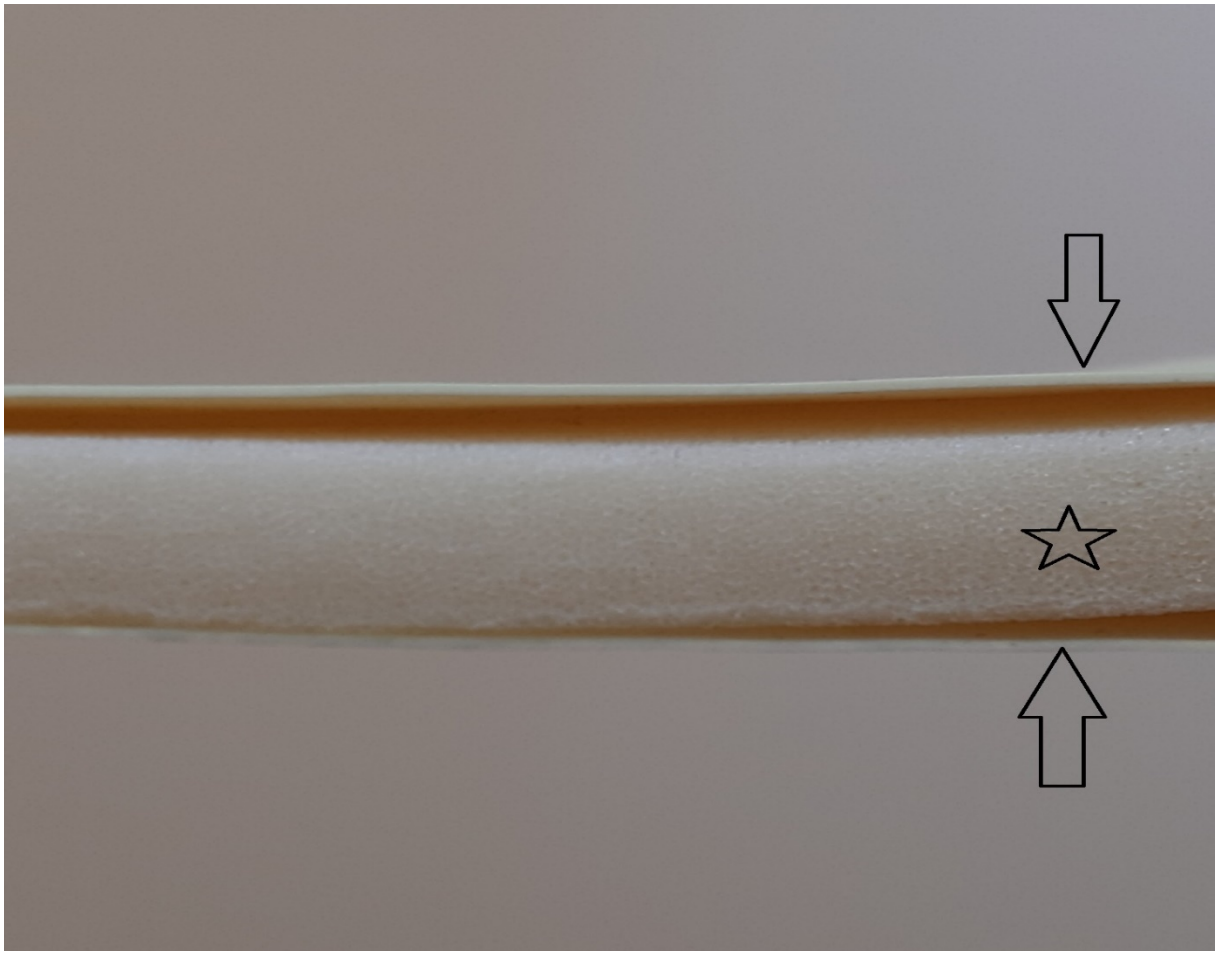

Figure 1. An in-plane bismuth shield. Open arrows show bismuth coated latex. Asterisk show foam

Statistical Analyses

The statistical analysis was performed using the SPSS (Statistical Package for Social Sciences for Windows) 15.0 program.Descriptive statistical methods (mean, standard deviation, frequency) were used while evaluating the study data.Paired samples t test was used to compare the normally distributed quantitative data. Pearson correlation analysis was used to evaluate the relationships between age, height and weight, and radiation dose.The significance level used to evaluate the results was $p<0.05$, with a 95% confidence interval.

Results

A pediatric radiologist evaluated the results of the MSCTexamination. The right breast tissue and skin, where the bismuth shield was positioned, showed minimal artifact.Between the sections with and without bismuth shielding, there was no difference in the image quality of the lung parenchyma and mediastinum.The age range for the cases in our study was 2 to 16 years, with a mean age of 10±4,2. The mean superficial radiation dose levels of the shielded right breast and unshielded left breast were determined to be 7,0075±5,187 mSv and 9,0730±6,382 mSv, respectively (Table 2). The mean superficial radiation dose of the shielded right breast was observed to be statistically significantly lower than the mean superficial radiation dose of the unshielded left breast($p<0,001$) (Table 3).These results revealed that bismuth shielding decreased the superficial radiation dose to the right breast by 22.76 %. There was no statistically significant relationship between age, height and weight, and mean radiation dose levels in the shielded and unshielded breasts ($p>0,05$) (Table 4).

Table 2. Standard deviations and min-max values of the mean superficial radiation doses of shielded right breast and unshielded left breast

Variables	Mean+SD (mSv)	Min-max values (mSv)
Shielded right breast	7.0075±5.187	3.59-21.70
Unshielded left breast	9.0730±6.382	4.30-29.60

Table 3. Comparison of mean superficial radiation doses of bismuth shielded right breast and unshielded left breast with Paired Sample T-test

Variables	TLD Mean dose (mSv)	*P*
Shielded right breast	7.0075±5.187	<0.001
Unshielded left breast	9.0730±6.382	

TLD: Thermolucent dosimeter, **mSv :** milisievert

Table 1. Correlation of age, weight and height, and mean superficial radiation doses of shieldeded right breast and unshielded left breast

Variables	Shielded right breast		Unshielded left breast	
	p	***r***	***p***	***r***
Age	0.201	0.395	0.236	0.316
Weight (kg)	0.026	0.913	0.108	0.652
Height (cm)	0.022	0.925	0.096	0.687

***r*:** pearson correlation coefficient

Discussion

Thorax MSCT is a non-invasive imaging method used in the diagnosis of lung, mediastinum, heart and chest wall diseases. The need for sedation in children is significantly reduced by short examination times.Although the breast is not the target of examination, the main drawback of this imaging technique is that it reveals it to ionizing radiation.In recent large-scale epidemiological studies, it has been shown that the risk of cancer in children and young adults increases due to radiation exposure after CT examination (6-9). Studies on women who survived the atomic bombing of Japan and on patients who underwent numerous radiographs due to benign conditions like tuberculosis and scoliosis resulted findings demonstrating that cancer develops in the breast tissue after exposure to ionizing radiation (4, 10-12).It is estimated that exposure to 10 mGy radiation in a woman younger than 35 years of age increases the lifetime risk of developing breast cancer by 13.6% (13).

Various methods are used to reduce the harmful effects of ionizing radiation originating from computed tomography.These can be listed as reducing the tube current, increasing the section thickness and pitch value, decreasing the tube voltage, shortening the gantry rotation time, increasing the table speed and using X-ray filters (14).The main drawback of these dose reduction methods is that the image quality may deteriorate and the diagnostic efficiency may decrease.In addition to these methods, bismuth shields can be used to reduce the radiation exposure of superficial organs such as breast, thyroid, lens and testis.With bismuth shields, some of the X-rays that may affect the superficial organs are prevented. In this study, we placed a bismuth shield on the right breast of pediatric female who underwent thorax MSCT. We used automatic tube current modulation protocol during shooting. We observed that bismuth shielding reduced the superficial radiation dose in the right breast by 22.76 %. We did not see any differencesin image quality between the shielded and unshielded lung.Fricke et al. showed that the mean dose protocol and the use of bismuth shielding in pediatric female with thoracic and abdominal CT reduced the radiation dose of the breast by 29%, similar to our study, and did not cause any deterioration in image quality (15). In the study conducted by Coursey et al. to investigate the effectiveness of automatic tube current modulation and bismuth shielding in reducing the breast radiation dose in thorax CT taken using an anthropomorphic phantom

representing a 5-year-old girl, bismuth shielding alone decreased the radiation dose by 26%, automatic tube current modulation and bismuth shielding together reduced the dose by 52% . In the same study, an increase in noise level was found (16). An increase in the noise level might have been observed because this study used a phantom and quantitative values to assess the image quality.
It has been demonstrated in the literature that bismuth shielding alone or in combination with various other dose reduction techniques can lower the breast radiation dose in adults by an average of 27.9% to 57% (17-24).We believe that the emergence of such disparate results across studies is a result of the use of other dose reduction techniques, such as automatic tube current modulation and low peak kilovoltage (kVp), in addition to bismuth shielding in some studies.In some of the aforementioned studies, it was determined that the image quality deteriorated after the use of bismuth shielding.The qualitative and quantitative evaluations created in various ways could be the consequence of the variations between the studies in image quality.The pediatric radiologist evaluated the diagnostic applicability of the thorax MSCT images we obtained for this study only qualitatively, and all of the patients in our study had quite images.

Limitations

The first limitation of the study was the relatively small number of patients. A phantom should be used to calculate the breast glandular tissue radiation dose. In this study, only the superficial radiation dose of the breast and the effectiveness of bismuth shielding were investigated. Not using phantom in this study can be considered as another limitation.We were also unable to objectively assess the image quality due to this limitation.

Conclusion

With the technological developments in CT, there is a significant increase in the number of MSCT examinations performed on children.In the light of current information, it is known that breast cancer secondary to radiation can develop.For this reason, it is important to follow the ALARA (as low as reasonably achievable) approach and administer MSCT at the lowest dose possible, especially in situations when the requirement of MSCT in children must be thoroughly assessed.In this study, we found that bismuth shielding effectively reduced the superficial radiation dose received by the breast in pediatric female who underwent thorax MSCT.We recommend the use of bismuth shielding in MSCT scans where superficial radiosensitive organs such as breast, thyroid, eyes and gonads are in the examination area.

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Orgınal Article

Comparison of the effects of Propofol. Dexmedetomidine and Midazolam on Sedation and Oxidative-Antioxidant System in Critically ill Patients

Yoğun Bakım Hastalarında Propofol, Deksmedetomidin ve Midazolam'ın Sedasyon. Oksidan – Antioksidan Sistem Üzerine Etkilerinin Karşılaştırılması

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Highlights

- Among sedative drugs, dexmedetomidine has better results in terms of oxidative stress parameters.

Abstract

Background: This study aimed to compare the impact of midazolam, propofol, dexmedetomidine infusions for 24th hour on total antioxidant status (TAS), total oxidant status (TOS), oxidative stres index (OSI) and prolidase levels.

Material and Method: 75 patient ICU patient who were mechanically ventilated enrolled to the study. Patients randomised to three groups. Group I (n=25, midazolam): 0.02 mg/ kg/h midazolam, Group II (n = 25, propofol): 1mg/kg/h propofol, Group III (n=25, dexmedetomidine): 0.2 µg/ kg/h dexmedetomidine infusions was started. Dosage were arrange to achieve Ramsay sedation score 3. Blood samples were collected in basal, 6.,12.,18., 24. hour, and hemodynamic parameters were also recorded in the same time intervals. **Results**: In midazolam group 24. hour TAS levels were significantly decreased and TOS, prolidase and OSI levels were significantly increased compared to the basal level ($p<0.05$). 24. hour TAS levels were significantly decreased and TOS, prolidase and OSI levels were significantly increased compared to basal level in propofol group ($p<0,05$). In dexmedotimidine groups 24.hour TAS and prolidase levels were significantly decreased, OSI levels were increased compared to the basal levels ($p<0.05$). Increase in TOS levels were not statistically significant ($p>0.05$). Basal TAS, TOS, prolidase, OSI levels were not statistically significantly between the different groups ($p>0.05$).**Conclusion:** Dexmedetomidine was found to be having statistically significant favorable results in comparison to others. However there results should be clinically and molecularity verified with large scale further studies. **Keywords**: Intensive care unit, sedation, oxidative stress, midazolam, propofol, dexmedetomidine

ÖZ

Amaç: Bu çalışmada yoğun bakımda sık kullanılan sedasyon ajanlarındanmidazolam, propofol ve deksmedetomidinin sedasyon amacıyla 24 saatlik infüzyonlarınıntotal antioksidan seviye (TAS), total oksidan seviye (TOS), oksidatif stres indeksi (OSI), ve prolidaz değerleri üzerine olan etkilerini karşılaştırmak amaçlandı.**Materyal ve Metod:** Çalışmaya yoğun bakımda yatmakta olan 75 erişkin hasta dahil edildi. Çalışmaya dahil edilen olgular üç gruba randomize edildi. Grup I'e (n=25, midazolam): 0,02 mg/kg/saatmidazolam, Grup II'ye (n = 25, propofol): 1mg/kg/saat propofol, Grup III'e (n=25, deksmedetomidin): 0,2 µg/kg/saat deksmedetomidin infüzyonuna başlandı. Hastaların bazal 6.,12.,18., ve 24. saatteki hemodinamik parametreleri kaydedilerek kan örnekleri alındı. **Bulgular:** Grup içi incelemelerde midazolam grubunda 24. saatte TAS değerleri bazale göre istatistiki olarak azalırken, TOS, prolidaz ve OSI değerleri istatistiki olarak artmıştır ($p<0,05$). Propofol grubunda 24. saat TAS değerleri bazale göre istatistiki olarak azalırken, TOS, prolidaz ve OSI artış tespit edilmiştir ($p<0,05$). Deksmedetomidin grubunda TAS ve prolidaz değerlerinde istatistiksel olarak anlamlı azalma görülürken ($p<0,05$), OSI değerlerinde istatistiksel olarak anlamlı artış görülmüştür ($p<0,05$). TOS değerlerindeki artış ise istatistiksel olarak anlamlı bulunmamıştır ($p>0,05$). **Sonuç:** Grup içi ve gruplar arası incelemelerde deksmedetomidin ile ilgiliistatistiksel olarak anlamlı olumlu sonuçlar elde edilmiştir. Sonuçların daha geniş çalışmalarlahem moleküler hem de klinik açıdan desteklenmesi gerektiğini düşünmekteyiz. **Anahtar kelimeler:** Yoğun bakım, sedasyon, oksidatif stres, midazolam, propofol, deksmedetomidin

Introduction

Patients who undergo mechanical ventilation (MV) in the Intensive Care Unit often need sedation. even if they are unconscious. There are still debates about which drug should be given in what dose. among the various agents routinely used for sedation. and their superiority over each other (1).

Providing sedation in intensive care patients receiving MV support is one of the important components of treatment. Being on a mechanical ventilator in the intensive care unit is a cause of anxiety in itself. In addition. pain and agitation may lead to increased myocardial oxygen consumption, immunosuppression, and hypercoagulopathy (1,2).

Disrupted sleep pattern/abnormal sleep rhythm in intensive care patients is also an important cause of orientation and psychological disorders. It is accepted that the fatigue caused by the deterioration in sleep rhythm in the critically ill is an important reason for the termination of MV and the prolongation of the time of discharge from the intensive care unit (3).

Hearing is the last sense to deteriorate in humans. and unusual sounds such as medical comments and monitor alarms heard by the intensive care patient are other serious causes of anxiety (2).

One of the scariest situations a person can find themselves in is being therapeutically paralyzed and fully aware of it. For this reason. sedation is strictly indicated in all paralyzed intensive care patients (4).

Another picture that can occur frequently in intensive care patients is agitation. This is probably a clinical condition of anxiety. disorientation and pain. However. the important thing here is to eliminate organic causes such as hypoxia, hypercarbia, hypoglycemia, drug or alcohol withdrawal and encephalopathy that cause agitation. Therefore. differential diagnosis is extremely important before intervening in agitation (5).

By providing sedation. these negative factors can be prevented and the length of stay of the patient in the mechanical ventilator and the length of stay in the intensive care unit can be shortened. For this purpose. various drugs are used today. Despite their clinically significant beneficial effects. drugs used for sedation have significant side effects. making it difficult for clinicians to choose appropriate drugs and doses. In this study. to compare the effects of the sedation agents of midazolam. propofol and dexmedetomidine. which are frequently used in intensive care units. on hemodynamics and total antioxidant level (TAS), total oxidant level (TOS), oxidative stress index (OSI) and prolidase values was intended.

Propofol, midazolam and dexmedetomidine are some of the commonly used intravenous agents for the induction and maintenance of general anesthesia. procedural and intensive care sedation. Dexmedetomidine. which is a candidate to be an alternative to frequently used midazolam-propofol or midazolam-opioid combinations; It is a sedo-analgesic with analgesic, sedative, anxiolytic properties. Although it was originally produced for the sedation of intensive care patients. It is increasingly used in non-operating room sedoanalgesia. Sedation without respiratory depression Its analgesic property is superior to other agents (6-10).

Methods

Patient Selection

Ethical approval was taken 03.12.2008/9 Ethics Committee of Harran University Faculty of Medicine Clinical Research Ethics Committee. Written consent was obtained from the parents or guardians of the unconscious patients, who were informed about the procedures to be done. Afterwards, 75 adult patients (18-70 years old) who were treated with MV between January 2009 and January 2010 in the General Intensive Care Unit of the Department of Anesthesiology and Reanimation were included. On the day they started to receive treatment, their physical examinations were performed and their hemograms and biochemical parameters were recorded.

Exclusion Criteria:

Those who are allergic to the drug, the patient or his family does not accept it, there is a drug interaction between the other drugs he uses and the drugs we will use.

The patients were randomly randomized and divided into 3 groups of 25 patients.

Group I (n=25. midazolam): The subjects were given 0.02 mg/kg/hour midazolam as an infusion.

Group II (n=25. propofol): The subjects were given 1mg/kg/hour of propofol as an infusion.

Group III (n=25. dexmedetomidine): The subjects were given 0.2 microgram/kg/hour of dexmedetomidine as an infusion.

Demographic Data

The day when the patients included in the study started to receive mechanical ventilator therapy. their name. surname. Age, weight, height, gender, smoking, diagnosis, whether there was any additional pathology other than the current diagnosis, and nutritional status were recorded. Basal 6.. 12.. 18. and 24. Hours at heart rate. mean arterial pressure values. arterial oxygen saturation. TAS. TOS. prolidase values were recorded.

Blood samples were sent to the biochemistry laboratory in a 5 cc biochemistry tube. The obtained samples were centrifuged at 3000 rpm for 5 minutes and stored in a deep freezer at -80ºC until the working time. On the study day, prolidase enzyme activity was thawed to evaluate TAS and TOS status. The newly developed optimized

modified Chinard Method (11. 12). a colorimetric measurement method for prolidase enzyme activity. and a fully automatic colorimetric method developed by Erel (Rel-Assay commercial kits) were used to measure TAS and TOS states (13-16).

Statistical Analysys

SPSS (Statistical Package for Social Sciences) for Windows 11.5 (SPSS Inc. Chicago USA) program was used for Statistical analysis.The normal distribution of the data was based on skewness and cortisis values. The data were distributed normally. Analysis of Variance in Repeated Measurements test was used to evaluate recurrent hemodynamic data within the group. One Way ANOVA test was used for quantitative comparisons between and within groups. and Chi-Square test was used for categorical data. Results were expressed as mean ± standard deviation. and $p<0.05$ was considered statistically significant.

RESULTS

Demographic Data

To this study; Seventy-five adult patients who were treated with mechanical ventilators between January 2009 and January 2010 in the Department of Anesthesiology and Reanimation, Department of Anesthesiology and Reanimation, Harran University were included. 51 of the patients (68%) were male and 24 were female (32%). The demographic data of the groups are given in **Table 1**.

Table.1 Cross-group demographic data

	Midazolam	Propofol	Deksmedetomidin
Age (years)	65.52 ± 17.26	58.96 ± 19.1	60.6 ± 23.59
Weight (kg)	73.76 ± 10.68	69.64 ± 11.30	68.52 ±12.46
Height (cm)	165.8 ± 8.42	166.32 ± 9.68	165.48 ± 7.01

Aberrations: cm:centimeter kg: kilogram Data are given as standard deviation from mean ±.SD

TAS. TOS. OSI. Prolidase basal. 6th. 12th and 24th hour values of the midazolam group are shown in Table 2. When the TAS values of the Midazolam Group patients were compared, a statistically significant decrease was found in the 6th. 12th and 24th hour values compared to the baseline value ($P<0.05$). When the TOS values of Midazolam Group Patients were compared. they were 6..12. Statistically significant increase was detected at 24th and 24th hours ($p<0.05$). When the Midazolam Group Prolidase values were compared, a statistically significant increase was found compared to the basal value at the 6th. 12th and 24th hours ($p<0.05$). When the OSI values of the patients in the Midazolam Group were compared. a statistically significant increase was found compared to the baseline value ($p<0.05$) **(Table 2).**

Table.2 Midazolam group TAS. TOS. OSI and Prolidase values

Parametres	BaSal	6.hours	12.hours	24.hours
TAS (mmol TroloksEqv./L**)**	1.3252±0.28475	1.2773±0.2853*	1.0245±0.23321*	0.9067±0.12984*
TOS(µmol H_2O_2 Eqv./L)	14.990±3.891	17.248±3.756*	23.408±4.924*	26.9464±5.1552*
OSI (AU)	1.2396±0.4081	1.4248±0.4575*	2.441±0.957*	3.0445±0.756*
Prolidaz (U/L)	686.649±12.559	690.0358±12.544*	693.174±18.226*	702.872±10.674*

Aberrations:* Statistically significant ($p<0.05$) when compared with baseline value. Data are given as mean ± standard deviation.TAS: Total Antioxidant Level TOS: Total Oxidant Level OSI: Oxidative Stress Index

Propofol group TAS, TOS, OSI, Prolidase basal, 6^{th}, 12th and 24th hour values are shown in Table 3. When the TAS values of the Propofol Group patients were compared, the decrease determined at the 6th hour value compared to the baseline value was not statistically significant ($p>0.05$). While the 12th and 24th hour values decreased statistically significantly compared to the baseline value ($p<0.05$). When the TOS values of the Propofol Group patients were compared, a statistically significant increase was found compared to the baseline value ($p<0.05$). When the Propofol Group Prolidase values were compared, a statistically significant increase was found compared to the basal value at the 6th. 12th and 24th hours ($p<0.05$). When the OSI values of the Propofol Group patients were compared. a statistically significant increase was found compared to the baseline value ($p<0.05$) **(Table 3).**

Table.3. Propofol group TAS. TOS. OSI and Prolidase values

Parametres	BaSal	6.hours	12.hours	24.hours
TAS (mmolTroloksEqv./L)	1.3196±0.28475	1.2283±0.2119	1.055±0.240*	0.9258±0.1694*
TOS (μmol H_2O_2 Eqv./L)	15.404±3.704	26.681±6.188*	28.010±6.466*	31.196±3.431*
OSI (AU)	1.2784±0.420	2.2118±0.611*	2.819±1.021*	3.49±0.79*
Prolidaz(U/L)	694.08±26.48	696.91±26.56*	698.42±14.51*	707.64±11.40*

Aberraions:* Statistically significant (p<0.05) when compared with baseline value. Data are given as mean ± standard deviation. TAS: Total Antioxidant Level TOS: Total Oxidant Level OSI: Oxidative Stress Index

Dexmedetomidine group TAS. TOS. OSI. Prolidase basal 6th 12th and 24th hour values are shown in Table 4. When the TAS values of the Dexmedetomidine Group patients were compared. a statistically significant decrease was found at the 6th hour value compared to the baseline value (p<0.05). Although there were lower levels compared to the baseline value at the 12th and 24th hour values. it was not statistically significant. A statistically significant increase was observed in the 12th hour value compared to the 6th hour p(<0.05). When the TOS values of the Dexmedetomidine Group patients were compared. there was a statistically significant increase in the 6th and 12th hour values compared to the baseline value (p<0.05). while no statistically significant difference was found between the baseline value and the 24th hour (p>0.05). When the Dexmedetomidine Group Prolidase values were compared. a statistically significant decrease was found between the baseline value and the 24th hour (p<0.05). When the OSI values of the Dexmedetomidine Group patients were compared. a statistically significant increase was found in the 6th. 12th and 24th hour values compared to the baseline value (p<0.05) **(Table 4).**

Table.4. Dexmedetomidine group TAS. TOS. OSI and Prolidase values

Parameters	BaSal	6.hours	12.hours	24.hours
TAS (mmolTroloksEqv./L	1.276±0.2824	0.89±0.20*	1.1857±0.344	1.067±0.34
TOS (μmol H_2O_2 Eqv./L)	16.81±5.81	23.15±6.13*	27.75±6.66*	20.34±5.96
OSI (AU)	1.40±0.64	2.76±1.04*	2.49±0.85*	2.14±0.95*
Prolidaz (U/L)	690.51±14.8	693.30±14.85	675.34±32.91	671.11±20.87*

Aberrations:* Statistically significant (p<0.05) when compared with baseline value. Data are given as mean ± standard deviation. TAS: Total Antioxidant Level TOS: Total Oxidant Level OSI: Oxidative Stress Index.There was no statistically significant difference between the groups in terms of demographic data (p>0.05).

Discussion

Approximately 1/3 of the patients hospitalized in the intensive care unit need MV and often require analgesia and sedation. Despite their clinically significant beneficial effects, drugs used for sedation have significant side effects, making it difficult for clinicians to choose drugs and doses (17). In patients undergoing MV, pain also has important side effects such as increased endogenous catecholamine activity,anxiety and delirium (18).

In the study conducted by Wunsch et al. (19) in the United States. 51.5% of 109.671 patients who underwent MV received one or more sedative infusions. sedative use increased from 39.7% in 2001 to 66% in 2007. They reported that it increased to 0.7. that 81% of those who received sedatives took propofol, 31% took benzodiazepine, 34% took dexmedetomidine. Nowadays. intensive care sedations are increasingly performed within the framework of protocols. However. Ethier et al. (20) found in their study that more than 50% of patients discharged from the intensive care unit, despite sedation protocols. recalled the pain. fear and anxiety they experienced, and severe or moderate events. Midazolam, propofol and dexmedetomidine used in this study are widely used for intensive care sedation.

In this study, it was aimed to investigate the effects of propofol, midazolam and dexmedetomidine on TAS, TOS, OSI and prolidase after 24 hours when used for sedation in the intensive care unit.

It is known that propofol has positive effects on oxidative stress and inflammation due to its chemical structure. Balyasnikova et al. (21) showed that propofol prevents oxidative damage in the lung. Tsuchiya et al. (22) examined the effects of propofol on oxidative damage on human erythrocytes and showed that propofol increases the resistance to hemodynamic and physical stress by increasing membrane flow in erythrocytes, protects against repetitive oxidative and physical stresses, and has an effective and safe antioxidant potential.

Tsuchiya et al. (23) compared the antioxidant activities of propofol and midazolam and showed that propofol has a greater potential to reduce oxidative stress compared to midazolam.

In one of the limited studies examining the effects of dexmedetomidine on inflammation, it was shown that subhypnotic doses of dexmedetomidine decreased IL-12 release from macrophages and decreased the Th1/Th2 ratio (24). Tasdogan et al. (25) compared the effects of propofol and dexmedetomidine infusions on the inflammatory response. intra-abdominal pressure values. and IL-1. IL-6. TNF-α levels in 40 adult patients hospitalized in the intensive care unit after abdominal surgery and dependent on mechanical ventilator. They showed that IL-1. IL-6 TNF-α and intra-abdominal pressure were lowered more. Qioa H. et al. (26) showed that dexmedetomidine and midazolam can reduce early mortality in severely septic rats. and the decrease in mortality indicates the low TNF-α levels in both groups. Venn et al. (27) in their study in which they compared the effects of dexmedetomidine and propofol on the endocrine, metabolic, inflammatory and cardiovascular systems of patients hospitalized in the intensive care unit after a major surgery (28). They randomly divided 20 patients in need of postoperative sedation into two groups and divided them into one group with dexmedetomidine 0.2-2.5 μg/kg. They gave 1-3 mg/kg/hour propofol to the other group/hour. Blood pressures. heart rate. and cortisol. ACTH, growth hormone. prolactin. insulin, glucose, and IL-6 levels were measured respectively. While the heart rate was lower in the dexmedetomidine group. while there was no difference between the two groups in arterial pressures, cortisol, ACTH, prolactin, and glucose concentrations. It was shown that IL-6 level was lower in the dexmedetomidine group. Aslan et al. (29) investigated the effect of dexmedetomidine after traumatic spinal cord injury, traumatic spinal cord injury was found to be associated with lipid peroxidase elevation and a decrease in enzymatic, non-enzymatic endogenous antioxidative defense system. It has been shown that dexmedetomidine inhibits lipid peroxidation and causes an increase in the endogenous antioxidant defense system in CSF and spinal cord tissue samples. Yagmur et al. (30) showed that dexmedetomidine significantly reduced hypoxanthine production in ischemia and malondiaaldehyde production in reperfusion period on ischemia-reperfusion injury due to tourniquet applied during upper extremity surgery on 40 patients.

In this study, in-group studies it was shown that TAS decreased within 24 hours in the propofol and midazolam group but did not change in the dexmedetomidine group. It was determined that OSI increased at the end of 24 hours in all three drugs, while prolidase increased after 24 hours in other groups and decreased in the dexmedetomidine group. In the examinations between the groups, it was determined that there was no difference in TAS at the end of 24 hours, and there was a significant decrease in TOS and OSI and prolidase values in the dexmedetomidine group.

The high OSI values in all three drug groups at the end of 24 hours indicate the severe oxidative stress that intensive care patients are exposed to. In particular. the decrease in TAS values and the increase in TOS values confirm this. In the comparison between groups, the fact that TAS and TOS values did not statistically change in the dexmedetomidine group and showed a change in the direction of increasing OSI in the other groups shows that dexmedetomidine is more preferable for sedation in intensive care patients.

In our study, we also examined prolidase enzyme activities in all three groups for 24 hours and examined whether collagen metabolism was changed. Collagen, one of the most common proteins in our body. can undergo metabolic changes in case of severe oxidative stress (6).

It was determined by the increased prolidase enzyme activity that the metabolism of this protein, which is likely to be mechanically damaged as well as oxidative damage in intensive care patients due to MV, accelerates in general. From this point of view, we demonstrated that the dexmedetomidine group did not accelerate the metabolism of collagen proteins, and therefore catabolism did not increase, with the decreased prolidase enzyme activity detected at the end of 24 hours. According to the results of this study; a statistically significant positive result was obtained with dexmedetomidine both in and between groups. The biochemical results obtained in this study at the end of 24 hours can be considered in terms of choosing between drugs for intensive care sedation. However, we think that the results should be supported by larger studies, both molecularly and clinically. Confirmation of our results by evaluating both oxidant-antioxidant and prolidase enzyme activity levels. especially in larger patient population and patients under longer follow-up. will make a great contribution to the medical literature.

Study Limitation

The biggest limitation of this study is the absence of a control group.

Conclusion

According to the results of this study. no significant difference was found between the groups in terms of hemodynamics. Statistically significant positive results were obtained with dexmedetomidine in the in-group and between-group examinations. We think that the results should be supported by larger studies. both molecularly and clinically.

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Ethical Approval: *Ethical approval was taken 03.12.2008/9 Ethics Committee of Harran University Faculty of Medicine Clinical Research Ethics Committee. We conducted this study according to the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants.*

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Orgınal Article

Relationship between Coronavirus Disease and Erythrocyte Morphology Parameters

Koronavirüs Hastalığı ile Eritrosit Morfoloji Parametreleri ile İlişkisi

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Highlights

- Coronavirus Disease causes changes in erythrocyte morphology
- Microcytosis value may help in diagnosing coronavirus disease

Abstract

Background: To determine the rates of Microcytosis (%), Macrocytosis (%), Hypochromia (%), and Hyperchromia (%) as erythrocyte morphological parameters in Coronavirus Disease 2019 **(**COVID-19) infection, using a new-generation hematological autoanalyser, and to evaluate the use of these parameters for diagnostic purposes. **Material and Methods:** This retrospective study included 66 patients (F:41, M:25) with COVID-19 infection confirmed by real-time Polymerase Chain Reaction (PCR) test positivity, and 67 age and gender-matched healthy individuals (F:40, M:27) as a control group. The COVID-19 patients were separated into two groups as those with pulmonary infiltration (n=35, F/M:20/15) and those without (n=31, F/M:21/10). The hematological parameters measured on the autoanalyzer were analyzed and compared between the groups. **Results:** Age and gender distribution were similar in both study groups (p=0.619, p=0.457). The White Blood Cell (p=0.040) Neutrophil (p<0.001), Lymphocyte (p<0.001), and Platelet (p <0.001) levels were statistically significantly lower in the COVID-19 patients compared to the control group and C-Reactive Protein (CRP) levels were significantly increased (p<0.001). In the comparisons of the erythrocyte morphology parameters, Microcytosis % (p=0.011) was significantly greater, and Macrocytosis % (p=0.009) and Hypochromia % (p=0.032) were significantly lower in the COVID-19 patients. An increase was determined in Hyperchromia %, but not at a statistically significant level (p=0.059).**Conclusion:** From the erythrocyte morphological findings determined with the new-generation devices, the Microcytosis percentage was determined to be significantly increased in COVID-19-positive patients, and this parameter was found to have 78.79% sensitivity and 50.75% specificity in the differentiation of COVID-19 patients from healthy individuals.

Keywords: COVID-19, Microcytosis, Macrocytosis, Hypochromia, Hyperchromia

ÖZ

Amaç: Yeni nesil hematolojik oto analizör cihazı ile tespit edilen eritrosit morfolojik parametreleri olan Microcytosis (%), Macrocytosis (%), Hypochromia (%), Hyperchromia (%) 'nin Koronavirüs Hastalığı 2019 (Covid-19) hastalığındaki oranları ve tanı amaçlı kullanılmasının tespiti amaçland.

Gereç ve Yöntem: Retrospektif olarak tasarlanan çalışmamıza real time- Polimeraz Zincir Reaksiyonu (PCR) testi pozitif olan 66 (K/E: 41/25) hasta ile yaş ve cinsiyet olarak benzer 67 (K/E: 40/27) sağlıklı birey alındı. Covid-19 hastaları daha sonra, akciğerde infiltasyon olanlar (n=35, K/E: 20/15) ve infiltrasyon olmayanlar (n= 31, 21/10) olarak iki gruba ayrıldı. Hastaların otoanalizatör cihazda ölçülen hematolojik parametreleri analiz edildi.

Bulgular: Çalışma gruplarının yaş (p=0.619) ve cinsiyet (p=0.457) olarak benzerdi. Covid-19 hastalarının; White Blood Cell (p=0.040) Neutrophil (p<0.001), Lymphocyte (p<0.001), Platelet (p <0.001) düzeylerinin sağlıklı kontrol grubuna gore anlamlı oranda azaldığı fakat C-Reaktif Protein (CRP) düzeylerinin ise anlamlı oranda arttığı tespit edildi (p <0.001). Ayrıca eritrosit morfolojilerinin karşılaştırıldığında Covid-19 hastalarında Microcytosis yüzdesinin (p=0.011) anlamlı oranda fazla, Macrocytosis yüzdesinin (p=0.009) ve Hypochromia yüzdesinin (p=0.032) ise anlamlı oranda az olduğu, Hyperchromia yüzdesinin ise arttığı fakat bu artisan istatistiksel olarak anlamlı olmadığı (p=0.059) tespit edildi **Sonuç:** Yeni nesil cihazlar ile tespit edilen eritrosit morfolojik bulgularından ise Microcytosis yüzdesinin Covid pozitif hastalarda anlamlı oranda arttığı ve Covid-19 hastalarını, sağlıklı bireylerden ayırt etmede sensitivitesinin %78.79 ve specificitesinin ise % 50.75 olduğu tespit edildi.

Anahtar kelimeler: COVID-19, Microcytosis, Macrocytosis, Hypochromia, Hyperchromia

Introduction

COVID-19 infection, caused by the SARS-CoV-2 virus, is a disease affecting many organ systems, which develops with a wide range of clinical signs and symptoms from asymptomatic infection to acute respiratory distress syndrome, multiple organ failure, and death. The clinical symptoms of COVID-19 are very similar to those of various other viral infections (1-3). The SARS-CoV-2 virus is known to enter the host cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors (4). Studies have reported that ACE2 is expressed in type 1 and 2 alveolar epithelial cells, in myocytes, in vascular endothelial cells, and some other cells including hematopoietic stem cells and progenitors (4, 5). It has been suggested that this may be related to a change in oxygen intake and/or oxygen binding and /or oxygen expression of red blood cells (RBC) in COVID-19 patients. A change in the hematological profile, and changes in RBC morphology, structure, and function that can occur during the acute phase of infection may explain the symptoms that emerge (6, 7). These changes may be related to damage in the beta chain of hemoglobin or to the formation of increasing methemoglobin which increases the oxygen affinity of undamaged hemoglobin (8). It has been shown in several studies that hematological parameters are changed in COVID-19 infection and may be associated with mortality (9,10). However, there is a limited number of studies related to the morphological changes in the blood cells of COVID-19 patients, and most of the publications are case reports (11, 12).

Peripheral blood smear analysis is an important diagnostic tool in RBC deteriorations, but there are very few studies giving detailed information about RBC morphology in COVID-19 patients (13). Hemoglobin (Hb) concentration tends to gradually reduce during the course of the disease. Both sepsis and hypoxia have profound effects on RBC morphology, rheology, and survival, and probably contribute to the complex pathogenesis of COVID-19 anemia (13).

New-generation hematology devices can provide neew data about erythrocyte morphology. In emergency situations, the hypochromia percentage (%), hyperchromia %, macrocytosis %, and microcytosis % can be sensitively measured automatically (14,15).

The hemogram autoanalyzer assesses the volume of erythrocytes of <60 fL as Microcytosis (%), >120 fL as Macrocytosis (%), and erythrocytes with hemoglobin concentrations of >42 pg and <17 pg as Hyperchromia (%) and Hypochromia (%), respectively).

The aim of this study was to compare the erythrocyte morphological parameters measured with a hemogram autoanalyzer in the Emergency Department between patients diagnosed with COVID-19 and healthy individuals, and to compare the COVID-19 patients with and without infiltrative involvement determined on thorax computed tomography.

Material and Methods

This case-control study included 67 patients diagnosed with COVID-19 infection confirmed by real-time PCR test positivity and 67 healthy individuals as a control group. The study was conducted in the Emergency Department of a University Faculty of Medicine Hospital in accordance with the Helsinki Declaration. Approval for the study was granted by the university Ethics Committee. Signed informed consent was obtained from all the study participants. After sample size was established, inclusion and exclusion criteria were defined. Patients were excluded if they were aged <18 years, had any hematological malignancy, or chronic lung disease. Non-Contrast Thorax Computed Tomography (CT) (Aquilion Prime SP, Canon Medical Systems, 9750 Irvine, USA) was performed on PCR positive patients. CT images were described using standard terminology using terms such as ground glass opacity, crazy-paving pattern, and consolidation(16).

Biochemical Analysis

Venous blood samples were taken from the patients presenting at the Emergency Department and from the control group subjects. The samples were analyzed using standard laboratory methods.The hemogram parameters of Microcytosis (%), Macrocytosis (%), Hypochromia (%), Hyperchromia (%), White Blood Cell (10e3/µL), Neutrophil (10e3/µL), Lymphocyte (10e3/µL), Monocyte (10e3/µL), Hemoglobin (g/dL), Hematocrit (%), Mean Corpuscular Volume (fL), Mean Corpuscular Hemoglobin (pg), Mean Corpuscular Hemoglobin Concentration (g/dL), Red Blood Cell Distribution Width , Platelet (10e3/µL), Mean Platelet Volume (fL), and Platelet Distribution Width (fL) were examined using an Alinity HQ (Abbott, USA) full automatic hemogram autoanalyzer. The biochemical parameters (Glucose (mg/dl), Urea (mg/dl), Creatine (mg/dl), C-Reactive Protein (mg/dL)) were examined using an Architect c16000 (Abbott, USA) full automatic biochemistry autoanalyzer.

Statistical Analysis

Data were analysed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA) and MedCalc (Version 10.1.6.0, Ostend, Belgium) packaged software. Numerical data were expressed as median (IQR) values, and qualitative data as number (n) and percentage (%). The Shapiro–Wilk test was used to examine the conformity of

continuous variables to normal distribution. Comparisons were made using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. Receiver operating characteristic (ROC) curve analysis was performed using the erythrocyte parameters for the differentiation of control subjects and COVID-19 patients. The ROC curve analysis results were given as % specificity, and % sensitivity [area under the ROC curve (AUC), p-value, 95% confidence interval (CI)]. A value of $p<0.05$ was accepted as the level of statistical significance.

Results

Evaluation was made of 66 patients with COVID-19 confirmed by real-time PCR test positivity and 67 healthy individuals. Age and gender distribution were similar in both groups (p=0.619, p=0.457, respectively). The White Blood Cell (p=0.040) Neutrophil (p<0.001), Lymphocyte (p<0.001), and Platelet (p <0.001) levels were statistically significantly lower in the COVID-19 patients compared to the control group and CRP levels were significantly increased (p<0.001). The basic data of the study groups are shown in Table 1.

Table 1. The basic data of the study groups.

Variabales	COVID-19 group	Control group	p
N (F/M)	66 (41/25)	67 (40/27)	0.457
Age (years)	46.00 (29.50-60.25)	45.00 (29.00-64.00)	0.619
White Blood Cell* (10e3/µL)	6.35 (5.55-9.05)	7.53 (6.65-8.52)	0.040
Neutrophil* (10e3/µL)	3.50 (2.16-4.43)	4.76 (3.68-5.28)	<0.001
Lymphocyte* (10e3/µL)	1.47 (1.03-1.84)	2.10 (1.68-2.64)	<0.001
Monocyte* (10e3/µL)	0.50 (0.42-0.68)	0.60 (0.48-0.71)	0.075
Hemoglobin* (g/dL)	13.80 (12.78-15.43)	14.00 (12.60-15.50)	0.993
Hematocrit* (%)	42.60 (39.40-47.43)	44.00 (39.00-46.50)	0.845
Mean Corpuscular Volume* (fL)	89.60 (86.18-92.75)	90.30 (86.20-93.80)	0.685
Mean Corpuscular Hemoglobin* (pg)	29.15 (28.20-30.23)	29.40 (28.00-30.20)	0.633
Mean Corpuscular Hemoglobin Concentration* (g/dL)	32.40 (32.00-32.83)	32.40 (31.80-32.90)	0.914
Red Blood Cell Distribution Width	12.55 (12.18-13.33)	12.80 (12.30-13.70)	0.084
Platelet* (10e3/µL)	229.50(190.75-262.25)	288.00 (226.00-335.00)	<0.001
Mean Platelet Volume* (fL)	8.20 (7.63-8.90)	8.11 (7.55-8.74)	0.253
Platelet Distribution Width* (fL)	13.40 (12.90-13.73)	13.20 (12.80-13.50)	0.187
Glucose (mg/dl)	93.00 (84.75-113.00)	96.00 (86.00-115.00)	0.369
Urea (mg/dl)	25.68 (21.40-29.96)	25.68 (19.26-32.10)	0.964
Creatine (mg/dl)	0.70 (0.59-0.89)	0.70 (0.50-0.80)	0.055
C-Reactive Protein* (mg/dL)	0.92 (0.43-2.50)	0.11 (0.05-0.31)	<0.001

* Median (IQR)

In the comparisons of the erythrocyte morphology parameters, Microcytosis % (p=0.011) was significantly greater, and Macrocytosis % (p=0.009) and Hypochromia % (p=0.032) were significantly lower in the COVID-19 patients. An increase was determined in Hyperchromia %, but not at a statistically significant level (p=0.059) (Table 2).

Table 2. Comparisons of the erythrocyte morphology parameters of the study groups

Variables	COVID-19 group	Control group	p
Microcytosis* (%)	1.35 (1.01-1.35)	1.00 (0.68-1.73)	0.011
Macrocytosis *(%)	0.66 (0.33-1.63)	1.21 (0.60-2.41)	0.009
Hypochromia* (%)	0.51 (0.34-0.96)	0.82 (0.44-1.62)	0.032
Hyperchromia* (%)	0.12 (0.06-0.16)	0.07 (0.03-0.16)	0.059

* Median (IQR)

According to the ROC curve analysis performed to evaluate the use of erythrocyte morphology parameters in the differentiation of COVID-19 patients from healthy control subjects, a cutoff value of >0.998 for the Microcytosis percentage was determined to have 78.79% sensitivity and 50.75% specificity. A cutoff value of >0.0666 for the Hyperchromia percentage was determined to have 72.73% sensitivity and 49.25% specificity (Table 3, Figure 1).

Table 3: ROC Curve analysis results for the differentiation of COVID-19 patients from healthy individuals

Varaibles	Cut Off	AUC	95% CI	Sensitivity	Specificity	PPV	NPV	P
Microcytosis* (%)	>0.998	0.628	0.540 - 0.711	78.79	50.75	61.2	70.8	0.008
Macrocytosis *(%)	≤0.727	0.632	0.544 - 0.713	54.55	70.15	64.3	61.0	0.007
Hypochromia* (%)	≤0.797	0.608	0.519 - 0.691	71.21	52.24	59.5	64.8	0.031
Hyperchromia* %)	>0.066	0.595	0.506 - 0.679	72.73	49.25	58.5	64.7	0.058

* Median (IQR)

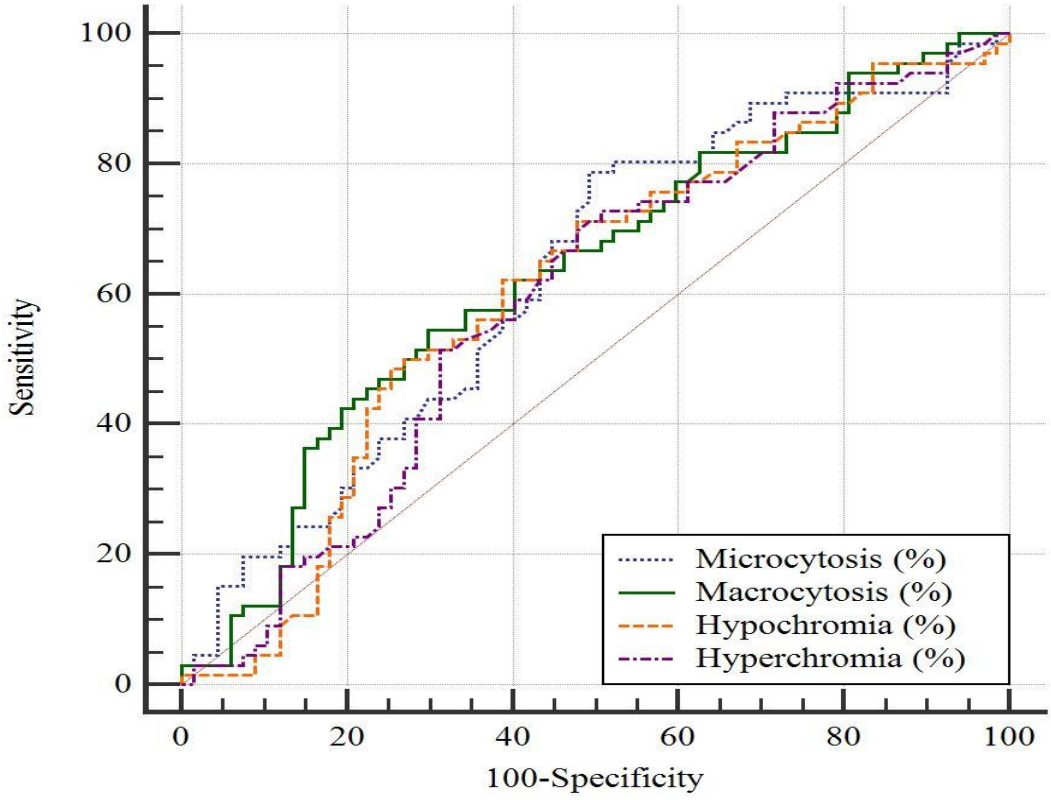

Figure 1: ROC curve analysis for the differentiation of COVID-19 patients from healthy control subjects

When the patients diagnosed with COVID-19 were separated into two groups as cases with and without infiltration on thorax CT, the age (p=0.001), WBC (p=0.043), glucose (p=0.008), urea (p=0.017), creatinine (p=0.010), and CRP (p<0.001) levels were determined to be significantly higher in the patients with infiltration on thorax CT, and the lymphocyte count was significantly lower (p=0.021). No significant difference was determined between the groups in respect of the erythrocyte morphological data (Table 4).

Table 4: Comparisons of the COVID-19 patients with and without infiltration on thorax CT

Thorax CT infiltration	Present	Absent	P
N (F/M)	35 (20/15)	31 (21/10)	0.264
Age (years)	48.00 (41-66)	32.00 (22-51)	0.001
Microcytosis* (%)	1.66 (1.04-2.17)	1.22 (0.88-2.78)	0.492
Macrocytosis *(%)	0.56 (0.29-1.46)	0.78 (0.35-1.71)	0.352
Hypochromia* (%)	0.58 (0.35-1.23)	0.46 (0.34-0.73)	0.225
Hyperchromia* (%)	0.11 (0.05-0.15)	0.12 (0.06-0.19)	0.581
White Blood Cell* (10e3/µL)	6.95 (5.82-9.23)	6.10 (5.05-7.53)	0.043
Neutrophil* (10e3/µL)	3.72 (2.19-4.67)	3.21 (2.05-4.34)	0.240
Lymphocyte* (10e3/µL)	1.36 (0.92-1.61)	1.66 (1.28-1.93)	0.021
Monocyte* (10e3/µL)	0.49 (0.40-0.75)	0.58 (0.46-0.67)	0.329
Hemoglobin* (g/dL)	13.70 (13.00-15.20)	13.90 (12.50-15.50)	0.729
Hematocrit* (%)	42.80 (40.20-46.70)	42.20 (38.50-48.40)	0.817
Mean Corpuscular Volume* (fL)	89.00 (85.80-91.90)	90.60 (86.30-93.80)	0.232
Mean Corpuscular Hemoglobin* (pg)	28.90 (27.90-29.60)	29.40 (28.30-30.50)	0.136
Mean Corpuscular Hemoglobin Concentration* (g/dL)	32.20 (31.80-32.70)	32.40 (32.10-32.90)	0.347
Red Blood Cell Distribution Width	12.80 (12.20-13.50)	12.40 (12.10-13.00)	0.234
Platelet* (10e3/µL)	223.00 (181.00-256.00)	241.00(198.00-275.00)	0.165
Mean Platelet Volume* (fL)	8.16 (7.59-8.91)	8.25 (7.64-8.83)	0.995
Platelet Distribution Width* (fL)	13.50 (13.00-13.80)	13.20 (12.70-13.60)	0.070
Glucose (mg/dl)	100.00 (88.00-120.00)	87.00 (80.00-97.00)	0.008
Urea (mg/dl)	27.82 (21.40-38.52)	23.54 (19.26-27.82)	0.017
Creatine (mg/dl)	0.83 (0.64-0.99)	0.62 (0.54-0.75)	0.010
C-Reactive Protein* (mg/dL)	1.73 (0.82-5.48)	0.60 (0.24-1.00)	0.001

* Median (IQR)

Discussion

The results of this study demonstrated that of the classic hematological parameters, the lymphocyte and platelet counts were significantly reduced in COVID-19-positive patients, and the CRP level was significantly increased. From the erythrocyte morphology findings determined with a new-generation device, the Microcytosis% was determined to be significantly increased in the COVID-19-positive patients, the Macrocytosis% and Hypochromia% were significantly reduced, and there was no significant difference between the patient and control groups in respect of the Hyperchromia%. The Microcytosis % was determined to have 78.79% sensitivity and 50.75% specificity in the differentiation of COVID-19 patients from healthy individuals. No significant difference was determined between the patients with and without infiltration on thorax CT in respect of the erythrocyte morphological findings.

Mean corpuscular volume (MCV) is defined as <80 fL (17). A small size of red blood cells is due to deficient hemoglobin production. The causes of microcytic anemia can be observed in vitamin B6 deficiency and in various diseases, including the absence of iron transmission to the group (iron deficiency anemia), the absence of the synthesis of α-globin or b-globin (thalassemia minor or major), limited iron transmission to the group (liver disease, chronic kidney disease, chronic inflammatory disease, tuberculosis, chronic inflammation) and defects in the synthesis of the hem group (sideroblastic anemias). It is also known that it may be related to race or causes of false positivity (hyponatremia, excessive EDTA) (18-22).

Pulmonary involvement of COVID-19 infection and the change in hematological parameters depends on the interaction between host cell receptors and proteases. The SARS-CoV-2 virus can enter into interaction with different molecules (furins, TMPRSS2, ACE2, cyclophils, hemoglobin) and erythrocyte receptors, and there has also been reported to be interaction with CD147 receptors in erythrocytes (23). Therefore, it has been claimed that COVID-19 could be evaluated as an oxygen deficient blood disease in addition to pneumonia. The SARS-CoV-2 virus binds to cell receptors using proteins and can enter cells by differentiating proteases and polypeptides. A compensatory increase in the number of erythrocyte receptors (CD147) associated with oxygen deficiency can cause more binding of the virus and a greater effect of the erythrocytes. There are

different and complex mechanisms affecting hematological parameters in COVID-19 patients. Impaired iron metabolism can be one type of process affected. There are known to be low hemoglobin levels and pathologically increased ferritin levels showing the presence of anemia in COVID-19 patients (9). The innate immune response can restrict the availability of iron during infections with deprivation from the pathogen, and this is a mechanism which can lead to anemia. Previous studies have reported a prevalence of iron deficiency of up to 59% in patients with heart failure who are not anemic. The iron status, independently of hemoglobin levels, has also been determined to be associated with a decrease in exercise capacity, diminished quality of life and death, and an increased risk of (re-) admission to hospital (24). Hematological abnormalites in COVID-19 patients are generally thought to occur because of iron deficiency, hypoxia, and inflammation.

Berzuini et al. evaluated the erythrocyte morphological appearance of peripheral blood smears of 20 patients with anemia who required blood transfusion, and the blood smears were determinedwith RBC shape abnormality (spherocyte and schistocyte), consistent with hemolytic mechanisms (13). These show that hematological changes in COVID-19 patients are a complex event occurring with the activation of many different mechanisms. The fact that there was no change in the hemoglobin levels in the patient and healthy control groups in the current study, and that there was an increase in the microcytosis level in patients without anemia could probably be due to the onset of a change in erythrocyte morphology because of the cellular response given before anemia develops.

Although the microcytosis level shows an increase in COVID-19 patients, the sensitivity and specificity have been determined to be very low for diagnostic use. In addition, the fact that there was no difference between patients with and without pulmonary infiltration in repect of erythrocyte morphology, suggests that these changes that occur could be related more to receptor interaction than to hypoxia.

Study Limitations

The primary limitation of this study is that it was conducted in a single centre. Another limitation could be said to be that no advanced laboratory tests were made to determine the reasons for the Microcytosis (%), Macrocytosis (%), Hypochromia (%), and Hyperchromia (%) values of the patients determined on new-generation devices. Nevertheless, it can be considered that this preliminary study will be of guidance for future prospective studies.

Conclusion

From the erythrocyte morphological findings determined with the new-generation devices, the Microcytosis percentage was determined to be significantly increased in COVID-19-positive patients, and this parameter was found to have 78.79% sensitivity and 50.75% specificity in the differentiation of COVID-19 patients from healthy individuals.

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***Ethical Approval**: Ethical approval was taken from the Bursa Uludag University, Faculty of Medicine, Clinical Research Ethics Committee (Date 17 August 2020; Number: HRU/20.14.18). We conducted this study according to the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants.*

***Author Contributions:** Concept:İHY. Literature Review:İHY,MY. Design: ESŞ,AÖ. Data acquisition:İHY,AÖ. Analysis and interpretation: MY, ESŞ. Writing manuscript:İHY,MY. Critical revision of manuscript:ESŞ,AÖ.*

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Orgınal Article

Burnout Syndrome in Urology Residents: A Multicenter Survey Study

Üroloji Asistan Doktorlarında Tükenmişlik Sendromu: Çok Merkezli Anket Çalışması

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Highlights

- Burnout syndrome is common among urology residents.
- It is important to investigate the causes of burnout syndrome in order to solve this problem.
- multidisciplinary approach from primary healthcare to occupational healthcare is essential.

Abstract

Background: The aim of this study is to determine the level of burnout syndrome in residents receiving urology training and determine factors that may cause it.
Materials and Methods: A cross-sectional descriptive study. A survey containing questions on sociodemographic characteristics and the Maslach Burnout Inventory were administered to 46 urology residents in different years of residency training at different clinics.
Results: The mean age of the urology residents participating in the study was 29.0±2.1 years. It was determined that most participants had high scores in the Maslach Burnout Inventory subscales. The mean subscales scores of the participants were determined as 24.7±6.3 for emotional exhaustion, 11±3.4 for depersonalization, 19.2±4.1 personal achievement. When the residents' sociodemographic characteristics, such as marital status, year of residency training, smoking status and alcohol consumption habits were separately examined, there was no significant difference in the Maslach Burnout Inventory subscale scores according to these variables (p>0.05). However, the participants who reported that they would not prefer urology again if they were given an opportunity to change their specialty had significantly higher scores in the emotional exhaustion and depersonalization subscales compared to those stated that they would have made the same choice (p=0.001 and p=0.02, respectively).
Conclusion: Burnout syndrome is frequently seen in residents undergoing urology specialty training. There is a need to carefully determine causes of burnout syndrome and establish policies that will increase the motivation of urology residents. It is important to determine how to spot it and take action with a multidisciplinary approach from primary healthcare to occupational healthcare.
Keywords: Burnout Syndrome, Urology, Resident, Primary Healthcare, Occupational Healthcare

ÖZ

Amaç: Bu çalışmada, üroloji alanında uzmanlık eğitimi alan asistan doktorlarda Tükenmişlik Sendromunun düzeyinin belirlenmesi ve buna sebep olabilecek etmenlerin saptanması amaçlandı.**Materyal ve Metot:** Kesitsel tanımlayıcı çalışma. Farklı kliniklerde ve farklı eğitim yıllarında 46 üroloji asistanı çalışmaya katılarak sosyodemografik özellikleri sorgulayan anket ile Maslach Tükenmişlik Ölçeği anketi uygulandı. **Bulgular:** Çalışmaya katılan üroloji asistanlarının yaş ortalaması 29.0±2.1 idi. Maslach Tükenmişlik Ölçeği alt boyutlarında büyük çoğunluğun yüksek puanlar aldığı görüldü. Katılımcıların alt ölçek puan ortalamaları duygusal tükenme için 24.7±6.3, duyarsızlaşma için 11±3.4, kişisel başarı için 19.2±4.1 olarak belirlenmiştir. Asistanların medeni durumu, asistanlık yılı, sigara veya alkol kullanımı gibi sosyodemografik özellikler ayrı ayrı incelendiğinde Maslach Tükenmişlik Ölçeği alt boyutlarında anlamlı farklılık göstermediği izlendi. (p>0.05) Tekrar uzmanlık seçme fırsatı verilse üroloji tercih etmeyeceğini söyleyenlerin yine üroloji tercih edeceğini söyleyenlere göre duygusal tükenme ve duyarsızlaşma skorları istatistiksel olarak anlamlı derecede yüksek saptandı (p=0.001 ve p=0.02).**Sonuç:** Üroloji uzmanlık eğitimi alan asistan doktorlarda Tükenmişlik Sendromu sık olarak görülmektedir. Buna yol açacak nedenlerin dikkatli bir şekilde belirlenmesi ve motivasyonu artıracak stratejilerin uygulanması gerekmektedir. Birinci basamaktan mesleki sağlık hizmetlerine multidisipliner yaklaşımla, bunun nasıl tespit edilip aksiyon alınabileceğinin belirlenmesi önemlidir. **Anahtar Kelimeler:** Tükenmişlik Sendromu, Üroloji, Asistan, Birinci Basamak Sağlık, Mesleki Sağlık Hizmetleri

Introduction

Individuals working in challenging conditions, especially in occupations involving intense human relations may experience work-related burnout at some point in their lives (1). Herbert Freudenberger was first to define the concept of burnout as a pathological picture characterized by emotional and physical exhaustion due to long-term work-related stress (2). The progressive response of the human body to chronic interpersonal stressors leads to work fatigue. Burnout Syndrome generally manifests with emotional exhaustion, reduced personal achievement, physical and emotional exhaustion, and depersonalization (1).

Maslach and Jackson defined Burnout Syndrome with three dimensions. The first dimension, emotional exhaustion, occurs when an individual feels drained to due to the demands of their work and loses the mental energy required to perform work-related tasks (3). In the context of health, when burnout progresses, the healthcare provider begins to see patients as objects rather than people. This second stage can actually be considered as a natural defense mechanism against stress and is called depersonalization. Ineffective coping and defense mechanisms often result in reduced personal achievement (4).

Physicians are at higher risk of burnout than the general population and are more likely to be dissatisfied with their work-life balance. It was reported that almost half of the physicians in the United States had at least one symptom of burnout, and the highest rates of burnout were found among front-line clinicians, such as family physicians and emergency physicians (5). In another study, it has been reported that residents in the surgical specialties leave their professions due to the uncontrollable lifestyle and heavy workload (5,6). Urology residents, on their way to becoming specialists receive extensive training, during which they are expose to a high risk of experiencing burnout syndrome (7,8). Therefore, there is a need to address the problem of work-related burnout among urology residents in order to ensure that patients receive high-quality healthcare services, minimize medical errors, and increase the satisfaction levels of patients and physicians in the field of urology (9). In this study, we aimed to examine burnout syndrome among urology residents from different clinics in different years of residency training.

Materials and Methods

This survey was a cross-sectional descriptive study conducted between March and September 2017 with 46 urology residents receiving residency training in different urology clinics. As data collection tools, a survey on sociodemographic characteristics and the Maslach Burnout Inventory (MBI) were administered via e-mail. The study was approved by the Ethics Committee (BEAH 2019/542) and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was taken from all the participants. Data were based on the responses of the participants to the questions in the survey and items in MBI. In the first part of the survey, sociodemographic and occupational characteristics were evaluated with 21 questions. In the second part, the burnout levels of the residents were determined using the Turkish version of MBI, consisting of 22 Likert-type items and three subscales (emotional exhaustion, depersonalization, and personal achievement) (10). The subscale scores were evaluated as follows: 0-11 points, low; 12-17 points, moderate; and >17 points, high for emotional exhaustion; 0-5 points, low; 6-9 points, moderate; and ≥10 points, high for depersonalization; and 0-21 points, low; 22-25 points, moderate; and ≥26 points, high for personal achievement. As questions addressing the measurement of personal achievement were phrased in a positive manner, high results for EE and DP scores and low ones for PA indicate presence of burnout syndrome.

As the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used. The distribution of variables was determined with the Kolmogorov-Smirnov test. The independent-samples t-test and Mann-Whitney U test were used in the analysis of quantitative independent data. SPSS v. 28.0 software package was used in statistical analyses.

The mean age of the 46 urology residents participating in the study was 29.0 ± 2.1 years. Of the participants, 67.4% (n = 31) were married. The participants were in different years of their five-year urology residency training. Residents doing seven or more monthly shifts constituted 30.4% (n = 14) of the sample. According to the responses of the participants to the survey questions, it was determined that 87% (n = 40) were not satisfied with the work life-social life balance, only three (6.5%) participants could spare sufficient time for their family and friends, and only two (4.3%) had enough personal time. Detailed data on the sociodemographic and professional characteristics of the residents and the distribution of their survey responses are shown in Table-1 and Table-2.

Table 1. Sociodemographic Characteristics and Maslach Burnout Inventory Subscale Scores

Age, Mean ± SD		29.0±2.1
Relationship status, n, (%)	Married	31 (67.4)
	Single, in a relationship	8(17.4)

	Single, not in a relationship	7(15.2)
Residency year, n, (%)	I	7(15.2)
	II	6(13.0)
	III	8(17.4
	IV	13(8.3)
	V	12(26.1)
Number of shifts, n, (%)	≤ 3	11(23.9)
	4-6	21(45.7)
	≥ 7	14(30.4)
Weekend shifts, n, (%)	0	11(23.9)
	I	12(26.1)
	II	18(39.1)
	III	5(10.9)
Weekly working hours, n, (%)	< 60	3(6.5)
	60-80	28(60.9)
	> 80	15(32.6)
Smoking status, n, (%)	Non-smoker	24(52.2)
	Smoker	22(47.8)
Alcohol consumption, n, (%)	Absent	16(34.8)
	Present	30(65.2)
Excess coffee/energy drink consumption, n, (%)	Absent	21(45.7)
	Present	25(54.3)
Total emotional exhaustion score, Mean ± SD		24.7±6.3
Emotional exhaustion score classification, n, (%)	Low	1(2.2)
	Moderate	3(6.5)
	High	42(91.3)
Total depersonalization score, Mean ± SD		11.0±3.4
Depersonalization score classification, n, (%)	Low	2(4.3)
	Moderate	15(32.6)
	High	29(63.0)
Total personal achievement score, Mean ± SD		19.2±4.1
Personal achievement score classification, n, (%)	Low	35(76.1)
	Moderate	8(17.4)
	High	3(86.5)

Table 2. Distribution of Survey Responses

Questions	Answers	n (%)
How many non-medical books do you read in a month?	None/I do not read books	23(50.0)
	Part of a book	14(30.4)
	1 book	6(13.0)
	2 books	2(4.3)
	≥3 books	1(2.2)
Are you satisfied with your work life/social life balance?	Dissatisfied	40(87.0)
	Satisfied	4(8.7)
	Undecided	2(4.3)
Do you have enough time to spend with family/friends?	No	43(93.5)
	Yes	3(6.5)
Do you meditate?	No	43(93.5)
	Yes	3(6.5)

Do you watch TV/films to relax?	No	7(5.2)
	Yes	39(84.8)
Do you think you have enough time for yourself?	No	44(95.7)
	Yes	2(4.3)
Do you exercise/do yoga?	No	35(76.1)
	Yes	11(23.9)
Are you currently using antidepressants?	No	40(87.0)
	Yes	6(13.0)
Did Have you ever used antidepressants during your urology residency training?	No	28(60.9)
	Yes	18(39.1)
Do you think you are receiving good training in the clinic where you work?	No	29(63.0)
	Yes	17(37.0)
What specialty would you chose if you took the medical specialty test again?	I would choose urology again	24(52.2)
	I would choose another specialty	4(8.7)
	I would not choose a surgical branch	12(26.1)
	I would choose to work as a general practitioner	6(13.0)

Table-1 presents the distribution of the participants' scores in the subscales of MBI. The mean subscales scores of the participants were determined as 24.7 ± 6.3 for emotional exhaustion, 11 ± 3.4 for depersonalization, 19.2 ± 4.1 personal achievement.

Table-3 and Table-4 show the distribution of the participants' scores in the MBI subscales according to their sociodemographic and occupational characteristics. The results revealed that the emotional exhaustion, depersonalization, and personal achievement scores did not show statistically significant differences according to the participants' marital status, whether they were within the first three or last two years of the residency training, and smoking status or alcohol use ($p > 0.05$). The emotional exhaustion scores of the residents that did more than three shifts per month and those that worked weekends were found to be higher, but it was not statistically significant ($p = 0.51$ and $p = 0.24$, respectively). When weekly working hours, reading non-medical books, engaging in exercise/yoga, and antidepressant use were evaluated separately, the emotional exhaustion, depersonalization, and personal achievement scores did not significantly differ ($p > 0.05$). However, the participants who reported that they would not choose urology again if they could change their specialty had significantly higher scores in the emotional exhaustion and depersonalization subscales compared to those stated that they would have made the same choice ($p = 0.001$ and $p = 0.02$, respectively).

Table 3. Comparison of Maslach Burnout Inventory Subscale Scores According to Sociodemographic Characteristics

		Emotional exhaustion (Mean ± SD)	p		Depersonalization (Mean ± SD)	p		Personal achievement (Mean ±SD)	p	
Marital status	Married	24.3±6.4	0.460	t	10.9±3.4	0.833	t	19.8±3.1	0.415	m
	Single	25.7±6.0			11.1±3.5			17.8±5.5		
Residency year	≤3	25.3±5.5	0.561	t	11.0±4.1	0.901	t	18.5±4.1	0.322	m
	4-5	24.2±6.9			10.9±2.9			19.8±4.1		

Smoking status	Non-smoker	25.1±4.6	0.702	t	11.5±3.1	0.247	t	18.9±4.3	0.877	m
	Smoker	24.4±7.8			10.4±3.7			19.5±4.0		
Alcohol use	Absent	24.6±5.4	0.929	t	10.2±3.5	0.256	t	19.3±4.3	0.963	m
	Present	24.8±6.8			11.4±3.4			19.1±4.1		
Excess coffee/energy drink consumption	Absent	24.5±4.9	0.798	t	10.6±3.4	0.519	t	19.1±3.9	0.633	m
	Present	25.0±7.3			11.3±3.5			19.2±4.3		

[t]Independent-samples t-test, [m]Mann-Whitney U test SD: standard deviation

Table 4. Comparison of Maslach Burnout Inventory Subscale Scores According to Occupational and Individual Characteristics

		Emotional exhaustion (Mean ± SD)	p		Depersonalization (Mean ± SD)	p		Personal achievement (Mean ± SD)	p	
Number of shifts	≤ 3	23.6±9.2	0.510	t	10.8±2.2	0.861	t	20.0±3.5	0.475	m
	> 3	25.1±5.1			11.0±3.7			18.9±4.3		
Weekend shifts	Absent	22.8±9.2	0.248	t	10.2±2.5	0.381	t	19.6±3.6	0.907	m
	Present	25.3±5.1			11.2±3.6			19.0±4.3		
Weekly working hours	≤60	28.7±6.7	0.266	t	10.0±1.7	0.613	t	19.0±1.7	0.929	m
	>60	24.5±6.2			11.0±3.5			19.2±4.2		
Reading non-medical books	No	26.5±5.8	0.053	t	10.5±3.6	0.371	t	19.1±4.1	0.587	m
	Yes	23.0±6.4			11.4±3.3			19.3±4.2		
Doing exercise/yoga	No	24.9±6.8	0.781	t	10.9±3.7	0.673	t	19.5±3.8	0.687	m
	Yes	24.3±4.4			11.4±2.3			18.2±5.0		
Current antidepressant use	No	24.7±6.5	0.860	t	10.9±3.6	0.788	t	19.5±3.5	0.316	m
	Yes	25.2±4.5			11.3±2.5			17.2±7.3		
	No	23.4±6.5	0.061	t	10.6±3.6	0.319	t	19.4±3.9	0.803	m

Antidepressant use at any time during residency	Yes	26.9±5.3			11.6±3.0			18.8±4.5		
Reporting receiving good residency training	No	25.2±6.4	0.484	t	11.6±3.4	0.096	t	18.3±4.1	0.121	m
	Yes	23.9±6.1			9.9±3.3			20.6±3.8		
Would choose urology specialty again?										
Yes		21.8±6.1	***0.000***	t	9.9±3.3	***0.026***	t	20.3±3.8	0.187	m
No		28.0±4.7			12.1±3.2			18.0±4.1		

[t]Independent-samples t-test, [m]Mann-Whitney U test SD: standard deviation

Discussion

Specialty training is an important period in which resident doctors acquire the knowledge and experience over many years to conduct their profession in the branch they have chosen. In addition, during this period, residents serve as an important workforce asset in hospitals where they receive training. Physical and emotional exhaustion is very common among resident physicians due to the intensity of training, high number of shifts, high demand in clinics, and heavy workload (8). The regulation of working conditions can have a positive or negative impact on physicians' own health, which can, in turn, affect their working lives and quality of work production in the same direction.

Lack of personal achievement is described as individuals considering themselves inadequate and unsuccessful whilst performing their job. At the beginning of their careers, people believe that they will gain accomplishments regarded significant professionally and socially. When their expectations are not met, the case of viewing themselves as incompetent and becoming unable to overcome problems occurs (11) . It is argued that the most important sub-dimension of burnout is 'emotional exhaustion', accompanied by the dimensions of depersonalization and lack of personal achievement. In the later stages of the burnout syndrome, the individual who defines himself as unsuccessful starts to think that he cannot progress, even regresses, despite the positive results he has achieved in his job, thinking that it is unnecessary to make an effort, that he is an inadequate individual, and enters the process of frustration (12). When the results obtained from our study were evaluated, it was determined that the participating urology residents scored high in emotional exhaustion and depersonalization, and low in personal achievement according to MBI, indicating that they were experiencing burnout syndrome.

Ocak et al. reported that gender, educational background, and history of COVID-19 infection might have an impact on burnout. They also observed that history of COVID-19 and gender are independent predictors of emotional exhaustion (13). Working conditions are among the most important factors leading to burnout syndrome among physicians. These working conditions are determined by the workload, working hours, number of shifts, and number of patients seen (14). In a meta-analysis published in recent years, young age, female gender, negativity in marital status, and heavy workload were determined as sociodemographic risk factors in burnout syndrome (15). Dündar et al. detected a high rate of burnout syndrome in resident doctors. When the authors examined possible effective factors, they found no significant difference in terms of gender, marital status, and drug use but reported that burnout scores were significantly higher in residents working in surgical branches and those that had not chosen medicine voluntarily (16). Similarly, in another study, it was stated that burnout syndrome was more common in surgical departments where working conditions are relatively more challenging and working hours are longer (8). Soler et al. also showed the association of smoking and alcohol use with burnout syndrome (17). However, in the current study, there was no statistically significant relationship between smoking and alcohol use.

While the workload and number of shifts in the residency process are generally higher in the first years of training, they gradually decrease in the last years. In a study conducted with anesthesia residents, Turgut et al. reported that the scores of the second-year residents in the emotional exhaustion and depersonalization subscales of MBI were significantly higher compared to the third- and fourth-year residents (18). In contrast, in our study, no statistically significant difference was found between the residents in their first three and last two years of training in relation to the MBI subscale scores. This may be due to the negativities resulting from the high

workload and number of shifts, as well as increased concerns about the future that has become more prominent in recent years and feeling inadequate in the profession in the early years of residency training.
Resignation during the residency process have certain negative consequences, such as lost time during training, loss of workforce due to resignation, and insufficient number of remaining resident physicians (19). In a study by Yaşayancan et al., a high rate (58%) of research assistants receiving specialty training in surgical branches considered resignation, despite 92% had chosen their branch voluntarily (20). In the current study, almost half the participants stated that they would not have chosen the same specialty if they had been given another choice, and this group had significantly higher scores in emotional exhaustion and depersonalization.
On the completion of this survey study, we determined that the majority of urology residents were not satisfied with their work-social life balance. In addition, only 4% of the participants considered that they could allocate sufficient time to their personal lives. The rate of antidepressant use during residency was determined as 39%. We consider that these findings are important signs indicating that burnout syndrome is very common among urology residents. The rate of participants who stated that they were receiving good training in the clinic at which they worked was 37%. We consider that the urology specialty training entails an intense and tiring process. In addition, it is important to examine and remedy sociodemographic and personal factors that cause burnout syndrome in urology residents, as well as other factors that may be present within the clinic and in the training process.
In the literature, the relationship between the amount of salary received and burnout syndrome has also been examined (21). However, since all the participants in the current study were urology residents and their salary levels were similar to each other, we were not able to evaluate salary as a variable.

Study Limitation

Our study has several limitations, including the small number of participants and absence of detailed evaluation of other factors that may be effective in the training process, e.g., number of patients encountered, and surgical operations attended. Since the general health status of residents was evaluated before they started their residency training in the Turkish health system, it was accepted that the individuals participating in the survey would not have psychiatric disorders; however, as a limitation of our study, some participants with undiognosed mild or moderate depression might have participation in the survey. In addition, in Turkiye, the number of female urology assistant physicians is still very low, although it is gradually increasing. Since all the urology residents participating in our survey were male, we were not able to evaluate the effect of gender on burnout syndrome.

Conclusion

The majority of urology residents experience Burnout Syndrome. This can result in poor patient care and major medical errors. Although differences in sociodemographic and personal factors have some effects on this situation, it is important to make changes to increase professional motivation in the prevention of burnout syndrome, make health policy decisions by taking into account the training and health of residents that will become specialist doctors of the future, and conduct further research in this area. Healthcare professionals should be aware of the risks. A multidisciplinary approach is required in its management from primary health care to occupational health care.

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Orginal Article

Relationship of Humerus Retroversion Angle with Morphometric Parameters

Humerus Retroversiyon Açısının Kemik Parametreleri ile İlişkisi

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Highlights

-Anthropometric measurements are very important clinically.

-In addition, the importance of anthropometric and morphometric measurements to be made, especially in forensic medicine cases, in age and/or gender determination becomes apparent.

-At this point, it is important to carry out anatomical and clinical studies together.

Abstract

Background: This study aims to perform an analysis of the morphometric anatomical measurements of the humerus to make clinically successful evaluations. **Material and Method:** A total of 42 dry bone humerus were included in the study. Measurement parameters: Length of the humerus (LH), circumference of the surgical neck (CSN), width of the intertubercular sulcus (WIS), depth of the intertubercular sulcus (DIS), width of the epicondyle (WE), width of the trochlea humeri (WTH), length of the trochlea of humerus (LTH), width of the olecranon fossa (WOF), depth of the olecranon fossa (DOF), height of the olecranon fossa (HOF), transvers diameter of the head of humerus (TDH), vertical diameter of the head of humerus (VDH), minimum diameter of the shaft of humerus (Min-DS), maximum diameter of the shaft of humerus (Max-DS), width of the capitulum of humerus (WC), length of the capitulum of humerus (LC), the height of the coronoideal arch (HCA), the width of the coronoideal arch (WCA), the retroversion angle of the humerus (RAH) were determined. **Results:** According to the study results, mean and standard deviation values, LH; 300, CSN; 72±8.7, WIS; 8.2±1.6, DIS; 5.7±0.9, WE; 59, WTH; 15.6±4.4, WOF; 22.7±2.2, DOF; 13.4±2.1, TDH; 42.5±2.8, VDH; 44.8±3.5, Min-DS; 18.7±1.8, Max-DS ; 21.8±2.1, WS; 16.2±4.1, LC; 20.6±1.7, LTH; 20.7±4.4, HCA; 6.3, WCA; 11, HOF; 13.4±2.2, RAH; 28.2.
Conclusion: It is very important to calculate the average values of the anatomical structures in this bone to know the humerus bone's normal anatomical structure and to guide the surgical procedures in this region.
Keywords: Humerus, morphometry, retroversion angle.

Öz

Amaç: Bu çalışmanın amacı, klinik açıdan başarılı yönlendirmeler yapılabilmesi için humerus'un morfometrik anatomik ölçümlerinin analizinin yapılmasıdır. **Materyal ve Metod:** Çalışmaya yaşı, cinsiyeti ve kimliği bilinmeyen toplam 42 adet kuru kemik humerus dahil edilmiştir. Ölçüm parametreleri: Humerus uzunluğu (HU), cerrahi boyun çevresi (CBÇ), sulcus intertubercularis genişliği (SIG), sulcus intertubercularis derinliği (SID), epicondyler genişlik (EG), trochlea humeri genişliği (THG), fossa olecranii genişliği (FOG), fossa olecranii derinliği (FOD), humerus başının transvers çapı (HBTÇ), humerus başının vertikal çapı (HBVÇ), minimum corpus çapı (MinCÇ), maximum corpus çapı (MaxCÇ), capitulum humeri genişliği (CHG), capitulum humeri uzunluğu (CHU), trochlea humeri uzunluğu (THU), coronoideal ark yüksekliği (CAY), coronoideal ark genişliği (CAG), fossa olecranii yüksekliği (FOY), humerus retroversiyon açısı (HRA) olarak belirlenmiştir. **Bulgular:** Çalışma sonuçlarına göre ortalama ve standart sapma veya median değerleri, HU; 300, CBÇ; 72±8,7, SIG; 8,2±1,6, SID; 5,7±0,9, EG; 59, THG ; 15,6±4,4, FOG; 22,7±2,2, FOD; 13,4±2,1, HBTÇ; 42,5±2,8, HBVÇ; 44,8±3,5, MinCÇ; 18,7±1,8, MaxCÇ ; 21,8±2,1, CHG; 16,2±4,1, CHU; 20,6±1,7, THU; 20,7±4,4, CAY; 6,3, CAG; 11, FOY; 13,4±2,2, HRA; 28,2 olarak bulunmuştur. **Sonuç:** Humerus kemiğinin normal anatomik yapısını bilmek ve bu bölgedeki cerrahi prosedürleri yönlendirmek için bu kemikteki anatomik yapıların ortalama değerlerini hesaplamak çok önemlidir.
Anahtar kelimeler: Humerus, morfometri, retroversiyon açısı.

Introduction

Humerus is the longest and thickest bone of the upper extremity and it is the only bone that makes up the arm skeleton (1). Humerus has a total of eight ossification centres, one from the corpus, one from the caput, one from the capitulum, one from the trochlea, two from the tubercle and two from the epicondyle (2). Humerus is also of great importance since it is formed by the combination of more than one joints, it has the widest range of motion in the human body and it participates in the formation of shoulder complex which enables hand movements to be made in a functional way (3). The shoulder, which has the ability of approximately 170° elevation, 60° extension and 120-180° rotation, provides this range of motion from medial to lateral through sternoclavicular, acromioclavicular, glenohumeral and scapulothoracic joints and subacromial region, respectively (4). On the other hand, elbow joint is a hinge and synovial joint formed by the combination of humero-radial, humero-ulnar and proximal radio-ulnar joints and elbow joints allow one of the two bones to move independently, thanks to the articulation of the humerus with the radius and ulna (5). Proximal humerus fractures constitute 4-5% of all fractures and this rate increases with advancing age and takes its place in the most common fracture group after wrist and femur fractures (1). The most common clinical presentation in proximal humerus fractures is surgical neck fractures. Half of the fractures are treated surgically. Fractures of the distal region of the humerus constitute 5% of all fractures and 30% of elbow region fractures (6). In addition, radial nerve and profunda brachii artery may be damaged in shaft of humerus fractures, while ulnar nerve may be damaged in epiconylus medialis fractures. The angle between the axis passing through the proximal articular surface of the humerus and the axis passing through the distal articular surface is defined as the retroversion angle. This angle is approximately between 10-40° in adults. In new-borns, this angle is greater and decreases with age (6). This angle differs among societies and individuals (7). Existing literature data show the importance of examining the morphometry of the humerus in detail. Therefore, the aim of the present study is to perform morphometric analyses of the bone and to calculate the retroversion angle, based on the clinical importance of the humerus. It is thought that the analysis results of the parameters determined in the study will add clinical depth to pathological conditions such as glenohumeral arthrodesis, internal fixation, fracture stabilization, lateral and medial epicondylitis, cubital tunnel syndrome in more accurate analysis of shoulder and elbow anomalies and fractures.

Material and Method

The study was initiated with the 2022/56 decision numbered ethics committee approval of Clinical Research Ethics Committee. The study was carried out on 42 (23 left, 19 right) dry humerus bones of unknown age and sex from the bone collection Bolu Abant İzzet Baysal University Anatomy Department. The length of the humerus (LH), the circumference of the surgical neck (CSN), the width of the intertubercular sulcus (WIS), the depth of the intertubercular sulcus (DIS), the width of the epicondyle (WE), the width of the trochlea humeri (WTH), the length of the trochlea of humerus (LTH), the width of the olecranon fossa (WOF), the depth of the olecranon fossa (DOF), the height of the olecranon fossa (HOF), the transvers diameter of the head of humerus (TDH), the vertical diameter of the head of humerus (VDH), minimum diameter of the shaft of humerus (Min-DS), maximum diameter of the shaft of humerus (Max-DS), the width of the capitulum of humerus (WC), the length of the capitulum of humerus (LC), the height of the coronoideal arch (HCA), the width of the coronoideal arch (WCA) and the retroversion angle of the humerus (RAH) were measured by placing on an osteometric board by using a digital calliper. Retroversion angle measurement design: the bones were photographed from a distance of 100 cm under artificial light with the help of osteometric board. Photography system was set up by fixing the camera at a distance of 100 cm with an adjustable tripod. Shots were taken with digital SLR (Canon EOS 80D; ISO 100 f/4.5) camera. The photos taken were transferred to ImageJ (version 153e) program, reference points were determined and measurements were made.

Determined parameters:

1- The length of the humerus (LH): The distance between the most proximal end of the humerus and the most distal end of the trochlea humeri.
2- The circumference of the surgical neck (CSN): Surgical neck circumference was measured as in Figure 1.
3- The width of the intertubercular sulcus (WIS): The transverse length between tuberculum majus and tuberculum minus.
4- The depth of the intertubercular sulcus (DIS): Depth of groove between tuberculum majus and tuberculum minus.
5- The width of the epicondyle (WE): The distance between the most medial end of the epicondylus medialis and the most lateral end of the epicondylus lateralis.

6- The width of the trochlea humeri (WTH): The distance between the most lateral and most medial of the trochlea humeri.
7- The length of the trochlea of humerus (LTH): The distance between the most proximal and most distal of the trochlea humeri.
8- The width of the olecranon fossa (WOF): The widest distance of olecranon fossa parallel to the epicondylar line.
9- The depth of the olecranon fossa (DOF): The distance from the deepest part of the olecranon fossa to the epicondylar line.
10- The height of the olecranon fossa (HOF): The longest distance between the most proximal and the most distal of the olecranon fossa.
11- The transvers diameter of the head of humerus (TDH): The distance between the most lateral and the most medial articular surfaces of the caput humeri.
12- The vertical diameter of the head of humerus (VDH): The distance between the most proximal and the most distal articular surfaces of the caput humeri.
13- Minimum diameter of the shaft of humerus (Min-DS): The shortest distance of the corpus humeri.
14- Maximum diameter of the shaft of humerus (Max-DS): The longest distance of the corpus humeri.
15- The width of the capitulum of humerus (WC): The distance between the most lateral and most medial of the capitulum humeri.
16- The length of the capitulum of humerus (LC): The distance between the most proximal and the most distal of the capitulum humeri.
17- The height of the coronoideal arch (HCA): The distance between the most proximal and the most distal of the coronoideal arch.
18- The width of the coronoideal arch (WCA): The distance between the most lateral and most medial of the coronoideal arch.
19- The retroversion angle of the humerus (RAH): The angle between the axis passing through the articular surface located proximal to the humerus and the axis passing through the articular surface located distal to the humerus.

Statistical Analyses

After the parameters were measured, statistical analyses were made with Minitab® 21.2 (64-bit) program. Whether the parameters measured showed a normal distribution was determined with Anderson Darling test. Minimum, maximum and median values were included for parameters which were not normally distributed, while mean and standard deviation values were included for parameters which were normally distributed. Two simple t-test was applied to parameters with normal distribution, while Mann Whitney U test was applied to parameters which did not show normal distribution. The correlation between parameters was found with Pearson correlation test.

Results

Table 1 and Table 2 show the descriptive statistics in the study. WIS, DIS and WC parameters were found to be statistically significant as a result of the analysis conducted. Table 2 shows the correlation coefficients between the parameters. As a result of Pearson correlation test, positive strong correlation was found between WTH-CSN, VDH-CSN, LTH-CSN, HOF-WTH, HOF-LTH, WTH-LH. Negative correlation was found between RAH and LH, DIS, WE, TDH, VDH, LH, HCA, WCA, HOF; while positive weak correlation was found between CSN, WIS, WTH, WOF, DOF, Min-DS, Max-DS, WC, LC.

Table 1. Minimum, maximum, median, mean, standard deviation and p values of the parameters (*).

	Mean±Std / Median		**Minimum**		**Maximum**		**P**
	R	L	R	L	R	L	R
LH	300	300	250	255	340	350	0.667
CSN	72±8.8	72.1±8.8	-	-	-	-	0.950
WIS	7.5±0.2	8.8±0.3	-	-	-	-	0.004
DIS	6.0±0.1	5.4±0.2	-	-	-	-	0.027

WE	59.0	59.0	45.9	46.2	63.9	73.1	0.723
WTH	14.7±0.9	16.4±0.9	-	-	-	-	0.216
LTH	20.1±4.1	21.2±4.7	-	-	-	-	0.411
WOF	22.7 ± 2.1	22.7 ± 2.4	-	-	-	-	0.928
DOF	12.9 ± 1.9	13.9±2.3	-	-	-	-	0.155
HOF	13.8 ± 2.2	13.0±2.3					0.228
TDH	42.1±2.3	43.0 ± 3.2	-	-	-	-	0.303
VDH	44.5 ± 2.9	45.1 ± 3.9	-	-	-	-	0.538
Min-DS	19.0 ± 1.8	18.5 ± 1.7	-	-	-	-	0.449
Max-DS	22.3 ± 1.9	21.3 ± 2.2	-	-	-	-	0.142
WC	15.7 ± 1.3	16.6 ± 1.4	-	-	-	-	0.033
LC	20.3 ± 1.0	20.8 ± 2.2	-	-	-	-	0.376
HCA	6.8	5.9	4.2	4.1	10.8	11.7	0.312
WCA	11.3	11.0	7.6	6.8	15.3	17.9	0.079
RAH	28.2	28.2	20.6	23.2	34.8	35.2	0.448

Abbreviations:(*)The length of the humerus (LH), the circumference of the surgical neck (CSN), the width of the intertubercular sulcus (WIS), the depth of the intertubercular sulcus (DIS), the width of the epicondyle (WE), the width of the trochlea humeri (WTH), the length of the trochlea of humerus (LTH), the width of the olecranon fossa (WOF), the depth of the olecranon fossa (DOF), the height of the olecranon fossa (HOF), the transvers diameter of the head of humerus (TDH), the vertical diameter of the head of humerus (VDH), minimum diameter of the shaft of humerus (Min-DS), maximum diameter of the shaft of humerus (Max-DS), the width of the capitulum of humerus (WC), the length of the capitulum of humerus (LC), the height of the coronoideal arch (HCA), the width of the coronoideal arch (WCA), the retroversion angle of the humerus (RAH), right (R), left (L) .

Table 2. Pearson correlation test results (*)

	LH	CSN	WIS	DIS	WE	WTH	WOF	DOF	TDH	VDH
CSN	0.143									
WIS	0.139	0.278								
DIS	0.191	0.357	0.067							
WE	0.413	0.166	0.215	0.027						
WTH	0.042	0.699	0.348	0.233	0.042					
WOF	0.351	0.012	0.283	-0.003	0.526	-0.028				
DOF	0.282	0.391	0.514	-0.040	0.156	0.299	0.362			
TDH	0.571	0.493	0.300	0.093	0.534	0.310	0.397	0.417		
VDH	0.590	0.678	0.421	0.335	0.355	0.504	0.286	0.518	0.713	
Min-DS	0.432	0.246	0.239	0.158	0.542	0.082	0.450	0.320	0.390	0.312
Max-DS	0.427	0.128	0.124	0.181	0.529	-0.081	0.426	0.266	0.346	0.224
WC	0.454	0.398	0.350	0.017	0.510	0.401	0.240	0.471	0.576	0.541
LC	0.197	0.066	0.295	-0.028	0.039	0.173	0.027	0.258	0.064	0.178
LTH	0.137	0.671	0.284	0.292	0.033	0.813	-0.061	0.321	0.404	0.566
HCA	0.139	-0.453	-0.178	-0.076	0.222	-0.696	0.375	-0.072	-0.067	-0.260
WCA	0.406	-0.270	-0.036	-0.024	0.544	-0.274	0.392	-0.078	0.069	0.083
HOF	0.339	-0.434	-0.125	-0.228	0.285	-0.617	0.453	0.093	0.083	-0.124
RAH	-0.159	0.192	0.288	-0.058	-0.067	0.049	0.098	0.254	-0.006	-0.093

	Min-DS	Max-DS	WC	LC	LTH	HCA	WCA	HOF
CSN								
WGI								
DGI								
WE								
WTH								
WOF								
DOF								
TDH								
VDH								
Min-DS								
Max-DS	0.836							
WC	0.336	0.272						
LC	0.027	0.084	0.352					
LTH	-0.025	-0.175	0.403	0.163				
HCA	0.232	0.371	-0.159	-0.195	-0.765			
WCA	0.399	0.460	-0.027	0.052	-0.424	0.393		
HOF	0.378	0.472	0.025	0.030	-0.668	0.743	0.523	
RAH	0.155	0.095	0.109	0.069	-0.035	-0.038	-0.324	-0.053

Abbreviations: (*)The length of the humerus (LH), the circumference of the surgical neck (CSN), the width of the intertubercular sulcus (WIS), the depth of the intertubercular sulcus (DIS), the width of the epicondyle (WE), the width of the trochlea humeri (WTH), the length of the trochlea of humerus (LTH), the width of the olecranon fossa (WOF), the depth of the olecranon fossa (DOF), the height of the olecranon fossa (HOF), the transvers diameter of the head of humerus (TDH), the vertical diameter of the head of humerus (VDH), minimum diameter of the shaft of humerus (Min-DS), maximum diameter of the shaft of humerus (Max-DS), the width of the capitulum of humerus (WC), the length of the capitulum of humerus (LC), the height of the coronoideal arch (HCA), the width of the coronoideal arch (WCA), the retroversion angle of the humerus (RAH).

Table 3. Comparison of literature data. HRA is measured in degrees, other values in millimeters. Right and left side values are written respectively (*)

	Akman et al, TR (17)	Desai et al., IND (13)	Niraj et al. SA (18)	Patil et al., IND (19)	Sinha et al. IND (12)	Andrin et al., F (15)	Goldberg et al, US(16)	Yılmaz, TR (1)	Kastamoni, TR (6)	Tellioğlu et al. TR (2)	This study, TR
N	120	90	200	250	49	70	1104	80	54	104	42
LH	307.1±20.8 307.8±18.9	292.3±22.9 289.4±21.8	308.5±19.1 307.2±16.1	311±3 303±5	290.17±18.67 283.36±22.80	-	-	298.5±3.08 311.6±2.44	320.04±30.44 307.13±28.15	292 (F) 313 (M)	300 300
TDH	-	-	-	-	-	-	-	-	-	37.0 (F) 41.9(M)	42.1±2.3 43.0±3.2
VDH	-	-	-	-	-	-	-	-	-	40.5±2.6 (F) 45.8±2.0 (M)	44.5±2.9 45.1±3.9
RAH	-	-	23.16 26.6	-	-	37	35±7	-	36.44±4.97 31.34±5.51	-	28.2 28.2
DIS	-	-	-	-	-	-	-	3.79±0.64 3.96±1.09	3.08±0.95 3.51±0.85	4.3±0.7 (F) 4.7±0.6 (M)	6.0±0.1 5.4±0.2
WIS	-	6.9±1.2 7.1±1.1	-	-	-	-	-	6.72±0.64 6.52±1	7.79±0.77 7.34±0.65	10.01±0.5 (F) 10.6±0.9 (M)	7.5±0.2 8.8±0.3
WE	-	-	-	-	57.64±5.33 56.11±5.41	-	-	58.21±5.24 57.07±4.78	57.44±4.87 56.18±4.86	54.7±3.5 (F) 61.3±3.4 (M)	59.0 59.0
Min-DS	-	-	-	-	-	-	-	-	-	15.8(F) 19.2 (M)	19.0±1.8 18.5±1.7
Max - DS	-	-	-	-	-	-	-	-	-	19.3(F) 21.8 (M)	22.3±1.9 21.3±2.2
WC	-	-	-	-	-	-	-	-	-	16.1(F) 18.3 (M)	15.7±1.3 16.6±1.4

LC	-	-	-	-	-	-	-	-	-	20.0(F) 22.2 (M)	20.3±1.0 20.8±2.2
WTH	-	-	-	-	-	-	-	-	35.91±5.24 35.31±5.42	22.7±1.5 (F) 22.9±1.3 (M)	14.7±0.9 16.4±0.9
LTH	-	-	-	-	-	-	-	-	-	23.4 (F) 25.5 (M)	20.1±4.1 21.2±4.7
WOF	-	21.2±1.8 20.7±2.1	-	-	-	-	-	-	22.32±2.34 22.34±2.95	-	22.7±2.1 22.7±2.4
DOF	-	-	-	-	-	-	-	5.34±0.97 5.35±1.05	6.86±1.4 6.65±1.3	-	12.9±1.9 13.9±2.3
CSN	-	-	-	-	-	-	-	-	75.3±9.5 75.5±8.6	91 (F) 92(M)	72±8.8 72±8.8

Abbreviations: (*)The length of the humerus (LH), the circumference of the surgical neck (CSN), the width of the intertubercular sulcus (WIS), the depth of the intertubercular sulcus (DIS), the width of the epicondyle (WE), the width of the trochlea humeri (WTH), the length of the trochlea of humerus (LTH), the width of the olecranon fossa (WOF), the depth of the olecranon fossa (DOF), the height of the olecranon fossa (HOF), the transvers diameter of the head of humerus (TDH), the vertical diameter of the head of humerus (VDH), minimum diameter of the shaft of humerus (Min-DS), maximum diameter of the shaft of humerus (Max-DS), the width of the capitulum of humerus (WC), the length of the capitulum of humerus (LC), the height of the coronoideal arch (HCA), the width of the coronoideal arch (WCA), the retroversion angle of the humerus (RAH), female (F), male (M), United State (US), France (F), Turkey (TR), India (IND), South Asia (SA).

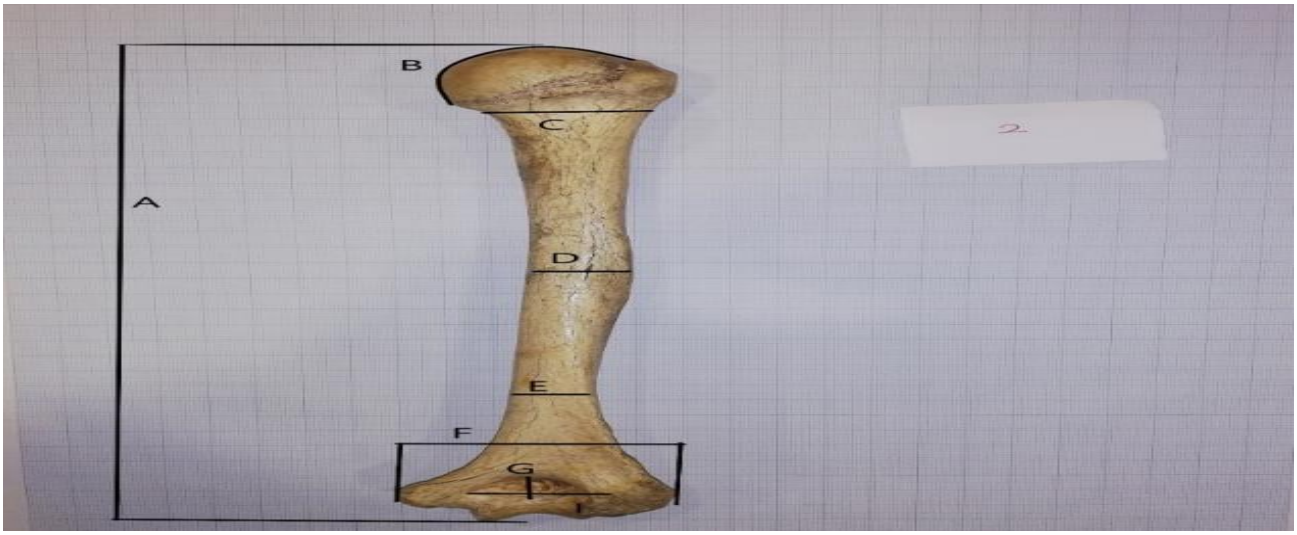

Figure 1. A: The humeral length, **B:** The vertical diameter of the head of humerus, **C:** The circumference of the surgical neck, **D:** The maximum diameter of the shaft of humerus, **E:** The minimum diameter of the shaft of humerus, **F:** The width of the epicondyle, **G:** The height of the olecranon fossa, **I:** The width of the olecranon fossa.

Figure 2. A: The height of the coronoideal arch, **B:** The width of the coronoideal arch, **C:** The length of the capitulum of humerus, **D:** The width of the capitulum of humerus, **E:** The length of the trochlea of humerus, **F**: The depth of the olecranon fossa, **G:** The depth of the intertubercular sulcus.

Discussion

Mobility and stability of shoulder depend on the amount of humeral retroversion (8–10). Retroversion movement also affects glenohumeral joint mechanism. Pain and pathologies in this region are among the most common symptoms in musculoskeletal system (11). Therefore, evaluation of the parameters of the humerus and especially retroversion angle is of great importance. When the literature is reviewed, the highest and the lowest HL values were measured in Turkish and Indian populations, respectively (6,12). While the data were 320.04±30.44 and 307.13±28.15 on the right and left, respectively in a study conducted on 54 dry bones in Turkey, they were 290.17±18.67 and 283.36±22.80 in a study conducted on 49 dry bones in India (6,12). In the present study, which was designed to make a detailed morphometric evaluation, a total of 19 different measurements were made, two on the humeral shaft, seven on the proximal end and ten on the distal end. LH value in the study was found as 300 on the right and on the left **(Table 1).** The study result is within the limits of literature data. The number of studies examining TDH and VDH is limited in literature **(Table 3).** In a study examining gender differences through humerus in Turkish population, TDH values were found as 37.0, 41.9 and VDH values were found as 40.5±2.6, 45.8±2.0 in women and men, respectively (2). The data obtained in this study were examined as right and left and they were found to be higher when compared with the literature. Since not knowing the gender of bones in the collection which were used as material in the study makes the validation of the data impossible, it seems to be a disadvantage. When DIS and WIS parameters were examined, the lowest DIS values were in a study conducted in 2021 as 3.08±0.95 and 3.51±0.85, respectively on the right and left (6). Similarly, in a study conducted in 2020, the lowest DIS values were found as 6.72±0.64 and 6.52±1, respectively on the right and left (1). The highest WIS values were found as 10.01±0.5 and 10.6±0.9, respectively for women and men in a study examining the differences between genders (2). When the literature is reviewed, as stated in Table 3, the highest DIS value is the data obtained in the present study (**Table 3).** WIS, WOF and LC values of the study are in parallel with the literature (2,6,13). In addition, although the results in literature for WE, Min-DS, Max-DS, DOF values were found to be close, the highest numerical values seem to be data obtained in the present study (1,2,6,12). On the other hand, when the literature was reviewed for CSN, WTH and LTH, the lowest numerical values were found to be in the present study (2,6). In a study conducted, it was stated that the changes in retroversion angle in the functional treatment of humeral fractures could easily be tolerated by patients as long as retroversion angle was within appropriate limits (14). When the results of this study were compared with HRA values in literature, although they were close to the results in a study conducted in South Asian population, they were found to be numerically lower than the studies conducted in France and America **(Table 3).** When the WTH-CSN, VDH-CSN, LTH-CSN, HOF-WTH, HOF-LTH, WTH-LH parameters, which have a strong positive correlation, are evaluated **(Table 2)**, the increase in the variables will provide valuable data in clinical prosthesis designs or in cases where identification is required in the field of forensic medicine (16, 20). It was also stated in a study conducted in 2022 that not only morphometric differences should be known, but also the differences between populations should be taken into account in prosthesis designs (20). Therefore, the differences between populations were examined. In studies on musculoskeletal system, occupations of individuals, working conditions required by these occupations and at the same time ergonomic conditions in work are important factors in the emergence of musculoskeletal system. It is thought that the reason why some parameters in the study are different from the results on Turkish population shown in **Table 3.** As a result, the results of the present study were in parallel with the data obtained from studies in literature. In addition, the difference between right and left bones for WIS, DIS and WC parameters were found to be significant. When the correlation of RAH with other parameters was examined, a negative weak correlation was found between LH, DIS, WE, Min-DS, Max-DS, LTH, HCA, WCA and HOF while a positive weak correlation was found between CSN, WIS, WTH, WOF, DOF, Min-DS, Max-DS, WC and LC.

Conclusion

The present study is a cross-sectional study and although it does not reflect the whole Turkey population, it gives a general information about Bolu sample. Morphometric data obtained from the humerus with various methods can be a reference in anthropology, radiology and physiotherapy-rehabilitation areas and in studies planned for problems in the clinic. They can also be a guiding source in understanding radiological anatomy of the humerus better, in humerus fractures and conditions that affect the shoulder and the arm, various surgeries such as shoulder joint prosthetic replacement arthroplasty and surgical interventions such as grafting. The data obtained in the field of forensic medicine provide data about the mean size of the humerus.

Study Limitation

The fact that no data were known about the age, gender of the bones used in the study and the life conditions of the individuals the bones belonged to were important parameters that limited the study. In addition, the presence of diseases that can affect the bone tissue and joints such as osteoporosis, rheumatoid arthritis and osteoarthritis are not known.

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Review Article

Negative Effects of Aflatoxin B1 on Sperm

Aflatoksin B1'in Sperm Üzerine Negatif Etkileri

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Abstract

Aflatoxins are secondary metabolites that produced by *Aspergillus* fungi which are soilborne and involved in the decomposition of plant materials in nature. *Aspergillus* species find opportunity to produce aflatoxins in high humidity and temperature conditions such as tropical and subtropical environment. Therefore, in changing climatic conditions caused by global warming, geographical distribution of these fungi to have changed day by day, and find out an opportunity to grow in different feed materials. Aflatoxin B1 (AFB1) is the most toxigenic mycotoxin in these group and threatens both human and animal health due to its carcinogenic and mutagenic properties. In cattle, commonly known adverse effects of AFB1 depending on the chronic exposure such as decreasing milk production and quality, reducing the feed efficiency in beef cattle, increase susceptibility to diseases following suppression of the immune system, compromise ruminal functions, disruption of ruminal microorganism growth and functions.

In this study, the negative effects of AFB1 on bull sperm has been examined. Topics such as negative effects of AFB1 on sperm proteomes, increase in the reactive oxygen species, changes in sperm DNA and plasma membrane integrity are discussed.

Key Words: Aflatoxin, Aflatoxin B1, Sperm

ÖZ

Aflatoksinler, toprak kaynaklı olan ve bitkisel materyallerin çürümesinde görev alan Aspergillus türü mantarlar tarafından üretilen sekonder metabolitlerdir. Aspergillus türleri, tropikal ve subtropikal ortamlar gibi yüksek nem ve sıcaklık koşullarında aflatoksin üretme fırsatı bulmaktadır. Bu nedenle, küresel ısınmanın neden olduğu iklim değişikliklerine bağlı olarak aflatoksin üreten mantarların coğrafi yayılışları değişmekte ve farklı yem materyallerinde üreme imkanı bulmaktadırlar. Aflatoksinler içerisinde en toksik olanı aflatoksin B1'dir (AFB1) ve karsinojenik ve mutajenik özelliğinden dolayı insan ve hayvan sağlığını tehdit etmektedir. Aflatoksin B1'e uzun süre maruz kalmaya bağlı olarak sığırlarda; süt veriminde ve kalitesinde azalma, besi sığırlarında yemden yararlanmada düşme, immun sistemin baskılanması ve buna bağlı olarak hastalıklara karşı duyarlılıkta artış, karaciğer fonksiyonlarının baskılanması, rumen fonksiyonlarında azalma, rumen mikroorganizmalarının gelişme ve fonksiyonlarının sekteye uğratılması gibi etkileri yaygın olarak bilinmektedir.

Bu çalışmada, AFB1'in boğa spermi üzerindeki olumsuz etkileri incelenmiştir. Boğa spermindeki proteomlar, reaktif oksijen türlerindeki artışlar ve plazma membran bütünlüğündeki değişiklikler, sperm DNA'sında meydana gelen değişiklikler gibi konular ele alınmıştır.

Anahtar Kelime: Aflatoksin, Aflatoksin B1, Sperm

Highlights

- AFB1 impairs the spermatozoa acrosome reaction and capacitation.
- AFB1 reduces PARK7 expression in spermatozoa and increases ROS generation.
- DNA fragmentation in spermatozoa is increased in males exposed to AFB1.

Introduction

Aflatoxin contamination in various feed materials such as corn, maize, sorghum, rice and wheat are common worldwide (1-3). Aflatoxin contamination of corns cause economic losses in U.S. corn industry between US$52.1 and US$1.68 billion (4). Estimates of the economic losses caused by mycotoxin contamination vary, nevertheless, neither of these estimates contain human health impact of aflatoxin contamination.

Aflatoxins are the secondary metabolites produced by fungi, *Aspergiluus flavus, A. parasiticus* and *Penicillium* species (5-7). Aflatoxins consist four main compounds called Aflatoxin (AF) B1, B2, G1 and G2 (6). Aflatoxin M1 and M2 which are found in milk and dairy products are hydroxylated forms of AFB1 and AFB2, respectively (8). According to the International Agency for Research on Cancer, AFB1 is classified as Group 1 carcinogen to humans (9).

In cattle, long term exposure to aflatoxins can reduce production performance, interrupt liver function, increase the susceptibility to diseases following suppression of immune function (10). The negative effects of aflatoxins such as production performance have been observed by researches using pure aflatoxins because it allows control of the dose applied and more contamination prevention. However, in nature, different fungi species can growth in the feedstuffs depending on the environmental conditions. Therefore, mycotoxins may cause more severe damage due to the synergistic or additive effects of different types of mycotoxin as well as other metabolites and their fungal sources (11-13). Applebaum et al (1982) observed that the pure AFB1 administration to dairy cows did not affect the milk productions whereas impure AFB1 administration reduced the milk production in dairy cows (14). Due to the synergistic or additive effects of different mycotoxin types, or aflatoxins, may exert their deleterious effects more severely in vivo or in vitro.

Aflatoxin B1 may have toxic to the male reproductive system in animal as well as human. The negative effects of AFB1 on male reproductive system are sorted as pathological changes in testis and epididymis, decreases in the number of leydig cells, and in the number of spermatogenesis, spermatocytes and spermatids (15). In addition, AFB1 exerts it's negative effects on human are reported as poor sperm quality and infertility (16).

Effect on sperm capacitation and acrosome reaction

The acrosome reaction is a prerequisite process of spermatozoa for fertilization. Acrosome-reacted spermatozoa are being capable to pass through the zona pellucida subsequently bind the oocyte plasma membrane and fuse with the oocyte (17). All mammalian spermatozoa including human undergo a series changes during their ascent in the female reproductive tract, is called capacitation (18). The acrosome reaction requires to release of hyaluronidase and acrosin enzymes (17). Ataman et al., (2014) have observed significant increase in semen hyaluronidase activity in rams exposed to aflatoxin from 3 week of the trial (19). Researchers had discussed on increase in semen hyaluronidase activity could be arise from an increase in the rate of abnormal or nonviable spermatozoa or could be explained by the transfer of hyaluronidase from the serum into the seminal plasma as a result of chronic intoxication. In contrast, chronic exposure to AFB1 of mammals in dose dependent manner cause low serum testosterone (20, 21). In another hand, the high testosterone levels in sheep results in high serum hyaluronidase levels (22). Therefore, the increase in hyaluronidase activity in semen could not be related to the transfer from the serum into the seminal plasma.

Komsky-Elbaz et al., (2018) reported that AFB1 causes significant decrease the proportion of sperm that reacts to Ca^{++} ionophore and underwent induced acrosome reaction in sperm obtained from the epididymis tail (23). In another study, the ubiquitin-proteosome systems (UPS) that involved in capacitation, acrosome reaction and zona pellucida penetration, have been found affected by the AFB1 (24).

Effect on mitochondria

Alterations in mitochondrial functions caused by the environmental substrates such as aflatoxins are associated with dysfunction male and female infertility (25). The mitochondria involve in ATP synthesis, reactive oxygen species (ROS) production, calcium signaling and apoptosis. Impairment of mitochondrial functions in cells exposed to AFB1 induce apoptosis following activating ROS generation by the mitochondria (29). Komsky et al., (2018) observed that AFB1 induced alterations in mitochondrial membrane potential in spermatozoa (23). In addition, AFB1 reduced expression of PARK7, a protein involved in cell protection against mitochondrial damage and high levels of ROS generation (24, 26). These results suggest that AFB1 reduces fertilization rate via mitochondrial damage. The ubiquitin C-terminal hydrolase L3 protein is located in the mitochondrial sheath and shows reduced expression in male infertility (24).

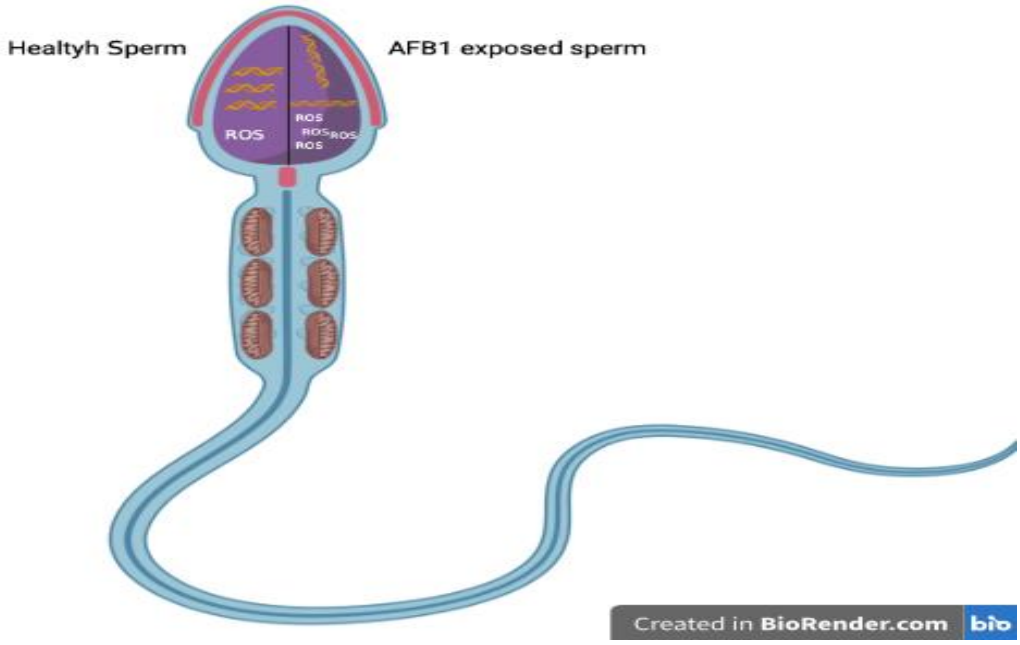

Figure 1: Effects of Aflatoxin B1 (AFB1) on sperm quality. Acrosome reaction is impaired, and apoptosis is induced following activated ROS generation. DNA fragmentation is increased.

DNA Fragmentation

Paternal components which are believed to be crucial for oocyte activation and zygote formation, are deliverd by spermatozoon. During fertilization, the proportion of sperm with DNA fragmentation is considered a practical parameter for characterizing semen quality (27, 28). DNA fragmentation reduces sperm fertilization and also effects embryonic development (29), but embryo can repair DNA damage of sperm origin. This process starts after fertilization (30). Komsky et al., (2018) reported DNA fragmentation in bull sperm exposed to AFB1 but no difference on the blastocyst formation between AFB1-treated group and control (23).

Cell membrane integrity is important on the cell viability. Komsky et al., (2018) reported that exposure of low concentrations of AFB1 (1 or 10 μM) reduced the viability of sperm (23). Ram spermatozoa exposed to AFB1 induced the higher rate of dead spermatozoa proportion in comparison with control group (19).

In conclusion, while aflatoxins are considered one of the risk factors for decrease in production performance such as milk production, feed efficiency in dairy and beef cattle, according to the data from the limited studies, they may also accepted as risk factor for male reproduction. These risk factors for male reproduction include decreasing sperm motility and viability, increasing the rate of fragmented DNA, and ROS in spermatozoa. Further studies are required for negative effects on male reproduction exposed to aflatoxins either alone or combined with other mycotoxins.

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Case Report

Metastasis of Renal Cell Carcinoma to the Urinary Bladder: Case Report

Böbrek Hücreli Karsinomun Mesaneye Metastazı: Olgu Sunumu

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Highlights

- Metastasis to the bladder may rarely be seen in renal cell carcinoma cases.
- Case management is difficult due to the lack of consensus on the treatment procedure in the case of renal cell carcinoma metastasis to the bladder.

Abstract

Renal cell carcinoma (RCC) is the most common malignant type among kidney tumors, with a rate of 90% in adults. Distant metastasis is seen in 30% of patients with Renal Cell Carcinoma at the time of diagnosis. In this study, we aimed to present two very rare cases of bladder metastases. Case 1; A 65-year-old male patient with nodular thickening and mass in the bladder wall around the right ureteral orifice. Case 2; The patient, who had undergone nephrectomy operation due to a mass in the left kidney, was hospitalized with the complaint of hematuria and a mass in the bladder was detected in the examination.Although metastasis of Renal Cell Carcinoma to the bladder is not common, it should be kept in mind in routine control examinations and investigated for metastasis.

Keywords: Renal cell carcinoma, Metastasis, Urinary bladder

ÖZ

Renal hücreli karsinom (RCC), yetişkinlerde %90 oranında böbrek tümörleri arasında en sık görülen malign tiptir. Renal Hücreli Karsinomalı hastaların % 30'unda tanı anında uzak metastaz görülmektedir. Bu çalışmada çok nadir görülen iki mesane metastazı olgusunu sunmayı amaçladık. OLGU 1; Sağ üreter ağzı çevresinde mesane duvarında nodüler kalınlaşma ve kitlesi olan 65 yaşında erkek hasta. OLGU 2; Sol böbrekte kitle nedeniyle nefrektomi operasyonu geçiren hasta hematüri şikayeti ile hastaneye yatırıldı ve yapılan muayenede mesanede kitle tespit edildi. Renal Hücreli Karsinomun mesaneye metastazı sık olmamakla birlikte rutin kontrol muayenelerinde akılda tutulmalı ve metastaz açısından araştırılmalıdır.

Anahtar Kelimeler: : Böbrek hücreli karsinom, Metastaz, Mesane

Introduction

Renal cell carcinoma (RCC) is the most common malignant type among kidney tumors, with a rate of 90% in adults. Distant metastasis is seen in 30% of the cases at the time of diagnosis (1). In 20% of the cases, metastases develop during follow-up (2). Radical nephrectomy is the gold standard approach in the treatment of RCC. Despite this radical surgical approach, early or late metastasis is seen in 20-30% of patients during follow-up (2). RCC tends to spread to almost every organ, but the most common sites of metastasis are lung, lymph node, bone, brain and liver.

Approximately 65 cases of metastatic RCC to the urinary bladder were identified so far. Among these, clear cell RCC was the most common histological type (92%) (3). As for the rest, only two cases of papillary RCC were reported (4).

In this study, we will present two clear cell RCC cases with metastasis to the urinary bladder.

Cases

Case 1; A 65-year-old male patient underwent right radical nephrectomy in 2019 due to a 6x5x3 cm right renal mass starting from the lower pole and filling the right renal pelvis, and a 9.5x5x2 cm right adrenal adenoma. Pathological examination revealed right adrenal cortical adenoma and clear cell RCC with invasion to perinephric tissue and pelvis. Invasion to the renal sinuses and veins was not detected. The pathological stage was determined as T3aN0M0. In the follow-up, cystoscopy was performed at the first year due to bladder related symptoms such as hematuria, burning in urination, and cystitis, and a solid mass of 4x3 cm was observed on the right orifice. Right kidney was not observed during upper abdominal CT. A nodular thickening and mass were determined in the bladder wall around the right ureteral orifice. The patient underwent Tur-B, and the pathology was determined as RCC and Clear Cell Type Metastasis (figure 1a).

Case 2; Our second case had left radical nephrectomy due to an 8x6x3 cm renal mass in the left kidney in 2013 in an external center. Pathology was reported asT2N0M0 clear cell RCC. The patient was hospitalized in 2021 due to the complaint of hematuria, and examination revealed a mass in the urinary bladder. A mass was detected in the superior of the left lateral wall of the bladder in the metastasis control CT (figure 2), and bladder resection was performed. The pathology of the specimen was identified as clear cell RCC, as seen in figure 1b.

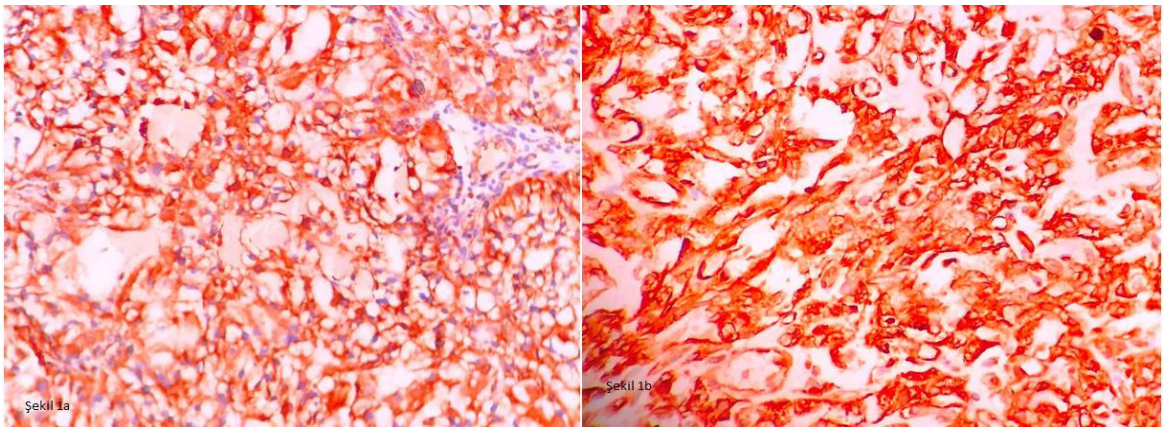

Figure 1 (a, b): (a): Clear Cell RCC specimen (H&Ex40) composed of tumor cells with alveolar and acinar pattern, displaying hemorrhage and a congested small fine vessel network between tumor islets, conspicuous cell membrane, clear eosinophilic cytoplasm in patches that lost lipid or glycogen content in most areas (H&Ex40). **(b):** Clear Cell RCC specimen (H&Ex40) consisting of cells with well-defined cellular borders, clear cytoplasm, and nuclei approximately twice the size of normal tubule cells at high magnification, and prominent nucleoli that can be distinguished at 40x magnification (H&Ex40).

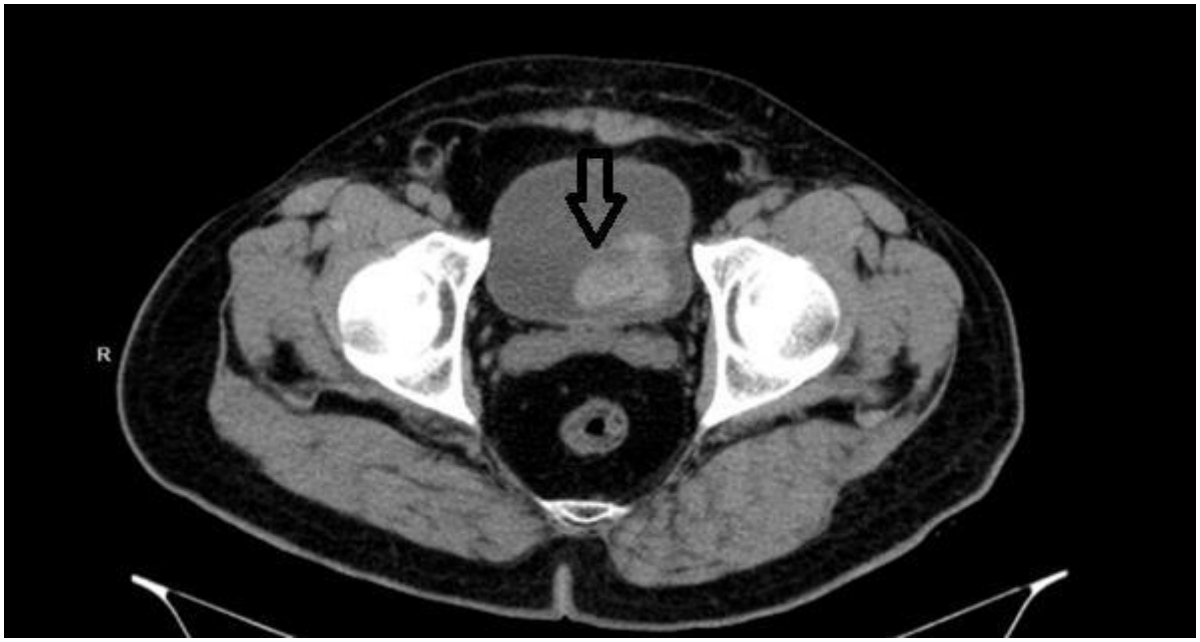

Figure 2: Computed tomography image of metachronous metastasis shown with the arrow.

Discussion

Metastasis of RCC to the urinary bladder is an extremely rare condition. Urinary bladder metastasis is seen in less than 1% of solid tumors (5), which can be synchronous or metachronous. In literature review, synchronous bladder metastases are less common and have a worse prognosis in comparison to metachronous bladder metastases. Of the RCC types, the clear cell carcinoma type is determined to metastasize more to the urinary bladder (3).

In general, probability of metastasis is lower and the prognosis is better in papillary renal cell carcinoma with respect to clear cell carcinoma (6). However, papillary RCC behaves more aggressively than metastatic clear cell RCC, in case metastasis develops (7). The reason for this could not be fully understood. The pathological mechanism underlying the spread of RCC to the urinary bladder is not exactly known. However, various possible mechanisms were observed, including hematogenous metastasis through the circulatory system, retrograde spread of the tumor mainly from the left renal vein or through the periureteral veins or lymphatics connecting the renal hilar lymphatics to the pelvic organs, and direct migration of tumor cells through the lumen (8). RCCs usually metastasize by hematogenous route, and this may cause observing different metastasis sites at the time at diagnosis. Conversely, urinary spread may be suspected if the primary tumor invades renal pelvis or collecting duct. In addition, lymphogenous metastases should also be kept in mind. Another metastasis route is the superficial antegrade spread of tumor, as drop metastases. And sometimes it can also be anticipated that several spread routes may be involved. However, none of these spread routes has been clarified so far. We consider that further studies are needed to shed light on the issue. In the literature, urinary bladder metastasis of clear cell type of RCC was reported more common with respect to the other RCC types (6). And in both of our cases, in consistency with the literature, RCC type metastasizing to the urinary bladder was determined to be clear cell subtype.

It was reported in the literature that, urinary bladder metastases of clear cell subtype of RCC usually manifested with macroscopic hematuria and lower urinary tract symptoms (9). Our cases also presented with macroscopic hematuria, in accordance with the literature. There is no consensus on the treatment of clear cell carcinoma because their metastases to the urinary bladder are not seen very often. Among the treatment options in the literature, systemic treatments including IL2 immunostimulant, tyrosine kinase were also seen, in addition to surgical treatment of multiple distant metastases (4). Shiraishi et al. recommended additional systemic therapy against metastasis in most cases (10). They suggested that the progression of another metastasis can be managed in combination with surgical resection and immunostimulatory therapy used in an outpatient setting, and long-term survival was possible (11). In their study, Gallmetzer et al. elaborated the long-term survival achieved after resection along with immunotherapy, and emphasized that surgical resection should not be considered as the only therapeutic tool against bladder metastasis of RCC. A combined treatment should also be considered in the treatment of solitary synchronous metastases of RCC (12). Nakanishi et al. reported a solitary metastatic

bladder tumor caused by RCC in a 48-year-old female patient (13). Maruo et al. reported two cases of bladder metastasis from RCC during molecular targeted therapy with pazopanib (14).

Gajasinghe et al. administered interleukin-2 or tyrosine kinase inhibitors along with resection, considering that systemic metastasis is likely to occur in such patients (4). Our cases were metachronous urinary bladder metastasis following a primary clear cell carcinoma surgery, consistent with the literature. Bladder metastasis was observed 9 years after -nephrectomy in our second case, and TUR-B was performed. No metastasis was determined in the systemic scanning of this patient with clear cell carcinoma. No recurrence or systemic metastasis was determined in the 1st year cystoscopy and imaging studies, is kept under monitoring with no systemic treatment. Urinary bladder metastasis was observed approximately two years after nephrectomy and TUR-B was performed in our first case. Tyrosine kinase was planned to be administered as a systemic treatment in this patient, due to the recurrence determined in the urinary bladder for the second time.

As a result, urinary bladder is one of the sites that should be kept in mind during routine control testing of the patients and should be investigated for metastasis, given that metastasis of RCC to the urinary bladder is not common. The fact that there is no consensus on the treatment procedure in case of metastasis of RCC to the urinary bladder, further complicates the management of such cases.

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