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Araştırma Makalesi / Research Article

Estimation of Gender by Using Decision Tree, a Machine Learning Algorithm, With Patellar Measurements Obtained From MDCT Images

MDBT Görüntülerinden Elde Edilen Patellar Ölçümler İle Bir Makine Öğrenme Algoritması Olan Karar Ağacı Kullanılarak Cinsiyet Tahmini

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Abstract

Aim: The present study aimed to analyze whether gender could be determined with the decision tree (DT) method, a machine learning algorithm, based on patellar multidetector computed tomography (MDCT) image measurements.

Material and Methods: The study was conducted on 219 male and 131 female MDCT images. The patellar anteroposterior (Ap), craniocaudal (Cc), transverse (Trv) length and volume (Vol), adjusted on the orthogonal plane by the radiologist, were calculated. In patellar length measurements, initially linear discriminant outliers were detected to clear the data for gender prediction. Accuracy (Acc), Sensitivity (Sen), Specificity (Spe), F1-Score (F1) and Matthew's Correlation Coefficient (Mcc) criteria were taken as the performance criteria for DT.

Results: It was determined that male Ap, Trv, Cc, and Vol values were higher when compared to the female values and there was a significant difference between these values based on gender ($p^{Ap, Trv, Cc, Vol} = 0.000$). Using the above-mentioned measurements, it was calculated that the prediction rate for male individuals was 98.2% and for female individuals, it was 98.4%.

Conclusion: DT analysis based on patella morphometry provided a simple, adequate and highly accurate approach for gender estimation. Furthermore, it was determined that it would provide an advantage for researchers in gender prediction using only branching and cut-off values on the tree structure without the need to use a computer.

Keywords: Decision tree; gender estimation; linear discriminant analysis; patella; multidetector computed tomography; osteometry

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Amaç: Bu çalışmanın amacı, patellanın multi-detektör bilgisayarlı tomografi (MDBT) görüntüleri üzerinden yapılan ölçümlerinden, bir makine öğrenmesi olan karar ağacı (KA) metodu kullanılarak cinsiyet belirlenmesi yapılıp yapılamayacağını ortaya koymaktır.

Materyal ve Metod: Çalışmaya 219 erkek ve 131 kadın bireye ait MDBT görüntüleri dahil edilmiştir. Radyolog tarafından, ortogonal düzleme getirilen patellanın anteroposterior (Ap), kraniokaudal (Kk), transvers (Trv) uzunlukları ölçüm aracıyla ölçülmüş ve volümleri (Vol) hesaplanmıştır. Patellar uzunluk ölçümlerine öncelikle lineer ayırt edici aykırı değer tespiti yapılmış, bu sayede cinsiyeti tahmin için veriler temizlenmiştir. KA için performans kriteri olarak karışıklık matrisi üzerinden hesaplanan Doğruluk, Sensitivite, Spesifite, F1-Skoru ve Matthew Korelasyon Katsayısı ölçütleri kullanılmıştır.

Bulgular: Erkeklerin Ap, Trv, Kk ve Vol değerleri kadınlardan daha yüksek olarak bulunmuş ve aralarında anlamlı fark tespit edilmiştir ($p^{Ap, Trv, Kk, Vol}=0.000$). Bu ölçümler ile erkek bireyleri tahmin etme oranı %98,2, kadın bireyleri tahmin etme oranı %98,4 olarak hesaplanmıştır.

Sonuç: Patella morfometrisine dayalı KA analizi, cinsiyet tahmini için basit, yeterli ve oldukça doğru bir yaklaşım sağlamıştır. Ayrıca araştırmacılara herhangi bir bilgisayara ihtiyaç duymadan sadece ağaç yapısı üzerinde dallanmaları ve cut-off değerleri kullanarak cinsiyet tahmini yapmak konusunda avantaj sağlamaktadır.

Anahtar Kelimeler: Karar ağacı; cinsiyet tahmini; lineer diskriminant analizi; patella; multi-dedektör bilgisayarlı tomografi; osteometri

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INTRODUCTION

Forensic anthropology requires accurate and reliable methodologies to determine the gender of human remains without a known gender (1). Thus far, gender identification has been conducted on skeletal remains to identify individuals in forensic sciences and to analyze populations in archaeology (2). When the entire skeleton is available for analysis, gender prediction is more reliable; however, in forensic cases, human skeletal remains are often partial or damaged (3). In a forensic case where all bones are not available, differential function equations should be derived using various bones to estimate the gender (2).

Generally, morphological and metric methods are used to estimate gender with skeletal remains. The morphological method includes observation of gender-specific properties of the bones, however accurate results are obtained only when the observer has sufficient experience. On the other hand, the metric method is based on measurements and statistical techniques that do not require expertise and could be repeated to confirm the results (2). Physical anthropology has conventionally used both qualitative and quantitative strategies to predict gender with skeletal remains, however, due to its variable nature, the osteometry has generally been considered a more reliable approach (4).

The skull, pelvis and long bones are often absent or disintegrated, thus gender prediction should be attempted with other skeleton parts. However, the accuracy of gender prediction using skeletal elements depends on the degree of sexual dimorphism exhibited by the skeleton (3). Patella is the largest sesamoid bone in the human body. It is articulated with the femur and covers and protects the anterior knee joint surface. Patella develops in quadriceps femoris tendon and ossifies from a single center (5). It has a triangular shape and front and rear surfaces, three sides and a top. Patella is a strong bone without a significant morphological feature for the determination of gender and significant differences based on race. However, as a sesamoid bone formed within the quadriceps femoris tendon, it is resistant to postmortem and taphonomy variations and therefore valuable in the prediction of gender with unknown human remains (2, 5).

The decision tree (DT) algorithm is one of the frequently used data mining classification algorithms. It is used to make a decision based on pre-determined parameters. It generates a set of rules for the decision (6). The decision tree algorithm is easy to understand and interpret, it can be easily processed without the need for missing values, it is easy to process heavy skewed data, and it can tolerate outlier values to some extent (7).

The present study aimed to analysis whether gender could be determined with DT, a machine learning algorithm, based on patella measurements conducted using multidetector computed tomography (MDCT) images.

MATERIAL AND METHODS

Study population and analysis

The present study was approved by the Ethics Committee for Non-Interventional Clinical Trials with protocol no. 6/22. CT images of the lower extremities that included the patella taken for various indications between January 2015 and May 2019 were reviewed. Images obtained from 219 male and 131 female subjects were included in the study without right-left discrimination. Subjects with significant bone deformity and a history of surgery were excluded from the study. All obtained CT images were taken with a 16-slice MDCT scanner (Aquilion 16; Toshiba Medical Systems, Tokyo, Japan). The cross-sectional thickness was 1 mm in all images.

All measurements were conducted by an experienced radiologist in a workstation (Vitrea v6.1, Vital Images, Plymouth, MN, USA). The images in the axial plane were analyzed with two- and three-dimensional reconstructions (Maximum Intensity Projection-MIP, Volume Rendering) in the bone window. Images that focused on the patella were adjusted to the orthogonal plane in three planes. Anteroposterior (Ap), craniocaudal (Cc), and transverse (Trv) length of the patella were measured with the measurement device after the cross-sectional thickness was maximized. The entire patella region was stained with the Volume (Vol) measurement instrument. The accuracy of the stained patella boundaries was checked with the field lines and required corrections were made and finally, the patella volume was calculated (Figure 1). All measurements were conducted in 3 replicates. Since the images of certain individuals included bilateral patella, a total of 6 measurements were taken in this group. For the DT model to be able to encounter the maximal variation the statistical differences that could potentially exist between the measurements at the different time were ignored.

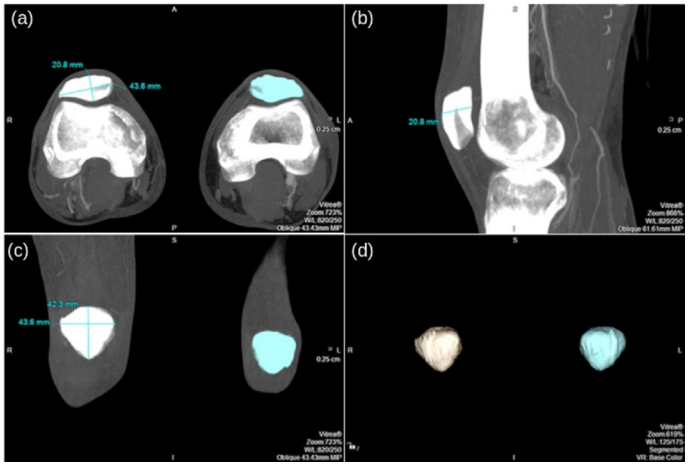

Figure 1. Patellar measurements. (a) Axial, (b) Sagital, (c) Coronal, (d) 3D image

In order to determine the gender based on patellar measurements, a framework structure was developed with Python programming language. Python programming language was selected since its structure is adequate

for scientific calculation, due to the simplicity of its syntax structure, and since it is an open development platform independent of the development environment (8). Statistical calculations were conducted with Stats models with a Python programming language statistical framework and Pandas with a data structure framework (9, 10). Also, scikit-learn framework was used for the DT algorithm. This framework was selected since it is an open source easy to use software with a commercial BSD license and has full compatibility with popular frameworks such as Numpy, Scipy and Matplotlib (11, 12).

Data structure

The data structure used for patellar measurements was the text format. This format is designed as a flat file that included comma-separated values (csv). The Pandas framework was used to read the measurements and convert them into structured data. Measurements conducted on the structured data structure were separated into Id, Name, Age, Gender, Ap, Trv, Cc, Vol, Out3 fields. Where, Id is a unique number used for measurement. Out3 parameter was denoted with 1 for males and 0 for females and used for classification.

Data cleaning, training and test sets, and performance criteria

Initially, patellar length measurements were conducted with linear discriminant outlier detection. Thus, data that would be used for gender prediction were cleared of outliers (13). The first 80% of the patellar length measurements were set as the training set and the remaining 20% were set as the test set. Training and test procedures were conducted using the selected training set by randomizing the patella data set for each procedure and the test was conducted with the test set that the DT model was never exposed to. The model developed for more realistic performance criteria, was tested on 500 different test sets. Thus, the probability that each data line was a training set element and that each data line was a test set element were increased. Furthermore, the distribution of performance criteria was determined as a result of repeated training and test procedures. The DT performance criteria included Accuracy (Acc), Sensitivity (Sen), Specificity (Spe), F1-Score (F1) and Mathew's Correlation Coefficient (Mcc) criteria, calculated with the confusion matrix. Performance criteria were calculated with the Equation-1 set.

$$Acc = \frac{TP}{TP + FP + FN + TN}$$

$$Sen = \frac{TP}{TP + FN}$$

$$Spe = \frac{TN}{TN + FP}$$

$$Mcc = \frac{TP \cdot TN - FP \cdot FN}{\sqrt{(TP + FP).(TP + FN).(TN + FP).(TN + FN)}}$$

$$F_1 = 2\frac{Sen.Spe}{Sen + Pre}$$

Eq. (1) DT performance criteria, Accuracy (Acc), Sensitivity (Sen), Specificity (Spe), F1-Score (F1) and Mathew's Correlation Coefficient (Mcc) calculated with the confusion matrix.

Decision tree

Decision trees are an algorithm that allows writing various rules between the existing data and the classes of data. In decision trees, the parameters are represented by branching and parent nodes. The results are the tree leaves and nodes (14). In order to provide an acceptable outcome success rate based on parameter values, a set of rules is written (the acceptable success rate is accepted as 0.85 in the present study). Thus, several clusters that include data and various classes are divided into smaller clusters and classified. The advantages of the method include is ease of use, ability to present clearly visualized rules, ability to develop rules to classify the dataset, ability to classify with less data, and ability to classify both numerical and semantic expressions. Its disadvantages include the fact that tree structures that best describe the data may be extremely complex in certain cases and they are not suitable to work with missing or lost data (15). In the present study, DT was used to predict gender based on 4 patellar parameters and to write a set of rules to determine gender based on patellar measurements. The models required for DT were developed and tested with the scikit-learn framework.

RESULTS

The reported study findings included comparative results obtained before and after outlier removal with linear discriminant analysis (LDA).

Main statistical findings before the outliers were removed with LDA

A total of 1166 measurements were conducted on images obtained from 219 males and 1007 measurements were conducted on images obtained from 131 females. Anderson Darling normality test was used to test whether Age, Ap, Trv, Cc, and Vol values exhibited normal distribution. The test findings demonstrated that Age, Ap, Trv, Cc and Vol values did not exhibit a normal distribution (for males: p^{Ap} = 0.008, $p^{Trv, Cc, Vol}$ = 0.000, for females: p^{Ap} = 0.0007 for women, p^{Trv} = 0.0000, p^{Cc} = 0.0002, p^{Vol} = 0.0023). Mann-Whitney U test was used to determine whether there was a difference between the values since they did not exhibit a normal distribution. The median male age was 64 (min 18, max 91), the median female age was 60 (min 18, max 91). There was no significant difference between the ages of male and female subjects (p = 0.011). It was found that male Ap, Trv, Cc, and Vol values were higher when compared to females and there were significant differences based on gender ($p^{Ap, Trv, Cc, Vol}$

= 0.000). The distribution of patellar Ap, Trv, Cc and Vol measurements for males and females are presented in Table 1.

Table 1. Distribution of patellar measurements based on gender before outliers were removed with LDA (min: Minimum, max: Maximum, Ap: Anterior to Posterior length, Trv: Transversal length, Cc: Cranio-Caudal length, Vol: Volume)

	Male	Female
Parameters	Median (min-max)	Median (min-max)
Ap	24.70 (20.20-31.80)	23.00 (17.80-28.20)
Trv	47.70 (37.10-57.20)	43.10 (34.70-49.50)
Cc	45.90 (37.70-56.70)	41.75 (31.90-50.50)
Vol	23.47 (14.32-39.42)	17.90 (8.91-24.62)

Main statistical findings after the outliers were removed with LDA

After the outlier removal conducted with LDA, 179 males and 119 females were included in the study. A total of 822 measurements obtained from 179 males and 849 measurements obtained from 119 females were included. The distribution of the ages of male and female subjects did not exhibit normal distribution (p^{Male} = 0.0000, p^{Female} = 0.0000). The median male age was 63 (min 18, max 91) and the median female age was 57 (min 18, max 91). It was observed that all measurements for males and females did not exhibit normal distribution (for males: p^{Ap} = 0.0234, $p^{Trv, Vol, Cc}$ = 0.000; for females: p^{Ap} = 0.0003, $p^{Trv, Vol, Cc}$ = 0.000). All measurements conducted on males were higher when compared to female measurements and there was a statistically significant difference between these figures ($p^{Ap, Trv, Cc, Vol}$ = 0.000). The distribution of patellar Ap, Trv, Cc and Vol measurements for males and females is presented in Table 2.

Table 2. Distribution of patellar measurements based on gender after outliers were removed with LDA (min: Minimum, max: Maximum, Ap: Anterior to Posterior length, Trv: Transversal length, Cc: Cranio-Caudal length, Vol: Volume)

	Male	Female
Parameters	Median (min-max)	Median (min-max)
Ap	25.20 (20.50-31.80)	22.80 (17.80-28.20)
Trv	48.90 (43.80-58.20)	42.10 (34.70-47.60)
Cc	46.80 (38.10-56.70)	40.97 (31.90-50.50)
Vol	25.04 (18.52-39.42)	16.98 (8.91-22.25)

It was calculated that there were significant statistical differences between the Age, Ap, Trv, Cc and Vol values before and after outlier removal was conducted with LDA based on gender ($p^{Age, Ap, Trv, Cc, Vol}$ = 0.0000).

Decision tree

DT and gender prediction findings are presented in two sections; the first section includes data obtained before the outlier removal with LDA and the second section includes the data after the outlier removal with LDA.

Findings obtained before the outlier removal with LDA

Various DT models with a max. depth of 3, 4, 5 and unlimited were tested. In none of these models, the total Acc value was greater than 0.82 (maximum depth of tree of 3, 4 and 5). In the present study, since the Acc was accepted as over 0.85, the pre-LDA dataset was not considered successful. The performance criteria are presented in Table 3.

Table 3. The performance criteria findings for the case where various maximum depth of tree was used in the DT method (Acc: Accuracy, Spe: Specificity, Sen: Sensitivity, F1: F1-Score, Mcc: Matthew's correlation coefficient)

	Maximum depth of tree			
Performance	3	4	5	None
Acc	0.810 (0.729-0.850)	0.811(0.722-0.854)	0.811 (0.765-0.854)	0.846±0.013
Spe	0.758 (0.570-0.911)	0.804 (0.580-0.894)	0.809 (0.600-0.901)	0.843±0.024
Sen	0.841 (0.579-0.971)	0.825 (0.581-0.971)	0.822 (0.696-0.957)	0.849±0.021
F1	0.804 (0.708-0.850)	0.808 (0.704-0.853)	0.809 (0.726-0.854)	0.846±0.013
Mcc	0.623 (0.487-0.699)	0.624 (0.489-0.709)	0.625±0.026	0.692±0.027

Maximum dept of tree was set to unlimited to prevent the limit on the depth of the tree. However, it is practically impossible to derive a set of rules from the resulting tree. Therefore, the maximum depth of tree with the highest Mcc value was accepted as 4 and called that the DT general solution model.

The DT general solution model was trained 500 times with different training sets selected from the dataset, tested 500 times with various test sets, and the resulting distribution of the performance criteria are presented in Figure. 2.

Findings obtained after the outlier removal with LDA

Various DT models with a max. depth of 3, 4, 5 and unlimited were tested. In all models, the total Acc value was greater than 0.97 and the models were accepted as successful. The performance criteria are presented in Table 4.

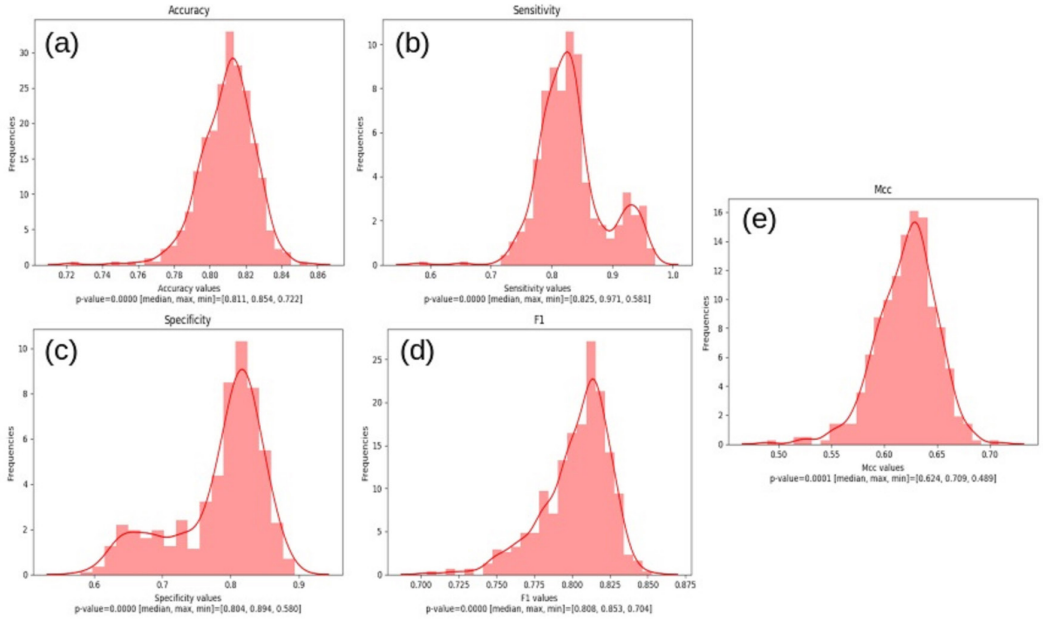

Figure 2. Distribution of performance criteria before LDA outlier removal, (a) Acc distribution, (b) Sen distribution, (c) Spe distribution, (d) F1 distribution, (e) Mcc distribution. Acc: Accuracy, Spe: Specificity, Sen: Sensitivity, F1: F1-Score, Mcc: Matthew's correlation coefficient.

Table 4. Performance criteria findings when DT method with different maximum depth of trees was used (Acc: Accuracy, Spe: Specificity, Sen: Sensitivity, F1: F1-Score, Mcc: Matthew's correlation coefficient)

Performance Criteria	Maximum depth of tree			
	3	4	5	None
Acc	0.972 (0.940-0.990)	0.982 (0.962-0.994)	0.984 (0.964-0.998)	0.984 (0.966-0.998)
Spe	0.975 (0.898-1.000)	0.984 (0.946-1.000)	0.985 (0.938-1.000)	0.987 (0.952-1.000)
Sen	0.973 (0.914-0.996)	0.980 (0.939-1.000)	0.984 (0.948-1.000)	0.984 (0.951-1.000)
F1	0.972 (0.940-0.990)	0.982 (0.961-0.994)	0.984 (0.965-0.998)	0.984 (0.966-0.998)
Mcc	0.944 (0.881-0.980)	0.964 (0.925-0.988)	0.968 (0.928-0.996)	0.968 (0.933-0.996)

Based on the findings presented in Table 4, the model where the maximum depth of tree was assigned as 4 was selected as the DT general solution model based on the fact that the set of rules could be easily created from this tree structure. The DT general solution model was trained 500 times with different training sets selected from the dataset and tested 500 times with various test sets and the resulting distribution of the performance criteria are presented in Fig. 3.

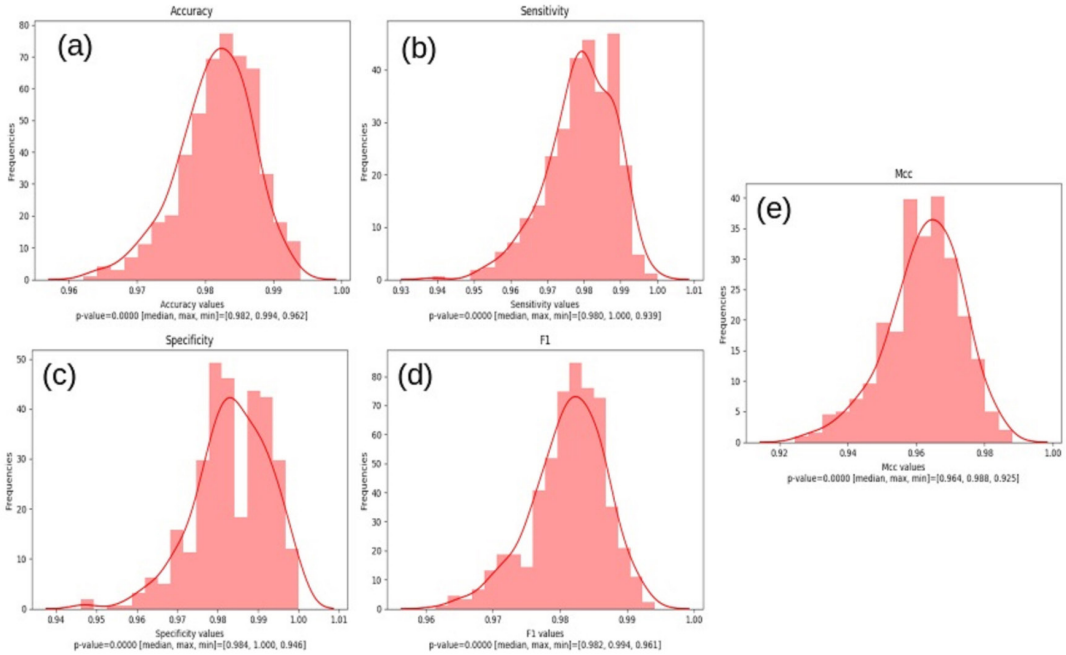

Figure 3. Distribution of performance criteria after LDA outlier removal (a) Acc distribution, (b) Sen distribution, (c) Spe distribution, (d) F1 distribution, (e) Mcc distribution. Acc: Accuracy, Spe: Specificity, Sen: Sensitivity, F1: F1-Score, Mcc: Matthew's correlation coefficient.

The confusion matrix obtained by running the DT general solution model on randomly selected test sets on each run is presented in Fig. 4. High Spe and Sen values were noted in the test set for both genders. In the predictions for males, the Sen value was calculated as 0.01 percent higher when compared to the predictions conducted with female measurements. The decision tree obtained after the LDA was conducted is presented in Fig. 5.

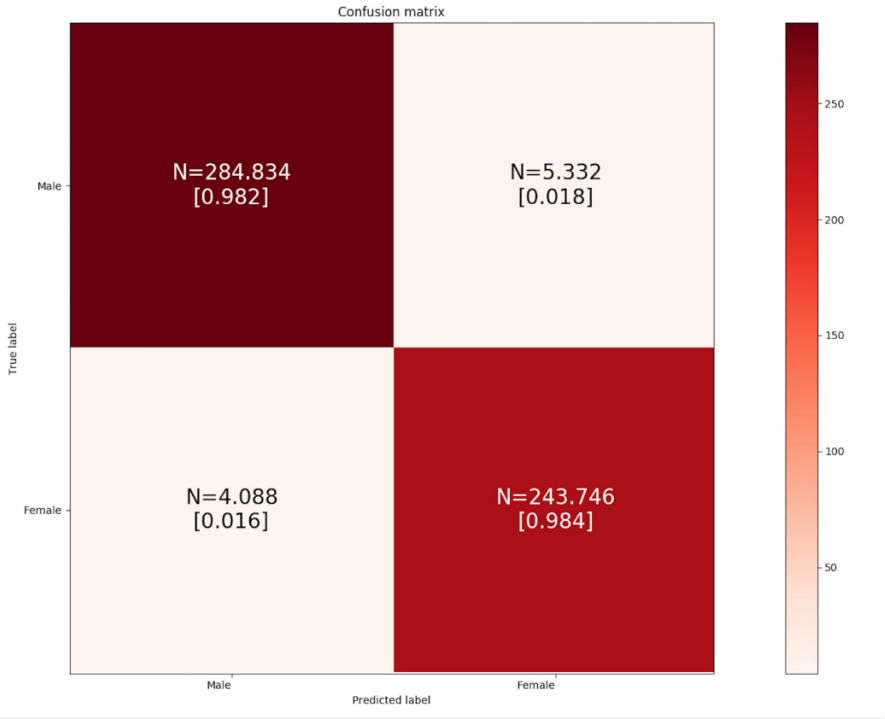

Figure 4. The confusion matrix for the test set (500 repetitions).

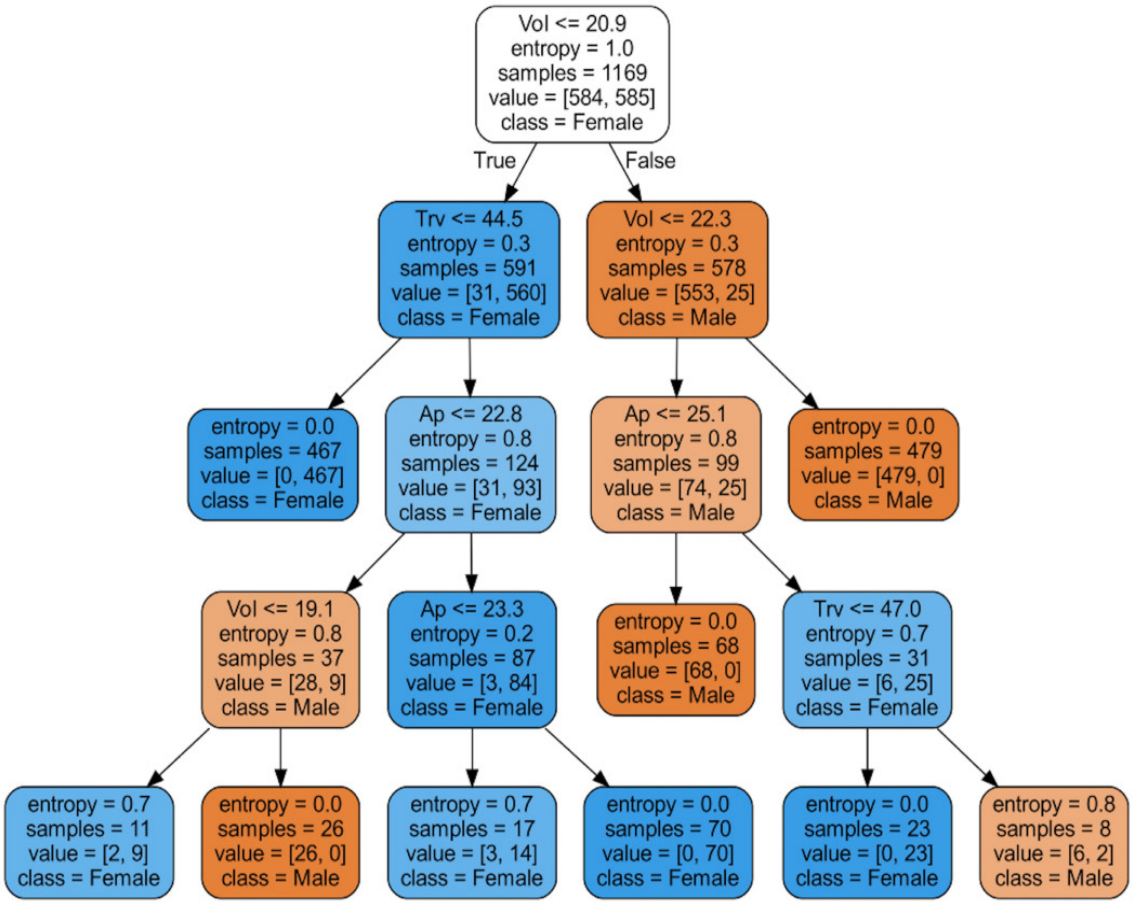

Figure 5. The rule set obtained after the DT. Ap: Anterior to Posterior length length, Trv: Transversal length, Cc: Cranio-Caudal length, Vol: Volume.

DISCUSSION

Gender determination plays an important role in the identification of human remains since it reduces the likelihood of identification (16). In forensic anthropology, it is essential to accurately define the measurement parameters. Thus, researchers using these parameters could understand the definitions and reproduce the measurements (1, 5). Previous studies showed that different populations have different bone characteristics, and these characteristics may affect the process of identifying sex (17-19) . Since the patella is resistant to postmortem and taphonomy changes and it is generally recovered in forensic cases (1), the patellar measurement parameters were used in the present study to predict gender.

In our study, it was found that the Sen value for male patellar measurements was 0.01 percent higher when compared to the predictions conducted with female patellar measurements. On the other hand, the Spe value for the predictions determined with female measurements was calculated as 0.01 percent higher when compared to the predictions determined with male measurements. The rate of the prediction of male individuals with patellar measurements was 98.2% and the rate of the prediction of female individuals was 98.4%.

Measurements conducted on most bones exhibited higher mean values for males when compared to those for females. Patellar findings have exhibited a similar pattern (20, 21). In the present study, it was found that patellar Ap, Trv, Cc, and Vol values were higher in males when compared to females.

In the present study, all four patellar variables demonstrated statistically significant differences based on gender. This revealed that the patella is dimorphic based on gender. Thus, discriminant function equations obtained with the variables could be used in gender determination (1). Similar findings were reported for South African white (20), South African black (22), Thai (23), Japanese (24), South Italian (25), and Medieval German (4) communities.

LDA method is one of the classically used methods for classification, and for revealing the relationship between parameters and classes, artificial neural network (ANN) are more successful. Missing, incorrect or unusually variable data are disadvantages of LDA (19, 26, 27). In contrast, DT, which is a machine learning algorithm, was used in the present study instead of LDA and ANNs for gender discrimination. DT allows forensic specialists, anthropologists, anatomists, and pathologists to make highly accurate decisions using dry bones or

reconstructed CT images. Furthermore, a scale was produced that could help them to obtain results using a DT based on measurements conducted without a computer.

In the study conducted by Curate et al., the data obtained with femur were analyzed for measurement errors using Technical Error of Measurement, Relative Technical Error of Measurement and Coefficient of Reliability (28). LDA has been used in several studies to predict gender using bone measurements (28, 29). Taking advantage of this feature of the LDA, values that reduce success during gender prediction were excluded in the present study. In the literature, LDA has been used as a good outlier detector due to this property (30). In the present study, LDA was used to improve the findings due to this particular property.

The sensitivity of predictions for males was 0.01 percent higher when compared to predictions for females in gender predictions based on male and female patellar measurements. The 0.01 difference was considered insignificant since it was a very low value. The fact that Acc value for the DT general solution model run on the test set after outlier removal with LDA was quite high demonstrated that there was no difference in the prediction of gender by the constructed model based on genders.

Although it was observed that the use of high maximum depth of tree values positively affected the success, it became a disadvantage when writing the set of rules for gender prediction. Thus, models with lower maximum depths of tree were preferred. This made it easier to predict gender by following the propositions available in tree branches. Selecting the maximum depth of tree value of 4 (Figure 4) provides an advantage for the researchers by allowing them to use the branches in the tree structure and gender cut-off values without the need for a computer.

When looking at gender prediction studies from the patellar bone measurement, it appears that studies focus on that the patella is a suitable bone for gender discrimination. In this study, it was found that the accuracy score was low before the outlier data was cleared with LDA. After removed outliers values from the set was found that the accuracy score was high. Because of that, it was thought that the data removed from the study via LDA decreased the success of gender discrimination due to effects such as demographic characteristics, physical characteristics such as height and weight, body type and factors affecting the remodeling processes of the bone. On the other hand, since this study does not use physical features such as demographic data, height and weight as a model, this idea could not be tested, and accepted as a constraint.

CONCLUSION

The application of DT analysis based on patella morphometry provided a simple and adequate approach with high accuracy in gender determination. The quite high Acc value seemed to prove the exact validity of gender accuracy. Furthermore, the method allows the specialists to make highly accurate decisions using image analysis method or dry bone measurements. Furthermore, a scale based on measurements conducted without a computer but the decision tree rules were produced. Exclusion of outlier values that could reduce the success during gender prediction with LDA improved the findings of the present study.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval

This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and permission was obtained from Ethics Committee of Karabuk Universityfor the use of patient data for publication purposes.

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MEDICAL RECORDS-International Medical Journal

Araştırma Makalesi / Research Article

Intra- and Inter-Observer Variability in Sonographic Measurement of the Cervical Nerve Roots of Healthy Volunteers

Sağlıklı Gönüllülerin Servikal Sinir Köklerinin Sonografik Ölçümünde Gözlemci İçi Ve Gözlemci Arası Değişkenlik

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Abstract

Aim: The aim of our study is to determine the normal values of mean cervical (C) nerve root diameter in millimeters (mm) in healthy volunteers and to show its relationship to age, gender, height, weight, body mass index (BMI), and the dominant hand.

Material and Method: Two observers measured the mean nerve root diameter of the bilateral C5, C6, and C7 nerve of all volunteers. Before the procedure, the age, sex, height, weight, BMI, and the dominant hand of all the participants were noted. Two measurements were taken by each of the two observers without one knowing about the other's noted values. The intraclass correlation coefficient (ICC) test was used to analyze intra-and inter-observer reliability.

Results: There was no statistically significant relationship between gender and dominant hand, and mean nerve root diameter. Moreover, when we compared the mean nerve root diameter for the nerves in the right and left sides of each participant, no significant statistical differences were identified. The mean diameter of the C6 nerve root was higher than that of C7, which was higher than that of C5 on both sides ($p < 0.001$). The ICC values for intra- and inter-observer were good or excellent for all diameter measurements (ICC > 0.8).

Conclusions: The normal range of cervical nerve root diameters should be determined to distinguish pathological conditions. In our study, the measurement of mean nerve root diameters of C5, C6, and C7 nerves is highly reproducible with excellent intra-observer and inter-observer agreement. Therefore, the measurement of nerve root diameter can be confidently performed in daily clinical practice.

Keywords: Brachial plexus; cervical nerve root; ultrasonography; diameters; healthy volunteers

Oz

Amaç: Çalışmamızın amacı sağlıklı gönüllülerde ortalama servikal (C) sinir kökü çapının normal değerlerini milimetre (mm) olarak belirlemek ve yaş, cinsiyet, boy, kilo, vücut kitle indeksi (VKİ) ve dominat el ile ilişkisini göstermektir.

Materyal ve Metod: İki gözlemci, tüm gönüllülerin bilateral C5, C6 ve C7 sinirinin ortalama sinir kökü çapını ölçtü. İşlem öncesi tüm katılımcıların yaş, cinsiyet, boy, kilo, VKİ ve dominant eli not edildi. Biri diğerinin not edilen değerleri bilmeden, iki gözlemcinin her biri tarafından iki ölçüm yapıldı. Gözlemci içi ve gözlemciler arası güvenilirliği analiz etmek için sınıf içi korelasyon katsayısı (ICC) testi kullanıldı.

Bulgular: Cinsiyet ile dominant el ve ortalama sinir kökü çapı arasında istatistiksel olarak anlamlı bir ilişki yoktu. Ayrıca, katılımcıların sağ ve sol taraf ortalama sinir kökü çap ölçümleri arasında istatistiksel olarak anlamlı farklılık izlenmedi. C6 sinir kökünün ortalama çapı, her iki tarafta da C7'den C7 ise C5'ten yüksekti ($p <0.001$). Gözlemci içi ve arası ICC değerleri tüm çap ölçümleri için iyi veya mükemmeldi (ICC> 0.8).

Sonuç: Patolojik durumları ayırt etmek için normal servikal sinir kökü çapları aralığı bilinmelidir. Çalışmamızda, C5, C6 ve C7 sinirlerinin ortalama sinir kökü çaplarının ölçümü, mükemmel gözlemci içi ve gözlemciler arası uyum göstermekte olup yüksek tekrarlanabilik göstermektedir. Bu yüzden servikal sinir kökü çap ölçümü, günlük klinik pratikte güvenle yapılabilir.

Anahtar Kelimeler: Brakiyal pleksus; servikal sinir kökü; ultrasonografi; çaplar; sağlıklı gönüllüler

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INTRODUCTION

Brachial plexus (BP), consisting of the roots of the cervical (C) nerve, provides sensorimotor innervation of the upper extremity (1). Anatomically, the nerve roots of C5 and thoracic (T) 1 usually form a brachial plexus, and the C4 or T2 nerve roots may also contribute to the formation of BP (2). The brachial plexus has four anatomical regions: paravertebral, interscalene, periclavicular, and retropectoral regions (3, 4). Ultrasonographic evaluation of the cervical nerve root is optimal during the anatomical course between anterior scalene and middle scalene muscles (5, 6).

Cervical nerve roots may possess pathological findings due to various systemic diseases, such as trauma, tumoral lesions, entrapment neuropathies, inflammatory-infectious causes, and secondary to radiation (7, 8). Ultrasound (US) and magnetic resonance imaging (MRI) methods can be used to evaluate the cervical nerve roots (9). MRI imaging is superior to the US with higher spatial resolution and high soft-tissue resolution (10). Ultrasound is an alternative imaging method to evaluate the roots of the cervical nerve as it is cheap, easily accessible, reproducible, and dynamic (5, 6).

Our aim in this study is to examine the normal values of cervical mean nerve root diameter in healthy volunteers and to show its relationship to age, gender, height, weight, body mass index (BMI), and dominant hand.

MATERIAL AND METHODS

The study period was from June 2019 to January 2020. A total of 84 participants were included in the study, of which 50 were women and 34 were men. All procedures performed in our study were in accordance with the ethical standards.

We included volunteers aged 18-60 years without any known disease. The exclusion criteria were receiving radiotherapy to the neck for any reason, previous neck surgery-trauma history, cervical disc herniation, brachial plexopathy finding on physical examination, and body mass index >35. Two observers participated in this study and both of them used the same ultrasound system (LOGIQ S8, GE Medical Systems, Wisconsin, USA) with a 9-11 MHz linear transducer. The first observer (Observer 1, IA, 10 years' experience in radiology and Head - Neck Imaging) and second observer (Observer 2, EG, 6 years' experience in musculoskeletal radiology and Head - Neck Imaging) performed the B-mode ultrasound and measured the mean nerve root diameter of bilateral C5, C6 and C7 nerves of all volunteers at the level of the root. The observers were blind to the participant's results. Participants were examined consecutively during the same visit. Two measurements were taken by each observer at a 1-hour interval in two separate settings.

Before the procedure, age, sex, height, weight, BMI, and the dominant hand of all participants were noted. The examination was performed in the supine position with the arms in anatomical position. In the posterior part of the longus colli muscle, between the anterior and posterior tubercles of the transverse process, the probe was moved up and down to identify the C5, C6, and C7 nerve roots, respectively. The C7 nerve root was recognized at this level by the absence of the anterior tubercle in the transverse process and being just inferior to C6. Nerve roots were scanned in the axial-longitudinal plane up to the truncus and cords. Two measurements, anteroposterior and mediolateral, were taken at the root level of the axial plane and their arithmetic mean was obtained (Figure 1). Imaging of the C8 and T1 was problematic due to the sternoclavicular joint and was not included in the analysis.

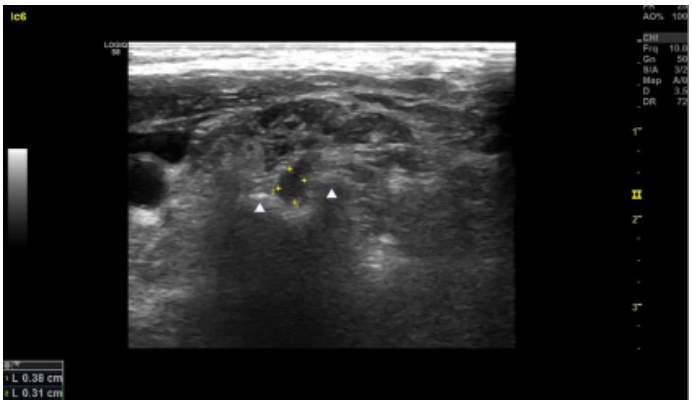

Figure 1. 44 years old healthy female volunteer. The mean diameter of the left C6 nerve root (yellow oval shape) was measured between the anterior and posterior transverse tubercles (arrowheads) of the C6 transverse process

Statistical analysis was performed via the SPSS v.22 package program (IBM SPSS Statistics, Chicago, IL, USA). The compatibility of the variables to normal distribution was examined using the Kolmogorov-Smirnov test. Mean and standard deviation values were used for descriptive statistics. The relationship of the nerve diameters to gender and dominant hand was evaluated using the Man Whitney U test. The correlation between the bilateral mean nerve root diameter and age, weight, BMI, and height was calculated with the Spearman correlation coefficient test. Friedman test was used to evaluate the within-group differentiation of nerve root diameter values. We used Wilcoxon's signed tests on different combinations of interest groups to analyze where the variations exist. The intraclass correlation coefficient (ICC) test was used to analyze intraobserver reliability for repeated measurements. Interobserver agreement regarding the diameter measurements between the two observers was assessed using the ICC with a 95% confidence interval in a two-way random model. ICC was interpreted as follows: below 0.50: poor, between 0.50 and 0.75: moderate between 0.75 and 0.90: good above 0.90: excellent. It was considered that $p<0.05$ was significant.

RESULTS

A total of 84 participants were included in the study. The demographic data of the participants are presented in Table 1. In 8 patients, the measurement could not be

obtained due to technical reasons, such as the short neck, deep localization of the nerve root, and the absence of rudimentary anterior tubercle, which is the anatomical landmark of the C7 nerve root. There was no statistically significant relationship between gender, hand dominance, and mean nerve root diameter (p=0.76). Besides, no statistically significant differences were identified when we compared the mean nerve root diameter at the right and left sides in each participant (p=0.12).

Tablo 1. The demographic characteristics of the participants

Variables	Participants (N = 84)
Age (range)	42.06±6.73(18-60)
Gender (male:female)	34:50
Weight (kg)	64.06±7.73
Height(cm)	166.61±6.30
Body mass index (kg/m²)	23.13±3.25
Dominant hand (right:left)	76:8

Data are expressed as the mean± standard deviation

The mean nerve root diameters of both sides of the first and second observers are shown in Table 2.

The ICC values for all diameter measurements were>0.80-0.90, indicating good and excellent agreement (Table 3a, b).

Spearman correlation analysis was performed for comparison of mean nerve root diameters and height, weight, BMI, and age. There was no statistically significant difference between C5, C6 and C7 mean nerve roots and weight, height, BMI, and age(p>0.05) (Table 4).

There was a statistically significant difference in the within-group differentiation of mean nerve root diameters ($\chi 2=278.225$, p<0.001, Friedman test). Post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied to were used to compare subgroups. The mean diameter of the C6 nerve root was higher than C7 and the mean diameter of the C7 nerve root was higher than C5 on both sides, according to both observer measurements (p<0.001) (Table 5).

Table 2. Measurement of cervical mean nerve root diameters(mm)

	Observer 1		Observer 2	
	Right	Left	Right	Left
C5	2.68 ±0.40	2.88±0.41	2.63 ± 0.38	2.66±0.42
C6	3.29 ± 0.56	3.15±0.56	3.30 ± 0.56	3.26±0.61
C7	2.88 ± 0.48	2.86±0.52	2.86 ± 0.52	2.90±0.50

Data are expressed as the mean± standard deviation

Table 3 a,b: Intraclass correlation coefficient for intra-observer(a) and inter-observer(b) measurement of mean nerve root diameters(mm).

Tablo 3a. Intraobserver variability

	Observer 1			Observer 2		
	ICC Value	%95 CI	P-Value	ICC Value	%95 CI	P-Value
R C5	0.901	0.845-0.936	<0.001	0.890	0.795-0.921	<0.001
R C6	0.935	0.901-0.957	<0.001	0.903	0.850-0.930	<0.001
R C7	0.905	0.858-0.937	<0.001	0.901	0.846-0.929	<0.001
L C5	0.823	0.702-0.911	<0.001	0.841	0.751-0.898	<0.001
L C6	0.870	0.788-0.919	<0.001	0.884	0.791-0.922	<0.001
L C7	0.870	0.806-0.914	<0.001	0.874	0.794-0.924	<0.001

R: Right, L: Left

Table 3b. Interobserver variability

	ICC Value	%95 CI	P-Value
R C5	0.948	0.916-0.967	<0.001
R C6	0.966	0.948-0.978	<0.001
R C7	0.950	0.923-0.968	<0.001
L C5	0.839	0.752-0.896	<0.001
L C6	0.931	0.881-0.958	<0.001
L C7	0.930	0.893-0.955	<0.001

ICC: Intraclass Correlation Coefficient; CI: Confidence Interval; p value significant at 0.05. R: Right, L: Left

Tablo 4. Spearman Rho correl ations between age, weight, height, and body mass index

			Observer 1						Observer 2					
			RC5	RC6	RC7	LC7	LC6	LC7	RC5	RC6	RC7	LC5	LC6	LC7
Spearman's rho	Age(years old)	Correlation Coefficient	.183	-.031	.118	-.021	.103	-.061	.173	.028	.007	.037	.128	-.050
		Sig. (2-tailed)	.096	.782	.284	.850	.351	.581	.116	.804	.947	.738	.246	.651
	Weight(kg)	Correlation Coefficient	-.027	-.093	-.242*	-.171	-.062	-.125	-.054	-.102	-.174	-.047	-.007	-.143
		Sig. (2-tailed)	.810	.400	.056	.119	.574	.256	.626	.355	.114	.668	.953	.195
	Height(cm)	Correlation Coefficient	-.079	.014	.067	-.108	.138	.097	-.131	.050	.064	.066	.127	.117
		Sig. (2-tailed)	.477	.896	.545	.329	.211	.379	.236	.654	.564	.550	.249	.287
	BMI (kg/m2)	Correlation Coefficient	-.073	-.184	-.196	-.086	-.018	-.209	-.024	-.167	-.201	-.071	-.004	-.184
		Sig. (2-tailed)	.512	.095	.074	.434	.871	.057	.829	.129	.067	.524	.973	.094
		N	84	84	84	84	84	84	84	84	84	84	84	84

Correlation is significant at the 0.05 level (2-tailed).

Table 5. Wilcoxon test for mean nerve root diameters

	Observer 1		Observer 2	
	Z-Value	P-Value	Z-Value	P-Value
R C6 – R C5	-7.257[b]	<0.001	-7.273[b]	<0.001
R C7 – R C6	-5.884[c]	<0.001	-5.502[c]	<0.001
R C7 – R C5	-3.530[b]	<0.001	-3.677[b]	<0.001
L C6 – L C5	-6.802[b]	<0.001	-6.977[b]	<0.001
L C7 – L C6	-6.037[c]	<0.001	-5.268[c]	<0.001
L C7 – L C5	-3.272[b]	<0.001	-3.824[b]	<0.001

a. Wilcoxon Signed Ranks Test b. Based on negative ranks c. Based on positive ranks R: Right, L: Left

DISCUSSION

Cervical nerve roots may be affected with some systemic diseases, such as tumors, neuropathies, inflammation, infection, and radiation (7, 8). Magnetic resonance imaging (MRI) and ultrasound (US) are commonly preferred imaging methods in the evaluation of cervical nerve roots (11). The main disadvantages of MRI are the long imaging times, the need for contrast material, they are expensive, and they are prone to motion artifacts (7). With its outstanding soft-tissue resolution and multiplanar examination characteristics, MRIs are still the most preferred method for evaluating the peripheral nervous system, and US can be used as a complementary method in selected cases (12).

In this prospective study, 84 healthy participants were recruited. To determine the reference values for the mean nerve root diameters of the cervical nerve roots, including the C5, C6, and C7 nerves, measurements were made immediately after their exit from the spinal foramina. The mean nerve root diameters of C5, C6, and C7 nerves were obtained on both sides. The association between the measurements and age, height, weight, body mass index (BMI), and hand dominance were then evaluated.

An important finding of this study was that the mean nerve root diameters of C5, C6, and C7 nerves could be evaluated by ultrasonography with an excellent intra- and interobserver reliability.

Sugimoto et al. (13), found no statistically significant correlation between C5, C6, and C7 mean nerve root diameters and sex in 60 healthy volunteers. In the same study, the relationships between the C6 and C7 nerve roots and the dominant hand were higher than

those of the non-dominant hand. Moreover, there was a statistically significant correlation between BMI and C6, while the same correlation with the C5 and C7 nerves could not be demonstrated (13). Perez et al. (14) found no statistically significant correlation between BMI and nerve root cross-sectional area (CSA) in 100 healthy volunteers. Moreover, they could not find a statistically significant relationship between the CSA values of the nerve roots and the dominant hand.

A correlation between age and mean nerve root diameter in the control group was not observed in the study conducted by Nodera et al. (15) in 35 patients with amyotrophic lateral sclerosis. They also failed to find a significant relationship between sex and mean nerve root diameters. A study by Boehm et al. (16) with 56 healthy subjects reported a weak negative correlation between the C6 mean nerve root diameter and age. Furthermore, there was no significant correlation between the C5 and C7 mean nerve root diameters and age. They also could not find a significant correlation between the C5, C6, and C7 nerve roots and height or weight. In another study by Takeuchi et al. (14), a correlation between the C5 nerve root transverse diameters and CSA values and height were observed bilaterally; however, no correlation was observed between the C6 and C7 measurements and height on either side. In our study, there were no significant relationships between the mean nerve root diameters of C5, C6, and C7, hand dominance, and sex. There were also no correlations between BMI and age and the mean diameters of the C5, C6, and C7 nerve roots. Therefore, there was no significant relationship between the diameters of the nerve roots of the C5, C6, and C7 and height on the right and left sides. Our study differs from other studies due to its interobserver structure and the fact that it included more participants and a wider range of ages. As a result, we consider our findings to be more accurate.

Takeuchi et al. (17) measured 219 cases of C5, C6, and C7 nerve root diameters, transverse diameters, and CSAs. They found that the nerve diameter of C5 was less than those of C6 and C7 on both the right and left sides. Similarly, in nerve root CSA measurements, the C5 nerve root was smaller than the C6 and C7 nerve roots. The C7 CSA was less than that of C6. Perez et al. (14) reported that the C5 nerve root CSA was less than that of C6 and C6 less than C7. Matsuoka et al. (18) examined 30 healthy volunteers and found the mean diameter of the C5 nerve roots was smaller than those of C6 and C7. Moreover, the mean C7 nerve root diameter was also greater than C6 in the same study. In our study, in accordance with Takeuchi et al. (17), the mean C6 nerve root thickness was greater than that of C7; however, the mean C7 nerve root thickness was greater than that of C5. We believe our study provides more accurate data on mean nerve root diameters due to its wider age range and the greater number of participants and interobserver assessments.

There were some limitations of our study. First, the number of cases was not sufficient to reach a definitive result. Second, the C8 and T1 nerve root measurements could not be included in the study due to technical problems. Third, as degenerative changes and osteophyte formations increase with older age, participants over 60 years of age were not included in the study. Finally, since our measurements were made only at the level of the nerve root, the measurements of the diameter at the fascicle and trunk levels may vary.

In summary, the normal range of cervical nerve root diameters should be determined to distinguish pathological conditions. In our study,the measurement of mean nerve root diameters of C5, C6, and C7 nerves is highly reproducible with excellent intra-observer and inter-observer agreement. Therefore, the measurement of nerve root diameter can be confidently performed in daily clinical practice.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval

The study was approved by the ocal ethics committee (approval number: 2019/1901). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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MEDICAL RECORDS-International Medical Journal

Araştırma Makalesi / Research Article

Romatoid Artrit Tanısı Almış Bireylerde Serum D Vitamini Seviyelerinin Hastalık Aktivitesi İle İlişkisi: Retrospektif Bir Çalışma

The Relationship of Serum Vitamin D Levels with Disease Activity in Individuals Diagnosed with Rheumatoid Arthritis: A Retrospective Study

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Oz

Amaç: Bu araştırmanın amacı, romatoid artrit tanısı almış bireylerde serum D vitamini seviyelerinin hastalık aktivitesi ile ilişkisini saptamaktır.

Materyal ve Metod: Kesitsel ve retrospektif olarak planlanan bu çalışma, Ekim 2019- Mart 2020 tarihleri arasında 337 romatoid artritli bireyin medikal dosyaları incelenerek tamamlandı. Araştırmaya, Romatoloji polikliniğinde takip edilen, hekim tarafından romatoid artrit tanısı konmuş ve en az 1 yıldır romatoid artrit rahatsızlığı olan bireyler dahil edildi. Veriler, araştırmacılar tarafından oluşturulan "Sosyodemografik ve Laboratuvar Tahlil Formu" ve "Hastalık Aktive Skoru-28" kullanılarak elde edildi. Verilerin analizi tanımlayıcı istatistikler, Kruskal Wallis, Mann-Whitney U testi ve Sperman korelasyon analizi ile yapıldı.

Bulgular: Araştırmaya katılan 337 romatoid artritli bireyin %83,4'ü kadın, yaş ortalaması 54,38±13,0, hastalık yılı ortalaması 4,08±3,67 ve hastalık akivitesi skor ortalaması 3,14±0,82 idi. Bireylerin %73,3'ünün D vitamini seviyesi ≤20 ng/mL'nin altındaydı. Romatoid artritli bireylerin D vitamini seviyesi ile yaş değişkeni arasında pozitif yönde zayıf bir ilişki, hastalık aktive skoru arasında ise negatif yönde zayıf bir ilişki olduğu belirlendi (p<0,05).

Sonuç: Bu çalışmada, romatoid artritli bireylerin büyük çoğunluğunda D vitamini eksikliği ve yetersizliği olduğu saptanmıştır. Romatoid artritli bireylerin D vitamini seviyelerinin değerlendirilip eksikliğin giderilmesine yönelik girişimlerin yapılması önerilmektedir.

Anahtar Kelimeler: Romatoid artrit; D vitamini; hastalık aktivitesi

Abstract

Aim: The aim of this study is to determine the relationship between serum vitamin D levels and disease activity in individuals diagnosed with rheumatoid arthritis.

Material and Method: This cross-sectional and retrospective study was completed between October 2019 and March 2020 by examining the medical files of 337 individuals with rheumatoid arthritis. Individuals with rheumatoid arthritis for at least 1 year who were followed up in the rheumatology outpatient clinic, diagnosed with rheumatoid arthritis by a physician, were included in the study. The data were obtained by using the "Sociodemographic and Laboratory Analysis Form" and "Disease Activity Score-28" created by the researchers. The analysis of the data was done by descriptive statistics, Kruskal Wallis and Mann-Whitney U tests and Sperman correlation analysis.

Results: Of the 337 individuals with rheumatoid arthritis participating in the study, 83.4% were female, the mean age was 54.38 ± 13.0, the mean year of illness was 4.08 ± 3.67 and the disease activity score was 3.14 ± 0.82. The vitamin D level of 73.3% of the individuals was below ≤20 ng / mL. It was determined that there was a weak positive relationship between the vitamin D level and age of individuals with rheumatoid arthritis, and a weak negative relationship with the disease activated score (p <0.05).

Conlusion: In this study, it was found that the majority of individuals with rheumatoid arthritis had vitamin D deficiency and insufficiency. It is recommended to evaluate the vitamin D levels of individuals with rheumatoid arthritis and to make attempts to eliminate the deficiency.

Keywords: Rheumatoid arthritis; Vitamin D; Disease activity

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GİRİŞ

Romatoid artrit (RA); eklem ağrısı, sertlik ve güçsüzlük ile karakterize olan, genellikle el ve ayaklarda deformite ve sakatlığa yol açabilen sistemik otoimmün bir hastalıktır (1). Dünya nüfusun yaklaşık % 1'ini etkilemekte ve kadın: erkek oranı 3: 1'dir (2, 3). RA'nın etiyolojisinde hormonal, çevresel ve enfeksiyöz faktörler gibi genetik ve genetik olmayan faktörler yer almaktadır (4). D vitamini, RA ile ilişkili çevresel faktörlerden birisidir ve D vitamini eksikliği veya yetersizliği birçok kronik hastalığın patogenezinde rol oynamaktadır (2). D vitamini eksikliğinde enfeksiyonlara ve otoimmün hastalıklara yatkınlık artmaktadır (5). Bu açıdan romatoid artrit gibi otoimmün hastalıkların oluşmasında D vitamini eksikliğinin rolü olduğu ileri sürülmektedir (6).

D vitamini, kemiğin sağlıklı mineralizasyonu, büyümesi ve yeniden şekillenmesi, anti mikrobiyal aktivite ve hücresel farklılaşmanın modülasyonuna kadar geniş bir biyolojik etki yelpazesine sahip önemli bir seko-steroid (pro) hormondur (3). Ayrıca D vitamininin kalsiyum homeostazı ve kemik metabolizması üzerindeki etkilerinin yanı sıra bağışıklık sistemi üzerinde de düzenleyici işlevlerinin olduğu ifade edilmektedir (5, 6). D vitaminin proinflamatuvar hücrelerin fonksiyonlarında azalma meydana getirerek immün toleransta artış olduğu, yani RA gelişimine doğrudan katılan hücreler üzerinde baskılayıcı işlevler uyguladığı bilinmektedir (3, 5).

Yapılan bazı çalışmalarda serum 25 (OH) D vitamini düzeyi ile hastalık aktivesi arasında ters bir ilişki olduğu saptanmıştır (3, 4, 7). Ayrıca düşük 25 (OH) D vitamini serum seviyeleri, tüm nedenlere bağlı mortalite açısından da yüksek risk ile ilişkilendirilmiştir. Şiddetli D vitamini eksikliği olan bireylerin ölüm oranı, D vitamini seviyesi ≥ 30 ng / mL olanlara göre neredeyse iki kat daha fazladır (2). Düşük serum 25 (OH) D vitamini düzeyi ile RA arasında bir ilişki olduğu ve D vitaminin düşük olması ile hastalık aktivitesinin de artacağı birkaç epidemiyolojik çalışmada gösterilmiştir (3, 8–10) ancak literatürde bunun aksini belirten çalışmalara da rastlanmıştır (4, 11–13). RA hastalarında hastalık aktivitesi ve D vitamini seviyesi arasındaki potansiyel ilişkiyi anlamak için hem objektif hem de subjektif hasta bazlı daha fazla çalışmaların yapılmasına ve yeni bulgulara ihtiyaç vardır. Bu nedenle bu araştırmanın amacı, RA tanısı almış bireylerde serum D vitamini seviyelerinin hastalık aktivitesi ile ilişkisini saptamaktır.

MATERYAL ve METOD

Araştırmanın Tipi: Bu araştırma, romatoid artrit tanısı almış bireylerde serum D vitamini seviyelerinin hastalık aktivitesi ile ilişkisini saptamak için kesitsel ve retrospektif olarak planlandı.

Araştırmanın Evren ve Örneklemi: Araştırmanın evrenini Ekim 2019- Mart 2020 tarihleri arasında bir üniversitenin Sağlık Uygulama ve Araştırma Hastanesi romatoloji polikliniğine muayene olmak için gelen, American College of Rheumatology (ACR) ve/veya American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) 2010 kriterlerine göre hekim tarafından RA tanısı konmuş ve en az 1 yıldır RA rahatsızlığı olan 360 birey oluşturdu. Hastaların bilgilerine ulaşmak için veri toplama tarihleri arasında hastane bilgi sistemindeki kayıtlar kullanıldı. Bilgi sistemindeki kayıtlar üzerinden formlar dolduruldu. Hastaların dosyalarından elde edilen veriler doğrultusunda dahil edilme kriterlerine uyan, DAS-28 skoru ve D vitamini düzeylerine bakılmış olan toplam 337 hasta örneklemi oluşturdu (Evrenin %93,6'sına ulaşıldı).

Verilerin Toplanması: Araştırmada veriler, araştırmacılar tarafından literatür incelenerek hazırlanan, hastaların sosyo-demografik verileri ve laboratuvar değerlerinin olduğu "Sosyodemografik ve Laboratuvar Tahlil Formu" ile hastalık aktivitesini değerlendirmek için kullanılan "Hastalık Aktivite Skoru -DAS-28 " ile toplandı.

Sosyodemografik ve Laboratuvar Tahlil Formu: Hastaların yaş, cinsiyet, hastalık süresi gibi sosyo-demografik ve D vitamini, ESH, WBC, CRP, Ca, AST, ALT, RF gibi klinik laboratuvar bilgilerini içeren toplam 12 sorudan oluşmaktaydı. Hastaların D vitamini seviyelerinin 20ng/ml altında olması "eksik", 21-29ng/ml arasında olması "yetersiz", "30ng/ml ve üzeri ise "normal" olarak değerlendirildi.

DAS 28 Skoru Hesaplama Formu: Hastalık aktivitesinin değerlendirilmesinde DAS28 skoru kullanıldı. Hastaların şiş eklem sayıları (ŞES), hassas eklem sayıları (HES) (28 eklem üzerinden), Vizüel ağrı skalası (VAS) ile eritrosit sedimantasyon hızı (ESH, mm/saat) verilerinden yararlanılarak DAS28 (Disease Activity Score) hesap edildi. Hesaplama DAS28=(0.56X HES 112)+(0.28 X ŞES l/2)+(0.7 X ESH)+ (0.014 X VAS) formülasyonu ile yapıldı. Hesaplama sonucunda 2,6 ve altında olması "remisyon", 2,6 ila 3,2 arasında olması "düşük hastalık aktivitesi", 3,2 ila 5,1 arasında olması "orta hastalık aktivitesi" 5,1 ve üzerindeki değerler ise "yüksek hastalık aktivitesi" olarak değerlendirildi (14).

Verilerin Değerlendirilmesi: Veriler, SPSS 21,0 paket programında analiz edildi. Veri dağılımının normalliğini değerlendirmek için Shapiro-Wilk testi kullanılmıştır. İstatistiksel değerlendirmede; tanımlayıcı istatistikler, Kruskal Wallis testi; Mann Whitney U testi, Ki-kare testi ve Spearman korelasyon analizinden yararlanıldı. Anlamlılık düzeyi, p değerinin 0.05'ten küçük olması şeklinde yorumlandı.

Araştırmanın Etik Yönü: Araştırmanın uygulanabilmesi amacıyla Burdur Mehmet Akif Ersoy Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik kurulundan etik kurul izni (Toplantı Tarihi: 04.09.2019; Karar No: GO 2019/135), araştırmanın yapıldığı hastane yönetiminden ve Romatoloji AD yazılı izin alındı.

BULGULAR

Araştırmaya katılan 337 RA tanısı almış bireyin %83,4'ü kadın, yaş ortalaması 54,38±13,0 (19-93), hastalık yılı ortalaması ise 4,08±3,67 (1-16) idi. DAS 28 skor ortalaması

3,14±0,82 (2-6,3) ve DAS-28 değerlendirmesinde %33,2'sinin orta şiddette hastalık aktivitesinde olduğu belirlendi. RA'lı bireylerin ESH, WBC, CRP, Ca, AST, ALT ve RF değerlerinin ortalaması sırasıyla 23,63±18,32mm/saat (2-111), 7,85±2,60 (3,6-19,23), 14,20±23,54mg/dl (1,20-200), 9,31±0,37 mg/dl (7,82-10,57), 23,57±12,01IU/L (6-133), 22,87±13,15U/L (5-103) ve 80,98±156,39 IU/ml (7-1050) idi. D vitamini ortalaması 17,51±11,01 (4,20-75,33) ve D vitamini seviyesi 20 ng/mL ve daha az olan 247 hasta (%73,3), 21-29 ng/mL arasında 58 hasta (%17,2) ve ≥30 ng/mL'nin üzerinde 32 (%9,5) hasta olduğu belirlendi (Tablo 1).

Araştırmaya katılan RA'lı bireylerin D vitamini düzeylerinin sosyo-demografik ve laboratuvar bulguları ile DAS-28 skoru karşılaştırılmasında, cinsiyet, hastalık süresi, DAS28 skoru, ESH, WBC, CRP, Ca, AST, ALT ve RF bulguları arasında anlamlı bir fark saptanmazken (p>0,05), yaş değişkeni ile anlamlı bir fark saptanmıştır (p<0,05) (Tablo 2).

Araştırmada yer alan RA'lı bireylerin D vitamini değerleri ile yaş arasında anlamlı pozitif yönde, DAS28 arasında ise anlamlı negatif yönde; yaş ile D vitamini, ESH, CRP ve AST arasında anlamlı pozitif yönde bir ilişki saptanmıştır. RA'lı bireylerin hastalık süresi ile ESH arasında anlamlı pozitif yönde, WBC arasında ise anlamlı negatif yönde; DAS28 ile D vitamini değerleri arasında ise anlamlı negatif yönde bir ilişki saptanmıştır. RA'lı bireylerin ESH, CRP ve WBC arasında anlamlı pozitif yönde; Ca ile WBC arasında anlamlı pozitif yönde; ESH ile yaş, hastalık süresi, DAS28, CRP ve WBC arasında anlamlı pozitif yönde bir ilişki saptanmıştır. RA'lı bireylerin CRP ile yaş, DAS28, ESH ve WBC arasında anlamlı pozitif yönde; WBC ile hastalık süresi arasında ise anlamlı negatif yönde bir ilişki saptanmıştır. RA'lı bireylerin DAS28, Ca, ESH, CRP ve RF arasında anlamlı pozitif yönde; AST ile yaş ve ALT arasında anlamlı pozitif yönde bir ilişki

Tablo 1. Hastaların sosyo-demografik ve laboratuvar değerleri

Özellikler	Sayı	Yüzde	Ort.±SS	Ortanca
Yaş			**54,38±13,0**	**55,00**
Cinsiyet				
Kadın	281	83,4		
Erkek	56	16,6		
Hastalık süresi, yıl			4,08±3,67	2,00
25 (OH) D Vitamini (ng/ml)			17,51±11,01	15,06
25 (OH) D Vitamini grubu (ng/ml)				
<20ng/ml (eksik)	247	73,3		
21-29ng/ml (yetersiz)	58	17,2		
30ng/ml ve üzeri (normal)	32	9,5		
DAS 28			3,14±0,82	2,90
DAS 28 grubu				
<2,6 (remisyon)	114	33,8		
2,6-3,2 (düşük hastalık aktivite-si)	93	27,6		
3,2-5,1 (orta şiddette hastalık)	112	33,2		
>5,1 yüksek hastalık aktivitesi	18	5,3		
ESH (mm/saat)			23,63±18,32	19,00
WBC			7,85±2,60	7,46
CRP (mg/dl)			14,20±23,54	5,91
Ca (mg/dl)			9,31±0,37	9,29
AST (IU/L)			23,57±12,01	21,00
ALT (U/L)			22,87±13,15	19,00
RF (IU/ml)			80,98±156,39	21,80

Ort±SS: Ortalama ± Standart sapma

Tablo 2. Hastaların verilerinin Vitamin D düzeyine göre karşılaştırılması

Özellikler	D Vitamini Düzeyi						*p*
	≤20ng/ml		21-29ng-ml		≥30ng/ml		
	Ort±SS	Ortanca	Ort±SS	Ortanca	Ort±SS	Ortanca	
Yaş (yıl)	53,21±13,23	54	56,82±12,31	57,5	59,03±11,01	57,5	**0,021**
Hastalık süresi (yıl)	4,21±3,77	2	3,98±3,65	2	3,28±2,88	2	0,646
DAS 28	3,14±0,81	2,90	3,16±0,88	2,85	3,06±0,83	2,90	0,751
Ca	9,33±0,37	9,29	9,25±0,32	9,28	9,26±0,44	9,29	0,407
ESH	23,11±19,02	18	24,68±17,20	22	25,75±14,60	20,5	0,143
CRP	13,39±22,14	5,83	16,58±29,57	6,42	16,17±22,12	7,58	0,814
WBC	7,89±2,61	7,56	7,48±2,54	7,07	8,21±2,65	7,44	0,188
AST	23,16±10,45	21	24,55±16,78	21	25,00±13,18	22	0,666
ALT	22,81±12,96	19	23,58±13,24	20	22,03±14,80	18,5	0,518
RF	84,53±161,96	20	59,05±120,21	23,6	93,28±170,87	25,3	0,906

Tablo 3. Hasta Verilerinin Korelasyon Analizi

Özellikler	Yaş	Hastalık Süresi	D Vitamini	DAS 28	Ca	ESH	CRP	WBC	AST	ALT	RF
Yaş	1	0,077	0,148	-,003	-,039	0,260	0,126	0,031	0,152	-,027	0,033
	-	0,160	0,006**	0,952	0,471	0,000**	0,021*	0,575	0,005**	0,624	0,551
Hastalık Süresi	0,077	1	0,029	-,055	-,053	0,153	-,018	-,118	0,090	-,004	0,019
	0,160	-	0,593	0,310	0,334	0,005**	0,745	0,030*	0,100	0,945	0,732
D Vitamini	0,148	0,029	1	-,104	-,072	0,077	-,024	-,063	0,066	0,023	-,020
	0,006**	0,593	-	0,046*	0,186	0,161	0,659	0,251	0,229	0,678	0,718
DAS 28	-,003	-,055	-,104	1	-,014	0,389	0,565	0,286	-,009	-,025	0,036
	0,952	0,310	0,046*	-	0,791	0,000**	0,000**	0,000**	0,866	0,641	0,506
Ca	-,039	-,053	-0,72	-,014	1	-,100	-,065	0,146	0,033	0,076	0,024
	0,471	0,334	0,186	0,791	-	0,066	0,230	0,007**	0,541	0,166	0,666
ESH	0,260	0,153	0,077	0,389	-,100	1	0,444	0,129	-,040	-,078	0,064
	0,000**	0,005**	0,161	0,000**	0,066	-	0,000**	0,018*	0,467	0,153	0,239
CRP	0,126	-,018	-,024	0,565	-,065	0,444	1	0,312	0,035	0,042	-,042
	0,021*	0,745	0,659	0,000**	0,230	0,000**	-	0,000**	0,521	0,438	0,438
WBC	0,031	-,118	-,063	0,286	0,146	0,129	0,312	1	-,029	0,064	0,144
	0,575	0,030*	0,251	0,000**	0,007**	0,018*	0,000**	-	0,598	0,244	0,008**
AST	0,152	0,090	0,066	-,009	0,033	-,040	0,035	-,029	1	0,581	0,013
	0,005**	0,100	0,229	0,866	0,541	0,467	0,521	0,598	-	0,000**	0,817
ALT	-,027	-,004	0,023	-,025	0,076	-,078	0,042	0,064	0,581	1	0,064
	0,624	0,945	0,678	0,641	0,166	0,153	0,438	0,244	0,000**	-	0,244
RF	0,033	0,019	-,020	0,036	0,024	0,064	-,042	0,144	0,013	0,064	1
	0,551	0,732	0,718	0,506	0,666	0,239	0,438	0,008**	0,817	0,244	-

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

bulunmuştur (p<0,05) (Tablo 3).

TARTIŞMA

Romatizmal hastalıklar alanında, D vitamininin, otoimmünitenin patofizyolojik mekanizmalarında önemli bir rol oynadığına dair kanıtlar artmaktadır (15-17). D vitamininin bağışıklık düzenleyici etkileri ve bağışıklık sistemi hücrelerinde D vitamini reseptörlerinin saptanması, D vitamini ve RA arasındaki ilişkiyi göstermektedir (2). Literatürde yapılan çoğu çalışmada otoimmün romatizmal hastalıklarda 25 (OH) D vitamini eksikliği prevalansının yüksek olduğu saptanmıştır (7-10, 17, 18). Mesci ve Geler Külcü (2017) yaptıkları çalışmada RA hastalarının D vitamini seviyelerinin 19,87±13,22 ng/mL olduğunu saptamışlardır (18). Ülkemizde son zamanlarda yapılan bir çalışmada RA'lı bireylerde D vitamin düzeylerinin sağlıklı kontrollerden anlamlı derecede düşük olduğu ve RA'lı bireylerin %73'ünde D vitamini eksikliği olduğu saptanmıştır (7). Sirbu ve ark. (2020) yılında yaptıkları çalışmada RA hastalarının %30'unda D vitamini seviyelerinin eksik ve %54'ünde ise yetersiz olduğunu saptamışlardır (17). Deng ve ark. (2020) yeni tanı konulan spondiloartrit hastalarında D vitamini düzeyleri ile ağrı ve hastalık aktivitesi arasındaki ilişki inceledikleri çalışmada, hastaların %35,1'inde D vitamini eksikliği olduğu ve hastaların %67'sinde serum 25 (OH) D seviyesinin 50 ile 75 nmol / L arasında olduğu belirlenmiştir (16). Bir başka çalışmada da RA hastalarının ortalama serum D vitamini düzeyinin 16,00 ± 8,91 ng / ml olduğu ve hastaların %62,5'inde D vitamini yetersizliği, %32,5'inde D vitamini eksikliği olduğu saptanmıştır (10). Çalışmamızda da RA'lı bireylerin D vitamini seviyelerinin düşük olduğu saptandı. Çalışmamız bu yönü ile literatür ile benzerlik göstermektedir.

Çalışmamız kapsamına alınan RA'lı bireylerin D vitamini düzeyleri ile cinsiyet, hastalık süresi, ESH, WBC, CRP, Ca, AST, ALT ve RF değerleri arasında istatistiksel olarak anlamlılık bulunmazken yaş değişkeni ile istatistiksel olarak bir anlamlılık bulunmuştur. Allam ve Radwan yaptıkları çalışmada RA'lı bireylerde D vitamini seviyesi ile yaş, hastalık süresi, ESH, CRP ve RF arasında anlamlı bir ilişki olmadığını saptamışlardır (4). Bir başka çalışmada da RA'lı bireylerin D vitamini seviyesi ile laboratuvar bulguları (Serum Ca, P, ALT, RF) arasında ilişki saptanmadığı belirlenmiştir (19).

Çalışmamız kapsamına alınan RA'lı bireylerin %27,6'sının düşük, %33,2'sinin orta ve %5,3'ünün yüksek hastalık aktivitesi gösterdiği saptandı. Ayrıca RA tanısı almış bireylerin serum D vitamini seviyesi ile DAS-28 skoru arasındaki ilişki incelediğinde; DAS28 ile D vitamini değeri arasında negatif korelasyon belirlendi. Literatür incelendiğinde birçok çalışma RA hastalarında yetersiz D vitamini seviyesi ile hastalık aktivasyonu arasında ters bir ilişkiden bahsetmektedir (10, 18, 20-22). Gupta ve ark. (2018) yılında yapmış oldukları çalışmada, D vitamini seviyesi ile hastalık aktivasyonu arasında anlamlı düzeyde ters bir ilişki saptandığı, hastalık aktivasyonunun yüksek olduğu grupta D vitamini düzeyinin daha düşük olduğunu bulmuşlardır (10). Borukar ve ark. (2017) RA hastalarının yaklaşık %69,0'ında "yüksek", % 30,9'unda "orta" düzeyde hastalık aktivite skoru olduğunu ve yüksek hastalık aktivite grubunda ortalama 25 (OH) D vitamini seviyesinin orta hastalık aktivite grubundaki hastalarından önemli ölçüde düşük olduğunu, serum D vitamini seviyesi ile DAS-28 skoru arasında negatif korelasyon olduğunu bildirmişlerdir (8). 150 RA hastası ve 150 sağlıklı bireyin serum D vitamini düzeyinin karşılaştırıldığı bir çalışmada RA hastalarının serum D vitaminin düzeyinin kontrol grubuna kıyasla anlamlı derece düşük olduğu ve D vitamini seviyesi düşük olan grupta hastalık aktivitesinin anlamlı düzeyde yüksek olduğu saptanmıştır (19). Maateen ve ark. (2017), Mesci ve Geler Külcü (2017) de çalışmalarında D vitamini seviyesi ile hastalık aktivasyonu arasında negatif yönde bir ilişki olduğunu saptamışlardır (18, 22). Literatürde çoğu çalışma RA'lı bireylerde serum D vitamini ile hastalık aktivitesi arasında negatif bir ilişki olduğunu bildirse de bunun aksini bildiren çalışmalar da mevcuttur (2, 7, 16, 17). Çalışmamızdan farklı olarak Deng ve ark. (2020) yaptıkları çalışmada yeni teşhis edilen spondiloartrit hastalarında D vitamini ile hastalık aktivitesi arasında bir ilişki olmadığını bildirmişlerdir (16). Bir başka çalışmada da 25 (OH) D vitamini düzeyi ve DAS28 skoru arasında anlamlı bir ilişki olmadığı, katılımcıların yaklaşık %19'unun yüksek, %40'ının orta ve %19'unun düşük hastalık aktivitesi gösterdiği saptanmıştır. Bununla birlikte, D vitamini seviyesinin ortalama değeri yüksek hastalık aktivite grubunda 14,24 ± 5,06 ng / mL, orta hastalık aktivite grubunda 22,37 ± 9,07 ng / mL ve düşük hastalık aktivite grubunda 22,55 ± 9,44 ng / mL olduğu bulunmuştur (17). Ülkemizde yapılan bir çalışmada da RA hastalarının %73'ünde D vitamini eksikliğinin saptandığı ancak D vitamini seviyesi ile hastalık aktivitesi arasında bir ilişki olmadığı saptanmıştır (7).

SONUÇ

Sonuç olarak, normal popülasyona kıyasla RA tanısı almış bireylerde D vitamini eksikliğinin daha sık olduğu görülmektedir. Ancak romatizmal hastalıklara sahip hastalarda D vitamini ile hastalık aktivitesi ilişkisini irdeleyen araştırmalarda çelişkili sonuçlarında elde edildiği görülmüştür. Çalışmamız mevcut literatürün çoğunluğu ile uyumlu olup RA'lı bireylerde serum D vitamini düzeyi ile hastalık aktivitesi arasında ters bir ilişkili olduğunu göstermiştir. Bu nedenle hem kemik sağlığının korunması hem de D vitamini eksikliği ile ilişkili hastalıkların riskini azaltmak için D vitamini seviyelerinin bilinmesi önemlidir. Bu doğrultuda RA'lı bireylerin tedavi protokollerinde D vitamini seviyelerinin de ölçülmesi ve eksiklik durumunda yerine konması gerekmektedir.

Araştırmanın Sınırlılıkları: Araştırma, RA'lı bireylerin dosyalarından elde edilen bilgilerle sınırlı tutulmuştur. Bu çalışma, ülkemizdeki romatoid artrit tanısı almış bireylerin genelini yansıtmamakta olup çalışmanın yapıldığı hastanedeki romatoid artrit tanısı almış bireyler ile sınırlıdır.

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MEDICAL RECORDS-International Medical Journal

Araştırma Makalesi / Research Article

Long-Term Effects of Neonatal LPS and Caspase -1 İnhibitor Administration on Gonadotropin Levels and Testicular Histology in Rats

Sıçanlarda Neonatal LPS ve Kaspaz-1 Inhibitörü Uygulamasının Gonadotropin Düzeyi ve Testis Histolojisi Üzerine Uzun Vadeli Etkleri

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Abstract

Aim: Endotoxins (lipopolysaccharides, LPS) negatively affect reproduction by decreasing gonadotropin levels in the acute period. The aim of this study is to investigate the long-term effects of re-injection of endotoxin in adulthood on gonadotropin release and testicular tissue in male rats injected with endotoxin with IL-1 beta inhibitor (Q-Vd-OPh; caspase-1 inhibitor, Cİ) in the neonatal period.

Material and Methods: On postnatal day 7, male rat pups were injected once with either Salin, LPS (50µg/kg), LPS (50µg/kg)+CI (1mg/kg). On postnatal 10 months, these rats were either injected with saline or LPS (50 µg/kg). 10 days after these injections, serum samples and testicular tissues were taken and the experiment was terminated.

Results: Respectively, control, Salin+LPS, LPS+Salin; LPS+LPS; LPS(CI)+Salin and LPS(CI)+LPS groups were 18.8±1.6; 11.3±1.2; 23.4±2.0; 22.2±1.2 ve 23.6±1.4 ng/ml for serum LH concentrations (p<0,05); while 33.4±2.5; 29.6±1.4; 32.1,6±2.0 28.7 0.8 and 35.5±3.3 ng/ml for FSH concentrations (p>0,05). Seminiferous tubule damage was observed in LPS groups (p<0,05).

Conclusion: This research demonstrates (1) neonatal LPS injections do not negatively affect gonadotropin release in the long term, (2) IL-1 β plays a critical role in the programming of reproduction, especially in terms of testicular histology.

Keywords: neonatal LPS; LH; FSH; seminiferous tubules; caspase-1 inhibitor

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Amaç: Endotoksinler (lipopolisakkaritler, LPS) akut dönemde gonadotropin seviyelerini düşürerek üremeyi negatif yönde etkilemektedir. Bu çalışmanın amacı, neonatal dönemde endotoksin ile birlikte IL-1 beta inhibitörü (kaspaz-1 inhibitörü, Cİ) enjekte edilen erkek sıçanlara erişkinlik döneminde tekrar endotoksin enjekte edilmesinin gonadotropin salınımı ve testis dokusu üzerine uzun vadeli etkilerini araştırmaktır.

Materyal ve Metod: Erkek sıçan yavrularına neonatal 7. günde Salin, LPS veya LPS+kaspaz-1 inhibitörü (Cİ) intraperitonal olarak enjekte edildi. Daha sonra 10. ayda her grup kendi içinde iki ayrı gruba ayrılarak yarısına salin diğer yarısına da aynı dozda LPS enjeksiyonu yapıldı. Bu enjeksiyonlardan 10 gün sonra serum numuneleri ve testis dokuları alınarak deney sonlandırıldı.

Bulgular: Sırasıyla kontrol, Salin+LPS, LPS+Salin; LPS+LPS; LPS(Cİ)+Salin ve LPS(Cİ)+LPS grupların için serum LH konsantrasyonları 18.8±1.6; 11.3±1.2; 23.4±2.0; 22.2±1.2 ve 23.6±1.4 ng/ml (p<0,05) iken FSH konsantrasyonları ise 33.4±2.5; 29.6±1.4; 32.1,6±2.0 28.7 0.8 ve 35.5±3.3 ng/ml (p>0,05) olarak tespit edildi. LPS gruplarında seminifer tübül hasarı görüldü (p<0,05).

Sonuç: Bu araştırma göstermektedir ki (1) neonatal LPS enjeksiyonları uzun vadede gonadotropin salınımını olumsuz yönde etkilememektedir, (2) IL-1 β, özellikle testis histolojisi açısından üremenin programlanmasında kritik bir rol oynamaktadır.

Anahtar Kelimeler: Neonatal LPS; LH; FSH; seminifer tübülleri; kaspaz-1 inhibitörü

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INTRODUCTION

It is well known that stressful stimuli, as infection or administration of endotoxin, can have profound negative effect on the activity of reproduction functions (1). Early life may shift the functional of bodily systems, and this contribute to later life health has been defined to as perinatal programming (2). Research investigating this fact has demonstrated long-term changes in immune, metabolic (2, 3), neuroendocrine function (4, 5) and behaviour (6-8). İt has been well to determined that the activity of hypothalamo-pituitary-gonadal (HPG) axis is disturbed by immunological stresses. LPS injection suppresses the activity of a GnRH pulse generator (9, 10), affects estrous cycle (9), delays puberty (11-13). İnterleukin-1 β has pivotal roles in the LPS induced suppression of the HPG axis (9, 14, 15). Recently, a broad spectrum caspase inhibitor has been developed in which a carboxy terminal phenoxy group is conjugated to the amino acids valine and aspartate (Q-VD-OPh). The administration of QVD-OPH, a caspase inhibitor (CI), causes a decrease in IL-1α and IL-1β (16).

In the present study, we examined the effects of neonatal and prepubertal LPS administration on response testicular histology, serum LH and serum FSH levels. In addition, we determined this effects of neonatal LPS administration role of interleukin-1 β inhibition with caspase-1 inhibitor.

MATERIAL AND METHODS

Animals and Experiment Protocols

Pregnant Wistar-Albino rats (INUDEHUM, Turkey) were housed under controlled conditions (12L:12D; 22±2 °C) and supplied with ad libitum food and water. This study was approved Animal Research Ethics Committee of Inonu University Medical Faculty (Protocol # 2010/54). On pnd 7, the pups were administered either saline, or 50 g/kg LPS (Escherichia coli O111:B4, Sigma L-2630), or 50 g/kg LPS plus 1 mg/kg Q-Vd-OPh (Biovision, California, USA) by intraperitoneal (i.p.) injection. C1i (50 L) was injected 60 min after LPS injection (see Figure 1). The timing of C1i administration in relation to the timing of the LPS injection and this dose were determined from the literature (17). At pnd 7, the control group received both the vehicle for Q-Vd-OPh (i.e., DMSO). At pnd 30, each group was further subdivided into 2 groups, and one of these 2 groups received sterile physiologic saline solution (50 L) and the other received LPS (50 g/kg, 50 L).

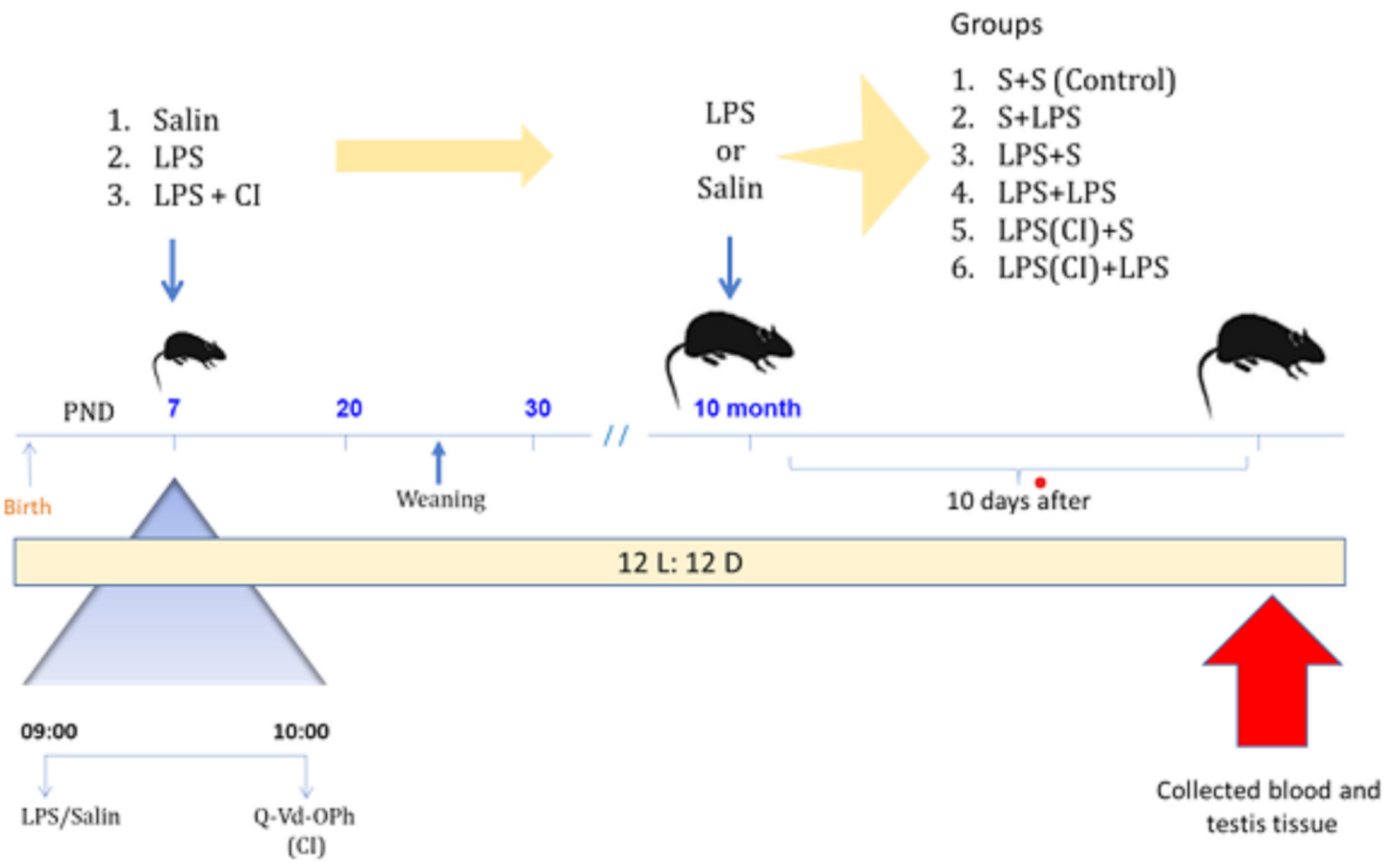

Figure 1. Experimental protocol

Histolopathologic Examination

Testis tissue was fixed in 10 % formol and was embedded in paraffin. Sections of tissue were cut at 5 µm, mounted on slides, stained with hematoxylin-eosin (H-E).

Semiquantitative Evaluation

The diameter and germinative cell layer thickness of the seminiferous tubule (ST) from twenty different areas of each testis were measured using a Leica Q Win Plus Image Analysis System (Leica Micros Imaging Solutions Ltd, Cambridge, United Kingdom) at 10X. Histopathological evaluations were performed according to Sayım F method except minor revision (18). Histological changes were detected by counting 100 tubules in slides stained with H-E. One hundred tubules per animal were examined and classified as normal, sloughing, spermatogenic arrest and germ-cell degeneration based on the degree of seminiferous tubule damage.

The tubules with sloughing were those that showed disrupted cell association. Tubules with anormal shaped cells were classified as tubules with germ cell degeneration. Tubules with interrupted spermatogenic cells at various stage of mitotic phase were classified as tubules with spermatogenic arrest.

LH and FSH enzymeimmunoassays

LH and FSH were analyzed according to Pappa et al. (19) with some modifications. Briefly, 96-well immunoplates (Nunc, Roskilde, Denmark) were coated with rat LH or rat FSH. Serum samples or standards were preincubated with primary antibodies and were then transferred into coated plates for competition with antigens on the solid phase. Plates were washed and the secondary antibody conjugated to streptavidin peroxidase was added into each well and color was developed by using tetramethylbenzidine as the substrate. Plates were read at 450 nm using a plate reader (Biotek, Synergy HT, USA). Rat LH, rat FSH and primary antibodies (rabbit anti-rat LH and rabbit anti-rat FSH) were obtained from Dr. A.F. Parlow (NIDDK, NIH, USA) and secondary antibodies (goat anti-rabbit IgG) conjugated to streptavidin peroxidase was purchased from Sigma (Sigma-Aldrich, Taufkirchen, Germany). Sensitivity of the assays was 1 ng/ml for LH and 2 ng/ml for FSH. Inter- and intra-assay coefficients of variations were below 8 % for both LH and FSH.

Statistical analysis

SPSS 25.0 program was used for statistical analysis. The results were compared with Kruskal-Wallis variance analysis. Where differences among the groups were detected, group means were compared using the Connover test. Values of $p<0.05$ were considered significant. All results were expressed as means ±standart error (SE).

RESULTS

There was no significant difference between the groups in terms of FSH levels. LH levels were found to be statistically lower in the Saline + LPS group compared to the control. The data of LH and FSH findings are presented in Table.3.

Morphological damage ranged from none (control) to slight LPS(CI)+S to moderate S+LPS and LPS+S and to severe LPS+LPS and LPS(CI)+LPS. In control group, the seminiferous tubules were intact and germ cells organized in concentric layers (Figure 2). Histopathological observation showed that LPS administration caused testicular damage characterized by sloughing, spermatogenic arrest and degenere germ cell. Numerous round germ cells which detected from spermatogenic layers were observed in the some seminiferous lumen in these groups (Figure 3A, 3B and 3C) Also seminiferous tubules containing arrested spermatogenic cells at various stage of division and degenerative changes in germinal cells were observed in LPS groups (Figure 4A, 4B and 4C). The most obvious damage was found in LPS+LPS group compare with LPS-S and S-LPS groups. The most affected group between the single dose LPS groups was detected as LPS-S group. ($p=0.009$). On the other hand, the number of affected seminiferous tubules in the LPS(CI)+S group was significantly lower according to LPS+S and S+LPS groups ($p<0.05$).

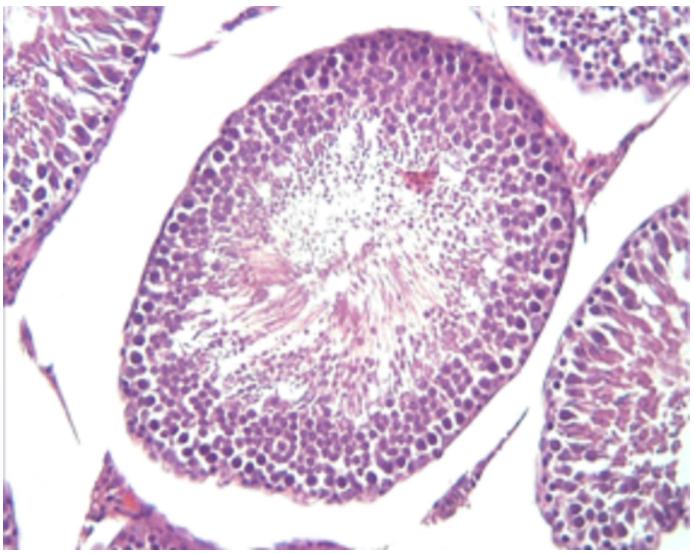

Figure 2. Control; Normal histological view of seminiferous tubules. H-E X66

In LPS(CI)+S group, seminiferous tubules were nearly similar to the control group except disintegration of spermatogenic layer observed in some of the tubules (Figure 5A).

Ci treatment was not found effective on given two dose LPS group. Although intact seminiferous tubular was recognized as increased in LPS(CI)+LPS group, the lesions did not completely ameliorate. Disordered testicular epithelium, degenerative changes in germinal cells and arrested spermatogenic cells were still present in this group (Figure 5B).

Moreover decreased mean seminiferous tubule diameter and decreased germinal cell layer thickness

were prominent in group given two dose LPS group. CI administration was not improved the decreased seminiferous tubule diameter and germinal cell layer. The results of the histopathological classification of the seminiferous tubules, diameters seminiferous tubules (DST) and germinal cell layer thickness (GCLT) were given Table 1 and Table 2.

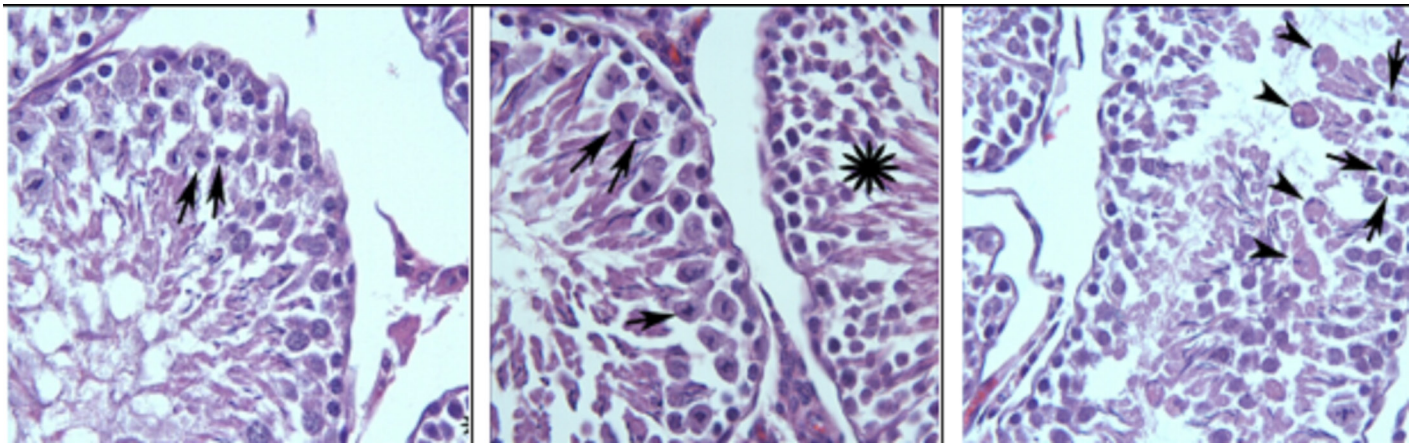

Figure 3. (A) S+LPS; disorder of testicular epithelium is seen in the tubule of top (B) LPS+S; notice the accumulation of immature germ cells in the lumen (C) LPS+LPS large number ofi immature germ cells in the lumen are present due to disruption of cell–cell contacts. H-E X66

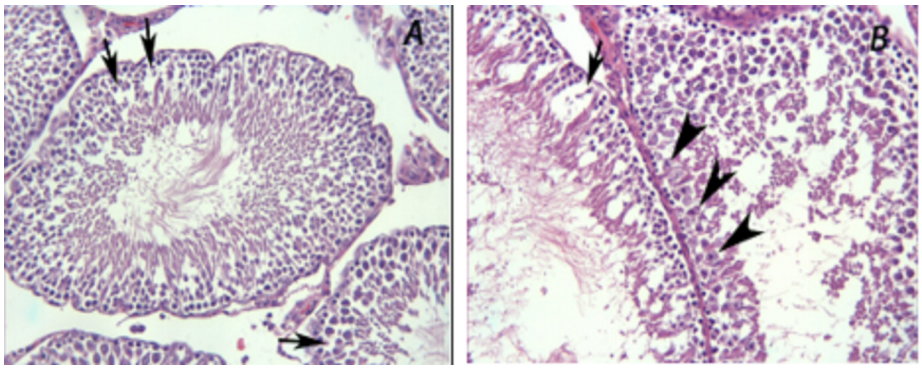

Figure 4. (A) S+LPS and (B) LPS+S; spermatogenic arrest (arrows) is observed in the tubule of left but the other tubules (stars) show nearly normal histologic appearance; (C) LPS+LPS; Degenere spermatogenic cells (head arrows) are visible in seminiferous tubule. H-E X132

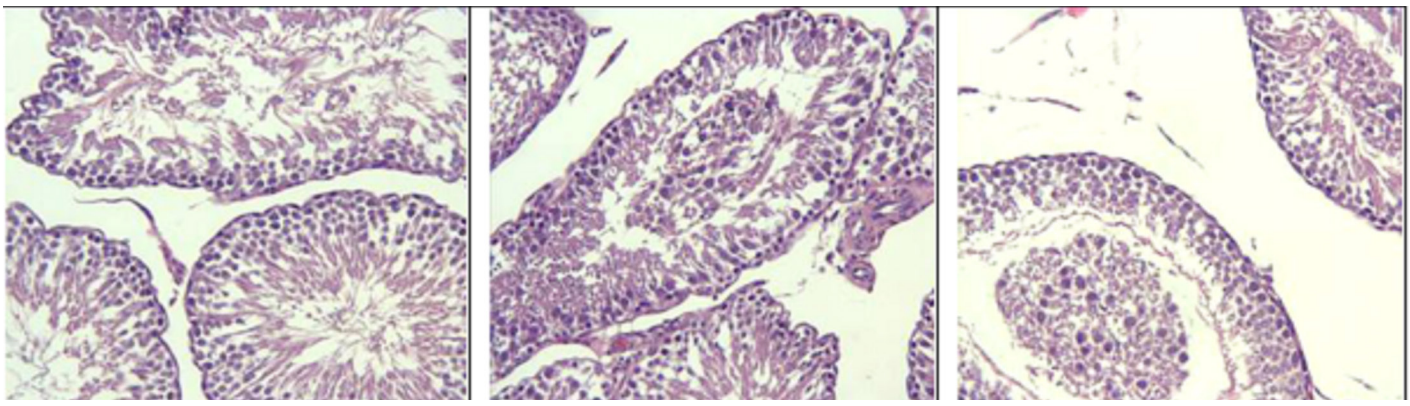

Figure 5. (A) LPS(CI)+S; testicular histology revealed normal except the disintegration of spermatogenic layer (arrows) of some tubules (B) LPS(CI)+LPS; Disordered testicular epithelium (arrow) and spermatogenic arrest (head arrows) are still evident. H-E X 66

Table 1. Percentage (%) of histopathological classification of the seminiferous tubules in the testis

	Control	S+LPS	LPS+S	LPS+LPS	LPS(CI)+S	LPS(CI)+LPS
Intact	99.0 ± 0.3	77.6 ± 0.7[a]	69.2 ± 0.3[a]	49.4 ± 1.8[a,b]	90.8 ± 0.5[a,c]	57.0 ± 0.6[a]
Sloughing	0.0 ± 0.0	7.6 ± 0.8	14.2 ± 1.1	15.0 ± 1.7	1.8 ± 0.3[b]	21.6 ± 0.5
SA	0.0 ± 0.0	10.4 ± 0.7	10.4 ± 0.8	27.0 ± 0.8[c]	6.8 ± 1.0	12.4 ± 0.9[d]
GCD	1.0 ± 0.4	4.4 ± 0.5	6.2 ± 0.5	8.6 ± 0.5	0.8 ± 0.3	9.0 ± 0.3

SA: Spermatogenic arrest; GCD: Germ-cell degeneration
[a]Significantly decreased when compared with control group (p<0.05).
[b]Significantly decreased when compared with S-LPS and LPS-S groups (p<0.05).
[c]Significantly increased when compared with S-LPS and LPS-S groups (p<0.05).
[d]Significantly decreased when compared with LPS-LPS group (p<0.05).

Table 2. Diameters seminiferous tubules (DST) and germinal cell layer thickness (GCLT)

	Control	S+LPS	LPS+S	LPS+LPS	LPS(CI)+S	LPS(CI)+LPS
DST	634,4 ± 6,4	642,9 ± 6,0	605,5± 7,0[a]	590,6± 6,8[a]	595,0 ± 6,6[a]	589,6 ± 5,8[a]
GCLT	100,6 ± 1,6	94,6 ± 1,6[a]	90,3 ± 1,4[a]	88,1 ± 1,5[a]	82,2 ± 1,1[a]	76,4 ± 0,9[a]

[a]Significantly decreased when compared with control group (p<0.05).

Table 3. Serum LH and FSH concentrations of the groups

	Control	S+LPS	LPS+S	LPS+LPS	LPS(CI)+S	LPS(CI)+LPS
LH	18.8 ± 1.6	11.3 ± 1.2[a]	23.4 ± 2.0	22.3 ± 1.5	22.2 ± 1.2	23.6 ± 1.4
FSH	33.4 ± 2.5	29.6 ± 1.4	32.1 ± 2.0	35.1 ± 2.6	28.7 ± 0.8	35.5 ± 3.3

[a]Significantly decreased when compared with control group (p<0.05).

DISCUSSION

Immune stress can cause reproductive dysfunction. Some hypothalamic factors such as pro-inflammatory cytokines play pivotal roles in reproductive disorders under immune stress conditions. According to the data we obtained from our study, the lowest LH level was seen in the S+LPS group, while the lowest FSH level was found in the LPS(CI)+S group. It was determined that the effect of LPS on gonadotropin production in the neonatal period was lower. LPS-induced changes does not alter the effects of LPS on the serum levels of LH or testosterone, in adult male rats (20). Another study reported that the reduction in sexual behavior induced by neonatal stress was not associated to androgen levels in male rats (21). Munkhzaya et al reported that immune stress did not suppress LH secretion in the early neonatal period in rats (22). According to the literature information, it is seen that a single LPS injection in the neonatal period does not affect androgen release in the long term. It was determined that the LH and FSH levels obtained in the present study were negatively affected by the second injection in the postnatal period rather than the neonatal period. In addition, it was determined that caspase inhibitor had no permanent effect on androgen levels.

In our study, it was determined that LPS administration caused testicular damage and the most damage was seen in the groups receiving double dose LPS. The seminiferous tubule diameters and the thickness of the germinal cell layer of the groups receiving double-dose

LPS decreased. The effect of the caspase inhibitor on this increase was not observed. In the neonatal period, the level of seminiferous tubules affected in the group in which caspase inhibitor was applied with LPS was similar to that of the control. Therefore, the group least affected by LPS was the LPS(CI) group. LPS+S was the most affected group in the single dose LPS groups. As a result, it has been observed that the caspase inhibitor has a protective role in the groups receiving a single dose of LPS, but it is not effective in preventing the degenerative effects of the second LPS on the testis in the later periods. In a study investigating the effect of LPS on spermatogenesis in adult mice at different times, it was reported that harmful effects were observed after 60 days on spermatogenesis (23). It has been reported that LPS-induced cytokine activation causes pathogenic damage in testicular tissue (24). Bacterial infection and inflammation of the testis impairs fertility, yet an understanding of inflammatory responses of the testis is incomplete (25).

According to our findings, neonatal LPS administration does not affect gonadotropin release in the long term. In addition, it is thought that IL1-beta secreted during immune challenge may have negative effects on testicular histology.

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Araştırma Makalesi / Research Article

The Role of Thiol-Disulfide Hemostasis in Predicting Renal İnjury After Coronary Artery Bypass Graft Surgery

Koroner Arter Bypass Greft Ameliyatı Sonrası Böbrek Hasarını Öngörmede Tiyol-Disülfid Hemostazın Rolü

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Abstract

Aim: EInflammation andoxidative stres play an active role in renal injury that develops after open heart operations as in many diseases. There is a balance between oxidants and antioxidant defense mechanisms, and in the morbidity of cardiac surgery patients, this balance is thought to change depending on many factors.

Materials and Methods: 76 patients scheduled for coronary artery bypass graft surgery were included in the study. Demographic and operation information of the patients were recorded. In addition to routine blood parameters, blood samples were taken forthiol / disulfid hemostasis parameters. Patients who did not develop acut kidney injury (AKI) after the operation were recorded as Group 1 and those who developed register as Group 2.

Results: Postoperative AKI developed in 19 (25%) patients included in the study. When the thiol-disulfide hemostasis parameter values obtained from the blood sample taken within the first 2 hours after the introduction of intensive care after the operation of the patients, there was no difference between the two groups in terms of native thiol, total thiol, disulfide / native thiol and native thiol / total thiol values. In Group 2, disufide and disulfide / total thiol values were significantly higher (P = 0.018, P = 0.009).

Conclusion: We believe that the values of disulfide and disulfide / total thiol ratio, which are among the parameters of thiol-disulfide hemostasis, in the postoperative period may be predictors for AKI.

Keywords: Oxidative stres parameters; thiol levels; disulfide; kidney injury; cardiac surgery

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Amaç: İnflamasyon ve oksidatif stres, birçok hastalıkta olduğu gibi açık kalp ameliyatları sonrası gelişen böbrek hasarında da aktif rol oynamaktadır. Oksidanlar ve antioksidan savunma mekanizmaları arasında bir denge vardır ve kalp cerrahisi hastalarının morbiditesinde bu dengenin birçok faktöre bağlı olarak değiştiği düşünülmektedir.

Materyal ve Metod: Koroner arter baypas cerrahisi planlanan 76 hasta çalışmaya dahil edildi. Hastaların demografik ve operasyon bilgileri kaydedildi. Rutin kan parametrelerine ek olarak tiyol / disülfid hemostaz parametreleri için kan örnekleri alındı. Ameliyat sonrası akut böbrek hasarı (AKI) gelişmeyen hastalar Grup 1, gelişen hastalar Grup 2 olarak kaydedildi.

Bulgular: Çalışmaya dahil edilen 19 (% 25) hastada postoperatif AKI gelişti. Hastaların operasyon sonrası yoğun bakıma alınmasından sonraki ilk 2 saat içinde alınan kan örneğinden elde edilen tiyol-disülfid hemostaz parametre değerleri incelendiğinde, iki grup arasında nativ tiyol, total tiyol, disülfid / nativ tiyol ve nativ tiyol / total tiyol değerleri açısından fark yoktu. Grup 2'de disülfid ve disülfid / total tiyol değerleri anlamlı olarak yüksekti (P = 0.018, P = 0.009).

Sonuç: Postoperatif dönemde tiyol-disülfid hemostaz parametreleri arasında yer alan disülfid ve disülfid / total tiyol oran değerlerinin AKI için öngörücü olabileceğine inanıyoruz.

Anahtar Kelimeler: Oksidatif stres parametreleri; tiyol seviyeleri; disülfid; böbrek hasarı; kalp cerrahisi

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INTRODUCTION

Open heart surgeries are common operations in many heart diseases, such as coronary and heart valve diseases. The use of the cardio pulmonary bypass (CPB) system in these surgeries increases technical success. However, as a result of using this system, the blood comes into contact with extravascular surfaces, thus inflammatory pathways are activated. This can lead to various complications such as cerebrovascular accident, mesenteric ischemia, renal failure and mortality.

Although acute kidney injury (AKI) is monitored at a rate of 5-30% after cardiac surgery, the need for renal replacement may occur in 1-2% of these patients (1). Many factors play a role in the emergence of this condition, such as prolonged perfusion times, increased age, presence of preoperative renal insufficiency and increased blood product transfusion (2,3). Inflammation and oxidative stres play an active role in renal injury that develops after open heart operations, as in many diseases. Various inflammatory markers in this area have been investigated in predicting postoperative AKI (4,5).

In recent years, it has been revealed that thiol-disulfide hemostasis can be an important biomarker of oxidative stres (6). Thiol is a compound containing sulfhydryl group (-SH), which plays an important role in preventing oxidative stress in cells. Thiol groups are converted to reversible disulfide structures by oxidant radicals. These disulfide structures can be reduced back to thiol groups, there by maintaining thiol-disulfide homeostasis, which is important for many cellular processes, such as the antioxidant defense system. Thiol-disulfide homeostasis can indirectly reflect the oxidative stres state of the organism. There is a balance between oxidants and antioxidant defense mechanisms and it is thought that this balance varies depending on many factors in the morbidity of cardiac surgery patients (7).

In this study, we aimed to investigate the role of thiol-disulfide hemostasis parameters in predicting AKI after coronary artery bypass graft (CABG) surgery accompanied by CPB.

MATERIAL AND METHODS

Study Design

In this prospective study, CABG patients with elective CPB in our clinic between March 15, 2019 and November 15, 2019 were included. The study started after the approval of the local ethics committee (HRU / 25.02.2019). Patients with emergency operations, those with creatinine>1.5mg / dl in the preoperative period, who underwent percutaneous coronary angiographic intervention in the last 24 hours, who had systemic inflammatory disease, reoperations and streorid treatment were excluded from the study. As a result of exclusion criteria, 76 consecutive patients were included in the study.

Demographic and preoperative features (Age gender, body mass index (BMI), hyperlipidemia, hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD) and current medical treatments (acetyl salicylic acid, angiotensin receptor blocker therapy) smoking, routine blood parameters etc.), as well as operative (cross clamp times, total perfusion times, graft counts, total amount of blood product used) and postoperative data (routine blood parameters, renal injury status as a result of creatinine measurement, total blood product usage, thorax tube drainage amounts, hospital and intensive care hospitalization times etc.) were recorded. In addition, for the thiol-dylsulfide hemostasis parameters, which is the main hypothesis of the study, blood samples were taken twice, after anesthesia induction before surgery and 2 hours after being taken to the postoperative intensive care unit. Patients who did not develop AKI after the operation were recorded as Group 1 and those who developed register as Group 2.

Anaesthesia Management

After routine anesthesia induction, the patients were intubated and ventilated with tidal volume of 6-8 ml / kg, end-tidal carbon dioxide (ETCO2) 30-40 mmHg in 50% O2-air mixture. Median sternotomy incision was applied to all patients. Vasopressor or vasodilator agents were given when mean arterial pressure (MAP) values were ± 20% from basal values during the CPB period. MAP values were adjusted to be in the range of 65-70 mmHg. In the nonpulsatile KPB period, 2.4 L / min / m2 flow was provided according to the body surface area. In this period, MAP values were adjusted to be 55-65 mmHg. ACT (activated clotting time) values were checked with 30-minute periodic measurements until the CPB was discontinued and the cannulas were removed. At the end of the operation, controlled extubation was planned by taking all patients to mechanical ventilation support in the intubated intensive care unit.

Identification of Postoperative RenalInjury

Renal injury status after the operation was determined according to the criteria of Acute Kidney Injury Network (AKIN) (8). This staging is done as follows:

Stage 1: 1.5-2 times increase or>0,3 mg / dl increase compared to basal value

Stage 2: 2-3 times increase in creatinine value

Stage 3: Creatinine increase more than 3 times or 4mg/dl increase or renal replacement therapy is required

Patients who met the above-mentioned criteria in the postoperative hospital were accepted as the group of patients developing AKI. This situation was accepted as the primary end point of the study.

Analysis of blood parameters

Routine blood parameters of the patients were evaluated from the blood samples taken from antecubital veins before the operation. Complete blood countand biochemical parameters were measured with automatic analyzers. Thiol-dylsulfide hemostasis parameters

were studied from the blood samples taken before the operation (t1) and upon arrival to the intensive care unit (t2). The sesamples were centrifuged at 3000 rpmfor 10 minutes and then stored at -80 °C until analysis. Thiol disulfide hemostasis parameters were measure dusing the spectrophotometric method developed by Erel and Neselioglu using commercially available kits (Rel Assay Diagnostics, Turkey) (9).

From the measured total thiol and native thiol values; disulfid, disulfide / native thiol ratio, disulfide / total thiol ratio and native thiol / total thiol ratios were calculated.

Statistical Analysis

All statistical analyses were performed using the Statistical Package fort the Social Science (SPSS) software (SPSS, Microsoft Inc. an IBM Company, Chicago, USA) version 21.0. "Kolmogorov-Smirnov test and Shapiro-Wilk test" were used for normality distribution. While "Student's t test" was used for the data with normal distribution, "Mann-Whitney U test" was used for the data that did not comply with the normal distribution. "Chi Square test" was used to compare nominal data. P value below 0.05 was considered significant. Logistic regression analysis was performed for the appropriate variables in predicting AKI emerging after CABG surgery. Receiving operating characteristic (ROC) curve analysis was performed for postoperative disulfide and disuffid / total thiol, and the area under the curve (AUC) was calculated.

RESULTS

A total of 76 patients were included in the study and 19 (25%) patients were found to develop postoperative AKI. Group 1 had 57 patients and their average age was 58.6 ± 9, while Group 2 had 19 patients and their average age was 61.7 ± 8.2. There was no difference between the groups in terms of age, gender, BMI, hyperlipidemia, HT, DM, COPD and their current medical treatments (such as acetyl salicylic acid, angiotensin receptor blocker therapy). The time from coronary angiography to operation was significantly less in Group 2 (P = 0.037) (Table 1).

Table 1. Preoperative variables and demographic datas of the patients

Characteristics	Group 1 (n=57)	Group 2 (n=19)	P value
Age (years) mean±sd	58.6±9	61.7±8.2	0.180†
Male gender, n(%)	40 (70.1)	11 (57.8)	0324 *
Previous PCI, n(%)	15 (26.3)	6 (31.5)	0.758*
Hypertension, n(%)	24 (42.1)	7 (36.8)	0.685*
Hyperlipidemia, n (%)	25 (43.8)	9 (57.8)	0.593*
PAD, n (%)	7 (12.2)	3 (15.7)	0.894*
COPD, n (%)	8 (14)	5 (26.3)	0.427*
BMI (kg/m2)	29.3±5.1	30.7±6.8	0.278†
Diabetes mellitus, n (%)	20 (35)	8 (42.1)	0.585*
Smoking, n (%)	21 (36.8)	6 (31.5)	0.676*
Angiography to operation time, (days)	3 (2, 85)	3 (2, 30)	0.037‡
ASA use, n (%)	50 (87.7)	16 (84.2)	0.812*
ACE-I/ ARB use, n(%)	19 (33.3)	5 (26.3)	0.447*
Ejection fraction (%)	50 (35-65)	50(30-60)	0.554
EuroScore II	1.8 (0.5- 4.8)	2.1 (0.5- 5.2)	0.077‡

Student's t test, * Chi-square test, ‡Mann Whitney U test (Data is expressed as median (interquartile range))ACE-I: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin-receptor blocker, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, PCI: Percutaneus coronary intervention, PAD: Peripheral artery disease

Preoperative laboratory parameters data of the patients are given in Table 2. There was no difference between the groups in terms of hemogram parameters, C-reactive protein, albumin and thiol hemostasis parameters in the preoperative period. Preoperative creatinine values were significantly higher in Group 2 (P = 0.016). Parameter values of thiol-disulfid hemostasis obtained from the blood sample taken with in the first 2 hours at the entrance to intensive care after the operation of the patients are given in Table 3. There was no difference between the two groups in terms of native thiol, total thiol, disulfide / native thiol and native thiol / total thiol. In Group 2, disufide and disulfide / total thiol values were significantly higher (P = 0.018, P = 0.009, respectively).

Other peroperative variables of the patients are given in Table 4. There was no difference between the groups in terms of distal anostomosis numbers, perfusion times, total postoperative drainage amounts, and time to postoperative extubation. Positive inotropic requirement rates, total amount of blood product used, intensive care and total hospital stay were significantly higher in Group 2

Table 2. Preoperative laboratory values of the patients

Characteristics	Group 1 (n=57)	Group 2 (n=19)	p value
Hemoglobin (g/dL)	13.5 (12.8- 15.7)	13.1(12.6-15.9)	0.418‡
White blood cell (103/µL)	7.9 (6.3- 9.9)	8.1 (6.4- 10.7)	0.554‡
Neutrophil (103/µL)	4.2 (3.3- 8.1)	4.5 (3.4- 9)	0.317‡
Lymphocyte (103/µL)	2.1 (0.8- 3.3)	1.9 (0.7-3.2)	0.259‡
Creatinine (mg/dL)	0.8 (0.3- 1.42)	1.2 (0.4- 1.49)	0.016‡
C Reactive protein (mg/dL)	8.7 (1.9- 33.7)	9 (2-35.2)	0.610‡
Albumin (g/L)	39 (35- 50)	38.7 (34.2- 54)	0.526‡
Nativethiol (µmol/L)	115.9 (12.9-273)	137.8 (31.9-245.3)	0.278
Total thiol (µmol/L)	186.1 (53.3-490.2)	208.4 (104.7-465.6)	0.305
Disulfide (µmol/L)	33.1 (1.1-131.5)	35.8 (10.4-110.2)	0.102
Disulfide/native thiol	29.4 (0.6-165.1)	35.4 (5.9-114.1)	0.976
Disulfide/total thiol	18.5 (0.6-38.4)	19.7 (5.3-34.8)	0.271
Native thiol/total thiol	63 (23.2-98.7)	58.6 (30.5-89.4)	0.981

†Student's t test (Data is axpressed as mean±sd), ‡Mann Whitney U test (Data is expressed as median (interquartile range)

Table 3. Admission to intensive care unit (t2) thiol-disulfide homeostasis parameters of the patients

Characteristics	Group 1 (n=57)	Group 2 (n=19)	P value
Native thiol (µmol/L)	134.2 (15.5-359.8)	131.8 (84.5-275.3)	0.606‡
Total thiol (µmol/L)	192 (33.9- 640.4)	206.4 (92.6- 529.5)	0.265‡
Disulfide (µmol/L)	26.7 (0.9-160.1)	37.6 (4.1-172.7)	0.018‡
Disulfide/native thiol	19.7 (0.6-104.1)	27.4 (4.6-69.8)	0.181‡
Disulfide/total thiol	14.8±7.9	19.4±7.1	0.009†
Native thiol/total thiol	70.3±15.8	65.1±14.3	0.193†

†Student's t test (Data is axpressed as mean±sd), ‡Mann Whitney U test (Data is expressed as median (interquartile range),

Table 4. Peroperative variables of the patients

Characteristics	Group 1 (n=57)	Group 2 (n=19)	P value
Distal anostomosis number	3 (1- 5)	3 (1- 5)	0.959‡
CCt (minutes)	92.8±34.5	98.8±34.1	0.516†
TPt (minutes)	117.2±33.2	127.8±35.7	0.242†
Total chest tube drainage (ml)	550 (250- 900)	500 (300- 1100)	0.211‡
Packed blood products (units)	5 (4, 12)	7 (4, 16)	0.018‡
Inotropic support, n (%)	12 (21)	11 (57.8)	0.002*
Extubation time (hours)	6 (3-9)	6 (5-12)	0.115‡
ICU stay (days)	2.2±0.8	3.8±1.3	0.019†
Total hospital stay (days)	6.4±1.3	8.3±1.4	0.011†

†Student's t test (Data is axpressed as mean±sd), ‡Mann Whitney U test (Data is expressed as median (interquartile range),

(P = 0.002, 0.018, 0.019, 0.011, respectively).

Logistic regression analysis was performed to predict AKI after the operation (Table 5). Preoperative creatinine height (Odds Ratio [OR]: 1.234, 95% Confidence interval [CI]: 1.090-1.578, P=0.030), less time to operation after angiography (OR:0.648, CI 95%: 0.554 -0.875, P=0.041), postoperative disulfide values (OR:0.718, CI 95%: 0.527-0.894 P=0.021), postoperative disulfide / total thiol ratio (OR:1.696, CI 95%: 1.472-1.987, P=0.013), total amount of blood product used (OR:1.012, CI 95%: 1.002-1.124, P=0.034) and need for inotropic drugs (OR:1.334, CI 95%: 1.021-1.539, P=0.004) significant correlation with postoperative AKI was detected. In multivariate analysis, preoperative creatinine height (OR:1.079, CI 95%: 1.007-1.434, P=0.039), postoperative disulfide / total thiol ratio (OR:1.336, CI 95%: 1.090-1.834, P=0.021) and inotropic drug need (OR:1.056, CI 95%: 1.009-1.318, P=0.019) were determined as independent predictors for predicting postoperative AKI.

In the ROC analysis, cut-off values were 32.9 (AUC: 0.701, 95% CI: 0.562-0.840 p = 0.009, 73.7% sensitivity and 43.9% specificity) for postoperative disulfide, and 15.3 (AUC: 0.746, 95% CI for postoperative disulfide / total thiol. (CI:0.636-0.857, p=0.001, 82.4% sensitivity and 51.9% specificity) (Figure 1).

Table 5. Logistic regression analysis to identify factors affecting postoperative acute kidney injury

	Univariate analysis			Multivariate analysis		
Variables	**P**	**Exp(B) Odds Ratio**	**95% C.I. Low-er Upper**	**P**	**Exp(B) Odds Ratio**	**95% C.I. Lower Upper**
Age	0.212	0.789	0.529- 2.140	--	--	--
Hypertension	0.710	0.334	0.248- 1.909	--	--	--
Creatinine	0.020	1.234	1.090-1.578	0.039	1.079	1.007-1.434
Angiography to operation time	0.041	0.648	0.554-0.875	0.214	1.002	0.897- 1.202
Disulfide/total thiol(t2)	0.013	1.696	1.472-1.987	0.021	1.336	1.090- 1.834
Disulfide (t2)	0.021	0.718	0.527- 0.894	0.114	0.875	0.678- 1.102
Packed blood products	0.034	1.012	1.002- 1.124	0.226	0.978	0.916- 1.354
Inotropic support	0.004	1.334	1.021- 1.539	0.019	1.056	1.009- 1.318
CCt	0.518	0.765	0.414- 1.718	--	--	--

CCt: Cross-clamp time

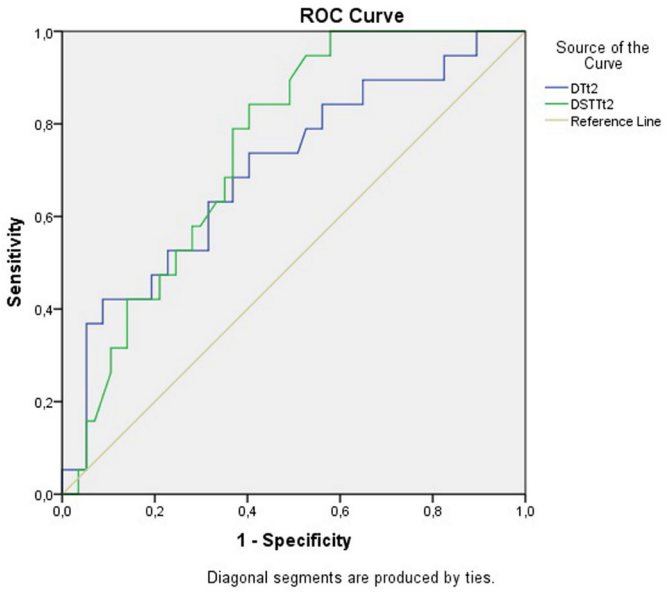

Figure 1. ROC (Receiver operation characteristic) curve and AUC (Are aunder the curve) for postcardiotomy Disulfide/total thiol (DSTTt2) and postcardiotomy Disulfide thiol (DTt2) for predicting postoperative acute kidney injury (DSTTt2: AUC: 0.746, 95% CI: 0.636-0.857,p = 0.001, cut-off=15.3, 82.4% sensitivity and 51.9% specificity) (DTt2: AUC: 0.701,95% CI: 0.562-0.840 p = 0.009, cut-off=32.9, 73.7% sensitivity and 43.9% specificity)

DISCUSSION

Today, open heart surgery is successfully used in the treatment of many cardiac diseases. In these surgeries, CPB systems are mostly used and one of the most important morbid results that can occur is postoperative AKI. The most important finding in this current study is that we determine that thiol-disulfid hemostasis values, which are among the new oxidative stres parameters, can be used to predict AKI after open heart surgery. In our multivariate analysis, we found that besides the disulfide / total thiolratio, preoperative creatinine height and inotropic drug use are independent predictors for predicting postoperative AKI.

Oxygen is an indispensable molecule for the human organism, and reactive oxygen radicals that occur during metabolic events are molecules that can be harmful. These reactive oxygen radicals are mostly composed of free radicals. There are antioxidant systems in our body to reduce the harmful effects of these free radicals. Organic compounds that contain a sulfhydryl (-SH) group are known as thiols to prevent any stress in our cells (10). The oxidation of these thiol groups leads to the formation of disulfide bonds (-SS). This dynamic equilibrium is a bidirectional reaction, known as thiol-

disulfide hemostasis. This dynamic hemostasis balance plays an important role in antioxidant defense, apoptosis, detoxification and transmission of cellular signals (11).

Although it is also caused by the existing disease in open heart operations, the formation of oxidative stres becomes inevitable with the use of CPB systems. In a recent study, the relationship of thiol-disulfide hemostasis parameters with cross-clamp times and their effectiveness in predicting postoperative rhythm disorders were investigated in CABG-guided CABG operations (12). 51 patients were included in the study and blood samples were measured 3 times, preoperatively, immediately after the cross-clamp was removed, and at the postoperative sixth hour. The authors found that as a result of this study, increased cross-clamp times and disulfide levels increased. In addition, in the multivaritae analysis, they stated that the disulfide / total thiol ratio observed after cross-clamp can be an independent predictor in predicting postoperative atrial fibrillation. In our study, although the number of patients was higher than this study, thiol-disulfide hemostasis parameters were evaluated at two different times as preoperative and postoperative 2nd hour. As a result, we determined the postoperative disulfide / total thiol ratio as an independent predictor in predicting AKI, which is an undesirable morbid condition such as postoeprative atrial fibrillation.

In another study conducted by Ozgunay SE et al. (13), in cardiac surgery operations using the CPB system, they divided patients in to two groups as those who were continuously ventilated and those who were not ventilated during CPB. In this study, it has been shown that thiol-disulfide hemostasis may be an indicator of increased oxidative stress. Accordingly, the relationship of thiol-disulfide hemostasis with coronary artery disease was also investigated. In the study conducted by Altıparmak et al. (14), native thiol values were found low in patients with severe coronary artery disease. Similar findings were supported by the study by Kundi et al (6).

AKI may be after cardiac surgery or it may develop depending on the medication given to the other patients under treatment in the hospital and the disease itself. In a study conducted by Qian et al. (15) with 160 patients, the effects of thiol groups on in-hospital developing AKI were investigated. In this study, serum thiol values were found lower in patients with AKI than healthy volunteers. At the same time, the 90-day over all mortality rate was found to be higher in AKI patients with high serum protein thiol levels than those with low thiol levels. However, dynamic thiol-disulfide hemostasis was not evaluated in this study. According to our information in the results of our literature review, our study is one of the rare studies investigating AKI after CABG surgery accompanied by CPB, and dynamic thiol-disulfide hemostasis parameters were measured. Another study investigating the relationship between AKI and thiol-disulfide hemostasis was done by Korkmaz et al. (16). In this study, which included a total of 302 patients, the location of oxidative parameters was investigated in predicting contrast nephropathy after coronary intervention in patients with myocardial infarction. In the multivariate analysis, the disulfide / total thiol ratio was determined as an independent predictor for contrast nephropathy. Gafney AM et al. (17) in his study, the main known risk factors for AKI that occur after open heart operations; They reported the use of CPB systems, blood product use, inotropic agent use, age, hypertension, and the presence of preoperative renal failure. The use of positive inotropic agents can lead to renal ischemia due to vasoconstrictor effects.

Due to the use of blood products, hemolysis increases, and increased hemolysis metabolites can cause renal injury. In the study conducted by Ramos et al. (18), increased blood transfusion and inotropic agent use in predicting AKI after open heart surgery were shown as independent predictors of AKI. In our study, we concluded that the increase in blood and blood product transfusion and the use of inotropic agents play an effective role in the development of AKI in accordance with this study. There are also studies that the operation time after coronary angiography may affect postoperative AKI development.

In the study conducted by Del Duca et al. (19), it was shown that the operations performed in the first five days after coronary angiography may increase the postoperative AKI. In another study conducted by Ranucci et al. (20), it was found that the risk of AKI may increase 3 times in the operations performed in the first day after coronary angiography. In our study, we found that the shorter time until surgery after coronary angiography may correlate with the development of AKI.

Our study has limitation ssuch as being single-centered, performing operations with more than one surgical team, and limited number of patients.

CONCLUSION

As a result; we believe that the values of disulfide and disulfide / total thiol ratio, which are among the thiol-disulfide hemostasis parameters, in the postoperative period may be predictors for AKI. We believe that multicentre studies with large patient groups are needed to support these results.

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Conflict of Interest: *The authors declare that they have no competing interest.*

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Araştırma Makalesi / Research Article

Kardiyopulmoner Bypass Eşliğinde Yapılan Kalp Cerrahisinde Vücut Kitle İndeksinin Morbidite ve Mortalite Üzerine Etkisi

The Effect of Body Mass Index on Morbidity and Mortality in Heart Surgery Accompanied by Cardiopulmonary Bypass

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Oz

Amaç: Açık kalp operasyonları endovasküler alanda olan gelişmelere rağmen önemini korumaktadır. Obezite birçok hastalık ile ilişkilendirilmektedir. Obezite ile ilişkili hastalıklar içerisinde kalp hastalıkları da bulunmaktadır. Bizim çalışmamızda da vücut kitle indeksinin kardiyak cerrahi sonrası sonuçlar üzerine etkilerini araştırmayı amaçladık.

Materyal ve Metod: Çalışmamıza 01 Ocak 2018 ile 01 Ekim 2019 tarihleri arasında kalp cerrahisi uygulanan toplam 215 hasta retrospektif olarak dahil edildi. Olgu verileri, operasyonda kullanılan teknikler, preoperatif, intraoperatif ve postoperatif veriler retrospektif olarak incelendi. Çalışma grupları obez olmayan hastalar (Grup 1 (VKİ<30 kg/m^2)) ve obez olan hastalar (Grup 2 (VKİ≥30 kg/m^2)) olmak üzere iki grup olarak belirlendi. Elde edilen veriler istatistiksel olarak analiz edildi.

Bulgular: Grup 1'de 123 ve Grup 2'de 92 hasta vardı. Grupların preoperatif (VKİ hariç) ve intraoperatif verileri benzerdi (p>0,05). Grupların postoperatif; renal yetmezlik, revizyon, intra-aortik balon pompası ihtiyacı, serebrovasküler olay, atriyal fibrilasyon, pnömoni, hastanede kalış süresi, mortalite ve taburcu sayısı verileri benzerdi (p>0,05). Ancak Grup 2'nin drenaj miktarı, entübasyon süresi ve yoğun bakım ünitesinde kalış süresi, Grup 1'e göre anlamlı olarak yüksekti (p<0,05).

Sonuç: Çalışmamızda vücut kitle indeksinin kalp cerrahisi sonrası mortalite ile ilişkili olmadığını ancak bu durumun kalp cerrahisi sonrası drenaj miktarını artırdığı, entübasyon süresini ve yoğun bakım ünitesinde kalış süresini uzattığını saptadık. Bu nedenlerden dolayı yüksek vücut kitle indeksinin morbiditeler ile ilişkili olduğunu düşünmekteyiz.

Anahtar Kelimeler: Kardiyopulmoner bypass; kalp cerrahisi; vücut kitle indeksi; morbidite; mortalite

Abstract

Aim: Open heart operations maintain their importance despite the developments in the endovascular department. Obesity is associated with many diseases. Heart diseases are among the diseases associated with obesity. In our study, we aimed to investigate the effects of body mass index on outcomes after cardiac surgery.

Material and Method: A total of 215 patients who underwent cardiac surgery between January 01, 2018 and October 01, 2019 were retrospectively included in our study. Case data, techniques used in the operation, preoperative, intraoperative and postoperative data were analyzed retrospectively. Study groups were determined as two groups as non-obese patients (Group 1 (BMI<30 kg/m^2)) and obese patients (Group 2 (BMI≥30 kg/m^2)).The data obtained were analyzed statistically.

Results: There were 123 patients in Group 1 and 92 patients in Group 2. Preoperative (except BMI) and intraoperative data of the groups were similar (p>0.05) . Groups postoperatively; data on renal insufficiency, revision, need for intra-aortic balloon pump, cerebrovascular stroke, atrial fibrillation, pneumonia, hospital stay, mortality and number of discharges were similar (p>0.05). However, the amount of drainage, intubation time and length of stay in the intensive care unit in Group 2 were significantly higher than Group 1 (p<0.05).

Conclusion: In our study, we found that body mass index was not related to mortality after cardiac surgery, but this situation increased the amount of drainage after cardiac surgery, extubation time and duration of stay in the intensive care unit. For these reasons, we think that high body mass index is associated with morbidities.

Keywords: Cardiopulmonary bypass; cardiac surgery; body mass index; morbidity; mortality

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GİRİŞ

Açık kalp operasyonları endovasküler alanda olan gelişmelere rağmen önemini korumaktadır. Kalp cerrahisinde ekstrakorporeal dolaşım tekniğinin kullanımı modern kalp cerrahisindeki en önemli olaylardan birisidir (1). Kardiyopulmoner bypass, kalp ve akciğer fonksiyonlarının devre dışı bırakıldığı ve bu süreçte yapay olarak kalp ve akciğer fonksiyonlarının kalp-akciğer makinesi kullanılarak sağlandığı ekstrakorporeal dolaşım tekniğidir (2,3). Bu tekniğin sağladığı en önemli yarar maksimum cerrahi görüşün sağlanması ve güvenliğin arttırılması amacı ile kalp ve akciğerlerin devre dışı bırakılarak mükemmel cerrahi görüş ve hareketsiz alanın sağlanmasıdır (4).

Kardiyak hastalıklar tüm dünyada morbidite ve mortalite nedenleri arasında önemli bir yer tutmaktadır. Bulaşıcı olmayan hastalıklar arasında ilk sıralarda bulunmaktadır ve yakın gelecekte de ilk sıralarda olmaya devam edecektir (5).

Obezite birçok hastalık ile ilişkilendirilmektedir ve dünyada ciddi bir şekilde artan bir problem haline gelmiştir. Obezite tanımı itibariyle vücutta aşırı derecede yağ dokusunun bulunmasıdır. Geçmişte sağlık, güç ve refah göstergesi iken günümüzde hastalık olarak görülmektedir. Obezitenin tanımlamasında vücut kitle indeksi (VKİ) kullanılmaktadır. Vücut kitle indeksi vücut ağırlığının metrekare olarak boya bölünmesi ile hesaplanmaktadır. Amerikan Ulusal Sağlık Enstitüleri VKİ'ye göre obeziteyi sınıflandırmıştır. Obezite birçok hastalık riskini de arttırmaktadır. Bu ilişkili olduğu hastalıklar içerisinde kalp hastalıkları da bulunmaktadır. Ayrıca obezite, morbidite ve mortalitenin de ciddi bir artış nedenidir (6).

Kardiyak cerrahi sonrası olumsuz etkenlerin önceden belirlenmesi ve bunlara çözümler üretilmesi önem taşımaktadır. Bizim çalışmamızda da kardiyopulmoner bypass eşliğinde yapılan kalp cerrahisinde vücut kitle indeksinin cerrahi sonrası sonuçlar üzerine etkilerini araştırmayı amaçladık.

MATERYAL VE METOD

Çalışmamıza 01 Ocak 2018 ile 01 Ekim 2019 tarihleri arasında kardiyopulmoner bypass eşliğinde kardiyak cerrahi uygulanan toplam 215 hasta retrospektif olarak dahil edildi. Olgu verileri, operasyonda kullanılan teknikler, preoperatif, intraoperatif ve postoperatif veriler retrospektif olarak incelendi. ÇalışmaHelsinki Deklarasyonunda belirtilen ilkelere uyularak yapıldı. Preoperatif veriler (Cinsiyet, yaş, vücut kitle indeksi (VKİ) (kg/m²), sigara kullanım öyküsü, ejeksiyon fraksiyonu (EF %), hipertansiyon (HT), diyabetes mellitus (DM), kronik obstrüktif akciğer hastalığı (KOAH) ve hiperlipidemi (HL)), intraoperatif veriler (Perfüzyon süresi, aortik krossklemp süresi, yapılan operasyon çeşitleri ve intraoperatif defibrilasyon ihtiyacı) ve postoperatif veriler (Postoperatif renal yetmezlik, revizyon, drenaj miktarı (ml), intra-aortik balon pompası (İABP) ihtiyacı, postoperatif serebrovasküler olay (SVO), postoperatifatriyalfibrilasyon(AF), postoperatif pnömoni, entübasyon süresi (saat), yoğun bakım ünitesi (YBÜ)'nde kalış süresi (saat), hastanede kalış süresi (gün), mortalite ve taburcu sayısı) hasta dosyalarından ve hastane kayıtlarından elde edildi.

Çalışma grupları obez olmayan hastalar (Grup 1 (VKİ<30 kg/m2))ve obez olan hastalar (Grup 2 (VKİ≥30 kg/m2)) olmak üzere iki grup olarak belirlendi. Çalışmada elde edilen veriler oluşturulan bu iki grup arasında değerlendirildi.

Ameliyat öncesi atriyal fibrilasyon öyküsü, bilinen sistemik inflamatuar hastalığı olanlar, acil ameliyat veya yeniden ameliyat geçirenler (daha önce kardiyak cerrahi operasyonu geçirenler) ve kronik hemodiyaliz hastaları çalışma dışı bırakıldı. Dışlama kriterleri uygulandıktan sonra ardışık olarak opere edilen hastalar çalışmaya dahil edildi.

İstatistiksel analizler

İstatistiksel analizler SPSS® 16.0 bilgisayar programı kullanılarak gerçekleştirilmiştir. Sürekli ve sıralı veriler için ortalama ve standart sapmalar hesaplandı. Normallik dağılımını değerlendirmek için KolmogorovSmirnov testi ve Shapiro-Wilk testi kullanıldı. Sırasıyla normal ve normal dağılmayan verileri değerlendirmek için Student t testi ve Mann Whitney U testleri kullanıldı. Nominal veriler için frekans ve yüzde analizleri yapılmış ve karşılaştırılmasında Chi-Square testi kullanılmıştır. Çalışmamızda p<0,05 değeri istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Çalışmamıza toplam 215 hasta dahil edildi. Grup 1 (obez olmayanlar) 123 hasta, ve Grup 2 (obez olan) 92 hastadan oluştu. Tablo 1'de görüldüğü gibi grupların preoperatif; cinsiyet, yaş, sigara kullanım öyküsü, ejeksiyonfraksiyonu (EF %), hipertansiyon (HT), diyabetesmellitus (DM), kronik obstrüktif akciğer hastalığı (KOAH) vehiperlipidemi (HL) verileri benzerdi (p>0,05). Ancak grupların vücut kitle indeksleri (kg/m²) arasında istatistiksel olarak anlamlı fark vardı. (p<0,05)

Tablo 1. Hastaların Preoperatif Verileri

Değişkenler	Grup 1 (Obez Olmayan) (n=123, % 57,2)	Grup 2 (Obez) (n=92, % 42,8)	P
n (%)	123 (57,2 %)	92(42,8%)	0,106
Kadın cinsiyet, n (%)	59 (47,96 %)	48(52,17 %)	0,456
Yaş (yıl), (ort±ss)	63,51±12,03	61,91±11,47	0,498
VKİ (kg/m²), (ort±ss)	25,35±3,23	34,34±2,71	0,041*
Sigara, n (%)	38 (30,89%)	28 (30,43%)	0,942
EF %, (ort±ss)	46,75±9.13	45,35±10.51	0,748
HT, n (%)	93(75,6 %)	61(66,30 %)	0,134
DM, n (%)	38(30,89%)	29(31,52%)	0,922
KOAH, n (%)	10(8,13 %)	8(8,69 %)	0,882
HL, n (%)	10(8,13 %)	8(8,69 %)	0,882

*:p<0,05, Ort±ss= Ortalama±standart sapma, n (%)= Sayı ve yüzde, VKİ: Vücut kitle indeksi, EF:Ejeksiyon fraksiyonu, HT: Hipertansiyon, DM: Diabetes mellitus, KOAH:Kronik obstrüktif akciğer hastalığı, HL: Hiperlipidemi.

Tablo 2'de de görüldüğü gibi grupların intraoperatif; perfüzyon süresi (dakika), aortik kross klemp süresi (dakika), yapılan cerrahi operasyon tipleri ve intraoperatif defibrilasyon ihtiyacı verileri benzerdi (p>0,05).

Tablo 2. Hastaların İntraoperatif Verileri

Değişkenler	Grup 1 (Obez Olmayan) (n=123, % 57,2)	Grup 2 (Obez) (n=92, % 42,8)	P
Perfüzyon süresi (dk), (ort±ss)	72,00±27,70	75,55±30,94	0,653
Kross klemp süresi (dk), (ort±ss)	52,60±23,13	54,45±23,81	0,836
Koroner arter bypass greft, n (%)	114 (92,6%)	85 (92,3%)	0,831
Kalp kapak replasmanı, n (%)	9 (7,3%)	7(7,6%)	0,842
İntraoperatif defibrilasyon ihtiyacı, n (%)	8(6,50%)	10(10,86%)	0,882

Ort±ss=Ortalama±standart sapma, n (%)=Sayı ve yüzde

Tablo 3'te de görüldüğü gibi grupların ameliyat sonrası; postoperatif renal yetmezlik, revizyon durumu, intra-aortik balon pompası (İABP) ihtiyacı, postoperatif serebrovasküler olay (SVO), postoperatif atriyal fibrilasyon (AF), postoperatif pnömoni, hastanede kalış süresi (gün), mortalite ve taburcu sayısı verileri benzerdi (p>0,05). Ancak Grup 2'de ki hastaların drenaj miktarı (ml), entübasyon süresi (saat) ve yoğun bakım ünitesinde(YBÜ) kalış süresi (saat), Grup 1'deki hastalara göre anlamlı olarak yüksekti (p<0,05).

Tablo 3. Hastaların Postoperatif Verileri

Değişkenler	Grup 1 (Obez Olmayan) (n=123, % 57.2)	Grup 2 (Obez) (n=92, % 42,8)	P
Postoperatif renal yetmezlik, n (%)	4(3,25 %)	1(1,08 %)	0,297
Revizyon, n (%)	3(2,43 %)	1(1,08 %)	0,468
Drenaj miktarı (ml) (ort±ss)	481,65±92,05	725,67±93,30	0,000*
İABP ihtiyacı, n (%)	3(2,43%)	4(4,34%)	0,603
Postoperatif SVO, n (%)	3(2,43 %)	2(2,17 %)	0,898
Postoperatif AF,n (%)	9(7,31%)	5(5,43%)	0,580
Postoperatif pnömoni, n (%)	2(1,62%)	4(4,34%)	0,635
Entübasyon süresi (saat),(ort±ss)	7,06±4,12	8,80±4,34	0,001*
YBÜ kalış süresi (saat),(ort±ss)	32,01±7,93	36,26±9,46	0,006*
Hastanede kalış süresi (gün), (ort±ss)	6,81±2,53	7,32±3,37	0,302
Mortalite, n (%)	5(4,06 %)	5(5,43 %)	0,637
Taburcu, n (%)	118(95,93 %)	87(94,56 %)	0,637

*:p<0,05, Ort±ss=Ortalama±standart sapma, n (%)=Sayı ve yüzde, İABP:İntra-aortik balon pompası, SVO:Serebrovasküler olay, AF:Atriyal fibrilasyon, YBÜ:Yoğun bakım ünitesi

TARTIŞMA

Obezite birçok hastalığın morbidite ve mortalite oranlarında artışa yol açabilmektedir. Ayrıca hipertansiyon ve birçok kalp hastalığı riski obezite ile birlikte artmaktadır. Açık kalp operasyonları major cerrahi operasyonlar olup obezite bu operasyonlarda da bir risk faktörü olarak karşımıza çıkmaktadır. Bu güncel çalışmada kardiyopulmoner bypass eşliğinde yapılan kalp cerrahisinde vücut kitle indeksinin morbidite ve mortalite üzerine etkisini araştırmayı amaçladık. Çalışmamızın üstün yanı; vücut kitle indeksinin kardiyak cerrahi sonrası mortalite ile ilişkili olmadığının saptanmasıdır. Ayrıca yüksek vücut kitle indeksinin açık kalp operasyonları sonrasında, kanama miktarını, entübasyon süresini ve yoğun bakım ünitesinde kalış süresini arttırdığının tespit edilmesi çalışmamızın diğer üstünlükleri arasında bulunmaktadır.

Yapılan çalışmalarda VKİ'nin kardiyak cerrahi sonrası bir çok morbid durum ile ilişkili olduğu bildirilmiştir (7-11). Bu çalışmalarda yüksek VKİ'nin kardiyak cerrahi sonrası artmış postoperatif renal komplikasyonlara, solunum sistemi sorunlarına, yoğun bakım ve total hastanede yatış süresinin artmasına ve inotrop ilaç ihtiyacının artmasına, lokal yara yeri enfeksiyonlarına, sternumun iyileşme süresinin artmasına, taze donmuş plazma ihtiyacının artmasına, atriyal fibrilasyon gibi problemlere neden olduğu bildirilmektedir (7-11). Yaptığımız çalışmada ise yüksek vücut kitle indeksinin postoperatif kanama miktarını, entübasyon süresini ve yoğun bakım ünitesinde kalış süresini arttırdığını saptadık. Literatürle benzer sonuçlar bulmakla berber yüksek vücut kitle indeksinin postoperatif birçok komplikasyonu ve olumsuz sonucu ortaya çıkardığı düşünmekteyiz.

Yüksek vücut kitle indeksinin kardiyak cerrahi sonrası mortalite ile ilişkisi üzerine bir çok çalışma yapılmıştır (8-10). Yüksek vücut kitle indeksinin kardiyak cerrahi sonrası mortalite ile ilişkili olmadığı, obez hastalar ile obez olmayan hastalar arasında mortalite açısından fark olmadığını bildiren çalışmalar bulunmaktadır (8-10). Yüksek vücut kitle indeksine sahip hastaların kardiyak cerrahi sonrası hastane içi mortalite oranlarının daha düşük olduğunu belirten çalışmalarda bulunmaktadır (11). Ayrıca farklı VKİ'ye sahip gruplar arasında morbidite ve mortalite oranlarının benzer olmasının, peroperatif ve postoperatif süreçte obez hastalara yapılan özellikli bakım ve tedavi ile ilişkili olduğu bildirilmektedir (9). Bizim çalışmamızda ise yüksek vücut kitle indeksinin kardiyak cerrahi sonrası mortalite ile ilişkili olmadığını saptadık.

Gramlich ve ark. obezitenin etkilerini araştırdıkları çalışmalarına koroner arter bypass greft cerrahisi uygulanan 61 hastayı dahil etmişlerdir. Obezitenin, enzimatik redoks modellerinde değişikliklere neden olarak kalp fonksiyonunu ve morbiditeyi etkilediği varsayımında bulunmuşlardır. Koroner arter bypass greft cerrahisi uygulanan hastalarda artan vücut kitle indeksinin, yetersiz antioksidan kompanzasyonu ile artmış oksidatif strese

işaret eden değişmiş miyokardiyal redoks paternleri ile ilişkili olduğunu ortaya koymuşlardır. Bu değişiklikler, koroner arter hastalığı olan obez hastaların miyokardının kardiyomiyopatiye ve kalp cerrahisi sırasında iskemi ve reperfüzyondan kaynaklanan olası hasara daha duyarlı olduğunu göstermektedir (12). Bizim çalışmamızda da obez hastalar adına elde ettiğimiz olumsuz sonuçlar bu durumlardan kaynaklanıyor olabilir.

Kardiyovasküler hastalıkların nedenleri arasında obezite de bulunmaktadır. Obezite, ateroskleroz ve koroner arter hastalığı için önemli bir role sahiptir. Obezite, kalpte yapısal ve fonksiyonel değişikliklere yol açarak kalp yetmezliğine neden olabilmektedir. Değişen miyokardiyal yapı, atriyal fibrilasyon ve ani kardiyak ölüm riskini arttırmaktadır. Bunun yanında obezite, kardiyovasküler anormalliklerin gelişimi için artmış risk içermesine rağmen, fazla kilo ve obezite halihazırda gelişmiş bir hastalık durumunda, olumlu bir prognoz etkisi de gösterebilmektedir. Bu durum obezite paradoksu olarak bilinmektedir (13). Bu paradoksu Borracci ve ark. yaptıkları bir retrospektif ve meta-analiz çalışmada incelemişlerdir. Çalışmalarında kalp cerrahisi geçirmiş 1823 yetişkin hastayı retrospektif olarak incelemişlerdir. Çalışmalarını; normal kilolu (18,5-24,9 kg/m^2), fazla kilolu (25-29,9 kg/m^2), sınıf I obez (30-34,9 kg/m^2), sınıf II obez (35-39,9 kg/m^2) ve sınıf III obez veya morbid obez (40-49,9 kg/m^2) olarak gruplandırmışlardır. Çalışmalarında aşırı kilolu ve obez hastaların, normal kilolu bireylere kıyasla kalp cerrahisinden sonra benzer ya da biraz daha düşük hastane içi mortalite oranlarına sahip olduğunu belirtmişlerdir. Ancak obez hastalarda postoperatif komplikasyon oranlarının daha yüksek olduğunu belirtmişlerdir. Yaptıkları sistematik meta-analiz serisinde de aşırı kilolu ve obez hastaların normal kilolu hastalarla aynı hatta daha düşük bir mortalite oranlarına sahip olduğunu ortaya koymuşlardır (14). Biz de çalışmamızda bu bilgiler ile uyumlu olarak iki grup arasında mortalite oranlarımızı benzer olarak tespit ettik. Çalışmamızda entübasyon süresi, yoğun bakım ünitesinde kalış süresi ve drenaj miktarı gibi morbid sonuçlar ise obez hastalarda daha yüksekti.

Yapılan diğer çalışmalarda da yüksek vücut kitle indeksinin kardiyak cerrahi sonrası birçok morbid durum ve komplikasyon ile ilişkili olduğu, ancak mortalite ile ilişkili olmadığı bildirilmektedir (15,16).Yaptığımız çalışmayı da tüm bu veriler desteklemektedir.Gao ve ark. 4740 hastayı dahil ettikleri retrospektif çalışmalarında vücut kitle indeksinin kardiyak cerrahi sonrası kısa dönem klinik sonuçlar üzerine etkisini araştırmışlardır. Hastaları VKİ'ye göre; düşük ağırlıklı (VKİ<18,5 kg/m^2), normal ağırlıklı (25>VKİ≥18 kg/m^2), aşırı kilolu (30>VKİ≥25 kg/m^2), sınıf I obez (35>VKİ≥30 kg/m^2), sınıf II obez (40>VKİ≥35 kg/m2) ve sınıf III obez (VKİ 40 kg/m^2 ve üzeri) olarak altı gruba ayırmışlardır. Çalışmalarının sonucunda aşırı obezite ve düşük kilonun erken dönem klinik sonuçlar üzerine olumsuz etkisi olduğunu belirtmişlerdir. Ancak fazla kilo veya sınıf I obezitenin cerrahi mortalite üzerinde olumlu bir etkisi olduğunu belirtmişlerdir (16). Bu çalışmada da kalp cerrahisi sonrası erken dönem mortalite üzerine "obezite paradoksu" olduğu görülmektedir. Bizim çalışmamızın bu çalışmadan en önemli eksikliği hastaları iki grupta incelememizdi. Biz de iki çalışma grubumuz arasında mortalite oranlarını benzer olarak tespit etmekle birlikte yoğun bakım yatış sürelerini ve ekstübasyona kadar geçen süreleri obez hastalarda daha yüksek olarak saptadık.

Çalışmamızın en önemli kısıtlayıcı noktaları tek merkezli, retrospektif çalışma olması ve buna bağlı hasta sayısının azlığıdır.

SONUÇ

Çalışmamızın sonucunda vücut kitle indeksinin kardiyopulmoner bypass eşliğinde yapılan kalp cerrahisi sonrası mortalite ile ilişkisi olmadığını ancak bu durumun kardiyak cerrahi sonrası drenaj miktarını artırdığı, entübasyon süresini ve yoğun bakım ünitesinde kalış süresini uzattığını saptadık. Bu nedenlerden dolayı yüksek vücut kitle indeksinin morbiditeler ile ilişkili olduğunu düşünmekteyiz. Bu vakalarda kardiyak cerrahi sonrası bakım ve tedavi sürecinin çok daha dikkatli takip edilmesi gerektiğini düşünmekteyiz.

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MEDICAL RECORDS-International Medical Journal

Olgu Sunumu / Case Report

Inflammatory Colitis Due to Methotrexate Toxicity in a Patient With Psoriasis: A Case Report

Psoriasis Tanılı Hastada Methotreksat Toksisitesine Bağlı Gelişen Inflamatuar Kolit Olgusu: Olgu Sunumu

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Abstract

Methotrexate is known as a folate antimetabolite. The side effects of methotrexate are not usually seen in low dosages. Here we present a patient with inflammatory colitis due to methotrexate use for psoriasis.

A 29 year-old male who was diagnosed with psoriasis 1 year ago and started to use methotrexate for 2 weeks; applied to emergency with acute abdomen symptoms. According to the tests and examinations the patient was diagnosed with inflammatory colitis due to methotrexate toxicity. The patient was observed for abdominal pain without surgical interventions and had folic acid therapy combined with empiric antibiotherapy. Methotrexate side effects are usually seen as bone marrow suppression and mucosal tissue inflammation therefore some side effects can be missed in clinical examinations. As a result, we should consider that in patients applying to emergency with acute abdomen symptoms drugs can be the cause of this clinical presentation.

Keywords: Methotrexate toxicity; inflammatory colitis; psoriasis

Oz

Methotreksat folat antimetaboliti olarak bilinen bir ilaç olmakla birlikte yan etkileri yüksek dozlarda görülmektedir. Bu olgu sunumunda psoriasis tanılı bir hastada methotreksat toksisitesine bağlı gelişen inflamatuar kolit tablosundan bahsedilecektir.

Bir sene önce psoriasis tanısı almış ve 2 hafta önce methotreksat tedavisi başlanmış 29 yaş erkek hasta acil servise akut karın semptomları ile başvurdu. Yapılan fizik muayene ve tetkikler sonucunda hastaya methotreksat toksisitesine bağlı inflamatuar kolit tanısı konularak folik asit replasmanı ve ampirik antibiyoterapi başlandı. Hasta opere edilmeden komplikasyonsuz taburcu edildi.

Methotreksatın bilinen yan etkileri kemik iliği baskılanması ve mukozalarda inflamasyondur. Acil servise başvuran hastalarda klinik tablonun nedeninin ilaçlar olabileceği akılda bulundurulmalıdır.

Anahtar Kelimeler: Methotreksat toksisitesi; inflamatuar kolit; psoriasis

INTRODUCTION

Methotrexate(MTX) was produced in 1940s and used as a systemic immunosuppressive agent in 1950s [1]. In course of time its' application was expanded and MTX was started to use for various malignancies, early ectopic pregnancy, chronic inflammatory diseases, some types of carcinoma, rheumatoid arthritis and psoriasis [2,3]. Methotrexate is known as a folate antimetabolite that binds to an enzyme named dihydrofolate reductase, which ultimately leads to inhibition of DNA synthesis. It can be taken as orally, subcutaneously or intramuscularly. MTX primarily bounds to serum albumin and is excreted with urine and can achieve toxic blood levels in patients with hypoalbuminemia and renal failure. In dermatology, typical starting doses of oral methotrexate range from 5 to 15 mg weekly [4]. Toxicity of the MTX at low doses was reported rarely in the literature . In this case report we present a patient with psoriasis diagnosed as inflammatory colitis due to MTX toxicity.

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CASE REPORT

A 29 year-old male applied to emergency with the symptoms of general abdominal pain, diarrhea and nausea. The patient had diagnosed with psoriasis one year ago and started MTX treatment three weeks before the admission to the emergency department. It was learned that the patient took the drug 20 mg per week for two weeks and stopped the treatment himself when the diarrhea was started. In physical examination defence and rebound was found in lower and upper quadrants of the right abdomen. Also psoriatic plaques were seen on the patient's whole body and limbs. Laboratory tests were analyzed and pancytopenia was found in complete blood count (CBC). The serum albumin and creatinine levels were found to be normal. Due to the acute abdomen symptoms intravenous contrast abdominal computed tomography(CT) was performed. In CT scan right colon wall was found to be thickened whereas no free fluid or air density was seen in abdominal cavity (Figure 1).

Figure 1. Thickened right colon wall in CT scan

The patient was diagnosed with inflammatory colitis due to MTX toxicity and was hospitalized for observing the abdominal pain. The patient's oral intake and MTX treatment was stopped and intravenous hydration was started. On follow up day 1 the patient had fever therefore blood, stool and urine cultures were sampled and empiric antibiotherapy was started as ceftriaxone combined with metronidazole. On follow up day 2, oral ulcers were occurred in the patient's oral mucosa and antifungal gargle was given for preventing infections. Dermatology consultation was also done for methotrexate toxicity and treatment of the psoriatic lesions. According to the dermatology consultation folic acid replacement therapy for bone marrow suppression and local pomades containing urea and corticosteroids for skin lesions were started. Colonoscopy was not performed due to the risk of colonic perforation in inflammatory colitis. On patient's follow-up no other complications were seen and the patient was started oral intake according to his regressed abdominal pain. Also CBC controls after folic acid replacement therapy and culture results were found to be normal. The patient was discharged on follow up day 7 without any complications and with planning colonoscopy control.

DISCUSSION

Although MTX is a relatively safe drug in dosages used in dermatological diseases, side effects associated with idiosyncratic or dose-dependent mechanisms can occur in use of low doses. MTX excrete with urine and can achieve toxic blood levels in patients with hypoalbuminemia and renal failure. Side effects of MTX can be defined as agranulocytosis and bone marrow suppression, mucosal tissue inflammation and necrotic changes, liver cell necrosis and hepatic cirrhosis, pulmonary fibrosis and severe renal dysfunction [5]. Drugs such as aminoglycosides, cyclosporine, nonsteroidal anti-inflammatory agents, sulfonamides, probenecid, salicylates, penicillins, colchicines, cisplatin, proton pump inhibitors can increase the risk of MTX toxicity by decreasing renal elimination of MTX. Also salicylates, probenecid, sulfonamides, barbiturates, phenytoin, retinoids, sulfonylureas, and tetracyclines can increase the risk of MTX toxicity by displacing MTX from protein binding sites in the plasma [6].

Treatment in MTX toxicity depends on the patient's status. Patients who have renal and liver failure, low glasgow coma scores, unstable vital signs must be followed in intensive care units. In treatment, at first step MTX therapy must be terminated and then folic acid replacement therapy must be started for bone marrow suppression. As a result of immunosuppression patients are usually have the risk of infections. In patients with colitis, Clostridium difficile is usually found as an agent in stool cultures. Therefore empiric anti biotherapies must be started for preventing sepsis after taking stool blood and urine cultures in patients with fever.

Whereas oral mucositis were common clinical findings in MTX toxicity, inflammatory colitis was occurred as a rare symptom in our patient. Also physical examination findings were like acute abdomen symptoms. Patient's abdominal pain, oral ulcers and diarrhea were decreased after discontinuation of MTX therapy. We started empiric antibiotherapy due to fever presented in follow up day 2, gastroenteritis and pancytopenia. Folic acid replacement therapy was also given for bone marrow suppression.

CONCLUSION

Patients applying to emergency with acute abdomen symptoms, drugs can be the cause of this clinical presentation. Methotrexate toxicity can occur in low doses and early ages therefore patients should be followed more often.

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MEDICAL RECORDS-International Medical Journal

Derleme / Review

A Review of Color Matching in Dentistry

Diş Hekimliğinde Renk Seçimi Derlemesi

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Abstract

The success of dental treatment is evaluated according to functional and esthetic results. The esthetics of prostheses considered one of the most important parameters of treatment that the patient is interested in. Color matching is an essential procedure to obtain an esthetic prosthesis. Color matching is influenced by several factors, and if not performed properly, it can have unsatisfactory results for both the clinician and the patient. This review discusses color science, factors associated with color perception, and color matching techniques.

Keywords: Shade guide; visual color matching; instrumental color matching; color system

Oz

Dental tedavinin başarısı, fonksiyonel ve estetik sonuçlarla değerlendirilir. Protez estetiği, hastanın ilgilendiği en önemli tedavi parametrelerinden biri olarak kabul edilmektedir. Renk seçimi, estetik bir protez elde etmek için gerekli bir prosedürdür. Renk seçimi çeşitli faktörlerden etkilenir, uygun şekilde gerçekleştirilmediğinde ise, hem klinisyen hem de hasta için tatmin edici olmayan sonuçlar doğurabilir. Bu derleme, renk bilimini, renk algısıyla ilişkili faktörleri ve renk seçim tekniklerini irdelemektedir.

Anahtar Kelimeler: Renk skalası; görsel renk seçimi; enstrümantal renk seçimi; renk sistemi

INTRODUCTION

The esthetic dental result is essential for fulfilling the high expectations of patients. Color and shape determine the esthetics of both restored and natural teeth (1). The importance of color research in dental science has improved significantly over the last decades (2). To provide esthetic prosthesis, the dentist should consider the color's scientific basis as well as the artistic aspects of color matching (3). Because of the great variety of natural teeth color, obtaining a close color match of a prosthesis with the natural teeth is a complex procedure. The dentist needs an understanding of color, light, and characteristics of resin and porcelain in addition to the ability to communicate with the technicians to achieve a natural-looking prosthesis (4). The understanding of the light's nature, how the eye perceives the light, and how the brain interprets light as color is essential for a favorable esthetic prosthesis (5). Color can be described by three primary attributes of color which are hue, chroma, and value. To facilitate communication with the technician, the dentist should be thoroughly familiar with these terms and their definitions (3). Color determination and replication are the greatest challenging parts of dental esthetic (6).

Tooth color is determined using either instrumental or visual methods (7). The most common technique for color matching is the visual method using a shade guide (2). Shade guides have been used to determine and communicate the color of tooth and prosthesis to obtain an optically satisfying prosthesis but misunderstanding could often happen since every human-eye is not capable to perceive it in a standardized way (8,9). Additionally, visual color matching relies on many subjective elements such

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as translucency, surface structure, lighting conditions, and the optical character of the material used (10). Since visual color matching relies on an individual assessment, which is subjective and consequently a clinically challenging procedure. So, this is one of the causes of developing standards for communicating shades and instruments that make it easier to measure them (11). However, instrumental color matching is concerned to be useful and reliable in obtaining color for clinical color matching in dentistry (6). The recommended protocol for visual and instrumental color matching should be followed for a better understanding of the difficulties involved in it (12).

Factors Affecting Color Perception

Sir Isaac Newton's experiments during the 18th century presented that white light passing through a prism is divided into a pattern of colors termed as spectrum and he proved that color does not exist without light (4). It is the interaction of light with the object that allows the perception of color (13). The perception of the color relies on the combination of three elements, which is a light source, an observer, and an object (14).

Light source

The light source is the most important element in color matching (1). There are three light sources commonly found in the dental office: natural, incandescent, and fluorescent (3). The natural light is the ideal light source, which occurs around the middle of the day for proper color matching (13). Natural sunlight itself is extremely variable (3). The use of artificial lighting is needed due to the absence of ideal circumstances for color matching (13). Artificial light sources are also lacking in an equal distribution of color. Incandescent light is mainly red-yellow and lacking in blue (3). The color temperature of 5500 Kelvin (°K) is a recommended standard for dental color matching (1). The "color corrected" is special lights that emit light with a more identical distribution of color. Initial color matching should be done using color-corrected lights, but any color matching should be done under more than one type of light to overcome the problem of metamerism (3).

Object

The objects have no color of their own (5). The object being viewed modifies the light that falls on it by reflecting, absorbing, transmitting, or refracting all or part of the light energy, thereby producing the quality of color (3). A white object reflects all wavelengths of light but a black object absorbs all wavelengths of light. For example, while a blue object absorbs all light wavelengths except blue, which are reflected; by this process, the eye determines the object as blue (15).

Observer

The eye is an organ that has receptors of images attained from electromagnetic radiation which we name as light. It corresponds to a narrow segment between the 400-800 nm wavelengths approximately of the entire spectrum (16) (Figure 1). The light reflected from an object can stimulate the cones and rods cells of the retina which enable perception of color (17). The rods cells are responsible for scotopic (monochromatic, low light level) vision while cones cells are responsible for photopic (medium/high light level) vision (14).

Color Systems

From the beginning of the 20th century to the present, there are many different systems developed to measure colors mathematically (18). Visually descriptive Munsell and the more quantitive CIE color systems are the most emphasized systems in terms of development principles, experiential technique, and qualifications (19).

Munsell Color System

Prof. Albert D. Munsell presented a color wheel that contains the dimension of Value, Chroma, and Hue at the beginning of the 20th century (20). The color quality that differentiates one color from another is called hue. Hue is the name of a color, e.g. red, orange, or yellow (3). Hue is represented on the Vita Classic shade guide by A, B, C, or D. Chroma define as the strength, intensity, or saturation of the hue (21). On the Vita Classic Shade Guide, the higher numbers represent increased chroma (16). Value is the color relative lightness or darkness or the object's brightness (13). According to Munsell, value is described as a black to white grayscale (16) (Figure 2-A). Often the most important dimension of color is the value, as the value decreased, the chroma is increased; value and chroma are inversely related (1, 13).

CIE Lab Color System

The Commission International de l'Eclairage (CIE), in 1931, introduced a system of instrumental color measurement for describing colors (14). One of the first color spaces defined is CIE XYZ. These models are created manually with the help of human judgment ability of appearances and visualization matching, and the chosen colorimetry is based on this matching process. While In 1976, CIELAB color model was introduced, the second uniform color space, was derived from CIE XYZ space, with a white reference point (22). The CIE color system represents a uniform color space, with equal distances corresponding to equal perceived color variances. In this three-dimensional color space, the three-axis are L*, a*, and b*. The L* represents the value which is a lightness measurement of an object and is quantified on a scale as a 100 L* of value for a perfect black. While the a* value is a quantity of greenness (negative a*) or redness (positive a*). Whereas the b* value is a quantity of blueness (negative b*) or yellowness (positive b*) (Figure 2-B). The a* and b* coordinates approach zero for natural colors and increase in degree for more intense or saturated colors (16). A more advanced and recent CIE formula, CIEDE2000, has been subsequently presented and it is increasingly used in dentistry for color research (17). CIE Lab system's main advantage is that color variances could be expressed in units that can be related to visual perception and clinical importance (16).

Color Measurement

There are two main methods for color matching, the visual method using shade guide, and the instrumental method using color matching devices (23).

Conventional Visual Method

Visual color matching involves a direct visual comparison of the different color samples in a shade guide with natural teeth in order to determine which tab, or combination of tabs, constitutes the best match (24). The Munsell color system is a common system for visual color assessment. Also, the visual color assessment of the patient's teeth is the most common method applied in dental practice (13). It is economical, commonly available, and it efficiently compares teeth color with a standardized reference shade guide (23). However, the visual method is very subjective, and usually, this method relies on many factors and the observer's psychological and physiologic responses to radiant energy stimulation (13, 25). Visual color matching is inconsistent, which may result from uncontrolled factors such as lighting conditions, emotions, aging, fatigue, metamerism, object and illuminant position, and previous eye exposure (13). Visual color matching tools are called shade guides (17). The shade guide's main advantage is that generally they can be used almost anywhere and less expensive (15). The most popular shade guides currently used are:

Vita Classic (Vita Zahnfabrik, Bad Sackingen, Germany)

It is a very popular shade guide and has been in use since the 1960s (5). VITA classical shade guide contains sixteen tabs. The (A to D) is the original tab arrangement (Figure 3-A). The four groups are created based on hue: A is reddish-brown (A1, A2, A3, A3.5, A4), B is reddish-yellow (B1, B2, B3, B4), C is gray (C1, C2, C3, C4), and D is reddish-gray (D2, D3, D4). Within the groups, tab arrangement is based on decreasing value and increasing chroma. The "value scale" is an alternative tab arrangement which is a gold standard for tooth whitening monitoring. For dental shade matching the "value scale" is more logical and preferred by many over the (A to D) arrangement (17) (Figure 3-B).

Vitapan 3D-Master (Vita Zahnfabrik, Bad Sackingen, Germany)

The 3D-Master shade guide was introduced by Vita In the early 1990s, to accurately assess color according to the three components of color: value, chroma, and hue. The 3D-Master attempts a three-dimensional analysis of tooth color, unlike the majority of dental shade guides. The tabs are arranged logically and systematically, rather than randomly as in the Classic guide (5). The 3D-Master have three shade guide type: Linearguide, Bleachedguide, and Toothguide. The VITA Toothguide 3D-Master contains twenty-nine tabs divided into six groups according to lightness. Within the groups, tabs are arranged horizontally according to hue and vertically to chroma (17) (Figure 3-C).

Chromascop (Ivoclar - Vivadent, Schaan, Liechtenstein)

Chromascop is a proprietary shade guide with the same group division principle as VITA classical (17). The Chromascop uses numbers to distinguish hue, for example, for white (100), for yellow (200), for orange (300), for gray (400), for brown (500). Chroma is determined by another set of numbers, 40 are high chroma with low value while 10 are low chroma with high value (5) (Figure 4).

Specific or custom chroma and value guides

A custom shade tab could be fabricated using porcelain if the teeth color fails to concur with any of the shade guide tabs (5).

Instrumental Method

The instrumental color matching was presented to the dental practice to reduce the inconsistencies and limitations of the visual color matching method (25). The instrumental methods offer a potential advantage over visual methods which are instrumental measurement is rapidly obtained, can be quantified, and more objective (26). Several studies have proved that computer-aided color analysis is more consistent and more accurate in comparison to the visual method (12). The cost of the instrument is the most significant disadvantage of an instrumental method (23). Visual and instrumental matching methods complement each other and their combined use can lead to more favorable esthetic results (17). All color matching instruments contain a signal conditioner, a detector, and software that processes the signal in a method that produces usable data for dental treatment (27). When using these instruments, the manufacturer guidelines must be followed (25). There are three basic types of devices used for color matching:

Colorimeter

Colorimeters were the first type of color measuring instrument which approximate the spectral function of the normal vision and are designed to directly measure color as the human eye perceives (14). The colorimeters are instruments for color measurement which are equipped with three or four special filters. The filters obtain RGB (red, green, and blue) values. Colorimeters are usually less accurate than spectrophotometers, but they are often preferred because of their low cost and easily operated (28). ShadeEye (NCC chroma meter) and ShadeVision (X-Rite, Grandville, MI) is an example of a colorimeter (2, 13).

Spectrophotometry

Spectrophotometry is a device that measures the amount of light energy reflected or transmitted from an object's surface at 1-25 nm intervals along the visual light spectrum "380-780 nm". For color matching in dental practice, the spectrophotometer can be the most accurate instrument (25). The spectrophotometer contains a source of optical radiation, a detector, a means of dispersing light, a means of converting light obtained to a signal that can be analyzed, and an optical system for measuring

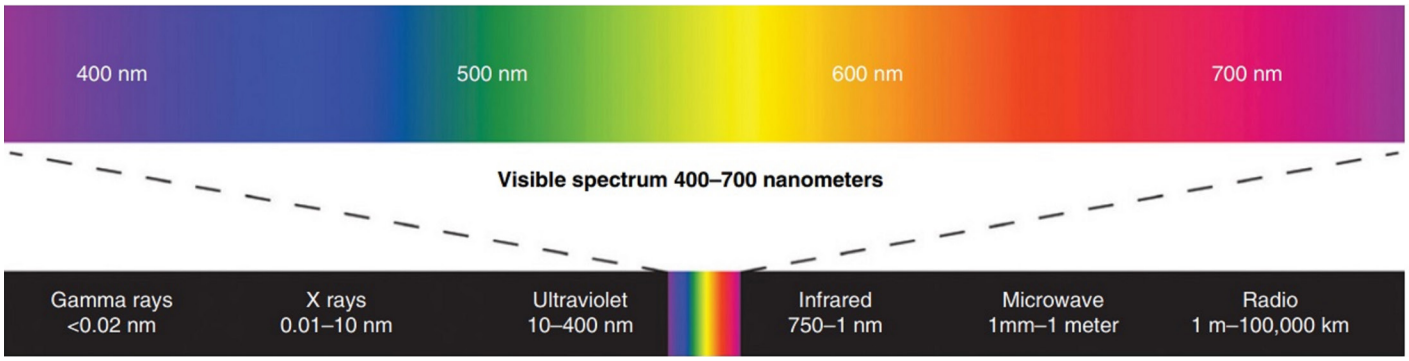

Figure 1. The visible wavelength of light (19).

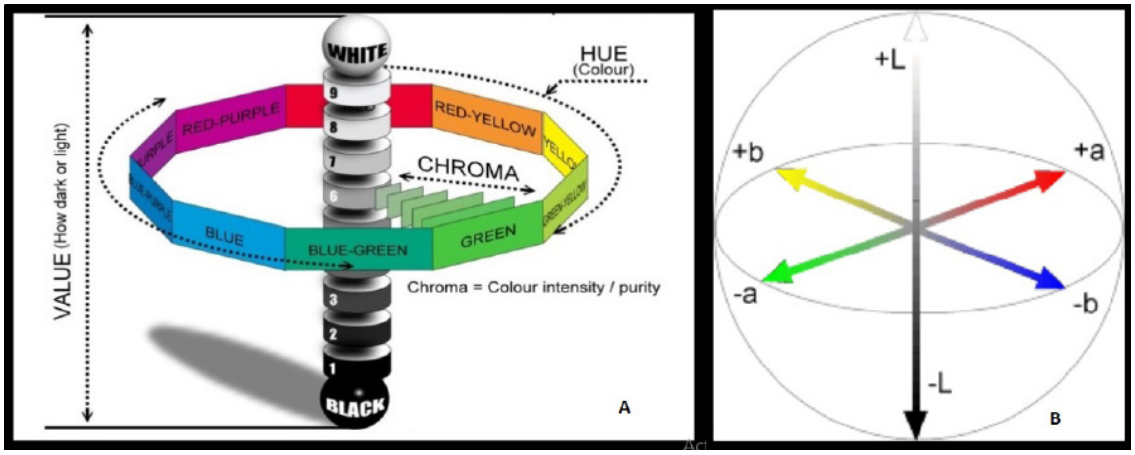

Figure 2. (A) Munsell color system wheel; **(B)** CIE LAB color system (18).

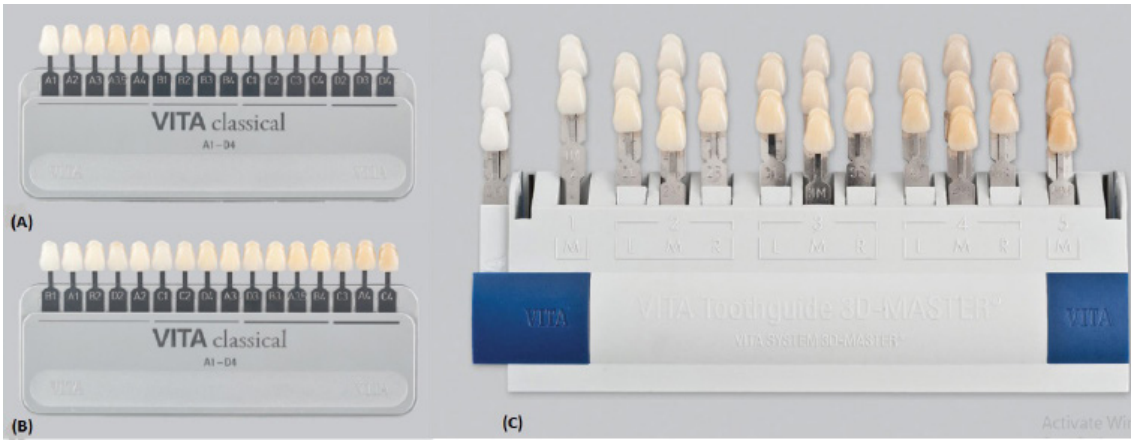

Figure 3. (A) Vita classic A-to-D tab arrangement; **(B)** value scale; **(C)** VITA Toothguide 3D-Master (19).

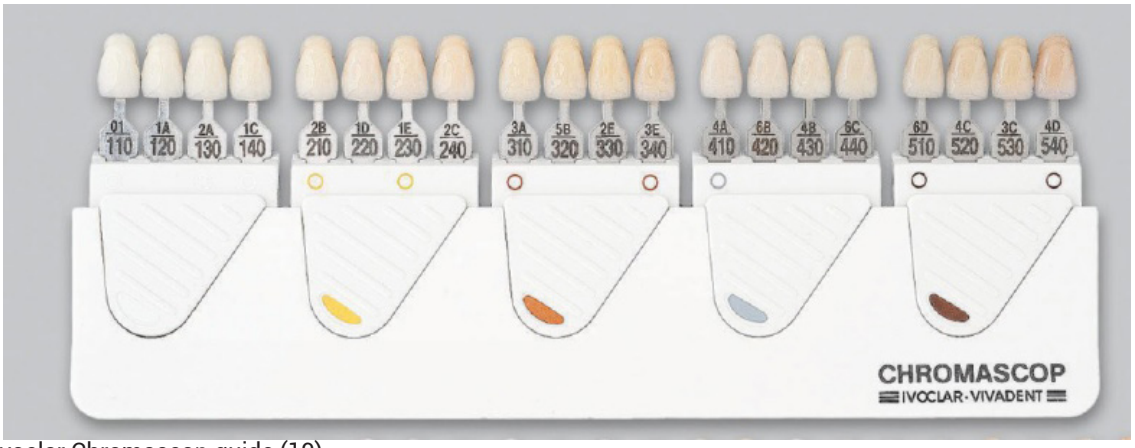

Figure 4. Ivoclar Chromascop guide (19).

(2). Several intraoral spectrophotometers are currently available (28). Vita Easyshade Compact (Vita Zahnfabrik, Bad Sackingen, Germany) is a color matching cordless device, portable, battery-operated, small, contact-type, and cost-efficient spectrophotometer which provides color measurement is based on the VITAPAN 3D-Master and VITAPAN Classical shades (2, 15). SpectroShade (MHT Optic Research, Niederhasli, Switzerland) and Crystaleye (Olympus, Tokyo, Japan) are examples of digital imaging with spectrophotometric analysis (2, 13). Reliability percentages are 96.9, for Spectro Shade and 96.4 for VITA Easyshade. The VITA Easyshade accuracy percentages are 92.6 which consider the highest (4).

Digital Camera

The digital cameras and imaging systems are the third classifications of instrumental color matching devices (25). Digital photography offers significant benefits to dental practices (13). The use of digital cameras in dental practice can be very appealing to the dentist because of their availability, cost, and ease of use (25). Scanners and digital cameras can provide a useful color mapping, used to record color information, and provide a detailed image of the teeth surfaces (17). Images provided through a digital camera can be analyzed using proper software that enables color values collection from parts or whole of those images, however, the digital scanners like those used in (CAD-CAM) systems are also being developed with tooth color matching capability (25, 29). ClearMatch (Smart Technology, Hood River, OR) is a software system which uses images with high resolution and compares color over the entire tooth. The system uses three basic color references (white, black, and shade tab) to calibrate and determine the color (28).

Recommended Color Matching Protocols

• Color matching should be done in different types of lighting conditions. Color matching must be completed between 10 am and 2 pm, due to the color temperature is around 5500 K – which is considered as the best value – at this time, after using color corrected light to ensure the accuracy of matched color (4, 13).

• Bright colors should be avoided in the working field, brightly colored clothing should be covered and lipstick or other makeup that could affect color matching should be removed (4).

• Tooth to be matched must be cleaned of all stains and debris. Also, the teeth should be cleaned by using prophylaxis paste before color matching.

• The patient has to be viewed at the level of the eye, in such a manner that the most sensitive part of the retina can be used, at a distance of 25 to 35 cm (5, 24).

• Color matching should be done at the beginning of the appointment before the eyes become fatigued and before the preparation of the tooth because the teeth become dehydrated and color changes during preparation (24, 26).

• Color matching has to be done quickly, with the color samples positioned under the lip directly next to the tooth being matched, the comparison should not lasting for more than 5 to 7 seconds at a time to avoid fatiguing the cones of the retina. The eye has to be rested by looking on a blue-gray surface immediately before and between a comparison because this will balance all the color sensors of the eye (3, 24, 26).

• The value must be analyzed first, followed by chroma and hue (4).

• During color matching, the tooth has to be divided into three areas. Incisal area (enamel is the thickest here and varies from translucent to transparent), body, and gingival area (which gives an accurate determination of dentinal chroma) (4).

• Once the best match has been selected, a brighter shade tab and a darker shade tab are photographed next to the teeth to be matched (24).

CONCLUSION

Patients expect the broken down and missing teeth to be restored with proper form, function, and an esthetic appearance. Color matching forms an important part in producing esthetics prosthesis. The tooth color determination and replication is a challenging task for every dentist. Understanding the science of color, color perception, color matching instrument usage, and limitations, and communication between technicians and dentists are essential for successful esthetics treatments. Accurate color matching that allows the prosthesis to match the natural teeth positively influences the appearance and esthetic self-confidence of the patient.

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Editöre Mektup / Letter to the Editor

Düşünce Özellikleri Ölçeği Bağlamında Bilişsel Hatalar

Cognitive Errors in the Context of the Cognitive Distortions Scale

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Değerli Editör

Bilginin işlenme biçimi, kişilerin olaylara verdikleri tepkilerde nedensel bir rol oynar. Olumsuz yönde işlenen bilgi, takip eden süreçlerdeki düşünce, duygu ve davranış ile ilgili çıktıları etkileyerek uyum sorunlarını artırır. Tepkilerimizi etkileyen çeşitli bilişler, bilişsel alanda çalışan klinisyenler tarafından araştırılmıştır (1). Düşünce içeriği açısından, duygu ve davranışları etkileyen birkaç farklı biliş seviyesi olduğu varsayılır. Birincisi, bireyin kişisel ve çevresel bilgiyi nasıl düzenleyeceğini belirleyen, bireyin kendisi, diğerleri ve dünyayla ilgili temel varsayımlarını içeren, geçmiş yaşantı ve deneyimler sonucu oluşmuş bilişsel yapılar olan temel inançlardır. Temel inançlar bilişsel yapının en derininde yer almaktadır (2). İkincisi, yaşantı ve gözlem yoluyla öğrenilen, davranışların soyut düzenleyicileri olan ve bilişsel yapıda temel inançların hemen üstünde yer alan ara inançlardır (3). Bilişsel yapının yüzeyinde yer alan üçüncü bilişsel yapı elemanı ise otomatik düşüncelerdir (Figür 1). Otomatik düşünceler, aklımıza kendiliğinden gelen, bizim özellikle düşünmeyi istemediğimiz düşüncelerdir. Sıklıkla fark edilmezler, sadece dikkatimizi verirsek onları tanımlayabilir ve anlayabiliriz. Otomatik düşünceler, herkeste bulunmasına karşılık ruhsal rahatsızlığı olan kişilerin otomatik düşüncelerinin bozuk, aşırı ve hatalı olduğu belirtilmektedir. Bu kişilerin otomatik düşünceleri, sağlıklı bireylere kıyasla daha hızlı, katı ve kusurludur (4).

Olumsuz otomatik düşünceler çarpık bir bilişsel sürecin ürünüdür. Otomatik düşünceler bilişsel çarpıtma ya da bilişsel hata olarak da adlandırılır. Bununla birlikte son yıllarda bilişsel davranışçı terapistler "hata" terimini "çarpıtma" terimine tercih etmektedir (5). Beck ve ark. (6) tarafından geliştirilen yedi farklı bilişsel hata, Burns (7) tarafından on farklı bilişsel hataya genişletilmiştir. Takip eden süreçte bu bilişsel hatalar kullanılarak çeşitli otomatik düşünce ve bilişsel hata ölçekleri geliştirilmiştir (8). Ancak bu ölçeklerin tamamı kişilerarası ilişkilerle ilgili bilişsel süreçleri sorgulamaktadır. Covin ve ark. (8) 2011 yılında on farklı bilişsel hatayı kişiler arası ilişkiler (IP) ve bireysel başarı (PA) gibi iki farklı alanda sorgulayan bir ölçek geliştirmiştir: Düşünce Özellikleri Ölçeği (DÖÖ, Cognitive Distortions Scale).

DÖÖ, Özdel ve ark. (5) tarafından 2014 yılında Türkçe'ye çevrilmiş her bir bölümünde on madde olan, iki ayrı bölümden oluşan yirmi maddelik bir ölçektir. On farklı maddede on farklı düşünce tarzı (hep ya da hiç tarzı düşünme, felaketleştirme, zihinsel filtreleme, zihin okuma, etiketleme, aşırı genelleme, kişiselleştirme, -meli -malı ifadeleri, olumluyu küçültme ya da yok sayma, duygudan sonuç çıkarma) bulunmaktadır. Öncelikle her düşünce tarzının ne olduğu açıklanır. Daha sonra her bir düşünce tarzının daha iyi anlaşılması amacıyla iki örnek durum anlatılır. Anlatılan bu iki durumdan bir tanesi sosyal ilişkilerle (IP, arkadaş, eş ve aile gibi) diğeri ise kişisel başarılarla ilgilidir (PA, bir sınavı geçmek ya da işte başarısız olmak gibi). Bu kurgu örneklerinin amacı her bir düşünce tarzının gerçek hayatta nasıl olabileceğini ölçeği dolduran kişinin anlamasını kolaylaştırmaktır. Ölçeği dolduran kişinin başta bu tanımlanan düşünüş tarzını anlaması ve bu düşünüş tarzını ne sıklıkta kullandığını 1-7 arasında Likert tipi bir puanlamaya yansıtması istenmektedir. Her ne kadar orijinal ölçekte "çarpıtma" kavramı kullanılmış olsa da Türkçe uyarlamanın aktarıldığı makalede Özdel ve ark. (5) "hata" kavramını tercih etmişlerdir.

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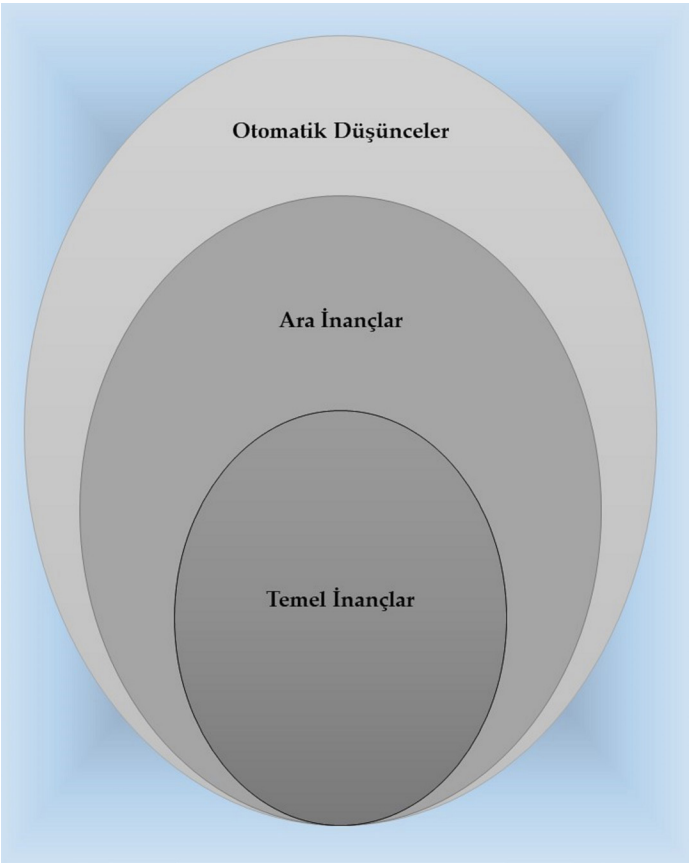
Majör depresif bozukluk, obsesif-kompülsif bozukluk (OKB) ve madde kullanım bozukluğu (MKB) bilişsel hataların araştırıldığı bazı psikiyatrik bozukluklardır. Örüm ve ark. (9), DÖÖ'yü kullanarak gerçekleştirdikleri çalışmada MKB hastalarının hem IP hem de PA alanlarındaki bilişsel hata düzeyinin sağlıklı insanlardan daha yüksek olduğunu, esrar kullanım bozukluğunun bilişsel hatalarla eroin kullanım bozukluğuna göre daha fazla ilişkili olduğunu bildirmiştir (10). DÖÖ, OKB hastalarındaki bilişsel hata düzeyinin hem IP hem de PA alanlarında sağlıklı kontrollere göre daha yüksek olduğunu göstermiştir (11). OKB'nin temizlik ve ruminasyon alt boyutlarının karşılaştırıldığı çalışmada ruminasyon boyutunda bilişsel hata düzeyinin anlamlı olarak daha yüksek olduğu bildirilmiştir (12). Yine, ruminasyon boyutunda kişilerarası ilişkilere ilişkin bilişsel hatalar (IP) temizlik boyutundan daha yüksek saptanmıştır. Benzer bulgu PA alanında saptanmamıştır. Bu çalışma, bilişsel hataların olay bazında rolünün olduğunu; bir alanda sık kullanılan bilişsel hatanın başka bir alanda kullanılamayabileceğini göstermesi bakımından değerlidir (12). Konversiyon bozukluğu, anksiyete bozukluğu ve panik bozukluk DÖÖ'nün kullanılabileceği bazı psikiyatrik bozukluklar olması açısından araştırmacıların ilgisini çekebilir. Psikiyatrik bozukluklardaki bilişsel hataların ortaya çıkarılması tedavi uygulamalarını yönlendirebilir. Özellikle ilaç tedavisine karşı aşırı ön yargısı olan hastalarda psikoterapi sırasında bilişsel hatalar üzerine yoğunlaşmak faydalı olabilir (12).



Figür 1. Bilişsel Yapı

Sonuç olarak, sağlıklı insanların da gündelik yaşantılarında sıklıkla kullandıkları bilişsel hataların aşırı, katı ve daha hızlı olduğu durumlar çeşitli psikiyatrik bozukluklarla ilişkili olabilir. Bilişsel hatalar tedavi süreçlerinin uygun şekilde ilerleyişinin önünde bir engeldir ve bilişsel hataların saptanması özellikle bilişsel davranışçı terapi gibi tedavi uygulamalarında tedavi başarısının artmasını sağlayabilir.

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