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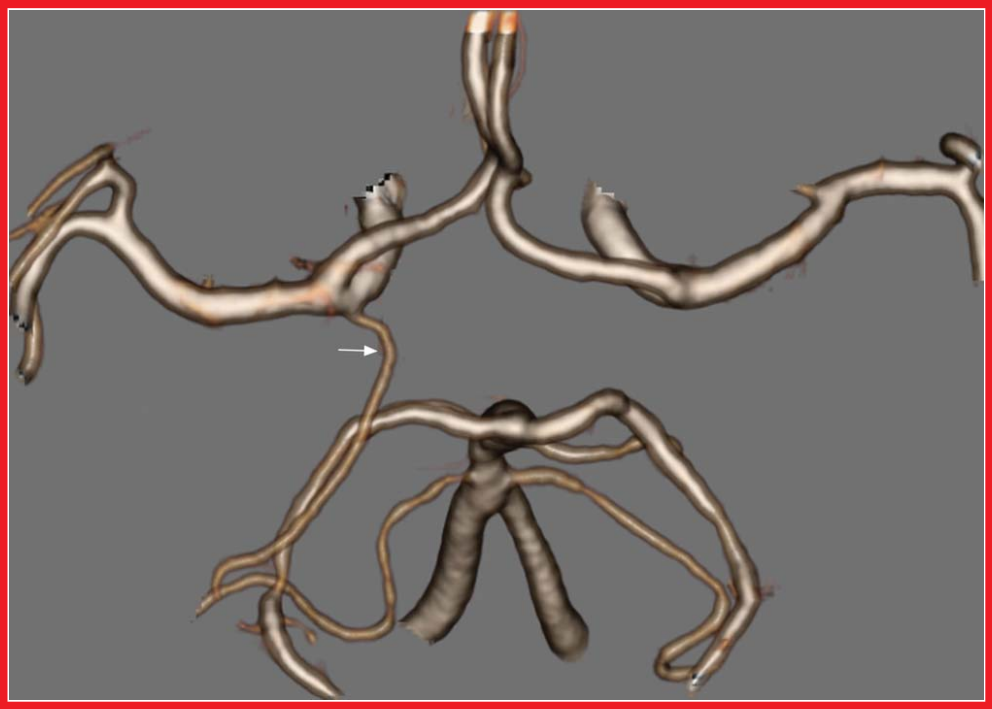

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Foetal hepatorenal toxicity and intrauterine growth retardation in pregnant Wistar rats treated with artemether

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Abstract

Objectives: Foetal hepatorenal toxicity and foetal morphology were evaluated following artemether administration to pregnant Wistar albino rats.

Methods: Twenty pregnant Wistar rats weighing between 180–200 g were divided into four groups (n=5, each) with Group 1 serving as the control. Groups 2, 3 and 4 received 1.1 mg, 2.2 mg and 3.3 mg per kilogram body weight artemether, respectively orally, twice daily for three days on day 7, 8 and 9 of pregnancy. The animals were sacrificed on day 20 of pregnancy and foetuses were harvested and evaluated for morphological changes. Foetal body weight and crown-rump length (CRL) were measured; alpha-fetoprotein (AFP) was assayed using amniotic fluid, and foetal kidney and liver were evaluated histologically for toxicity.

Results: There was a significant decrease in body weight, CRL and AFP of the treated groups compared to the control. The foetal liver of the treated groups revealed distorted cytoarchitecture, marked hepatocyte inflammation and hepatic necrosis. The foetal kidney of artemether-treated groups also showed disorganised renal structure, atrophic and degenerated glomeruli with acute tubular necrosis.

Conclusion: Artemether administration to pregnant albino rats causes intrauterine growth retardation or stunted growth, as well as foetal hepatorenal toxicity.

Keywords: alpha-fetoprotein; artemether; foetal hepatorenal toxicity; pregnancy

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Introduction

Malaria is one of the commonest tropical diseases which is a major source of concern to the developing world in terms of morbidity and mortality in children and pregnant women, especially with the emergence of the resistance of the Plasmodium parasite[1] to common, affordable and readily available anti-malarial drugs. In 1998, about 373 million people were infected with malaria. In 2008, about 247 million cases of malaria were reported and nearly one million deaths were recorded annually among children living in Africa.[2] The World Malaria Report of 2014 showed that children under the age of 5 years are at high risk of malaria and they account for about 78% of deaths resulting from malaria.[1] Recent occurrence of malaria is estimated at 198 million (uncertainty range 124 million to 283 million) cases with estimated 367,000 to 755,000 deaths annually, 90% of them in Africa.[1] These statistics have shown a decrease in both the occurrence and mortality of malaria over the years, but the figures are still alarming and a cause for major concern.

Plasmodium falciparum is the most virulent of all Plasmodium species that cause malaria and is known to have the highest morbidity and mortality rate.[3] Malaria is transmitted from one infected person to another through a bite of an infected female Anopheles mosquito as vector. However, the intensity of transmission is dependent on factors related to the parasites, the vector, human host and the environment. Malaria is however a preventable and curable disease. Pregnant women are also very susceptible to malaria infection hence it constitutes a threat to both women and the foetuses.

The prevalence of *Plasmodium falciparum* resistance to antimalarials especially in endemic regions further narrows the spectrum of antimalarial drugs available for use during pregnancy. The World Health Organization (WHO) has recommended the use of artemisinin-based combination therapy (ACT) for treatment of malaria in second and third trimesters of pregnancy.[2] Readily available, WHO-recommended ACTs include artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine, dihydroartemisinin-piperaquine and artesunate-sulfadoxine-pyrimethamine. These drugs have been known to be very effective in the treatment and management of malaria, and several studies have been carried out to evaluate the effect of these therapies on the biological system.[4–8]

Studies have focused on the effect of artemisinins during pregnancy in experimental animals.[9] The effect of artemether during different phases of pregnancy has been investigated in blastogenesis, organogenesis and foetal period.[10] At doses of 3.5 and 7 mg/kg/bw, artemether was observed to be lethal to embryos during organogenesis, and foetal growth retardation without incidence of malfunction was also observed. Furthermore, severe embryotoxicity has been reported for artemisinins, especially injectable artesunate at low doses in rodent, but embryotoxicity has not been convincingly observed in humans in clinical trials.[11] Embryo lethality and foetal cardiovascular as well as skeletal abnormalities have been observed for all derivatives of artemisinin at high doses.[12] Longo et al.[13] studied the effect of dihydroartemisinin on rat embryos and suggested that embryotoxicity of artemisinins may be due to oxidative stress induced by the drug.

Alpha-fetoprotein (AFP) is measured in pregnant women using maternal blood or amniotic fluid as a screening test for a subset of developmental abnormalities. AFP is particularly increased in open neural tube defect (NTD) and decreased in Down syndrome. It has also been used as a biomarker to detect tumours.[14] Foetal crown-rump length and body weight give an indication of foetal growth.

This study was designed to evaluate the foetal hepatorenal toxicity and intrauterine growth retardation following administration of artemether to pregnant Wistar albino rats.

Materials and Methods

Twenty pregnant female Wistar albino rats weighing between 180–200 g were used for the study. The rats were obtained from the animal house of the Department of Pharmacology, University of Calabar, Calabar, Nigeria and acclimatized for two weeks at the Animal House of Faculty of Basic Medical Sciences, University of Uyo, Nigeria. The approval for the study and the use of animals was obtained from the Faculty Animal Care and Use Committee of the Faculty of Basic Medical Sciences of University of Uyo, Uyo, Nigeria. Rules and regulations of Institute for Animal Ethical Committee (IAEC) were strictly followed and ethical standards from 1964 declaration of Helsinki were followed. The rats were fed with pellets and clean drinking water *ad libitum*. The rats were randomly divided into 4 groups of 5 per group. Female rats in proestrus phase of their cycle were transferred into a cage overnight with matured sexually active male Wistar albino rats. The vaginal aspirates were taken and smear done following overnight mating to demonstrate the presence of spermatozoa and this was taken to signify day zero of pregnancy. Group 1 served as control while Groups 2–4 received 1.1 mg, 2.2 mg, 3.3 mg of artemether per kilogram of body weight (bw) daily for five days between day 7 and day 11 of pregnancy.

Artemether manufactured by Greenlife Pharmaceuticals, Lagos, Nigeria was purchased from a registered pharmaceutical store in Uyo, Akwa Ibom State, Nigeria. Stock solution was prepared from the tablets and aliquots administered to the animals using cannula bypassing the oesophagus and delivered into the stomach based on the body weight.

The animals were sacrificed on the 20th day of the pregnancy under chloroform anaesthesia. The uterus was examined for the number of implantation sites, number of resorption sites and viable foetuses. The foetuses were delivered by uterotomy and examined for abnormal external features. Crown-rump length of each foetus was measured and the foetuses were weighed. The foetal liver and kidney were harvested and fixed in 10% formalin for histological studies using haemotoxylin and eosin techniques. Amniotic fluid was also collected for analysis of AFP using the alpha fetoprotein kits.

The preserved tissues were dehydrated with ascending grades of alcohol (70%, 90%, 95% and 100%) 1h/each concentration. The tissues were then cleared in two changes of xylene for one hour and then infiltrated with molten paraffin wax at 60°C two changes for an hour. The tissues were further embedded in molten paraffin and sectioned at 5 µm using a rotary microtome. The tissue sections were then stained using haemotoxylin and eosin. Light microscopic examinations were performed and presented as plates.

Statistical analysis was performed using analysis of variance (ANOVA) and Student's t-test. Experimental data were presented as mean ± standard deviation (SD). Values of $p<0.05$ were considered to be statistically significant.

Results

Effects of Artemether on the Morphology of Rat Foetuses and AFP

The mean crown-rump length (CRL) of the foetuses in the treated groups were 4.47 cm, 3.84 cm and 3.66 cm for Groups 2, 3 and 4, respectively. The means of Groups 3 and 4 showed a significant decrease when compared to control (4.74 cm) at p=0.05. The number of viable foetuses ranged between seven and ten which corresponded to the number of placental site noted. No dead foetuses and resorption sites were observed in any of the experimental groups. Significant reduction (P<0.05) was observed in rats in Groups 2, 3, and 4 compared to the control with respect to foetal body weight, CRL and AFP (**Table 1**). There was a dose-dependent reduction in the CRL of the foetuses.

Table 1
Effect of artemether on foetal body weight, crown-rump length and alpha fetoprotein.

Groups	Foetal weight (g)	CRL (cm)	AFP
Group 1 (control)	5.15±0.54	4.74±0.07	76.32±0.91
Group 2 (1.1 mg/kg)	4.85±0.45*	4.47±0.02	42.50±1.43*
Group 3 (2.2 mg/kg)	3.46±0.13*	3.84±0.13*	40.18±2.1*
Group 4 (3.3 mg/kg)	3.48±0.13*	3.66±0.07*	40.86±1.72*

*Data presented as mean ± standard deviation (SD) *p<0.05. **AFP:** alpha-fetoprotein; **CRL:** mean crown-rump length.

Effects of Artemether on the Histology of the Liver of Rats Foetuses

Effects of artemether on the cytoarchitecture of the foetal liver of rats are shown in **Figure 1**. The cytoarchitecture of liver of Group 1 was not altered. The cen-

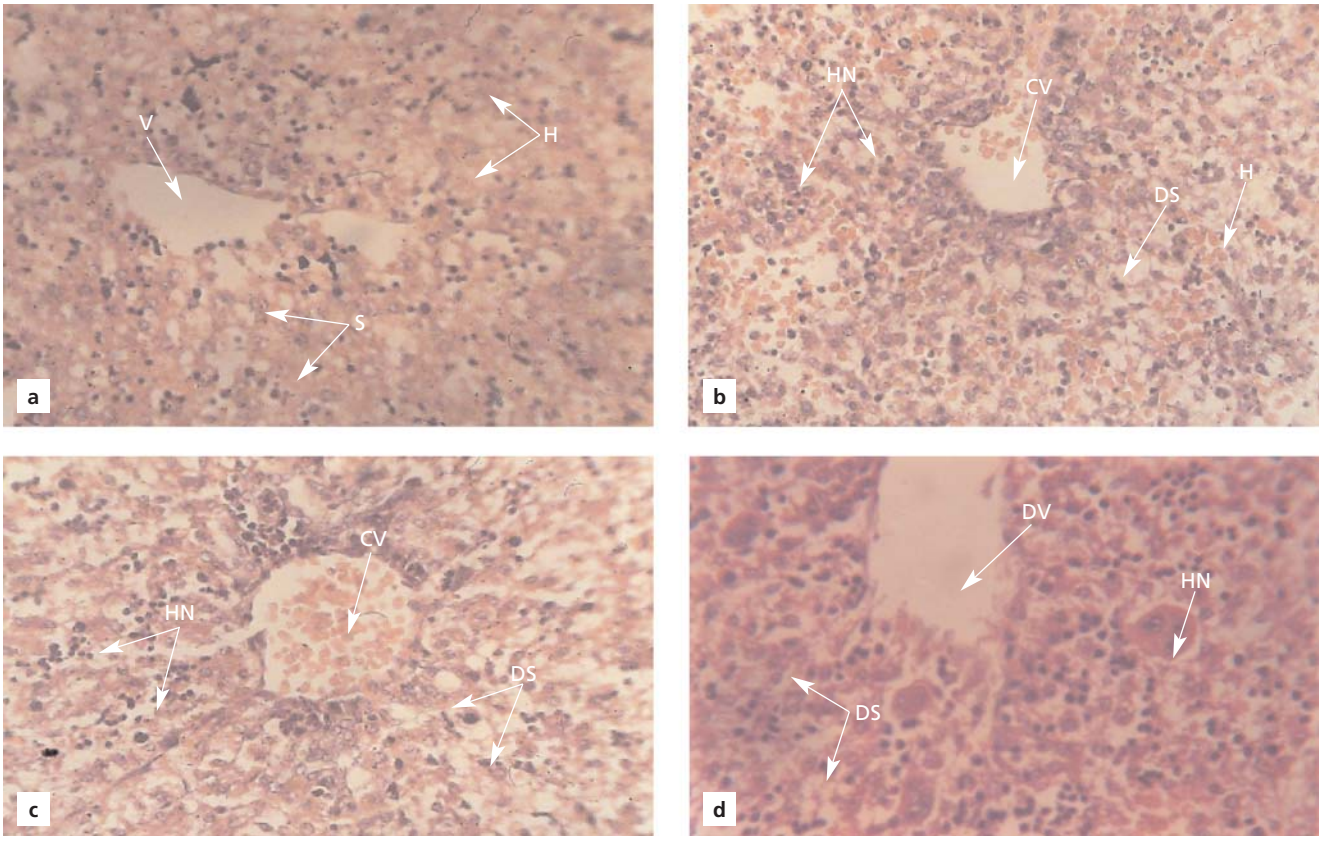

Figure 1. Foetal liver of (**a**) Group 1 (control group) showing normal preserved lobular architecture of the liver with normal hepatic cells, normal hepatic veins, and sinusoids. (**b**) Group 2 treated with 1.1 mg/kg of artemether showing moderately distorted architecture with focal hepatic necrosis, congested hepatic veins, dilated sinusoids, and haemorrhage. (**c**) Group 3 treated with 2.2 mg/kg of artemether showing moderately distorted architecture with focal hepatic necrosis, extensive congested hepatic veins, and dilated sinusoids. (**d**) Group 4 treated with 3.3 mg/kg of artemether showing severely distorted architecture with focal hepatic necrosis, severe hepatic vein dilation, dilated sinusoidal space and multinucleated giant cells. Haematoxylene and eosin stain, ×400. **CV:** congested hepatic veins; **DS:** dilated sinusoids; **H:** normal hepatic cells; **He:** haemorrhage; **HN:** hepatic necrosis; **MG:** multinucleated giant cells; **S:** sinusoids; **V:** normal hepatic veins. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

tral veins and the sinusoids were prominent while the hepatocytes were well outlined (**Figure 1a**). The foetal liver from Group 2 animals (**Figure 1b**) treated with therapeutic dose (1.1 mg/kg) of artemether showed distorted architecture with marked inflammation. The central veins were dilated and congested. The sinusoids showed mononuclear infiltrate, and extensive hepatic necrosis was observed when compared to the control. There was an extensive hepatotropic necrosis with dilated sinusoidal spaces infiltrated with mononuclear inflammatory cells in the liver of Group 3 (**Figure 1c**), while the liver of Group 4 showed distorted liver cytoarchitecture with extensive macrovesicular steatosis and hepatic necrosis with multinucleated cells (**Figure 1d**).

Effects of Artemether on the Histology of the Kidney of Rat Foetuses

Effects of artemether on the cytoarchitecture of the foetal kidney of rats are shown in **Figure 2**. The foetal kidney of Group 1 (**Figure 2a**) showed distinct cortical medullary region, while moderate degeneration of glomeruli and narrowing of the capsular space were observed in Group 2 (**Figure 2b**). The foetal kidney of Group 3 showed disorganised renal structural details, atrophic and degenerated glomeruli with acute tubular necrosis (**Figure 2c**). Severe degenerated glomeruli with periarterioler haemorrhages and acute tubular necrosis were observed in foetal kidney of Group 4 (**Figure 2d**).

Discussion

In this study, foetal body weight and CRL were used to evaluate foetal growth morphology. The result revealed a reduction in the weight and CRL of the foetuses following administration of artemether. This is suggestive of intrauterine growth retardation. Similar observation was also made when artesunate was administered to pregnant Wistar rats in order to study its effect on the morphometry of foetal central nervous system.[15] Observations on the foetal weight and CRL of Wistar albino rats have been reported following the administration of artesunate, artemether and arteether,[9] *Aloe vera*,[16] or pyrimethamine.[17] Ekanem et al.[18] also reported that pyrimethamine had a deleterious effect on the foetal epiphysis leading to growth retardation and developmental anomalies.

AFP is measured in pregnant women using maternal blood or amniotic fluid as a screening test for a subset of developmental abnormalities. It is particularly increased in open neural tube defect and decreased in Down syndrome. It has also been used as a biomarker to detect tumours.[14] There has been a correlation between amniotic fluid AFP

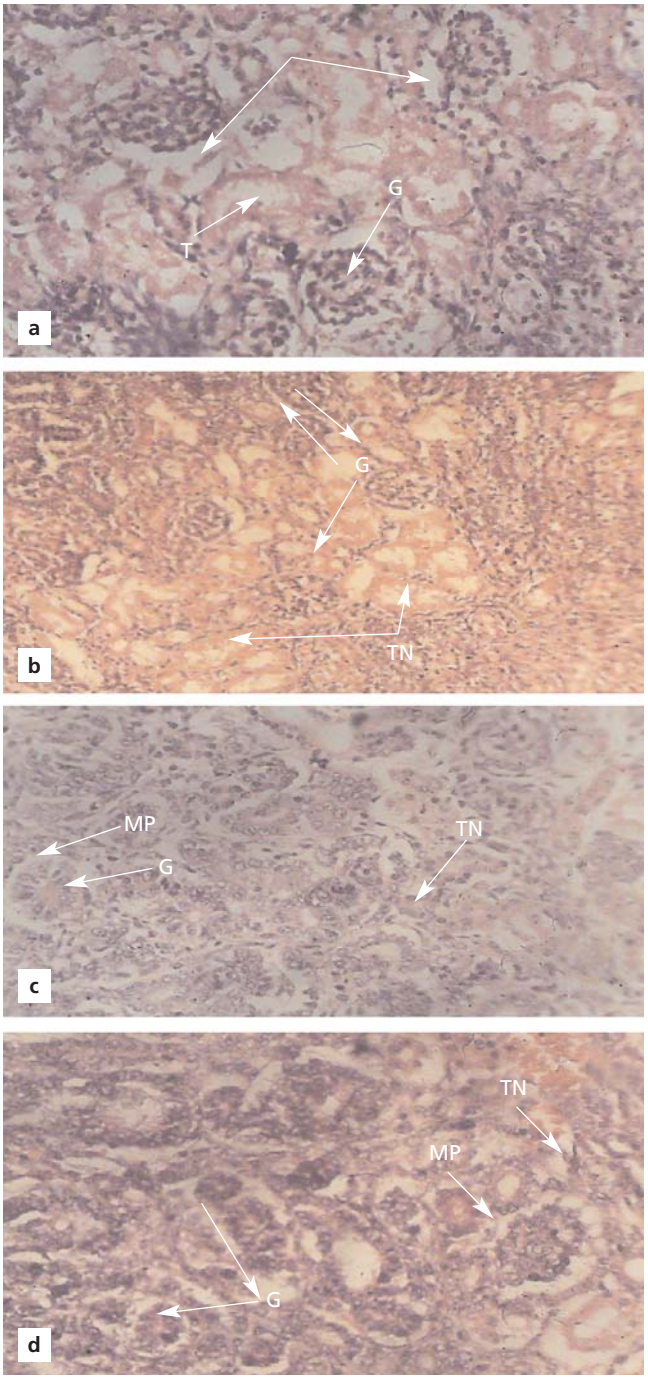

Figure 2. Foetal kidney of (**a**) Group 1 (control group) showing normal preserved architecture with normal glomeruli and tubules, and no tubular necrosis. (**b**) Group 2 rats treated with 1.1 mg/kg of artemether showing mildly distorted architecture with paucity of glomeruli, mesangial proliferation and tubular necrosis. (**c**) Group 3 rats treated with 2.2 mg/kg of artemether showing mildly distorted architecture with few glomeruli, mesangial proliferation and tubular necrosis. (**d**) Group 4 rats treated with 3.3 mg/kg of artemether showing severely distorted architecture with paucity of glomeruli, mesangial proliferation, tubular necrosis and peritubular arterioler haemorrhage. Haematoxylene and eosin stain, ×400. **G:** glomeruli, **MP:** mesangial proliferation; **PH:** peritubular arterioler haemorrhage; **T:** tubules; **TN:** tubular necrosis. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

and occurrence of neural tube defects.[19] The AFP in this study was significantly reduced in treatment groups compared to the control, implying that there was no gross foetal malformation except histologically, the liver which is another source of AFP had been significantly affected in the treated groups. This findings support the study by Bhabagrahi et al.[9] which reported that artemisinin has significant embryo-foetal toxicity in rats without any gross malformation. Elevation of AFP has been reported to result from the leakage of foetal serum through a disrupted and necrotic nervous tissues into the amniotic fluid.[20]

Most drugs are metabolised and eliminated in the liver and kidney, but the liver is more susceptible to drug toxicity.[21] Teratogenic effects of drugs have been well documented.[19] Hepatocyte necrosis, hepatitis, cholestasis and fibrosis are common manifestations of liver toxicity. In this study, we observed derangements and degenerations in the foetal liver of the rats with increasing doses of artemether compared to the control. Cellular damage and a progressive cytoarchitectural damage of the foetal liver were observed in the treated animals. Congested and dilated sinusoids and central veins, hepatocytic necrosis and microvesicular steotosis were observed. Toxicological study of *Ginkgo biloba* in mice foetus by Zehra et al.[22] also reported similar findings.

The kidney filters and removes toxic substances from the body. Certain drugs have been found to be nephrotoxic. Mild to severe alteration in the histology of the foetal kidney was observed in this study following the administration of artemether. The degeneration of renal glomeruli and the disorganisation of the renal structural details in this study were similar to other studies where teratogenic nephrotoxicity of *Aloe vera*,[16] beer and palm wine[23] were reported.

Conclusion

The results of this study showed that artemether crosses the uteroplacental barrier to cause intrauterine growth retardation or stunted growth, as well as foetal hepatotoxicity and nephrotoxicity in Wistar albino rats.

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Nose asymmetry correlates with external nose volume and area: 3D analysis of nasal dimensions in a young Turkish population

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Abstract

Objectives: The nose is a critical facial feature from the cosmetic and functional point of view. The effect of size and symmetry of the nose on beauty and function is a matter of concern for surgeons. In the present study, we performed 3D analysis of nose dimensions and investigated the correlation among them.

Methods: Facial mask of 40 (20 males and 20 females) young Turkish adults aged between19 and 26 years were recorded with a 3D scanner. Nose asymmetry, external nose volume, nose area, anatomical nasal index, nasal protrusion index, body height, body weight and body mass index were measured. The correlations among these measurements were investigated.

Results: The external nose surface area was measured as 18.2±2.1 cm^2 and external nose volume as 8.1±1.3 cm^3. A significant correlation was found between nose asymmetry value and external nose surface area (r=0.33, p=0.03), and also between nose asymmetry value and external nose volume (p=0.34, r=0.03).

Conclusion: Our study presents 3D quantitative data regarding nasal dimensions and correlation between the nose size and symmetry.

Keywords: 3D analysis; external nose area; external nose volume; nose asymmetry

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Introduction

The nose is a prominent feature of the face and located in the center. Its shape and therefore dimensions, like other parts of the human face, vary among human populations. Besides the basic physiological tasks of the nose, the size of the nose plays an important role in facial beauty. The smaller size of nose area and dimensions in women, or the averageness size of nose in man were perceived as attractive by men and women respectively.[1] Furthermore, as in other facial parts, the nose symmetry is another important parameter which contributes to facial expression and beauty.[1–3] Therefore, nose size and symmetry should be considered together.

Assessment of nasal dimensions and asymmetry is important for craniofacial and plastic surgery in order to restore the facial esthetics. Surgeons need accurate and reliable anatomical measurements obtained from the patients for planning and evaluating the outcome before and after the surgery.[4] The traditional analysis of facial features is performed using 2D photography method which has limitations. The emerging technologies enable more accurate and reliable measurements over 3D scans.[5] Additionally, these technologies allow more complicated surface analyses using thousands of facial soft tissue landmarks.[6] In both 2D and 3D methods, cephalometric analyses of facial soft tissue are performed by using soft tissue landmarks defined in previous studies.[7] The accurate placement of the soft tissue landmarks is an important issue in order to obtain reliable data.[8–10]

The aim of the present study was to measure nose asymmetry, external nose volume, external nose area, anatomical nasal index, nasal protrusion index, body height, body weight, body mass index and afterwards, to investigate the correlation among these measurements.

Materials and Methods

Ethical approval for this study was obtained from the Ethics Committee of Clinical Research of Akdeniz University (approval number 70904504/143). Written, informed consent for participation was obtained from the volunteers. Three-dimensional face scans of 40 volunteers (20 males and 20 females) aged between 19 and 26 years (mean age 22±2) were performed with a hand held light scanner (Artec™ Eva, Artec Group, Luxembourg). All volunteers were of Caucasian ethnic origin and with no history of underlying trauma, craniofacial disease or previous orthodontic treatment or surgery.

Face of each volunteer was scanned using the scanner. The volunteers were seated on a chair and asked to keep a natural head position determined by the volunteers own feeling of a natural head balance. In order to avoid motion artefacts, the volunteers were asked to remain still during scanning. Each face scanning took around 5 seconds. The ideal scan distance was determined by the distance adjustment indicator available in the Artec Studio 10 Software (version 9.2.3.15; Artec Group, Luxembourg, licensed). Using the distance indicator, true localization of the scanner was adjusted, either moving it closer or farther away to obtain the best possible face scan. The scanning was performed at a speed of 15 frames per seconds and the depth of the scanning field was adjusted to 400 mm for near and 1000 mm for far. The given data of the scanner by the manufacturer is between 0.4-1 m for work distance, up to 0.1 mm for 3D accuracy and up to 0.5 mm for 3D resolution. The three-dimensional surfaces were created by Artec Eva Studio 10 software in STL file format.

The scanned masks of each subject were imported into the same work space of Artec Eva Studio 10 Software (version 9.2.3.15; Artec Group, Luxembourg, licensed). Unwanted extraneous data except from the nose region were excluded. The upper borders of nose region were the planes connecting the landmarks "nasion" and "endocanthion" on both sides, the lateral borders were the planes connecting the landmarks "endocanthion" and "alar curvature" on both sides, and the lower border was determined by the horizontal plane passing through the landmark "subnasale".

Five anthropometric soft tissue landmarks which have been used in the present study were as follows:

1. The soft tissue nasion (N) which was marked on the deepest concavity of the dorsum of the nose.
2. Pronasale (Prn) was identified as the most prominent point in the tip of the nose.
3. Subnasale (Sn) was identified at the base of the columella.
4. Right and left alar curvature point (AcR and AcL) were identified as the attachment point of right and left ala of the nose (**Figure 1**).

Eight nasal parameters calculated by using five anthropometric soft tissue landmarks were as follows:

1. Nose height (N-Sn): Length between soft-tissue nasion and subnasale
2. Nose length (N-Prn): Length between soft-tissue nasion and pronasale
3. Anatomical width of the nose (nose width) (AcR-AcL): Length between attachment point of right and left nasal curvature
4. Nasal tip protrusion (Prn-Sn): Length between subnasale and pronasale
5. Anatomical nasal index (AcR-AcL/N-Sn): The ratio of nose width to nose height

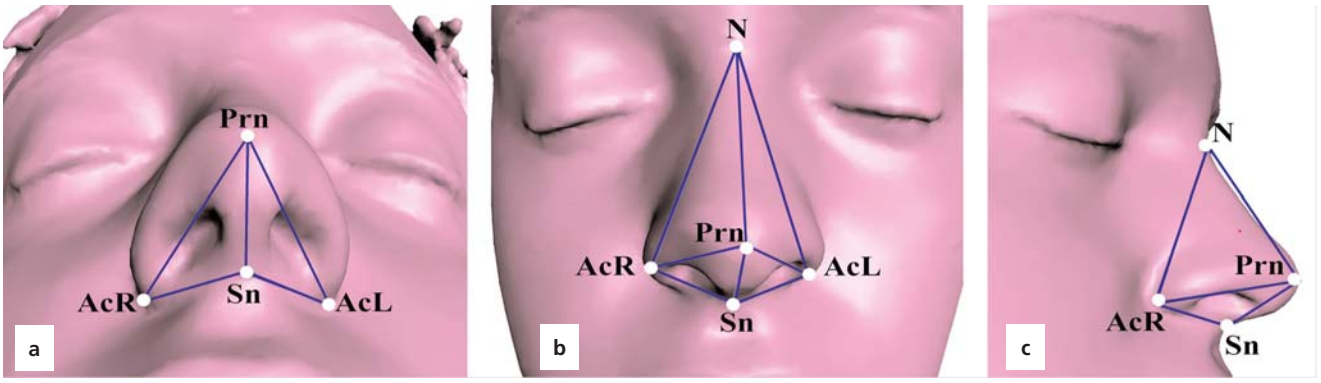

Figure 1. Nasal soft tissue landmarks and linear measurements. Inferior (**a**), anterior (**b**) and lateral (**c**) view of scanned nose. **AcL:** left alar curvature; **AcR:** right alar curvature; **N:** nasion; **Prn:** pronasale; **Sn:** subnasale. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

6. Nasal protrusion index (Prn-Sn/N-Sn): The ratio of nasal tip protrusion to nose height
7. External nasal volume: This was approximated from the volumes of two tetrahedra. The base of the first tetrahedron was defined as the plane AcR-AcL-Prn, and vertex was defined in (N). The second tetrahedron had the same base and vertex was defined in (Sn)
8. Extemal nasal surface: The four surfaces forming the nose area were N-Prn-AcR, N-Prn-AcL, Prn-Sn-AcR, and Prn-Sn-AcL

A mirror image of nose region was generated for each subject with Autodesk Netfabb software (Netfabb, Parsberg, Germany, Free trial version) and superimposed on the original nose image. Afterwards, for quantitative nose asymmetry analyses, the distance between the original nose and its mirrored nose image was automatically computed by the Artec Studio 10 Software. Namely, the asymmetry value of the nose was indicated by using the root mean square (RMS) value of the distance between the original nose and the mirror nose surfaces. The volume or shape differences between two surfaces are evaluated using RMS value.[11–13] This value is the indicator of the variation between two surfaces in 3D and shows the disparity or similarity between the compared shapes. While the lower values indicate a more similar shape, the higher values indicate greater diversity. For a perfect overlapping, the value should optimally be as close to zero as possible. For the further detail of RMS see the study of Ozsoy (**Figure 2**).[14]

The Graphpad software (GraphPad Prism version 6.05, GraphPad Software Inc, San Diego, CA) was used for statistical analyses. In order to analyze intra-observer reliability, soft tissue measurements of randomly selected 10 subjects (5 males and 5 females) were measured two times by the same operator with a one-week gap.

To investigate the correlation between nasal asymmetetry and the measured external nose volume, external nose area, anatomical nasal index, nasal protrusion index, body mass index, height and weight the correlation coefficient between these values were calculated. For normally distributed data, a Pearson's correlation coefficient was calculated, while a Spearman's correlation coefficient was computed for any abnormally distributed data.

Student t-test was used to compare gender differences. A p-value of less than 0.05 was considered statistically significant. Values were expressed as mean ± standard deviation (SD).

Results

We first examined the intra-observer reliability of our method. The correlation coefficient ($r=0.96$, $p<0.001$) showed that the intra-observer reliability of the method was very high. Descriptive statistically analyzed results for the measured parameters in both genders are represented in **Tables 1** and **2**.

Significant difference was observed between male and female in external nose volume and surface area. The mean value of external nose volume was approximately 30% higher and external nasal area is 12% larger in males compared to females. Additionally, mean nose width and height of male nose was 10% and 4% higher than the mean female nose, respectively. Mean body height, weight and BMI of male were 4%, 35% and 20% higher than the mean female values respectively.

A significant correlation was found between nose asymmetry value (as RMS) and external nose surface area ($r=0.33$, $p=0.03$) and also between nose asymmetry value (as RMS) and external nose volume ($p=0.34$, $r=0.03$). We did not find correlation in any other parameters. We further assessed the evidence of correlation according to the genders and no significant differences were found (**Table 2**).

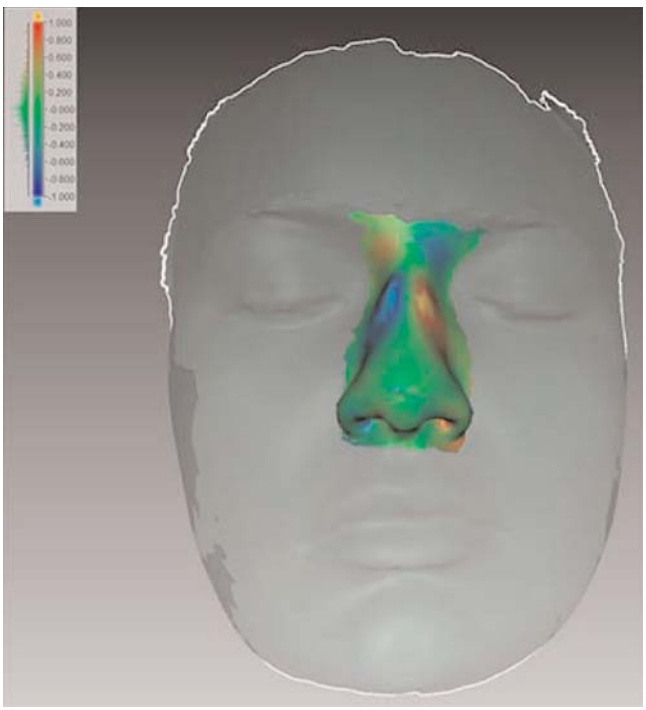

Figure 2. Image showing the deviation color maps after superimposition of original and mirrored facial scans of the same subject. The colored deviation map legend in the upper left corner shows the millimeter scale. The map changes in color from blue, which corresponds to negative distance, to red, which corresponds to positive distance; green means that the distance between surfaces at that particular point is close to zero. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

Table 1
Means and standard deviations of the measurements compared by sex using t-test.

Gender	Nose asymmetry	Nose volume (cm^3)	Nose surface area (cm^2)	Nose width (mm)	Nose height (mm)	Anatomic nasal index (%)	Nasal protrusion index (%)	Body height (m)	Body weight (kg)	Body mass index (BMI)
Males	0.52±0.2	9±1*	19.5±1.7*	34.7±2.5*	53.9±3.5*	64±8	32±4	1.76±0.06*	77.5±12.9*	24.7±3.4*
Females	0.43±0.1	7.19±0.9	17.1±1.7	31.6±1.6	51.7±3	61±4	34±39	1.69±0.04	57.9±6.3	20.3±1.75
Total	0.48±0.16	8.1±1.3	18.2±2.1	33.1±2.6	52.8±3.4	63±6	33±4	1.72±0.07	67.7±14.2	22.5±3.5

*Indicates significant difference between male and female ($p<0.05$).

Discussion

In this study, we analyzed the anthropometric parameters of the nose with a 3D method and reported the external nasal volume and area of young Turkish males and females for the first time in the literature. Examination of the correlation among the measurements showed that nasal asymmetry corelates with nasal volume and area.

We demonstrated the nasal asymmetry using surface topography measurement method. In this method, the asymmetry of the nose was calculated by comparing the whole surface with the mirror image of the surface, instead of comparing a few determined landmarks between the right and left sides. The advantage of the present method is that, every point composing the surface can be included to the calculation and a quantitative data can be obtained. Additionally, colored surface maps demonstrate a visual data which makes it easy to understand the alteration at any points of the surface. Another advantage of our method is that all measurements were performed on a single scanned data in contrast to 2D methods. In 2D methods, the measurements are performed from several images which are captured from different aspect of the nose. This may cause increment of variability cussed by different landmark identification or caliper positioning in every aspect.

There are several non-invasive techniques for facial analyses using 3D reconstruction. They offer significant changes in the process of diagnosis, such as structured light scanner, laser scanning, contact digitization, magnetic resonance imaging and stereo photogrammetry.[6] The most important advantage of such systems is the speed in data acquisition. Quick acquisition of the image reduces the effect of subject movements, and therefore increase accuracy of the measurements. The accuracy and reproducibility of 3D imaging systems have been confirmed by several studies.[5,15,16]

Table 2
Correlation between nose asymmetry and determined nasal measurement.

	Males		Females		Total	
	r	p	r	p	r	p
Nose volume	0.19	0.43	0.34	0.14	0.34	0.03*
Nose surface area	0.22	0.34	0.27	0.26	0.33	0.03*
Nose width	0.10	0.66	0.19	0.42	0.26	0.11
Nose height	0.09	0.7	0.41	0.07	0.25	0.11
Anatomic nasal index	0.07	0.78	-0.16	0.05	0.08	0.61
Nasal protrusion index	0.37	0.11	-0.11	0.63	0.13	0.41
Body height	-0.39	0.09	0.17	0.46	-0.02	0.88
Body weight	-0.23	0.33	-0.03	0.9	0.06	0.71
Body mass index	-0.06	0.81	-0.09	0.71	0.13	0.44

*$p<0.05$

There are several studies focusing on nasal morphometric parameters which differ among the races and genders. Most of them provide data concerning basal values which are obtained from a local population.[17–21] Such anthropometric data play a key role in clinical evaluations, in point of providing a precise diagnosis for different syndromes and evaluating and planning surgical treatment.

The result of a recent study describing the average values of the nasal anthropometric measurements in a young Turkish male population (ranging in age from 18 to 30 years) reported the mean height (N-Sn) of the nose as 56.92±0.44 mm, width of nose (AcR-AcL) as 23.14±0.28 mm.[17] In another study, the authors analyzed facial soft tissue of healthy Turkish young adults (ranging in age from 18 to 24 years) with a photographic method and reported the mean height (N-Sn) of the nose as 5.19±0.75 mm.[22]

The external nasal volume and area measurements are other parameters in evaluation of nasal dimensions. In the literature, there is no study reporting the external nasal volume and nasal area of Turkish population. For the estimation of nasal volume and area, different geometric approximations were used. By using two defined tetrahedral method, Ferrario et. al.[19] approximated the external nasal volume and area. They reported the volume as 11.16±1.33 cm^3 and the area as 22.6±2.15 cm^2 in adults (aged 19 to 32 years). With the same approximation method, in an anthropometric study which measures the external nose in 18–25 year old Sistani and Baluch aboriginal women in southeast of Iran, the external nose surface area was measured as 17.52±2.12 cm^2 in Sistani group, and 18.94±1.6 cm^2 in Baluch group.[20] In the same study, the nasal volume was reported as 4.79±0.35 cm^3 and 5.23±0.45 cm^3 in Sistani and Baluch groups, respectively. External nasal parameters of 1000 healthy Egyptians aged 20–70 years were analyzed with a photogrammetric method and the external nasal volume was reported as 4.58±3.57 cm^3 in males and in 4.02±2.93 cm^3 in females for a 20–30 years age group.[18] The value of external nasal area was 17.67±1.6 cm^2 in males and 15.58±1.7 cm^2 in females. External nose volume in fifty young adults was calculated as 9.06±1.3 cm^3 in males and 7.03±1.2 cm^3 in females using a formula developed by mathematician David Bash.[23] The findings of Bash are very close to our measurements. In a mix longitudinal study, Burke et al.[24] approximated the nasal volume by using facial contour map created by stereometrics camera and contour plotting machine. In the aforementioned study, the nasal volume of the 26 boys and 26 girls between the ages of 9 and 16 years were reported as 15.2 cm^3 and 11.2 cm^3, respectively.

The contribution of symmetry and averageness of facial features to facial beauty is matter of concern. Thornhill et al.[25] noted that averageness and symmetry could both contribute to the attractiveness of averaged composites. Langlois et al.[26] rejected the symmetry hypothesis. They argued that facial symmetry is not attractive and, therefore, cannot be in charge of the attractiveness of averaged composites. By using the photographic images which were rated by the subjects, they showed that there was no correlation between symmetry and attractiveness. Additionally, Kowner et. al.[27] showed that perfectly symmetrizing using a software make the faces less attractive than the originals. However, in contrast to aforementioned works, several studies reported significant correlations between facial symmetry and attractiveness.[1,28,29]

Although the face is generally one of the most revealing parts of body, evidence suggests that most people focus on the region of the nose, eyes and mouth.[30] Size of the facial features is important factor for attractiveness and the average face features are perceived more attractive.[31,32] Grammer et al. showed that while the women rate larger nose as healthy and attractive, men rate smaller nose as attractive.[1] Men whose noses are near the means of the distributions received higher ratings than men whose noses were either smaller or larger than average.[33] In our study, in order to investigate the correlation among symmetry and size, we performed quantitative measurements instead of inspecting rating of participants in photographs. We believe that our data contributes to the literature by presenting new quantitative data.

Conclusion

The effect of nose size and asymmetry on facial beauty has been discussed in several studies. In our study, we inspected both parameters and presented quantitative data concerning nasal dimensions and correlation among them. The limitation of our study is the number of subjects; therefore, the findings of the present study needs to be confirmed with large cohort studies.

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Sella turcica variations in lateral cephalometric radiographs and their association with malocclusions

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Abstract

Objectives: Classification of the skeletal facial types is performed using certain reference points and planes in lateral cephalometric radiographs to plan orthodontic treatments. One of these reference points is sella turcica which is closely associated with craniofacial bone development. The aim of this study was to identify the association between the sella turcica variations and skeletal Class I, II, and III malocclusions.

Methods: This study retrospectively evaluated 94 orthodontic patients (48 males and 46 females) between 14–26 years of age. Lateral cephalometric radiographs of the patients with skeletal Class I, II, and III malocclusions were classified into six groups according to sella turcica morphology: normal sella turcica, oblique anterior wall, double contour of the floor, sella turcica bridge, irregularity in the posterior part, and pyramidal shape of sella turcica. The length, depth, and diameter of sella turcica were measured. Sella turcica variations and radiographs of patients with Class I, II, and III malocclusions were compared statistically.

Results: The correlation between the sella turcica variations and skeletal sagittal classification was statistically significant (p=0.017). 36.8% of the radiographs, which were classified as normal sella turcica were classified as Class I patients. There were no statistically significant differences between the skeletal Class I, II, and III malocclusions and sella turcica variations in terms of the length, depth, and diameter.

Conclusion: For adequate patient referral and management, orthodontists should recognize sella turcica variations in lateral cephalometric radiographs, and these findings should arise an index of suspicion for associated pathologies, especially of the hypophyseal gland.

Keywords: sella turcica; lateral cephalometric radiography; malocclusion; skeletal class I, II, III

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Introduction

The sphenoid bone which is located in the middle of the skull base articulates with most of the bones forming the skull. The so-called corpus sphenoidale is the body of sphenoid bone. The concavity in the middle part of the upper surface of corpus sphenoidale is the hypophyseal fossa, in which the hypophysis lies.[1,2]

The hypophyseal fossa is limited by the tuberculum sellae anteriorly and dorsum sellae posteriorly. The two small processes on both sides of the tuberculum sellae are named as middle clinoid processes and the small processes on the superior lateral corners of the dorsum sellae are the posterior clinoid processes. The hypophyseal fossa is examined in three parts, namely, the anterior wall, poste-

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rior wall, and the floor. Because these three structures resemble a Turkish saddle, this region is named as sella turcica.[1–6] Development of sella turcica is closely associated with the development of the hypophysis. The size of the sella turcica will vary depending on the normal or pathological development of the hypophysis,[3,4] which is the primary endocrine gland controlling most of the endocrine functions. 25% of the anomalies diagnosed in the lateral cephalometric radiograms by the orthodontists account for the glandular anomalies. The most common radiologic manifestation of these anomalies is enlarged sella turcica due to a hypophyseal adenoma.[2,7] Besides its importance endocrinologically, the hypophysis is also important due to its anatomical location, including its proximity to the hypothalamus, optic chiasm, sphenoid sinus, cavernous sinus and its internal anatomic structures.[4,5] The recent developments in endoscopy allowed transnasal endoscopic approaches performed in the sellar region and its surroundings. The anatomical structures, especially the shape of the posterior clinoid processes, are of importance during this process. As the advanced radiological investigations are required for three-dimensional evaluations of the anatomic structures in the pre-operative period, identifying the presence of any variations of sella turcica in the lateral cephalometric radiographs may be beneficial as a preliminary information, providing a guide for the patient management.[8]

Embryological development of sella turcica is associated with the development of craniofacial bones with its anterior part developing from the neural crest cells, and its posterior part developing from the paraxial mesodermal cells. Sella turcica plays a key role in the migration of neural crest cells towards the frontonasal and maxillary areas under embryologic development. While the anterior wall anomalies of the sella turcica are associated with the anomalies in the frontonasal region, the ones belonging to the posterior wall are associated with the cerebral developmental defects.[2] Studies in monozygotic twins have shown that genetic factors are not solely responsible for the genesis of the sella turcica morphology.[9]

Certain reference points and planes are used as landmarks in lateral cephalometric radiographs for sagittal classification of facial types and for the planning of orthodontic treatments. In this aspect, sella is important because of its central location as a reference point in cranial morphology and its relation with the intermaxillary suture.[2,3,7] Therefore, the S point, where the sella turcica is located, bears importance for the practice of orthodontists. On the other hand, the anterior wall structure is more reliable in cases when variations of the sella turcica are present.[10]

One of the measurements, which shows the sagittal relation between maxilla and mandibula is the 'ANB' angle. This angle is formed by the arbitrarily named points A, N, and B defining the cephalometric landmarks as follows: First, point A is the deepest point in the bony concavity, extending from the anterior nasal spine to the first upper incisor. Secondly, the point N (nasion) is the union point of the frontal and nasal bones. And finally, the third one, point B is the deepest point of the mandibular concavity extending from the lower incisors of mandibula to the tip of the chin (**Figure 1**).

The size and shape of the sella turcica may be variable ranging from 4 to 12 mm vertically and from 5 to 16 mm anteroposteriorly in size.[3] Assessment of these variabilities in the size of the sella turcica in terms of malocclusions may be beneficial in planning the treatment.

For the assessment purposes, morphological variations of the sella turcica may be classified under the following headings: normal sella turcica, oblique anterior wall, double contour of the floor, sella turcica bridge, irregularity in the posterior part of the sella turcica, and pyramidal shape of dorsum sella.[11–15]

The most common variation of the sella turcica in the orthodontic literature is the sella turcica bridge - the manifestation of the union of the anterior and posterior structures of the sella turcica. The image of this variation may be the display of the calcification of the interclinoid liga-

Figure 1. ANB angle. **A:** deepest point in bony concavity extending from the anterior nasal spine to the first upper incisor; **B:** deepest point of the mandibular concavity which extends from the lower incisors of mandibula to the tip of the chin; **N:** nasion, the union point of frontal and nasal bones.

ment or it may be formed by the superimposition of the sellar structures.[2] It is reported in the literature that the sella turcica bridge is associated with local dental anomalies.[16]

The aim of this study was to define the sella turcica variations and determine the associations of skeletal Class I, II, and III malocclusions to the sella turcica variations.

Materials and Methods

This study included 94 patients (48 males and 46 females) between 14–26 years of age admitted to Başkent University, School of Dentistry between 2013–2017, whose lateral cephalometric radiographs were obtained by the same imaging device (Veraviewepocs®, Morita, CA, USA). The radiographs included in this study were randomly selected from a pool of 3517 patient records. The radiographs were excluded from the study if the following were present including any signs of a syndrome, cleft lip-palate, history of a previous maxillofacial surgery or previous orthognathic surgery, or any known endocrine diseases. In addition, the radiographs of patients that went under endocrinologic treatment were excluded. Furthermore, the radiograms with a double view or if the sella turcica could not be visualized clearly were also excluded. The drawings, measurements, and filtrations on the cephalometric radiographs were performed with Dolphin Imaging software (Vers 11.5 Premium, Patterson Dental, St. Paul, MN, USA) using the appropriate criteria.

Skeletal classification of the cephalometric radiographs was made using the ANB angle. Patients with an ANB angle between 0° to 4° were accepted as skeletal Class 1, the patients with an angle above 4° were accepted as skeletal Class II, and the patients with an angle below 0° were accepted as skeletal Class III. The results of the Wits' analysis were evaluated in order to eliminate the possibility of the mandibular posterior rotation obscuring any skeletal anomalies in the patients with increased perpendicular direction values. For this purpose, the radiographs were excluded if the results from the ANB angle measurements and Wits' analysis did not coincide. To eliminate the effects of growth-related changes in the post-pubertal period, the patients, who completed or who were about to complete their growth processes were included in the study. Therefore, the lower limit of the age range of the study patients was determined to be 14 years in females, and 16 years in males. The upper limit of the age range was 26 years.

According to these inclusion and exclusion criteria, 94 individuals were included in the study. Of these, 30 were classified as skeletal Class I, 31 skeletal Class II, and 33 skeletal Class III. The magnification ratio was eliminated by calibration by means of a radioopaque ruler image with a known spatial size, located at the upper right corner of the radiographs.

Radiographs of the patients with skeletal Class I, II, III malocclusions were classified in six groups according to sella turcica variations as follows: a) normal sella turcica, b) oblique anterior wall, c) double contour of the floor, d) irregularity in the posterior part of the sella turcica, e) sella turcica bridge, and f) pyramidal shape of dorsum sella (**Figure 2**).[4]

The measurements of sella turcica were performed on the radiographs. Calculated variables including the length, depth, and diameter values of sella turcica were illustrated in **Figure 3**. The length was measured as the distance between the tuberculum sellae and dorsum sellae. The

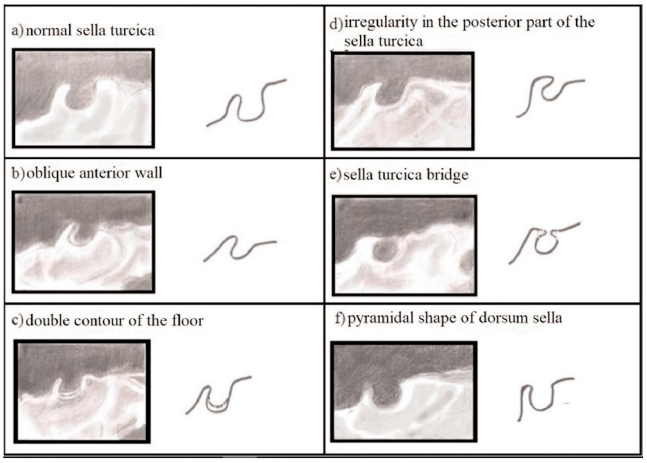

Figure 2. Morphological variations of sella turcica in six groups.

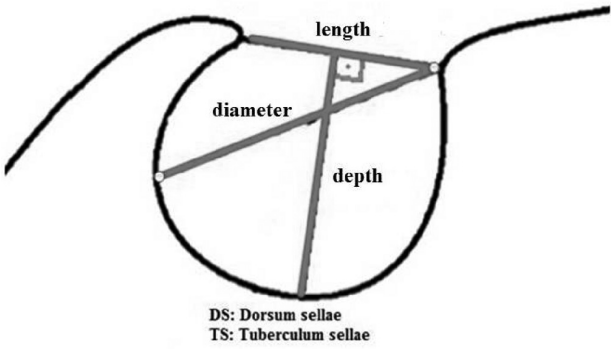

Figure 3. Measurements of sella turcica.

Table 1
Dependence of Classes I, II, III malocclusions and sella turcica variations.

Sella turcica variants	Class I	Class II	Class III	Total	p
Normal	14 (46.7%)	10 (30.3%)	14 (45.2%)	38 (40.4%)	0.017*
Oblique anterior wall	0 (0%)	3 (9.1%)	3 (9.7)	6 (6.4%)	
Double contour of the floor	7 (23.3%)	2 (6.1%)	0 (0%)	9 (9.6%)	
Sella turcica bridge	3 (10%)	4 (12.1%)	0 (0%)	7 (7.4%)	
Irregularity in the posterior part	4 (13.3%)	8 (24.2%)	9 (29%)	21 (22.3%)	
Pyramidal shape of dorsum sellae	2 (6.7%)	6 (18.2%)	5 (16.1%)	13 (13.8%)	
Total	30 (100%)	33 (100%)	31 (100%)	94 (100%)	

*Fisher-Freeman-Halton exact test

depth was measured as the distance extending from the length line to the deepest point of the hypophyseal fossa. And finally, the diameter was measured as the distance between the tuberculum sellae and the most posterior point inside the fossa.

Descriptive statistics were expressed as mean and standard deviation values when the parametric assumptions were satisfied. If these assumptions were not satisfied, the descriptive statistics were expressed as median (minimum-maximum) values. The descriptive statistics for the categorical variables were given as frequency (n) and percentage (%).

To evaluate the intra-rater reliability, 30 radiographs were randomly selected 30 days later than the initial evaluations. Then, the length, depth, and diameter of the sella turcica were measured, determining the variants. To evaluate the correlation between two measurements, the Intraclass Correlation Coefficient (ICC) was calculated. The Kappa coefficient was calculated to test for the agreement of nominal categorical variables between two measurements.

For continuous dependent variables, Student's t-test was used to detect the differences between the gender groups because the parametric test assumptions were satisfied. The Kruskal-Wallis test was used to detect the differences between the skeletal classes and variation groups because the parametric test assumptions were not satisfied. As significant differences were found in length between the variant groups, the Mann-Whitney U test was used to make multiple comparisons with Bonferroni's correction. For the categorically dependent variables, Pearson Chi-Square or Fisher-Freeman Halton Exact test was used for testing the independence. The probability of a Type I error (alpha) was chosen as 5% in all tests. Statistical Analysis was performed using the Statistical Package for Social Sciences (SPSS for Windows, version 17.0, Chicago, IL, USA).

This study was approved by Başkent University Medical and Health Sciences Research Council and Ethics Committee (Project No: KA17 / 49).

Results

A moderate level of agreement was calculated between the two rater assessments for sella turcica variations. For all numeric variables, the correlations between the two rater measurements were detected to be strong.

In this study, 38 (40.4%) of the lateral cephalometric radiographs were evaluated as the images of normal sella turcica. Irregularity in the posterior part of sella turcica was observed in 21 (22.3%), pyramidal shape of dorsum sellae was observed in 13 (13.8%), double contour of the floor was observed in 9 (9.6%), sella turcica bridge was observed in 7 (7.4%), and oblique anterior wall was observed in 6 (6.4%) cases (**Table 1**).

There was a significant relationship between sella turcica variations and skeletal classes (p=0.017). Normal sella turcica was the most common (46.7%) variant in patients who had skeletal class I malocclusions. This ratio was 30.3% and 45.2% in the skeletal Class II and III patients respectively, with the most common variant being the normal sella turcica in these patients. 24.2% of the Class II patients were had irregularity in the posterior part of sella turcica. The least common variation in patients with Class II malocclusion was the double contour of the floor (6.1%). In patients with Class III malocclusion, the second most common variant after normal sella turcica was an irregularity in the posterior part of sella turcica (29%). The double contour of the floor and sella turcica bridge variants were not found in this group (**Table 1**). There was a significant relationship between sella turcica variations and gender (p=0.358) (**Table 2**).

In the sella turcica measurements of 94 cases, the mean length was 9.74 mm±2.09, the mean depth was 8.03±1.34, and the median diameter was 11.65 mm (7.4–16.7). No

Table 2
Number of patients by sella turcica variations and genders.

Sella turcica variants	Female	Male	Total	p
Normal	21 (45.7%)	17 (35.4%)	38 (100%)	0.358*
Oblique anterior wall	1 (2.2%)	5 (10.4%)	6 (6.4%)	
Double contour of the floor	4 (8.7%)	5 (10.4%)	9 (9.6%)	
Sella turcica bridge	4 (8.7%)	3 (6.3%)	7 (7.4%)	
Irregularity in the posterior part	12 (26.1%)	9 (18.8%)	21 (22.3%)	
Pyramidal shape of dorsum sellae	4 (8.7%)	9 (18.8%)	13 (13.8%)	
Total	46 (100%)	48 (100%)	94 (100%)	

*Fisher-Freeman-Halton exact test

statistically significant difference was found between males and females for the length, depth, and diameter (p=0.069; p=0.280; p=0.951, respectively) (**Table 3**).

There was a statistically significant difference between the sella turcica variants in terms of length (p=0.023). Among the variants, the highest values in length were observed for the oblique anterior wall variant. In order to determine which individual variant groups resulted in these differences, Mann-Whitney U test was used for multiple comparisons with Bonferroni's correction. These tests demonstrated the significant differences between first, the oblique anterior wall and double contour of the floor variants; and secondly between the double contour of the floor and pyramidal shape of dorsum sellae variants. On the contrary, there were no statistically significant differences between the sella turcica variations in terms of depth and diameter (p=0.598; p=0.179, respectively) (**Table 4**).

The differences between the skeletal classification types and the length, depth, and diameter values of the sella turcica were not statistically significant (p=0.060, p=0.492, and p=0.077, respectively) (**Table 5**).

Table 3
Length, depth and diameter measurements of sella turcica according to gender.

	Female (Mean±SD)	Male (Mean±SD)	p
Length (mm)	9.34±1.75	10.12±2.33	0.069*
Depth (mm)	7.88±1.3	8.18±1.38	0.280*
Diameter (mm)	11.65±1.35	11.63±1.9	0.951*

*Student's t test. **SD:** standart deviation.

Discussion

In our study, the linear measurements and morphological structures of the sellae turcica were examined and compared in patients with different skeletal classes. We observed normal sella turcica in 40.4% of the patients. Valizadeh et al.[7] found normal sella turcica in 24.4% of their patients which was lower than our study. Al Kofide[14] found normal sella at a percentage of 67% which was higher than our study. The difference in percentages may be due to varying ethnic origins.

The sella turcica bridge is one of the variants and is defined as the ossification in dura mater between the

Table 4
Descriptive statistics for length, depth, and diameter in sella turcica variations.

Sella turcica variants	Length (mm) Median (min–max)	Depth (mm) Median (min–max)	Diameter (mm) Median (min–max)
Normal sella turcica	9.45 (6.30–15.4)	8.1 (4.7–11.7)	11.9 (8.9–16.2)
Oblique anterior wall	10.9 (9.7–16.4)	7.35 (4.8–10.2)	12.7 (11–16.7)
Double contour of the floor	8.9 (5.5–10.3)	7.7 (5.7–9.8)	10.9 (8.8–12.8)
Sella turcica bridge	8.7 (7.7–11.6)	8.7 (5.6–9.9)	11.8 (7.4–13)
Irregularity in the posterior part of sella turcica	9 (6–13.5)	7.4 (6.4–10.8)	11.1 (9.5–14.4)
Pyramidal shape of dorsum sellae	10.4 (7.4–15.1)	8 (5.8–9.6)	11.3 (9.2–13.2)
p	**0.023***	0.598*	0.179*

*Kruskal-Wallis test.

anterior and posterior clinoid processes. This malformation can also be seen in healthy individuals.[15] In the present study, the sella turcica bridge was seen in 3.2% of the Class I patients; in 4.3% of the Class II patients, and at a 7.4% frequency in total. But this variant was not observed in the Class III patients. Sella turcica bridge rate was found to be close to the rate found in our study: 5.5% by Axelson et al.,[11] 23.3% by Valizadeh et al.,[7] and 1.1% by Al Kofide et al.[14]

Meyer-Marcotty et al.[17] found the sella turcica bridge more commonly in Class II patients (16.8%) compared to Class I patients (9.4%). Similarly, in their study involving adult women, Marşan and Öztaş[18] found sella turcica bridge more commonly in Class III patients (18%). In our study, this variation was not seen in Class III patients. These different results in the literature may be due to the number of included subjects and their existing malformations. The sella turcica bridge is also associated with the deviation developing during the dentation.[17,18] Studies in pediatric populations demonstrated an association between this malformation and the craniofacial deviations, and also reported that the treatment of malocclusions was more complex in these patients.[2,15]

Similar to the findings of Al Kofide et al.,[14] the differences in length, depth, and diameter were not statistically significant between the males and females in our study. In our study, there was no statistically significant difference in length, depth, and diameter measurements among patients with Class I, II, and III malocclusions. In contrast, Valizadeh et al.[7] found higher values in terms of length in Class III cases compared to those values observed in Class I and II patients. Al Kofide[14] also found a statistically significant difference in diameter measurements between Class II and Class III patients.

In a study by Canigur Bavbek and Dincer,[12] lower rates of normal sella morphology were observed in diabetic patients compared to healthy individuals. Sella turcica enlarges with increased age. However, in our study, patients with endocrine disorders were excluded and age limits were defined for the study patients to evaluate the measurements.

Rai et al.[19] analyzed the shape and size of sella turcica, and four groups were described according to the shape of the hypophyseal fossa and posterior clinoid process, which was a different methodology compared to our study. Then, the sizes were examined according to the gender and age. All values in women were observed to be higher than the values measured in males. However, in our study, there was no statistically significant difference according to gender.

Table 5
Descriptive statistics of length, depth, and diameter measurements of sella turcica in Classes I, II, III malocclusions.

Skeletal classes	Class I Median (min–max)	Class II Median (min–max)	Class III Median (min–max)	p
Length (mm)	10 (5.5–13.3)	8.3 (4.7–11.7)	12.25 (8.8–15.2)	0.06*
Depth (mm)	8.9 (6–12)	7.7 (4.8–9.9)	11.1 (7.4–15.1)	0.492*
Diameter (mm)	10 (6–16.4)	7.9 (6.3–10.8)	11.8 (9.1–16.7)	0.077*

*Kruskal-Wallis test.

Some congenital syndromes, such as Down syndrome, trisomy 21, myelomeningocele, Meckel-Gruber syndrome, anencephaly, trisomy 18, chondrodystrophy, hydrocephaly, Williams syndrome, and Seckel syndrome may affect the shape and size of sella turcica. Small sella turcica may result from a necrosed hypophysis due to infarction. Sella turcica may enlarge due to the enlargement of the hypophysis. An enlarged sella turcica may also be observed in empty sella syndrome, where the herniation of the subarachnoid space with cerebrospinal fluid occurs.[6,10,19]

Yasa et al.[4] used cone beam computed tomography to examine the sella turcica morphology. Using a different classification system, they found that 69.5% of the cases had a circular morphology, 16.4% were flat, and 14% were oval in shape.

Due to their common embryological origins, the association between various dental anomalies and the sella turcica bridge variant has received the attention from the investigators. Ali et al.[16] found a higher rate of sella turcica bridge in patients with buried canine teeth. In this study, sella turcica bridge is seen more commonly in Class II patients. The morphology and size of the anterior and posterior clinoid processes are important for vascular surgery and trans-sphenoidal endoscopic procedures. To decrease the risk of intraoperative complications, the anatomy of this region should be evaluated thoroughly.[8]

Conclusion

Results of this study in regards to sella turcica variations and associated measurements will contribute to the normal reference standards which will be used by future studies on craniofacial malformations and syndromes. Furthermore, the results of the study are of importance in terms of raising the awareness of orthodontists to identify the sella turcica variations in lateral cephalometric radiographs used in the diagnosis and treatment planning, as these findings will allow considering the associated pathologies and patient referrals accordingly.

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Anatomical variations of the circle of Willis: evaluation with CT angiography

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Abstract

Objectives: The aim of this study was to investigate anatomic variants and anomalies of the circle of Willis using computed tomography angiography (CTA).

Methods: CTA images of 770 patients obtained from Tepecik Training and Research Hospital between January 2012 to January 2017 were retrospectively reviewed to identify the anatomical vascular variations of the circle of Willis.

Results: After exclusion, 751 patients (348 females, 403 males, mean age 54.6 years, range 18–90 years) were enrolled into the study. The anatomical variations related to the posterior communicating artery (PcoA) were the most common, whereas anatomical variations related to the middle cerebral artery (MCA) were the least common variations among arteries. Hypoplasia of the A1 segment was the most common (14.6%) variation of the anterior cerebral artery (ACA) and fenestration of this artery was the least common variation (1,06%) observed only in A1 segment. Bilateral absence of the PcoA was seen in 27.56% of the patients. Fenestration was more commonly detected in anterior communicating artery (AcoA) (10.12%), followed by MCA (1.06%), ACA (1,06%) and PCA (0.67%). Duplication was the least common variation which was detected in MCA, AcoA and PcoA.

Conclusion: Arterial variations of the circle of Willis are not rare and can be non-invasively evaluated using CTA.

Keywords: angiography; cerebral arteries; circle of Willis; computed tomography; variation

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Introduction

Multidetector computed tomography angiography (CTA) has proven to be a valuable tool for initial evaluation of the cerebral circulation for acute stroke and subarachnoid hemorrhage. A comprehensive CTA facilitates better visualization of cerebral vessels due to high spatial resolution and with recent advances in computed tomography (CT) technology, it has partially replaced the digital subtraction angiography.[1,2] It does not only show the pathologies of the cerebral vasculature, but may also display clinically relevant vascular variations.

Recognizing variations of the intracranial arteries has clinical relevance. Fenestrations and duplications may predispose patients to aneurysm development. Moreover, the occlusion of an azygos or bihemispheric anterior cerebral artery (ACA) may result in ischemia of both hemispheres. Patients with fetal origin of posterior cerebral artery (PCA) and concomitant atherosclerotic disease of the carotid artery are prone to ischemic events in the PCA territory. Although the majority of normal variations have no major clinical impact, their appreciation may aid planning of the surgical and interventional procedures and may explain uncommon and unexpected findings after treatment.[1,3]

To be able to interpret the cerebral CTA correctly, we should be familiar with normal anatomy and anatomical variations of the cerebral arteries, and their cross-sectional appearances. In this study, we aimed to systematically evaluate the anatomical variations of the circle of Willis and to determine their frequency.

Materials and Methods

CTA images of 770 patients who underwent multidedector cerebral CTA in our institution from January 2012 to January 2017 were retrospectively reviewed to identify the cerebral anatomy and to determine anatom-

ical vascular variations. Patients were referred for cerebral CTA because of known or suspected cerebral aneurysm, intracerebral hemorrhage and suspected arteriovenous malformation. We excluded all patients with a history of surgical or interventional treatment of the circle of Willis, with a cerebral occlusive disease and with poor image quality mainly due to patient movement and technical problems. The study was approved by the Tepecik Training and Research Hospital review board.

All CT examinations were performed by 2 different scanners: a 64-slice CT scanner (Aquillon 64, Toshiba Medical Systems, Tochigi, Japan) and a 128-slice CT scanner (SOMATOM Definition Edge, Siemens Healthcare, Erlangen, Germany). For venous access, an upper extremity vein (antecubital vein of the right arm) and a 20-gauge IV cannula was used. After precontrast images a total of 80–85 mL of contrast media with high iodine concentration (370–400 mg/mL) was injected with a flow rate of 5 mL/s, followed by a 20 mL saline chaser. The scanning parameters included 120 kV, 225 mA, section thickness of 0.5 mm and reconstruction interval of 0.3 mm. The scan revolution time was 0.4 seconds. Data for CTA were obtained in a caudocranial direction.

In preparation of the study readings, all multidetector CTA data were transferred from the archive to a workstation (Aquarius workstation, TeraRecon, San Mateo, California, USA), via internal network connections, providing 3D postprocessing options, multiplanar image reformatting (MPR) and maximum intensity projections (MIP). We reviewed the MIP and three-dimensional volume-rendering (3D VR) images. All examinations were evaluated by two radiologists independently with respect to the anatomy of the circle of Willis. In cases of discrepancy, the CTA images were evaluated again, to reach a consensus on all variations.

We assessed the anatomy and variations of the circle of Willis and classified our findings to describe the results of our analyses. The terms of arterial variations found in our assessments are listed and explained below.[1,3–5]

- **Fenestration** is used for an arterial lumen that divides into distinctly separate lumens with distal convergence (they may or may not share an adventitial layer).
- **Duplication** is used for two distinct arteries with separate origins and no distal arterial convergence.
- **Absence and hypoplasia** are used for absence and small size of the vessel, respectively.
- **Accessory middle cerebral artery (MCA)** is used for a vessel that originates from anterior cerebral artery (ACA), courses parallel to the main MCA and supplies the anterior-inferior of the frontal lobe.
- **Trifurcation of the ACA** is used for presence of three ACA A2 segments. Third artery represents persistence of the median callosal artery.
- **Bihemispheric ACA** is used for hypoplasia of one of the ACA A2 segment. Bilateral major arterial supply is from the other, dominant A2 segment.
- **Azygos ACA** is used for single midline ACA A2 segment that represents persistence of the median callosal artery.
- **Hyperplastic anterior choroidal artery (AChA)** is used for prominent AChA, larger than usual.
- **Infundibulum** is used for cone-shaped dilatation at the origin of the posterior communicating artery (PcoA) and AChA that are smaller than 2 mm. Those arteries arise from the apex of a cone-shaped dilatation.
- **Fetal origin of the posterior cerebral artery (PCA)** is used when PcoA is prominent with ipsilateral the same size or hypoplastic PCA P1 segment (partial type fetal PCA) or absent PCA P1 segment (full type fetal PCA)

Results

From 770 patients evaluated, after exclusion of the 19 patients, finally a total of 751 consecutive patients (348 females, 403 males, mean age 54.6 years, range 18–90 years) enrolled into the study. The frequency of the detected anatomical variations was outlined in **Tables 1–4**. The anatomical variations related to the PcoA were the most common and anatomical variations related to the MCA were the least common variations (**Figures 1** and **2**). Among ACA variations, hypoplasia of the A1 segment was the most common (14.6%) and fenestration,

Table 1
Middle cerebral artery (MCA) anatomical variations.

Anatomical variation	Number and incidence (%) (n=751)
Fenestration (M1 segment)	8 (1.06)
Right	4 (0.53)
Left	4 (0.53)
Accessory MCA	7 (0.93)
Right	2 (0.27)
Left	5 (0.67)
Duplication	8 (1.06)
Right	1 (0.13)
Left	7 (0.93)

Table 2
Anterior cerebral artery (ACA) anatomical variations.

Anatomical variation	Number and incidence (%) (n=751)
Hypoplasia	110 (14.6)
Right	47 (6.26)
Left	63 (8.39)
Aplasia	19 (2.53)
Right	12 (1.6)
Left	7 (0.93)
Fenestration*	8 (1.06)
Right	7 (0.93)
Left	1 (0.13)
Trifurcation	34 (4.53)
Azygos ACA	11 (1.46)
Bihemispheric ACA	9 (1.2)

*All fenestrations were in ACA A1 segment.

Table 3
Anterior communicating artery (AcoA) anatomical variations.

Anatomical variation	Number and incidence (%) (n=751)
Fenestration-duplication*	76 (10.12)
Absence	29 (3.86)

*Only one patient identified as duplication.

Table 4
Posterior communicating artery (PcoA) and posterior cerebral artery (PCA) anatomical variations.

Anatomical variation	Number and incidence (%) (n=751)
Absent PcoA	355 (47.3)
Right	64 (8.52)
Left	84 (11.19)
Bilateral	207 (27.56)
Partial type fetal origin of the PCA*	190 (25.3)
Right	87 (11.58)
Left	57 (7.59)
Bilateral	46 (6.13)
Total type fetal origin of the PCA†	6 (0.79)
Right	3 (0.39)
Left	2 (0.27)
Bilateral	1 (0.13)
PCA Fenestration‡	5 (0.67)
Right	3 (0.39)
Left	2 (0.27)
PCoA Duplication	1 (0.13)
Right	1 (0.13)
Left	0 (0)

*Partial type: prominent PcoA with ipsilateral the same size or hypoplastic P1 segment of the PCA; †Total type: Prominent PcoA with ipsilateral absent P1 segment of the PCA; ‡PCA fenestrations were P1 segment in all patients.

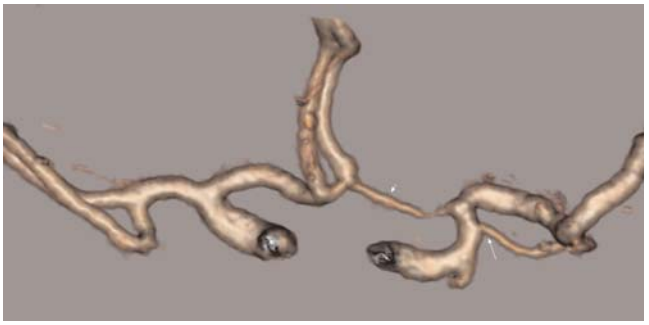

Figure 1. 3D VR image shows a duplicated MCA (**long arrow**). A smaller branch arises from ICA just before its terminal bifurcation and courses parallel to the main branch. Left A1 segment of the ACA is hypoplastic (**short arrow**). [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

which was observed in only A1 segment, was the least common (1.06%) variation (**Figures 3–7**). Bilateral absence of the PcoA was seen in 207 of 751 patients (27.56%) (**Figure 8**). Fenestration was more commonly detected in anterior communicating artery (AcoA) (10.12%), followed by MCA (1.06%), ACA (1,06%) and PCA (0.67%). Duplication was the least common variation which was detected in MCA, AcoA and PcoA.

Discussion

The reported prevalence of most of the vascular variants and anomalies is derived from cadaveric or angiographic studies. The knowledge of the segmental anatomy and the prevalence of the arterial variants is important while evaluating multidedector CTA images. We evaluated anatomical variations of the cerebral arteries in 751 patients and found that those anatomical variations are frequent and could be evaluated correctly by CTA.

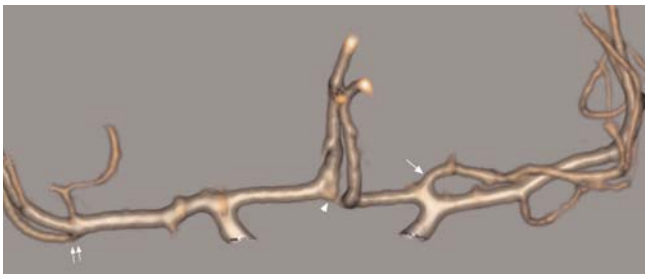

Figure 2. 3D VR image depicts an accessory MCA (**arrow**), a smaller branch arises from A1 segment of the ACA. There is also anterior communicating artery fenestration (**arrowhead**) and trifurcation of the right MCA (**double arrows**). [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

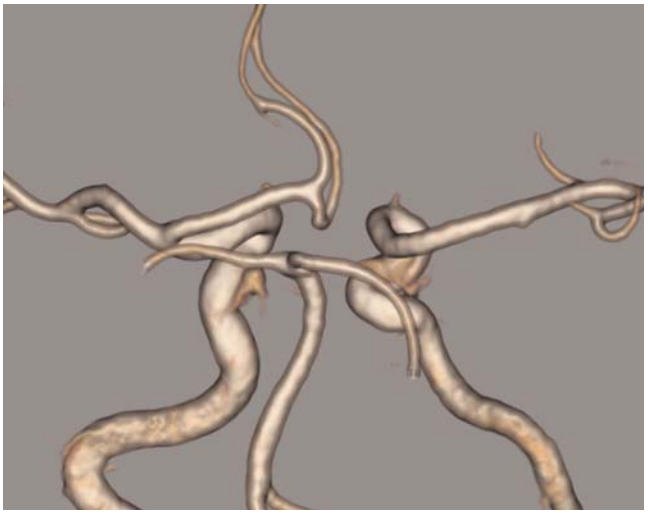

Figure 3. 3D VR image demonstrates absence of the A1 segment of the ACA. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

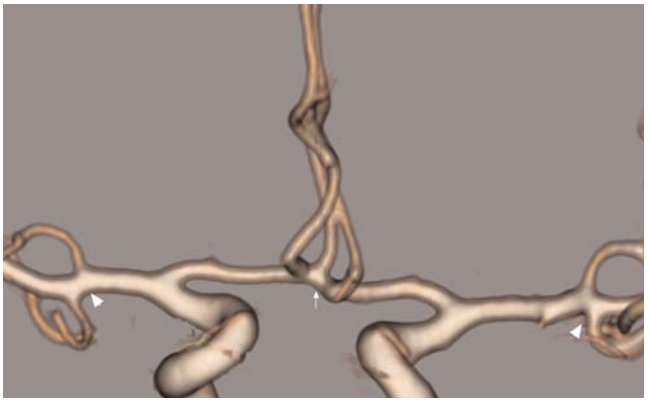

Figure 4. 3D VR image shows trifurcation of the ACA, two normal A2 segments and one A2 segment that arises from the anterior communicating artery (**arrow**). Bilateral trifurcation of MCA (**arrowhead**) accompanies to this anomaly. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

DSA, used for visualization of the cerebral arterial system for several decades, has disadvantages in detecting cerebral artery anomalies because of the 2D projection of the images. Most anomalies are only visible from one specific angle, that is likely not present in the limited available projections of conventional angiography. Any desired viewing angle is possible with 3D imaging. Although 3D rotational angiography has higher spatial resolution than CTA, it is invasive and lack of soft tissue information.[6,7] CTA is not affected by flow-related inhomogeneities, which is very commonly seen at MR angiography. CTA is performed in seconds, as opposed to minutes, effectively eliminating MR angiography which is limited by the patients' motion and it offers more complete intracranial coverage in less time than does MR angiography.[7] Furthermore, CTA enables better visualization of small vessels and vascular variations.[8]

Anatomical variations of the middle cerebral artery were not found seen frequently in our study. An accessory MCA was observed in 0.93% of the patients and the frequency of accessory MCA is reported as 0.3% to 4%.[4] Duplication of the MCA is reported as 0.2% to 2.9%.[3,4] In our study it was found in 1.06% of the patients. Both variations may change arterial blood supply regions.[8,9] These variations should be considered in evaluating ischemic lesions and clinical symptoms in stroke patients.[8,10] The clinical significance of MCA fenestration might be due to its relationship with aneurysm formation.[11,12] But none of our patients with MCA fenestration (8 patients, 1.06%) had an aneurysm.

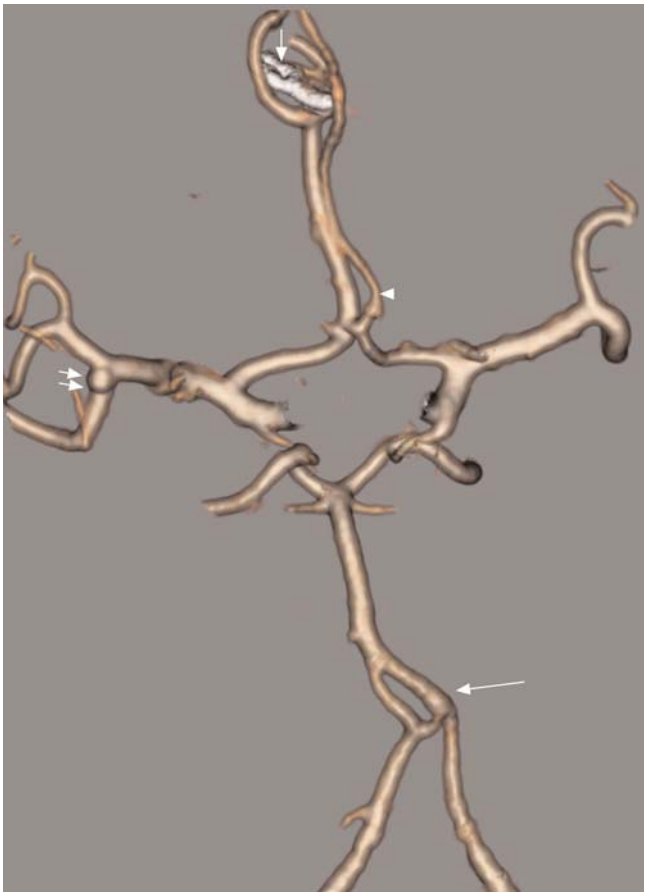

Figure 5. 3D VR image demonstrates bihemispheric ACA. Dominant A2 segment that supplies both ACA territories has operated aneurysm at the level of furcation (**short arrow**). The smaller caliber, non-dominant A2 segment (**arrowhead**) courses parallel to the dominant segment. There is small aneurysm at MCA bifurcation (**double arrows**). Basilar artery fenestration (**long arrow**). [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

Anterior cerebral artery A1 segment hypoplasia and absence was found 14.6% and 2.53%, respectively. The reported incidence in cadaveric studies, 10% for hypoplasia and 1–2% for absence, is similar with our findings.[1,3] These anatomical variations cause decreased collateral supply in the event of thromboembolic disease. Two normal A2 segment with persistence of the embryonic median artery of the corpus callosum defined as ACA trifurcation. Its incidence varies from 2 to 13%.[3] In the present study, it was found in 4.53% of the patients. Bihemispheric ACA represents one hypoplastic A2 segment with the other A2 segment provide the major blood supply to both hemispheres. The prevalence of this variation is 2–7% in cadaveric studies and we observed 1.2% of the patients in our study.[3] The frequency was less than both cadaveric and angiographic studies.[13] This anatomical variation may be related to aneurysm formation.[14] We had only one patient with aneurysm at bifurcation of the normal A2 segment, that ruptured and was treated with surgical clips. Azygos ACA is defined as a single unpaired A2 segment that represents persistence of the median artery of the corpus callosum. The prevalence of azygos ACA is between 0.2% and 4% and it was found in 1.46% of patients in our study. Azygos ACA have been reported to be associated with many congenital anomalies like holoprosencephaly and an increased risk of aneurysm formation.[15] Both bihemispheric and azygos ACA are clinically important anomalies and should be reported because occlusion of the ACA from whatever cause affects both hemispheres.[1,3]

Fenestration was the most frequently observed in AcoA (10.12% of patients) in our study. The reported incidence of AcoA fenestration from anatomic, 3D angiographic and CT angiographic studies is 12–20%, 5.3% and 5.32%, respectively.[16,17] Anterior communicating artery is so small that recognition of its anomalies may be difficult on CTA in comparison to the cadaveric studies. On the other hand, our higher incidence when compared previous studies with angiography and CTA is probably due to the recent improvements in CT technology that allows obtaining thinner images with higher resolution.[6,8] The clinical significance of fenestration comes from its association with the aneurysm formation. It is postulated that in addition to arterial wall weakness, the hemodynamic factors result in formation of an aneurysm at the proximal end of arterial fenestrations.

Figure 6. 3D VR image depicts azygos ACA, a single midline A2 trunk (**arrow**). [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

Figure 7. 3D VR image shows the absence of the anterior communicating artery. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

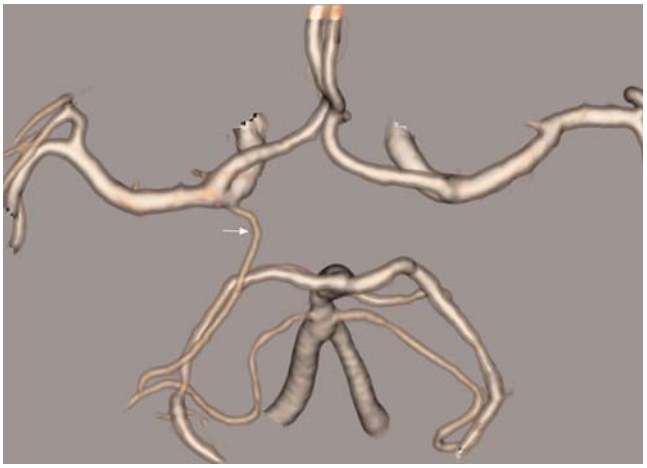

Figure 8. 3D VR image shows the absence of both posterior communicating arteries. Note that the anterior choroidal artery is prominent, so called as hyperplastic in 3D VR image (**arrow**). [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

An absence of AcoA occurs in 5% of surgical dissections.[1,3] In our study, the percent of absence of AcoA was 3.86%, which was lower than anatomical studies in the literature.

The posterior communicating arteries are usually small and may not be depicted at CTA, but this does not necessarily mean that the arteries are absent. Hypoplasia of PCoA is seen in one fourth of MR angiograms and one third of all anatomic dissections.[3] In our study, it was the most frequent anatomical variation and observed in 47.3% of the patients. Bilateral absence was higher than unilateral absence and unilateral absence was more common on the left side. Posterior communicating arteries are main collaterals of the circle of Willis and knowing their patency is important before any surgical and interventional procedure.

Fetal origin of the posterior cerebral artery occurs when the embryonic posterior cerebral artery fails to regress.[1] When the prominent PcoA is observed with the same size or hypoplastic ipsilateral P1 segment of the PCA, it is named as partial type fetal origin of the PCA.[18] But if the ipsilateral P1 segment of the PCA is absent, it is called full or total type fetal origin of the PCA.[1,18] Prevalence of partial type from cadaveric, DSA and MR angiographic studies have wide range, 11–29% for unilateral and 1–9% for bilateral.[18,19] It may occur 10% on the right side and 10% on the left side and 8% bilaterally.[19] In the present study, we observed partial type fetal origin of PCA in 25.3% of the patients, 11.58% on the right and 7.59% on the left side and 6.13% bilaterally. Total type fetal origin of the PCA is very uncommon.[18] In our study, 0.79% of the patients had this anatomical variation. Most of them were unilateral with exception of one bilateral patient. Reporting of either type of this variant is clinically important because dominant blood supply to the occipital lobes comes from internal carotid artery and PCA territory stroke may be caused by atheromatous disease of the anterior circulation.[17–19] Posterior cerebral artery fenestration is extremely rare.[1,19] We observed it only in five patients (0.67%). Posterior communicating artery duplication was the least common variation in the present study with 0.13% prevalence rate which is also extremely rare.

This study also has some limitations. First of all, very small arteries may not be detected via CTA. The absence or hypoplasia of an artery was decided by the consensus of two observers in the study. Secondly, in patients with a silent occlusive arterial disease, the occluded artery could be misdiagnosed as absent. To overcome this limitation, contrast enhanced images were compared with the non-enhanced images.

Conclusion

According to our large study group, we believe that the arterial variations of the circle of Willis are not rare, clinically important and can be noninvasively evaluated by CTA.

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Correlation between gross morphology of the human placenta and birth weight in normotensive and pre-eclamptic pregnancies in Northwest Ethiopia

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Abstract

Objectives: The objective of this study was to investigate correlation of gross morphology of human placenta with birth weight in normotensive and pre-eclamptic pregnancies obtained from Bahir Dar, Northwest Ethiopia.

Methods: Institutional based comparative cross-sectional study was carried out on 200 term placentas (37 to 42 weeks of gestation) between October and January 2015. 150 placentas from normotensive and 50 from pre-eclamptic pregnancies were collected and examined for weight, diameter, thickness and number of cotyledon. Birth weight and placental-fetal weight ratio also measured.

Results: The mean birth weight in pre-eclamptic pregnancies (2.6 kg) was significantly (p=0.0001) reduced as compared to birth weight (3.1 kg) in normotensive pregnancies. However, placental-fetal weight ratio had no significant (p=0.658) difference between normotensive (6.34:1) and pre-eclamptic (6.41:1) groups. Birth weight was correlated with placental weight (r=0.572), diameter (r=0.583), thickness (r=0.192) and number of cotyledons (r=0.647) in the pre-eclamptic group. Birth weight was also correlated with placental weight (r=0.572), diameter (r=0.583), and number of cotyledons (r=0.647) in the normotensive group. However, no correlation was found between placental thickness (r=0.192) and birth weight in the normotensive group.

Conclusion: Birth weight was significantly reduced in pre-eclamptic pregnancies as compared to normotensive pregnancies. Morphology of placenta such as weight, diameter and number of cotyledons were correlated with birth weight in both groups, but placental thickness was only correlated with birth weight in pre-eclampsia, but not in normotensive group. Placental-fetal weight ratio had not significant difference between the groups. Examination of placental morphology prenatally using ultrasound and observation immediately after delivery is important for better management of this and subsequent pregnancies.

Keywords: birth weight; morphology; placenta; pre-eclampsia

Anatomy 2018;12(1):27–32

Introduction

The placenta is temporary vital organ situated between mother and developing fetus until the end of pregnancy.[1] It is the fusion of feto-maternal tissue derived from decidual basalis and villous chorion, respectively.[2] Placenta is sentinel predictor of the intrauterine health status of fetus.[3,4] It acts as vital body organs like the lung, kidney, heart and digestive organs for transfer of nutrients and gases from the mother to the fetus; removal of waste products from the fetus to the mother. It is also a temporary endocrine organ that produces hormones for maintaining pregnancy.[5–7] The healthy survival of fetus depends on the placenta for normal growth and development.[8,9] Fetal weight is a very useful determinant of fetal survival, healthy growth and development[8] and is directly associated with placental morphology. When the formation, growth and functioning of placenta are compromised by diseases, maternal and fetal well-being fall at risk.[10] At term, the normal human placenta is discoid in shape, 500

g in weight, 18.5 cm in diameter, 2.5 cm thick and has 15 to 30 number of cotyledons.[11] These features of human placenta can be affected by pre-eclampsia. Pre-eclampsia is a pregnancy related metabolic disease which affects the placenta macroscopically as well as microscopically.[12] It is described as the occurrence of new onset of elevated blood pressure in previously normal pregnant women after 20 weeks of gestation. Pre-eclampsia complicates 5 to 10% pregnancies world-wide[13] and is a major contributor for maternal and child morbidity and morbidity.[5] In developed countries like Ethiopia, the health care system is overwhelmed by preventive, control, investigation and therapeutic challenges of pre-eclampsia. Even though placenta is important for the survival and wellbeing of the fetus and mother, the influence of it on placenta, fetus and mother has not been well investigated. Immediately after delivery, the placenta is discarded as a waste without examining its morphology, as well as its relation with birth weight. Placental morphology and its association with birth weight are under-investigated also in Ethiopia. With these view, this study aimed to assess the correlation between gross morphology of human placenta and birth weight in Northwest Ethiopia.

Materials and Methods

This institutional based comparative cross sectional study was conducted between October and January 2015 in Gondar, Northwest Ethiopia. The study participants were term pregnant women who attended labour at obstetrics ward during the study period. Those normal and pre-eclamptic women were included in the study. Normotensive women were pregnant mothers who were diagnosed as normal or without pre-eclampsia and other acute and chronic diseases. Pre-eclamptic women were pregnant mothers who were diagnosed with pre-eclampsia, but free of other acute and chronic diseases. The diagnosis of pre-eclampsia was based on one or more of pre-eclampsia diagnostic investigations, i.e. new onset of elevated blood pressure and presence of proteinuria in urine microscopy.

The study was designed to have 80% statistical power with level of significance at 5% and normotensive to pre-eclampsia ratio of 3:1. Sample size was estimated using mean difference formula by taking the mean of placental weight (478.8 g) among normotensive and (385.4 g) among pre-eclamptic mothers. The variances of placental weight were 292.12 among normotensive and 82.21 among pre-eclamptic mothers. The calculated sample size was 200 (150 for normotensive and 50 for pre-eclampsia). The sample size was also calculated for placental diameter, thickness, number of cotyledons and birth weight, and the largest sample estimate was taken. At the University of Gondar Referral Hospital Obstetric Ward, Gondar, Ethiopia, approximately a total of 20 normotensive mothers were giving birth per day. We used systematic random sampling with sampling interval of five to select normotensive mothers. All pre-eclamptic mothers who were attending labour during the study period were included.

A total of 200 term placenta (150 from normotensive and 50 from pre-eclamptic mothers) were collected immediately after delivery at the obstetrics ward. The collected placentas were checked for their completeness, and trimmed membrane. Then placentas were washed with tap water to remove any blood clot and prepared for measurement.

Placenta weight and birth weight were measured by directly placing the placenta and newborn over standardized weight scale.

To measure the diameter of the placenta, the placenta was placed in a flat tray after trimming the membrane. The first maximum diameter was measured with a plastic measuring scale graduated in centimeter, then the second maximum diameter was taken at right angle to the first one (**Figure 1**). The mean of the two measurements was considered as the diameter of the placenta.

Placental thickness was measured at five points using a long needle. The placenta was divided into three equal parts by drawing two circles on the maternal surface of the placenta. These circles cut the radius of the placenta into three equal parts. One thickness was measured from the center of central zone, two from the middle zone and two from the peripheral zone. The peripheral points were

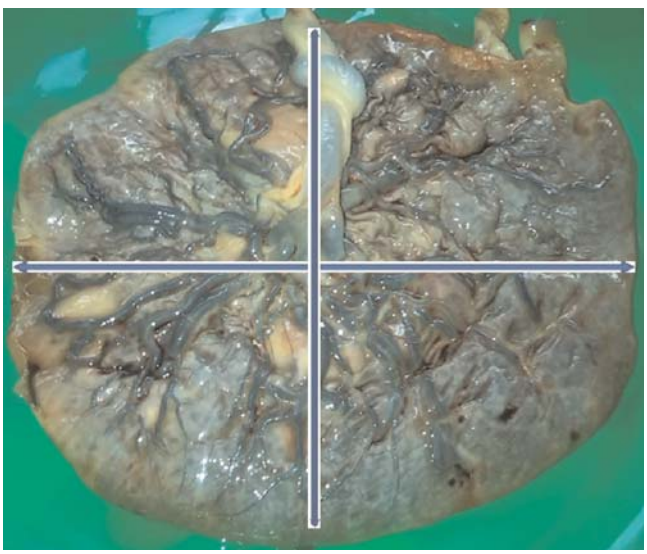

Figure 1. Measurement for diameter of the placenta. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

taken within the outer zone on a line perpendicular to the previous imaginary line in the middle zone (**Figure 2**). Finally, the mean of all five measurements were calculated as the thickness of the placenta.

The placenta was placed in 10% formalin solution for 24 h in order to make the placenta groove visible to count the cotyledon. Then, gentle pressure was applied on the center of the fetal surface of the placenta. As a result, the cotyledon on the maternal surface became prominent. The placenta was placed on a fetal surface with maternal surface facing upward. Counting of the cotyledon was started from the left side of the one end of the placenta and then going to the right and again turning back to the left in a loop (**Figure 3**). Finally, total number of cotyledons was counted and recorded.

Data were entered into Epi statistical software for epidemiology version 7 (Atlanta, GA, USA) and analysis was done by using IBM SPSS Statistics for Windows (Version 20, Armonk, NY, USA). Frequencies and proportions were used to describe the study subjects in relation to the studied variables. A value of $p<0.05$ was used to identify statistical significant results. Pearson correlation test was used to investigate correlation of birth weight with placental morphology in normotensive and pre-eclamptic pregnant mothers.

Ethics approval a was obtained from the Ethical Review Board of School of Medicine, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia. Communication with the Department of Obstetrics and Gynecology was made through a formal letter obtained from Department of Human Anatomy. After the purpose of the study was informed, written consent was obtained from each participant. Confidentiality was maintained by making the data collection anonymous. Participation was on voluntary basis.

Results

In this study, 43.3% of study subjects were in the age group 18–25 years among normotensive mothers, while 54% of study subjects were in the age group of 18–25 years in pre-eclamptic mothers. Among pre-eclamptic mothers, 54% were primigravida and 46% were multigravida. Similarly, 49.3% study subjects were primigravida and 50.7% were multigravida among normotensives. Among 150 normotensive placentas, majority (78.7%) was delivered by spontaneous vaginal delivery, 6.6% by assisted forceps delivery, and 14.7% by cesarean section. Likewise, of 50 pre-eclamptic placentas, 52% were delivered by spontaneous vaginal delivery, 10% by assisted forceps delivery and 38% by cesarean section (**Table 1**).

In normotensive and pre-eclamptic groups, mean fetal weight was 3.1 kg and 2.6 kg, respectively. The difference was highly significant ($p=0.0001$) (**Table 2**).

From normotensive groups, 96% of the newborns placental weight was more or equal to 2.5 kg and in 4% less than 2.5 kg, while in pre-eclampsia, in 62% of the newborns placental weight was more or equal to 2.5 kg and in 38% less than 2.5 kg (**Table 3**). Normal birth weight is between 2.5–4 kg, overweight is >4 kg, and low birth weight is <2.5 kg.

In the present morphometric study, placental-fetal weight ratio in normotensive and pre-eclampsia were

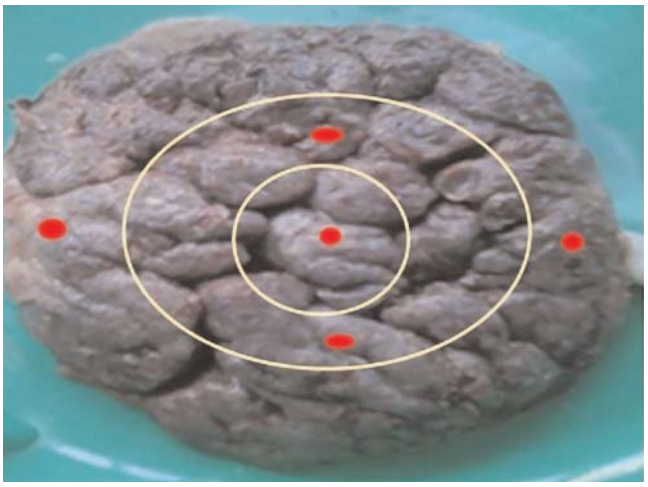

Figure 2. Measurement points for placental thickness. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

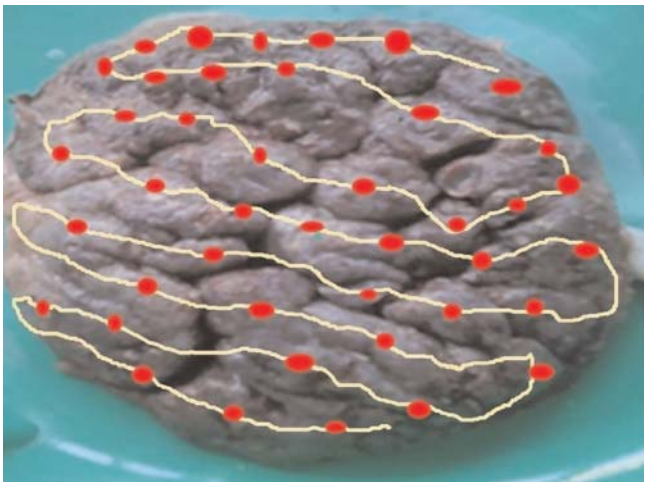

Figure 3. Counting the cotyledons of placenta. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

Table 1
Demographic and obstetric characteristics of the study subject.

Parameters		Normotensive (n=150)		Preeclampsia (n=150)	
		Number	%	Number	%
Maternal age in years	18–25	65	43.3	27	54
	26–32	65	43.3	19	38
	33+	20	13.3	4	8
Gravidity	Primigravida	74	49.3	27	54
	Multigravida	76	50.7	23	46
Mode of delivery	SVD	118	78.7	26	52
	Forceps	10	6.6	5	10
	C/S	22	14	19	38

C/S: caesarean section; **SVD:** spontaneous vaginal delivery.

6.34:1 and 6.41:1, respectively (**Table 4**). This difference was not statistically significant (p=0.658).

Overall, there was a significant positive correlation between birth weight and placental weight, diameter, thickness and number of cotyledons [(r=0.752, p=0.0001), (r=0.583, p=0.0001), (r=0.192, p=0.007) and (r=0.647, p=0.0001)], respectively (**Table 5**). Comparatively, Pearson correlation test showed that birth weight was moderately correlated with placental weight (r=0.666, p=0.0001) and number of cotyledons (r=0.566, p=0.0001), and fairly correlated with placental diameter (r=0.439, p=0.0001) in the normotensive group. In pre-eclampsia, birth weight was strongly correlated with placental weight (r=0.809, p=0.0001) and moderately correlated with diameter, thickness and number of cotyledon. However, birth weight had no significant correlation with placental thickness in normotensive (r=0.115, p=0.165) (**Table 5**).

Discussion

In the present study, the mean birth weight of pre-eclamptic cases (2.62±5.87 kg) was less than as compared to normotensive cases (3.12±4.36 kg). This difference was significant (p=0.0001). The results were in accordance with studies carried out in India (3.14 kg and 2.44 kg)[14] and Kamataka (3.02 kg and 2.61 kg).[15] However, lower values were reported in India (2.8 kg and 2.1 kg)[12] in both normotensive and pre-eclamptic pregnancies, respectively. This may be due to genetic, maternal weight, height and nutritional variation among study participants.

Placental-fetal weight ratio represents the balance between fetal and placental growth. It is the predictor of developing disease later in adult life. Large British cohort study suggested that having a discordance larger placenta with small baby may lead to circulatory adaptation in the fetus, altered arterial structures in the child and hypertension in the adult. This may have important implications for the prevention of adult hypertension which appear to have its origin in fetal life.[16]

Table 2
Comparison of fetal weight in normotensive and preeclamptic groups by using independent two samples t-test.

Variables	Group	Range	Mean	SD	t-value	p-value
Birth weight	Normotensive	1.6–4.4	3.12	0.436	6.20	0.0001
	Pre-eclampsia	1.3–3.9	2.62	0.587		

Table 3
Comparisons of birth weight category between normotensive and preeclampsia.

Birth weight	Normotensive group (n=150)		Preeclampsia group (n=50)	
	n	%	n	%
<2.5 kg	6	4	19	38
2.5–4 kg	144	96	31	62
>4 kg	0	0	0	0

Table 4
Comparison of placental-fetal weight ratio between normotensive and pre-eclamptic pregnancies.

Parameters	Normotensive (n=150)	Preeclampsia (n=50)	t-value	p-value
	Mean±SD	Mean±SD		
Weight of placenta	497.95±89.1	417.6±102.41	5.32	0.0001
Birth weight	3.12±0.436	2.62±0.587	0.2	0.001
Placental-fetal weight ratio	6.34±0.89	6.41±1.03	-0.443	0.658

Table 5
Correlation between birth weight and placental weight, diameter, thickness and number of cotyledon by using Pearson correlation test.

	Variables		Placental weight	Placental diameter	Placental thickness	Number of cotyledons
Birth	Over all	r	0.572	0.583	0.192	0.647
		p	0.0001*	0.0001*	0.007*	0.0001*
Weight	Normotensive pregnancy	r	0.666	0.439	-0.115	0.566
		p	0.0001*	0.0001*	0.165	0.0001*
	Pre-eclamptic pregnancy	r	0.809	0.732	0.548	0.647
		p	0.0001*	0.0001*	0.0001*	0.0001*

*Correlation is significant at ≤0.05 levels (2-tailed)

The normal birth weight to placental weight ratio ranged from 6.5 to 7.1 at term 37–42 weeks of gestation. In cases with pre-eclampsia, this ratio was found to be significantly (p=0.001) smaller as compared to normotensive cases 6.60 vs. 7.40.[16]

In the present study, the mean feto–placental weight ratio was 6.34±0.89 in normotensive cases and 6.41±1.03 in pre-eclampsia. The difference was not statistically significant (p=0.658). This is in accordance with findings noted in Rajindra Hospital in Punjab, India which found almost constant fetal placental weight ratio in normotensive (6.308±0.364) and pre-eclamptic (6.343±0.953) pregnancies at p=0.8598.[13]

In the present study birth weight was positively correlated with placental weight (r=0.75, p=0.0001), diameter (r=0.583. p=0.0001), thickness (r=0.192, p=0.007), and number of cotyledon (r=0.647, p=0.0001) in both normotensive and pre-eclamptic group as a whole (**Table 5**). This finding of Pearson correlation indicates that when placental weight, diameter, thickness and number of cotyledons increase, birth weight also increases and vice versa.

Comparatively, Pearson correlation showed that birth weight was moderately correlated with placental weight and number of cotyledons and fairly correlated with placental diameter in the normotensive, while in pre-eclampsia, it was strongly correlated with placental weight and moderately correlated with diameter, thickness and number of cotyledons. However, birth weight did not have a statistical significant (p=0.165) correlation with placental thickness in the normotensive group (**Table 5**).

In normotensive cases, placental weight is directly proportional to birth weight. When birth weight becomes large, placental weight and size also increase to accommodate the large fetus. As placental size increases, the placental thickness becomes small. This result was supported by reports from Pakistan (r=0.413, p=0.003),[17] Norwich (r=0.78, p=0.001)[18] and India (r=0.759, p<0.01)[8] which showed that birth weight was significantly associated with placental weight. This confers that the higher the birth weight, higher is placental weight and vice versa.

Another morphological comparative study of placenta in normotensive and pre-eclampsia was performed in Kamataka; India showed that mean placental weight (r=0.96 and r=0.98), diameter (r=0.92 and 0.92) and number of cotyledons (r=0.9 and 0.86) were strongly correlated with fetal weight.[19]

There are some limitaions for this study. Since this study was conducted in a health institution, placentas from both groups who delivered at home could not be studied. Although the range of 37–42 weeks is a large interval in which the dimensions and weight of the placenta continues to grow, this study does not consider the normotensive and pre-eclamptic groups in terms of distribution of the delivery time within 37–42 weeks. Also, some pre-eclamptic cases were diagnosed at the time of delivery and others were diagnosed at variable times between 34 to 35 weeks as the individual mother told. Due to this, it was difficult to determine for how long the placenta was exposed to the disease. Therefore, this study did not consider the length of time in which placenta exposed to pre-eclampsia.

Conclusion

Birth weight was significantly reduced in pre-eclamptic pregnancies as compared to normotensive pregnancies. Morphology of placenta such as weight, diameter and number of cotyledons were correlated with birth weight in both groups, but placental thickness was only correlated with birth weight in pre-eclampsia, but not in the

normotensive group. Placental-fetal weight ratio did not have a significant difference between the two groups. Examination of placental morphology prenatally by using ultrasound and observation immediately after delivery is important for better management of such and subsequent pregnancies.

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Intervertebral disc heights and concavity index of the lumbar spine in young healthy adults

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Abstract

Objectives: The aim of this study was to investigate lumbar intervertebral disc heights and concavity index of the lumbar spine, and the influence of age, gender, weight, height and body mass index (BMI) on these parameters.

Methods: The study was conducted on 150 health young subjects (age 18 to 27) without any disorder which affects the lumbar spine and the discs. Subjects underwent standard standing lateral lumbar radiography. Mann-Whitney U test and Spearman's correlation test were used for statistical analysis.

Results: Of the 150 subjects (age range, 18–27 years), 80 (53.3%) were women and 70 (46.7%) were men. Men presented higher lumbar disc values than women. In both genders, disc height increased from T12–L1 to L4–L5, and then decreased at L5–S1. The heights of all lumbar discs increased with age, weight, height and BMI in both genders. Women demonstrated a higher concavity index at L2, L3 and L4 vertebrae compared to men, whereas men showed a higher concavity index value at L5 vertebra. The concavity index of T12, L1, L2, L3 and L4 vertebrae decreased with age.

Conclusion: Our results will serve as guidelines and references for further studies, radiologists and spinal surgeons.

Keywords: concavity index; intervertebral disc; lumbar vertebrae; radiography, spine

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Introduction

The demands on the lumbar spine in daily, professional and recreational activities is very strong. Lumbar spine is supposed to be stable and bear high static and dynamic axial loads and also demonstrate flexibility to ensure a high degree of mobility of the entire spine. Junghanns[1] defines the segment of movement as the smallest structural and functional unit of the lumbar spine. The intervertebral (IV) disc is a dynamic structure which lies between the vertebrae and consists of anulus fibrosus, nucleus pulposus and end plates.[2] The IV disc is one of the largest avascular tissues in the body with no blood vessels, neurons and lymphatic structures. Discs are supplied by vessels in the subchondral bone adjacent to the hyaline cartilage of the end plate. Therefore, the discs show a slow and limited healing process after injury. Progressive and serious changes also occur with increasing age.[3,4] The most common cause of low back or upper neck pain problems are degenerations that occur in the IV discs. The causes of these degenerations are fluid loss in nucleus pulposus, rupture of annulus fibrosus, weakening of the connections between the intervertebral foramen and loss of function. These alterations will reduce the ability to absorb forces and durability with advancing age. They also lead to a decrease in the disc height, and disc herniation or bulging over time.[5] Biomechanical changes in the discs with aging also affect the height due to their location.[6] Over the years, various diagnostic methods have been developed for early detection of these and similar degenerative changes to improve the treatment strategies.[3] Computed tomogra-

phy (CT), magnetic resonance imaging (MRI), ultrasonography (US) and radiography (X-ray) techniques are widely used for imaging and diagnosis of spinal disorders.[5] Especially, radiography is the simplest and cost-effective method that can be applied even in primary health-care services. This is currently the most frequently used imaging technique to detect vertebral and discal disorders.[7,8]

In this study, we aimed to establish reference values for disc height and concavity index of lumbar vertebral bodies in healthy young Turkish population on radiographic examination, as well as to determine the influence of age, gender, weight, height and BMI on aforementioned values.

Materials and Methods

This study was conducted at Orthopedics and Traumatology Departments of Sütçü İmam University and Kilis State Hospital. X-ray images were selected from 180 healthy young adults (90 women, 90 men) without low back pain or hip disorders who underwent standardized standing lateral lumbar radiography for various reasons from the hospital archive database. The age of subjects ranged from 18 to 27 years old. In addition, the demographic data (sex, age, body weight, height, BMI) of each subject and the phone number was recorded. Subjects with spinal disorders such as Bechterew disease, Scheuermann's disease, scoliosis, spinal metastasis, spondylolisthesis, low back pain, osteoporosis, hip disorder and history of trauma were excluded. Of the 180 subjects assessed according to the protocol, 150 subjects (80 women, 70 men) were included; 21 subjects did not come for an interview about their clinical condition and the remaining patients matched one or more of the exclusion criteria. This study was approved by the Faculty of Medicine Clinical Research Ethics Committee of Kahramanmaraş Sütçü İmam University, and voluntary informed consent forms were obtained from the participants. The radiographic cassette was placed to right side of each participant in relaxed standing position, with joining their hands behind the neck.

X-ray images were taken with the beam focused on the third lumbar vertebrae, with anode-film distance between 100 to 120 cm. The height of the lumbar discs were measured according to the Leivseth et al.[9] protocol, and the concavity index for each vertebra was calculated, dividing the central vertebral height with the anterior vertebral height (**Figure 1**).[10] We used Image J software (National Institute of Mental Health, Bethesda, Maryland, USA) to measure the disc height and concavity index of the lumbar spine on the digitized lateral radiographs.

Table 1
Demographic characteristics of the groups using Mann-Whitney U test.

	Male (n=70)	Female (n=80)	Total (n=150)	p
Age (years)	20.97±1.7	20.73±1.87	20.83±1.8	0.192
Weight (kg)	72.85±10.54	55.97±6.95	63.76±12.15	p<0.001*
Height (cm)	176.69±6.03	162.81±4.94	169.30±8.85	p<0.001*
BMI (kg/m²)	23.29±2.79	21.10±2.25	23.30±2.73	p<0.001*

*p<0.001

Statistical analysis was performed using SPSS Version 16.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of the data was assessed by Kolmogorov-Smirnov test and homogeneity of variance of the data was assessed by Levene's test. Mann-Whitney U test was used to compare the groups. Correlation between parameters was determined by Spearman's correlation test. p<0.05 was accepted to be statistically significant. Data were presented as mean ± SEM.

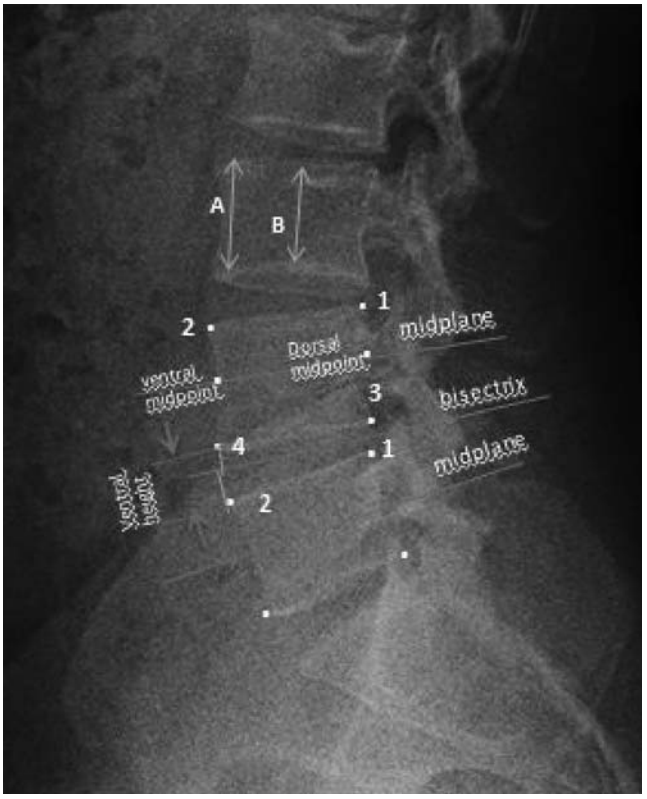

Figure 1. Schematic representation of measurements of ventral intervertebral disc height and concavity index (B/A) on lateral radiography.

Results

Of the 150 subjects included in this study, 80 (53.3%) were women and 70 (46.7%), were mean; mean age was 20.83±1.80 (range: 18 to 27) years. They had a mean height of 169.3±8.85 (range: 151 to 190) cm, mean body weight of 63.76±12.15 (range: 43 to 97) kg, and mean BMI of 23.30±2.73 (range: 18.99 to 29.43) kg/m^2. The demographic characteristics of the groups are given in **Table 1**.

Disc height values of the groups are given in **Table 2**. Men presented higher lumbar disc values (T12–L1, L1–L2, L2–L3, L3–L4, L4–L5, and L5–S1) than women (p<0.001). In both gender, disc height values increased from T12–L1 to L4–L5 and then slightly decreased at L5–S1.

Correlation coefficients and statistical evaluation of interrelation between demographics and disc height are given in **Table 3**. The heights of lumbar discs increased with advancing age (p<0.001), weight (p<0.001), height p<0.001) and BMI (p<0.001) in both genders. Concavity index values of the groups are given in **Table 4**. Women demonstrated a higher concavity index (L2, L3 and L4 vertebrae) than men (p<0.001). However, men showed a higher concavity index value at L5 vertebra than women (p<0.001). Correlation coefficients and statistical evaluation of interrelation between demographics and concavity index are given in **Table 5**. The concavity index of vertebrae (T12, L1, L2, L3 and L4) decreased with advancing age (p<0.01). The concavity index of L2, L3 and L4 vertebrae decreased with advancing weight, height and BMI of the subjects (p<0.01). On the other hand, the concavity index of L5 vertebrae increased with advancing weight, height and BMI of the subjects (p<0.01).

Table 2
Disc height values of the groups using Mann-Whitney U test.

Disc height (mm)	Male (n=70)	Female (n=80)	Total (n=150)	p
T12–L1	6.14±0.56	5.16±0.37	5.61±0.67	p<0.001*
L1–L2	7.97±0.61	7.16±0.4	7.54±0.65	p<0.001*
L2–L3	9.71±0.72	9.04±0.35	9.35±0.65	p<0.001*
L3–L4	11.91±0.29	10.43±0.52	11.11±0.85	p<0.001*
L4–L5	11.98±0.33	11.44±0.55	11.69±0.54	p<0.001*
L5–S1	11.52±0.5	10.59±0.74	11.02±0.79	p<0.001*

*p<0.001

Discussion

IV discs have an important role in posture, biomechanics, and balancing of the body. They show morphological and functional changes throughout life starting from birth according to the body's needs, which mostly occur due to genetic and hormonal effects in up to three decades.[11] Therefore, we aimed to determine the segmental disc height and concavity index of the lumbar spine in a young healthy Turkish population. In determining the changes in the IV discs, disc height measurements are usually used. Previously, decreases in disc heights with age have been evaluated as pathological[12,13] and reported mostly in men.[14] However, subsequent studies have shown that the anterior disc height increased steadily in first five decades in both age in both genders and decreased afterwards.[15–17] Berlemann et al.,[6] in their cadaver study, indicated that degenerative changes due to aging might reduce disc height. On the other hand, Twomey and Taylor[18] reported in their radiographic study on people aged 20–35 years and over 60 years that there was a clear upward trend in disc heights with increasing age. Moreover, in succeeding studies, the lumber discs of participants in each decade showed gradual increase from L1–L2 to L5–S1 in the craniocaudal direction.[10,19–21] In other studies, it was reported that with aging, the disc height increase in each segment was 10%.[14,22] The present study demonstrated lumbar disc

Table 3
Correlations between demographics and disc height using Spearman's correlation coefficient.

	Age		Weight		Height		BMI	
	r	p	r	p	r	p	r	p
T12–L1	0.505	p<0.001*	0.649	p<0.001*	0.679	p<0.001*	0.385	p<0.001*
L1–L2	0.566	p<0.001*	0.556	p<0.001*	0.56	p<0.001*	0.317	p<0.001*
L2–L3	0.422	p<0.001*	0.477	p<0.001*	0.5	p<0.001*	0.18	p<0.001*
L3–L4	0.38	p<0.001*	0.705	p<0.001*	0.741	p<0.001*	0.431	p<0.001*
L4–L5	0.552	p<0.001*	0.456	p<0.001*	0.407	p<0.001*	0.336	p<0.001*
L5–S1	0.634	p<0.001*	0.554	p<0.001*	0.520	p<0.001*	0.393	p<0.001*

*p<0.001

height increased in the craniocaudal direction from T12–Ll to L4–L5 with age in both genders, which was more significant in men. L4–L5 disc height was also greater compared to L5–S1 disc height. Kapakin and Akşit[23] and Malkoç et al.[21] in their MR studies, reported increase in lumbar disc height with age, as well as in craniocaudal direction for each decade depending on age in both genders. Disk heights of the participants in third decade of life were examined. Kapakin and Akşit[23] measured the L4–L5 level as 11.9 mm for both genders, and the L5–S1 level as 12.8 mm for men and 12.7 mm for women.

Furthermore, Malkoç et al.[21] measured mean disc heights at the L4–L5 level as 14.3 mm in men and 13.6 mm in women, and the L5–S1 level as 13.92 mm for men and 14.45 mm for women. In another study, Berlemann et al.[6] evaluated 13 L4–L5 and 10 L5–S1 level intervertebral discs of cadavers under the age of 40, with no history of lumbar region disorders. They measured the mean height of the discs as 12.7 mm in both L4–5 and L5–S1 levels. In our study, referring to measurements on radiographic examination of healthy adults, mean heights were measured for L4–L5 11.98 mm and L5–S1 11.52 mm in men while L4–L5 11.44 mm and L5–S1 10.59 mm in women. The decrease in disc height at L5–S1, which was determined in the present study, was consistent with the results of Humzah and Soames.[11] There are also different studies reporting a decrease in disc height at the L5–S1 level. Various studies, in which study populations consisted of obese individuals, heavy-duty workers or professional athletes, found a decrease in L5–S1 disc height as well.[24–26] This difference in the L5–S1 level may be due to the shape of the disc, its connection with the sacrum, involvement of the lordosis angle to the formation and rupture of the annulus fibrosis due to the disruption of the superior and inferior endplate as a result of great axial forces (loads) affecting the discs related to performing heavy duties or heavy sports activities.[27] A limitation of the present study is the lack of information on profession and involvement of participants in sports activities. Another limitation is the absence of obese participants in this study which includes normal and overweight participants according to BMI.

Table 4
Concavity index values of the groups using Mann-Whitney U test.

	Male (n=70)	Female (n=80)	Total (n=150)	p
T12	0.9855±0.01	0.9861±0.01	0.9859±0.01	0.879
L1	0.9806±0.01	0.9796±0.01	0.9801±0.01	0.342
L2	0.9614±0.01	0.9673±0.01	0.9646±0.01	**p<0.001***
L3	0.9546±0.02	0.962±0.01	0.9586±0.01	**p<0.001***
L4	0.9408±0.02	0.9636±0.01	0.953±0.02	**p<0.001***
L5	0.886±0.02	0.868±0.01	0.8764±0.02	**p<0.001***

*p<0.001

Another parameter that was evaluated in our study was the concavity index. Concavity index is the evaluation of the changes on the surface between the disc and vertebral body due to aging.[10] Currently, the concavity index is used for radiographic diagnosis of osteoporosis and lumbar spinal anomalies.[10,25,28] Change in concavity index with aging is controversial because both increase and decrease in concavity index with aging were reported in the literature.[6,10,17,20,29] The present study demonstrated decrease in concavity index with aging in both genders.

Conclusion

We observed that the disc height increased with age from T12–L1 to L4–L5 in the craniocaudal direction; in contrast, L5–S1 disc height decreased. Decrease in concavity index of lumbar vertebrae with aging was also observed. This study is a cross-sectional one, because of

Table 5
Correlations between demographics and concavity index using Spearman's correlation coefficient.

	Age		Weight		Height		BMI	
	r	p	r	p	r	p	r	p
T12	-0.362	p<0.001*	-0.112	0.189	-0.052	0.389	-0.087	0.308
L1	-0.431	p<0.001*	-0.052	0.545	0.034	0.774	-0.09	0.291
L2	-0.529	p<0.001*	-0.385	p<0.001*	-0.326	p<0.001*	-0.233	0.006
L3	-0.469	p<0.001*	-0.329	p<0.001*	-0.220	0.009*	-0.171	0.043
L4	-0.339	p<0.001*	-0.647	p<0.001*	-0.633	p<0.001*	-0.254	0.002
L5	-0.147	0.162	0.479	p<0.001*	0.580	p<0.001*	0.255	0.002

*p<0.05

this, the results cannot be applied to the whole of this age group population. However, these results will serve as guidelines for radiological evaluation of lumbar spine in young healthy adults.

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A detailed cadaver donation form

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Abstract

Objectives: Cadavers are the basic part of anatomy education; however, the number of donations does not meet the necessity for qualified education. Donation process is regulated by laws and professional regulations. In order to avoid possible negative effects of wrong applications, it is important that the donation process should be conducted very carefully. In this study, we aimed to structure a detailed cadaver donation form for daily practice.

Methods: Responsibilities imposed by laws and regulations have been revealed by scanning the High Court jurisprudence. For application examples, a literature search in Index Medicus was made for previous studies regarding cadaver donation and ethical perspectives.

Results: In the light of regulations of laws, ethical rules and experienced legal problems a detailed consent form was structured.

Conclusion: This study will contribute to donation process and provide detailed information on consent forms.

Keywords: cadaver; donation; informed consent form

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Introduction

Anatomy is one of the branch of the basic sciences focused on human body. It is concerned with the macroscopic structures of human body. Besides other health education programs such as nursing or vocational colleges, anatomy education is a corner stone for medical education and teaching anatomy is based on cadaver training. Thus, medical education needs to be supported by sufficient number of cadavers, in order to obtain well-trained healthcare personnel.

As in other developed countries, cadaver donation is an important issue in our country and number of donations does not meet the need for qualified medical education. The legislation related to the importation and transplantation of tissues and organs is carried out within the scope of the law no. 2238, in Turkey.[1] The 7th article of this law gives responsibility of informing to the physician who is responsible for receiving the donation. Therefore, an informed consent form regarding cadaver donation should be submitted to the donor. The informed consent forms are extensively used for surgical procedures. Due to malpractice cases, scope of each type of consent forms expands. It is obvious that a malpractice situation about cadaver donation will affect negatively the number of donations which are already low.

In this study, we aimed to structure a detailed informed consent form for cadaver donation in the light of malpractice cases and High Court jurisprudence about organ donations and informed consent forms.

Materials and Methods

All medical procedures require the legal consent of the person to undergo medical intervention. There are two dimensions of consent forms: legal dimension described by laws and regulations, and medical dimension which regulates the ethical perspectives.[2]

In the context of the responsibilities imposed by the relevant laws and regulations, wrong applications concerning informed consent have been revealed by scanning the High Court jurisprudence. An anonymous literature search in Index Medicus was performed for previous studies regarding cadaver donation and ethical perspectives. Cadaver donation, informed consent form, malpractice, organ donation, donation ethics were the keywords used in literature search. A detailed consent form has been structured taking into account both the

legal provisions and good application examples. This study has been carried out according to Declaration of Helsinki updated in 2013.

Results

Physicians perform their duties within the framework of legal and professional ethics regulations. Informed consent forms are part of the medicolegal process of the medical profession.

The concept of informed consent form has been existed for a long time in High Court jurisprudence. The decision of the Court dated 1977 states that the physician is responsible for informing the patient before medical interventions.[3] The decisions taken in 2008 and 2014 also state that this information needs to be elaborated and the patient has to know what the procedure is and the patient must know how the medical process can develop. Briefly, the patient should be aware of what he/she is consenting.[4,5] Responsibility of this issue is imposed by the relevant laws and regulations to the physician.

When the legal cases of informed consent forms were examined in the light of these regulations, these main topics were confronted:

- Inadequate or no information: especially complications are not explained in detail.
- The medical terms make it difficult to understand.
- Lack of medical documentation: verbal affirmation in the presence of witnesses is not sufficient.

In the light of regulations of laws, ethical rules and experienced legal problems, the cadaver donation form should be given by the physician including detailed information about the process. It should be written in simplicity for better understanding by the donor. The donor must be voluntary, not forced, the consent must be taken in writing and the documents must be well protected. In this context, a detailed consent form for cadaver donation is structured. English version of the detailed consent form is presented in **Supplement 1**, and Turkish version is presented in **Supplement 2**.

Discussion

Physicians conduct their professional activities within the framework of laws and professional regulations. One of the professional activities of the anatomists is cadaver donation. In our country, body-organ and tissue donations are regulated by the law no. 2238.[1]

As a part of our legal system, European Convention on Human Rights and Biomedicine and Law no. 2238 gives physicians responsibility for informing about any intervention in the field of health, including research.[1,6]

Recent High Court jurisprudence states that information in the consent form must be elaborated and detailed. Literature research revealed that good application examples involve detailed information about the donation process (from acceptance of the body to funeral procedures). We suggest that the following headings should be included in the donation form when the donors' opinions were taken into consideration:

The person who gives information should be a physician: The informing process must be done by a competent staff, preferably by a physician. In this way, the donor will be able to take accurate information about the processes and donor will not be hesitated. On the other hand, the donor must also be competent. Underage or donors with inadequate mental capacity should not be accepted. If the donor is dead, written consent of *all legal heirs* must be taken in terms of legal issues (this point should be well questioned for legal complications that may arise later).

The consent form must be clear and understandable: The processes to be performed must be expressed in detail. It must be avoided from medical terms or medical terms must be explained in a way that the donor can understand. In an earlier study, donors stated that they refused or hesitated donations not because they were against the donation, but due to lack of information they demanded.[7]

The relatives who are informed about the donation, relatives to whom the funeral will be delivered after the completion of the process must be recorded: A number of relatives should be informed about the donation. Thus, after the death of the donor, there will be no time loss during the transfer of the funeral to the institution. Also, a number of relatives should be recorded for the delivery of the funeral after completing use of cadaver.

The form should include information about the nature of dissections or scientific researchers: Cadavers are mainly used for medical education and scientific research. In the dissection of the cadaver for medical education, body cavities may be opened, organs or body parts may be removed. When the funeral is delivered, its integrity will be impaired. Scientific researches on cadavers may include surgical procedures, implantation applications, trauma exercises, disarticulations, imaging methods, histopathological, cytological or microbiological examinations.

Donors must be voluntary and must consent to donation: Cadaver donation process should be conducted on volunteering and the donor should not be forced.[7]

There should not be any kind of interest between the institution and the donor or next-of-kins: In Turkey, tissue and organ trading is prohibited, thus cadaver donation should be made without any interest.

Donation-related records must be in hand-writing: In order to avoid legal problems, consent for donation should be written and witnessed. All the records should be well-kept.

The contact information of the institution should take place in the consent form: The communication information should be easily accessible. Donors or those seeking information should be able to access to anatomy department easily.

Use of cadavers is an indispensable part of medical education and cadaver donation process should be carried out carefully. Because a legal problem that may be experienced in this regard will affect the donations which are already low and inadequate.

We hope that this study will contribute to donation process and provide a detailed information on the consent forms for all anatomists and other medical staff.

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Supplements to this article containing English and Turkish versions of the cadaver donation form are given on the following four pages.

Supplement 1. English version of the detailed consent form for cadaver donation.

CADAVER DONATION FORM

This form consists of two parts.

Part One: General information on cadavers and donations

Part Two: Cadaver Donation Information

1. GENERAL INFORMATION

What is a cadaver?	It is a dead human body that has been specially treated to prevent its deterioration, is used for training in anatomy class.
What is the cadaver used for?	It is used to teach the structure of the human body in student education, especially medical education or other health sciences (dentistry, nursing, FTR, Health Vocational Schools). It is also used in postgraduate training, scientific research, surgical intervention studies.
How is cadaver used?	All anatomical structures are revealed by dissection in the direction of the relevant course and/or researcher. The revealed structures are used for training and/or research purposes. Both instructors and students continue to work with awareness of the value of the sacrifices our donors. The care and respect required during these studies are maintained and followed without any concessions.
Who can make cadaver donation?	Anyone who is not mentally ill od who is not under age can donate before two witnesses. Persons who want to donate a deceased person as a cadaver may donate again in the presence of two witnesses with the approval of all legal representatives. Cadaver donation is acceptable for Islamic religion (Presidency of Religious Affairs)
How does the donation process work?	After the donor's death, the funeral is quickly transferred to the relevant Anatomy AD or related institution's morg unit. It is subjected to a fixation process to stop the deterioration. The funeral is then held in formaldehyde for about 6 months to complete the fixation process.
What is fixation?	The cadaver is protected by using chemical fluids, so that the tissue properties remain similar to that of living organisms. The aim here is to stop the deterioration of the cadaver so that it can be examined for a long time. In Turkey, formaldehyde liquid is generally used for this process.
What are Scientific Researches?	These are the studies for the development of medical science. Investigations using cadavers include surgical procedures, implant procedures, trauma studies, disarticulations, imaging methods, histopathological, cytological, biochemical, microbiological examinations.
Terminology	Fixation (Old-style Embalming): Permanent medication to prevent deterioration
	Dissection: Opening the cadaver by cutting to examine the internal structure.
	Disarticulation: Separation of bones from joints
	Extremity: Limb (arm or legs)

2. CADAVER DONATION INFORMATION

Donor's Identity Information

Name-surname

Identification number

Father name

Birth Place / Date

Identity Serial Number

Contact information

Adress

I informed the following people about the donation I made.

Name-surname	Contact information	Kinship
Name-surname	Contact information	Kinship

I read and understand the information about cadavers and donation in this form, given by department of Anatomy.

Name-surname

Signature:

Date:

University of.....Department of Anatomy Contact Information

Supplement 1. ***[Continued]*** English version of the detailed consent form for cadaver donation.

CADAVER DONATION FORM

PLEASE READ CAREFULLY THE INFORMATION BELOW. ASK TO THE PHYSICIAN WHO IS INFORMING YOU FOR WHAT YOU DO NOT UNDERSTAND.
I understand the following explanations as a condition for donation and funeral procedures

I make this donation voluntarily, without any coercion or restriction and without any financial interest.

Accepting of donation depends on the criteria specified by Department of Anatomy. The donation does not always mean that the body will be accepted as a cadaver. The donation can be refused for reasons such as not being suitable for fixation (the beginning of deterioration) or delays in transporting the funeral.

Fixation (embalming) will be done for protection to long term use of the cadaver. Detailed surgical procedures will be conducted for education and scientific studies. During these examinations, body organs can be removed or disarticulation can be performed for body parts such as extremities, head, spine. Tissue samples can be taken for histopathological examination. I allow to Department of Anatomy that part of my body to be kept indefinitely for educational and/or scientific purposes.

All or part of the donated cadaver can be moved for research purposes, such as training courses or radiological imaging in the institution or to another institution, with permission provided from the administration.

The cadaver will not be used for any purpose other than educational and scientific research. It will be protected with respect and care. It will not be exhibited in any way.

The tissues, organs, parts or all of the cadaver can be used unlimitedly in scientific research, student education or postgraduate training. Scientific publications (such as articles, case reports) or lecture presentation materials can be prepared with the data obtained as a result of researches on cadavers. For such academic studies, scientific publications or course presentations, photographs or videos may be taken by hiding the donor's identity. The donor's identity will not be shared with anyone under the responsibility of "Physician's keeping secrets of patients".

As a result of using the body as a cadaver, body integrity will be impaired. During the return of the body; the tissues and organs will not be complete due to the dissections made during educational activities or scientific researches.

DONATION CERTIFICATE
In the light of the information given and in the presence of witnesses, after my death I donate my body as cadaver to the Department of Anatomy of .....University, without any financial interest.
Signature:

Purpose of use: Educational activities/Scientific Activities/In both educational and scientific activities
Please indicate by handwriting:

Donation Time: 3 Years / Other / No time limit
Please indicate by handwriting:

Funeral procedures: After the use of my body as cadaver is completed;
1. I want my body to be delivered to my family.
The person i would like my body to be delivered to is;

Name-Surname:	Contact Information:	Kinship:
Name-Surname:	Contact Information:	Kinship:

2. I want to be buried in a graveyard which will be determined by the municipality. I want the funeral ceremony will be done in accordance with ..... religion / I do not want funeral ceremony
Please indicate by handwriting:

Donor	**Name-Surname**	**Signature**	**Date**
Witness	**Name-Surname**	**Signature**	**Date**
Witness	**Name-Surname**	**Signature**	**Date**
Physician	**Name-Surname**	**Signature**	**Date**

Donor's Medical Story (Optional): **Height:** **Weight:**
Profession: **Orthotics-Prosthetics:**
Previous surgeries:
Other (if present):

Supplement 2. Turkish version of the detailed consent form for cadaver donation.

KADAVRA BAĞIŞ FORMU

Bu form iki kısımdan oluşur.

Birinci Kısım: Kadavra ve bağış konusunda genel bilgiler

İkinci Kısım: Kadavra Bağış Bilgileri

1. GENEL BİLGİLER

Kadavra nedir?	Anatomi dersinde eğitim amacıyla kullanılan, bozulmasını önlemek için özel işleme tabi tutulmuş cansız insan vücududur.
Kadavra ne için kullanılır?	Başta tıp eğitimi olmak üzere, sağlık bilimlerinde (diş hekimliği, hemşirelik, FTR, Sağlık Meslek Yüksekokulları gibi) öğrenci eğitiminde insan vücudunun yapısını öğretmek amacıyla kullanılır. Mezuniyet sonrası eğitimlerde, bilimsel araştırmalarda, cerrahi girişim çalışmalarında da kullanılır.
Kadavra nasıl kullanılır?	İlgili dersin ve/veya araştırmanın konusu doğrultusunda, diseksiyon yapılarak tüm anatomik yapılar ortaya konulur. Ortaya çıkarılan yapılar, eğitim ve/veya araştırma amacıyla kullanılır. Gerek eğitmenler, gerek öğrenciler bağışçılarımızın değeri ölçülemeyecek olan fedakarlıklarının farkında olarak çalışmalarını sürdürürler. Bu çalışmalar esnasında gerekli olan özen ve saygı korunur ve hiç bir taviz verilmeden takip edilir.
Kimler kadavra olabilir?	Akli melekeleri yerinde ve reşit olan herkes, iki şahit huzurunda bağışta bulunabilir. Vefat etmiş bir yakınını kadavra olarak bağışlamak isteyen kişiler, tüm yasal vasilerin onayı ile yine iki şahit huzurunda bağışta bulunabilir. Kadavra bağışı İslam dini açısından caizdir (Diyanet İşleri Başkanlığı)
Bağış süreci nasıl işler?	Bağışçının vefatı sonrası cenaze, süratle ilgili Anatomi AD.'a ya da ilgili kurumun morg ünitesine nakledilir. Ölü çürümesini durdurmak amacıyla cenaze fiksasyon işlemine tabi tutulur. Cenaze daha sonra, yaklaşık 6 ay fiksasyon işleminin tamamlanması için formaldehit isimli sıvı içerisinde bekletilir.
Fiksasyon nedir?	"Tespit" olarak da bilinir. Kadavranın kimyasal sıvılar kullanılarak, doku özelliklerinin canlıdakine benzer şekilde kalması için korunmasıdır. Burada amaç, kadavranın uzun süre incelenebilmesi için bozulmasını durdurmaktır. Türkiye'de genellikle bu işlem için formaldehit sıvısı kullanılır.
Bilimsel Araştırmalar nedir?	Tıp biliminin gelişimi için yapılan araştırmalardır. Kadavra kullanılarak yapılan araştırmalar; cerrahi girişimleri, implant işlemlerini, travma çalışmalarını, disartikülasyonları, görüntüleme yöntemlerini, histopatolojik, sitolojik, biokimyasal, mikrobiyolojik incelemeler gibi yöntemleri kapsar.
Terimler	Fiksasyon (Eski dilde Tahnit): Bozulmaması için ölüyü ilaçlama
	Diseksiyon: Kadavranın iç yapısını incelemek üzere kesip açma olayı.
	Disartikülasyon: Kemiklerin eklem yerlerinden kesilerek ayrılması
	Ekstremite: Uzuv (kol ya da bacaklar)

2. KADAVRA BAĞIŞ BİLGİLERİ

Bağışçının Kimlik Bilgileri

Adı Soyadı

TC Kimlik No

Baba Adı

Doğum Yeri/Tarihi

TC Kimlik Seri No

İletişim Bilgileri

Adres

Yaptığım bağış hakkında şu kişileri bilgilendirdim.

Adı Soyadı	İletişim Bilgileri	Yakınlığı
Adı Soyadı	İletişim Bilgileri	Yakınlığı

Bu formda yer alan, Kadavra Bağışı ve Kullanımı hakkında
tarafıma, Anatomi AD. Başkanlığınca verilen bilgileri okudum, anladım.

Adı Soyadı:
İmza:
Tarih:

……..Üniversitesi Anatomi AD. İletişim Bilgileri:……

Supplement 2. ***[Continued]*** Turkish version of the detailed consent form for cadaver donation.

KADAVRA BAĞIŞ FORMU

LÜTFEN AŞAĞIDA VERİLEN BİLGİLERİ DİKKATLİCE OKUYUNUZ. ANLAMADIĞINIZ HUSUSLARI BİLGİ VEREN HEKİME SORUNUZ.

Aşağıdaki açıklamaları bağış ve cenaze işlemleri için koşul olarak anlıyorum.

Bu bağışı herhangi bir zorlama ya da kısıtlama olmadan kendi rızamla, gönüllü olarak, maddi kazanç olmadan yapıyorum.

Bağışın kabulü Anatomi AD. tarafından belirtilen kriterlere bağlıdır. Bağış yapılmış olması, her zaman cenazenin kadavra olarak kabul edileceği anlamına gelmez. Fiksasyon için uygun olmaması (ölü çürümesinin başlamış olması) ya da cenazenin naklinde olabilecek gecikmeler gibi nedenlerden ötürü bağış reddedilebilir.

Kadavrayı uzun süre korumak ve kullanmak amacıyla fiksasyon (tahnit) işlemi yapılacaktır. Yapılacak eğitsel faaliyetlerde ve bilimsel çalışmalarda ayrıntılı cerrahi incelemeler yapılacaktır. Bu incelemeler esnasında vücut organları çıkarılabilir veya ekstremiteler, baş, omurga gibi vücut bölümleri için disartikülasyon yapılabilir. Kadavradan histopatolojik inceleme için doku örnekleri alınabilir. Anatomi AD.'nın bedenimin bir bölümünü, eğitim ve/veya bilimsel amaçlar için süresiz olarak saklamasına izin veriyorum.

Bağışlanan kadavranın tümü veya bir bölümü sadece eğitim ya da kurs, radyolojik görüntüleme gibi araştırma amacıyla, bağışlandığı kurum içinde ya da başka kuruma idareden izin alınmak kaydıyla taşınabilir.

Kadavra, eğitim ve bilimsel araştırma dışında herhangi bir amaçla kullanılmayacaktır. Saygı ve özenle korunacaktır. Her hangi bir şekilde sergilenmeyecektir.

Kadavranın dokuları, organları, bir parçası ya da tümü, bilimsel araştırmalarda, öğrenci eğitimi ya da mezuniyet sonrası eğitimlerde sınırsız olarak kullanılabilir. Kadavra üzerinde yapılan araştırmalar sonucunda elde edilen veriler ile bilimsel yayınlar (makale, olgu sunumu gibi) ya da ders sunum materyalleri hazırlanabilir. Bu tür akademik çalışmalar, bilimsel yayınlar ya da ders sunumları için fotoğraf ya da videolar bağışçının kimliğini gizleyecek şekilde çekilebilir. Bağışçının kimliği "Hekimin sır saklama" sorumluluğu kapsamında kimseyle paylaşılmayacaktır.

Cenazenin kadavra olarak kullanımı sonucunda vücut bütünlüğü bozulmuş olacaktır. Cenazenin geri teslimi sırasında; yapılmış olan diseksiyonlar, bilimsel araştırmalar ya da eğitsel faaliyetlerdeki incelemelerden dolayı doku ve organlar tam olmayacaktır.

BAĞIŞ TUTANAĞI

Bana verilen bilgiler ışığında, vefatımdan sonra bedenimi; .....Üniversitesi Anatomi Anabilim Dalı'nda kadavra olarak kullanılması amacıyla hür irademle, maddi karşılık beklemeden şahitler huzurunda bağışlıyorum.

İmza:

Kullanım amacı: Eğitim faaliyetleri / Bilimsel Araştırma / Hem eğitim hem bilimsel araştırma faaaliyetlerinde
Lütfen el yazısı ile belirtiniz:

Bağış Süresi: 3 Yıl / Diğer / Süre sınırı yok
Lütfen el yazısı ile belirtiniz:

Cenaze işlemleri: Cesedimin, kadavra olarak kullanılması tamamlandığında;
1. Aileme teslim edilmesini istiyorum.
Cenazemin Teslim edilmesini istediğim Kişi:
Adı Soyadı: İletişim Bilgileri: Yakınlığı:
Adı Soyadı: İletişim Bilgileri: Yakınlığı
2. Belediye tarafından tespit edilecek bir mezarlığa defnedilmesini istiyorum. Cenaze törenimin .....
dinine uygun şekilde yapılmasını istiyorum / yapılmasını istemiyorum.
Lütfen el yazısı ile belirtiniz:

Bağışçının	**Adı Soyadı**	**İmza**	**Tarih**
Şahit	**Adı Soyadı**	**İmza**	**Tarih**
Şahit	**Adı Soyadı**	**İmza**	**Tarih**
Sorumlu Hekim	**Adı Soyadı**	**İmza**	**Tarih**

Bağışçının Tıbbi Öyküsü (Opsiyonel): **Boy:** **Kilo:**

Mesleği: **Ortez-Protez:**

Geçirdiği Ameliyatlar:

Diğer Hususlar (varsa belirtiniz):

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Evaluation of attitudes and knowledge of Kocaeli University medical students on dissection, brain death and organ donation

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Abstract

Considering organ donation, cadaver supply routes and procurement rates, it seems that resources are limited. It is discussed from a broad perspective that the evaluation of ethical approaches in terms of cadaver needs in anatomy education and research areas, and the use of bodies obtained through donation are more appropriate. Healthcare workers' knowledge and attitudes on organ donation and transplantation are the main factors for making a positive impact on the society and raising the donation rate. In this study, the questions directed to the students were designed to assess their views on cadaveric and organ donation, their awareness of the issue, and their attitudes in case the person or his/her relatives need organ donation. When the obtained data were evaluated, statistically significant changes were observed between medical students' attitudes before and after the anatomy laboratory education ($p<0.05$). Although many of the students stated that their ideas did not change, this study shows that medical school students change their attitudes towards cadaver and organ donation issues after anatomy laboratory training.

Keywords: cadaver donation; medical students; organ donation

Anatomy 2018;12(1):45–48

Introduction

Cadaver and organ donation issues have become very important in terms of medical education and treatment of chronic diseases. It is also seen that resources are limited when organ donation, cadaver supply routes and acquisition rates are considered.[1,2] Throughout the history of anatomy, acquiring cadavers became a major problem and the ethical debate on cadaver supply routes dates back to ancient history. Among these ways of supply, the most ethically correct method is thought to be donation of the human body or part of it voluntarily.[3,4]

As is known, anatomy knowledge is very important for most medical students. Anatomy education is carried out for two years, theoretical and practical. This situation can also affect students' attitudes towards cadaver donation. This questionnaire study among medical students who will become doctors of the future aimed to evaluate the effect of anatomy laboratory education on the knowledge, attitudes and behaviors of the medical students towards organ and cadaver donation.

Materials and Methods

Our questionnaire evaluation study was carried out between 2015–2016 and 2016–2017 academic year on students of Kocaeli University Faculty of Medicine. The attitudes of the Term-I students which have not yet received anatomy laboratory training, on cadaver and organ donation were questioned again on the same students in Term-II after the anatomy laboratory training. A total of 166 students (80 females and 86 males) participated in the study. The students were asked 12 questions answers of which were including "Yes", "No" and "Undecided" choices. Before the questionnaire was re-applied to the Term-II

students, the question "Do you think that medical education has changed your mind about organ and / or cadaver donation?" was added at the end of the questionnaire (**Figure 1**). The questions directed to the students were designed to assess their views on cadaveric and organ donation, their awareness of the issue, and their attitudes in case the person or his/her relatives need organ donation. The data obtained from the study were transferred to the computer and statistically analyzed using the IBM SPSS Statistics for Windows (Version 20.0, Armonk, NY, USA). Dependent samples t-tests were applied on the responses of the participants to the questionnaires after the descriptive statistics (mean value, standard deviation) were made. The answers given by each group for every question were analyzed by Pearson chi-square test according to pretest / posttest variables. The statistical significance was set at $p<0.05$.

Results

When gender, age and demographic characteristics are examined from the 166 students who participated in the

Questionnaire on Cadaver and Organ Donation Attitudes for Preclinic Medical Students

Date of birth:
Gender: ☐ Woman ☐ Man

In which region your family live?
a. Mediterranean Region b. Eastern Anatolia Region c. Aegean Region d. Southeast Anatolia Region
e. Central Anatolia Region f. Black Sea Region g. Marmara Region

1. Do you want to donate your organs when brain death takes place?
☐ Yes ☐ No ☐ Undecided

2. Do you want to donate the organs of anybody from yourr family when brain death takes place?
☐ Yes ☐ No ☐ Undeceded

3. Would you donate one of your own kidneys to any of your relatives or loved ones if it were necessary?
☐ Yes ☐ No ☐ Undeceded

4. Are you a registered organ donor?
☐ Yes ☐ No

5. Would you accept organ donation from another person whose brain death takes place in case of need?
☐ Yes ☐ No ☐ Undecided

6. I think that the donation of the organs caried oud after death disturbs the peace of the dead.
☐ Yes ☐ No ☐ Undecided

7. I believe that it's not appropriate form my religion to donate organs after death.
☐ Yes ☐ No ☐ Undecided

8. Do you think organ donation after death disturbs body intergrity of the dead and harms that person?
☐ Yes ☐ No ☐ Undecided

9. Have you ever seen a cadaver used in medical education?
☐ Yes ☐ No

10. Would you consider donating your body as a cadaver for medical education purpose?
☐ Yes ☐ No ☐ Undecided

11. Do you want someone from your family donate himself/herself as a cadaver?
☐ Yes ☐ No ☐ Undecided

12. I think it's "....." to work in the anatomy laboratory,
a. Frightening b. Disgusting c. Exciting d. Interesting e. Something normal

*Do you think that medical education has changed your mind about organ and /or cadaver donation?
☐ Yes ☐ No

Figure 1. Questionnaire on cadaver and organ donation attitudes for preclinic medical students. *Extra question in the second questionnaire.

Table 1
Percentages of answers that differ significantly from year to year for organ and cadaver donations (p<0.05).

Questions	2015–2016 academic year			2016–2017 academic year		
	Yes	No	Undecided	Yes	No	Undecided
1. Do you want to donate your organs when brain death takes place?	38.6% (64)	21.1% (35)	40.4% (67)	54.8% (91)	18.1% (30)	27.1% (45)
2. Do you want to donate the organs of anybody from your family when brain death takes place?	31.9% (53)	24.7% (41)	43.4% (72)	44% (73)	27.7% (46)	28.3% (47)
3. Would you accept organ donation from another person whose brain death takes place in case of need?	72.9% (121)	4.8% (8)	22.3% (37)	84.9% (141)	3% (5)	12% (20)
4. Do you think organ donation after death disturbs body integrity of the dead and harms that person?	7.8% (13)	70.5% (117)	13.3% (22)	10.2% (17)	80.1% (133)	9.6% (16)
5. Would you consider donating your body as a cadaver for medical education purpose?	8.4% (14)	59% (98)	24.1% (40)	9% (15)	79.5% (132)	11.4% (19)
6. Do you want someone from your family donate himself/herself as a cadaver?	7.8% (13)	65.1% (108)	19.3% (32)	5.4% (9)	77.7% (129)	16.9% (28)

study, 48.2% (n=80) were males and 51.8% (n=86) were females. The average age of the students in the academic year of 2015–2016 was 20.6. The geographical region in which the students' families resided was mostly %60.8 (n=101) the Marmara region. When the distributions of the answers according to years were taken into account, a total of 6 questions were observed with statistically significant difference (p<0.05) (**Table 1**).

When the obtained data were evaluated, it was observed that the anatomy laboratory education caused changes in the attitudes of medical students on cadaver and organ donation. When students were asked as "Do you want to donate your organs when brain death takes place?", 38.6% (n=64) of them replied as "Yes". This ratio increased to 54.8% (n=91) in the following year (p<0.05).

Likewise, 31.9% (n=53) of the students answered yes to "Do you want to donate the organs of any one of your family members when the brain death takes place?" then this ratio increased to 44.0% (n=73) (p<0.05). Similar differences were also found in the increase in acceptance of organ donation (p<0.05).

In another question directed to the students, "How was the feeling of working with the cadaver in the anatomy laboratory" the answer choices were frightening, nauseating, exciting, interesting or normal. Statistically significant differences were determined when the answers given by the students in Term-I and Term-II were evaluated separately (p<0.05). In 2015–2016 education year, while 34.3% (n=57) of the students in Term-I described working in the anatomy laboratory as "normal", this ratio increased to 63.9% (n=106) among the same students in the following year (**Table 2**).

"Do you think that medical education has changed your mind about the organs and / or cadaveric donation?" When this question is directed to the Term-II students in anatomy laboratory training; 45.1% (n=75) answered "Yes" and 54.9% (n=91) answered "No" (**Table 3**).

Discussion

Healthcare professionals' knowledge and attitude to organ donation and transplantation are importantl factors to promote a positive influence and rise the donation rate. In parallel with the development of medical sciences, cadaver needs are increasing in the fields of anatomy and medical

Table 2
Distribution of the views of students participating in the research about the anatomy laboratory studies by years.

	I think it's "....." to work in the anatomy laboratory				
	Frightening	Disgusting	Exciting	Interesting	Something normal
Term-I (2015–2016)	0.6% (1)	1.8% (3)	24.7% (41)	30.7% (51)	34.3% (57)
Term-II (2016–2017)	0% (0)	3% (5)	10.2% (17)	22.3% (37)	63.9% (106)

Table 3
Response for 'Do you think that medical education has changed your mind about organ and / or cadaver donation?'

	Do you think that medical education has changed your mind about organ and / or cadaver donation?	
2016–2017 academic year	**Yes**	**No**
Term-II	45.1% (n=75)	54.9% (n=91)

research. In the history of medicine, there are various ways to supply cadavers.[5,6] The view that the use of the cadavers obtained by donation being more appropriate is discussed from a broad perspective in terms of ethics.[7,8] Statistically significant changes were observed between medical students' attitudes before and after anatomy laboratory education ($p<0.05$).

When the results obtained were evaluated, it was observed that, in case of brain death, students did not have a high enough positive attitude for them or their families to donate organs and bodies. However, it was also found that the rate of donation acceptance is higher when the same situation is questioned according to the needs of themselves or their families.

Intercalarily, a question was added to the questionnaire study after the anatomy laboratory training "Do you think that medical education changes your opinion on organ and / or cadaver donation?" at the same time. 54.9% (n=91) of the answers given to this question constituted "No" (**Table 3**). However, when the answers given by the same medical students in Term-I and Term-II were evaluated, there were significant differences according to years ($p<0.05$), **Table 1**.

Although majority of students declared that there was no change in their attitudes, the results showed that their attitudes towards cadaveric and organ donation changed after the anatomy laboratory study.

Conclusion

When the obtained data were evaluated, anatomy laboratory studies could be seen as a reason for the change in the attitudes of medical students towards cadaver and organ donation. When the respondents' attitudes towards donation of organs and cadavers were evaluated, an increase in the positive direction for the donation of the students' organs and a decrease in the cadaver donation orientations of the persons was observed. It is known that the cadaver needs are increasing day by day in terms of cadaver use periods and the importance of anatomy laboratory education.

In this context, healthcare professionals have the greatest responsibility in terms of creating social awareness on organ and cadaver donation issues. Given the responsibilities and duties of health workers in this regard, the promotion of this level is critical to increase the quality of community health and health education.

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Case Report

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Unusually located inferior lateral genicular artery and an abnormally attached soleus with the absence of plantaris muscle

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Abstract

In this report, two male cadavers (ages 54 and 68) are presented with a variative inferior lateral genicular artery passing superficial to the plantaris muscle instead of passing deep to it. A soleus muscle attached to popliteus tendon with the absence of plantaris was encountered in the other extremity of one of these cases. The cases were evaluated regarding clinical and developmental aspects. This case is the first to our knowledge to describe the inferior lateral genicular artery passing superficial to the plantaris. Positional variations of the inferior lateral genicular artery should be taken into account during radiological assessments to avoid misdiagnosis. The case with soleus attached to the popliteus tendon in the absence of plantaris muscle has not been described previoulsly in the literature.

Keywords: inferior lateral genicular artery; plantaris, soleus; popliteus; positional variation

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Introduction

Inferior lateral genicular artery (ILG) arises from popliteal artery at posterolateral corner of the knee. It reaches infrapatellar fat pad by running superficial to popliteus and deep to fibular collateral ligament.[1–3] ILG supplies the important structures of the knee, *e.g.* the anterior and posterior cruciate ligaments, and the lateral meniscus. It is an important clinical landmark for the ligaments of posterolateral part of knee.[4,5] Post-operative hematoma due to the injury of artery can be significant during surgical interventions.[1,6]

Plantaris muscle (PM) originates from the lower part of supracondylar line and the oblique popliteal ligament. At the proximal part, it is fusiform in shape and descends as a long and slender tendon between gastrocnemius and soleus. PM can be double or absent in about 7.4–13% of the cases.[2,3,7] PM is supplied by lateral sural and popliteal arteries superficially and lateral superior genicular artery deeply.[2] No report has been encountered about variations regarding positional relation of the ILG with PM.[3]

Soleus origins from posterior aspect of fibular head, soleal line, 1/3 part of tibia and interosseous membrane. Together with gastrocnemius, they form the calcaneal tendon.[2] The cases with soleus attached to popliteus tendon is rare in literature.[3]

In this study, two cases with variative course of ILG and in one of these cases positional variation of soleus with the absence of PM were observed and evaluated regarding to clinical and developmental aspects.

Case Report

During dissection of the popliteal region of 10 formalin-fixed male cadavers with a mean age of 66.9±18.9 (range: 45 to 104) years in the Department of Anatomy, School of Medicine, Mersin University, Mersin, Turkey, posi-

tional variations of ILG, PM and soleus were encountered in two cases (ages of 54 and 68).

Case 1

During the dissection of popliteal fossa and posterolateral corner of the knee at the left lower extremity, PM was observed as completely covered by lateral head of gastrocnemius, and the muscle fibers started from deep surface of lateral head as a separate entity. Its width in the origin was 2.2 cm and length of its venter was 4.9 cm. PM tendon continued its normal form inferiorly. ILG, arising from the popliteal artery, ran laterally by passing superficial to the PM, instead of deep to it (**Figure 1a**). Then, ILG continued deep to fibular collateral and fabellofibular ligaments. ILG was passing between superficial and deep parts of arcuate popliteal ligament as usual. The artery gave small branches to the joint capsule, fibular head and continued along the lateral meniscus.

On the right side, PM was absent, but the origin of soleus was attached to the both of muscle-tendon junction of the popliteus and popliteofibular ligament (**Figure 1b**). Soleus then continued as its normal form below. No other variation was determined in the region.

Case 2

In the left lower extremity, PM was originating deep to lateral head of gastrocnemius and it was partially covered by that muscle. PM was exceeding 5 mm the medial margin of lateral head. Its width in the origin was measured as 1.5 cm and length of its venter was 9.1 cm. PM tendon was in a normal form towards below. ILG, emerging from the popliteal artery, was on the superficial surface of PM instead of deep to it (**Figure 1c**). Then, as normal, ILG passed deep to the fibular collateral, fabellofibular and between the two layers of arcuate popliteal ligaments. No variations related to those structures were seen on the right side and the attachment of soleus was normal.

Discussion

It has been previously reported that branching pattern of genicular arteries and their diameters are quite variable.[3,8] It was underlined that the preservation of vascu-

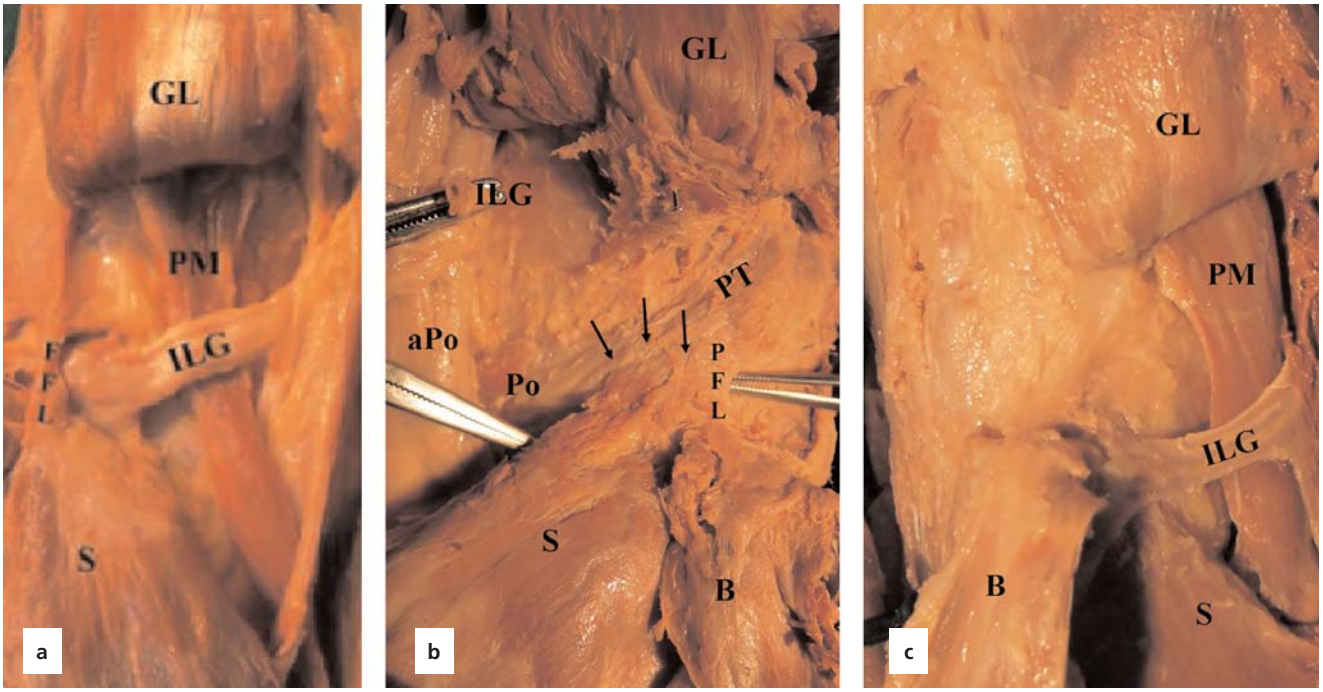

Figure 1. Posterolateral corner of the knees showing the positional variations of ILG and soleus. (**a**) ILG is running superficial to plantaris on the left side; (**b**) Soleus is attaching superiorly to the popliteus and popliteofibular ligament on the right; (**c**) ILG is running superficial to plantaris on the other knee. **aPo:** popliteal artery; **B:** biceps femoris (retracted inferiorly); **FFL:** fabellofibular ligament; **GL:** lateral head of gastrocnemius (retracted superiorly); **ILG:** inferior lateral genicular vessels; **PFL:** popliteofibular ligament; **PM:** plantaris; **Po:** popliteus; **PT:** popliteus tendon; **S:** soleus; **black arrows:** superiorly attached muscle fibers of soleus. [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

lar structures of the knee is essential in the recovery of surgical interventions such as the anterior cruciate ligament reconstruction, popliteal aneurysm repair and anterior horn meniscectomy of external meniscus.[8,9] The antero-proximal region of patellar tendon is maintained by ILG and it can be damaged during total knee arthroplasty and Hoffa's fat pad removal.[10] ILG can be unnoticed in posterolateral corner surgeries, but 3D images can be beneficial in understanding this region.[4] This vascular bundle is between superficial and deep parts of arcuate popliteal ligament. This placement is used as a guideline in the identification of ligamentous structures on posterolateral corner during surgery.[5] In our study, ILG passed from superficial surface of PM instead of deep surface in 2 out of 20 sides. A similar case has not been found in the literature.

It is known that at the early stages of embryonic development, femur articulates with the fibula and tibia. Then, the mesenchymal tissue including fibula and the attached lateral portion of the joint capsule shift inferior. At the end of that shift, the popliteus tendon attach to both distal femur and head of fibula and the fibular attachment is called as popliteofibular ligament.[11] Also, plantaris is reported to be a remnant of the superficial layer of the common flexors of the digits, and the soleus is suggested be a derivative of the lateral head of the gastrocnemius.[3] It seems that the popliteus, plantaris and soleus originate from the lateral portion of the embryonic mesenchymal tissues around the knee joint. Accordingly, variative relation of soleus, plantaris and popliteus can be associated with development of those three components. We suggest that in the absence of plantaris, attachment of the soleus to the popliteus and popliteofibular ligament can be the result of two possibilities in the early stages. Deviated fibers of plantaris can drift inferiorly and attach to the head of fibula instead of lateral condyle of femur and then fuse with the mass of soleus and popliteus, or there can be any deviation in the movement of soleus resulting into high origin of the muscle. Nevertheless, these suggestions need to be confirmed by studies with large series that evaluate the origin of soleus within the absence and presence of plantaris.

Freeman et al.[7] stated that PM is defined as normal form in 56%, varied form in 30.4% and absent in 13% of the cases. Unilateral absence of PM is reported to affect the main foot choice, therefore the leg with PM is likely to be chosen. In addition, the authors reported that absence of PM might also cause weakness in initiation of flexion movement in knee ankle, that laxity can be seen during medial and lateral rotations and related increase in primary ligament sprains which stabilize the knee. A congenital absence is reported to cause serious functional losses in sportive tasks in young people.

In another study, it was reported that removal of PM did not affect lower extremity functions when both soleus and gastrocnemius were present.[12] Tendon of this muscle is used successfully as a graft in flexor tendon replacements in hand and atrioventricular valve repair surgeries. While tears of PM can be the primary cause for unidentified lower extremity pain, it may not be distinguished by ultrasonography (USG) or magnetic resonance imaging (MRI).[12] On the other hand, we suggest that misplaced ILG, similar to our case, may cause misinterpretation of USG or MRI. It is also proposed that PM supports gastrocnemius activity.[2] Nevertheless, it should be investigated whether, in the absence of PM, the fibers of soleus anchoring to the popliteus tendon support the activity of gastrocnemius *via* this tendon or not.

Consequently, cases with ILG passing superficial to the PM should be kept in mind in the evaluation of posterolateral knee by MRI and USG. While any developmental and functional relations of the absence of PM with soleus anchoring to popliteus muscle have not been addressed previously, we suggest the possibility of such relations is worth investigating.

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Case Report

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anatomy
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A rare anastomotic artery between right and left common iliac arteries: iliac anastomotic artery

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Abstract

Congenital abdominal aortoiliac arterial abnormalities are not as common as aortic arch anomalies. Incidentally observed abdominal arterial and venous variations and anomalies are increasingly encountered due to widespread use of multislice CT for abdominal and vascular diseases. Knowledge of these variations or pathologies is crucial, especially before surgery to repair occlusive diseases, aneurysms and transplant surgeries, in order to reduce complications such as vascular injury and bleeding. Here we present an aortoiliac variation observed during abdominal CT examination of a 27-year-old female. This variation appeared as an anomalous arterial structure coursing obliquely and transversely between the right and left proximal common iliac arteries and binding them just below the bifurcation. Physicians should also be familiar with such a case, which appears as a triangular aortoiliac arterial window and which has only been reported in the old anatomical literature.

Keywords: anomaly; common iliac artery; variation

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Introduction

Congenital abdominal aortoiliac arterial variations are not as common as aortic arch anomalies.[1,2] Incidentally observed abdominal arterial and venous variations and anomalies are being encountered increasingly with the widespread use of multislice CT for abdominal and vascular diseases. Knowledge on these variations is crucial especially before surgeries to repair occlusive diseases, aneurysms, and transplant surgeries in order to reduce complications such as vascular injury and bleeding. Here we present an extremely rare common iliac artery variation observed during an abdominal CT examination.

Case Report

Abdominal CT examination of a 27 year old woman was performed in Gaziantep Dr. Ersin Arslan State Hospital with a 16 row multislice CT device (Siemens, Erlangen, Germany) and obtained in arterial phase for suspected renal artery stenosis. The patient was referred to Department of Radiology in School of Medicine, SANKO University, Gaziantep, Turkey. Renal arteries, bilateral adrenal glands and other abdominal organs were evaluated as normal. An anomalous arterial structure between the proximal common iliac arteries in the aortoiliac region was noticed (**Figure 1**). This appeared as an anastomotic artery coursing obliquely and transversely between right and left proximal common iliac arteries, connecting them just below the bifurcation and causing an appearance of a triangular aortoiliac arterial window. The bifurcation was at L4–L5 disc level as usual, the iliac bifurcation angle was measured as 24°, narrower than expected. There were no atherosclerotic plaques, aneurysm, stenosis or other accompanying variations or pathologies. Other abdominal and pelvic arte-

This study was presented at XXIV International Symposium on Morphological Sciences, 2–6 September, 2015, Istanbul, Turkey.

rial and venous structures were normal. The images were final at the level of internal-external iliac bifurcation. The patient had no signs of limb ischemia or claudication, so we did not perform any other CT study not to expose the patient to further ionizing radiation. The arterial system of both limbs was normal in Doppler sonography examination.

Discussion

Congenital malformations of the iliac bifurcation and iliac arteries are seldom encountered in man. In a previous study including 8000 angiograms, only 6 cases of aortoiliac and iliofemoral variations were found.[2] Besides the origin, angulation, course, length, diameter and branching variability, the described anomalies associated with the common iliac artery include its congenital absence or hypoplasia and the persistent sciatic artery.[3–9] The absence of common iliac artery in most of mammals is a normal pattern. On the contrary, absence of common iliac artery in humans has only been described in a few isolated case reports.[10–15]

Although a very rare anomaly, the persistent sciatic artery is also a well-known entity. As a branch of the umbilical artery, the earliest fetal blood supply to the developing lower extremity, it persists in the adult and is associated with a high incidence rate of complications that include aneurysm formation, embolism and nerve compression.[12,14] Based on angiograms, the incidence of persistant sciatic artery has been reported as 0.025% to 0.04%, and it is concluded that the persistent sciatic artery is a branch of the internal iliac artery and can occasionally originate from common iliac artery.[16]

According to the classical textbooks the common iliac artery in adults does not give any substantial branch.[6] In a large series of cadavers, only 35% had at least one lateral branch of common iliac artery.[3] However, it is known that common iliac artery sends small branches to the peritoneum, psoas major, ureter, adjacent nerves and surrounding areolar tissue. The common iliac artery occasionally gives rise to the iliolumbar artery and accessory or replaced renal arteries if the kidney is ectopic.[6,11] Initially, the renal arteries are branches of common iliac arteries, later the kidneys receive their blood supply from the aorta.[17]

Embryological development of aorta is formed during the third week of gestation. Two pairs of aortas are present at this stage. The dorsal aortas unite to form the descending aorta that passes the length of the embryo with 3 mm crown-heal length.[10] The abdominal part of aorta has five posterolateral intersegmental (lumbar) branches. The lumbar arteries remain segmental arteries, but the more important fifth artery forms the main artery for the leg, the common iliac artery. Caudal to the fifth lumbal artery, the aorta regresses to the small median sacral artery. At the embryo stage of crown-heal length of 10 mm, several side branches of the fifth lumbar artery can readily be identified: external iliac, sciatic, superior gluteal and internal pudendal arteries. One of these, the sciatic artery is the main artery of the lower extremity.[5–7,12,17] The umbilical arteries are one of the paired ventral branches of fetal abdominal aorta. They are much larger than all other brunches of aorta and remain paired vessels. Longitudinal anastomoses to the fifth lumbar artery develop and initial aortic origins disappear.[12]

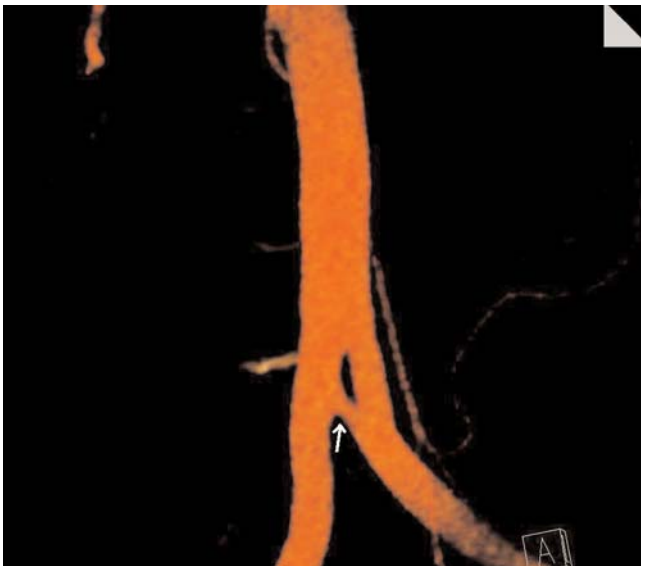

Figure 1. Coronal colored maximum intensity projection (MIP) image demonstrates an anomalous anastomotic artery between proximal common iliac arteries (**arrow**). [Color figure can be viewed in the online issue, which is available at www.anatomy.org.tr]

This anomaly in our case may be due to incomplete coalescence of the distal parts of dorsal aorta pairs, or a possible persisting transverse anastomosis between the umbilical arteries during the development of longitudinal connections to the fifth lumbar artery.

The classical works on arterial variations never describe such a variant.[6,10,12] An anatomic abnormality similar to our case has only been reported in the old anatomical literature.[11] To our knowledge, this is the first radiologic anatomic report of this extremely rare anomaly between two common iliac arteries. Physicians

should be familiar with such a case, and consideration of such arterial variation may provide better outcomes in retroperitoneal surgeries, in the placement of large access catheters and devices used for interventions.

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Book Review

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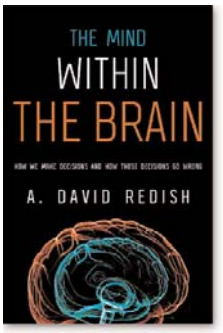
The Mind Within the Brain: How We Make Decisions and How Those Decisions Go Wrong



***by* David Redish**

Hard cover, 23.4x3.3x16.5 cm, 377 pages, ISBN: 978-1118570708; Oxford University Press, 2013

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"Your brain is a decision-making machine, a complex but physical thing. Like any physical process, there are multiple ways in which decisions can go wrong. Being a physical being does not diminish who you are, but it can explain some of the irrational choices you make." As in this quote from the chapter *The Tale of the Thermostat*, this book details the science behind decision-making in humans, and claims that understanding how the human decision-making works has enormous implications for understanding who we are, what we do, and why we do what we do.

The author A. David Reddish is a distinguished McKnight University Professor in Neuroscience at the University of Minnesota, Twin Cities, USA with expertise on behavior, decision-making and information processing in neural systems.

With an easily readable style, and including personal studies and humor, the author A. David Redish makes the difficult concepts in decision making understandable. The book focuses on how we make decisions, and what is known about how that decision-making can fail under certain conditions to explain irrationality, addiction, and other strange behavior.

The Mind Within the Brain is infour sections: "Decisions and the brain", "Decision making systems", "Brain with a mind of its own" and "The human condition." The first section begins with Redish's basic definition of a decision: "the selection of actions, and explains how are values are determined by multiple interacting systems. The brain is compared to a complex decision-making machine based on negative feedback.The second section focuses on four action-selection systems in decision-making system - reflexive, Pavlovian, deliberative, and procedural, and four support systems – taking physical action, perception, situation-recognition and motivation. Redish claims that some decisions are made by emotional (Pavlovian) systems, while others are reactive action-chains (procedural), and others taken only after extensive consideration of the options (deliberative) is that each of these systems has advantages and disadvantages. And if you can steer yourself from one system to another at the right time, you can improve your decision-making. The third section *'The Brain with a Mind of its Own'* explores the consequences of the physical nature of the brain and how mind and brain are related, and dysfunctions in decision making such as addiction and gambling. The fourth section deals with the philosophical questions of what makes us human, morality and free-will.

This book is s clear and concise discussion of what we currently know about brain processes involved in decision making. Clearly written and not too technical, *The Mind Within the Brain* answers a lot of questions about our decision making and offers fresh insight into one of the most complex aspects of human behavior.

***Review by* Gülgün Şengül**
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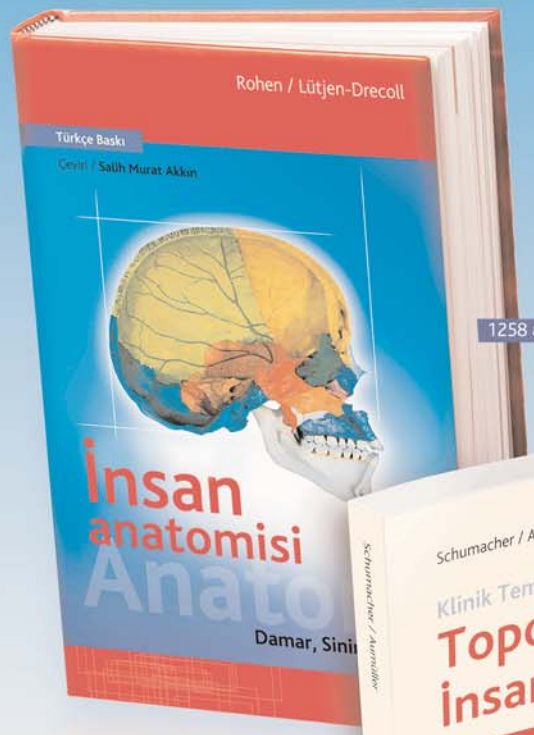

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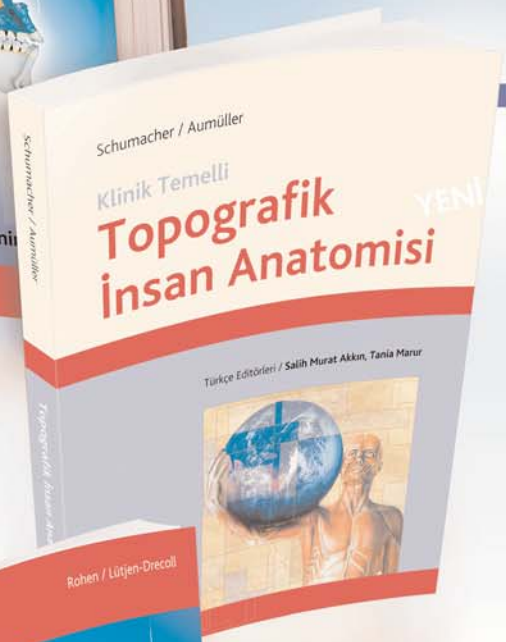

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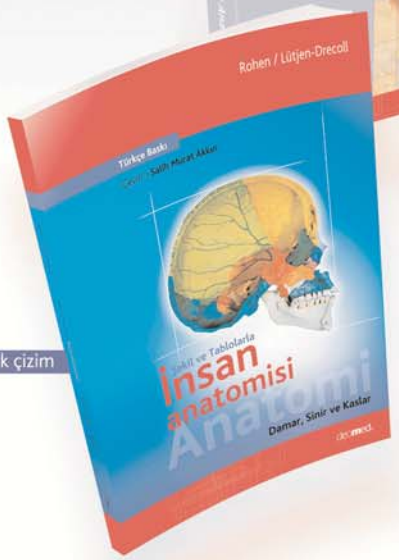

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