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ARAŞTIRMA / RESEARCH

Quantitative assessment of visceral and subcutaneous fat with hepatosteatosis by computed tomography in metabolic syndrome

Metabolik sendromda visseral ve subkutan yağ miktari ve hepatosteatozun bilgisayarli tomografi ile kantitatif değerlendirilmesi

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Abstract

Purpose: We aimed to evaluate visceral and subcutaneous fat tissue and its association with hepatosteatosis on computed tomography (CT) scans to determine cut-off criteria for metabolic syndrome, measure abdominal obesity directly based on the visceral fat tissue area (VFTA) rather than indirectly based on waist circumference and obtain supportive findings by density measurements in addition to the VFTA measurements.
Materials and Methods: The Hounsfield unit (HU) values, visceral, subcutaneous fat areas and HU values of 108 patients diagnosed with metabolic syndrome (MS) were determined according to the National Cholesterol Education Program Adult Treatment Panel III 2001 Criteria by retrospectively analyzing their abdominal CT images taken for various reasons. The relationships of the obtained values with each other and to MS were evaluated.
Results: The strongest predictor of MS was VFTA, and 156.47 cm² was the most significant value with 74.1% sensitivity and 58.6% specificity. An HU value of -102.99 for visceral fat tissue density (VFTD) was found as the second most significant finding with 75% sensitivity and 57.6% specificity. The VFTA values of the patients with hepatosteatosis were higher, and increased VFTA values were associated with lower VFTD values.
Conclusion: The most important supportive finding was the demonstration of the possibility of measuring abdominal obesity, which has an important place among criteria, directly by measuring VFTA, rather than indirectly based on waist circumference.
Keywords:. Metabolic syndrome, computed tomography, hepatosteatosis, visceral fat tissue.

Öz

Amaç: Bu çalışmada, metabolik sendrom hastalarında bilgisayarlı tomografi ile visseral ve subkutan yağlı doku alanı, dansitesi ve karaciğer yağlanmasında eşik değerleri elde etmek, metabolik sendromla vücut yağ dağılımı ve hepatosteatoz ilişkisini değerlendirmek amaçlandı .
Gereç ve Yöntem: Çeşitli nedenlerle çekilmiş kontrastsız abdomen bilgisayarlı tomografi (BT) görüntüleri retrospektif olarak taranıp National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII)-2001 kriterlerine göre Metabolik sendrom tanılı 108 hastanın karaciğere yönelik Hounsfield Unit (HU) değeri, visseral, subkutan yağ doku alanı ve HU değerleri, Osirix Dicom Viewer programı ile belirlendi. Elde edilen değerlerin birbiri ve metabolik sendromla ilişkisi değerlendirildi.
Bulgular: En güçlü prediktör visseral yağlı doku alanı (VYDA) bulunmuş olup 156.47 cm² değerinin %74.1 sensitivite ve %58.6 spesifiteye sahip en anlamlı değer olduğu saptanmıştır. Ayrıca visseral yağlı doku dansitesi (VYDD) için -102.99 HU değeri %75 sensitivite, %57.6 spesifite ile ikinci en önemli bulgu olarak saptanmıştır. Hepatosteatoz saptanan hastalarda VYDA'nın daha fazla olduğu ve VYDA artışı ile birlikte VYDD'nin de daha düşük dansitede ölçüldüğü saptanmıştır.
Sonuç: En önemli destekleyici bulgu: kriterler içinde en önemli yere sahip olan abdominal obezitenin indirek olarak bel çevresi ile değil direk olarak visseral yağlı doku alanının ölçülebilmesi ile gösterilmesi olmuştur.

Anahtar kelimeler: Metabolik sendrom, bilgisayarlı tomografi, hepatosteatoz, visseral yağlı doku.

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INTRODUCTION

For the first time in 1988, Reaven pointed out that various risk factors can often be found together, and this combination, which was called syndrome X (metabolic syndrome, MS), increased the risk of developing cardiovascular diseases. The main components of MS are abdominal obesity, impaired glucose metabolism, increased blood pressure, and dyslipidemia. Studies on the main sources of the pathogenesis of MS, which have a very wide range, have mainly focused on insulin resistance and hyperinsulinemia. In a study on MS, it was revealed that there was a disorder in the response of tissues to insulin, beta cells of the pancreas secreted excessive amounts of insulin due to insulin resistance, and eventually, hyperinsulinemia developed. Accordingly, hypertension, dyslipidemia, obesity and diabetes form the components of MS by originating from insulin resistance and hyperinsulinemia[1].

The clinical implications of MS are diabetes, essential hypertension, abdominal obesity, osteoporosis, polycystic ovary syndrome, dyslipidemia, hypercoagulability, hyperuricemia, fatty liver disease, and sleep apnea[2]. Abdominal obesity includes both subcutaneous and visceral fat. Sex hormones in male and female individuals induce fat tissue accumulation in different areas of the body. The measurement of waist circumference (WC) has been thought to be an imprecise method in determining the degree and amount of visceral fat. WC is composed of both subcutaneous and visceral fat, while visceral fat is much more closely related to MS. Visceral fat is located in the abdominal cavity and packed in between organs[3].

Visceral fat can be measured and evaluated using several techniques, including WC measurements, abdominal sonography, CT and magnetic resonance imaging (MRI), or bioelectrical impedance analysis. CT and MRI are optimal techniques for the accurate assessment of intraabdominal fat[3].

Considering today's point of view that started to shape after Ludwig defined its histopathological findings as Nonalcoholic Steatohepatitis (NASH) in 1980, fatty liver disease is a disease that is observed in people who do not consume alcohol even though this disease resembles alcoholic liver disease. This definition contains some subgroups as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis. NAFLD is considered an important marker of insulin resistance. According to recent evidence, NAFLD is associated with many systemic diseases such as visceral obesity, cardiovascular diseases, type 2 diabetes mellitus, and metabolic syndrome[4].

This study aimed to measure visceral and subcutaneous fat tissue areas and density values, identify a threshold based on the obtained values for MS, determine whether there was a significant difference between patients with and without hepatosteatosis in terms of their data, obtain supportive findings for the diagnosis of MS according to the threshold determined by unenhanced CT images, and use it as a cardiovascular risk marker in patient groups with MS diagnosis.

MATERIALS AND METHODS

This study was conducted retrospectively after obtaining approval from the Clinical Research Ethics Committee at Abant İzzet Baysal University with the decision numbered 2013/60 and selecting patients who were examined with unenhanced abdomen CT images for any reason between 1 January 2008 and 31 December 2012 in a tertiary hospital by using the hospital's picture archiving and communication system (PACS). Patients who were diagnosed with MS according to the National Cholesterol Education Program Adult Treatment Panel III 2001 (NCEP ATP III-2001) criteria were included in the patient group, while patients who were not diagnosed with MS were chosen randomly, forming the control group. Verbal and written informed consent was obtained from the participants. The power analysis showed that a sample size of 141 patients was sufficient to determine the significance of the correlation with a Cohen's effect size of d=0.6, a type I error of 5% and a power of 80%.

Diagnostic criteria for metabolic syndrome according to NCEP ATP III-2001

1. Abdominal obesity (waist circumference: >102 cm in males, >88 cm in females)
2. Hypertriglyceridemia (≥150 mg/dl)
3. Low HDL (<40 mg/dl in males, <50 mg/dl in females)
4. Hypertension (blood pressure ≥130/85 mmHg)

5. Hyperglycemia (fasting blood glucose ≥110mg/dl)

CT images had been taken with a two-detector CT device (Siemens Somatom Emotion Duo, 2001, Germany). The images were obtained in the supine position, in a way that the entire liver and the bottom of the bladder were included in the image without the administration of oral or intravenous contrast material, in a transverse plane, with sections of 5 mm thickness, with the settings of 110 kilowatt (kV) and 70 milliamp seconds (mAs).

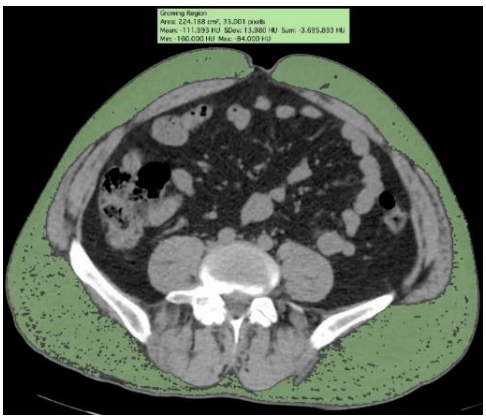

Figure 1. Measurement of subcutaneous fat area and density

Measurements

Subcutaneous and visceral fat tissue area and Hounsfield unit (HU) measurements were performed on a single cross-section passing through the L3-L4 vertebrae[5]. The attenuation values for subcutaneous fat tissue area and visceral fat tissue area were determined as -30 and -190, respectively. and the measurement was made by the 2D growing Region of Interest (ROI) technique.

This technique performs a density measurement in a vast area by marking other equivalent density pixels in the same cross-section in the range appropriate for the pixel density of a selected point. With this technique, both the area and the HU value of the same region were determined at the same time[6,7] (Figure 1,2). Hepatosteatosis was diagnosed when the parenchymal density of the liver was lower than 40 HU alone, or when the parenchymal density of the liver created a difference of at least 10 HU or more than the spleen parenchyma[8].

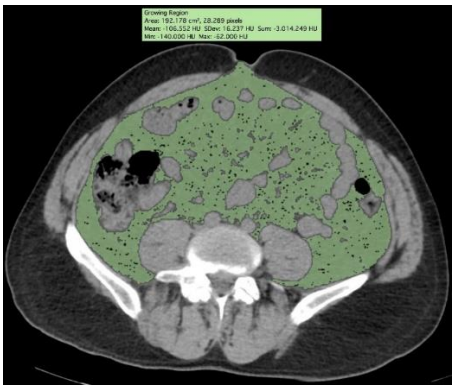

Figure 2. Measurement of visceral fat area and density.

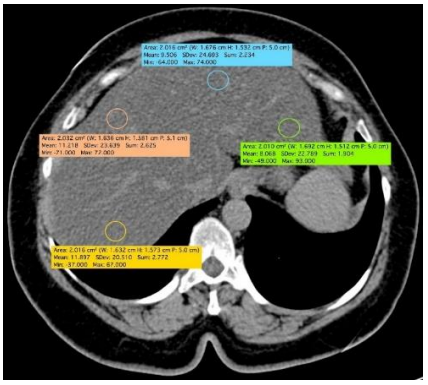

Figure 2. Measurement of liver density from 4 segments

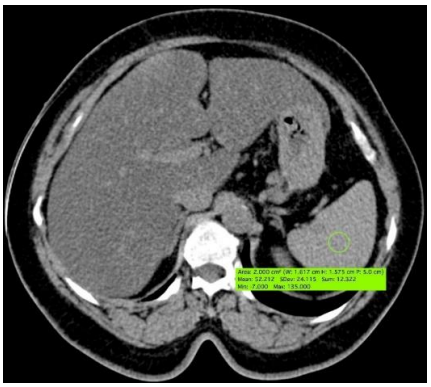

Figure 3. Measurement of spleen density

In this study, the liver parenchymal density was considered to be below 40 HU for the diagnosis. For values determined at the border (i.e., 39, 40 HU), hepatosteatosis was radiologically diagnosed based on whether it met the criterion of a 10 HU difference between the liver parenchyma and the spleen parenchyma. The ROI area for the liver and spleen

was determined as 2±0.1 cm². Measurements were performed in every anatomical region away from the intraparenchymal main vascular structure and from the central area inside the related region at the anterior and posterior of the right lobe of the liver, as well as the medial and lateral segments of the left lobe (Figure 3). Measurements were made in the spleen parenchyma from the central area with a single ROI (Figure 4). All measurements were performed using OsiriX DICOM Viewer version 3.6. by one radiologist (M.M.A.) with 7 years of experience in abdominal radiology.Patients who did not have abdominal CT images, those who had Hepatitis B, Hepatitis C, those who had a known malignancy, those who received or were receiving chemotherapy, those who had diseases that could diffusely affect the liver parenchyma, those who had chronic alcohol use and those with a history of abdominal surgery were excluded from this study even though they met the metabolic syndrome criteria in the screening performed in the hospital's information system.

Statistical analysis

The statistical analyses were carried out using the SPSS (Statistical Package for the Social Sciences, 20.0) package program. The descriptive statistics are presented as mean ± standard deviation. Student's t-test was used to compare the measurement of the continuous variables and evaluate data of the groups with and without metabolic syndrome. Mann-Whitney U-test and Student's t-test were applied in the pairwise comparisons of the control group and the subgroups of patients with metabolic syndrome. The correlations of visceral fat density, visceral fat area, subcutaneous fat density, subcutaneous fat area, hepatosteatosis were investigated by Spearman's correlation test. ROC curve analysis was also performed. The value of $p<0.05$ was considered statistically significant.

RESULTS

The sample of the study consisted of 108 patients diagnosed with MS and 33 patients who formed the control group. The demographic data of the patients are shown in Table 1. There was no statistically significant difference between the patient and control groups in terms of their age ($p>0.05$) and sex ($p=0.42$) distributions (Table 1).The mean visceral and subcutaneous fat tissue area and density values of the patient and control groups are shown in Table 2.

Table 1. Age and sex distribution

	Metabolic syndrome group		Control Group	
	Frequency (%)	Mean age (year)	Frequency (%)	Mean age (year)
Female	61 (56.5%)	61.73±13.29	16 (48.5%)	45±19.09
Male	47 (43.5%)	56.19±12.37	17 (51.5%)	60.29±11.43
TOTAL	108	59.32±13.3	33	52.87±15.07

Table 2. Mean VFT and SFT area and density of the groups

	Metabolic syndrome group	Control Group
VFTA (cm²)	196.04±67.85	135.27±69.61
VFTD (HU)	-98.77±5.62	-101.11±11.32
SFTA (cm²)	300.62±116.77	240.87±123.99
SFTD (HU)	-102.60±6.03	-99.42±7.35

VFTA: Visceral Fat tissue Area, VFTD: Visceral Fat tissue Density, SFTA: Subcutaneous Fat tissue Area, SFTD: Subcutaneous Fat tissue Density

According to the ROC curve analysis of factors that could predict MS, the most significant predictor of MS was VFTA. In terms of VFTA, a cut-off value of 156.47 cm² was the most significant value with 74.1% sensitivity and 58.6% specificity. Additionally, for VFTD, a HU value of -102.99 was found the most significant cut-off value with 75% sensitivity and 57.6% specificity ($p=0.03$). A cut-off value of 238.71 cm² was the most significant for SFTA with 69.4% sensitivity and 48.5% specificity ($p=0.00$), while this value for SFTD was a HU value of -102.91 with 40.7% sensitivity and 27.3% specificity ($p=0.00$) (Table 3).

Table 3. ROC values

	AUC	CI	p
VFTA (cm^2)	0.716	0.616-0.816	0.000
VFTD (HU)	0.619	0.486-0.752	0.039
SFTA (cm^2)	0.656	0.546-0.766	0.007
SFTD (HU)	0.339	0.220-0.458	0.005

VFTA: Visceral Fat tissue Area, VFTD: Visceral Fat tissue Density, SFTA: Subcutaneous Fat tissue Area, SFTD: Subcutaneous Fat tissue Density

Table 4. Relationships among hepatosteatosis and VFTA, VFTD, SFTA and SFTD values of the groups.

	Metabolic syndrome group				Control Group		
	Hepatosteatosis (+)	Hepatosteatosis (-)	p		Hepatosteatosis (+)	Hepatosteatosis (-)	p
VFTD (HU)	-101.08	-98.17	0.009		-107.93	-99.60	0.058
VFTA (cm^2)	245.56	183.37	0.000		151.61	121.14	0.002
SFTD (HU)	-103.08	-102.47	0.576		-104.21	-98.36	0.060
SFTA (cm^2)	298.72	301.11	0.912		170.22	91.64	0.067

VFTA: Visceral Fat tissue Area, VFTD: Visceral Fat tissue Density, SFTA: Subcutaneous Fat tissue Area, SFTD: Subcutaneous Fat tissue Density

Table 5. Correlation values

Metabolic syndrome group	**VFTD (HU)**	**VFTA (cm^2)**	**SFTA (cm^2)**	**SFTD (HU)**	**Waist circumference**	**Hepatosteatosis**
VFTD (HU)	-	-0.58**	-0.09	-0.46**	-0.22*	- 0.20*
VFTA (cm^2)	-0.58**	-	0.07	0.07	0.50**	0.35**
SFTA (cm^2)	-0.09	0.07	-	-0.24**	0.75	0.02
SFTD (HU)	-0.46**	0.07	-0.24**	-	-0.05	-0.01
Waist circumference	-0.22*	0.50**	0.75**	-0.05	-	0.22*
Hepatosteatosis	-0.20*	0.35**	0.02	0.01	0.22*	-
Control group	VFTD (HU)	VFTA (cm^2)	SFTA (cm^2)	SFTD (HU)	Waist circumference	Hepatosteatosis
VFTD (HU)	-	-0.37*	-0.22	0.18	-0.32	-0.36*
VFTA (cm^2)	-0.37*	-	0.47**	-0.31	0.67**	0.44**
SFTA (cm^2)	-0.22	0.47**	-	-0.53**	0.77**	0.42*
SFTD (HU)	0.18	-0.31	-0.53*	-	-0.33	-0.36*
Waist circumference	-0.32	0.67**	0.77**	-0.33	-	0.29
Hepatosteatosis	-0.36*	0.44**	0.42*	-0.36	0.29	-

VFTA: Visceral Fat tissue Area, VFTD: Visceral Fat tissue Density, SFTA: Subcutaneous Fat tissue Area, SFTD: Subcutaneous Fat tissue Density; ** p:0.01; * p:0.05

There was a significant positive correlation between hepatosteatosis and waist circumference in the patient group (p=0.02). There was no significant correlation between hepatosteatosis and waist circumference in the control group (p>0.05) (Tables 4 and 5). There was a significant positive correlation between hepatosteatosis and VFTA in the patient group (p:0.00). VFTA was higher in the patients with hepatosteatosis. In the control group, there was also a significant positive correlation between hepatosteatosis and VFTA (p=0.00) (Tables 4 and 5).

There was a significant negative correlation between hepatosteatosis and VFTD in the patient and control groups (p=0.03 and p=0.03, respectively). The VFTD values of the patients with hepatosteatosis were lower (Tables 4 and 5).

There was no statistically significant difference between patients with and without hepatosteatosis in terms of their SFTA and SFTD values in the patient group (p>0.05). There was also no statistically significant difference between the patients with and

without hepatosteatosis in terms of SFTA and SFTD in the control group (p>0.05) (Tables 4 and 5).

In the patient group, there was a statistically significant negative correlation between waist circumference and VFTD (p=0.02). VFTD was higher in the patients with greater waist circumference values. Moreover, waist circumference increased as VFTA increased (p=0.00) (Tables 4 and 5). There was a significant positive correlation between waist circumference and SFTA in the patient group (p=0.00). Waist circumference increased as SFTA increased (Tables 4 and 5). There was a significant positive correlation between waist circumference and the parameters of VFTA and SFTA in the control group (p=0.00). In the control group, there was no significant correlation between waist circumference and the parameters of VFTD and SFTD (p>0.05 and p>0.05, respectively) (Table 4 and 5). A significant negative correlation was also found between VFTA and VFTD. VFTD decreased as VFTA increased (Tables 4 and 5).When patients with hepatosteatosis in the metabolic syndrome group were compared in terms of their liver segmental fat deposition, there was no statistically significant difference in the liver's right lobe anterior segment, left lobe posterior segment, left lobe medial segment, or left lobe lateral segment (p>0.05). However, when the group was divided into two subgroups as female and male patients, there was a significant difference in the fat deposition values in these four areas. The fat deposition amounts were significantly higher in the male patients in the liver's right lobe posterior segment (p:0.04). There was no statistically significant difference in females.

DISCUSSION

Factors such as higher levels of education and income, change in eating habits, control of contagious diseases across the world have led to an increase in the expected lifespan of a person. Although a longer lifespan is desired, it has increased the prevalence of non-communicable diseases. Cardiovascular diseases come to the fore among such diseases[9]. Metabolic syndrome is known to increase the risk of developing cardiovascular diseases[10]. Considering the increased waist circumference with obesity and the body mass index within the MS criteria, the prevalence of this syndrome increases due to an increase in the fat tissue. The most important reason for an increase in WC is considered to be an increase in visceral fat tissue[11,12,13]. Previous studies have found that an increase in VFTA is significant in terms of MS and cardiovascular risk factors[10,11,14]. This study found that a VFTA value of above 156.47 cm^2 was the most significant predisposing factor for metabolic syndrome with 74.1% sensitivity and 58.6% specificity.

Increased WC and increased VFTA are correlated with lower HU values of visceral fat tissue, excessive amounts of free fatty acids that come with nutrition, fat accumulation in adipocytes, increased cell volume, and hypertrophy, affecting cell function, which are commonly known as cardiometabolic risk factors[15]. This is explained by the negative relationship of these variables to adipocyte volumes, insulin sensitivity, and adiponectin secretion[16].

The study conducted by Rytka et al. on rats revealed that free fatty acids from visceral fat tissue cause hepatosteatosis as a result of the excessive flow of adipocytokines to the liver through the portal venous system under the effects of autocrine and paracrine signaling, resulting in hepatosteatosis due to the development of insulin resistance according to the portal theory[17]. Nakajima et al. reported that increases in VFTA and lower HU values resulted from excessive lipid deposition, and as a result of this deposition, an increase was observed in the amount of fat stored as an energy surplus in visceral fat tissue[18]. In this study, it was observed that as the number of patients with hepatosteatosis increased in the MS patient group, the WC of these patients increased. There was also an increase in VFTA in these patients, and as VFTA increased, VFTD decreased. In this study, an HU value of -102.99 was the second most significant predisposing factor regarding VFTD with 75% sensitivity and 57.6% specificity.

Considering all patients with MS diagnosis, it was understood that the increase in the VFTA was higher in patients with hepatosteatosis, and VFTD was lower in these patients[16,19]. Additionally, in the MS patients with hepatosteatosis, liver segmental fat depositions were higher in the male patients in the right lobe posterior, while they were not different in the female patients. D. Mathieu et al. explained their finding that geographic steatosis was present only in the right lobe in some patients with their hypothesis that lipogenic nutritional factors in the blood carried by the superior mesenteric vein are predominantly distributed in the right lobe of the liver[15].

There was no significant difference in the

subcutaneous fat tissue area and density values when the groups were divided in two as patient groups with and without hepatosteatosis. This suggested that subcutaneous fat tissue does not have an effect on the pathogenesis of hepatosteatosis. Like our study, İdilman et al. did not find a significant relationship between subcutaneous adipose tissue and hepatosteatosis grade, nonalcoholic fatty liver disease activity score, or hepatic fibrosis[20].

Accordingly, VFTA is a significant risk factor for MS. Therefore, it is possible to measure VFTA and VFTD noninvasively in patients diagnosed with MS whose unenhanced CT images taken for any reason are available and comment on whether this group of patients has a predisposition to cardiometabolic risk.

The most important supportive finding in this study was that abdominal obesity, which has an important place among the criteria of MS, was shown directly by being able to measure VFTA, as opposed to its indirect measurement based on waist circumference. This result was supportive for many publications in the literature. The VFTA cut-off value of 156.47 cm^2 that was identified in this study can be indicated as an additional factor that is highly significant as a MS criterion with 74.1% sensitivity and 58.6% specificity. Accordingly, VFTA values higher than this cut-off value may indicate a risk factor for MS. Additionally, it is possible to obtain supportive findings for risk factors by density measurements while making VFTA measurements. Approaches to reducing VFTA can prevent the development of cardiovascular diseases. For this purpose, lifestyle changes, drug treatments and obesity surgeries can be considered.

Patients whose applicable MS diagnostic criteria were not found due to deficiencies in the hospital information system were excluded from the study. Therefore, the number of patients forming the sample cannot reflect the actual incidence of metabolic syndrome.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ED, MMA, ZC; Veri toplama: MMA, ZC; Veri analizi ve yorumlama: ED, MMA, ZC; Yazı taslağı: MMA; İçeriğin eleştirel incelenmesi: ED, ZC; Son onay ve sorumluluk: MMA, ED, ZC; Teknik ve malzeme desteği: MMA, ZC; Süpervizyon: ED, MMA, ZC; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Abant İzzet Baysal Üniversitesi Klink Araştırmalar Etik Kurulundan 25.04.2013 tarih ve 2013/60 sayılı kararı ile etik onay alınmıştır.
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Author Contributions: Concept/Design : ED, MMA, ZC; Data acquisition: MMA, ZC; Data analysis and interpretation: ED, MMA, ZC; Drafting manuscript: MMA; Critical revision of manuscript: ED, ZC; Final approval and accountability: MMA, ED, ZC; Technical or material support: MMA, ZC; Supervision: ED, MMA, ZC; Securing funding (if available): n/a.
Ethical Approval: For this study, ethical approval was obtained from Abant Izzet Baysal University Klink Research Ethics Committee with the decision dated 25.04.2013 and numbered 2013/60.
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