ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/cardiosci.2022-92530

Hemoglobin A1c is a Predictor of Poor Collateral Development in Non-Diabetic Patients with Coronary Chronic Total Occlusion: Retrospective Clinical Trial

Hemoglobin A1c, Koroner Kronik Total Oklüzyonu Olan Diyabetik Olmayan Hastalarda Zayıf Kollateral Gelişiminin Bir Prediktörüdür: Retrospektif Klinik Çalışma

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ABSTRACT Objective: Collateral circulation plays an important role for the nutrition of the myocardium in the region of chronic total occlusion (CTO), and affects clinical prognosis. It has been accepted that increased hemoglobin A1c (HbA1c) is a risk factor for cardiovascular events and subclinical atherosclerosis in individuals without diabetes mellitus. In this study, we aimed to reveal the effect of HbA1c level on coronary collateral development in the non-diabetic adult population with CTO. **Material and Methods:** The study included 208 non-diabetic patients out of 487 patients diagnosed with CTO on coronary angiography between March 2014 and January 2019. The patients were classified into two groups based on the Rentrop classification. Group 1 (Rentrop 0-1) (poor collateral) (90 patients) and Group 2 (Rentrop 2-3) (good collateral) (118 patients). This is a retrospective analysis. **Results:** The two groups were similar in terms of male gender, age, hypertension and previous history of myocardial infarction (78.9% vs. 75.4%, p=0.557; 58.9±9.9 vs. 60.8±11.2, p=0.194; 26.7% vs. 33.0%, p=0.321; and 18.9% vs. 12.7%, p=0.221; respectively). HbA1c value was statistically higher in Group 1 (5.85±0.45) than in Group 2 (5.22±0.84) (p<0.001). The ideal HbA1c cut-off value was 5.65 that was calculated by the Youden index had 77% sensitivity, and 75% specificity (Receiver operating characteristic area under curve: 0.780, 95% confidence interval: 0.717-0.844, p<0.001) for poor collateral development of CTO. **Conclusion:** HbA1c is a parameter that affects coronary collateral development even in non-diabetic patients. In non-diabetic patients with CTO, high HbA1c levels correlate with poor collateral development.

Keywords: Chronic total occlusion; collateral development; coronary artery disease; hemoglobin A1c

ÖZET Amaç: Kollateral dolaşım, kronik total oklüzyon (KTO) bölgesindeki miyokardın beslenmesinde önemli bir rol oynar ve klinik prognozu etkiler. Diabetes mellitusu olmayan bireylerde artan hemoglobin A1c (HbA1c) düzeylerinin kardiyovasküler olaylar ve subklinik ateroskleroz için risk faktörü olduğu kabul edilmiştir. Bu çalışmada, KTO tespit edilen diyabetik olmayan erişkin popülasyondaki HbA1c seviyesinin kollateral gelişimine etkisini öğrenmeyi amaçladık. **Gereç ve Yöntemler:** Çalışmaya Mart 2014-Ocak 2019 arasında koroner anjiyografide KTO tanısı konulan 487 hastadan diyabetik olmayan 208 hasta dâhil edildi. Hastalar Rentrop sınıflamasına göre 2 gruba ayrıldı: Grup 1 (Rentrop 0-1) (kötü kollateral) (90 hasta) ve Grup 2 (Rentrop 2-3) (iyi kollateral) (118 hasta). Bu bir retrospektif analizdir. **Bulgular:** İki grup yaş, erkek cinsiyet, hipertansiyon ve geçirilmiş miyokard infarktüsü öyküsü açısından benzerdi (sırasıyla %78,9'a karşı %75,4, p=0,557; 58,9±9,9'a karşı 60,8±11,2, p=0,194; %26,7'ye karşı %33,0, p=0,321 ve %18,9'a karşı %12,7, p=0,221). HbA1c değeri Grup 1'de (5,85±0,45) Grup 2'den (5,22±0,84) istatistiksel olarak anlamlı derecede daha yüksekti (p<0,001). Youden indeksi ile hesaplanan ideal HbA1c eşik değeri 5,65 saptandı ve %77 duyarlılık ve %75 özgüllük (eğri altındaki alıcı çalışma karakteristiği alanı: 0,780, %95 güven aralığı: 0,717-0,844, p<0,001) ile KTO'da zayıf kollateral gelişimi için bir öngördürücü faktör olarak saptandı. **Sonuç:** HbA1c, diyabetik olmayan hastalarda dâhi koroner kollateral gelişimini etkileyen bir parametredir. KTO'su olan diyabetik olmayan hastalarda yüksek HbA1c düzeyi zayıf kollateral gelişimi ile ilişkilidir.

Anahtar Kelimeler: Kronik total oklüzyon; kollateral gelişim; koroner arter hastalığı; hemoglobin A1c

Chronic total occlusion (CTO) is a type of macrovascular disease that occurs due to severe coronary artery disease (CAD) and late atherosclerotic lesions.[1] However, coronary collateral circulation (CCC), is a type of microcirculation, plays an important role in the nutrition of the myocardium in CTO

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Peer review under responsibility of Turkiye Klinikleri Cardiovascular Sciences.

Received: 16 Jul 2022 ***Received in revised form:*** 13 Aug 2022 ***Accepted:*** 15 Aug 2022 ***Available online:*** 22 Aug 2022

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localization and has an impact on clinical prognosis. Coronary collateral formation is the primary determinant of myocardial injury severity and mortality after coronary artery obstruction.[2] Although these collaterals do not restore coronary blood flow to normal physiologic levels, well-developed coronary collaterals may partially supply the distal perfusion area via arteriolar junction. Thus, it can prevent or reduce myocardial ischemia, preserve left ventricular function, and even reduce mortality.[3,4]

In Type 2 diabetes mellitus (DM), diffuse coronary atherosclerosis limits collateral vessel growth and function by reducing the pressure gradient between the coronary and collateral arteries. The interaction between advanced glycation end products (AGEs) and their receptors increases oxidative stress and exacerbates the inflammatory process.[2] Previous studies have shown that CCC is corrupted in diabetic patients.[2,5] Particularly in diabetic patients, reduction of hemoglobin A1c (HbA1c) to less than 7.0 was associated with a less incidence of major adverse cardiac events that indicating a reduction in revascularization. It has been shown that better glycemic control can improve the clinical prognosis, especially in diabetic patients with non-revascularizable CTO.[6]

Coronary collaterals are arterio-artery anastomoses that develop in the newborn and are physiologically present at birth. These anastomoses occur when a blockage develops in a coronary artery. It transforms into arteries with a diameter 20 times larger than the original arterioles. However, many acquired factors influence arterial turnover, which ultimately manifests as differences in the quality of the CCC.[7]

HbA1c is a marker that reveals the average glycemic index in long-term follow-up. It has been accepted that increased HbA1c level is a risk marker for cardiovascular (CV) events and subclinical atherosclerosis in non-diabetic patients.[8,9] HbA1c level significantly correlates with the number of diseased vessels during coronary angiography (CAG).[10] It has been reported that HbA1c is strongly associated with CAD in addition to the diagnosis of DM and can be shown as a predictor of CAD.[11-13] However, the relationship between HbA1c and CCC development has not been demonstrated in the non-diabetic patient with CTO. We aimed to reveal the effect of HbA1c on collateral development in non-diabetic patients with CTO of at least one vessel in CAG.

MATERIAL AND METHODS

The study included 208 non-diabetic patients out of 487 patients who were admitted to Dicle University Faculty of Medicine, Department of Cardiology between March 2014 and January 2019, were diagnosed with chronic coronary syndrome and/or had myocardial ischemia in stress tests, therefore underwent CAG and CTO was detected in CAG. This is a retrospective analysis.

There were 2 groups formed according to Rentrop classification: Rentrop 0-1 Group 1 (poor collateral development) (90 patients), Rentrop 2-3 Group 2 (good collateral development) (118 patients). The study was designed in accordance to the Declaration of Helsinki, and ethics committee approval was obtained from the Bakırçay University Çiğli Training and Research Hospital Ethics Committee (date: July 8, 2022, no: 655). Demographic and comorbid features such as age, gender, history of myocardial infarction (MI), hypertension (HT) were recorded. Blood tests were taken from the patients after at least eight hours of fasting. Written informed consent was obtained from all patients included in the study.

Patients with a history of DM or HbA1c level >6.5%, any coronary intervention, severe renal and/or liver failure, and cases in which optimal angiographic examination could not be performed were excluded from the study. Anemic patients (Hb values below 10) were excluded from the study. Therefore, it cannot be thought that it will affect the HbA1c value.

CAG IMAGE EXAMINATION AND RENTROP CLASSIFICATION

CAG images recorded in multiple projections were analyzed from a digital system. Images of right and left coronary angiograms of sufficient quality to evaluate CCC (with filling of main epicardial coronary arteries and lateral branches) were included.

CCC was classified semi-quantitatively between 0 and 3 according to the Rentrop classification.[12,14] The patients were classified into 2 groups according to the degree of collateral vessel formation: poor collateral (Rentrop 0-1), good collateral (Rentrop 2-3).[12,14] In the presence of more than one coronary artery lesion and more than one coronary collateral, the highest Rentrop grade was used.

STATISTICAL ANALYSIS

IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA) program was used for statistical analyses. Numerical variable parameters are given as mean and standard deviation. To compare groups in terms of numerical variables, independent samples t-test was used if normal distribution was achieved, and Mann-Whitney U test was used if normal distribution could not be obtained. Categorical variables were expressed as number (n) and ratio (%). Univariate and multivariate analyzes were used to demonstrate the predictive power of HbA1c values for collateral development. Odds ratios (OR) and 95% confidence interval (CI) values were recorded. In addition, Receiver Operating Characteristic (ROC) analysis was used to determine the HbA1c cut-off value.

G Power 3.1.9.7 programme (Heinrich-Heine-Universitat Düsseldorf, Germany) was done for the sample size calculation. Estimated sample size was calculated using Student's t-test with 0.95 (1-β err probe) power, α=0.05 error level and Cohen (d) effect size=0.5. Accordingly, it was found appropriate to complete the study with at least 176 (Group 1=88 patients, Group 2=88 patients) patients.

RESULTS

The mean age of the patients in the study population was 60.0±10.7 years, and the male gender ratio was 76.9%. Mean age and male gender ratio were similar between groups (58.9±9.9 vs. 60.8±11.2 years, p=0.194, male gender ratio 78.9% versus 75.4%, p=0.557).

The rate of smoking was higher in poor collateral development group compared to the good collateral development group (28.0% versus 51.1%, p=0.002). However, no significant difference in HT (26.7% vs. 33.0%, p=0.321) and history of previous MI (18.9% vs. 12.7%, p=0.221). The groups were similar in terms of the drug used before the procedure. The success procedure of the CTO lesion revascularization was high in both groups and were similar between groups (81.1% vs. 79.7%, p=0.795). Demographic, clinical data and drug used by the patients are given in Table 1.

When the biochemical and hemogram parameters are examined; there was a statistically significant difference between the two groups in terms of platelet (p=0.041), HbA1c (p<0.001), triglyceride (p<0.001) and high density lipoprotein (HDL) cholesterol

TABLE 1: Demographic, clinical and comorbid characteristics of the study population.

	Group I (n=90)	Group II (n=118)	Total (n=208)	p value
Age (years) X±SD	58.9 (9.9)	60.8 (11.2)	60.0 (10.7)	0.194
Male gender, n (%)	71 (78.9)	89 (75.4)	160 (76.9)	0.557
Smoking, n (%)	46 (51.1)	33 (28.0)	84 (40.4)	0.002
Hypertension, n (%)	24 (26.7)	39 (33.0)	63 (30.3)	0.321
Previous MI, n (%)	17 (18.9)	15 (12.7)	32 (15.4)	0.221
Success of interventional procedure, n (%)	73 (81.1)	94 (79.7)	167 (80.3)	0.795
Betablockers, n (%)	23 (25.6)	20 (16.9)	43 (20.7)	0.129
ACEi, n (%)	35 (38.9)	37 (31.4)	72 (34.6)	0.258
CCB, n (%)	9 (10.0)	13 (11.0)	22 (10.6)	0.813
Long acting nitrate, n (%)	12 (13.3)	9 (7.6)	21 (10.1)	0.176
Statine, n (%)	20 (22.2)	26 (22.0)	46 (22.1)	0.974
ASA, n (%)	15 (16.7)	13 (11.0)	28 (13.5)	0.237
Clopidogrel, n (%)	3 (3.3)	9 (7.6)	12 (5.8)	0.188

SD: Standard deviation; MI: Myocardial infarction; ACEi: Angiotensin converting enzyme inhibitor; CCB: Calcium channel blocker; ASA: Acetyl salicylic acid.

(p=0.001). Left ventricular ejection fraction (LVEF) values (48.3±8.5 vs. 49.6±10.9, p=0.340) were similar between groups. Hemogram, biochemical and echocardiographic parameters of the study population are summarized in Table 2.

In the univariable regression analysis performed among the factors affecting the quality of collateral in CTO; smoking (OR: 0.406; 95% CI: 0.228-0.722, p=0.002), platelet (OR: 0.997; 95% CI: 0.993-1.00, p=0.051), HbA1c (OR: 0.233; 95% CI: 0.137-0.398, p<0.001), triglyceride (OR: 0.986; 95% CI: 0.981-0.991, p=<0.001), total cholesterol (OR: 0.994; 95% CI: 0.988-1.001, p=0.078) and HDL (OR: 1.058; 95% CI: 1.023-1.093, p=0.001) was a predictor. In the multivariable regression analysis; smoking (OR: 0.455; 95% CI: 0.228-0.910, p=0.026), triglyceride (OR: 0.989; 95% CI: 0.983-0.996, p=0.001) and HbA1c (OR: 0.297; 95% CI: 0.174-0.506, p<0.001), parameters were found to be independent predictors (Table 3).

The mean HbA1c value was 5.49 (±0.76). HbA1c was higher in poor collateral development group than in good collateral development group (5.85±0.45 vs. 5.22±2.47, p<0.001). HbA1c>5.65 with 77% sensitivity and 75% specificity (ROC area under curve: 0.780, 95% CI: 0.717-0.844, p<0.001) predicts poor collateral development in nondiabetic patients with CTO (Figure 1).

DISCUSSION

In this study, we found that coronary collateral development was relatively poor in non-diabetic patients who underwent CAG and had higher HbA1c levels. HbA1c reflects the long-term mean glucose concentration. In addition, HbA1c has more advantages compared to plasma glucose. In particular, it is not affected by acute variations in glucose levels. Previous studies have shown that even if blood sugar levels are below the threshold required to diagnose

TABLE 2: Biochemical and imaging findings of the patients.

	Group I (n=90)	Group II (n=118)	Total (n=208)	p value
WBC, ×10^9/L	9.42 (±3.34)	8.64 (±2.77)	8.98 (±3.05)	0.065
Hemoglobin, g/dL	13.80 (±2.57)	14.00 (±1.99)	13.92 (±2.25)	0.522
Hct	43.02 (±5.27)	42.29 (±5.84)	42.61 (±5.60)	0.352
MCV	86.29 (±5.48)	85.84 (±5.28)	86.04 (±5.36)	0.554
Platelet, ×10^9/L	263.73 (±106.89)	238.43 (±70.43)	249.37 (±88.74)	0.041
MPV	8.76 (±1.63)	8.62 (±1.66)	8.68 (±1.65)	0.545
Lymphocyte, x10^9/L	2.29 (±0.83)	2.17 (±0.92)	2.22 (±0.88)	0.355
Monocytes	0.69 (±0.29)	0.64 (±0.26)	0.66 (±0.27)	0.219
Neutrophil, x10^9/L	6.18 (±2.99)	5.52 (±2.47)	5.81 (±2.72)	0.083
Fasting glucose, mg/dL	116.48 (±28.07)	111.87 (±27.07)	113.86 (±27.54)	0.233
HbA1c	5.85 (±0.45)	5.22 (±0.84)	5.49 (±0.76)	<0.001
Urea	38.40 (±17.29)	39.16 (±17.76)	38.83 (±17.52)	0.758
Creatinine, mg/dL	0.97 (±0.24)	1.13 (±1.08)	1.06 (±0.83)	0.157
GFR	84.76 (±19.83)	78.89 (±26.25)	81.43 (±23.81)	0.078
Albumin, g/dL	3.70 (±0.44)	3.72 (±0.42)	3.71 (±0.43)	0.718
Total cholesterol, mg/dL	171.62 (±41.32)	161.02 (±43.27)	165.60 (42.66)	0.076
Triglyceride, mg/dL	172.84 (±59.81)	120.97 (±58.62)	143.42 (±64.37)	<0.001
HDL, mg/dL	40.35 (±9.95)	44.71 (±8.04)	42.82 (±9.16)	0.001
LDL, mg/dL	94.42 (±38.23)	94.74 (±33.65)	94.60 (±35.61)	0.948
Sodium, mEq/L	137.40 (±2.18)	137.69 (±3.19)	137.57 (±2.79)	0.452
Potassium, mmol/L	4.35 (±0.39)	4.37 (±0.46)	4.36 (±0.43)	0.823
Calcium, mg/dL	9.22 (±0.42)	9.12 (±0.64)	9.16 (±0.56)	0.198
LVEF, %	48.30 (±8.52)	49.63 (±10.86)	49.05 (±9.91)	0.340

WBC: White blood cell; Hct: Hematocrit; MCV: Mean corpuscular volume; MPV: Mean platelet volume; HbA1c: Hemoglobin A1c; GFR: Glomerular filtration rate; HDL: High density lipoprotein; LDL: Low density lipoprotein; LVEF: Left ventricular ejection fraction.

TABLE 3: Univariable and multivariable regression analysis for determine predictor of chronic total occlusion collateral development in non-diabetic patients.

Variables	Univariate, OR (95% CI)	p value	Multivariate, OR (95% CI)	p value
Smoking	0.406 (0.228-0.722)	0.002	0.455 (0.228-0.910)	0.026
Platelet	0.997 (0.993-1.000)	0.051	0.998 (0.994-1.003)	0.461
Triglyceride	0.986 (0.981-0.991)	<0.001	0.989 (0.983-0.996)	0.001
Total cholesterol	0.994 (0.988-1.001)	0.078	0.998 (0.989-1.007)	0.701
HDL	1.058 (1.023-1.093)	0.001	1.021 (0.979-1.064)	0.340
HbA1c	0.233 (0.137-0.398)	<0.001	0.297 (0.174-0.506)	<0.001

OR: Odds ratios; CI: Confidence interval; HDL: High density lipoprotein; HbA1c: Hemoglobin A1c.

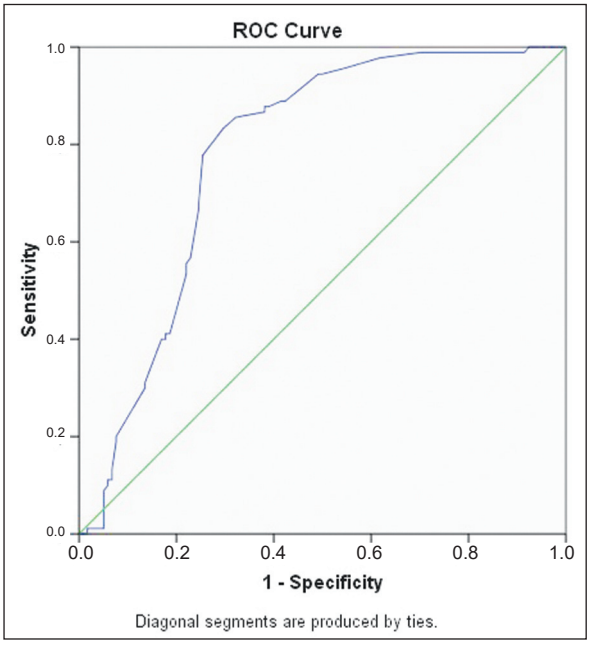

FIGURE 1: ROC analysis of the sensitivity and specificity of hemoglobin A1c, an indicator of poor collateral development in patients with chronic total occlusion. ROC: Receiver Working Characteristic.

diabetes, it carries a certain risk in terms of CV diseases.[8-10,13,15]

Coronary collateral development plays an important role in the nutrition of the myocardium in the CTO region and affects the clinical prognosis. The development of good collateral circulation can reduce the infarct area and preserve left ventricular systolic function in case with coronary CTO.[3]

It has been shown that among patients undergoing coronary CTO revascularization, patients with good CCC development have a lower risk of CV events than patients with poor CCC development.[3] Therefore, to perform coronary revascularization in CTO patients should not only based on clinical symptoms, but should also comprehensively consider the patient's vascular status. One of the most crucial factors indicating vascular status in patients with CTO is quality of CCC.[3] Many acquired factors can cause differences in the quality of CCC.[7] In a study that included 176 patients with CTO, it was shown that homocysteine level was independently associated with poor CCC (p=0.018).[14] In addition, smoking, HT and LVEF were not found to be associated with collateral development. In our study, mean LVEF value and HT frequency were similar between groups. However, in our regression analysis, smoking was higher in poor collateral development group than good collateral development group.

It can be thought that HT will positively affect collateral development. In some studies examining the correlation between HT and the presence of coronary collateral, some conflicting results were reported.[13,16,17] In our study, the incidence of HT was higher in the good collateral development group than in the poor collateral development group, but there was no statistically significant difference between the groups.

AGEs are products formed by the combination of carbonyl groups of carbohydrates and free amino groups of amino acids, and oxidative stress is one of the factors that trigger AGE formation.[18] Increasing AGE production also increases oxidative stress with superoxide formation.[19] Superoxide anions inactivate the most important endogenous vasodilator, endothelium-derived nitric oxide, this caused vasoconstriction.[20] Oxidative stress contributes to vascular remodeling by causing increased inflammation, hy-

pertrophy, apoptosis, cell migration, fibrosis, and angiogenesis.[21] HbA1c, is one of the endogenous AGEs and is a marker that reveals the average glycemic index. HbA1c level is a risk marker for subclinical atherosclerosis and correlates with the number of diseased vessels determined by CAG.[8-10] In our study, mean HbA1c levels were higher in the weak collateral development group than good collateral development group (p<0.001).

One of the parameters affecting the HbA1c value is the Hb value. A low Hb value may decrease the HbA1c level, which may affect the results of the study.[22] One of the advantages of our study was that the mean value of Hb values was within the normal reference range in both groups. In addition, we did not observe a statistically significant difference between the groups.

In a previous study, it was reported that there was a correlation between high HbA1c level and prevalence of CAD. Here, the ideal threshold value for HbA1c to predict the presence of CAD was found to be 5.6% (sensitivity: 60.5%, specificity: 52%).[16] In our study, the HbA1c cut-off value was similarly found to be 5.65% in the development of coronary collateral. However, it differs from the above-mentioned study with a sensitivity of 77% and a specificity of 75%.

In a study examining the effect of HbA1c on CV disease and total mortality, including 4,662 men and 5,570 women aged between 45 and 79, the relationship between HbA1c and CV disease and all-cause mortality was significant in both men and women without known diabetes. A 1% increase in HbA1c was associated with a 24% increase in all-cause mortality in men and a 28% increase in women (p<0.001). This relative increase in reported risk was reported to be independent of CV risk factors and/or disease. Results were similar when diabetic patients, HbA1c levels above 7%, or those with atherosclerotic heart disease were excluded (p=0.02).[15]

STUDY LIMITATIONS

The primary limitation of our study is that angiographically visualized collaterals constitute only a fraction of the total collateral vessel development, because very small collateral vessels cannot be visualized. The fact that HbA1c is based on a single measurement may underestimate any association between collateral development and HbA1c. Since the HbA1c value was not measured in every non-diabetic CTO patient, the patients could not be taken consecutively. In order to support our study results, there is a need for larger-scale studies on the predictor of HbA1c in collateral development.

CONCLUSION

HbA1c is a parameter that affects coronary collateral development. In non-diabetic patients with coronary CTO, high HbA1c levels were correlated with poor collateral development. The results of the study may contribute to the search for potential new therapeutic targets to specifically lower the HbA1c, which indicate long-term mean glycemic index, even in non-diabetic patients.

Acknowledgment

We would like to thank Oktay ŞENÖZ, who performed the statistical analysis in this study.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Mehmet Kış; **Design:** Mehmet Kış; **Control/Supervision:** Mehmet Kış, Tuncay Güzel; **Data Collection and/or Processing:** Tuncay Güzel; **Analysis and/or Interpretation:** Mehmet Kış; **Literature Review:** Mehmet Kış; **Writing the Article:** Mehmet Kış; **Critical Review:** Tuncay Güzel; **References and Fundings:** Tuncay Güzel; **Materials:**Tuncay Güzel.*

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