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Atherogenic index of plasma as a Novel Biomarker to Predict Retinal Vein Occlusion

Retinal Ven Tıkanıklığı Risk Belirteci Olarak Aterojenik Plazma İndeksi

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Abstract

Objective: Atherogenic index of plasma is a relatively new index used to predict the risk of cardiovascular diseases in the general population. Our aim was to investigate association between the development of retinal vein occlusion and atherogenic index of plasma.

Material and Method: A total of 24 patients with retinal vein occlusion and 24 age-sex matched healthy individuals were included in this retrospective study. The demographic characteristics and laboratory findings of the patients and control subjects were obtained from the electronic medical records. Atherogenic index of plasma was calculated as the logarithmical ratio of molar concentrations of triglycerides to high density lipoprotein cholesterol as. The association among atherogenic index of plasma, lipid metabolism parameters, and retinal vein occlusion was analyzed.

Results: The median age was 69.5 (range, 48-86) in the patient group and 71.5 (range, 50-84) in the control group ($p=812$). Although there were no significant differences in terms of total cholesterol and low-density lipoprotein cholesterol between two groups ($p=0.458, 0.88$), atherogenic index of plasma was significantly higher in the patient group ($p<0.05$).

Conclusion: Elevated atherogenic index of plasma values might aid clinicians raise suspicion against a possible retinal vein occlusion attack and take precautions accordingly to prevent complications related to retinal vein occlusion.

Keywords: Atherogenic index of plasma, lipid profile, retinal vein occlusion.

Özet

Amaç: Aterojenik plazma indeksi kardiyovasküler hastalık riskini tahmin etmek için kullanılan yeni bir indekstir. Amacımız retinal ven tıkanıklığı ile aterojenik plazma indeksi arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Retinal ven tıkanıklığı olan 24 hasta ve bu hastalarla yaş-cinsiyet ile uyumlu 24 sağlıklı birey retrospektif olarak incelendi. Hasta ve kontrol grubunun demografik özellikleri ve laboratuvar bulguları hastane veri tabanından elde edildi. Aterojenik plazma indeksi trigliseritin molar konsantrasyonunun yüksek yoğunluklu lipoprotein kolesterolüne logaritmik oranı olarak hesaplandı. Aterojenik plazma indeksi, lipid metabolizma parametreleri ve retinal ven tıkanıklığı arasındaki ilişki analiz edildi.

Bulgular: Hasta grubunun yaş ortancası 69,5 (48-86), kontrol grubunun 71,5 (50-84) idi ($p=812$). İki grup arasında total kolesterol ve düşük yoğunluklu lipoprotein kolesterol açısından anlamlı fark olmamasına rağmen ($p=0.458, 0.88$), aterojenik plazma indeksi, hasta grubunda anlamlı olarak yüksekti ($p<0.05$).

Sonuç: Yüksek aterojenik plazma indeksi, klinisyenlere olası retinal ven tıkanıklığı ve retinal ven tıkanıklığına bağlı komplikasyonların önlenmesi için yol gösterici olabilir.

Anahtar Sözcükler: Aterojenik plazma indeksi, lipit parametre, retinal ven tıkanıklığı.

Introduction

Retinal vein occlusion (RVO) is caused by the occlusion of retinal venous vasculature resulting in potential vision loss and long-term sequelae. RVO can be classified as branch RVO (BRVO) and central RVO (CRVO) according to the site of occlusion. CRVO typically occurs at or near the lamina cribrosa of the optic nerve, whereas BRVO occurs at an arteriovenous intersection. The prevalence of BRVO is estimated to be around 0.4% with equal distribution between men and women. The risk of having a RVO episode increases with older age and systemic diseases (1,2). Although the pathogenic mechanisms of RVO are not yet fully understood, a combination of complex elements is believed to contribute to the development of RVO, including compression of the retinal vein at an arteriovenous crossing, increased arterial rigidity and arteriosclerosis, thrombus formation, dysregulated hematologic factors, and elevated levels of proinflammatory mediators and decreased levels of anti-inflammatory cytokines in the vitreous fluid of patients. Previous studies have reported the risk factors for RVO as old age, hypertension, diabetes mellitus (DM), myocardial infarction, cerebral vascular accidents, and chronic kidney disease (CKD) (3-5). A meta-analysis suggested that factors known to contribute to the risk for atherosclerosis might also be important for pathogenesis of RVO (6). However, the precise role of dyslipidemia in the pathogenesis of RVO has not yet been fully identified, and only very limited data on low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and total cholesterol levels in patients with RVO is available (7-9).

Atherogenic index of plasma (AIP), is a novel marker of cardiovascular disease and dyslipidemia (10). AIP is calculated as the logarithmically transformed ratio of molar concentrations of triglycerides (TG) to HDL-C. AIP is accepted as a strong predictor of cardiovascular mortality and it has been shown to increase significantly in coronary artery disease (CAD) and acute coronary syndrome (11,12). Due to the similar etiopathogenesis of CAD and RVO, we hypothesized a possible relation between elevated AIP levels and RVO incidence. To our knowledge, there are no published studies evaluating this relationship.

Material and Method

Twenty-four patients who had the diagnosis of RVO in our department between August 2018 and August 2022 were included in this study. Age and gender matched 24 subjects without retinal vascular pathologies were enrolled for the control group. Exclusion criteria were the presence of liver, kidney and malignant diseases, thyroid dysfunction, and hypolipidemic medication use within the last 2 months. Hospital medical records and patient charts were reached to detect the demographic properties, chronic illness types and laboratory test results of the RVO patients and control subjects. Presence of DM, HT, and CAD was noted. AIP was calculated as the logarithmical ratio of molar concentrations of triglycerides (TG) to HDL-C as [log (TG/HDL-C)].
The study was approved by the Ethics Committee of Ankara Oncology Training and Research Hospital (2022-01/36). All tenets of the declaration of Helsinki have been followed.

Statistical Analysis

Statistical analysis was performed using SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to analyze the normal distribution of the data and Mann-Whitney U test was used to compare two groups. Due to the non-normal distribution of parameters revealed in the test results, the median value, along with the interquartile range, was utilized. To determine the cut-off value and to quantify the parameter accuracy, a receiver operating characteristic curve (ROC) analysis was performed. A statistical significance was considered with a P-value less than 0.05.

Results

Both the RVO and control groups consisted of 24 subjects (14 female, 10 male). All 24 patients included in the study had BRVO. Median age was 69.5 (range, 48-86) in the RVO group and 71.5 (range, 50-84) in the control group ($p=812$). The median value for the LogMAR visual acuity was 1 (0.775-1.3) in the RVO group and 0 (0-0.1) in the control group ($p<0.001$). Of the 24 patients in the RVO group; 22 (91.6%) had HT, 8 (33.3%) had DM, and 7 (29.1%) had CAD. The median value for AIP was 0.586 (0.502-0.614) in the RVO group and 0.295 (0.149-0.433) in the control group ($p<0.001$). Median triglyceride values were also significantly higher in the RVO group compared to the control group (169 (156.25-205) vs. 106 (85-124)), ($p<0.001$). Median HDL-c values were significantly lower in the RVO group compared to the control group (46.45 (41.23-54.25) vs. 53.00 (45.25-64.25)), ($p=0.031$). There were no significant differences between the RVO and the control group median total cholesterol and LDL-c values ($p>0.05$). Biochemical characteristics of the subjects in the RVO group and the control group are summarized in Table I.The ROC analysis revealed a cut off value of 0.425 for AIP to predict RVO incidence with a sensitivity of 95.8% and a specificity of 75% (Figure I).

Table I. Biochemical characteristics of the subjects in the RVO group and the control group

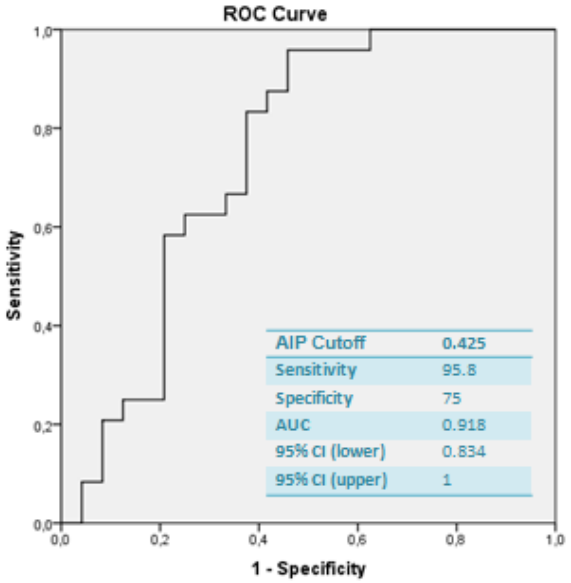
	RVO (n=24)	Controls (n=24)	*p*
Triglycerides (median (interquartile range))	169 (156.25-205)	106 (85-124)	**<0.001**
Total cholesterol (median (interquartile range))	199 (174.27-224.25)	188 (160.75-238.25)	0.458
LDL-c (median (interquartile range))	129 (96.5-166,5)	115.5 (104.5-158)	0.88
HDL-c (median (interquartile range))	46.45 (41.23-54.25)	53.00 (45.25-64.25)	0.031
AIP (median (interquartile range))	0.586 (0.502-0.614)	0.295 (0.149-0.433)	**<0.001**

RVO: Retinal vein occlusion, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol, AIP: Atherogenic index of plasma, SD: Standart deviation, **p<0.05*

Discussion

RVO is the second most common retinal vascular disorder following diabetic retinopathy, and it is a major cause of visual impairment (13). RVO is commonly associated with increased cardiovascular morbidity and mortality. Moreover, cardiovascular risk factors such as hypertension, hypercholesterolemia and atherosclerosis have been also implicated in the pathogenesis of RVO (14-16). Epidemiologically, hypertension is the strongest risk factor for RVO. In our study, 91.6% of the RVO patients were detected to have systemic hypertension. Atherosclerosis and dyslipidemia are the two other major risk factors for the development of RVO (2,3). AIP, suggested by Dobiasova and Frohlich in 2000, is a simple atherogenic index calculated as the logarithm of the molar ratio of circulating triglycerides to HDL-C concentrations. Additionally, AIP is inversely related to LDL particle size. In this regard, it has been demonstrated that small dense LDL-C are very vulnerable to oxidative damage and consequently to induce atherosclerotic lesions (17). Furthermore, several scientific studies have used AIP as a prognostic CVD biomarker. AIP is suggested as a potential biomarker (cheap, quick, specific) for the early diagnosis of CVD events (18,19). In our study, considering the role of dyslipidemia as a risk factor for both CVD and RVO, we speculated that AIP could potentially be a biomarker for RVO. As AIP levels were found to be increased in dyslipidemia, we aimed to investigate the predictive role of AIP in RVO incidence, and we found highly elevated AIP levels in RVO patients compared to control subjects. Numerous studies have previously reported that RVO is associated with atherosclerosis which is a chronic inflammatory disease of the arteries (2). Hyperlipidemia is a major risk factor for atherosclerosis and LDL-c is the most abundant atherogenic lipoprotein in the plasma (20). LDL-c leads to the initiation and progression of the atherosclerotic plaque formation in a dose-dependent manner. Therefore, LDL-c is believed to play an important role in the development of RVO (7,8). LDL-c and total cholesterol levels were found to be elevated in the RVO group in our study; however, statistical significance was not reached. In contrast to LDL-c, HDL-c is believed to employ atheroprotective effects. Evidence from various previous reports indicates an association between decreased levels of HDL-c and increased risk of RVO (21). Reverse cholesterol transport mediated by HDL-c deters the accumulation of cholesterol in the arterial wall; hence, prevents the progression of atherosclerosis. HDL-c also inhibits the endothelial inflammatory response and oxidation of LDL-c (22). In our study, we found that RVO patients had significantly lower HDL-c levels

Figure I. The ROC curve analysis for the diagnostic values of Atherogenic index of plasmato differentiate the Retinal Vein Occlusion group from the control group. when compared with the control group.



In recent years, there has been a consensus that non-conventional serum lipid ratios compared to single conventional lipid parameters are better in discriminating the atherogenic events (7-10). It has been also shown that AIP is more effective in predicting cardiovascular disorders and dyslipidemia than the single lipid parameters (11,12). As atherosclerosis is a common risk factor for both CAD and RVO, we aimed to evaluate the predictive value of AIP for RVO

(23). Although AIP was not previously evaluated in RVO patients, there is a study where AIP was found to be highly associated with the severity of visual loss and the second eye involvement in patients with non-arteritic ischemic optic neuropathy (NAİON) (24). It is known that atherosclerosis, DM, HT, and hyperlipidemia also play a major role in the etiopathogenesis of NAİON (24). In parallel, studies involving individuals with type 2 diabetes have revealed a noteworthy connection between the development and severity of diabetic retinopathy and the AIP level (25,26). We found that RVO patients had significantly higher AIP levels than the control group. We also found that AIP levels greater than 0.425 were highly associated with RVO, with a sensitivity of 95.8% and specificity of 75%. Although our study is the first to report a cut off value of AIP for RVO, literature search yields various AIP cut off values reported for systemic diseases. Thus, a cut-off value of 0.54 for AIP in predicting metabolic-associated fatty liver disease in patients with type 2 DM has been reported (sensitivity = 57.8%, specificity = 54.4%) (27). In another study, a cut off value of 0.318 was detected to predict the prognosis of percutaneous coronary intervention, higher AIP indicating unfavorable prognosis (28).

Regarding the pathogenesis of RVO, no treatment has been proved to reverse the obstruction in the vascular system (1,2). The prognosis of RVO is highly variable depending on the location of the vascular occlusion, degree of ischemia, and development of sequelae. Intravitreal injections of the anti-vascular endothelial growth factor (anti-VEGF) agents remains the mainstay of RVO management. Anti-VEGF treatment has been shown to improve vision and to reduce vision-limiting macular edema. However, it is known that 50% of CRVO patients and 30% of RVO patients do not respond to anti-VEGF treatment for macular edema (29). Therefore, as well as the early treatment of RVO, prevention is of the utmost importance. Detection of the accompanying systemic factors might help to prevent the occurrence and subsequent recurrent attacks of RVO. In this study, we aimed to evaluate the predictive role of lipid parameters and AIP for the occurrence of RVO and found a possible relation. We believe that elevated AIP values which is a marker of dyslipidemia might aid clinicians raise suspicion against a possible RVO attack and take precautions accordingly to prevent complications related to RVO.

Retrospective design and small study population are the major limitations of our study. Another limitation of our study is the absence of patients with CRVO in our dataset. Although a multicenter study with larger scale might provide a better insight of the predictive value of AIP in RVO occurrence; our study still provides data of a possible relation between elevated AIP levels and RVO incidence.

Conclusion

To the best of our knowledge, this study is the first to show that AIP, a novel biomarker of dyslipidemia and a strong predictor of cardiovascular mortality, is also associated with the development of RVO. Our study suggests that AIP can aid clinicians to prevent development of RVO and related complications in patient groups under risk.

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