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PRİMER AÇIK AÇILI GLOKOMDA KAN LİPİD PROFİLİ: BİR BİYOKİMYASAL ANALİZ ÇALIŞMASI

BLOOD LIPID PROFILE IN PRIMARY OPEN-ANGLE GLAUCOMA: A BIOCHEMICAL ANALYSIS STUDY

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ÖZET

AMAÇ: Primer açık açılı glokomda (POAG) kan lipit profilinin araştırılması.

GEREÇ VE YÖNTEM: Bu çalışmada, 50'si POAG hastası ve 50'si POAG olmayan hasta olmak üzere oftalmoloji kliniğine başvuran 100 katılımcı vardı. Total kolesterol, düşük yoğunluklu lipoprotein (LDL), yüksek yoğunluklu lipoprotein (HDL) ve trigliserit (TG) dahil olmak üzere kan lipit seviyeleri araştırıldı. Veriler t testi, Mann Whitney U, Fischer korelasyonu ve Ki-kare testi ile karşılaştırıldı. p <0,05 istatistiksel olarak anlamlı kabul edildi.

BULGULAR: POAG hastalarının yaş ortalaması 65.7 ± 11.09 iken POAG olmayan hastaların yaş ortalaması 66.2 ± 10.44 idi. Çalışmada kullanılan laboratuvar testlerinin normal sınırları total kolesterol için 0-200 mg / dl, LDL için 0-130 mg / dl, HDL için 35-70 mg / dl ve TG'ler için 35-160 mg / dl idi. POAG ve POAG dışı hastalarda sırası ile kan lipit düzeyleri; total kolesterol: 199 ± 47 mg / dl ve 202 ± 46 mg / dl (p> 0.05), LDL: 114 ± 37 mg / dl ve 112 ± 43 37 mg / dl (p> 0.05), HDL: 51 ± 14 mg / dl ve 54 ± 19mg / dl (p> 0.05) ve TG: 170 ± 69 mg / dl ve 146 ± 102 mg / dl (p <0.05) idi.

SONUÇ: Bu çalışmada POAG ve POAG olmayan hastalar arasında total kolesterol, LDL ve HDL düzeyleri açısından fark bulunmadı. Bununla birlikte, kan lipit profilindeki değişiklikler sadece hastaların yaşı ile değil, aynı zamanda yaygın sistemik hastalıklarla da ilişkili olabilir. Bu çalışma POAG hastalarında TG düzeyinin genel popülasyona göre daha yüksek olduğunu dikkat çekici bir bulgu olarak göstermiştir.

ANAHTAR KELİMELER: Kan lipit profili, Primer açık açılı glokom, Trigliserit

ABSTRACT

OBJECTIVE: Investigation of blood lipid profile in primary open-angle glaucoma (POAG).

MATERIAL AND METHODS: In this study, there were 100 participants, of whom 50 were patients with POAG and 50 were non-POAG patients consulted in the ophthalmology clinic. Levels of blood lipids including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) were investigated. Data were compared with t-test, Mann Whitney U, Fischer correlation and Chi-square test. p<0.05 was considered statistically significant.

RESULTS: While the mean age of the POAG patients was 65.7±11.09 years, the mean age of the non-POAG patients was 66.2±10.44 years. The normal reference ranges for laboratory tests in this study were 0-200 mg/dl for total cholesterol, 0-130 mg/dl for LDL, 35-70 mg/dl for HDL, and 35-160 mg/dl for TGs. The blood lipid levels in POAG and non-POAG patients were as following: total cholesterol 199±47 mg/dl and 202±46 mg/dl (p>0.05), LDL 114±37 mg/dl and 112±43 37 mg/dl (p>0.05), HDL 51±14 mg/dl and 54±19mg/dl (p>0.05), and TG 170±69 mg/dl and 146±102 mg/dl (p<0.05), respectively.

CONCLUSIONS: In this study, no statistically significant difference was found between POAG and non-POAG patients regarding total cholesterol, LDL, and HDL levels. Yet, changes in the blood lipid profile may be associated with not only the patients' age but also prevalent systemic diseases. The present study demonstrated a remarkable finding that the level of TG was higher in the POAG patients compared to the general population.

KEYWORDS: Blood lipid profile, Primary open-angle glaucoma, Triglyceride

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INTRODUCTION

Glaucoma is an optic neuropathy resulting from elevation of intraocular pressure (IOP) due to increased resistance in the drainage of the aqueous humor from the trabecular mesh (TM) and Schlemm's canal (1). Primary open-angle glaucoma (POAG) is chronic, painless, and often presents no symptoms until advanced stages. Biological cause underlying pathogenesis of POAG remains uncertain (2). Since the TM endothelium functions like a vascular endothelium, recent studies have reported increased association of the TM disruption and endothelial dysfunction-causing diseases such as atherosclerosis (2, 3).

Elevated IOP is considered the main risk factor for glaucoma development. In some patients, however, glaucoma develops when IOP is at normal levels, while in some patients, elevated IOP does not lead to glaucoma. Since elevated IOP alone is not sufficient to explain the etiology of glaucoma (4), other risk factors have been identified including vascular diseases such as diabetes mellitus, cardiovascular diseases, retinal vein occlusion, family history, migraine, vasospasm as well as high myopia(5, 6). Vascular dysfunction in glaucoma patients was recently noted in a clinical study, the Leuven Eye Study (7).

Primary open-angle glaucoma is the most common type of glaucoma. It is normally associated with slow progressive loss of visual field and optic disc pitting. Although its prevalence above the age of 40 has been reported to vary from 1.3% to 2.1%, Scandinavian and Mediterranean countries have been associated with rather higher prevalence rates. In addition, the disease is 3-6 times more common in blacks and starts at a younger age accompanied with more blindness. Both cholesterol and triglyceride (TG) elevation are increased risk factors for atherosclerotic diseases of coronary and peripheral arteries. Since vascular factors are associated with perfusion pressure of the optic nerve head, these factors are considered relatively effective in the glaucoma etiology.

High levels of both blood lipids and lipoprotein have been shown in normotensive glaucoma (8). Even though, hyperlipoproteinemia and ischemic vascular diseases are more commonly related to patients with ocular hypertensive and chronic open-angle glaucoma than in healthy subjects (9). Hypertriglyceridemia is often seen in patients with metabolic syndrome and type 2 diabetes (10). The role of TGs in the pathogenesis and progression of glaucoma remains unclear. Relationship of TGs with intraocular pressure (11, 12) and glaucoma; It has been reported in several case-control studies (13, 14). However, this was not confirmed in all studies (15, 16) and a recent study by Ko et al. (17) even found a significant inverse relationship between glaucoma and high TG levels .

This study aimed to investigate whether the levels of plasma TG, LDL, HDL, and total cholesterol in POAG patients constitute the risk factors, and to compare the blood lipid profile to non-POAG patients.

MATERIAL AND METHOD

This study included 100 participants, of whom 50 were POAG and 50 were non-POAG patients (control group) that were consulted to the ophthalmology clinic at Afyonkarahisar State Hospital. Blood lipid profile examination was performed prior to inclusion.

Presence of previously diagnosed POAG and ≥18 years of age were among inclusion criteria for POAG patients. On the other hand, exclusion criteria for POAG patients consisted of: (a) presence of other diseases causing secondary glaucoma such as proliferative diabetic retinopathy, high myopia, and ocular trauma, (b) presence of vascular diseases interfering with ocular blood flow, (c) β-blocker therapy due to systemic diseases, (d) antihyperlipidemic therapy, (e) alcohol intake, and (f) females on hormone replacement therapy.

Further, absence of POAG or glaucoma with any other etiology and ≤18 years of age constituted inclusion criteria for non-POAG patients. Whereas, exclusion criteria for non-POAG patients were: (a) β-blocker therapy due to systemic diseases, (b) antihyperlipidemic therapy, (c) presence of vascular diseases interfering with ocular blood flow, and (d) presence of other ocular diseases such as high myopia and ocular trauma. Both groups were randomized according to systemic vascular diseases, age, and gender.

The control group was evaluated in terms of age and gender by Student-t test and Chi-square test, respectively. Distributions of HDL, LDL, TG and cholesterol in both control and study groups were tested separately for normal distribution with Colmogrov-Simirnov. The mean values of variables with normal distribution were compared with Student-t test, while non-normally distributed values were compared with Mann-Whitney U test. Limit levels of the serum lipoprotein values were <200 mg/dl for cholesterol, <140 mg/dl for TG, <160 mg/dl for LDL, and <40 mg/dl for HDL. Chi-square and Fischer exact tests were used for statistical evaluation of the data. Number of drugs used in the study group and the levels of HDL, LDL, TG and cholesterol were evaluated by Pearson correlation test. Depending on the number of drugs used, HDL, LDL, TG, and total cholesterol values that were higher than the limit values were evaluated with the Chi-square test. Total Cholesterol, Triglyceride, LDL and HDL measurements in serum were studied in Roche Cobas C501 autoanalyzer using Roche branded commercial kits (Roche Diagnostics International Ltd., Rotkreuz, Switzerland).

Ethical Committe

All procedures were performed by the tenets of the Declaration of Helsinki. Afyonkarahisar Health Sciences University Ethics Committee of Clinical Research approved the study protocol. Signed informed consent was obtained from each participant before initiation of the study (no.2020/8).

RESULTS

Mean ages of the POAG and non-POAG patients were 65±11.0 and 66±10.4 years, respectively. There were 29 (58%) females and 21 (42%) males in the POAG patient group, 32 (64%) females and 18 (36%) males in the non-POAG control group. This study revealed statistically non-significant difference between the two groups in terms of gender (Chi-square; p=0.539) and age (T-test; t=0.214, p=831).

The levels of HDL, LDL and cholesterol showed normal distribution in both groups. However, TG level did not show normal distribution in non-POAG control group.

The groups were compared with Student-t test for HDL, LDL and cholesterol levels, and with Mann-Whitney U tests for TG levels **(Table 1)**.

Table 1: Comparison of the groups for blood HDL, LDL, cholesterol, and TG levels

	Study group	Control group	
Variable	Average value	Average value	Statistical analysis
HDL	51.3±14.85	53.6±19.19	t=-0.664; p=0.508
LDL	114.1±37.07	112.1±42.80	t=-0.257; p=0.798
Cholesterol	198.8±46.93	202.9±46.08	t=-0.447; p=0.656
TG	170.1±69.21	146.2±101.93	Z=-2.641; p=0.042

Distributions of HDL, LDL, TG and cholesterol in both groups were tested with Colmogrov-Simirnov.

They were also compared with Chi-square test in terms of height from the limit values **(Table 2).**

Table 2: Comparison of the groups with Chi-square test in terms of height from the limit values. (N=normal, P=number of pathological patients)

Variable		Study group	Control group	P-value
HDL	N	40	41	P=0.79
	P	10	9	
LDL	N	48	43	P=0.81
	P	2	7	
Cholesterol	N	25	24	P=0.84
	P	25	26	
TG	N	23	33	
	P	27	17	P=0.44

Chi-square test

It was observed that the antiglaucomatous agents used in controlling IOP values in the POAG patients contained 72% active ingredient of timolol **(Table 3)**.

Table 3: Distribution of antiglaucomatous drugs used by the POAG patients. (PGA: Prostaglandin Analogue, CAI: Carbonic Anhydrase Inhibitor)

Topical drug used		Number of patients	Value (%)
Combined therapy	PGA+β-blocker	15	30
	CAI+β-blocker	7	14
	α2-agonist+β-blocker	2	4
PGA		8	16
α2-Agonist		5	10
β-blocker		1	2
Combined therapy+PGA		7	14
Combined therapy+α2-Agonist		5	10

While HDL values lower than limit values were considered pathological, the values of other variables greater than limit values were considered pathological. Correlations between the number of drugs used and HDL, LDL, Cholesterol and TG levels were evaluated with Pearson correlation test. The statistical significance and correlation values of the blood lipids were; HDL: p=0.337, r=-0.1212, LDL: p=0.695, r=-0.064, cholesterol: p=0.571, r=0.082, and TG: p=0.829, r=0.031.

DISCUSSION

The lipoproteins contain varying proportions of TGs, lipoproteins as well as protein. The LDL contains 50% cholesterol, 10% TGs, whereas

VLDL contains up to 75% TGs and around 10% cholesterol. Usually, there is an enzymatically controlled continuous change among the lipoproteins. The levels of different plasma lipids differ from day to day, not only in any particular population, but even in the same person. Amount of fat and carbohydrates in the diet, alcohol intake, acute trauma, stress, smoking and some medications may affect the acute or chronic lipid and lipoprotein levels. The levels of the plasma lipids often increase gradually until the age of 50 in both sexes, though there is a tendency of being higher in females after 50 years.

Changes in the plasma lipid profile, especially in development of coronary artery disease and atherosclerosis, are considered as risk factors especially in HDL-cholesterol level decrease and TG-HDL cholesterol level increase. Atherosclerosis is not often considered as a risk factor for glaucoma incidence.(18 -19) Hypertension, bacterial toxins, atherogenic lipoproteins damage to the vascular wall and uncontrolled smooth muscle cell proliferation caused by factors such as aggregation facilitates the atherosclerotic plaque formation process. Reduced level of endothelial substances exhibiting a relaxing activity is also worth mentioning (20 - 21). The aforementioned risk factors, including also genetic predisposition to low HDL (<35 mg/dl), as well as free radical oxidation of LDL and lipoprotein Lp (a) fractions, homocystinuria, hyperbetalipoproteinemia, oxidative modifi cation of LDL, together with the so-called uninhibited stimulated inflammatory response of leukocytes/endothelial cells, induce the cascade of atherosclerotic processes (22 - 24). It has been shown in the experimental studies that oxidized LDL, which is the compound index of hypercholesterolemia, leads to production of endothelin-1 which consequently causes local vasoconstrictive stimulation of ciliary arteries (25, 26). Apart from lipid-related factors, the role of disturbances in the level of vasodilatory nitric oxide and vasoconstrictive endothelin-1 agents affecting the retino-choroidal microcirculation is emphasized in literature. Th e results of decreased nitric oxide and increased endothelin-1 levels in glaucoma patients have been widely described (18, 21, 27, 28, 29). Elevated IOP does not seem sufficient to solely explain the pathogenesis of glaucoma (4). Other risk factors, especially the dysfunction of the vasculature supplying the optic nerve and the surrounding tissue, have therefore been implicated. Although TGs are an independent risk factor for cardiovascular disease, their role in the pathogenesis of atherosclerosis is controversial (30). Patients diagnosed with glaucoma have been shown to have an increased risk of cardiovascular mortality (31) which is primarily explained by common risk factors such as hypertriglyceridemia (32, 33). Although there are studies indicating that glaucoma drugs have an effect on lipid levels, there is limited evidence to support this (33, 34) Winder et al., (10) reported the association of ocular hypertension and chronic open-angle glaucoma patients with ischemic vascular diseases as well as abnormal lipoprotein levels. Likewise, Walker et al. (35) reported abnormal lipoprotein levels in 44% of 45 patients with ocular hypertension and 52% of 50 patients with chronic open-angle glaucoma. On the contrary, the study of 182 ocular hypertensive patients published by Chisholm (36) revealed no difference in frequency of glaucoma between patients with and without abnormal lipid profile.

Topical β-blockers commonly used in glaucoma therapy are known to be absorbed from the conjunctiva, nasal and pharyngeal mucosa, and participate in circulation, causing systemic side effects. Timolol causes lipoprotein lipase enzyme inhibition and hence increases and decreases serum TG and HDL levels, respectively (37). Elgin et al. (38) divided 536 POAG patients and 298 normal individuals into 3 subgroups according to their ages, and compared both the two groups in terms of diabetes mellitus, systemic hypertension, and blood lipid levels with respect to age groups. The comparison of the patients with age less than 50 years revealed only high levels of blood lipid cholesterol in the POAG patients. This result was related to the majority of glaucoma patients being on topical β-blockers. Additionally, Pertl et al (39) study found that patients with glaucoma had higher mean TG levels than non-glaucoma patients. They suggested, however, that not only co-medications may modify the association of TGs and glaucoma, but also medications used for glaucoma treatment. Importantly, topical

β-blockers, which are a cornerstone treatment for glaucoma, have been shown to increase systemic TG levels in a study on 28 healthy volunteers taking topical timolol (40). Consistently, the present study revealed significantly higher TG levels in POAG patients than in the control group. Also, 72% of the patients were on combined therapy containing timolol. Consequently, it has been thought that the difference in TG levels has been associated with the use of timolol.

Although IOP is the main the risk factor for the development of glaucoma, other risk factors such as vascular dysfunction might play an additional pathogenic role. Hypertriglyceridemia, which may lead to vascular dysfunction, has been implicated in the development of glaucoma. In the present study, comparison of the lipid profile of POAG patients revealed significantly high TG levels, corresponding with previous studies in the literature. Still, there was no difference in other blood lipid parameters. It is noteworthy that this study yielded meaningful results in terms of TG levels compared to previous studies. The blood cholesterol, however, can give different results even during repeated measurements in the same person during the day. Thus, studies with large number of participants concerning this subject will be more useful in supporting the results of the present study.

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