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Original Article

Effect of The Atherogenic Index of Plasma on Microvascular Complications Associated with Type 2 Diabetes Mellitus

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Abstract

Objective: The aim of this study was to evaluate the effects of the atherogenic index of plasma (AIP) on the microvascular complications of type 2 diabetes mellitus (DM) patients who applied to our internal medicine clinic.

Methods: The study included 212 type 2 DM patients and 34 healthy controls who were compatible according to age and sex. Age, sex, duration of illness, treatment for diabetes and other illnesses associated with diabetes, height, weight, retinopathy, nephropathy, neuropathy, hypertension, and hyperlipidemia were recorded at the beginning of the study. AIP is calculated as the logarithm of the ratio between the triglyceride value and high density lipoprotein value (in mg/dL).

Results: AIP and triglyceride levels of the type 2 DM patients were higher than those of the control group. Also, the study determined that 25.7% of the patients have retinopathy, 31.6% have neuropathy, 29.1% have microalbuminuria, and 3.9% have macroalbuminuria. If we accept that there is a complications who have one of these complications in this three, there is 62.6% of the patients have complications. A statistically significant correlation was determined with these complications and lipid subgroups such as AIP and low density lipoprotein (LDL).

Conclusion: The relationship between AIP and only nephropathy, which is a complication in type 2 DM patients, was determined.

Keywords: Diabetes, microvascular complication, atherogenic index

Introduction

Diabetes Mellitus (DM) is a metabolic disease that is characterized by a decrease in insulin released from beta cells (or insulin deficiency) or hyperglycemia occurring because of insulin insensitivity in the peripheral tissue. The developments in technology, sedentary lifestyle, and increasing obesity have caused DM to be widespread (1, 2). DM is important not only because of its complications in the acute period, which are associated with an increased blood glucose level, but also more importantly, because of its long-term complications in many organ systems, most of which can be prevented with a successful treatment. Vascular complications can appear as micro- or macroangiopathy. Retinal and renal microangiopathies play an important role in diabetic retinopathy and diabetic nephropathy, respectively. Moreover, microangiopathy of the vasa nervorum has a role in diabetic neuropathy (3-5). Atherogenic dyslipidemia refers to a frequent coexistence of increased fasting serum triglyceride and decreased high-density lipoprotein cholesterol (HDL-C) levels. Adult Treatment Panel III defines this situation as an important risk factor for coronary artery disease (6). It has been demonstrated that the atherogenic index of plasma (AIP), a new indicator of atherogenity, significantly increases with atherogenic risk (7). Dobiasova and Frohlich (8, 9) defined the atherogenic index as the logarithm of the ratio of plasma triglyceride to HDL-C levels. It is suggested that AIP values of <0.1 are related to low cardiovascular risk, between 0.1 and 0.24 are related to moderate cardiovascular risk, and >0.24 are related to high cardiovascular risk (10). Furthermore, there is no consensus regarding the possible mechanisms of the relationship between the mentioned lipid subgroups and microvascular complications.

This study aimed to evaluate the effect of the atherogenic index on microvascular complications in patients with type 2 DM who applied to our Outpatient Clinic of Internal Medicine.

Methods

This study was conducted with patients who applied to the Outpatient Clinic of Internal Medicine in the Gaziosmanpaşa Taksim Trainin and Research Hospital between January and June 2014 and those who accepted to participate in the study. The study included 212 patients with type 2 DM and 34 healthy control individuals who were compatible in terms of age and gender. The diagnosis of type 2 DM was established in accordance with the ADA criteria. At the beginning of the study, the patients' age; gender; duration of illness; treatment for DM and accompanying diseas-

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es; height and weight; and presence of retinopathy, nephropathy, neuropathy, hypertension, and hyperlipidemia were recorded. Patients with a history of cardiovascular disease, malignancy, angina pectoris, myocardial infarction, revascularization, and stroke were excluded. Before beginning the study, patients were informed regarding the study, and their written informed consents were obtained. The study was approved by the Gaziosmanpaşa Taksim Training and Research Hospital's Ethics Committee.

After patients had rested for 10 min, using a mercury sphygmomanometer with a cuff, their tensions were measured from both arms in the supine position on the basis of Korotkoff phase I and V sounds. Systolic and diastolic blood pressures were recorded. The patients' weight, height, and waist circumference were measured by the same person using standard measurement devices when patients were hungry in the standing position. Waist circumference was measured by considering the narrowest diameter between the arcus costarum and spina iliaca. Body mass index (BMI) was calculated by dividing the patient's weight by height squared (weight/height^2, kg/m^2). After 12-h fasting, glucose, creatinine, low-density lipoprotein (LDL), HDL, total cholesterol, triglyceride (TG), HbA1C, and C-reactive protein (CRP) levels were measured and recorded in the patients' files. Coagulation time for blood samples that were collected in dry flat tubes was measured and after being centrifuged for 3000 cycle/min, serum was collected. Complete urinary analyses were performed for all patients. Moreover, patients were requested to collect 24-h urine in plastic bottles following the first urination in the morning for evaluating creatinine clearance and microalbuminuria. Patients were told to avoid exercising before urine collection. Urinary infection and heart failure were ruled out. While evaluating microalbuminuria, the following values were taken as the basis: (1) Normoalbuminuria: <30 mg/24 h; (2) Microalbuminuria: 30–300 mg/24 h; (3) Macroalbuminuria: >300 mg/24 h.

All patients were referred to the Outpatient Clinic of Ophthalmology for ophthalmologic examination, which is recommended routinely to patients with type-2 DM, and the presence of retinopathy was recorded. All patients were questioned for the existence of neuropathy; patients with complaints were referred to the Outpatient Clinic of Neurology. Moreover, the presence of diabetic neuropathy was noted.

Patients with serum cholesterol level of >200 mg/dL and LDL level of >100 mg/dL, female patients with HDL level of <50 mg/dL, male patients with HDL level of <40 mg/dL, patients with triglyceride levels of >150 mg/d L or patients who had been treated for proven hyperlipidemia were accepted as hyperlipidemia. AIP was calculated as the logarithm of the ratio of the plasma triglyceride to HDL-C levels (8).

Statistical analysis

For statistical analyses, Number Cruncher Statistical System 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software was used. While evaluating the data, the convenience of quantitative data to normal distribution was assessed and the descriptive statistical methods and logarithmic transformation were applied for non-normally distributed triglyceride/HDL-C ratio. In the comparison between two groups with regard to normally distributed variables, Student's t-test was used. In the evaluation of three groups and over, which were non-normally distributed because of the number of cases, Kruskal–Wallis test was used. Furthermore, the Yates' continuity correction test was used for comparing qualitative data. Pearson correlation analysis was used for evaluating the relationships among parameters. Significance was evaluated at p values of <0.01 and <0.05.

Table 1. Evaluation of descriptive features between groups

	Patient group (n=212)	Control group (n=34)
	Mean±SD/n, %	Mean±SD/n, %
Age	55.53±10.42	54.44±3.25
Duration of diabetes	7.54	0
BMI (kg/m^2)	32.09±6.41	27.34±3.99***
Systolic pressure (mmHg)	130.03±21.78	118.52±8.39**
Diastolic pressure (mmHg)	75.16±11.93	73.97±7.86
Fasting blood glucose (mg/dL)	189.02±87.201	85.47±11.34***
HbA1c (%)	11.55±4.01	5.43±0.50*
Triglyceride (mg/dL)	193.39±150.98	154.91±64.53*
Total cholesterol (mg/dL)	213.61±36.35	208.40±49.06
LDL-C (mg/dL)	127.94±31.70	124.79±46.57
HDC-C (mg/dL)	48.40±12.59	48.47±13.04
T.Chol/HDL-C	4.62±1.13	4.4961±1.29
LDL-C/HDL-C	2.77±0.84	2.67±0.99
TG/HDL-C	4.12±3.04	3.59±2.09
AIP (log TG/HDL-C)	0.53±0.25	0.44±0.23*
CRP (mg/L)	10.44±5.15	2.62±1.08*
Creatinine Clearance (mL/min)	91.74±40.88	158.54±83.23***
OAD	60.1%	0%
OAD and insulin	23.8%	0%
Insulin	6.3%	0%
Antihypertensive drug	44.2%	0%
Antilipid drug	37.4%	0%

Student's t-test, Yates' continuity correction test, Mann–Whitney U test
Statistical significance: *p<0.05, **p<0.01, ***p<0.001
BMI: Body mass index; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; AIP: atherogenic index of plasma; OAD: oral anti-diabetic

Results

The study was conducted on 212 patients and a control group, including 34 individuals, in the Outpatient Clinic of Internal Diseases in the Gaziosmanpaşa Taksim Training and Research Hospital between January and June 2014. The ages of the patients varied between 26 and 81 years, and the mean age was 54.70±10.71 years. The mean duration of DM was found to be 7.51±7.43 years.

As seen in Table 1, the values of BMI, fasting blood glucose, HbA1C, triglyceride, CRP, AIP (log TG/HDL), and systolic blood pressure were found to be significantly higher in the DM group than in the control group (p<0.001; p<0.001; p<0.05; p<0.05; p<0.05; p<0.005, respectively). It was observed that creatinine clearance levels were significantly lower in the DM group than in the control group (p<0.001). Of the patients in the DM group, 60.1% used only OAD

Table 2. Biochemical features of patients with type 2 DM according to AIP (log TG/HDL)

	Low risk (<0.11) (n=8)	Moderate risk (0.11-0.24) (n=26)	High risk (>0.24) (n=178)
Fasting blood glucose	125.00±35.82[a**]	189.60±86.29	192.12±88.31[c*]
HbA1C	6.35±0.60[a*]	8.71±2.67	12.20±4.73
Microalbuminuria	4 (50%)	1 (3.8%)	58 (32.5%)
Neuropathy	4 (50%)	6 (23%)	56 (31.4%)
Retinopathy	4 (50%)	5 (19%)	48 (27%)

AIP: atherogenic index of plasma; DM: diabetes mellitus; HDL: high-density lipoprotein [a]; between low and moderate risk; [b]: between moderate and high risk; [c]: between low and high risk; statistical significance: *<0.05,** <0.01, ***<0.001

Table 3. Correlation between lipid profile and microvascular complications

	Patient group	
	R	p
Microalbuminuria and AIP (log TG/HDL)	0.221	0.01**
Microalbuminuria and T. cholesterol	-0.072	0.296
Microalbuminuria and LDL-C	-0.153	0.027*
Neuropathy and AIP (log TG/HDL)	-0.010	0.886
Neuropathy and T. cholesterol	-0.064	0.361
Neuropathy and LDL-C	-0.074	0.292
Retinopathy and AIP (log TG/HDL)	0.005	0.940
Retinopathy and T. cholesterol	-0.001	0.984
Retinopathy and LDL-C	0.017	0.809

Statistical significance: *p<0.05, **p<0.01, ***p<0.001
AIP: atherogenic index of plasma; LDL-C: low-density lipoprotein cholesterol; HDL: high-density lipoprotein

(oral antidiabetic), 23.8% used AOD and insulin, 6.3% only used insulin, 44.2% used antihypertensive drugs, and 37.4% used an antilipid.

Among the patients in the DM group, 25.7% had retinopathy, 31.6% had neuropathy, 29.1% had microalbuminuria, and 3.9% had macroalbuminuria. Considering that a patient having at least one of these disorders had complications, 62.6% of patients had complications.

Fasting blood glucose and AIP values were found to be significantly lower in the low-risk group than in the moderate-high risk group ($p<0.01$ and $p<0.05$, respectively) (Table 2). The value of HbA1C was lower in the low-risk group than in the moderate-risk group, which was statistically significant ($p<0.05$). Moreover, while 50% of patients in the low-risk group had microalbuminuria, neuropathy, and retinopathy, the rates of these diseases were 3.8% for microalbuminuria, 23% for neuropathy, and 19% for retinopathy in the moderate-risk group and 32.5% for microalbuminuria, 31.4% for neuropathy, and 27% for retinopathy in the high-risk group.

As shown in Table 3, a statistically significant correlation was detected between microalbuminuria and AIP ($p<0.01$). In addition, there was a statistically significant correlation between microalbuminuria and LDL-C ($p<0.05$). No correlation was found between other microvascular complications and the lipid profile.

Discussion

Diabetes mellitus is a chronic disease with rapidly increasing prevalence in our country and worldwide, which is observed among all age groups. It requires lifelong medical care and has important chronic complications (11). Although the development and progression of diabetic vascular complications can be delayed with a regular glycemic control in patients with DM, this strategy is insufficient for all patients (12). Therefore, different concepts must be focused on for preventing and treating DM complications.

In this study, the effect of AIP, which was detected to have a relationship with cardiovascular risk, on microvascular complications of DM was investigated. In our study, triglyceride level and AIP were higher in patients with type 2 DM than in the control individuals. Moreover, of patients with type 2 DM, 25.7% had retinopathy, 31.6% had neuropathy, 29.1% had microalbuminuria, and 3.9% had macroalbuminuria. The studies conducted for revealing the relationship between dyslipidemia and microvascular complications are inadequate because of short research duration and small study group; they could not be generalized (13). Moreover, the evidence obtained demonstrates that abnormal changes in lipid subgroups increase the risk for microvascular event (14). In the study of Zoppini et al. (15), which was currently performed with 979 Caucasian patients with type 2 DM and which demonstrated that high TG/HDL ratio almost doubled the risk for microvascular complications during a 5-year follow-up, it was suggested that there was a relationship between high plasma TG level and/or low plasma HDL-C level and microvascular complications. The study conducted by Hermans et al. (16) set-up a substructure for the study that will be performed for determining the best predictive model for evaluating the risk for microvascular complications.

In our study, in the evaluation of AIP according to the risk groups, fasting blood glucose and HbA1C values were found to be significantly lower in the low-risk group than in moderate-high risk groups. Furthermore, in 50% of the low-risk group, microalbuminuria, neuropathy, and retinopathy were detected. However, the rates were 3.8% for microalbuminuria, 23% for neuropathy, and 19% for retinopathy in the moderate-risk group and 32.5% for microalbuminuria, 31.4% for neuropathy, and 27% for retinopathy in the high-risk group. It was considered that these findings were associated with few cases in the low- and moderate-risk groups and the use of an antilipid drug by 37.4% of patients. In addition, the relationship between microvascular complications and lipid subgroups was investigated in our study, and a statistically significant correlation was detected between microalbuminuria and AIP and LDL-C. However, there was no relationship between retinopathy and neuropathy and the lipid profile. In an approximately 8-year follow-up of 574 patients with type 2 DM, low HDL-C levels were found to be independently correlated with the development of microalbuminuria (17). Moreover, in the study conducted on 2000 patients with type 2 DM, whose renal functions were normal or near normal, it was revealed that the frequency rate of chronic renal failure increased with low HDL-C levels, and this situation was independent of the presence of classical risk factors, such as diabetic retinopathy and other possible potential factors (18). Some small observational studies performed with patients with DM support the relationship between HDL-C or TG levels and the progression of renal disease (19). It was detected that high plasma

total cholesterol and TG levels were correlated with diabetic nephropathy and a decrease in renal functions (20). The study group of the Diabetes Atherosclerosis Intervention Study reported that fenofibrate therapy provided a significant decrease in the progression of albuminuria compared with the placebo (21).

In a study conducted in Europe, the severity of diabetic retinopathy increased with high plasma total cholesterol levels and low HDL-C levels; however, there was no statistically significant relationship between serum TG level and retinopathy (14). In contrast, some prospective studies demonstrated that a high total cholesterol level and other plasma lipid abnormalities were significantly correlated with the appearance and progression of diabetic retinopathy that was observed in the participants (22-24). Similarly, no relationship was found between HDL-C and TG levels and the risk for diabetic retinopathy in the Early Treatment Diabetic Retinopathy Study (24). The number of studies, which support that abnormal plasma lipid levels have a role in the pathogenesis of diabetic retinopathy and nephropathy and suggest possible benefits of lipid-lowering drugs in the prevention of these complications, is increasing (23-29). In the Fenofibrate Intervention and Event Lowering in Diabetes study, a significant reduction of risk was observed in the lower extremity amputation, albuminuria, and nephropathy progression, and laser application that was performed because of proliferative retinopathy in patients receiving fenofibrate therapy compared with patients receiving the placebo (30-32).

Similarly, in the Action to Control Cardiovascular Risk in Diabetes study investigating a strict glycemic control and combination therapy in dyslipidemia, the progression of diabetic retinopathy was found to decrease in patients receiving the fenofibrate therapy compared with those receiving the placebo (33). The interaction between diabetic neuropathy and abnormal levels of lipid subgroups have not yet been sufficiently investigated; however, a weak relationship was found only in one study (34). The EURODIAB IDDM Complication Study reported that autonomic neuropathy was related to a high fasting TG level and low HDL-C level in patients with type 1 DM.

Conclusion

In our study, no relationship was found between nephropathy with respect to microvascular complications and AIP in patients with type 2 DM. Further larger and prospective studies that will support the findings of our study and enable us to evaluate whether TG/HDL ratio is a potential treatment target for treating microvascular complications and preventing their development in patients with type 2 DM are required.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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