



Correlation of serum lipid profile and glycemic control parameters in patients with type 2 diabetes mellitus

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ABSTRACT

Introduction: Diabetes mellitus type 2 has become a global health-care problem of modern society due to a pronounced increase of prevalence to pandemic proportions and vascular complications. At present, glycosylated hemoglobin (HbA1c) is widely accepted as a measure of glycemic control in established diabetes. The aim of this study was to analyze the lipid profile in serum of patients with diabetes mellitus type 2, and its relationship with HbA1c levels.

Methods: The observational cross-sectional study included 60 diabetic patients, 30 men, and 30 women, age 32–94 years. Patients were assigned into two groups based on HbA1c values; Group 1: HbA1c \leq 7% (good glycemic control) and Group 2: HbA1c $>$ 7% (poor glycemic control). We analyzed the concentration of glucose, HbA1c, and lipid profile including total cholesterol levels, triglycerides (TAG), low-density lipoproteins (LDL), and high-density lipoproteins (HDL).

Results: Significantly lower values of glucose concentration, TAG and the ratio TAG/HDLc were obtained in the group of patients with good glycemic control. ($p < 0.0005$) Patients with good glycemic control had lower values of Castelli 1 and Castelli 2 index, and atherogenic index of plasma, compared to patients with poor glycemic control, but this difference was not significant. ($p > 0.005$) Our study revealed a significant positive correlation between HbA1c and triglyceride level ($r = 0.375$; $p = 0.003$) and HbA1c and ratio triglyceride/HDLc ($r = 0.335$; $p = 0.009$).

Conclusion: HbA1c can also be used as a predictor of dyslipidemia in type 2 diabetics in addition to as a glycemic control parameter.

Key words: diabetes mellitus type 2, DMT2, HbA1c, LDL, HDL, lipid profile

INTRODUCTION

UN Resolution of 2006 acknowledged diabetes as a global pandemic and infectious disease which

made it an important medical and public health issue (1). Diabetes is defined as a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (2). Chronic hyperglycemia is associated with significant long-term complications and affects many organ systems. The risk of chronic complications increases as a function of the duration of hyperglycemia and they usually become apparent in the

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second decade of hyperglycemia (3). Cardiovascular disease (CVD) is the major cause of morbidity and mortality in diabetes mellitus (4). It has been shown that the estimated risk of CVD increases by 18% for each 1% increase in absolute glycated hemoglobin (HbA1c) value in the diabetic population (5).

Furthermore, it has been reported that reducing the HbA1c level by 0.2% could lower the mortality by 10% (6). The level of HbA1c is used as a measure of the glycemic control of diabetic patients during the previous 2–3 months. Glycemic control with a decreased level of HbA1c is essential in preventing diabetic complications (7).

HbA1c test shows the long-term control of blood glucose levels in patients with diabetes mellitus. Glucose binds to hemoglobin in red blood cells at a steady rate. Since red blood cells last 3–4 months, the HbA1c test shows how much glucose is in the plasma. This test shows how well has been the diabetes mellitus controlled in the past 2–3 months. HbA1c may be increased falsely in certain medical conditions. These conditions include uremia (kidney failure), chronic excessive alcohol intake, and hypertriglyceridemia. Medical conditions that may falsely decrease HbA1c include acute or chronic blood loss, sickle cell disease or thalassemia (6,7).

The glycemic control of the patient has got a significant impact on the serum lipid level, and dyslipidemia is frequently encountered in those people with diabetes who have got poor glycemic control (8). Dyslipidemia is an important component of the metabolic syndrome defined in type 2 diabetes mellitus, and it is defined as a disorder of lipoprotein metabolism, including lipoprotein overproduction, or deficiency (9). Primary changes include not only just hypertriglyceridemia and decreased high-density lipoprotein (HDL) cholesterol levels but also abnormalities that can be seen in the structure of lipoprotein particles. In diabetes, the predominant form of low-density lipoprotein (LDL) cholesterol is the small, dense form. Small LDL particles are more atherogenic than large LDL particles because they can more easily penetrate and form stronger bound to the arterial wall, forming atherosclerotic plaque, and promoting atherosclerosis (10). Diabetic patients with elevated HbA1c values and dyslipidemia can be considered as a very high-risk group for CVD (11).

Therefore, the aim of this study was to analyze lipid profile in serum of patients with diabetes mellitus type 2, and its relationship with HbA1c levels.

METHODS

This cross-sectional, observational study was performed at the Clinical Center University of Sarajevo, Laboratory of Clinical Chemistry and Biochemistry. The study included 60 patients (30 females and 30 males) with a history of type 2 diabetes mellitus for at least five years. Exclusion criteria were: type 1 diabetes mellitus, lipid-lowering drugs, familial hypercholesteremic syndromes, chronic renal failure, ischemic heart disease, erythrocyte abnormalities conditions such as hemoglobinopathies, anemia, heavy bleeding, and liver disease. Patients were assigned to two groups depending on their glycated hemoglobin values: Group 1, patients with good glycemic control (HbA1c \leq 7%) (32 patients, 18 females and 14 males, age 38–94 years); Group 2, patients with poor glycemic control (HbA1c $>$ 7%) (28 patients, 12 females and 16 males, age 32–87 years). All patients underwent standard diagnostic protocol comprised of the detailed medical history questionnaire and physical examination. Blood samples from all patients were obtained in the morning after the 12-h fasting period. The blood samples were collected into empty tubes and immediately stored at +4°C. Biochemical analyses were performed the same day.

Serum glucose levels were determined by spectrophotometric hexokinase/G-6-PDH method. Serum total cholesterol (TC) was determined using spectrophotometric cholesterol oxidase/4-aminoantipyrene method. Triglyceride (TAG) levels were determined by spectrophotometric glycerol phosphate oxidase method. The LDL-cholesterol value was analyzed using an enzymatic method with cholesterol-esterase and cholesterol oxidase. The HDL-cholesterol value was determined in serum by cholesterol oxidase/phenol aminoantipyrene method. HbA1c was determined in whole blood by enzymatic method.

All analyses were performed at ARCHITECTc8000 Systems analyzer.

Castelli risk index 1 (TC/HDL-cholesterol), Castelli risk index 2 (LDL/HDL-cholesterol), atherogenic index of plasma (AIP) (\log [TAG/

HDL-cholesterol)], as well as the ratio of triglycerides (TAG) to HDL-cholesterol were calculated.

The study protocol was performed following the Helsinki Declaration as revised in 2000. All patients have signed written consent to participate in this study on a careful explanation of the study procedure. The study protocol was approved by the Ethics Committee of Faculty of Pharmacy, Sarajevo.

Statistical analysis

For statistical analysis of the data obtained, we used software package SPSS for Windows (version 19.0, SPSS Inc., Chicago, Illinois, USA).

Shapiro–Wilk test was used for testing the significance of deviation from a normal distribution. Results of descriptive statistics for numeric variables were represented as a median with 25th–75th percentiles, mean \pm standard deviation or mean \pm standard error of the mean.

Differences in variables between the groups were determined by the nonparametric Mann–Whitney U-test (TAG and HDL-cholesterol). The correlation coefficient between variables (HbA1c and glucose and HbA1c and ratio TAG/HDL-c) was assessed by Pearson's test. The correlation coefficient between variables HbA1c and TAG was assessed by Pearson's test. Difference between values of numeric variables two groups, which was normally distributed, was analyzed with an independent *t*-test (age, glucose, TC, LDL-cholesterol, and Castelli risk index 1 [TC/HDL-cholesterol], Castelli risk index 2 [LDL/HDL-cholesterol], and AIP [log[TAG/

HDL-cholesterol]]). Statistical significance was set at $p < 0.05$.

RESULTS

The biochemical characteristics of patients are shown in Table 1. Among total 60 types 2 diabetic individuals included in this study, 30 were male, and 30 were female. The mean age of male and female subjects was 63.83 ± 12.33 and 63.40 ± 12.35 years, respectively.

Results showed that patients with good glycemic control were significantly older compared to patients with poor glycemic control. ($p = 0.023$) The mean age of patients with good glycemic control was 67 ± 12.88 years, and on the other hand, the age of patients with poor glycemic control was 59.7 ± 10.4 years.

Patients with good glycemic control had significantly lower blood glucose levels, compared to patients with poor glycemic control. ($p < 0.0005$) Median glucose concentration in the serum of patients with good glycemic control was 6.99 ± 1.65 mmol/L, and for the group of patients with poor glycemic control, it was 13.63 ± 4.48 mmol/L.

Median serum triglyceride concentrations in the group of patients with good glycemic control were 1.48 (1.15 – 2.22) mmol/L and in patients with poor glycemic control 2.15 (1.4 – 3.32) mmol/L. Patients with good glycemic control had significantly lower median serum triglyceride concentrations when compared to a group of patients with poor glycemic control ($p = 0.03$).

TABLE 1. Biochemical parameters categorized by patients' glycemic control (HbA1c)

Parameter	HbA1c $\leq 7\%$ ($n=32$)	HbA1c $>7\%$ ($n=28$)	p value
Age (years)	67 ± 12.88	59.7 ± 10.4	0.023*
Glucose (mmol/l)	6.99 ± 1.65	13.63 ± 4.48	0.0005*
TC (mmol/l)	5.12 ± 1.20	5.34 ± 1.59	0.117
TAG (mmol/l)	1.48 (1.15–2.22)	2.15 (1.4–3.32)	0.03*
LDL cholesterol (mmol/L)	3.10 ± 1.18	3.20 ± 1.54	0.104
HDL cholesterol (mmol/L)	1.10 (0.82–1.36)	1.00 (0.80–1.97)	0.332
Castelli risk index 1 (TC/HDL-cholesterol)	4.86 ± 1.68	5.39 ± 2.21	0.073
Castelli risk index 2 (LDL/HDL-cholesterol)	3.02 ± 1.33	3.27 ± 1.75	0.076
AIP (log[TAG/HDL-cholesterol])	1.75 ± 0.19	2.79 ± 0.42	0.025*

*statistically significant, *TC: Total cholesterol, TAG: Triglycerides, AIP: Atherogenic index of plasma, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

The significantly lower value of the ratio TAG/HDL-cholesterol was found in the group of patients with good glycemic control. ($p = 0.025$) The median value of the ratio TAG/HDL-cholesterol in a group of patients with good glycemic control was 1.75 ± 0.19 and in the group of patients with poor glycemic control was 2.79 ± 0.42 .

Female patients had significantly lower values of Castelli risk index 1 compared to male patients ($p = 0.023$). Median value of Castelli risk index 1 in female patients was 4.53 ± 1.51 and in male patients 5.67 ± 2.18 .

Female patients had significantly lower values of the ratio TAG/HDL-cholesterol compared to male patients. ($p = 0.023$) The median value of the ratio TAG/HDL-cholesterol in female patients was 1.72 ± 0.16 and in male patients 2.76 ± 0.41 .

There was a significant positive correlation between the concentration of glycosylated hemoglobin with serum glucose concentrations ($r = 0.560$) in patients with type 2 diabetes mellitus (Figure 1). Furthermore, there is a significant positive correlation between the concentration of glycosylated hemoglobin and serum triglyceride concentrations ($r = 0.375$) (Figure 2), and significant positive correlation between the concentration of glycosylated hemoglobin with a ratio of TAG/HDL-c ($r = 0.335$) (Figure 3).

DISCUSSION

Diabetes represents global endemic with rapidly increasing prevalence in both developing and developed countries (4). Hemoglobin A1c is not only an important indicator of long-term glycemic control, but it also correlates well with the risk of long-term diabetes complications (11). CVD is the major cause of death in patients with type 2 diabetes mellitus. It begins with the process of atherosclerosis in which atherogenic plaque builds up inside arteries (9). Clinically, dyslipidemia is highly correlated with atherosclerosis, and up to 97% of patients with diabetes are dyslipidemia (12). Khan and associates reported that severity of dyslipidemia increases in patients with higher HbA1c value (13).

The aim of this study was to determine the glycemic status of patients with diabetes mellitus type 2, and its link to serum lipid parameters. Analysis of the age difference showed that the patients with good glycemic control were significantly older compared to patients with poor glycemic control. Similar findings reported Al Lawati and associates demonstrating that younger Omani diabetic patients exhibit worse glycemic levels compared to older patients (14). Furthermore, the results of the Hawaiian study showed that the patients under age 35 were significantly associated with sustained poor glycemic control, compared to patients between ages 50 and 64 years (15). However, Roy et al. in

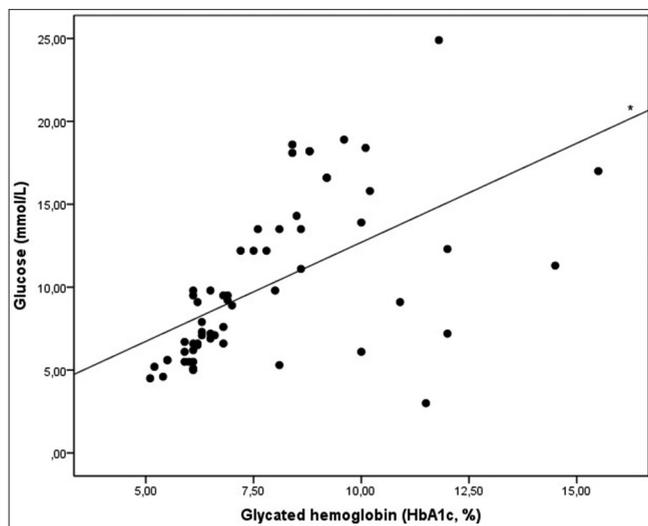


FIGURE 1. Correlation between concentrations of serum glucose and glycosylated hemoglobin (* $r=0.560$, $p<0.0005$).

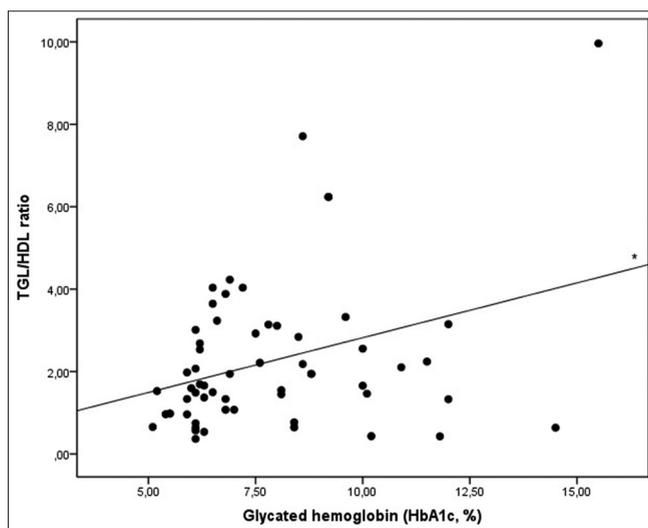


FIGURE 2. Correlation between concentrations of serum triglycerides and glycated hemoglobin (* $p=0.298$, $p=0.021$).

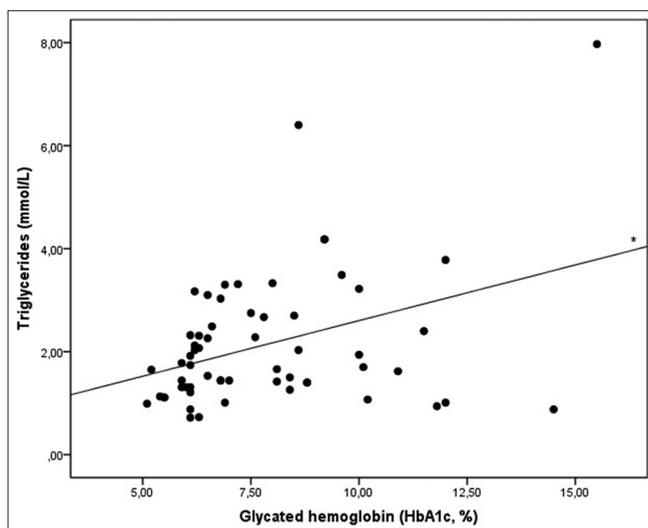


FIGURE 3. Correlation between triglyceride/HDL cholesterol ratio and concentration of glycated hemoglobin (* $r=0.335$, $p=0.009$).

their study showed that the patients older than 40 years had poorer glycemic control, compared to older patients (16). Possible reasons for poor glycemic control of younger adult patients may be the fact that they are less motivated to manage their diabetic condition, as they may be busy with their job, and have less time to comply with a healthy lifestyle, medication, and clinic visits (17).

Furthermore, the results of our study showed that patients with good glycemic control had significantly

lower serum concentrations of glucose and TAG compared to patients with poor glycemic control. TC levels were lower in patients with good glycemic control, compared to those with poor glycemic control, but no significant differences were found. Although levels of LDL-cholesterol were lower and HDL-cholesterol higher in patients with good glycemic control, there was no significant difference.

Rashid and Haider in their study showed that the serum levels of TC, TAG, and LDL-cholesterol were

significantly lower in patients with good glycemic control, while HDL-cholesterol was significantly higher (7). In a similar retrospective cohort study, all lipid fractions were deranged in patients with uncontrolled type 2 diabetes mellitus (18). Aboola-Abu from Nigeria also came up with similar findings and emphasized that good glycemic control and control of dyslipidemia could delay atherosclerosis and prevent coronary heart disease (19).

Our study showed that the serum concentrations of glucose, TC, TAG, and LDL-cholesterol were lower, as well as the value of HbA1c, and HDL-cholesterol was higher in female compared to male patients, but without statistical significance. Furthermore, female patients were mildly older than male patients, but there was no significant difference.

In a similar trial by Al-Alawi, serum concentrations of HDL-cholesterol were higher in female compared to male patients (20). Samantha and associates in their study showed conflicting results than ours. First of all, male patients were mildly older than female patients. Serum concentrations of glucose, TC, TAG, LDL-cholesterol, and HDL-cholesterol were higher in male patients; however, there was no significant difference (21). Possible cause of these differences may be the fact that the estrogens have an impact on lipid metabolism, so women at the younger age have lower serum values for TC compared to men. Furthermore, women are more conscious than men, and they may dedicate more attention on healthy lifestyle and prevention of disease. Studies have shown that the women develop CVD 7–10 years later than men (16).

In the assessment of risk for developing vascular complications in type 2 diabetes mellitus, size of LDL-cholesterol particles plays an important role, not just quantitative estimation of serum concentration. Quantitation of LDL-cholesterol particle size is possible with reliable, indirect, and a feasible marker of LDL-cholesterol particle size measured as TAG/HDL-cholesterol ratio (22). The higher values of the TAG/HDL-cholesterol ratio have been associated with the higher risk of cardiovascular events, even though serum concentrations of LDL-cholesterol are low (23). In our study, significantly lower values of the TAG/HDL-cholesterol ratio were found in the group of patients with good glycemic control and female patients.

In the case of normal lipid profile in patients with type 2 diabetes mellitus, the possibility of developing coronary heart disease cannot be excluded. Therefore, it is suggested to determine AIP, Castelli risk indexes 1 and 2 to predict and monitor coronary heart disease (24).

Results of our study showed that the AIP value was lower in patients with good glycemic control than in patients with poor glycemic control and the difference was at the limit of significance. Patients with good glycemic control had lower values of Castelli risk indexes 1 and 2, compared to patients with poor glycemic control, but this difference was not significant. Furthermore, the value of Castelli risk index 1 was significantly lower in female patients than in male, while the values of Castelli risk index 1 also were lower, but without significant differences.

Patil et al. in their study showed that the AIP value was significantly higher in patients who had coronary heart disease and diabetes mellitus, compared to patients who did not have coronary heart disease as an associated disease (24).

In our study, we also demonstrated the significant positive correlation between HbA1c value and TAG, and HbA1c, and TAG/HDL-cholesterol ratio.

The results of previous studies emphasize the importance of glycemic control on serum lipid profile levels and atherosclerosis in diabetic patients. Early diagnosis of dyslipidemia can be used as a preventive measure for the development of CVD in these patients (25–28).

CONCLUSION

Our study showed a statistically significant positive correlation between HbA1c and TAG, as well as HbA1c and TAG/HDL-cholesterol ratio, indicating that HbA1c is associated with dyslipidemia in patients with type 2 diabetes mellitus in addition to as glycemic control parameter. Improving glycemic control may improve the serum lipid profile, and thus significantly reduce the risk of cardiovascular events in this population of patients.

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CONFLICT OF INTERESTS

Authors declare no conflict of interest.

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