

Serum lipoprotein(a) and high sensitivity C reactive protein levels in Saudi patients with type 2 diabetes mellitus and their relationship with glycemic control

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Aim: To study serum lipoprotein(a) [Lp(a)] and high sensitivity C reactive protein (hsCRP) levels in Saudi patients with type 2 diabetes mellitus (DM) and their relationship with glycemic control.

Materials and methods: A total of 201 subjects were selected for the study. The final selection included 103 patients with type 2 DM (64 males and 39 females) and 98 healthy control subjects (58 males and 40 females). Fasting venous blood samples were analyzed for glucose, glycosylated hemoglobin (HbA1c), lipids, Lp(a), and hsCRP levels.

Results: Subjects with poor glycemic control showed significantly higher levels of fasting blood glucose levels (10.29 ± 3.56 vs. 7.05 ± 1.64 , $P = 0.0001$) and HbA1c (9.72 ± 2.54 vs. 6.56 ± 0.51 , $P = 0.0001$). Moreover, subjects with poor glycemic control were more obese than those with good glycemic control (BMI 30.63 ± 5.32 vs. 28.52 ± 4.93 , $P = 0.04010$). It was observed that the diabetics with poor glycemic control had significantly higher levels of serum triglycerides (2.32 ± 1.26 vs. 1.67 ± 1.37 , $P = 0.0426$), and hsCRP (5.16 ± 3.29 vs. 3.97 ± 2.5 , $P = 0.0423$) compared with the good glycemic control group. While the difference for TC, LDL, HDL, and Lp(a) was nonsignificant, significant positive correlations were observed between HbA1c, BMI ($r = 0.247$, $P = 0.038$), TG ($r = 0.247$, $P = 0.044$), and hsCRP ($r = 0.326$, $P = 0.006$).

Conclusion: Diabetic patients have higher levels of hsCRP and Lp(a) than healthy individuals. Diabetic patients with poor glycemic control have significantly higher hsCRP levels compared to those with good glycemic control. However, there is no effect of glycemic control on Lp(a) levels.

Key words: Type 2 diabetes mellitus, glycemic control, high sensitivity C reactive protein, lipoprotein(a)

1. Introduction

Diabetes mellitus (DM) is an established risk factor for cardiovascular disease (CVD) and is considered to be CVD equivalent. Glycosylated hemoglobin (HbA1c) concentrations predict CVD risk in diabetic patients and it is reported that good blood glucose control is associated with reduction in CVD. Elevated HbA1c levels are also associated with increasing CVD risk independent of classical risk factors in a continuous relationship across the whole normal distribution (1). Accelerated atherogenesis in DM is attributed to the dyslipidemic triad of higher levels of low density lipoprotein cholesterol (LDL), very low density lipoprotein cholesterol (VLDL), and lower levels of high density lipoprotein cholesterol (HDL) (2). It has been found that LDL lowering therapy and its assessment at baseline and follow ups reduces

the risk of subsequent coronary events even in patients with advanced atherosclerotic disease (3,4). Small dense LDL particles have been suggested to be associated with an increased risk of CVD more than other lipids (5,6). Strict metabolic control is recommended to reduce the risk of diabetic morbidity and premature mortality (7). Data from the United Kingdom Prospective Diabetic Study (UKPDS) conclusively demonstrated that improved blood glucose control in type 2 diabetics reduced microvascular complications by 25% (8). However, still the true pathogenic mechanism that leads to accelerated atherogenesis in DM is still not known because of its multisystem ramifications. Elevated lipoprotein(a) [Lp(a)] levels confer genetic predisposition to CVD and may be one of the links to accelerated atherogenesis in DM (9). Because of its structural similarity to plasminogen, it

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competes with its receptors on endothelial cells and fibrin, thus decreasing the fibrinolytic activity by decreasing formation of plasmin. This is responsible for a procoagulant state in such cases (10).

Several mechanisms linking Lp(a) and CVD have been proposed. In arterial intima, Lp(a) is located in atherosclerotic plaques, but not in the intact tissues. Lp(a) captured in the atherosclerotic plaque stimulates smooth muscle cells' proliferation and its binding to the extracellular matrix enhances lipid accumulation. As a nonfunctional structural homologue of plasminogen it can decrease fibrinolysis tendency in circulation (11,12). There is a significant correlation between the plasma concentration of Lp(a) and the severity of coronary artery disease (13). A large body of evidence has shown that the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) is an independent predictor of cardiovascular events and it also predicts risk of incident hypertension and diabetes (14). Both in type 1 and type 2 DM, HbA1c significantly correlates with hsCRP levels and future cardiovascular risk. Furthermore, hsCRP levels increase with progressive stages of beta cell dysfunction in insulin resistance syndromes (15). Serum glycated albumin and hs-CRP levels are reported to be independent predictors of cardiovascular events in patients with type 2 diabetes and existing CVD (16). Epidemiologic studies have shown that an increased cardiovascular risk exists in diabetics, even when TC, HDL, arterial blood pressure, and smoking habits are corrected. The explanation for the excess macrovascular complications is not yet readily apparent. There are different views regarding these complications in DM, like qualitative abnormalities in plasma proteins, hyperinsulinemia, platelet dysfunctions, and procoagulant state (17). The purpose of the present project was to study serum Lp(a) and hsCRP levels in Saudi patients with type 2 DM and their relationship with glycemic control.

2. Materials and methods

2.1. Subjects

This cross-sectional study was conducted in the Department of Physiology College of Medicine and King Khalid University Hospital, King Saud University, Riyadh. Patients were recruited from the outpatient clinics of King Khalid University Hospital. The project was approved by the College of Medicine ethics review board. Patients were recruited after they signed the consent form, which was designed in both Arabic and English. A total of 201 individuals were selected for the study. They included 103 patients with type 2 DM (64 males and 39 females) and 98 healthy control subjects (58 males and 40 females). Diagnosed patients with type 2 DM were recruited based on the American Diabetes Association (ADA) criteria (18). All the subjects were in stable metabolic condition.

All those with nephrotic syndrome, renal failure, thyroid problems, infections, stroke, diabetic ketoacidosis, and nonketotic hyperosmolar diabetes were excluded. The patients were divided into good and poor glycemic control groups based on a cutoff HbA1c value of 7.5%. The control group consisted of healthy subjects who were not suffering from any acute infection, or metabolic or psychological disorder. They had no history of familial hypercholesterolemias or DM.

2.2. Laboratory analysis

Overnight fasting blood samples were collected, and analyzed for fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL), Lp(a), and hsCRP. TC, TG, LDL, and HDL were analyzed by enzymatic colorimetric method with Dimension (USA) kits. HbA1c was measured by HbA1c Clover analyzer, by reflectance spectrophotometry. Human hsCRP and Lp(a) immunoassays were performed by quantitative standard sandwich ELISA technique using monoclonal antibody specific for these analytes with kits supplied by IBL International GMBH, Germany. The results of patients with hsCRP values >10 $\mu\text{g/L}$ were discarded and were re-evaluated after 2–3 weeks. We followed the guidelines of the American Heart Association for measurement, evaluation, and expression of hsCRP (19).

2.3. Statistical analysis

The data were analyzed with the Statistical Package for the Social Sciences (SPSS Version 19, Chicago, IL, USA). Descriptive characteristics of the study patients were calculated as mean \pm standard deviation (SD) for continuous variables. The tests applied for statistical analysis were Student's t test and Spearman's correlation analysis. Lp(a) data, due to its extreme skewness, was analyzed by a nonparametric statistical test, the Mann-Whitney U test. A P value of <0.05 was taken as statistically significant.

3. Results

This study examined the effect of glycemic control on cardiovascular risk markers. The participants were 103 subjects with DM and 98 healthy individuals. The descriptive characteristics of the diabetic and control subjects are shown in Table 1. The diabetic group significantly differed from the control group in fasting blood glucose level (5.04 ± 0.91 vs. 8.8 ± 3.28 , $P = 0.0001$) and HbA1C% (5.01 ± 0.60 vs. 7.66 ± 1.51 , $P = 0.0001$).

In Table 2 the lipid profile, Lp(a), and hsCRP are compared between the diabetic and control subjects. It shows that the diabetic subjects have significantly higher levels of serum TC (4.40 ± 1.08 vs. 4.85 ± 0.95 , $P = 0.0408$), TG (2.09 ± 1.63 vs. 1.38 ± 1.03 , $P = 0.0263$), and Lp(a) (27.51 ± 22.96 vs. 21.68 ± 16.98 , $P = 0.0326$).

Table 1. Comparison of descriptive characteristics and glycemc status between control and diabetic subjects.

M/F	Control N = 98 (Mean ± SD) 58/40	DM N = 103 (Mean ± SD) 64/39	P value
Age (years)	50.16 ± 11.81	52.07 ± 11.23	0.1745
Height (cm)	167.42 ± 8.21	165.79 ± 13.54	0.2735
Weight (kg)	78.85 ± 14.17	84.19 ± 20.43	0.0232
WHR	0.94 ± 0.11	1.00 ± 0.09	0.0000
BMI (kg/m ²)	28.13 ± 4.80	29.67 ± 5.23	0.0227
FBG (mmol/dL)	5.04 ± 0.91	8.8 ± 3.28	0.0001
HbA1c (%)	5.01 ± 0.60	7.66 ± 1.51	0.0001

BMI, body mass index; WHR, waist hip ratio; FBS, fasting blood glucose; HbA1c, glycosylated hemoglobin. P < 0.05 is significant

Table 2. Comparison of lipoprotein(a), hsCRP, and lipid profile between control and diabetic subjects.

M/F	Control (Mean ± SD) 58/40	DM (Mean ± SD) 64/39	P value
TC mmol/L	4.85 ± 0.95	4.4 ± 1.08	0.0415
TG mmol/L	1.38 ± 1.03	2.09 ± 1.63	0.0263
LDL mmol/L	2.98 ± 0.86	2.66 ± 0.92	0.1089
HDL mmol/L	1.14 ± 0.22	1.03 ± 0.37	0.1442
Lp(a) mg/dL	21.68 ± 16.98	27.51 ± 22.96	0.0326
hsCRP µg/mL	3.79 ± 2.47	4.76 ± 3.14	0.0096

TC, total cholesterol; TG, triglycerides; LDL, low density lipoprotein; HDL, high density lipoprotein; Lp(a), Lipoprotein(a); hsCRP, high-sensitivity C-reactive protein.

Differences were studied by Mann–Whitney U test for Lp(a) and Student's t test for other parameters. P < 0.05 is significant

The diabetic subjects were divided into good glycemc and poor glycemc control groups based on HbA1c cutoff of 7.5% (Table 3). Subjects with poor glycemc control had higher BMI than those with good glycemc control (BMI 30.63 ± 5.32 vs. 28.52 ± 4.93, P = 0.0401). Subjects with poor glycemc control showed significantly higher levels of fasting blood glucose (10.29 ± 3.56 vs. 7.05 ± 1.64, P = 0.0001) and HbA1c (9.72 ± 2.54 vs. 6.56 ± 0.51, P = 0.0001).

Table 4 shows a comparison of lipid profile, Lp(a), and hsCRP between the 2 diabetic groups. Diabetics with poor

glycemc control had significantly higher levels of serum TG (2.32 ± 1.26 vs. 1.67 ± 1.37, P = 0.0426) and hsCRP (5.16 ± 3.29 vs. 3.97 ± 2.5, P = 0.0423), while the difference for TC, LDL, HDL, and Lp(a) was nonsignificant.

Spearman's correlation analysis of HbA1c with descriptive characteristics, lipid profile, Lp(a), and hsCRP levels revealed significant positive correlations between HbA1c, BMI (r = 0.247, P = 0.038), TG (r = 0.247, P = 0.044), and hsCRP (r = 0.326, P = 0.006) (Table 5).

Table 3. Comparison of descriptive characteristics and glycemic status between good and poor glycemic control.

M/F	HbA1c < 7.5 N = 50 (Mean ± SD) 75/44	HbA1c ≥ 7.5 N = 53 (Mean ± SD) 71/39	P value
Age (years)	53.41 ± 10.95	50.93 ± 11.44	0.2577
Height (cm)	167.38 ± 6.18	164.47 ± 17.38	0.2771
Weight (kg)	78.6 ± 17.57	88.8 ± 21.59	0.0106
WHR	0.99 ± 0.07	1.01 ± 0.09	0.1613
BMI (kg/m ²)	28.52 ± 4.93	30.63 ± 5.32	0.0401
FBG (mmol/dL)	7.05 ± 1.64	10.29 ± 3.59	0.0001
HbA1c (%)	6.56 ± 0.51	9.72 ± 2.54	0.0001

BMI, body mass index; WHR, waist hip ratio; FBS, fasting blood glucose; HbA1c, glycosylated hemoglobin. P < 0.05 is significant.

Table 4. Comparison of serum lipoprotein(a), hsCRP and lipid profile in patients with type 2 diabetes mellitus with good and poor glycemic control.

	HbA1c < 7.5 N = 50 (Mean ± SD)	HbA1c ≥ 7.5 N = 53 (Mean ± SD)	P value
TC mmol/L	4.28 ± 0.91	4.53 ± 1.25	0.3277
TG mmol/L	1.67 ± 1.37	2.32 ± 1.26	0.0426
LDL mmol/L	2.63 ± 0.91	2.71 ± 0.94	0.6913
HDL mmol/L	1.00 ± 0.24	1.07 ± 0.48	0.4669
Lp(a) mg/dL	29.52 ± 23.11	25.82 ± 22.9	0.4042
hsCRP µg/mL	3.97 ± 2.5	5.16 ± 3.29	0.0423

TC, total cholesterol; TG, triglycerides; LDL, low density lipoprotein; HDL, high density lipoprotein; Lp(a), lipoprotein(a); hsCRP, high-sensitivity C-reactive protein. Differences were studied by Mann-Whitney U test for Lp(a) and Student's t test for other parameters. P < 0.05 is significant.

Table 5. Spearman's correlations analysis of HbA1c with descriptive characteristics, lipid profile, Lp(a), and hsCRP levels.

	Age	BMI	HbA1c	TG	TC	HDL	LDL	Lp(a)	hsCRP
Age	1.000	0.056	-0.004	-0.165	-0.218	-0.084	-0.148	-0.074	-0.092
BMI		1.000	0.247*	0.068	-0.011	-0.182	0.034	-0.136	0.417**
HbA1c			1.000	0.247*	0.232	0.192	0.136	-0.164	0.326**
TG				1.000	0.421**	-0.030	0.100	0.052	0.164
TC					1.000	0.202	0.733**	0.195	0.081
HDL						1.000	0.162	0.020	-0.131
LDL							1.000	0.152	0.161
Lp(a)								1.000	-0.042
hsCRP									1.000

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level.

4. Discussion

This study reports that diabetic patients with poor glycemic control have significantly higher hsCRP levels compared to those with good glycemic control. However, there is no effect of glycemic control on Lp(a) levels. hsCRP correlated significantly with poor glycemic control. In current strategies of global risk assessment, lipid testings are mostly the blood tests that are routinely recommended. However, hsCRP and Lp(a) evaluation may have the potential to improve cardiovascular risk prediction models when used in addition to traditional lipid profiles (20). Elevated hs-CRP levels have been associated with other indicators of diabetes-related cardiovascular risk, but had no correlation with disease duration or glucose control (21). However, we observed a positive correlation between HbA1c and hsCRP levels. In line with our study, Roopakala et al. reported that hsCRP levels showed a positive correlation with HbA1c in diabetic patients with nephropathy. These results suggest that estimation of serum hsCRP levels and aiming for good glycemic control may help in early intervention and prevention of further complications in diabetic patients (22). The predictive value of CRP for cardiovascular events and death has been reported to be much higher than traditional risk factors or parameters of metabolic control in type 2 diabetic patients.

The effect of hyperglycemia on the rate of synthesis, transcription, and translation of apo(a) is still not exactly known. The concentration of glycosylated Lp(a) is increased in the circulation in diabetic subjects (23,24). It is evident from many studies that glycosylation prolongs the half-life of lipoproteins and this may be true for Lp(a), which may lead to higher levels of Lp(a) in diabetes. In the present report Lp(a) levels were higher in poorly controlled diabetics than in well controlled diabetics, but the difference was not significant. This may be because

glycosylation may be affecting Lp(a) concentrations to a lesser extent than genetic determination. The effect of various other factors like insulin, exercise, estrogens, and niacin may be additive enough to affect Lp(a) magnitude significantly (25–27). A report from Kuwait revealed significantly higher levels of Lp(a) in children with poor glycemic control than in the good control group. However, the cutoff value used for HbA1c was 11%, unlike our cutoff point of 7.5% (28). Similar to our results, Smaoui et al. reported that no significant association of Lp(a) with glycemic control (HbA1c or fasting blood glucose) was noted in Tunisian type 2 diabetic patients. Additionally, positive correlations were observed between Lp(a) levels and total cholesterol and LDL-C (29). It is also reported that dyslipidemia prevalence increases with increasing blood glucose levels and thus the likelihood of cardiovascular risk would be high with poor glycemic control (30). In the present study it was observed that poor glycemic control was correlated significantly with higher values of BMI, TG, and hsCRP levels. However, there was no correlation of glycemic control with Lp(a) levels.

5. Conclusions

Diabetic patients have higher levels of hsCRP and Lp(a) than healthy individuals. Diabetic patients with poor glycemic control have significantly higher hsCRP levels compared with those with good glycemic control. However, there is no effect of glycemic control on Lp(a) levels.

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