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A Study of Nontraditional Biochemical Markers and Their Relation to the Level of Fasting Glycemia in Patients with Type 2 Diabetes Mellitus

Tip 2 Diabetes Mellituslu Hastalarda Geleneksel Olmayan Biyokimyasal Belirteçlerin ve Açlık Glisemi Düzeyleri ile İlişkilerinin İncelenmesi

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Abstract

Objective: Diabetes mellitus, a chronic metabolic disorder, is associated with the risk of cardiovascular disease in developing countries. Certain nontraditional cardiovascular risk factors have been associated with diabetes mellitus. The increased level of lipoprotein (a) [Lp (a)] is a genetically determined, independent risk factor for cardiovascular disease. The elevated levels of high-sensitive C-reactive protein frequently correlate with well-established risk factors of Type 2 diabetes mellitus. However, the association between Lp (a), high-sensitive C-reactive protein levels, and Type 2 diabetes mellitus remain uncertain. The aim of this study was to measure the nontraditional biochemical markers of cardiovascular risk regarding the level of fasting glycemia in patients with Type 2 diabetes mellitus compared with nondiabetic persons.

Material and Methods: This cross-sectional study was conducted in four groups (n=50 each group) considering the current levels of fasting plasma glucose. The groups were as follows: group 1 included nondiabetic healthy controls with the current fasting plasma glucose level of less than 100 mg/dL, group 2 included patients with Type 2 diabetes mellitus with fasting plasma glucose level in the range of 100-130 mg/dL, group 3 included patients with Type 2 diabetes mellitus with fasting plasma glucose level of greater than 130 mg/dL but less than 200 mg/dL, and group 4 included patients with Type 2 diabetes mellitus with fasting plasma glucose level of greater than 200 mg/dL.

Results: Lp (a) levels were significantly elevated in the patients with various glycemic levels compared with nondiabetic persons ($p<0.001$).

Conclusion: The results of this study conclude that Lp (a) and high-sensitive C-reactive protein levels are elevated in patients with Type 2 diabetes mellitus compared with that in healthy controls. The elevated levels of nontraditional cardiovascular risk factors reflect the glycemic status by showing an association between fasting plasma glucose, Lp (a), and cardiovascular disease.

Keywords: Cardiovascular disease risk; diabetes mellitus; glycemia; lipoprotein (a); high-sensitive C-reactive protein

Özet

Amaç: Kronik bir metabolik bozukluk olan diabetes mellitus, gelişmekte olan ülkelerde kardiyovasküler hastalık riski ile ilişkilidir. Bazı geleneksel olmayan kardiyovasküler risk faktörleri diabetes mellitus ile ilişkili bulunmuştur. Artan lipoprotein (a) [Lp (a)] düzeyi, kardiyovasküler hastalık için genetik olarak belirlenmiş bağımsız bir risk faktörüdür. Yüksek duyarlı C-reaktif proteinin yüksek düzeyleri, Tip 2 diabetes mellitusun iyi bilinen risk faktörleri ile sıklıkla korelasyon göstermektedir. Bununla birlikte, Lp (a), yüksek duyarlı C-reaktif protein düzeyleri ve Tip 2 diabetes mellitus arasındaki ilişki hâlâ belirsizdir. Bu çalışmada, diyabetik olmayan kişilere göre Tip 2 diabetes mellituslu hastalarda açlık glisemi düzeyiyle ilişkili olarak kardiyovasküler riskin geleneksel olmayan biyokimyasal belirteçlerinin ölçülmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu kesitsel çalışma, mevcut açlık plazma glukozu düzeyleri göz önünde bulundurularak dört grupta gerçekleştirildi (her grupta n=50). Gruplar şu şekildeydi; grup 1: mevcut açlık plazma glukozu düzeyi 100 mg/dL'nin altında olan nondiyabetik sağlıklı kontroller, grup 2: açlık plazma glukozu düzeyi 100-130 mg/dL aralığında olan Tip 2 diabetes mellituslu hastalar, grup 3: açlık plazma glukozu düzeyi 130 mg/dL'den büyük, ancak 200 mg/dL'den küçük olan Tip 2 diabetes mellituslu hastalar ve grup 4: açlık plazma glukozu düzeyi 200 mg/dL'den yüksek olan Tip 2 diabetes mellituslu hastalar.

Bulgular: Çeşitli glisemik düzeylere sahip hastalarda Lp (a) düzeyleri, diyabetik olmayan kişilere göre anlamlı olarak yüksek bulunmuştur ($p<0,001$).

Sonuç: Bu çalışmada, sağlıklı kontrollere kıyasla Tip 2 diabetes mellitus olan hastalarda, Lp (a) ve yüksek duyarlı C-reaktif protein düzeylerinin yüksek olduğu sonucuna varılmıştır. Geleneksel olmayan kardiyovasküler risk faktörlerinin artmış düzeyleri, açlık plazma glukozu, Lp (a) ve kardiyovasküler hastalık arasında bir ilişki ortaya koyarak, glisemik durumu yansıtmaktadır.

Anahtar kelimeler: Kardiyovasküler hastalık riski; diabetes mellitus; glisemi; lipoprotein (a); yüksek duyarlı C-reaktif protein

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Introduction

Type 2 diabetes mellitus (T2DM) has a higher risk of cardiovascular disease (CVD) leading to morbidity and mortality. CVD in patients with T2DM cannot be attributed solely to the higher prevalence of traditional risk factors. Therefore, other nontraditional risk factors may be crucial in patients with T2DM. Some of the nontraditional cardiovascular risk factors that have been associated with diabetes mellitus (DM) were high-sensitive C-reactive protein (hsCRP), lipoprotein (a) [Lp (a)], fibrinogen, uric acid, homocysteine, and microalbuminuria (1). Lp (a) is a unique low-density lipoprotein (LDL) produced by liver cells that contains a plasminogen-like glycoprotein, apolipoprotein (a) (apo (a)), which is covalently bound to apolipoprotein B–100 (2). Among the general population, Lp (a) has been proposed as a causal risk factor for CVD (3). Although the genetic variations in the LPA gene are the main determinants to affect Lp (a) concentrations, nongenetic factors can also influence Lp (a) concentrations (4). In the general population as well as in patients with diabetes, the increased level of Lp (a) has been identified as a major risk factor for atherosclerosis (5). Both the high concentrations of serum Lp (a) and T2DM increase the risk of CVD (6). However, the relationship between the elevated levels of serum Lp (a) and T2DM is poorly characterized. The association between the concentrations of Lp (a) and T2DM remains uncertain. Previous studies have reported the elevated concentration of Lp (a) in patients with T2DM with poor metabolic control and that with an improvement in the metabolic control, the serum Lp (a) concentration decreases (7). However, some studies have also reported an unchanged or decreased serum Lp (a) concentrations in patients with T2DM with poor metabolic control (8). Because of the structural similarity to an LDL particle, Lp (a) is found to contribute to lipid-induced atherogenesis (9). The similarity of Lp (a) to an LDL particle and its ability to undergo oxidation are the reason associated with the atheroma development, and hence, it may be involved in foam cell formation, smooth cell proliferation, endothelial dysfunction, and vascular inflammation (10). Lp (a) interferes with the function of plasminogen because of its unique structural homology with plasminogen and thus increases the risk of thrombosis. Lp (a) competes with plasminogen receptors present on the endothelial cells leading to a diminished formation of plasmin, thereby delaying the clot lysis and promoting thrombosis. Hence, Lp (a) is considered an independent risk factor for atherosclerosis (11). Among the population, Lp (a) levels were found to vary from less than 0.5 mg/dL to 200 mg/dL. The cutoff value of Lp (a) to classify subjects as being at an increased risk of CAD varies greatly among studies and ranges from 20 to 40 mg/dL (12,13); however, in the Indian population, the optimal level of Lp (a) concentration was greater than 20 mg/dL (14). The elevated levels of C-reactive protein are the major factor in the development of CVD, independent of traditional risk factors (15). Studies have suggested that hsCRP independently predicts CVD, but whether it can lead to cardiovascular risk in patients with T2DM is not well documented (16,17). The relationship between Lp (a) concentrations and lipid and glycemic levels and inflammation remains poorly characterized, and there are limited studies on the South Indian population. Hence, to determine whether diabetes mellitus (DM) and its degree of glycemic status are associated with elevated levels of Lp (a), this study was conducted to estimate the serum Lp (a) and hCRP concentrations in patients with T2DM with varying levels of fasting glycemia compared with nondiabetic persons.

Material and Methods

This was a prospective cross-sectional study conducted on blood samples collected for the analysis of fasting plasma glucose (FPG) along with plain serum for other biochemical investigations received in the clinical biochemistry laboratory, the Department of Biochemistry, at Sri Venkateswara Institute of Medical Science, Tirupati, India. This study included 200 subjects (n=50 each) of both the genders between the age group of 36 and 70 years who were categorized into the following four groups: group 1 included nondiabetic healthy controls with FPG of less than 100 mg/dL, group 2 included patients with T2DM with FPG of 100–130 mg/dL (well-controlled diabetes), group 3 included patients with T2DM with FPG of greater than 130 mg/dL but less than 200 mg/dL (moderately well-controlled diabetes), and group 4 included patients with T2DM with FPG of greater than 200 mg/dL (grossly uncontrolled diabetes). The patients with T2DM, chronic kidney and liver diseases, any inflammatory disease, and acute infection and those taking any medication known to affect the levels of Lp (a) or hCRP were excluded from this study. The study was conducted after obtaining approval from the institutional ethics committee.

Sample Collection

Fasting plasma samples from patients with T2DM (n = 150) and healthy individuals (n = 50) were collected in the clinical biochemistry laboratory. Identified samples were transferred into appropriately labeled aliquots and stored at −80 °C until further biochemical analysis. The files of the patients were reviewed for obtaining information on their age, the presence or absence of DM, and the history of infections and medications.

Laboratory Analysis

FPG, serum creatinine, total cholesterol, triglycerides, and high-density lipoprotein cholesterol were estimated using glucose oxidase-peroxidase method, modified Jaffe's rate kinetic method, cholesterol oxidase-peroxidase method, enzymatic colorimetric method, and polymer detergent method, respectively (18-20). LDL cholesterol and very LDL cholesterol were calculated using Friedewald's formula (21). All the above parameters were analyzed on clinical chemistry autoanalyzer Beckman Coulter DXC 600 Synechron, USA. Lp (a) and hCRP were estimated using immunoturbidimetric method using the commercial kits on ChemWell autoanalyzer (22,23).

Statistical Analysis

All the continuous variables were tested for data distribution using the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ±standard deviation for continuous variables and as frequency (number [%]) for categorical variables. The means across the groups were compared using the analysis of variance, followed by post hoc analysis. Pearson's rank correlation was used to determine the correlations of Lp (a) with other variables. All the statistical analyses were performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered significant.

Results

This study included 150 patients with T2DM and 50 controls. The mean ±standard deviation of the biochemical parameters was estimated using one-way analysis of variance for comparison of various parameters among different groups as shown in Table 1. A significantly higher level of FPG, serum lipids, Lp (a), and hCRP was observed in patients with T2DM than that in the controls (p<0.001). Serum creatinine levels were not considerably different in patients with T2DM when compared with the controls. The significance of the difference between the means within the groups using the Bonferroni post hoc analysis is shown in Table 2. Lp (a) levels progressively increased in patients with various glycemic levels compared with that in nondiabetic individuals (p<0.001). Lp (a) levels were considerably higher in patients with T2DM with FPG of 100-130 mg/dL than hCRP, which was significantly higher in patients with T2DM with FPG of greater than 130 but less than 200 mg/dL. The correlation of Lp (a) with other cardiovascular risk factors using Pearson's correlation analysis is shown in Table 3. In this study, Lp (a) was found to have

Table 1. Mean±SD of the various biochemical parameters across the groups of the present study by using one way ANOVA.

Parameter	Group 1	Group 2	Group 3	Group 4	p value
FPG (mg/dL)	86.96±8.36	112.14±8.09	154.26±22.86	266.94 ±63.82	0.000*
S. CHOL (mg/dL)	171.78±24.67	165.46±38.93	155.28±43.43	185.22 ±44.23	0.002*
S. TGL (mg/dL)	106.82±31.29	146.66 ±50.93	140.18 ±64.73	174.56±68.30	0.000*
S. HDL-C (mg/dL)	53.36± 6.79	39.80±6.15	41.08±8.33	41.28±5.94	0.000*
S. VLDL-C (mg/dL)	21.45±6.34	29.34±10.19	28.03±12.94	35.10 ±13.74	0.000*
S. LDL-C (mg/dL)	99.66±27.25	96.32±34.04	117.91±40.49	108.83±43.67	0.017*
S. LP (a) (mg/dL)	20.77±7.81	31.91 ±17.49	36.88 ±19.42	56.24±21.21	0.000*
hs- CRP (mg/L)	0.40 ±.0.37	0.69±0.46	0.90±.72	1.30±0.856	0.000*
S. Creat (mg/dL)	0.82±0.18	0.67.± 0.22	0.76±0.41	0.76 ±.028	0.077†

Group 1: Non- diabetic healthy controls (<100 mg/dl), Group 2: Well controlled diabetes (80-130 mg/dl), Group 3: Moderately well controlled diabetes (> 130 but < 200 mg/dl), Group 4: Grossly uncontrolled diabetes (>200 mg/dl). FPG:Fasting plasma glucose; Crea: Creatinine; CHOL: Cholesterol; TGL: Triglycerides; HDL: High density Lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density Lipoprotein; LP (a): Lipoprotein (a), hs-CRP: High sensitivity C-reactive protein.
* Significant at the 0.05 probability level. †NS, Not significant at the 0.05 probability level.

Table 2. Showing the significance of changes between the groups of the present study by Post Hoc Bonferroni analysis.

Parameter	Group 1 vs 2	Group 1 vs 3	Group 1 vs 4	Group 2 vs 3	Group 2 vs 4	Group 3 vs 4
FPG (mg/dL)	0.002*	0.000 *	0.000*	0.000*	0.000*	0.000*
S. CHOL (mg/dL)	1.000†	0.191 †	0.501†	1.000†	0.068†	0.001*
S. TGL (mg/dL)	0.003*	0.019 *	0.000*	1.000†	0.079†	0.014*
S. HDL-C(mg/dL)	0.000*	0.000 *	0.000*	1.000†	1.000†	1.000†
S. VLDL-C (mg/dL)	0.003*	0.022 *	0.000*	1.000†	0.064†	0.011*
S. LDL-C(mg/dL)	1.000†	0.060 †	1.000†	0.023*	0.549†	1.000†
S. LP (a) (mg/dL)	0.009*	0.000 *	0.000*	0.913†	0.000*	0.000*
S.hs- CRP (mg/L)	0.157†	0.000 *	0.000*	0.596†	0.000*	0.010*
S. Creat (mg/dL)	0.060†	1.000 †	1.000†	0.749†	0.593†	1.000†

Group 1: Non-diabetic healthy controls (<100 mg/dl) ,Group 2: Well controlled diabetes (80-130 mg/dl), Group 3: Moderately well controlled diabetes (>130 but <200 mg/dl), Group 4: Grossly uncontrolled diabetes (>200 mg/dl). FPG: Fasting plasma glucose; Crea: Creatinine; CHOL: Cholesterol; TGL: Triglycerides; HDL: High density Lipoprotein; LDL: Low density Lipoprotein; VLDL: Very low density Lipoprotein; LP (a): Lipoprotein(a); hs-CRP: High sensitivity C-reactive protein.
* Significant at the 0.05 probability level. †NS, Not significant at the 0.05 probability level.

Table 3. Showing the Pearson correlation analysis of LP(a) with biochemical markers

Parameter	r	p
FPG (mg/dL)	0.412	0.000*
S. CHOL (mg/dL)	0.165	0.043*
S. TGL (mg/dL)	0.147	0.072†
S. HDL-C (mg/dL)	0.050	0.542†
S. VLDL-C (mg/dL)	0.033	0.684†
S. LDL-C (mg/dL)	0.128	0.117†
S hs- CRP (mg/L)	0.427	0.000*
S. Creat (mg/dL)	0.103	0.208†

Group 1: Non-diabetic healthy controls (<100 mg/dl), Group 2: Well controlled diabetes (80-130 mg/dl) , Group 3: Moderately well controlled diabetes (>130 but <200 mg/dl), Group 4: Grossly uncontrolled diabetes (>200 mg/dl). FPG: Fasting plasma glucose; Crea: Creatinine; CHOL: Cholesterol; TGL: Triglycerides; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; hs-CRP: High sensitivity C-reactive protein.
* Significant at the 0.05 probability level. † NS, Not significant at the 0.05 probability level.

a significant positive correlation with FBS (r=0.412, p<0.001), total cholesterol (r=0.165, p=0.042), and hCRP (r=0.423, p<0.001) in the entire pool of patients with diabetes, although it does not correlate with other lipid parameters (p>0.05). Figure 1 shows the proportion of patients with Lp (a) greater than 20 mg/dL in all the groups using a bar diagram. The proportion of patients with elevated Lp (a) levels of greater than 20 mg/dL was highest in poorly controlled diabetes group (56%), followed by moderately controlled and well-controlled diabetes groups (37% and 31%, respectively). The association of Lp (a) with FPG and hCRP is shown in Figure 2 using scatter plots.

Discussion

In this study, a progressive increase was observed in the levels of serum Lp (a) with the worsening of glycemic control. This study results showed that patients with well-controlled diabetes had elevated Lp (a) values compared with healthy controls. However, the levels increased further with worsening glycemic status. This indicates that these patients are more prone to atherogenesis than the other glycemic groups. In agreement with the findings of this study, elevated serum Lp (a) levels in diabetes have been reported in some studies (24) but

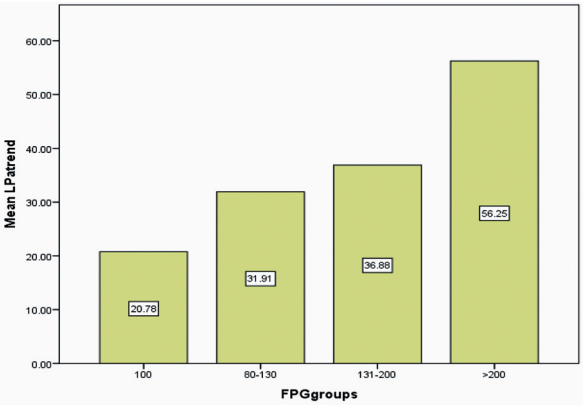

Figure 1: Bar diagram showing the proportion of patients with Lp(a) > 20 mg/dL in varied glycaemic ranges.

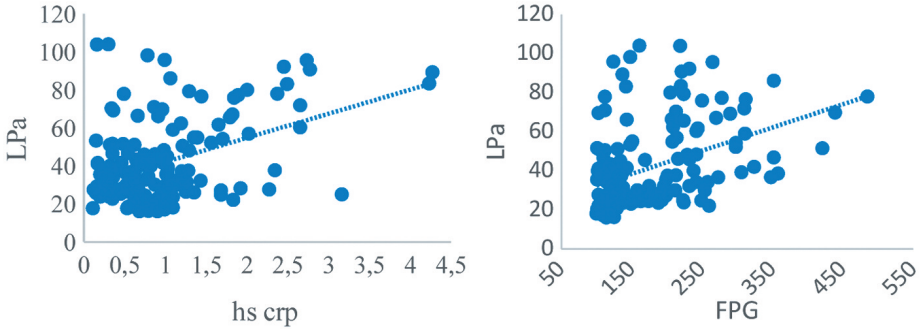

Figure 2: Scatter plots showing association of LPa with FPG and hs CRP.

not in all studies (12,25). In this study, a significant positive correlation was observed between Lp (a) and FPG in patients with diabetes as a whole ($p<0.001$). The increase in the rate of Lp (a) synthesis is dependent more on the rate of its synthesis rather than its catabolism. The increased rate of secretion of apolipoprotein B-100 from the liver may contribute toward the increase of LDL and Lp (a) concentrations. In patients with diabetes, the decreased rate of LDL catabolism leads to a decrease in the clearance of apolipoprotein B-100. As Lp (a) is constituted by apolipoprotein (a) and LDL, a decrease in the catabolism of LDL may naturally reflect on the level of Lp (a) (26). Simultaneous Lp (a) and apolipoprotein B kinetic studies may help to elucidate the mechanism of Lp (a) elevation. As reported by King et al., elevated C-reactive protein, a marker of chronic inflammation, is a major factor causing an increase in CVD, independent of traditional risk factors, which is in agreement with this study (27). Low-grade inflammation may be closely involved in the pathogenesis of dyslipidemia and atherosclerosis in T2DM (28). From the above findings, the elevated Lp (a) and hCRP levels may be the factors that have the potential to enhance coagulation and thrombotic process, triggering the vascular events in T2DM.

Conclusion

This study concludes that Lp (a) and hCRP levels are higher in patients with T2DM than healthy controls. Furthermore, the levels of Lp (a) increase with worsening glycemia. Hence, the elevated nontraditional cardiovascular risk factors may be responsible for the increased risk in patients with T2DM.

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Authorship Contributions

Idea/Concept: Harini Devi Nimmanapalli, Pullaiah Pasupuleti, Suresh Vakkakara, Srinivasa Rao PVLN; Design: Harini Devi Nimmanapalli, Pullaiah Pasupuleti, Suresh Vakkakara, Srinivasa Rao PVLN; Control/Supervision: Harini Devi Nimmanapalli, Pullaiah Pasupuleti; Data Collection and/or Processing: Harini Devi Nimmanapalli, Pullaiah Pasupuleti; Analysis and/or Interpretation: Harini Devi Nimmanapalli; Literature Review: Harini Devi Nimmanapalli, Pullaiah Pasupuleti, Suresh Vakkakara, Srinivasa Rao PVLN; Writing the Article: Harini Devi Nimmanapalli; Critical Review: Harini Devi Nimmanapalli, Suresh Vakkakara; References and Fundings: Harini Devi Nimmanapalli; Materials: Harini Devi Nimmanapalli, Pullaiah Pasupuleti.

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