Atherogenic dyslipidemia in diabetic nephropathy: lipoprotein (a), lipid ratios and atherogenic index

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ABSTRACT

Background: Atherogenic lipid profile is reported to become pronounced with onset of nephropathy. Lipid ratios also indicate atherogenic dyslipidemia. Lipoprotein (a) [(Lp(a)] considered as an independent risk factor for cardiovascular diseases (CVD), may play an important role in development and progression of nephropathy in type 2 diabetes mellitus (T2DM). The present study aimed to assess atherogenic dyslipidemia in T2DM and diabetic nephropathy patients.

Methods: Total cholesterol (TC), triglycerides(Tg), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), Lp(a), lipid ratios: TC/HDL, Tg/HDL, LDL/HDL, non-HDL cholesterol and atherogenic index (AI) was assessed in T2DM (n=35), diabetic nephropathy (n=30) and healthy individuals (n=30). Means of biochemical parameters were compared by ANOVA (analysis of variance). Pearson correlation was performed to study the association between parameters. Receiver operating characteristics (ROC) curve analysis was done to assess the predictive ability of the variables.

Results: Atherogenic dyslipidemia with elevated Lp(a), TC, Tg, VLDL, LDL, non-HDL cholesterol, lipid ratios, AI and low HDL levels were observed in both T2DM patients with and without nephropathy when compared to controls. Significantly high Tg/HDL, TC/HDL and AI were observed in diabetic nephropathy when compared to T2DM.

Conclusion: T2DM and diabetic nephropathy are associated with dyslipidemia which was more pronounced in diabetic nephropathy. Elevated Lp(a) levels may be considered as an independent CVD risk marker in T2DM and diabetic nephropathy patients along with atherogenic lipid ratio indicators.

Keywords: Atherogenic dyslipidemia, Lipid ratios, Atherogenic index, Cardiovascular disease, Diabetic nephropathy

INTRODUCTION

Diabetes mellitus is a well known cause for cardiovascular diseases (CVD). Atherogenic dyslipidemia of diabetes also known as diabetic dyslipidemia is characterized by elevated very low density lipoprotein (VLDL), small dense low density lipoprotein (LDL) and low high density lipoprotein (HDL) levels, which constitute the lipid triad and are considered as traditional risk factors for CVD.¹ Lipid ratios have also been found to indicate an atherogenic risk and are said to better predictors of coronary artery diseases than lipids alone. The ratio of triglycerides to HDL-cholesterol (Tg/HDL-c) is said to correlate inversely with the level of small, dense LDL particles and atherogenic index (AI) calculated as log of Tg/HDL is a strong predictor of CVD events.² Non-HDL cholesterol is an indicator of atherogenic apolipoprotein B (apo B) containing lipoproteins such as LDL, VLDL and Lp(a) and is accepted as a marker of apo B.³ One of the common complications of diabetes mellitus is nephropathy. Diabetic nephropathy is characterized by proteinuria, hypertension, progressive loss of renal
function, and a high incidence of cardiovascular morbidity and mortality. The risk of death from CVD is substantially increased in diabetic nephropathy patients when compared with diabetic patients without nephropathy. Atherogenic lipid profile which persists in diabetic nephropathy may contribute to the increased risk of CVD.

Lipoprotein(a)(Lp(a)) molecule is structurally similar to low density lipoprotein(LDL), with apolipoprotein(a) bound to apolipoprotein B-100 by a disulfide bond. It has also been found to contribute to the microvascular complications and an elevated level of serum Lp(a), is a significant risk factor for atherothrombogenesis in both diabetic and nondiabetic subjects. Lp(a) is said to be an independent risk factor for progression of diabetic nephropathy in type 2 diabetic patients (T2DM) with overt proteinuria.

Hence, the present study aimed to evaluate the atherogenic risk by assessing lipid profile, Lp(a), non-HDL cholesterol, lipid ratios and AI in patients with T2DM and diabetic nephropathy in comparison with healthy controls. We further wanted to assess the severity of atherogenic dyslipidemia in diabetic nephropathy group in comparison with the diabetic patients.

METHODS

Subjects: A total of ninety five (n=95) subjects (51 males and 44 females, aged 22-72 yrs) were recruited into the study. The study was approved by the institutional ethical committee. Informed consent was obtained from the patients and controls. Thirty (n=30) healthy age and sex matched individuals having no history of diabetes mellitus, coronary heart disease, hypertension and active infection were enrolled as control group. Thirty five (n=35) T2DM patients were enrolled in group-I. Thirty (n=30) type 2 diabetes mellitus patients with nephropathy evidenced by proteinuria >500 mg/day were enrolled in group-II.

Sample collection: Five ml of venous blood samples were collected from the subjects in plain bottles after an overnight fast of 12 hours. The samples were allowed to stand for half an hour following which they were centrifuged for 15 minutes at 2000rpm and the serum was separated and stored at -80°C until biochemical analysis.

Laboratory analysis: Serum total cholesterol, triglycerides (Tgl), high-density lipoprotein cholesterol (HDL), Lp(a), urea and creatinine were measured using commercially available kits on Beckman Synchron CX9 chemistry analyzer (USA). Low-density lipoprotein cholesterol (LDL) and very low density lipoprotein cholesterol (VLDL) was calculated using Friedewald's formula.: Lipid ratios were calculated as TC/HDL, LDL/HDL, Tgl/HDL. AI calculated as logTgl/HDL and non-HDL cholesterol calculated as a difference between total cholesterol and LDL cholesterol.

Statistical Analysis: Data distribution was tested using Kolmogorov-Smirnov test. Data was expressed as mean and standard deviation (±SD). Statistical comparisons of the means between the three groups were made using one way analysis of variance (ANOVA) with post hoc LSD test. Pearson correlation analysis was performed to study the association between parameters. Receiver operator characteristic (ROC) curve was constructed to study the strength of the variables in predicting CVD risk. A p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using statistical software, SPSS version 16.0.

RESULTS

Table 1 shows the mean and standard deviation of the biochemical parameters between the groups. One way ANOVA revealed a significant elevation in cholesterol, Tgl, LDL, VLDL and Lp(a) levels (p<0.01) in group I (T2DM) and group II (diabetic nephropathy) patients when compared to controls. A significant decrease in HDL levels (p<0.01) were found in group I and group II patients when compared to controls. Post hoc test did not reveal any significant difference in Lp(a), lipids and lipoprotein variables between group I and group II (p>0.05).

<table>
<thead>
<tr>
<th>Parameter (mg/dl)</th>
<th>Controls (n=30)</th>
<th>Group-I (n=35)</th>
<th>Group-II (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>135.4 ± 20.5</td>
<td>157.6 ± 29.3*</td>
<td>171.1 ± 39.09*</td>
</tr>
<tr>
<td>TGL</td>
<td>110.7 ± 27.9</td>
<td>147.6 ± 76.4*</td>
<td>176.3 ± 84.39*</td>
</tr>
<tr>
<td>HDL</td>
<td>44.0 ± 6.0</td>
<td>40.3 ± 6.1*</td>
<td>38.7 ± 7.2*</td>
</tr>
<tr>
<td>LDL</td>
<td>68.3 ± 22.2</td>
<td>89.2 ± 27.5*</td>
<td>97.0 ± 6.5*</td>
</tr>
<tr>
<td>VLDL</td>
<td>22.1 ± 5.5</td>
<td>29.5 ± 15.2*</td>
<td>35.27 ± 16.88*</td>
</tr>
<tr>
<td>Lp (a)</td>
<td>15.3 ± 6.0</td>
<td>24.0 ± 9.8*</td>
<td>27.5 ± 9.3*</td>
</tr>
<tr>
<td>Urea</td>
<td>23.3 ± 6.4</td>
<td>24.9 ± 4.6</td>
<td>84.7 ± 44.0*†</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9 ± 0.16</td>
<td>1.0 ± 0.19</td>
<td>3.3 ± 1.2*†</td>
</tr>
</tbody>
</table>

Statistical significance * p<0.01 compared to controls; †p<0.05 compared to Group I patients)
Table 2 shows the mean and standard deviation of the lipid ratios, non-HDL cholesterol and AI between the groups. A significant increase in the non-HDL cholesterol, TC/HDL, LDL/HDL, Tgl/HDL and AI was observed in group I and group II patients when compared to controls. When the lipid ratios and AI were compared between the groups, a significant increase was observed in Tgl/HDL, TC/HDL ratio and in the AI (p<0.05) in group II when compared to group I.

Table 2: Mean and standard deviation for the lipid ratios and atherogenic index among controls, T2DM (group I) and diabetic nephropathy (group II) patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=30)</th>
<th>Group-I (n=35)</th>
<th>Group-II (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC/HDL</td>
<td>3.08±0.70</td>
<td>3.94±0.84*</td>
<td>4.51±1.10*</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>1.58±0.64</td>
<td>2.24±0.79*</td>
<td>2.60±1.10*</td>
</tr>
<tr>
<td>TGL/HDL</td>
<td>2.50±0.71</td>
<td>3.78±2.20*</td>
<td>4.52±1.95*</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>90.46±22.70</td>
<td>117.22±27.96*</td>
<td>132.33±37.90*</td>
</tr>
<tr>
<td>AI</td>
<td>0.38±0.12</td>
<td>0.52±0.20*</td>
<td>0.61±0.20*</td>
</tr>
</tbody>
</table>

Statistical significance * p<0.01 compared to controls; †p<0.05; compared to Group I patients AI: Atherogenic index

Table 3 shows the ROC curve analysis for the lipid and lipoprotein levels. However we found a significant increase in Tgl/HDL, TC/HDL ratio and in the AI (p<0.05) in group II when compared to Group I.

Table 3: ROC curve analysis for lipids, lipid ratios and atherogenic index.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC</th>
<th>95% CI</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGL</td>
<td>0.822</td>
<td>0.597 - 1.047</td>
<td>0.005</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.822</td>
<td>0.597 - 1.047</td>
<td>0.005</td>
</tr>
<tr>
<td>Lp (a)</td>
<td>0.746</td>
<td>0.553 - 0.940</td>
<td>0.032</td>
</tr>
<tr>
<td>TGL/HDL</td>
<td>0.883</td>
<td>0.721 - 1.044</td>
<td>0.001</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>0.777</td>
<td>0.604 - 0.949</td>
<td>0.016</td>
</tr>
<tr>
<td>AI</td>
<td>0.883</td>
<td>0.721 - 1.044</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Statistically significant, AI: Atherogenic index; AUC: Area under the curve; CI: Confidence interval

DISCUSSION

Diabetic nephropathy is one of the most serious complications in T2DM. It is well known that patients with diabetes have a high incidence of CVD, the risk of which becomes substantially elevated when nephropathy develops. Though the pathogenesis of CVD in diabetes is multifactorial, dyslipidemia is yet found to be a powerful risk factor. In diabetes, blood glucose is not utilized by tissues resulting in hyperglycemia. Consequently fatty acids are mobilized from adipose tissue to meet the energy demands and in the process excess fatty acid accumulates in the liver leading to increased triglyceride and VLDL production. Further, long-term hyperglycemia causes generalized vascular endothelial damage, which reduces functional lipoprotein lipase, leading to increase in triglycerides and a decrease in HDL. Increased levels of cholesterol, LDL and triglycerides mediate the progression of atherosclerosis.

It has been reported that hypercholesterolemia contributes to the deterioration of renal function. Apart from the effect of dyslipidemia on CVD, dyslipidemia has also been found to contribute to the progression of diabetic nephropathy. The characteristic dyslipidemia which we observed in our study is elevated total cholesterol, triglycerides, VLDL, LDL and decreased HDL levels in T2DM patients with and without nephropathy when compared to controls. In diabetic nephropathy, hypoproteinemia markedly increases LDL, and renal failure specifically causes an increase in remnant lipoproteins and a decrease in HDL levels. Hypertriglyceridemia is associated with diabetic nephropathy. The incidence of nephropathy has been reported to be range from 15-17% even in newly diagnosed T2DM, which was found to have a strong correlation with poor glycemic control, hypertension and dyslipidemia.

Lipid ratios and AI index have been reported to indicate atherogenic dyslipidemia. Similarly in the present study we observed significant elevation in the lipid ratios, non-HDL cholesterol and AI in both T2DM patients with and without nephropathy when compared to controls. Non-HDL cholesterol is an accepted marker of Apo B in clinical practice as it is reliable even when measured in the nonfasting state. Non-HDL cholesterol serves as an index of cardiovascular risk in diabetic patients in whom LDL may not be elevated.

The dyslipidemia of diabetic nephropathy group when compared to T2DM did not show any significant change in the lipid and lipoprotein levels. However we found a significant increase in Tgl/HDL, TC/HDL ratio and AI in the diabetic nephropathy group when compared to T2DM. A decrease in HDL levels reflects in an increase in the TC/HDL ratio, which are an indicator of atherogenic dyslipidemia and a marker of CVD. The Tgl/HDL ratio is an independent risk factor for development of coronary artery disease, myocardial infarction and also an indicator of extensive coronary diseases in high risk patients. The AI has been applied as an additional cardiovascular risk assessor even in the presence of insignificant changes in the individual lipid parameters.
An elevated Lp(a) is another feature of dyslipidemia that can be accompanied by renal dysfunction or increased albuminuria in diabetic and non diabetic patients. Elevated serum Lp(a) is associated with vascular disease in both renal disease and diabetic nephropathy. In the present study elevated Lp(a) levels were observed in both the T2DM patients with and without nephropathy when compared to controls. Elevated Lp(a) levels might adversely affect the progression of diabetic nephropathy. Lp(a) competes with plasminogen for binding sites, resulting in decreased synthesis of plasmin and inhibition of fibrinolysis. This antifibrinolytic effect of Lp(a) causes the occlusion of small blood vessels leading to propagation of atherosclerosis. Therefore elevated serum Lp(a) may play an important role in development and progression of diabetic nephropathy. It has been reported that an elevated level of Lp(a) can be accompanied by renal dysfunction in diabetic and non diabetic patients. Lp(a) exerts its atherogenic effect by also causing an increased deposition of cholesterol in the artery walls, promotion of smooth muscle cell proliferation and induction of monocyte chemo tactic activity in endothelial cells. However Lp(a) is not associated with the LDL, HDL, cholestrol, Tgl and serum creatinine and the mechanism of its interaction in the metabolic pathways is not clear. Similarly in the present study we did not observe any significant correlation of Lp(a) with the lipid variables or creatinine. ROC curve analysis revealed significant areas under the curve for the lipid parameters Tgl, VLDL and Lp(a) and for the lipid ratios of Tgl/HDL, TC/HDL and AI. Tgl and Lp(a) are accepted independent risk factors for CVD. The lipid ratios are also found to predict risk in the diabetic nephropathy group.

CONCLUSION

Dyslipidemia is a common feature in T2DM and diabetic nephropathy. Our study supports the finding that the diabetic dyslipidemia comprising of elevated total cholesterol, Tgl, VLDL, LDL, non-HDL, Lp(a) and low HDL levels persists in diabetic nephropathy and appears to be more pronounced as indicated by higher Tgl/HDL, TC/HDL ratios and AI in the diabetic nephropathy group when compared to T2DM. Lp(a) may be considered as an important independent risk marker for indentifying T2DM patients who may develop nephropathy. Lipid ratios and AI may serve as additional or better indicators of atherogenic risk in patients with diabetic nephropathy when compared to lipids alone.

Metabolic control of diabetes mellitus along with monitoring of the risk factors would help in preventing onset of diabetic nephropathy thereby reducing the associated morbidity and mortality due to CVD.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES


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