
High Lipoprotein (a) Concentration Is Associated with Diabetic Nephropathy

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Abstract: *Aims:* Lipoprotein (a) [Lp(a)] has been well recognized as a risk factor for both micro and macrovascular complications in diabetes, due to its atherogenic effects. Studies suggested that serum lipoprotein (a) [Lp(a)] concentration may take part in the aggravation of diabetic nephropathy. Accumulating evidence suggests that higher serum Lp(a) may be associated with impaired renal function in populations. Therefore this study comprehensively evaluates the association between Lipoprotein (a) and diabetic nephropathy in patients with type 2 diabetes mellitus. *Methods:* One hundred subjects (50 with diabetic nephropathy and 50 type 2 diabetes mellitus without nephropathy) were studied. The examination used blood serum where lipoprotein a used the ELISA method. Nonpara- metric Mann–Whitney U-tests were used to compare the levels of lipoprotein a in diabetic nephropathy and Type 2 DM without diabetic nephropathy. *Results:* Lipoprotein a in the diabetic nephropathy group was higher when compared to the type 2 DM group without nephropathy (OR = 2.8; 95%; CI = 1.84-12.07). *Conclusion:* High lipoprotein (a) concentration are associated with diabetic nephropathy. Lipoprotein may reflect chronic underlying pathophysiological processes involved in development of complications of T2DM and serum Lp(a) can be considered as a promising predictive factor for the diagnosis of earlier diabetic nephropathy.

Keywords: Lipoprotein (a), Diabetic Nephropathy, Type 2 Diabetes Mellitus

1. Introduction

Patients with type 2 diabetes mellitus (T2DM) are vulnerable to kidney dysfunction, namely diabetic nephropathy [1]. The increasing incidence of diabetes mellitus globally causes many people with type 2 diabetes mellitus to develop diabetic nephropathy [2]. Diabetic nephropathy has become one of the leading causes of end-stage renal disease (ESRD) As a common complication of T2DM all over the world [3]. It has been reported that currently, over 20% of patients with diabetes ultimately develop diabetic nephropathy, which has become a major cause of mortality in these patients [4]. Age, race, diabetes duration, hyperglycemia,

dyslipidemia, and hypertension are among the risk factors for diabetic nephropathy. However, determining residual risk factors for diabetic nephropathy remains clinically relevant for stratification and management of the disease [5].

Lipoprotein (a) [Lp(a)] has been well recognized as a risk factor of of both micro and macrovascular complications in diabetes, due to its atherogenic effects. Glycation of lipoproteins has been implicated to play a role in the pathogenesis of micro- and macro-vascular complications [6]. Lipoprotein (a) [Lp(a)], discovered in 1963, is plasma-based but has a special structure. It comprises a lipid-rich apolipoprotein (apo) B-containing lipoprotein and apo(a) [7]. The apo(a) gene is highly homologous to the plasminogen

gene, and it mainly encodes two tricyclic domains (KIV and KV), and an inactive proteasome domain. Plasma Lp(a) levels are not changed by the environment, but primarily depend on genetic factors, for example, chromosomal mutation of the LPA gene. [8]

Studies suggested that serum lipoprotein (a) [Lp(a)] concentration may take part in the aggravation of diabetic nephropathy. It has been shown that serum Lp(a) is associated with impaired renal function in populations with higher levels of serum Lp(a) and these studies also demonstrated that serum Lp(a) has a strong correlation with increased risk of complications in individuals with Type 2 diabetes [9-13]. It seems that serum Lp(a) can be considered as a promising predictive factor for the diagnosis of earlier diabetic nephropathy. Therefore, relationship between Lp(a) level and diabetic nephropathy remains undetermined. Further research is needed to investigate the exact role of Lp(a) in the progression of diabetic nephropathy. Additionally, more studies should be conducted to explore the potential of Lp(a) as a biomarker for early diagnosis of the disease.

Accordingly, in this study, we performed a case control study to comprehensively evaluate the association between Lp(a) and diabetic nephropathy in patients with T2DM.

2. Subjects, Materials and Methods

2.1. Subjects and Blood Collection

One hundred Type 2 diabetes mellitus patient as research subjects were divided into two groups, the case group of 50 patients who had been diagnosed with diabetic nephropathy and the control group of 50 patients who were diagnosed with type 2 diabetes mellitus without diabetic nephropathy. Collection of research sample data and blood samples was carried out at the Endocrine Polyclinic of the Government General Hospital (RSUP) H. Adam Malik Medan.

Inclusion criteria for the case group were patients who had been diagnosed with diabetic nephropathy, have history of diabetes for more than 7 years, diabetic retinopathy or impaired kidney function in family and lab results 2x persistent proteinuria in 3-6 months, which found microalbuminuria (30-300mg/g), macroalbuminuria (> 300mg/g), decreased eGFR (> 60ml/min/1.73m²). Inclusion criteria for the control group, patients diagnosed with type 2 diabetes mellitus without nephropathy and willing to sign an informed consent. Exclusion criteria were patients with end state renal disease, patients with impaired liver function, hematuria, pyuria and pregnant.

2.2. Intervention

In the study, anamnesis was carried out, looking at medical records, taking blood and urine samples and laboratory tests. Anamnesis, medical records, laboratory tests are used to

diagnose patients in the control and case groups. Diabetes duration, fasting blood glucose levels and 2 hours post prandial, urine microalbumin on the spot, HbA1C, creatinine and eGFR were also measured to assess subject characteristics. The examination used blood serum where lipoprotein a used the ELISA method. Examination of fasting blood sugar levels and 2 hours post prandial, HbA1C, creatinine using the COBAS automated analyzer and eGFR using the Modification of Diet in Renal Disease (MDRD) method.

2.3. Statistic Analysis

Statistical analyses were performed with SPSS 21.0. The values were expressed as mean standard deviation (SD). The normality test uses the Kolmogorov-Smirnov normality test. Nonparametric Mann-Whitney U-tests were used to compare the levels of lipoprotein a in diabetic nephropathy and Type 2 DM without diabetic nephropathy. The unpaired t test was used for analyzing other variables between the groups. A value of $p < 0.05$ was considered as statistically significant.

2.4. Ethical Clearance

The research protocol was approved by the Health Research Ethics Committee, Faculty of Medicine, University of North Sumatra. All study subjects signed written informed consent after being informed about the aims and benefits of the study.

3. Result

There were differences in subject characteristics between the diabetic nephropathy group and the type 2 DM group without nephropathy. Age in the diabetic nephropathy group was 59.40 ± 8.48 years, while in the type 2 DM group without diabetic nephropathy was 56.56 ± 9.72 years ($p = 0.472$). The duration of diabetes in the diabetic nephropathy group was 13.12 ± 5.26 years, while in the type 2 DM group without diabetic nephropathy was 2.96 ± 1.62 years ($p=0.000$). HbA1c in the diabetic nephropathy group was $8.07 \pm 2.15\%$ while in the type 2 DM group without diabetic nephropathy was $6.32 \pm 0.62\%$ ($p=0.000$). The fasting KGD in the diabetic nephropathy group was 170.72 ± 82.85 mg/dl while in the type 2 DM group without diabetic nephropathy it was 132.32 ± 24.66 mg/dl ($p=0.132$).

Postprandial blood sugar in the diabetic nephropathy group was 257.28 ± 100.88 mg/dl while in the group Type 2 DM without diabetic nephropathy was 212.52 ± 70.36 mg/dl ($p=0.171$). The creatinine in the diabetic nephropathy group was 0.92 ± 0.17 mg/dl while in the type 2 DM group without diabetic nephropathy it was 0.71 ± 0.13 mg/dl ($p=0.000$). eGFR in the diabetic nephropathy group was 73.72 ± 11.08 mL/min/1.73m² whereas in the type 2 DM group without diabetic nephropathy it was 103.76 ± 22.72 mL/min/1.73 m² ($p=0.000$) (Table 1).

Table 1. Subject characteristics.

Subject characteristics	Diabetic nephropathy	Type 2 DM without diabetic nephropathy	P Value
Age (years)	59.40 ± 8.48	56.56 ± 9.72	
Diabetes duration (years)	13.12 ± 5.26	2.96 ± 1.62	0.000*
HbA1c (%)	8.07 ± 2.15	6.32 ± 0.62	0.000*
Fasting blood sugar level (mg/dl)	170.72 ± 82.85	132.32 ± 24.66	0.132
Postprandial blood sugar (mg/dl)	257.28 ± 100.88	212.52 ± 70.36	0.171
Hemoglobin (g/dl)	10.87 ± 1.38	12.19 ± 1.33	0.001*
Creatinine (mg/dl)	0.92 ± 0.17	0.71 ± 0.13	0.000*
eGFR (mL/min/1.73 m ²)	73.72 ± 11.08	103.76 ± 22.72	0.000*

The lipoprotein a level in the diabetic nephropathy group was 46.12±26.92mg/dl while the lipoprotein a level in the type 2 DM group without diabetic nephropathy was 25.08±19.24mg/dl (p=0.040). The odds ratio (OR) for lipoprotein a is 2.8, this indicates that patients with diabetic

nephropathy tend to have lipoprotein a levels 2.8 times higher than in type 2 DM without nephropathy. From the results of the coefficient interval (CI) on the odds ratio, it can be seen that lipoprotein A plays a very significant role in diabetic nephropathy because the CI number is above 1 (table 2).

Table 2. Differences levels of bilirubin and lipoprotein a in the two groups.

	Diabetic nephropathy	Type 2 DM without diabetic nephropathy	P Value	OR Value
Lipoprotein a (mg/dl)	46.12 ± 26.92	25.08 ± 19.24	0.040	2.8 (95% CI=1.84-12.07)

4. Discussion

We demonstrated subject characteristic between diabetic nephropathy and type 2 diabetes mellitus without diabetic nephropathy. In This study show that, significant differences were found in the initial characteristics of the study subjects where the duration of diabetes tended to be longer than 10 years, HbA1c was found to be uncontrolled, fasting KGD and 2-hour PPG were high, hemoglobin and eGFR levels decreased and creatinine levels increased. It is appropriate that the increased duration of diabetes, uncontrolled HbA1c is known to be a risk factor for the progression of diabetic nephropathy [14].

Lipoprotein a has a greater role in the progression of diabetic nephropathy. This can be seen statistically from the results of the confidential interval (CI) on the odds ratio which shows that lipoprotein a has a strong influence. Lp(a) has an affinity for various components of the subendothelial matrix including proteoglycans, fibrinogen and fibronectin. Lp(a) also binds to lipoprotein-rich lipoproteins triglycerides, which can lead to accumulation of lipids in the artery walls. Research also shows that Lp(a) is more easily oxidized and accumulates in the artery walls causing atherosclerosis. Just like LDL, Lp(a) will undergo oxidative modification to become a substrate which is then captured by macrophages to form foam cells. Lp(a) can trigger inflammation leading to monocyte chemotaxis and expression of vascular adhesion molecules. Apo(a) has similarities with plasminogen which can trigger fibrinolysis so that it can interfere with the work of plasminogen and trigger thrombosis [15].

The lipoprotein (a) level in the diabetic nephropathy group was higher when compared to the type 2 diabetes mellitus group. This is because impaired kidney function can cause impaired excretion of lipoprotein a, so albuminuria sufferers will find an increase in serum lipoprotein a. As it is known that the kidney is the main excretion site of lipoprotein a [16]. This

is in accordance with Toro et al. Whereas type 2 diabetes patients show that microalbuminuria (nephropathy in the subclinical phase) or proteinuria (nephropathy in the advanced phase) is associated with increased levels of Lp(a) [17].

The mechanisms underlying the potential association between Lp(a) and diabetic nephropathy could also be multifactorial. the foremost explanation is that serum Lp(a) levels reflect a balance of Lp(a) synthesis within the liver and catabolism possibly involving the kidney [9]. Lp(a) levels were significantly increased compared to healthy controls, which were rapidly decreased after kidney transplantation but not after the initiation of hemolysis. As a result of the loss of functioning renal tissue, the increase in Lp(a) observed in CKD may be attributed to the involvement of the kidney in Lp(a) catabolism. This suggests that the kidney plays an important role in modulating plasma Lp(a) concentrations and that renal dysfunction could be a major contributing factor to the elevated levels of Lp(a) observed in CKD patients [18]. Besides, it has also been suggested that the increase in Lp(a) associated with protein-losing-related renal disease is likely to be a result of a general increase in protein synthesis by the liver due to high urinary protein loss rather than decreased catabolism. It remains unclear whether increased Lp(a) plays a key role in the pathogenesis of diabetic nephropathy or it is just a marker of impaired renal function [19].

Given the atherogenic role of Lp(a) and therefore the importance of glomerular atherosclerosis within the pathogenesis of diabetic nephropathy [20]. Lp(a) could also be involved in the progression of diabetic nephropathy via its atherogenic effect. An early study in vitro study showed that low concentrations of Lp(a) stimulated the expansion of mesangial cells, whereas higher concentrations had antiproliferative or toxic effects, which can both hurt the course of renal disease [21]. Another study showed that Lp(a) stimulated the growth of human mesangial cells and induced the activation of phospholipase C, which may therefore contribute to pathophysiology of renal disease [22]. Moreover,

oxidative stress has been confirmed that play a key role in the pathogenesis of diabetic renal complications [23]. Lp(a) was reported to induce the generation of oxygen-free radicals in vitro, which may partly contribute to kidney injury in diabetes [24]. Besides, Lp(a) is vulnerable to oxidative modification, resulting in the extensive formation of pro-inflammatory oxidized phospholipids, oxysterols, and oxidized lipid-protein adducts in Lp(a) particles, which can perpetuate kidney injury [25].

5. Conclusion

High lipoprotein (a) concentration are associated with diabetic nephropathy. Lipoprotein may reflect chronic underlying pathophysiological processes involved in development of complications of T2DM and serum Lp(a) can be considered as a promising predictive factor for the diagnosis of earlier diabetic nephropathy.

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