

High Lipoprotein (a) Concentration is Associated with Diabetic Nephropathy

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Abstract: *Aims:* Lipoprotein (a) has been well known as a risk factor for micro and macrovascular complications in diabetes, because of its atherogenic effects. Research finding indicate that serum lipoprotein (a) concentration may take role in the escalation of diabetic nephropathy. Research suggests that reduced renal function in certain populations may be linked to elevated serum levels of lipoprotein (a). Thus, this study thoroughly assesses the relationship between Lipoprotein (a) and diabetic nephropathy in individuals with type 2 diabetes mellitus. *Methods:* One hundred subjects (fifty subject with diabetic nephropathy and fifty subject type 2 diabetes mellitus without nephropathy) were studied. The examination used blood serum where lipoprotein a used the ELISA method. Nonparametric tests were used to compare the levels of lipoprotein a in nephropathy and Type 2 DM without nephropathy. *Results:* Lipoprotein a in the 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 level of lipoprotein (a) concentration are correlated 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.

Keyword: Lipoprotein a, Diabetic Nephropathy, Type 2 Diabetes Mellitus

1. Introduction

Patients with type 2 diabetes mellitus 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]. Umamah dkk showed that "Diabetic nephropathy has become one of the leading causes of end-stage renal disease As a common complication of T2DM all over the world" [3]. Zhang dkk showed that "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. "Risk factors for diabetic nephropathy must be determined clinically for the stratification and management of the disease" [5].

Lamina dkk showed that "Lipoprotein (a) has been recognized known 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) discovered in 1963, is plasma-based which has special structure. It comprises a apo(b) and apo(a) [7]. The apo(a) gene has a same structure with 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, LPA gene chromosomal mutation.[8]

Studies suggested that serum lipoprotein (a) [Lp (a)] concentration may take role in the diabetic nephropathy aggravation. It has been shown that serum Lp (a) is correlated with impaired function of renal in populations with higher concentration of serum Lp (a) and these studies also showed

that increased risk of complications in individuals with Type 2 diabetes has a strong correlation with serum Lp (a) [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, Case group with 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 pandrial, 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 pandrial, HbA1C, creatinine using the COBAS automated analyzer and eGFR using the Modification of Diet in Renal Disease (MDRD) method.

2.3. Statistic Analysis

With SPSS 21.0, statistical analyses were carried out. Standard deviation (SD) was used to express the values. The Kolmogorov and Smirnov normalcy test is used in the normalcy test. Concentration of lipoprotein A in people with diabetic nephropathy and Type 2 diabetes without nephropathy were compared using nonparametric tests. Other factors between the groups were analyzed using the unpaired t test. It was determined that a value of $p < 0.05$ was 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 nephropathy group and the type 2 DM group without nephropathy. Age in diabetic nephropathy group was 59.40 ± 8.48 years, while in 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 type 2 DM group without nephropathy was 2.96 ± 1.62 years ($p=0.000$). HbA1c in the diabetic nephropathy group was $8.07 \pm 2.15\%$ while in type 2 DM group without nephropathy was $6.32 \pm 0.62\%$ ($p=0.000$). Fasting KGD in diabetic nephropathy group was 170.72 ± 82.85 mg/dl while in type 2 DM group without nephropathy it was 132.32 ± 24.66 mg/dl ($p=0.132$).

Postpandrial blood sugar in diabetic nephropathy group was 257.28 ± 100.88 mg/dl while in group Type 2 DM without nephropathy was 212.52 ± 70.36 mg/dl ($p=0.171$). Creatinine in diabetic nephropathy group was 0.92 ± 0.17 mg/dl while in type 2 DM group without nephropathy was 0.71 ± 0.13 mg/dl ($p=0.000$). eGFR in diabetic nephropathy group was 73.72 ± 11.08 mL/min/1.73m² whereas in type 2 DM group without nephropathy 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
Postpandrial 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*

Concentration of lipoprotein in diabetic nephropathy group was 46.12 ± 26.92 mg/dl while lipoprotein in type 2 DM group without nephropathy was 25.08 ± 19.24 mg/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. 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 part in diabetic nephropathy progression. 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. Rhices dkk showed that "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].

It has been compared that Lipoprotein (a) level in the diabetic nephropathy group was higher than 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 correlated with increased levels of Lp(a) [17].

There are more multifactorial underlying mechanisms that correlate between Lp (a) and diabetic nephropathy. The foremost explanation is that serum Lp (a) concentration reflect a balance of Lp (a) synthesis within the liver and catabolism possibly involving the kidney [9]. Rosas dkk showed that "Lp (a) concentration 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, Increasing Lp (a) concentration that observed in CKD may be attributed to the kidney involvement in catabolism of Lp (a)". The kidney plays an crucial role in controlling plasma Lp (a) concentrations and that renal failure may be a primary cause of the high Lp (a) concentration seen in patient with chronic kidney disease. [18]. Kronenberg showed that " Furthermore, rather than a decrease in catabolism, it has also been proposed that the increase in Lp (a) linked to renal illness connected to protein loss is most likely the consequence of a general increase in liver protein synthesis brought on by high urine protein loss. Elevated Lp (a) may be a marker of reduced renal function, but its exact significance in the development of diabetic nephropathy remains unknown" . [19].

Research by Hung dkk showed that "given the Lp (a) atherogenic role and therefore glomerular atherosclerosis's significance in the pathogenesis of diabetic nephropathy" [20]. Greiber dkk showed that "The progression of diabetic nephropathy involve Lp (a) 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]. Mondorf dkk "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]. Charlton dkk "Moreover, oxidative stress has been confirmed that play a key role in the pathogenesis of diabetic renal complications" [23]. Hansen dkk showed that "Lp (a) was reported to induce the generation of oxygen-free radicals in vitro, which may partly contribute to kidney injury in diabetes" [24]. Orso dkk also showed "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 corelated with diabetic nephropathy. Serum lipoprotein a has the potential to be a useful predictive indicator for the identification of early diabetic nephropathy, and persistent underlying pathophysiological processes that is indicated by lipoprotein can cause the development of complications of T2DM.

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