The Role of Lipoprotein A-I in Chronic Kidney Disease Patients; A Possible Marker for Atherosclerosis and Renal Dysfunction

Katsuhide Toyama¹, Tori Suzuki¹, Satoshi Kondo¹, and Kenjiro Kimura²

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Abstract

Background. A decrease in high density lipoprotein (HDL) is known to be one of the risk factors for atherosclerotic vascular disease. HDL is divided by its apoprotein (apo) composition into lipoprotein (Lp) A-I, which contains apo A-I only, and LpA-I: A-II, which contains both apo A-I and apo A-II. It is considered that the anti-atherogenic effect of HDL is due to LpA-I. Various lipid parameters were measured, including Lp A-I in patients with chronic kidney disease (CKD), and an analysis was performed on the relationship with renal dysfunction.

Methods. Twenty-three CKD patients (8 patients with IgA nephropathy and 15 patients with other etiologies) were included in this study. They were divided by their 24 hour creatinine clearance levels (Ccr24h) into Group 1 (14 patients; 30 < Ccr < 70 ml/min), and Group 2 (9 patients; Ccr > 70 ml/min). LpA-I and LpA-I: A-II were measured by rocket immunoelectrophoresis.

Results. 1) The LpA-I level was significantly lower (p<0.01) in Group 1 (36.3±5.4 mg/dl) compared to Group 2 (69.0±17.3 mg/dl). 2) The LpA-I: A-II levels were 76.7±17.3 mg/dl in Group 1 and 80.1±15.0 mg/dl in Group 2 (p>0.05). 3) There was a significant positive correlation between LpA-I level and Ccr24h (r=0.516, p<0.05).

Conclusions. Recently, it has been noted that CKD is an independent risk factor for cardiovascular disease (CVD). In CKD patients, the LpA-I level decreased as renal function deteriorated, suggesting that a decrease in LpA-I may play a role in the development of CVD in CKD patients.

Key Words

Lipoprotein A-I, Atherosclerosis, Chronic kidney disease

Introduction

It is known that a decrease in high density lipoprotein (HDL) is one of the risk factors for atherosclerotic vascular disease. HDL can be fractionated into two components by ultracentrifugation into HDL₂ (specific gravity 1.063–1.125) and HDL₃ (specific gravity 1.25–1.210). Recently, a new method for classifying HDL by its apoprotein (apo) composition has been developed. By this method, HDL is classified as lipoprotein A-I (LpA-I) which contains apo A-I but not apo A-II, and Lp A-I: A-II which contains both apo A-I and apo A-II. LpA-I plays a central role in the reverse cholesterol transport system. A decrease in the serum level of LpA-I level has been correlated with the development of coronary artery disease (CAD) and regarded as a new marker of atherogenesis.
Atherosclerotic lesions are frequently seen in chronic kidney disease (CKD). Increases of chylo-
imcron remnant, very low density lipoprotein (VLDL) and low density lipoprotein (LDL) and decrease of HDL are characteristics of this dyslipidemia. Many large-scale epidemiological and drug intervention studies have shown that hyperlipidemia is an important risk factor for the onset and advancement of CAD. In addition, it has been pointed out that hyperlipidemia itself plays a role in glomerulosclerosis. In this study, we measured various lipid parameters, including LpA-I, in CKD patients and analyzed their correlation with the progression of renal dysfunction.

Methods

Subjects
Twenty-three CKD patients (13 males and 10 females, average age 53.1±18.8 years, who were treated at the outpatient clinic of our hospital and had given informed consent, were included in this study. The primary diseases consisted of 8 patients with IgA nephropathy and 15 patients with other glomerulonephropathies. Diabetic patients were excluded. All patients had proteinuria of less than 1 gm / day. Corticosteroids, immunosuppressive drugs, and antilipemic drugs were not given. The 23 CKD patients were divided into 2 groups based on their 24 hour creatinine clearance (Ccr) levels. Group 1 had 6 males and 8 females (average age 55.0±23.0 years) with 30<Ccr<70 ml/min. Group 2 had 7 males and 2 females (average age 51.9±16.4 years) with Ccr>70 ml/min. There was no significance in age between the two groups. Fasting blood samples were collected in the early morning.

Lipid parameter analysis
Total cholesterol, cholesteryl esters, triglycerides and HDL cholesterol were measured by the enzyme method. Apolipoprotein was measured by turbidimetric immunnoassay (TIA).

Lp A-I, Lp A-I: A-II analysis
LpA-I and LpA-I:II particles in serum were quantified by electroimmunodiffusion methods in agarose gel, containing a mixture of specific anti apoA I and A II antibodies (The hydragel LpA-I particles kit; Cosmo-Bio Co.,Ltd., Tokyo). A 5 ul serum sample which had been diluted 100 times with saline was inserted into the antigen pore and electrophoresed for 4 hours under conditions of 12.5 V/cm. After electrophoresis, the samples were deproteinized, dried, and stained with Coomassie Brilliant Blue R-250. After destaining, the height of the sedimentation line was measured and the serum concentration was calculated with a standard curve.

Results

Lipid parameters
The test results of general lipids in the sera showed no significant differences in total cholesterol, triglycerides, and cholesteryl esters between Groups 1 and 2. However, HDL cholesterol was significantly lower in Group 1 (p<0.05) (Table 1).

Apolipoprotein parameters and Lp A-I, Lp A-I: A-II
Apoprotein parameters of apo C-II and apo E were significantly higher in Group 1 than in Group 2, whereas apo C-III was higher in Group 2 than in Group 1. Other parameters did not show significant differences. The serum LpA-I level was 36.3±5.4 mg/dl in Group 1, which was significantly less compared to Group 2 (69.0±17.7) (p<0.01). On the other hand, there was no significant difference in the LpA-I: A-II levels (Table 2). A significant positive correlation between the serum LpA-I level and the Ccr level was seen (r=0.576, p<0.05) (Figure 1). There was no correlation between the serum LpA-I: A-II level and the Ccr level (r=0.210, p=0.317) (Figure 2). In addition, there was no significant correlation between the Ccr level and other lipid parameters.

Discussion
Virchow et al. had pointed out in the late 1800’s that dyslipidemia accompanied renal diseases. Although this was confirmed by many researchers in the 1900’s, until very recently dyslipidemia was con-

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<th>Table 1. Lipid Parameters</th>
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<tr>
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<td>Total cholesterol (mg/dl)</td>
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<td>Cholesterol-ester (mg/dl)</td>
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<td>Triglyceride (mg/dl)</td>
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<td>HDL-cholesterol (mg/dl)</td>
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Values are means±SD. *p<0.05, Group1 vs. Group2
sidered as a secondary change to the primary disease and its etiologic significance was unknown. In 1982, Moorhead et al. introduced a concept of lipid nephrotoxicity. Since then dyslipidemia has been recognized in the progression of nephritis. Diamond studied the homology and analogy between atherosclerosis and glomerulosclerosis, and noted similar histochemical properties. Further, mesangial cells, which play a central role in glomerulosclerosis, have many homologous characteristics to vascular smooth muscle cells as to the origin, structure, and function in atherosclerosis. In the early stages of atherosclerotic lesion development, monocytes/macrophages play an important role. Likewise, the importance of monocytes/macrophages in the development of glomerulosclerosis is also known. In fact, studies in various hyperlipidemic animal models have confirmed that the number of macrophages infiltrating in the glomerulus increases prior to the formation of glomerulosclerosis. LDL is a primary risk factor for atherosclerosis and many large-scale studies have recently shown that LDL-cholesterol lowering therapy is effective in primary and secondary prevention of CAD. Also in renal diseases, there have been reports pointing out the involvement of oxidized LDL in the development of glomerulosclerosis. The prevailing idea is that in glomeruli, as LDL passes between endothelial cells it is oxidized by some factor in the mesangial region and the oxidized LDL causes renal injury. On the other hand, it is well known that HDL plays a role as an anti-atherogenic factor. However, little has been reported regarding the relationship between glomerulosclerosis, the progress of renal dysfunction, and HDL.

Free cholesterol effluxed into the extracellular fluid of peripheral tissues by serum HDL is esterified by lectin cholesterol acyl transferase (LCAT) and reverse transported to the liver by the action of cholesteryl ester transfer protein (CETP). HDL plays an important role in anti-atherogenic action. Recently, it has been determined from the composition of apoA-I and apoA-II, which are the main apoproteins of HDL, that there are LpA-I lipoprotein particles which contain only apoA-I and LpA-I:A-II lipoprotein particles which contain both apoA-I and apoA-II. LpA-I is considered to have anti-atherogenic activity and its main action in peripheral tissues by serum HDL is esterified by lectin cholesterol acyl transferase (LCAT) and reverse transported to the liver by the action of cholesteryl ester transfer protein (CETP). Thus HDL plays an important role in anti-atherogenic action.

Table 2. Apolipoprotein Parameters and LpA-I, LpA-I; A-II

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<tr>
<td>Group1</td>
<td>123.2 ± 17.3</td>
<td>32.7 ± 6.2</td>
<td>6.4 ± 2.3</td>
<td>5.6 ± 7.4</td>
<td>8.5 ± 3.6</td>
<td>96.3 ± 5.4</td>
<td>76.7 ± 17.3</td>
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<tr>
<td>Group2</td>
<td>140.7 ± 27.1</td>
<td>32.0 ± 7.3</td>
<td>3.9 ± 1.7</td>
<td>9.0 ± 4.5</td>
<td>102.6 ± 26.0</td>
<td>5.8 ± 1.8</td>
<td>69.0 ± 17.7</td>
<td>80.1 ± 15.0</td>
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Abbreviations: apo=apolipoprotein
Values are means±SD
*p<0.05, **p<0.01 Group1 vs. Group2

Fig. 1. The correlation between LpA-I and Ccr.

Fig. 2. The correlation between LpA-I: A-II and Ccr.
has been shown to be cholesterol efflux from tissues, as seen in experiments using cultured cells\textsuperscript{19}.

Clinically, the reports regarding LpA-I measurement have come mostly from studies on CAD\textsuperscript{24,25,10}. Recently, it has been reported that LpA-I decreases in type II diabetes mellitus in Japan\textsuperscript{19}. However, to the best of our knowledge, there are no reports regarding LpA-I and CKD. A recent clinical study showed that CKD is an independent risk factor for the onset and progression of cardiovascular disease (CVD). This has been confirmed in a statement by the American Heart Association\textsuperscript{26}. It has been reported that the risk of CVD onset increases approximately 1.7 fold when GFR declines to less than 60 ml/min, 5.4 fold when GFR is 30–44 ml/min, and more than 10 fold when GFR is less than 30 ml/min\textsuperscript{27}. A recent epidemiological study in Japan also showed that the onset of a cardiovascular event is significantly increased in CKD patients\textsuperscript{28}. The mechanism underlying this relationship is unknown. However, it has been suggested that general risk factors such as hypertension, diabetes mellitus, or hyperhomocysteinemia are not involved\textsuperscript{29}. The details as to why CKD is an independent risk factor of CVD remain to be determined.

We evaluated apoprotein, LpA-I and LpA-I: A-II in CKD patients. Studies using transgenic mice have shown that the expression of apoA-I suppresses atherosclerosis and apoA-II aids the development of atherosclerosis\textsuperscript{30}. In our study, there was no significant difference in the levels of apoA-I and apoA-II between Groups 1 and 2. However, the study of lipoprotein showed that LpA-I is significantly lower in Group 1 (i.e., patients with renal dysfunction). Furthermore, as renal dysfunction advanced (decrease of Ccr), LpA-I decreased significantly (p<0.01) and a significant positive correlation developed (r=0.516, p<0.05). However, there was no significant correlation between the other lipid parameters, including apo A-I and Ccr. Our study suggests that measuring LpA-I rather than apoprotein is useful in determining the severity of the disease in CKD patients. Furthermore, it is suggested that a decrease in LpA-I may play a role in the development of CVD in CKD patients. This leads to the possibility that a decrease in LpA-I will be recognized as a new risk factor for CVD in CKD patients. Further accumulation of cases and studies corroborating the results reported here await the realization of this promising potential.

In summary, various lipid parameters including LpA-I were measured and evaluated in CKD patients. The results showed that LpA-I levels were significantly decreased in the group with renal dysfunction and as renal dysfunction progressed, LpA-I levels decreased significantly. This suggested the involvement of a decrease in LpA-I in the progression of CKD. A decrease in LpA-I can be a new risk factor for CVD in CKD patients.

An abstract of this article was presented at the 29th Annual Meeting of The American Society of Nephrology in November, 1996.

References

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慢性腎臓病における血中リポ蛋白 A-I 測定の意義
—腎機能障害のマーカーとしての可能性—

外山 勝英1 鈴木 信理1 近藤 聡1 木村健二郎1

抄録
【目的】高比重リポ蛋白 (high density lipoprotein; HDL) の低下は動脈硬化性疾患の危険因子の一つとして知られているが、HDL はアポ蛋白 (apo) の組成により apoA-I のみを含むリポ蛋白 (Lp) A-I と apoA-I と apoA-II の両者を含む LpA-I: A-II の二つに分類される。HDL の抗動脈硬化作用は LpA-I によるものと考えられている。そこで本研究では慢性腎臓病 (Chronic kidney disease; CKD) 患者における LpA-I をはじめ脂質パラメーターを測定し腎機能障害との関連について比較検討した。
【方法】CKD 患者 23 名 (IgA 腎症 8 名、他の原因 15 名) を対象とし、24 時間 creatinine clearance 値 (Ccr24h) によって、Group 1 (14 名; 30 < Ccr < 70 ml/min)、Group 2 (9 名; Ccr > 70 ml/min) の 2 群に分けた。LpA-I、LpA-I: A-II の測定はロケット免疫電気泳動法にて行った。
【結果】1) LpA-I 値は、Group 1 で 36.3 ± 5.4 mg/dl で Group2 (69.0 ± 17.7) に比べ有意に (p < 0.01) 低下していた。2) LpA-I: A-II 値は、Group1 で 76.7 ± 17.3 mg/dl で Group2 (80.1 ± 15.0) の間に有意差はなかった。3) LpA-I 値と Ccr24h の間には有意な正の相関関係 (r = 0.516, p < 0.05) が認められた。
【結論】近年、CKD それ自体が心血管系合併症 (cardiovascular disease; CVD) の独立した危険因子である指摘され注目されている。CKD 患者では腎機能障害の進展に伴い LpA-I は低下しており、CKD 患者における CVD 発症の原因に LpA-I の低下が関与する可能性が示唆された。

索引用語
リポ蛋白 A-I、動脈硬化、慢性腎臓病

1 聖マリアンナ医科大学横浜市西部病院 内科学(腎臓・高血圧内科)
2 聖マリアンナ医科大学 内科学(腎臓・高血圧内科)