Metabolic aspects of dietary sodium restriction as a therapeutic intervention

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Antiproteinuric therapy decreases LDL-cholesterol as well as HDL-cholesterol in non-diabetic proteinuric patients: relationships with cholesteryl ester transfer protein mass and adiponectin

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Dyslipidemia contributes to increased cardiovascular risk in nephrotic syndrome. We questioned whether reduction in proteinuria not only lowers low-density lipoprotein cholesterol (LDL-C), but also high-density lipoprotein cholesterol (HDL-C) and cholesteryl ester transfer protein (CETP) mass and whether changes in HDL-C were related to changes in plasma adiponectin.

Thirty-two non-diabetic proteinuric patients (12 on statin therapy), were followed during two double blind 6-week periods of placebo and treatment (low sodium + 100 mg losartan + 25 mg hydrochlorothiazide).

With placebo HDL-C was lower but LDL-C and CETP were not different in proteinuric patients compared with matched controls. LDL-C, HDL-C and CETP decreased upon proteinuria reduction. The decrease in LDL-C correlated with the drop in CETP and the degree of proteinuria reduction. HDL-C also decreased in proportion to proteinuria lowering. Individual changes in HDL-C were correlated with changes in adiponectin.

LDL-C lowering upon robust reduction of proteinuria may be affected by changes in plasma CETP mass, but this treatment also decreases HDL-C in relation to the degree of proteinuria reduction. This adverse effect on HDL-C may in part be attributable to changes in adiponectin.
Introduction

The risk of myocardial infarction is more than five times higher whereas the risk of coronary death is almost three times elevated in non-diabetic patients with proteinuria (1;2). This increased cardiovascular risk can probably at least in part be attributed to the dyslipidemia accompanying heavy proteinuria. High plasma total cholesterol and low-density lipoprotein cholesterol (LDL-C) and elevated triglycerides are well documented in such patients (3;4). Nonetheless, the effects of proteinuria on high-density lipoprotein cholesterol (HDL-C) are inconsistent, with levels being lower, unchanged or even higher compared with control subjects (3;5;6).

Upon anti-proteinuric therapy, total cholesterol and LDL-C are decreased (6-9). This lowering effect on apolipoprotein B (apo B)-containing lipoproteins is closely linked to the efficacy of antiproteinuric therapy (8;10), irrespective of the way by which proteinuria is reduced, be it with inhibitors of the renin angiotensin aldosterone system (RAAS) or non steroidal anti-inflammatory drugs (NSAID’s)(2). Interestingly, some studies have suggested that proteinuria lowering may also be associated with a decrease in HDL-C (7;9), an effect which could possibly blunt the beneficial effect of such treatment on cardiovascular risk.

Among other factors, cholesteryl ester transfer protein (CETP), which has the ability to transfer cholesteryl esters from HDL towards apo B-containing lipoproteins (11-13), plays a pivotal role in lipoprotein metabolism. Thus, abnormalities in the plasma cholesteryl ester transfer process are likely to contribute to the dyslipidemia associated with proteinuria. Indeed, previous studies have demonstrated high plasma CETP mass and activity in subjects with proteinuria of diabetic (14;15) or non-diabetic origin (4;6;16;17). Plasma CETP mass is also higher in childhood idiopathic nephrotic syndrome (18). Furthermore, the plasma CETP level is lower during glucocorticoid treatment of the underlying kidney disease (17;18), but CETP activity does not respond to a 40% decrease in proteinuria with angiotensin converting enzyme inhibition alone (6). These findings (6;17;18), therefore, suggest that the magnitude of proteinuria response determines whether CETP is decreased. Remarkably, no longitudinal data are available with respect to the effect of robust anti-proteinuric regimens on the plasma CETP level in adult subjects with non-diabetic renal disease.

The mechanisms behind this possible effect of anti-proteinuric therapy on HDL-C lowering are poorly understood. Importantly, recent in vitro data suggest a direct regulatory role of adiponectin in the synthesis of apo A-I, which is the main apolipoprotein constituent of HDL-C (19;20). In humans, a high plasma adiponectin level is a major determinant of low apo A-I catabolism (21). Both findings probably contribute to the positive relationship between HDL-C and adiponectin. Furthermore, we have recently shown that a low sodium intake, resulting
in endogenous stimulation of the RAAS, as well as exogenous angiotensin II (ang II) infusion decrease plasma adiponectin levels (22). These findings suggest a direct interaction between the RAAS and adiponectin, which is probably mediated by ang II. Thus, a lower HDL-C through intervention in the RAAS could in part be attributed to effects on circulating adiponectin.

The present study aimed to document the LDL-C, HDL-C and CETP responses to rigorous anti-proteinuric treatment, and to establish whether plasma CETP predicts the levels of these lipoproteins during anti-proteinuric therapy. Also, in a subset of patients, we investigated whether changes in HDL-C during maximal anti-proteinuric therapy are related to changes in plasma adiponectin levels.

Materials and Methods

Subjects

The study population consisted of 32 patients with proteinuria of non-diabetic origin and 32 healthy non-diabetic age- and sex-matched controls. This cohort of non-diabetic proteinuric patients has been described elsewhere (23). The study protocol was approved by the local ethical committee and conducted according to the guidelines for good clinical practice and the declaration of Helsinki. Written informed consent was obtained from each subject before inclusion.

Proteinuric patients were allowed to participate if they met the following inclusion criteria: stable proteinuria > 2 g/day and < 10 g/day, stable renal function (24 h creatinine clearance > 30 mL/min and < 6 mL/min/year decline), age between 18 and 70 years. Diabetes mellitus, uncontrolled hypertension (diastolic blood pressure > 100 mmHg), serum potassium > 5.5 mmol/L, cardiovascular events within 6 months prior to inclusion, contraindication for angiotensin 1 (AT-1) receptor antagonists or diuretic use, as well as the regular use of NSAID's (> 2 doses per week) were exclusion criteria. Antihypertensive drugs except for RAAS-blocking agents or diuretics were allowed during the study for additional blood pressure control. These drugs were continued during the study period. Twelve out of the 32 proteinuric patients were on long-term statin treatment, and this medication was kept unchanged during the study.

Control subjects were recruited by advertisement in local newspapers. None of these subjects used any medication except for oral contraceptives or had previously diagnosed renal disease or hypertension. Serum creatinine was within reference limits in all of them, and they did not have microalbuminuria (urinary albumin < 10 mg/L). They were studied while consuming their habitual diet.
Protocol

The original study protocol was a prospective, randomized, placebo-controlled, crossover protocol in which patients were treated for 6-week periods with placebo, losartan (LST; 100 mg) and LST plus hydrochlorothiazide (HCT) (100 and 25 mg respectively) in random order. In addition patients were randomized to either a high-sodium (200 mmol Na⁺/24h) or a low-sodium diet (50 mmol Na⁺/24h). To test the hypothesis of the present study the data from two out of the six treatment periods, high-sodium placebo (placebo) and maximal antiproteinuric therapy with low sodium +, losartan + HCT (treatment) were compared.

A sodium intake of 200 mmol/24h corresponds to the average habitual dietary intake of sodium in the Western societies (24), and is also observed in our region (25). During the whole study, patients were closely counseled by a dietician in order to achieve the target intake of sodium. Patients were furthermore instructed to keep a stable intake of protein (1.1 g/kg/day), carbohydrate and fat. Every two weeks, patients collected 24-h urine in order to monitor dietary compliance. Blood pressure was measured at one-minute intervals for 15 min under standardized conditions with the patient in a semi-supine position. The mean of the last four readings was used for further analysis. Mean arterial pressure (MAP) was calculated as diastolic pressure plus one-third of the pulse pressure. Body mass index (BMI, in kg/m²) was calculated as body weight divided by length squared. On each occasion, all subjects were studied after an overnight fast for measurement of plasma lipids and CETP. Plasma adiponectin was measured in a subset of proteinuric patients from whom previously unthawed samples were available.

Laboratory analysis

Urinary protein was determined using the pyrogallol red-molybdate method. Urinary sodium and creatinine were measured with an automated multi-analyser (MEGA, Merck). Plasma for determination of lipids, CETP and adiponectin was frozen at -80°C until analysis. Cholesterol and triglycerides were assayed by routine enzymatic methods (Roche/Hitachi catalogue numbers 1187023 and 11875540 respectively) HDL-C was measured with a homogenous enzymatic caloric test (Roche/Hitachi catalogue number 03030024). Plasma CETP was analyzed using a double-antibody sandwich ELISA (26). A combination of monoclonal antibodies TP1 and TP2 was employed as coating antibodies and monoclonal antibody TP20, labeled with digoxigenine, as the secondary antibody. The CETP control samples were validated using a radioimmunoassay (carried out by Dr RM McPherson, Montreal, Canada). Plasma CETP mass is closely correlated with CETP activity measured using an exogenous substrate assay (26;27). Plasma adiponectin was measured by enzyme linked immunosorbent
assay using a kit from Linco Research (catalogue number EZHADP-61K) with an within assay coefficient of variation of 3.4%.

Statistical analysis

All statistical analyses were performed using SPSS 16.0. Parametric data are expressed as mean and standard deviation (SD). Non-parametric data are expressed as median and interquartile range. Differences between the two treatment periods were analyzed with a paired t-test for parametric data and Wilcoxon’s signed rank test for non-parametric data. Healthy controls were compared with the proteinuric subjects (high-sodium-placebo period) using Student’s t-tests or Mann–Whitney tests where appropriate.

To assess the effect of baseline CETP-mass on the total cholesterol, LDL-C, HDL-C and triglyceride before and during antiproteinuric therapy, the data were divided according to tertiles of CETP as measured during placebo. Differences between these tertiles were analysed using an ANOVA and the Kruskall–Wallis test for parametric and non-parametric data, respectively.

The effect of CETP-mass and proteinuria response to treatment on the response of cholesterol and lipoproteins was assessed by Spearman’s rank correlation analysis. Multivariate analysis was performed to assess possible confounding by statin-use. A two-sided p-value < 0.05 was considered statistically significant.

Results

Subject characteristics, dietary compliance, blood pressure and proteinuria

Thirty-two proteinuric patients (24 male, 8 females) and 32 healthy controls (24 males, 8 females) were included in the study (p = 1.0). All subjects were of Caucasian descent. Mean age (range) was 50 (23 - 69) years in the proteinuric patients and 52 (29 - 69) years in control subjects (p = 0.591). BMI was 27.5 ± 4.5 and 27.0 ± 4.4 kg/m² in patients and control subjects, respectively. Proteinuric patients had a higher MAP, 105 ± 15, compared with 98 ± 11 mmHg in control subjects (p = 0.024).

Renal diagnosis in proteinuric patients were: membranous glomerulopathy (n = 7), focal segmental glomerular sclerosis (n = 6), hypertensive nephropathy (n = 5), IgA nephropathy (n = 5), membranoproliferative glomerulonephritis (n = 2), minimal change disease with secondary glomerulosclerosis (n = 2), Alport syndrome (n = 1) and non-conclusive diagnosis.
Table 1: Clinical characteristics, serum creatinine, serum albumin and proteinuria during anti-proteinuric treatment (low sodium diet + losartan + hydrochlorothiazide) in 32 patients with non-diabetic proteinuria.

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>91 ± 17</td>
<td>89 ± 16 *</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>105 ± 15</td>
<td>90 ± 8 *</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>125 ± 44</td>
<td>140 ± 56 *</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>39 ± 4</td>
<td>41 ± 3 *</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>89 ± 27</td>
<td>76 ± 30 #</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/24h)</td>
<td>200 ± 57</td>
<td>93 ± 44 *</td>
</tr>
<tr>
<td>Urinary protein excretion (g/24h)</td>
<td>3.7 (1.9-5.5)</td>
<td>0.9 (0.5-1.4) *</td>
</tr>
</tbody>
</table>

* p < 0.001 versus placebo, # p < 0.01.

(n = 4). Twelve out of the 32 proteinuric subjects were on statin treatment (atorvastatin 20 - 80 mg/day, n = 5; simvastatin 20 - 40 mg/day, n = 3; pravastatin, 10 - 40 mg/day, n = 4) during the study period. There were no significant differences in total cholesterol, LDL-C, HDL-C, triglycerides and CETP mass during either treatment period between the statin and non-statin user subjects (p > 0.13 for all, data not shown). Moreover, no significant differences in response to antiproteinuric therapy were observed (p > 0.20, data not shown). We, therefore, analyzed all proteinuric patients together.

In table 1 body weight, blood pressure, kidney function and urinary excretion of sodium and protein during placebo and treatment are shown. The table shows first that body weight was significantly reduced by treatment, consistent with a negative volume balance. The data on urinary sodium excretion indicate that our subjects achieved an adequate compliance to the low sodium diet. Treatment resulted in a significant decrease in MAP and proteinuria. This effect was accompanied by a decrease in creatinine clearance and a slight rise in serum albumin, indicating an improvement of systemic nephrosis.

Total cholesterol, LDL-C, HDL-C, triglycerides and CETP

Figure 1, shows total cholesterol, LDL-C, HDL-C, triglycerides and CETP mass levels in healthy controls and in the proteinuric patients during placebo and treatment. There were no significant differences in total cholesterol, LDL-C and CETP-mass between controls and proteinuric subjects during placebo administration. In contrast, HDL-C was lower and triglycerides were higher in proteinuric patients.

Antiproteinuric treatment resulted in an average reduction in total cholesterol of 8% (figure
Figure 1: Serum levels of total cholesterol (chol), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides and cholesteryl ester transfer protein (CETP). *p < 0.05 versus proteinuric patients during placebo. # p < 0.05 during treatment (low sodium diet + losartan + hydrochlorothiazide) versus placebo.

1A), in LDL-C of 10% (figure 1B), in HDL-C of 11% (figure 1C) and in CETP of 10% (figure 1E). No effect on triglycerides (figure 1D) was observed. The plasma total cholesterol:HDL-C ratio did not change during treatment being 5.4 ± 1.6 and 5.5 ± 1.4 during placebo and treatment respectively (p > 0.40).

To investigate the influence of plasma CETP levels as measured during placebo administration on the response of cholesterol, LDL-C, HDL-C and triglycerides to treatment, the data were divided according to tertiles of CETP during placebo (Table 2). The table demonstrates that a higher CETP during placebo was associated with a higher CETP during treatment. It is further shown that a higher CETP was associated with a higher total cholesterol and LDL-C during both treatment regimens. There were no significant relationships of HDL-C and triglycerides
Table 2: Cholesteryl ester transfer protein (CETP) mass, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides during placebo and antiproteinuric treatment (low sodium diet + losartan + hydrochlorothiazide) according to CETP tertiles measured during placebo administration.

<table>
<thead>
<tr>
<th>Tertiles of CETP mass placebo</th>
<th>CETP mass placebo (range, mg/L)</th>
<th>Mean ± SD (mg/L)</th>
<th>CETP mass treatment (mg/L)</th>
<th>Total cholesterol placebo (mmol/L)</th>
<th>Total cholesterol treatment (mmol/L)</th>
<th>LDL-C placebo (mmol/L)</th>
<th>LDL-C treatment (mmol/L)</th>
<th>HDL-C placebo (mmol/L)</th>
<th>HDL-C treatment (mmol/L)</th>
<th>Triglycerides placebo (mmol/L)</th>
<th>Triglycerides treatment (mmol/L)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.24-1.75</td>
<td>1.56 ± 0.18</td>
<td>1.43 ± 0.20</td>
<td>4.54 ± 0.94</td>
<td>4.33 ± 0.62</td>
<td>2.57 ± 0.65</td>
<td>2.25 ± 0.51</td>
<td>0.94 ± 0.32</td>
<td>0.87 ± 0.24</td>
<td>2.27 ± 1.01</td>
<td>2.68 ± 1.23</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.78-2.28</td>
<td>2.02 ± 0.11</td>
<td>1.92 ± 0.25</td>
<td>5.53 ± 1.15</td>
<td>5.07 ± 0.94</td>
<td>3.36 ± 1.27</td>
<td>3.04 ± 0.82</td>
<td>1.19 ± 0.48</td>
<td>1.05 ± 0.32</td>
<td>2.20 ± 1.36</td>
<td>2.16 ± 0.97</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.22-3.29</td>
<td>2.71 ± 0.38</td>
<td>2.27 ± 0.41</td>
<td>6.53 ± 1.27</td>
<td>5.90 ± 1.35</td>
<td>4.34 ± 1.29</td>
<td>3.90 ± 1.29</td>
<td>1.18 ± 0.40</td>
<td>1.03 ± 0.28</td>
<td>2.24 ± 0.74</td>
<td>2.17 ± 0.58</td>
<td>by default</td>
</tr>
</tbody>
</table>

during placebo or treatment with CETP mass during placebo.

Spearman’s correlation coefficients of the changes in total cholesterol, LDL-C, HDL-C and triglycerides with the changes in CETP and UP are provided in table 3. The decreases in total cholesterol and LDL-C, but not those in HDL-C were correlated with the decrease in CETP. On multivariate analysis the correlation between the decrease in CETP and the decrease in total cholesterol and LDL-C was unaffected by statin use (p = 0.48 and p = 0.84 respectively). Table 3 also shows that the decreases in total cholesterol, LDL-C and HDL-C were related to the proteinuria response. Figure 2 demonstrates the positive relationship of the relative decrease in HDL-C with the relative decrease in urinary protein excretion in response to treatment (R = 0.492, p < 0.01). Changes in triglycerides were not related to the drop in proteinuria and in CETP. Changes in plasma CETP were not correlated with changes in proteinuria (R = 0.286, p = 0.12).

Adiponectin

In 17 patients adiponectin was measured. Median adiponectin levels were 18 (12 - 21) µg/mL.
Table 3: Relationship between changes in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides with changes in cholesteryl ester transfer protein (CETP) mass and proteinuria (UP) during antiproteinuric treatment (low sodium diet + losartan + hydrochlorothiazide) compared with placebo.

<table>
<thead>
<tr>
<th>Δ</th>
<th>Δ CETP</th>
<th>Δ UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Total cholesterol</td>
<td>0.63, p&lt;0.001</td>
<td>0.38, p&lt;0.05</td>
</tr>
<tr>
<td>Δ LDL-C</td>
<td>0.53, p&lt;0.01</td>
<td>0.39, p&lt;0.05</td>
</tr>
<tr>
<td>Δ HDL-C</td>
<td>0.28, p=0.13</td>
<td>0.40, p&lt;0.05</td>
</tr>
<tr>
<td>Δ Triglycerides</td>
<td>-0.01, p=0.98</td>
<td>-0.24, p=0.120</td>
</tr>
</tbody>
</table>

Figure 2: Correlation of changes in high-density lipoprotein cholesterol (HDL-C) with changes in proteinuria (UP) during antiproteinuric treatment ($R = 0.492$, $p < 0.01$).

Figure 3 shows that there was a positive relationship between the change in HDL-C and adiponectin as induced by treatment ($R = 0.670$, $p < 0.001$). Multivariate analysis revealed that this relationship was independent of statin use ($p = 0.21$) with high-sodium and 15 (13 - 19) µg/mL with low sodium, losartan + HCT ($p > 0.40$).
Discussion

This study has demonstrated a decrease in plasma total cholesterol and LDL-C upon rigorous anti-proteinuric therapy in patients with non-diabetic nephrotic range proteinuria, even though their plasma cholesterol at baseline was not higher compared with control subjects. The magnitude of this drop in apolipoprotein B-containing lipoproteins was significantly related to the decrease in urinary protein excretion. Anti-proteinuric treatment also resulted in a decrease in HDL-C, which was correlated with the decrease in proteinuria as well. Thus, the degree of proteinuria reduction determines lowering of both atherogenic and anti-atherogenic lipoproteins, thereby suggesting that beneficial effects on LDL-C lowering may be offset by a decrease in the HDL fraction. Accordingly, there was no change in the plasma total cholesterol/HDL-C ratio.

In the currently studied proteinuric patients, HDL-C levels were lower and plasma triglycerides were higher, but plasma total cholesterol and LDL-C were similar compared with age- and sex-matched control subjects. Twelve out of the 32 patients with nephrotic-range proteinuria were on long-term statin treatment before entry into our protocol, and it was considered clinically necessary to continue this medication during the study. It is conceivable that statin treatment had been preferentially given to those subjects with the most pronounced
elevations in atherogenic plasma lipoproteins. Therefore, the chronic use of statin therapy by a considerable number of patients most probably explains why plasma total cholesterol and LDL-C were not elevated in our cohort of proteinuric patients compared with age- and sex matched control subjects. In this context it is also relevant that statin treatment lowers plasma CETP mass and activity (12;26) via down regulation of CETP gene expression (28). This probably provides an explanation why plasma CETP mass was not elevated in the presently studied proteinuric patients. The concomitant use of statins in a subset of patients could be considered to be a limitation of our study. However, no differences in proteinuria reduction nor in any of the plasma lipoprotein and CETP effects of anti-proteinuric therapy were present between patients with and without receiving statin treatment, thus improving generalization of our findings.

High plasma levels of LDL and triglyceride-rich lipoproteins in nephrotic range proteinuria are commonly attributed to abnormalities in hepatic lipoprotein production and lipoprotein clearance (8), but the responsible mechanisms are still not fully understood. As expected, we showed that the degree of proteinuria reduction in response to treatment, predicted the drop in plasma total cholesterol and LDL-C (8). This study, furthermore, demonstrates that the plasma CETP level predicts plasma total cholesterol and LDL-C concentrations both before and during anti-proteinuric intervention. A potentially important novel observation is that anti-proteinuric treatment decreased plasma CETP mass, and that the decrease in LDL-C was related to the drop in plasma CETP. The CETP-mediated cholesteryl ester transfer process provides an important metabolic intermediate between a high cholesterol content in apo B-containing lipoproteins and a low HDL cholesterol (12;13). This process is influenced by the composition and concentration of lipoproteins involved in this reaction as well as by the CETP level itself (29). This raises the possibility that plasma CETP lowering may have contributed to the decrease in LDL-C during amelioration of proteinuria.

To our knowledge, this report is the first to demonstrate that the magnitude of the HDL-C decrease is determined by the degree of proteinuria reduction during treatment. It therefore appears that lowering of HDL-C is inherent to rigorous inhibition of urinary protein excretion. In our study, a trend towards lower HDL-C at higher plasma CETP was observed, but the difference in HDL-C levels across plasma CETP mass tertiles did not reach significance before as well as during treatment. The drop in HDL-C was unrelated to the decrease in plasma CETP during anti-proteinuric treatment, as can be predicted considering the effect of this lipid transfer protein on promoting transfer of cholesteryl esters out of HDL particles (12). Interestingly, a clear positive relationship was observed between the individual changes in HDL-C and the changes in adiponectin levels, albeit in a subset of participants. Evidence is accumulating that adiponectin is regulated by RAAS components (22), in such a way that endogenous RAAS
activation by lowering dietary sodium intake decreases plasma adiponectin (22). Conversely pharmacological inhibition of the RAAS increases plasma levels of this adipokine (22). As a result, median plasma adiponectin levels did not change significantly during anti-proteinuric intervention combining low sodium diet with hydrochlorothiazide and losartan, although large interindividual differences in responses were observed. In view of recent data showing that adiponectin may play a direct regulatory role in apo A-I metabolism (19;20), our data suggest that the adverse HDL-C response to antiproteinuric therapy, may be in part be ascribed to changes in adiponectin levels, as induced by intervention in the RAAS.

The present results suggest that HDL-C lowering is inherent to robust anti-proteinuric therapy when combining low-sodium diet with diuretic and angiotensin-II inhibitor treatment. Plasma CETP mass predicted LDL-C levels during treatment. Moreover, the decrease in LDL-C was strongly correlated to the decrease in CETP, possibly implicating effects of the cholesteryl ester transfer process on lowering of atherogenic lipoproteins upon anti-proteinuric intervention.

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Reference List


