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Relationship between apolipoprotein C-III concentrations and high-density lipoprotein subclass distribution

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Abstract

High-density lipoprotein (HDL) subclasses have different antiatherogenic potentials and functional properties. This work presents our findings and discussions on their metabolic implications on apolipoprotein (apo) C-III together with other apolipoprotein levels and HDL subclass distribution profile. Apolipoprotein A-I contents of plasma HDL subclasses were quantitated by 2-dimensional gel electrophoresis coupled with immunodetection in 511 subjects. Concentrations of triglycerides and of apo B-100, C-II, and C-III were higher, whereas those of HDL cholesterol were lower, for subjects in the highest tertile of apo C-III levels group, which presented a typical hypertriglyceridemic lipid profile. Subjects in the middle and highest tertile of apo C-III levels groups had increased preβ_1-HDL, HDL_{3c}, HDL_{3b} (only in the highest tertile of apo C-III group), and HDL_{3a}, but decreased HDL_{2a} and HDL_{2b} contents compared with subjects in the lowest tertile of apo C-III levels group. With the elevation of apo C-III together with apo C-II levels, contents of small-sized preβ_1-HDL increased successively and significantly; but those of large-sized HDL_{2b} reduced successively and significantly. With a rise in apo C-III and apo A-I levels, those of preβ_1-HDL increased significantly. Moreover, subjects with high apo A-I levels showed a substantial increase in HDL_{2b}; on the contrary, HDL_{2b} declined progressively and obviously for subjects in the low apo A-I levels with the elevation of apo C-III levels. Correlation analysis illustrated that apo C-III levels were positively associated with preβ_1-HDL, preβ_2-HDL, and HDL_{3a}. The particle size of HDL shifted toward smaller sizes with the increase of plasma apo C-III levels, and the shift was more remarkable when the elevation of apo C-III and apo C-II was simultaneous; and besides, higher apo A-I concentrations could modify the effect of apo C-III on HDL subclass distribution profile. Large-sized HDL_{2b} particles decreased greatly for hypertriglyceridemic subjects who were characterized by elevated apo C-III and C-II accompanied with significantly lower apo A-I, which, in turn, blocked the maturation of HDL.

1. Introduction

High-density lipoprotein (HDL) is a heterogeneous mixture of metabolically related particles differing in lipid and apolipoprotein compositions. The apolipoproteins not only could stabilize lipoprotein structure, they also play an essential function in regulating lipoprotein metabolism. For example, apolipoprotein (apo) A-I, which is the major apolipoprotein of plasma HDL, accounts for 65% to 70% of HDL protein and is a stimulator of the activity of lecithin-cholesterol acyltransferase (LCAT) in vitro [1-3]. Apolipoprotein A-II, which makes up about 25% of plasma HDL protein, appears to be primarily a structural protein [4].

Apolipoprotein C_s consists of 3 distinct proteins—apo C-I, apo C-II, and apo C-III—that together make up about 10% of HDL proteins. Apolipoprotein C-II is a major activator of lipoprotein lipase (LPL) [5] and therefore regulates triglyceride (TG) levels by stimulating TG hydrolysis. Apolipoprotein C-III inhibits the lipolysis of TG-rich lipoproteins (TRLs) and interferes with their clearance from the

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circulation [6,7]. High levels of apo C-III have been associated with increased risk of arteriosclerosis and cardiovascular events [8]. A high apo C-III level was also found in subjects with hypertriglyceridemia as part of the metabolic syndrome [9,10]. In the Monitored Atherosclerosis Regression Study and the Cholesterol Lowering Atherosclerosis Study, the high level of apo C-III was strongly related to atherosclerotic lesion progression [11,12].

Because of the importance of these apolipoproteins in HDL metabolism, in this work, we investigated mainly the apo C-III influence on the characteristics of HDL subclass distribution, which may contribute to understanding the mechanism by which altered apo C-III exerts its effect on metabolism of HDL subclasses.

2. Subjects and methods

2.1. Subjects

Six hundred nineteen subjects were recruited to participate in a study examining plasma lipid and apolipoprotein concentrations in West China Medical Center, Sichuan University. To reduce the impact of other factors on this study, the screening criteria applied the following: (1) presence of nephrosis, diabetes hypothyroidism, or hepatic impairment; (2) presence of major cardiovascular event, coronary heart disease, or stroke; (3) treatment by lipid-lowering drugs in the previous 1 month; and (4) consuming alcohol and smoking in the previous 1 week. According to the above exclusion criteria, 511 subjects (315 men; mean age, 56.5 ± 8.4 years; 196 women; mean age, 56.9 ± 7.8 years) were included in the present work. The institutional ethics committee on human approved the study, and all subjects gave informed consent.

To investigate the impact of apo C-III levels and the combined influence of apo C-III and apo C-II as well as apo C-III and apo A-I on HDL subclass distribution, we divided apo C-III, apo C-II, and apo A-I into tertiles.

The apo C-III concentration was entered as a categorical variable with 3 levels. Firstly, the apo C-III was arranged in ascending sequence on the basis of its concentrations. Afterward, subjects 1 to 170 were designated as the *lowest tertile of apo C-III group* (apo C-III range, 25-117 mg/L); subjects 171 to 340 were designated as the *middle tertile of apo C-III group* (apo C-III range, 118-170 mg/L); and subjects 341 to 511 were designated as the *highest tertile of apo C-III group* (apo C-III range, 172-498 mg/L). The methods used for the levels of apo C-II along with apo A-I were the same as those for the levels of apo C-III.

2.2. Specimens

Whole blood specimens were drawn after a 12-hour overnight fast into EDTA-containing tubes. Plasma was separated within 1 to 2 hours. Plasma was stored at 4°C and used within 24 hours for lipid and apolipoprotein analyses. An aliquot of plasma was stored at −70°C for the determination of HDL subclasses.

2.3. Plasma lipid and apolipoprotein analyses

Plasma TG, total cholesterol (TC), and HDL cholesterol (HDL-C) were measured by standard technique. The TC and TG were determined with enzymatic kits (Beijing Zhongsheng Biotechnological, Beijing, People's Republic of China). The HDL-C was determined after precipitation of the apo B–containing lipoproteins by phosphotungstate/magnesium chloride [13]. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula (TG <4.52 mmol/L) [14]. When plasma TG was at least 4.52 mmol/L, LDL-C was determined following the precipitation method with polyvinyl sulfate (enzymatic kits). Plasma apo A-I, B-100, C-II, and C-III were determined by radial immunodiffusion methods [15] using kits developed at the Apolipoprotein Research Laboratory, West China Medical Center, Sichuan University. The intraassay coefficient of variation for apolipoprotein concentrations was between 2.1% and 4.8%; interassay coefficient of the variation was 3.5% to 7.9% [16].

2.4. HDL-C subclass analyses

Apolipoprotein A-I–containing HDL subclasses were measured by nondenaturing 2-dimensional gel electrophoresis associated with immunodetection method as described previously [17]. Briefly, 10 μL of plasma was first separated by charge on 0.7% agarose gel into preβ and α mobility particles. In the second dimension, the 2 fractions of HDL were further separated according to size by 2% to 30% nondenaturing polyacrylamide gradient gel electrophoresis. To determine HDL subclasses, Western blotting was conducted after electrophoresis using horseradish peroxidase–labeled goat anti-human apo A-I immunoglobulin G. The HDL particle sizes were calibrated using a standard curve that includes bovine serum albumin, ferritin, and thyroglobulin (Pharmacia, Uppsala, Sweden). The calculation of each HDL subclass relative percentage was based on the density of electrophoresis spots. Afterward, the apo A-I contents (in milligrams per liter) of the HDL subclasses were calculated by multiplying the percentage of each subclass by the plasma total apo A-I concentrations. The interassay coefficients of variation of the relative concentration of preβ_1-HDL, preβ_2-HDL, HDL_{3c}, HDL_{3b}, HDL_{3a}, HDL_{2a}, and HDL_{2b} in plasma saple were 9.4% 9.8% 4.9% 6.2% 7.3% 11.1% and 7.9% respectively (n = 5).

2.5. Statistical analysis

All statistical analyses were performed using the statistical package SPSS Version 11.0 (SPSS, Chicago, IL). Data are expressed as mean ± SD. The significant differences between 2 groups were analyzed by 1-way analysis of

Table 1
Concentrations of plasma lipids, apolipoproteins, and the apo A-I contents of HDL subclasses among subjects categorized by apo C-III levels

	Low apo C-III group	Middle apo C-III group	High apo C-III group
n	170	170	171
Age(y)	55.4 ± 9.6	55.7 ± 9.1	57.0 ± 9.1
Female/male	67/109	64/102	65/104
Sex ratio(%)	61.5	62.7	62.5
BMI (kg/m^2)	24.4 ± 2.8	24.3 ± 3.1	24.6 ± 3.3
TG (mmol/L)	1.2 ± 0.5	2.2 ± 0.9‡	3.5 ± 1.8‡
TC (mmol/L)	5.2 ± 0.8	5.6 ± 0.9†	5.8 ± 1.1‡
LDL-C (mmol/L)	3.2 ± 0.9	3.3 ± 1.1	3.4 ± 1.0
HDL-C (mmol/L)	1.4 ± 0.4	1.3 ± 0.4	1.0 ± 0.3‡
TG/HDL-C	0.9 ± 0.5	2.1 ± 1.2‡	3.8 ± 2.2‡
TC/HDL-C	4.0 ± 1.2	4.9 ± 1.5†	6.0 ± 1.5‡
Apo A-I (mg/L)	1291.1 ± 186.8	1258.9 ± 194.3	1222.8 ± 144.7
Apo B-100 (mg/L)	767.9 ± 135.3	899.4 ± 100.8†	1061.9 ± 107.8‡
Apo C-II (mg/L)	38.7 ± 10.2	61.3 ± 11.7‡	110.6 ± 39.6‡
Apo C-III (mg/L)	93.2 ± 17.7	140.3 ± 13.6‡	223.8 ± 69.7‡
Preβ_1-HDL (mg/L)	83.7 ± 31.7	106.7 ± 40.8†	136.9 ± 46.6‡
Preβ_2-HDL (mg/L)	56.1 ± 18.4	59.5 ± 20.7	62.0 ± 25.8
HDL_{3c} (mg/L)	68.1 ± 24.9	77.0 ± 30.9	85.4 ± 32.4*
HDL_{3b} (mg/L)	139.8 ± 53.4	148.8 ± 53.8	160.1 ± 55.5†
HDL_{3a}(mg/L)	253.7 ± 68.6	294.3 ± 89.8‡	316.6 ± 91.1‡
HDL_{2a} (mg/L)	275.8 ± 67.0	258.5 ± 70.0*	217.8 ± 73.7‡
HDL_{2b} (mg/L)	371.6 ± 107.9	328.6 ± 102.4‡	251.4 ± 86.9‡

Values are expressed as mean ± SD. The highest and middle tertiles were compared with the lowest tertile of apo C-III levels group. BMI indicates body mass index.

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

variance. Linear regression was used to examine the associations between apolipoproteins and other variables. In all comparisons, P less than .05 (2-sided) was regarded as statistically significant.

3. Results

3.1. Concentrations of plasma lipids, apolipoproteins, and apo A-I contents of HDL subclasses according to apo C-III levels

As indicated in Table 1, concentrations of TG, TC, apo B-100, apo C-II, and apo C-III as well as ratios of TG/HDL-C and TC/HDL-C rose steadily; in contrast, those of HDL-C fell successively with the elevation of apo C-III levels.

In addition, in the subjects in the middle and highest tertile of apo C-III groups, preβ_1-HDL, HDL_{3c}, HDL_{3b} (only in the highest tertile of apo C-III group), and HDL_{3a} contents were significantly higher, whereas HDL_{2a} and HDL_{2b} contents were significantly lower, in comparison with the subjects in the lowest tertile of apo C-III group.

3.2. Apo A-I contents of HDL subclasses according to the apo C-III along with the apo C-II levels

Fig. 1 shows that, when apo C-III and apo C-II were elevated simultaneously, the contents of preβ_1-HDL rose significantly, whereas those of HDL_{2b} fell significantly. Furthermore, the contents of HDL_{2b} were noticeably lower for subjects in the high apo C-II levels, regardless of whether the apo C-III levels increased or not; and those of HDL_{2b} had no difference in the groups with low, middle, and high apo C-III levels.

3.3. The apo A-I contents of HDL subclasses among subjects categorized by apo C-III and apo A-I levels

As seen from Fig. 2, the contents of small-sized preβ_1-HDL increased gradually and markedly with a rise in the apo C-III along with apo A-I levels. It is worth noting that the subjects with high apo A-I levels showed a substantial increase in HDL_{2b}; on the contrary, HDL_{2b} declined progressively and obviously for subjects in the low apo A-I levels with the elevation of apo C-III levels.

3.4. The contents of HDL subclass coefficients with the levels of plasma apolipoproteins

To investigate the relationship between apo levels and contents of HDL subclasses, after adjustment for lipid (TG, TC) variables, the correlation analysis illustrated that the plasma apo C-III levels were positively associated with preβ_1-HDL, preβ_2-HDL, and HDL_{3a}. The apo A-I levels were positively correlated with all HDL subclasses; apo C-II levels were positively correlated with preβ_1-HDL, HDL_{3c}, and HDL_{3a} but inversely correlated with HDL_{2b}. In addition,

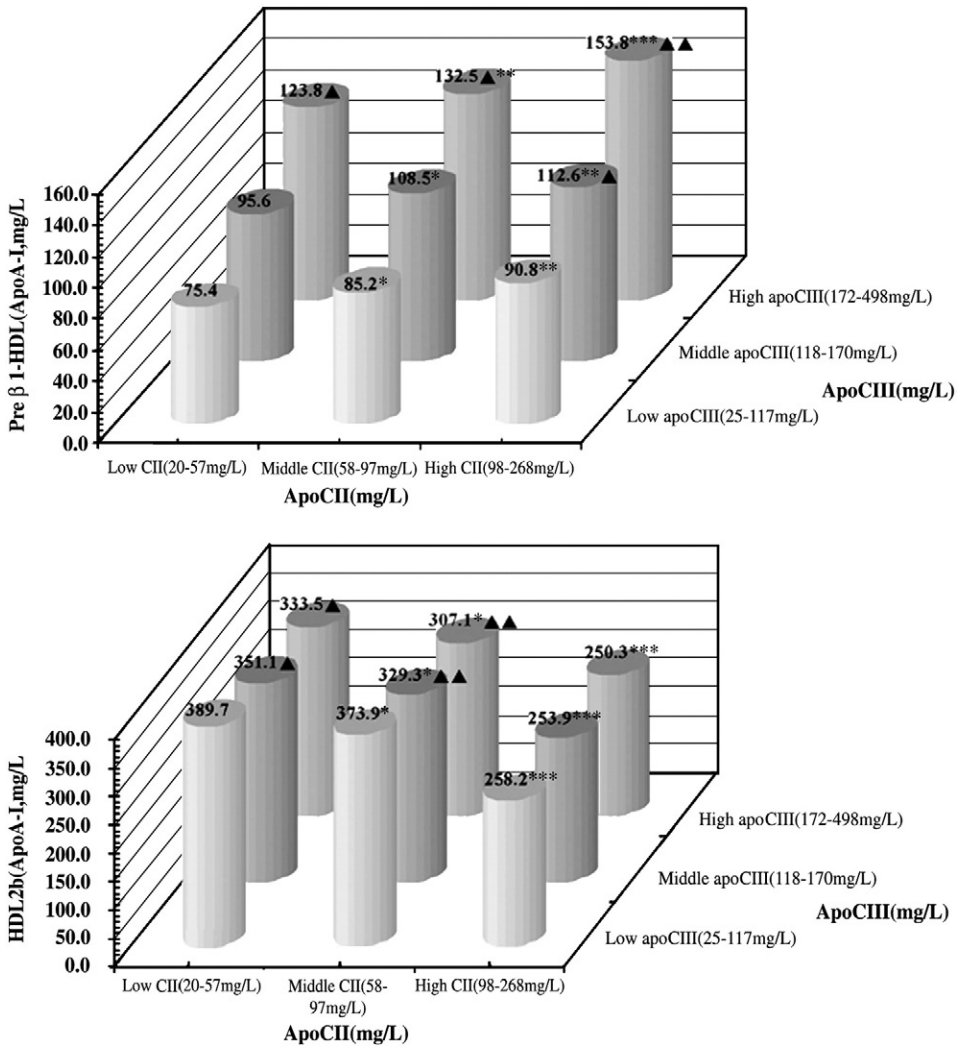

Fig. 1. The apo A-I contents of preβ_1-HDL and HDL_{2b} according to apo C-III together with apo C-II levels in whole subjects. *$P < .05$, **$P < .01$, and ***$P < .001$; compared with the low apo C-II subgroup within the same apo C-III group. ▲$P < .05$ and ▲▲$P < .01$; compared with the low apo C-III subgroup within the same apo C-II group.

the apo B-100 levels were positively related to preβ_1-HDL and negatively associated with HDL_{2b} (Table 2).

4. Discussion

The protein moiety of plasma lipoproteins consists of different apolipoproteins, which play key roles in the synthesis of lipoproteins, transport, and catabolism of plasma lipids. In addition to binding and transporting lipid, plasma apolipoproteins stimulate or inhibit lipolytic enzymes and mediate the interaction of lipoproteins with cell membrane receptors [18,19]. We have reported previously that concentrations of plasma lipids along with apo A-I levels have important effects on HDL subclass distribution pattern [20-24]. However, relatively little is known concerning the effects of other apolipoproteins that HDL contained, particularly the C apolipoproteins, in relation to alteration of HDL subclass distribution. In this work, we mainly investigated the apo C-III along with other apolipoprotein levels and HDL subclass distribution pattern.

Our main finding was that apo C-III is also an important impact factor for HDL subclass distribution. The present data show that large-sized HDL_{2a} and HDL_{2b} decreased significantly, whereas small-sized preβ_1-HDL and HDL_3 (HDL_{3c}, HDL_{3b}, and HDL_{3a}) increased significantly, in high apo C-III subjects vs middle and low apo C-III subjects.

The mechanism responsible for redistribution of HDL subclasses was likely related to the alteration of plasma apolipoprotein levels along with lipid levels. Compared with the lowest tertile of apo C-III levels group, a (240%) growth in apo C-III occurred in the highest tertile of apo C-III levels group. In vitro studies have implicated apo C-III as a noncompetitive inhibitor of LPL activity [25,26]; when catabolized by LPL, chylomicrons and very low-density

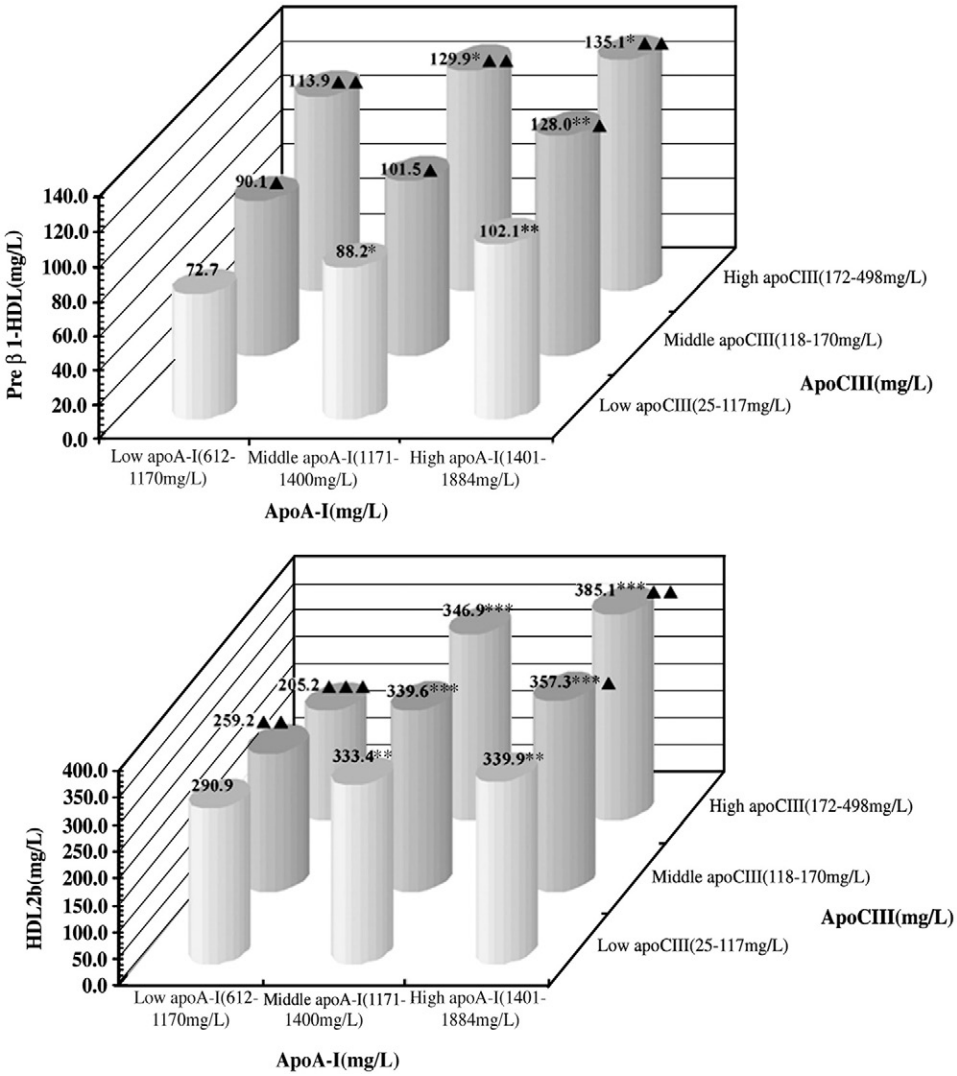

Fig. 2. The apo A-I contents of preβ_1-HDL and HDL_{2b} according to apo C-III together with apo A-I levels in whole subjects. *$P<.05$, **$P<.01$, and ***$P<.001$; compared with the low apo A-I subgroup within the same apo C-III group. ▲$P<.05$, ▲▲$P<.01$, and ▲▲▲$P<.001$; compared with the low apo C-III subgroup within the same apo A-I group.

lipoprotein (VLDL) release TG, TC, apo A-I, and apo Cs. Subsequent binding of these products to HDL_3 results in the formation of HDL_2 particles.

Furthermore, preliminary studies as discussed by Sparks and Pritchard [27] demonstrate that apo C-III stimulates cholesterol ester transfer protein (CETP) activity by using recombinant HDL particles. The CETP mediates exchange of core lipids between VLDL-TG, LDL-TG, and HDL-CE and brings about the generation of small HDL particles. In accordance with these, plasma-increased apo C-III levels

Table 2
The apo A-I contents of HDL subclass coefficients with the levels of plasma apolipoproteins (controlling for TG and TC)

	Apo C-III		Apo A-I		Apo C-II		Apo B-100	
	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
Preβ_1-HDL	0.156	.002	0.491	.000	0.147	.002	0.152	.001
Preβ_2-HDL	0.133	.007	0.476	.000	0.021	.759	−0.020	.731
HDL_{3c}	0.021	.681	0.362	.000	0.128	.016	0.094	.068
HDL_{3b}	−0.011	.891	0.525	.000	0.041	.419	0.080	.102
HDL_{3a}	0.092	.041	0.557	.000	0.090	.035	0.011	.886
HDL_{2a}	−0.020	.713	0.590	.000	−0.056	.279	−0.044	.357
HDL_{2b}	−0.023	.715	0.463	.000	−0.102	.029	−0.091	.038

favor the reduction of large-sized HDL particles and the production of small-sized HDL particles.

On the other hand, we divided the whole study population into tertiles of plasma apo C-III levels and showed that there was a 3-fold rise in TG and an approximately 40% decrease in HDL-C. Furthermore, apo C-II, C-III, and B-100 also increased in subjects in the highest tertile of apo C-III levels vs those in the lowest tertile of apo C-III group. According to the *Third Report of the National Cholesterol Education Program (Adult Treatment Panel III)* [28], the above alteration of lipid, lipoprotein, and apolipoprotein levels showed a typical hypertriglyceridemic lipid profile. Most studies have demonstrated that higher plasma TG levels not only impair LPL and LCAT but also enhance CETP and hepatic lipase activities [29-31]. The LCAT may catalyze unesterified cholesterol to CE and promote the conversion of preβ_1-HDL to HDL_2. As the excess TG is hydrolyzed by hepatic lipase, the HDL particle size shifted toward smaller sizes and the contents of the large HDL_{2b} were reduced. In view of these, we suggest that concentrations of TG also seriously interfere in the HDL subclass metabolism.

The contents of preβ_1-HDL and HDL_{2b} based on apo C-III along with apo C-II levels among whole subjects were discussed in the current study as well. The outcome presented that, when apo C-III and apo C-II were elevated simultaneously, contents of preβ_1-HDL rose significantly, whereas those of HDL_{2b} went down obviously. Interestingly, we found that, in the high apo C-II levels group, HDL_{2b} contents were reduced more markedly, regardless of whether the apo C-III levels increased or not, and were not different among low, middle, and high apo C-III level groups. It is well known that apo C-II mediates the activity of LPL and exists in a dynamic equilibrium between HDL and TRL [32]. Concentrations of plasma TG along with total apo C-II were elevated in parallel with the reduction of apo C-II in HDL plasma fraction. When TG levels increase, HDL is progressively depleted of apo C-II, which would lead to limited reserves in HDL for transfer to apo C-II to VLDL to facilitate catabolism of newly synthesized VLDL and chylomicron lipid. Because of insufficient transfer from HDL, this could bring about a decreased LPL activation of these TRLs. In addition, excess apo C-II on the lipoprotein particle has been shown to inhibit LPL-mediated hydrolysis of TGs [33]. Given these investigations, we think that plasma apo C-III and apo C-II may have a cooperative action on the redistribution of HDL subclasses. As for the high apo C-II levels group, HDL_{2b} contents were predominately reduced whether or not apo C-III increased; and those of HDL_{2b} were kept coincident among low, middle, and high apo C-III level groups, implicating that higher apo C-II levels may be more significant to influence the component of large-sized HDL_{2b} than plasma apo C-III levels. The correlation analysis revealed that apo C-II levels were negatively associated with HDL_{2b}, which conforms to our observation.

Besides, we want to know whether the changes in apo C-III and apo A-I could exert an impact on the distribution of preβ_1-HDL and HDL_{2b} contents. As apo C-III along with apo A-I levels rise, preβ_1-HDL contents gradually increased. In addition, with the increase of apo C-III levels, HDL_{2b} contents were elevated significantly in the high apo A-I levels group, but were reduced obviously in the low apo A-I levels group and in the middle apo A-I levels group, where higher concentrations remained, distinct from the alteration of apo C-III and apo C-II levels influence on the HDL subclass distribution. Studies in human apo A-I transgenic mice have demonstrated that the distribution of apo A-I among the HDL subclasses was similar, suggesting that the content of apo A-I in the major HDL subspecies was fixed and apo A-I levels might reflect the number of HDL particles [34-37]. Likewise, our previous investigation also showed that, with the elevation of apo A-I concentrations, all HDL subclasses tend to increase and higher apo A-I concentrations are associated with significant increase in HDL_{2b} [38]. Thus, it can be seen that apo A-I plays a lead role in HDL subclass metabolism and that higher apo A-I concentrations could correct the effect of apo C-III levels on HDL subclass profile.

When adjusting for lipid variables (TG, TC), the correlation analysis displayed that apo A-I levels were positively correlated with all HDL subclasses, which confirmed that apo A-I is an independent impact factor for the profile of HDL subclass distribution. Apolipoprotein C-II levels were positively correlated with preβ_1-HDL, HDL_{3c}, and HDL_{3a}, but inversely correlated with HDL_{2b}; and the plasma apo C-III levels were positively associated with preβ_1-HDL, preβ_2-HDL, and HDL_{3a}. These confirmed that the effect of apo C-III on change in HDL subclass distribution is closely related to plasma other apolipoproteins and lipid variables metabolism.

Thus, on the basis of these findings taken together, it indicated that the particle size of HDL shifted toward smaller sizes with increase of plasma apo C-III levels; and the shift was more remarkable when the elevation of apo C-III and apo C-II was simultaneous. Besides, the higher apo A-I concentrations could modify the effect of apo C-III on HDL subclass distribution profile. Large-sized HDL_{2b} particles decreased greatly for hypertriglyceridemic subjects who were characterized by elevated apo C-III and C-II accompanied with significantly lower apo A-I, which, in turn, blocked the maturation of HDL.

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