Dynamics of reverse cholesterol transport: protection against atherosclerosis

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Abstract

This review considers the antiatherogenic function of high density lipoprotein (HDL) from the point of view of its dynamics within the sequential steps of reverse cholesterol transport (RCT). It is postulated that the efficiency of cholesterol flux through the RCT pathways is clinically more relevant than the HDL cholesterol concentration. The particular role of preβ1-HDL is reviewed drawing attention to the relationship between its concentration and the flux of cholesterol through the RCT system.

Keywords: High density lipoprotein; Reverse cholesterol transport; Atherosclerosis; Preβ1-HDL

1. Introduction

Reverse cholesterol transport (RCT) is a pathway transporting cholesterol from extrahepatic cells and tissues to the liver, and perhaps intestine, for excretion. A key element of RCT is high density lipoprotein (HDL), a subfraction of human plasma lipoproteins with apolipoprotein A-I (apoA-I) as its principal apolipoprotein. By reducing accumulation of cholesterol in the wall of arteries reverse cholesterol transport may prevent development of atherosclerosis. That process is determined at least partially by the HDL concentration in the blood, since the plasma concentration of HDL cholesterol and apoA-I correlate negatively with the incidence of coronary heart disease (CHD). An alternative interpretation is that since the plasma HDL concentration reflects the activities of a number of metabolic pathways, it is the flow of cholesterol through these pathways that may determine the level of protection against atherosclerosis. This view may be particularly relevant for establishing the role of minor HDL subfractions, such as preβ1-HDL, in the reverse cholesterol transport and the diagnostic significance of their concentration in the evaluation of the risk of CHD.

2. High density lipoprotein concentration, atherosclerosis and coronary heart disease

The inverse relationship between plasma levels of HDL and CHD has been demonstrated in a number of observational epidemiological studies, such as Framingham Heart Study [1], and Prospective Cardiovascular Munster Study (PROCAM) [2] (for review of other studies see [3,4]), as well as in several intervention studies, for example Familial Atherosclerosis Treatment Study (FATS) [5], which showed that increased HDL concentrations independently predicted lowered risk of CHD. Results of the High-Density Lipoprotein Intervention Trial (VA-HIT) study also suggest that the rate of coronary events may be reduced by raising HDL...
cholesterol and lowering triglyceride concentration independent of LDL cholesterol levels in subjects with CHD whose primary lipid phenotype was low HDL—high triglyceride [6].

It is widely believed that this relationship between plasma HDL concentration and CHD is that of causation, not correlation, and is explained by the role of HDL in reverse cholesterol transport. The RCT concept was originally suggested by Glomset [7] and consists of a centripetal movement of cholesterol from extracellular tissues including the vessel wall, for excretion by the liver. The RCT consists of five steps: (i) uptake of cholesterol from cells by specific acceptors (cholesterol efflux); (ii) esterification of cholesterol within HDL by lecithin:cholesterol acyltransferase (LCAT); (iii) transfer of cholesterol to the apoB-containing lipoproteins (cholesterol transfer); (iv) remodeling of HDL and (v) uptake of HDL cholesterol by the liver and possibly also by kidney and small intestine through lipoprotein receptors (cholesterol uptake) [8]. HDL is involved in all RCT steps, but it need not follow that it is its concentration in plasma that is the key determinant of the rate of RCT.

First, most reports on cell cholesterol efflux agree that the concentration of apoA-I required for maximum recruitment of cellular cholesterol is far below the concentration of apoA-I in plasma [9,10]. Concentrations of apoA-I required for the activation of LCAT [11] and saturation of HDL binding to the known receptors [12] is also well below its concentration in the blood. Since even modest variations in cholesteryl ester transfer protein (CETP) and hepatic lipase (HL) concentration affect HDL cholesterol content in plasma [13], CETP and HL but not HDL, are more likely to be rate-limiting in the transfer and remodeling steps. The concentration of HDL within the vessel wall, where most processes associated with atherogenesis occur, may differ from its circulating concentration. However, even the concentration of HDL in lymph (about 15% of that in the blood [14]) that is likely to be closest to the concentration in tissue, is still almost an order of magnitude higher than that required for any step in RCT.

Second, Dietschy et al. [15,16] have recently reported that the in vivo rate of RCT did not depend on HDL concentration. Stein et al. [17] have also demonstrated in apoA-I transgenic mice that elevating the concentration of apoA-I was not accompanied by higher cholesterol efflux in vivo. In apoA-I knockout mice, the flux of cholesterol from the peripheral tissue to the liver was decreased, but did not lead to accumulation of cholesterol in peripheral tissues nor to cholesterol deficit in the liver [18]. This suggests that the plasma HDL concentration in vivo is not necessarily linked with cholesterol balance in extrahepatic cells.

Third, although high concentrations of apoA-I protect against development of atherosclerosis, apoA-I deficiency is not necessarily associated with an increased risk of atherosclerosis. ApoA-I knockout mice do not develop atherosclerosis even on an atherogenic diet despite absence of HDL [19,20]. Patients with Tangier disease [21], with familial hypoalphacholesterolemia [22,23] or with mutations in apoA-I [24,25] or LCAT [26] that are associated with severe decrease of plasma HDL, do not inevitably develop atherosclerosis and CHD. However, the patients with mutations associated with impaired apoA-I synthesis or apoA-I/apoC-III deficiency usually do have severe CHD [24,27].

Fourth, the strength of association between HDL levels and protection against CHD varies significantly from one study to another depending on ethnic background, gender and presence of other risk factors (reviewed in [28,29]). Moreover, in patients with very high plasma triglyceride concentration [30] or with CETP polymorphism [31], even high HDL levels may fail to protect against CHD or even be atherogenic [32].

3. Alternative hypotheses of HDL function

Several hypotheses have been suggested to explain the apparent paradoxes between relationships of HDL, RCT and risk of CHD.

The ‘permissive’ hypothesis postulates that high HDL might not be an independent anti-atherogenic factor, whereas low HDL may be a permissive trigger for development of atherosclerosis due to concomitant pro-atherogenic factors. Most evidence, however, points against this hypothesis. In both observational and intervention studies, level of HDL and incidence of CHD remain inversely correlated even when adjusted for other risk factors [2,4,6,33], supporting HDL as an independent protective factor.

The ‘Non-RCT’ hypothesis postulates that properties and functions of HDL other than RCT are the major protective factor. The following properties of HDL are potentially anti-atherogenic: (1) HDL down-regulates expression of adhesive molecules on the surface of vascular endothelium [34], thus being anti-inflammatory. (2) HDL has antioxidant property [35,36] ascribed to the enzyme paraoxonase that is associated with HDL [37], or to antioxidant properties of apoA-I itself [38]. (3) HDL inhibits platelet aggregation and thus has anti-thrombotic properties [39]. (4) HDL prevents inhibition of nitric-oxide synthase by oxidized LDL [40], apparently helping to maintain normal vessel functions. (5) HDL activates a number of intracellular signaling events [39,41,42], which can potentially lead to stimulation of cholesterol efflux [43,44] or up-regulation of ABCA1 [45]. Although these properties are well documented in vitro and may be important, it is presently
difficult to assess the contribution of ‘Non-RCT’ properties of HDL to its overall anti-atherogenic effect in vivo.

The ‘Subfraction’ hypothesis is based on the fact that HDL consists of a number of subfractions and that the concentration of one or several subfractions is rate-limiting for RCT thus determining the level of protection against atherosclerosis. Earlier studies divided HDL into two subfractions based on their flotation density, lighter and larger HDL₁ and denser and smaller HDL₃ (for review see [46]). However, not all studies have showed that this differentiation into two subfractions has improved the quantitation of the protective effect of HDL [47,48]. It was later suggested that particles containing only apoA-I (LpA-I) were anti-atherogenic whereas particles containing both apoA-I and apoA-II (LpA-I/A-II) were either neutral or pro-atherogenic [49]. In vitro, LpA-I particles were more effective than LpA-I/A-II particles in promoting cholesterol efflux [50,51], in the uptake and esterification of cholesterol [52], and in transferring cholesteryl esters to the liver [53]. Transgenic mice expressing apoA-I were more protected against atherosclerosis compared with mice expressing both apoA-I and apoA-II [51]. Other studies, however, could not confirm a difference between LpA-I and LpA-I/A-II in promoting cholesterol efflux [54]. Whether the negative association between LpA-I particles and atherosclerosis is superior to whole HDL remains to be confirmed. A further classification of the HDL particles based on separating apoA-I containing lipoproteins on non-denaturing two-dimensional electrophoresis may better reflect the functional properties of HDL with respect to cholesterol flux through metabolic pathways and may be a better predictor of CHD. Thus, Asztalos et al. have reported that the concentrations of large \( \alpha_1 \)-HDL and pre-\( \alpha_1 \)-HDL were relatively more decreased than that of HDL-C and of apoA-I in patients with CHD [55]; the same particles were also severely depleted in patients with heterozygous Tangier disease (familial hypoalphacholesterolemia) [56].

4. Dynamics of HDL cholesterol transport through metabolic pathways

Assuming that the anti-atherogenic property of HDL is substantially determined by its role in RCT, which is a dynamic process, it follows that it is the efficiency of the whole metabolic pathway and the rates of the individual steps in RCT that define the protective role of HDL. Thus, the concentrations of the components of the RCT pathway may in some situations determine the velocity of the pathway as a whole, at other times merely reflect the rates of individual steps. For example, if the efficiency of the middle stages of RCT were greater than the rates of cholesterol recruitment from cells, the concentration of the RCT intermediates might be low, but the overall efficiency high. In contrast, if HDL remodeling during its catabolism were slow, accumulation of HDL cholesterol may occur yet reflect reduced efficiency of RCT. From the standpoint of this hypothesis the concentration of HDL per se is less significant in forecasting the level of atheroprotection than the efficiency of cholesterol transport through RCT, and knowledge of its dynamics would provide better predictive power. That requires information on sequential steps, such as rate constants of cholesterol flux through HDL subspecies, activity of enzymes, transfer proteins and receptors. The in vivo rate of plasma cholesteryl ester turnover was shown to correlate more closely with LCAT activity than with the plasma cholesterol concentration [57]. Even without considering subdivision of HDL into functional subspecies, a significant body of evidence has accumulated since then to support the basic principle of the hypothesis. Inherited disorders in humans and transgenic animals offer the opportunity to examine simultaneously modifications in the individual steps of RCT on HDL concentration and atherogenic outcome.

4.1. Turnover of HDL subspecies and cholesterol efflux

Since HDL comprises of a number of minor and major subspecies, probably having different functional roles, the effective flux of cholesterol through RCT clearly requires coordinated metabolic regulation of HDL species and cholesterol. The following scheme of HDL inter-conversion derives from the work of Fielding [8,58,59], von Eckardstein [60] and Asztalos [61–63] (Fig. 1). Small discoid lipid-poor particles, pre\( \beta \)-HDL, are an initial acceptor of cellular cholesterol. Upon accumulation of cholesterol these particles are transformed into bigger particles, pre\( \beta \)-HDL, which are a substrate for LCAT. Esterification of cholesterol in pre\( \beta \)-HDL and probably acquisition of additional apoA-I molecules lead to the formation of spherical \( \alpha_1 \)-HDL particles. These particles acquire more cholesterol from pre\( \beta \)-HDL and possibly also from cells [64] that transforms these particles into larger \( \alpha_2 \)-HDL and \( \alpha_1 \)-HDL. The next step involves exchange of accumulated cholesteryl esters for triglycerides through the action of CETP, transfer of phospholipid through the action of phospholipid transfer protein (PLTP) and hydrolysis of triglyceride and phospholipid by HL. As a result, particles are remodeled into smaller \( \alpha_2 \)-HDL particles and lipid-free apoA-I [65,66], the latter becoming rapidly re-lipidated by cellular phospholipid and cholesterol to form pre\( \beta \)-HDL particles.

Disruption of the cycle severely impairs RCT. The most striking effect is seen when cholesterol efflux is reduced, either by probucol [67] or by mutation in the
ABCA1 transporter in patients with Tangier disease [68], which reduces lipidation of apoA-I and impairs formation of preβ1-HDL. Consequently, the level of HDL and RCT decline dramatically. This indicates that the rate of formation of preβ1-HDL might be critical for the functioning of RCT. Changes in HDL concentration in heterozygotes carrying mutations in ABCA1, which determines the rate of the initial lipidation of apoA-I [45,69], have been strongly associated with the rates of cholesterol efflux and risk of CHD [70].

Mice, transgenic for human CETP and apoA-I, have significantly higher levels of preβ1-HDL, α2-HDL and α3-HDL, greater LCAT activity and stimulated cholesterol efflux [71], probably because of increased availability of lipid-free apoA-I, the substrate for the formation of preβ1-HDL. Similar effects have been observed in mice transgenic for human PLTP and apoA-I [72]. Interplay between concentrations of substrate (apoA-I) and lipidation tool (ABCA1) may be the strongest determinant of the initial rate of RCT.

4.2. Cholesterol esterification

In humans, LCAT deficiency leads to a dramatic fall in HDL levels but not to a significant increase in the CHD risk [26]. In rabbits made transgenic with human LCAT, HDL levels rose, LDL levels fell [73]. HDL catabolism decreased while LDL catabolism was enhanced [74] and the level of protection against diet-induced atherosclerosis was enhanced [75]. However, in mice, transgenic with human LCAT, the HDL concentration also rose and the capacity of plasma from these mice to promote cholesterol efflux and esterification in vitro increased [76], yet the mice became more susceptible to diet-induced atherosclerosis [77]. Whereas rabbits express CETP, but mice do not, the necessary transport of cholesteryl esters and subsequent remodeling of HDL was lacking in mice. When this route of ‘disposal’ of cholesteryl esters is inefficient, excess esterification apparently leads to the formation of dysfunctional HDL and to decreased rather than increased activity of the reverse cholesterol transport pathway [77]. This condition is reversed in double transgenic mice expressing both human LCAT and CETP [78].

4.3. Cholesterol transfer

Enhancing cholesterol transfer from HDL to LDL, however, does not necessarily result in improved RCT activity: mice transgenic with CETP have lower HDL, higher LDL and increased susceptibility for atherosclerosis [79]. Mice transgenic with both LCAT and CETP resulting in enhancement of both cholesterol esterification and cholesterol transfer and high RCT efficiency show increased protection against atherosclerosis [78]. In humans CETP defects may result in either increased or decreased susceptibility to atherosclerosis. Inherited CETP deficiency, which was initially thought to explain partly the lower rate of CHD in Japan, was later found to be associated with increased risk of coronary events.

Fig. 1. Turnover of HDL subspecies during reverse cholesterol transport. RCT starts with ABCA1-dependent efflux of cellular cholesterol into lipid-free apoA-I with the formation of preβ2-HDL (hollow block arrow). Upon accumulation of cholesterol these particles are transformed into preβ1-HDL particles (filled block arrow). Esterification of cholesterol in preβ2-HDL by LCAT leads to the formation of spherical α2-HDL particles (filled block arrow). These particles acquire more cholesterol, with continuing esterification through LCAT, that transforms these particles into larger α3-HDL and α1-HDL (filled block arrow). The next step involves exchange of cholesteryl esters for triglycerides through the action of CETP, transfer of phospholipid through the action of PLTP and hydrolysis of triglyceride and phospholipid by HL. As a result, particles are remodeled into smaller α2-HDL particles and lipid-free apoA-I (thin arrows). Underlined are the names of the particles, italicized are the names of the conversion factors. The two major factors leading to the formation of preβ1-HDL are the availability of apoA-I and efflux of cellular cholesterol (thick arrows); overproduction of either potentially leads to raised preβ1-HDL. Whether inhibition of conversion of preβ1-HDL to preβ2-HDL particles (dashed arrow) also influencing preβ1-HDL levels is unknown, but possible.
Changes in lipoprotein profile also be involved in cholesterol efflux and efflux is unclear, but demonstrates that HDL concentration at least 9 days. The mechanism of the prolonged effect is that diminished cholesterol transfer and remodeling lead to the formation of dysfunctional HDL and decreased efficiency of RCT, whereas if the remodeling step is not impaired the outcome is atheroprotection.

4.4. Remodeling of HDL

Hepatic lipase deficient mice and HL transgenic mice, genetic manipulations associated with correspondingly increased and decreased HDL levels, paradoxically both showed increased atheroprotection [83,84]. In humans, HDL deficiency is associated with hyperalphacholesterololemia and with higher [85] or lower [86] prevalence of CHD compared with subjects with similar HDL levels and normal HL.

4.5. HDL uptake

There is a number of HDL binding proteins implicated in the uptake and degradation of HDL [12], two emerging as likely candidates scavenger receptor type BI (SRBI) in liver [87] and cubilin–megalin pair in kidney [88–91]. SRBI knockout mice show raised HDL concentration and are not susceptible to atherosclerosis [92,93]. Yet modest overexpression of SRBI in mice that is associated with increased biliary cholesterol secretion and very low HDL levels also confess atheroprotection [94–96]. The inference is that increased uptake of HDL decreased its concentration in plasma, but enhanced the flow of cholesterol through RCT. However, high overexpression of SRBI was pro-atherogenic, reflecting complexity of relationship between SRBI and atherogenesis [96]. In addition, SRBI may also be involved in cholesterol efflux, the first step of RCT [97]. Megalin knockout mice showed symptoms of cholesterol deficiency in a number of organs, but no changes in lipoprotein profile or susceptibility to atherosclerosis were reported [98].

An interesting example of stimulating RCT (judged by increased fecal sterol excretion) by infusing apoA-I/ phospholipid complexes was recently reported by Eriksson et al. [99]. Despite only small and transient rises in plasma HDL concentration over 24 h after the infusion, cholesterol excretion appeared stimulated for at least 9 days. The mechanism of the prolonged effect is unclear, but demonstrates that HDL concentration and efficiency of RCT are not necessarily firmly linked.

These few examples demonstrate that the plasma HDL concentration and the activity of the individual steps of RCT are influenced by multiple factors that affect susceptibility to atherosclerosis by mechanisms which can be unrelated to HDL level. Thus, HDL concentration does not necessarily predict the outcome of RCT activity nor the level of protection against CHD.

5. Preβ1-HDL and atherosclerosis

Identification of preβ1-HDL as the most active particle in removing cholesterol from cells [58] gave foundation to the ‘shuttle and sink’ model [100]. According to this model small preβ1-HDL particles (‘shuttle’) take cholesterol from cells and deliver it to larger HDL particles (‘sink’), where cholesterol accumulates before being transferred along the reverse cholesterol transport pathway. According to this model, transfer of cholesterol from the cells is normally the rate-limiting step in RCT and it is the concentration of preβ1-HDL (‘shuttle’) that would primarily determine or reflect the overall rate of RCT. Several in vitro studies seem to confirm this suggestion: depletion of preβ1-HDL from plasma [59,101] significantly reduced its capacity to promote cholesterol efflux. It might be expected that in vivo, in conditions associated with enhanced development of atherosclerosis and reduced activity of RCT, the concentration of preβ1-HDL would also be decreased. Available data suggest the opposite. The concentration of preβ1-HDL in several clinical settings are summarized in Table 1. Patients with coronary heart disease appear to have elevated levels of preβ1-HDL [55,102], as do patients with hypercholesterolemia [103–105], patients with high levels of LDL [106] and with hypertriglycerideremia [55,103,105]. Although these conditions represent a heterogeneous group of diseases instigated by different metabolic mechanisms the effect of these conditions on preβ1-HDL concentration is surprisingly consistent. However, there is no currently agreed standardization of preβ1-HDL measurements, limiting definitive conclusions. In studies of obese subjects in our laboratory, such subjects also have elevated preβ1-HDL. Moreover, the initial capacity of preβ1-HDL particles to acquire cellular cholesterol was greater in obese than in lean subjects [64,107] and we did not find a correlation between concentration of preβ1-HDL and the ability of plasma to promote cholesterol efflux in vitro [64]. The higher levels of preβ1-HDL were reversible: the concentration of preβ1-HDL was reduced with weight reduction [108]. Previously we had reported that the turnover of plasma esterified cholesterol measured in vivo was proportional to body weight [57]. We have also observed that treating patients with non-insulin dependent diabetes with insulin increased their
Table 1  
Preβ1-HDL levels and some other lipid parameters at different cardiovascular conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preβ1-HDL concentration</th>
<th>HDL concentration</th>
<th>Cholesterol in plasma</th>
<th>CETP activity</th>
<th>Cholesterol synthesis</th>
<th>Reference (for preβ1-HDL)</th>
</tr>
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<tbody>
<tr>
<td>CHD</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>N.D.</td>
<td>N.D.</td>
<td>[55,102]</td>
</tr>
<tr>
<td>Obesity</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>[64,107]</td>
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<tr>
<td>Weight reduction</td>
<td>↑</td>
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<td>↑</td>
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<td>↓</td>
<td>[108]</td>
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<tr>
<td>Hypertriglyceridemia</td>
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<td>N.D.</td>
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<td>Hypercholesterolemia</td>
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<td>[103–105]</td>
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<tr>
<td>Treatment with simvastatin</td>
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<td>Unpublished observationa</td>
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<tr>
<td>Diabetes treatment with insulin</td>
<td>↑</td>
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<td>N.D</td>
<td>N.D</td>
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</table>

a In this study, ten hypercholesterolemic patients were treated for 4 weeks with 20 mg simvastatin daily and relative changes in preβ1-HDL concentration were evaluated by non-denaturing two-dimensional electrophoresis.

preβ1-HDL concentration [109] and that treating hypercholesterolemic patients with simvastatin resulted in lower preβ1-HDL (unpublished observation).

Overall, the clinical data reveal higher preβ1-HDL concentrations in conditions that are known to be related to increased risk of CHD. This does not appear to be consistent with the concept that higher concentrations of preβ1-HDL are protective against atherosclerosis and are associated with lower cardiovascular risk. There could be a number of explanations for this. First, accumulation of preβ1-HDL may be a result of inefficient conversion of preβ1-HDL into preβ2-HDL or the esterification of cholesterol (Fig. 1). Thus, higher levels of preβ1-HDL have been found in congenital LCAT deficiency [103]. On the other hand, in our studies the activity of preβ2-HDL (i.e. rate of transfer of cholesterol to and from the subfraction) was positively correlated with preβ1-HDL concentration [64]. If accumulation of preβ1-HDL is the result of inefficient stages of RCT beyond preβ2-HDL formation, then higher concentrations of potentially dysfunctional preβ1-HDL would have a negative impact on the antiatherogenic capacity of HDL.

Second, increased levels of preβ1-HDL may reflect increasing formation of preβ1-HDL either due to enhanced cholesterol efflux or increased formation of its substrate, lipid-free apoA-I, derived from remodeling of large α1-HDL particles (Fig. 1). Indirect evidence in favor of this possibility is that the increase of preβ1-HDL concentration in obese subjects occurred at the expense of α1-HDL [64] and activation of HL with bezafibrate raised preβ1-HDL also at the expense of large HDL2b particles [110]. Loading of cells with cholesterol stimulates cholesterol efflux [43,45,111] and formation of preβ2-HDL, possibly contributing to the higher levels of preβ1-HDL in hypercholesterolemia [103–106] (Fig. 1). If accumulation of preβ1-HDL results from increased cholesterol efflux, then higher concentration of preβ1-HDL would impact favorably on anti-atherogenic potential of HDL. However, in Tangier disease patients, in whom cholesterol efflux is severely impaired, preβ1-HDL is the sole HDL subspecies [56,112]. Nevertheless, the absolute concentration of preβ1-HDL in Tangier patients is still much lower than in normal subjects and it is not clear if those particles are of the same composition and origin in Tangier patients and normal subjects. They may represent HDL synthesized de novo in the liver and intestine and containing proapoA-I; catabolism of proapoA-I containing particles is significantly delayed compared with mature apoA-I [112,113].

Comparing preβ1-HDL levels with other lipid parameters in patients with different disorders shows that the preβ1-HDL concentration usually correlates positively with plasma total cholesterol concentration, cholesterol synthesis and CETP activity and negatively with HDL concentration (Table 1). CETP is essential for the remodeling of HDL, a source of lipid-free apoA-I, which is substrate for preβ1-HDL formation. CETP is known to be raised in obese subjects [114,115], in hypertriglyceridemic patients [115] and reduced during weight reduction and statin therapy [116]. Preβ1-HDL formation may also be driven by excess synthesis of cholesterol necessitating efflux from sites of extrahepatic synthesis. Obesity is a major cause of cholesterol overproduction [117], which is reversed with weight loss or treatment with simvastatin. In the various disorders shown in Table 1 in which preβ1-HDL have been measured, the direction of changes for preβ1-HDL, CETP and cholesterol synthesis is similar. This represents presumptive evidence that at least CETP and cholesterol production are two determinants of preβ1-HDL levels. Overall the preβ1-HDL concentration may reflect the activities of three steps of RCT:HDL remodeling with the release of lipid-free apoA-I, apoA-I lipidation by cells and conversion of preβ1-HDL into preβ2-HDL and α-HDL particles (Fig. 1).

In conclusion, it seems likely that the antiatherogenic effect attributed to RCT might be better predicted by assessing the flow of cholesterol through that pathway,
than by the concentration of HDL itself. The particular relevance of the plasma concentration of preβ2-HDL in assessing predisposition to atherovascular disease, might also be better described in terms of activity in the RCT system.

References


