commentary

Investigations of apoC-III metabolism using stable isotopes: what information can you acquire and how can you interpret your results?[1]

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Apolipoprotein C-III (apoC-III) is one of the "exchangeable" apolipoproteins; it is found in all of the major lipoprotein classes in varying amounts. Although the exchangeability of apoC-III has been well established and accepted, it was clear early on that this apolipoprotein, as well as several others, were not present on every lipoprotein particle (1). Moreover, work by Sacks and colleagues (2–4) has demonstrated that the metabolism of apoB-containing lipoprotein subfractions is affected by their apoC-III content. Despite the complexities inherent in these findings, studies of the metabolism of apoC-III are needed, particularly because of recent reports indicating potential apolipoprotein-independent actions of this protein that are pro-atherogenic (5). The relevance of apoC-III for understanding the pathophysiology of dyslipidemia, atherosclerosis, and possibly insulin resistance is clear (6).

In a study of apoC-III metabolism published recently in the *Journal of Lipid Research*, Ooi et al. (7) reported that increased levels of plasma and VLDL apoC-III resulted from decreased fractional clearance rates (FCRs) of apoC-III from plasma, without alterations in plasma apoC-III production rate (PR). In their commentary in this issue of the *JLR*, Sacks, Zheng, and Cohn raise issues related to the use, by Ooi et al., of plasma FCRs and PRs for the analysis of apoC-III metabolism rather than of apoC-III metabolic parameters in individual lipoproteins. Indeed, in earlier studies, Barrett, Watts, and colleagues (8, 9) presented results of apoC-III turnover in VLDLs and HDLs, and this led to an editorial by us (10) criticizing that approach because the enrichment curves of apoC-III in VLDL and HDL were indistinguishable from each other. In fact, that group had concluded in earlier studies that apoC-III turnover was the same in VLDL and HDL (9, 11). We realize that Batal et al. (12) (Cohn and colleagues) reported differences in the enrichment of VLDL and HDL apoC-III, and based on those data, appropriately presented separate results for the turnover of apoC-III in each lipoprotein class. However, because Barrett, Watts, and colleagues find the same enrichments in the two lipoproteins, they must, we believe, restrict themselves to presenting plasma turnover parameters (10).

An important issue raised by Sacks et al. in their commentary stems from their demonstration in multiple reports in recent years that apoB on apoC-III-containing particles has distinct kinetics from apoB on particles without apoC-III. If apoC-III were moving freely among all apoB-containing particles, Sacks et al. would not have found distinct kinetics between particles with and without apoC-III. This leads them to pose the question: how can one rationalize *1*) the findings of different proportions of apoC-III on subpopulations of apoB and apoA-I containing lipoproproteins, and *2*) the effects of the presence or absence of apoC-III on the metabolism of apoB (and probably apoA-I) containing lipoproteins, with the presence of a single, exchangeable pool of apoC-III? However, though it may seem counterintuitive, the existence of many kinetically distinct apoB pools, some with apoC-III and others without apoC-III, is not in conflict with a single PR and a single FCR for this protein. Thus, the presence of particles with and without apoC-III in both VLDL and HDL does not conflict with its exchangeability; it simply means that apoC-III exchange occurs within pools of lipoproteins containing apoC-III, perhaps by one-for-one exchange of apoC-III between pairs of particles. There would be no movement of apoC-III to a particle that does not contain apoC-III, thus providing consistency with the findings of kinetically distinct apoB pools by Sacks et al. Indeed, the finding by Sacks and colleagues that VLDL with apoC-III are metabolically converted to VLDL without apoC-III seems, to us, to support our concept of restricted exchange. The fact that the presence or absence of apoC-III affects the metabolism of apoB-containing (or apoA-I-containing) lipoproteins does not conflict with a model in which apoC-III has a single kinetic pool with one FCR,

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although this pathway remains to be characterized. Indeed, what Sacks et al. term the "Actual apoC-III distribution" in their figure is quite consistent with a single pool for apoC-III, provided we understand that the transfer rate constants for apoC-III among their CIII+ pools are very rapid with no apoC-III transfer to or among CIII- pools, whereas apoB transfers among the pools at measurable, nonzero rates. What they term "Inferred apoC-III distribution" in their figure is not at all required for a single apoC-III pool in plasma.

Sacks et al. suggest that for apoC-III exchange to be "restricted to apoC-III-containing lipoprotein subtypes … would require an unknown property of apoC-III-containing lipoproteins that permitted apoC-III to transfer freely among them and not to nonapoC-III containing lipoproteins." We agree with this observation, which we believe is both fully compatible with the finding of Sacks and colleagues of metabolically distinct apoB pools, some with and others without apoC-III, and the finding by Barrett and colleagues of indistinguishable apoC-III enrichment curves in VLDL and HDL. Finally, as we noted in our earlier commentary on this matter, the possibility that there may be multiple pathways whose FCRs, in various combinations, generate the same kinetic parameters is moot; until methods are available that can consistently identify individual FCRs in lipoprotein subpopulations, we must be frugal and present the simplest results that fit the data.

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