Elevated levels of circulating high-density lipoprotein cholesterol (HDL-C) have long been thought to be associated with reduced coronary artery disease (CAD) risk. This concept has led to the HDL hypothesis: increasing HDL-C would be a key addendum in the prevention of CAD, in addition to reducing circulating low-density lipoprotein cholesterol levels. In theory, increasing HDL-C should improve the anti-atherosclerotic process of reverse cholesterol transport (RCT). However, repeated attempts to increase HDL-C pharmacologically have shown no changes to the risk of CAD. Although discouraging, the concept of HDL functionality, or its ability to efflux cholesterol from extrapaphelic tissues during the RCT process, was shown to be a negative correlate of CAD. Thus, studies of interventions that attempt to target HDL functionality are highly desirable.

In this issue of Circulation, O’Reilly et al5 examined how HDL function changes in response to high-fat diets enriched with saturated fatty acids (SFAs) or monounsaturated fatty acids (MUFAs). Using a mouse model that received 45% of calories from either SFA or MUFA over a 24-week period, the authors found that, in comparison with mice fed the MUFA-enriched diet, mice fed the SFA-enriched diet exhibited impaired macrophage-to-feces RCT. Interestingly, although there was an increase in plasma concentrations of small HDL particles in SFA-fed mice, the small HDL particles from these mice had an impaired ability to efflux cholesterol from macrophages via the transport ATP-binding cassette A1. In support of their animal studies showing that a high-fat diet enriched with SFAs negatively influences HDL functionality, O’Reilly et al5 also showed that the HDL from human subjects receiving >10% of calories from SFAs had an impaired ability to efflux cholesterol from macrophages via ATP-binding cassette A1. They also showed that the HDL from human subjects with insulin resistance had an impaired ATP-binding cassette A1–mediated cholesterol efflux ability.

Reducing SFAs in the diet by replacing them with MUFAs can improve disease outcomes in human subjects, including CAD risk. The effect of diet on the risk of CAD is further evidenced by studies examining the Mediterranean diet, which is low in SFAs and high in MUFAs. The majority of studies to date suggest that the Mediterranean diet improves disease outcomes, although more long-term studies are necessary. Several animal studies also support the human studies. For instance, Morrison et al8 found that replacing a cocoa butter diet (enriched in SFAs) with a pumpkin seed oil diet (enriched in PUFAs) in the apolipoprotein E3-Leiden mouse model led to a reduction of atherosclerotic lesion area, as well as an attenuation of nonalcoholic fatty liver disease. Overall, studies to date are in favor of reducing dietary SFAs, with the goal of ameliorating the burden of diseases associated with metabolic syndrome. However, some controversy exists regarding how PUFA-enriched diets may influence HDL functionality; a crossover study with human male subjects fed a SFA-enriched diet over 4 weeks, followed by a PUFA-enriched diet over 4 weeks, revealed that the cholesterol efflux capacity of HDL was unaffected.9 However, a longer length of time on each diet might influence HDL functionality.

Using a proteomics approach, O’Reilly et al5 showed that the protein content of small HDL particles differed between mice fed the high-fat diet enriched with SFAs versus the mice fed the high-fat diet enriched with MUFAs. Of note, the authors identified an increase in the amount of the acute-phase inflammatory protein serum amyloid A (SAA) 1 and SAA2 that were associated with the small HDL particles from mice fed the high-fat diet enriched with SFAs versus the MUFA-fed mice. Recently, Vaisar et al10 showed that HDL isolated from human subjects treated with low doses of an Escherichia coli O:113 endotoxin had an increase in SAA1 and SAA2 content, which was tied with a decrease in the ability of the HDL to efflux cholesterol from macrophages, despite no changes to plasma HDL-C levels. They further showed that the HDL from acutely inflamed mice had a 40% reduction in cholesterol efflux capacity versus acutely inflamed mice that were deficient in both SAA1 and SAA2.

In addition, O’Reilly et al5 showed an increase in the amount of paraoxonase 1 (PON1) that was associated with the small HDL particles from MUFA-fed mice versus SFA-fed mice. PON1, together with glutathione peroxidase, can prevent the oxidation of HDL phospholipids.11 HDL subfractions from human subjects with acute coronary syndrome have a high inflammatory index and high lipid hydroperoxide levels, which are accompanied with significantly lower levels of PON1 and cholesterol efflux ability. In line with the observations of O’Reilly et al, diets supplemented with olive oil have been shown in a mouse model to increase PON1 activity and the cholesterol efflux ability of HDL. Moreover, in a small study with 8 human male subjects, a Mediterranean diet was also shown to increase plasma carotenoids and PON1 activity, as well as a decrease of C-reactive protein. Overall, these studies suggest that MUFA-enriched diets may improve HDL.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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functionality and CAD risk, in part, by increasing the PON1 available to associate with HDL.

SAA1, SAA2, and PON1 may in fact be suitable biomarkers of HDL functionality and CAD risk, but the HDL proteome is complex because of the exchangeable nature of its associated proteins. The day-to-day variation of diet could influence the snapshot of any lipoprotein proteome, in part, by influencing the lipid composition of a lipoprotein. The effects of the lipoprotein lipidome on HDL functionality and CAD risk are not well understood, because of the number of lipid classes and the overwhelming number of individual species of lipid within each class. Changes to a lipoprotein lipidome can minutely influence the charge and structure of a lipoprotein surface, and subsequently influence the lipoprotein proteome. It is likely that the SFA and MUFA diets affected the HDL lipidome in the study by O’Reilly et al., but more work is necessary to address how changes to the lipidome in vivo may influence HDL functionality and RCT.

Although the SFA-fed mice in the study by O’Reilly et al. had a significant increase of plasma HDL-C, which translated into an increased movement of radioabeled cholesterol from macrophages to the plasma in an in vivo RCT assay, it did not translate into improved fecal cholesterol excretion versus the MUFA-fed mice. This appeared to be attributable to cholesterol accumulation in the livers of the SFA-fed mice. This impairment of RCT was likely due to the observed reduction in the expression of the hepatic cholesterol transporters ATP-binding cassettes G5 and B11. Other studies have shown that HDL functionality may be improved, but RCT as a whole remained unaffected. For example, Brown et al. examined RCT in a mouse model that was deficient in both endothelial lipase and hepatic lipase, 2 lipases involved in the remodeling of circulating HDL. The authors showed that the levels of HDL-C were increased and the HDL functionality was improved in vivo, but the selective uptake of the HDL lipid by the liver was impaired, which translated into no change in RCT versus wild-type mice. Recently, Zanoni et al. identified a rare variant of the bidirectional cholesterol transporter scavenger receptor Bi in human subjects with high HDL-C (>95th percentile) that results in a reduction of selective uptake and is also associated with CAD risk; although an assessment of RCT in vivo was not reported, it would be expected to be impaired. The process of RCT requires not just HDL with a good cholesterol efflux capacity, but the HDL must be capable of delivering cholesterol to the liver effectively, and the cholesterol needs to be transported out of the liver for excretion. Thus, a dietary or pharmacological intervention meant to improve HDL functionality may not translate into an improvement of the complete RCT process, what we wish to coin as RCT functionality. Future work is necessary to assess RCT functionality in human subjects, and how RCT functionality may be influenced through dietary interventions.

An understanding of the biochemical mechanisms through which SFAs affect the cholesterol efflux capacity of HDL and the hepatic secretion of cholesterol for fecal excretion is needed. In addition, the effects of different dietary lipids, including MUFAs and PUFAs, on the biochemistry of RCT functionality remain to be fully elucidated. In answering the title question, can we make HDL great again, it appears that the answer is yes. The dietary replacement of SFA with MUFA, as demonstrated by O’Reilly et al., improves the antioxidant properties of small HDL particles without detrimentally affecting ATP-binding cassette A1-mediated cholesterol efflux to small HDL particles, and ultimately the diet improves RCT. What remains to be solved is how to improve the movement of hepatic cholesterol out of the body.

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References


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