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EDITORIAL COMMENT

Inflammatory Effects of Triglycerides

Relevant or Redundant?*

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Discussing the true impact of hypertriglyceridemia, a central component of the metabolic syndrome, on cardiovascular risk is more relevant than ever. On the one hand, observational and Mendelian randomization studies have consistently underscored the relevance of hypertriglyceridemia as a most likely causal factor for atherosclerotic cardiovascular disease (ASCVD). On the other hand, recent data from the PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) study emphasized that solely enhancing the metabolism of large triglyceride particles into atherogenic but smaller triglyceride-rich remnants and low-density lipoprotein-cholesterol (LDL-C) particles by fibrate administration does not translate into a lower major adverse cardiovascular event rate.[1] This raises the question: what drives the atherogenicity of triglyceride-rich particles: the "remnant cholesterol" payload in these apolipoprotein (apo)B-containing particles, or do triglycerides themselves also mediate atherogenic effects? Epidemiologic data revealed a correlation between high triglyceride levels and C-reactive protein, also after adjustment for confounding factors, whereas LDL-C levels did not correlate with C-reactive protein, implying a distinct impact of high triglycerides or derived free fatty acids on the inflammatory axis.[2] In support, elevated triglyceride remnant particles in patients with familial dysbetalipoproteinemia resulted in proinflammatory monocytes in plasma as well as heightened arterial wall inflammation,[3] lending further support to an association between triglyceride-rich particles and atherogenic inflammation. Last but not least, postprandial hypertriglyceridemia (after a high-fat meal) was also shown to elicit increased lipid droplet formation in circulating monocytes, which coincided with proinflammatory skewing of monocytes.[4] Collectively, these data substantiate a direct adverse effect of high triglyceride levels potentially contributing to the propagation of a systemic proinflammatory state, an effect that appears to be independent from LDL-C and/or the apoB component of the triglyceride-rich particles.

In this issue of *JACC: Basic to Translational Science*, Lian et al[5] evaluated the impact of a high-saturated fat diet (HSFD) vs a low-saturated fat diet (LSFD), followed by a fat-loading test comprising either high-saturated fat or low-saturated fat, on triglycerides and inflammatory changes. Using a randomized crossover design, they compared the effects in 19 subjects with features of the metabolic syndrome and elevated triglyceride levels. Whereas fasting triglyceride levels did not differ between groups 4 days after diet initiation, the high-saturated fat load at day 5 produced significantly higher plasma triglyceride levels 4-6 h after ingestion compared with the low-saturated fat load. Plasma levels of saturated fatty acids (SFAs) were comparable after HSFD and LSFD loading. HSFD resulted in increased lipid accumulation in plasma monocytes postprandially, which coincided with higher CD11c expression by monocytes. Functional significance of this finding was substantiated ex vivo, showing increased firm adhesion of monocytes from HSFD subjects on vascular cell adhesion molecule-1 compared with monocytes from LSFD subjects. Monocytes obtained from HSFD subjects also displayed increased uptake of oxidized LDL-C particles ex vivo. Based on the marked differences between HSFD and LSFD loading, the authors attributed these

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proinflammatory effects predominantly to an adverse effect of the SFAs as opposed to the polyunsaturated fatty acids (PUFAs) administered to LSFD subjects.

In this elegant study, Lian at al[5] provide consistent evidence of a proinflammatory effect after an oral load containing saturated fats in patients with the metabolic syndrome. Strong aspects of the study design comprise direct comparison of fat composition (SFA vs PUFAs), fat dose (baseline diets combined with a separate loading dose at day 5), and the comprehensive evaluation of monocyte function as a crucial player in atherogenic inflammation. Several aspects, however, merit further discussion.

First, the major differences observed between HSFD and LSFD relate to the lipid loading test on day 5. Here, it should be taken into account that the total caloric intake as well as the total fat and cholesterol intake were significantly higher in the HSFD compared with the LSFD group, reflecting mainly a much higher SFA intake in the HSFD subjects. This automatically translates into a higher area under the curve for postprandial plasma triglyceride levels. Therefore, the only valid conclusion that can be drawn is a proinflammatory effect of a higher total fat load on circulating monocytes, whereas no clear distinction can be made with respect to the difference between SFAs and PUFAs. The latter would require a study with equal caloric and fat quantity, differing in fat composition only (SFAs vs PUFAs).

Second, although this study convincingly shows a relationship between high triglyceride levels, monocyte lipid accumulation, and proinflammatory skewing of circulating monocytes, the relevance of these phenomena for atherosclerotic cardiovascular disease remains to be established. The majority of triglycerides resides in the large very-low-density lipoprotein (VLDL) particles, which usually determine >80% of the total plasma triglyceride concentration. Hence, if the plasma triglyceride concentration is lowered, invariably due to a reduction of large VLDL particles, one would predict a concomitant reduction of the triglyceride-associated inflammatory phenomena as suggested by Lian et al.[5] In the PROMINENT study, triglyceride levels were reduced by 55 mg/dL without a change in non- high-density lipoprotein-cholesterol levels, reflecting enhanced VLDL catabolism in the absence of an increased removal of apoB-containing lipoproteins.[2] Most importantly, the incidence of cardiovascular events was not affected by pemafibrate treatment.[2] The explanation for this apparent paradox can be 2-fold. First, the absolute reduction in triglyceride levels by pemafibrate on top of (predominantly) high-intensity statin therapy was too modest (-22.6%) to translate into a clinically meaningful cardiovascular benefit in these type 2 diabetic patients with mild-to-moderate hypertriglyceridemia. Second, it can be argued that triglycerides themselves are not of major importance because they only reflect the payload of cholesterol in the triglyceride-rich particles. Despite the significant triglyceride reduction in the PROMINENT study, the total plasma cholesterol concentration was not reduced as the absolute reduction in VLDL-cholesterol of 9 mg/dL was compensated for by an absolute increase in LDL-C of 9 mg/dL.[2] A lesser importance of the triglyceride content of lipoproteins in causing ASCVD is underscored by genetic analyses performed by Ference et al,[6] who reported that the association between cholesterol and ASCVD could be completely attributed to changes in apoB levels irrespective of whether the cholesterol load was carried by triglyceride-poor LDL-C particles or triglyceride-rich VLDL-cholesterol particles. Collectively, these findings do not support an overriding role of triglyceride-induced inflammation contributing to ASCVD.

The final proof of the pudding is in the eating. By combining more potent triglyceride reductions with increased clearance of the (smaller) apoB-containing particles, both angiopoietin-like 3 and apoC-III inhibition hold the promise to resolve apoB-mediated residual cardiovascular risk of VLDL, triglyceride-remnants, and LDL-particles. Detailed studies on systemic inflammation and particularly monocyte activation after these potent triglyceride and apoB-lowering interventions will be instrumental to dissect whether and to what extent triglyceride-associated inflammatory changes contribute to ASCVD risk. Only then will we be able to pass a judgement on the relevance of pleiotropic “inflammatory effects” of triglycerides as truly relevant or largely redundant.

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