Triglyceride-Rich Lipoproteins and Vascular Function

William G. Haynes

The epidemic of obesity in the developed and developing world has resulted in a considerable increase in the number of patients with high plasma triglyceride concentrations. There has been considerable debate about the role of triglyceride-rich lipoproteins (TRLs) in atherosclerosis. These lipoproteins include chylomicrons, VLDL, IDL, and various remnant particles. Although elevated triglyceride levels are common in patients with atherosclerotic disease, establishing a clear link has been made difficult by a number of factors.

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First, elevated triglycerides are usually found in lipoprotein particles that also contain cholesterol. A role for cholesterol in these particles is supported by the fact that non-HDL cholesterol appears to be a more powerful marker of cardiovascular risk than even LDL cholesterol.1 Second, elevated TRLs are strongly associated with low HDL cholesterol concentrations. This association is so powerful that it is very difficult to dissect out the relative contributions of HDL and TRLs, although low HDL is commonly believed to have a greater impact on the atherosclerotic process. Third, triglyceride concentrations have high biological variability, which obscures the statistical strength of any association with cardiovascular disease, particularly when compared with the less variable HDL. Fourth, patients with high TRL levels often possess other risk factors that may explain their predisposition to atherosclerosis, especially those that comprise the metabolic syndrome.2 Finally, the lack of an established pathophysiological mechanism linking TRLs to atherosclerosis has hindered consideration of triglycerides as a cause of atherosclerosis, as opposed to being a marker for other risk factors (ie, insulin resistance, visceral obesity, or hypertension). Identification of a plausible mechanism would help resolve this debate.

Meta-analyses of observational studies have suggested that a 1-mmol/L (89 mg/dL) elevation in triglycerides is associated with a 14% to 37% higher incidence of cardiovascular disease independent of other risk factors, with the highest risk in women.3 However, given the variability in plasma triglyceride concentrations, observational studies may considerably underestimate the cardiovascular consequences of elevated TRLs. Unfortunately, large-scale randomized outcome trials examining pharmacological interventions that alter triglycerides have not provided a clear resolution of this issue. The benefits of fibrate therapy in the Helsinki Heart study and Veterans Affairs High-Density Lipoprotein Intervention Trial have been attributed to decreases in non-HDL cholesterol or increases in HDL.4,5 Similar findings have been observed for therapy with niacin.6 One difficulty in interpreting outcome trials has been that the relatively limited number of cardiovascular events, even in large studies, makes detailed subgroup analyses underpowered and prone to error. Thus, it has been difficult to identify substantial numbers of patients who manifest changes in only one lipid parameter with an intervention and then track their cardiovascular events.

An alternative experimental approach is to focus on a plausible quantitative intermediate phenotype for atherosclerosis that exhibits changes in a relatively short period of time. Relatively small studies with sophisticated analysis of intermediate phenotypes can then test the effects of pharmacological interventions for dyslipidemia. When patients are carefully selected (ie, isolated hypertriglyceridemia), these studies can provide mechanistic and clinical insights that large-scale outcome trials cannot.

One potentially powerful intermediate phenotype is vascular function. During experimental induction of atherosclerosis in monkeys, changes in endothelial function precede structural lesions.7 Conversely, dietary regression of experimental atherosclerosis in monkeys is preceded by improvements in endothelial function.8 In humans, endothelium-dependent dilatation is impaired in hypercholesterolemia,9–11 hypertension,12 tobacco use,13 and in patients with established coronary atherosclerosis.14 Patients with diabetes exhibit impaired vascular smooth muscle function, possibly related to reduced NO activity.15,16 Normalization of risk factors produces rapid improvements in vascular function.17,18 Most importantly, impaired vascular function appears to predict complications of atherosclerosis, independently of atherosclerosis burden or other risk factors. This is true for endothelium-dependent,19 as well as endothelium-independent, responses.20,21

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Capell and colleagues22 describe the effect of fenofibrate-induced reductions in triglycerides on vascular function. Patients were selected to have elevated triglycerides, but relatively normal cholesterol (including LDL and HDL). As a result, two weeks of therapy with fenofibrate had most effect on triglyceride concentrations (reduced by 45%) with no change in HDL or LDL cholesterol. Total cholesterol and apolipoprotein B concentrations decreased by ≈15%, consistent with reduction in TRLs. Fenofibrate produced a global improvement in vascular function, with significantly increased forearm vasodilatation to brachial artery infusion of acetylcholine, an endothelium-dependent vasodilator. Interestingly, endothelium-independent vascular smooth muscle dilatation to nitroprusside and verapamil also improved after

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fenoﬁbrate treatment. Fenoﬁbrate modestly reduced free fatty acid concentrations, particularly after activation of lipoprotein lipase by heparin infusion. However, insulin sensitivity was not changed by fenoﬁbrate, and its beneﬁts did not differ between hypertriglyceridemic subjects with and without evidence of the metabolic syndrome.

There have been only a few other reports of the vascular effects of stimulation of nuclear peroxisome proliferator activated (PPAR-α) receptors by fibrate. Two of these studies were performed in patients with type 2 diabetes and showed improvements in endothelial function.23,24 One study was performed in patients with combined hyperlipidemia; like the current study, this showed improvement in endothelium-dependent and -independent dilatation.25 Interestingly, HMG-CoA reductase therapy in the same population only improved endothelium-dependent dilatation.25 However, in all three previous studies, there were substantial increases in HDL cholesterol,23–25 making it diﬃcult to prove that the vascular effects were due to reduction in TRLs.

The ﬁndings in the present and previous studies with PPAR-α agonists are consistent with the concept that triglycerides directly impair dilatation of vascular smooth muscle. Capell and colleagues22 suggest one potential triglyceride-mediated mechanism may have been reduction in formation of free fatty acids from TRLs by endothelial lipoprotein lipase. This explanation is strengthened by the fact that severely hypertriglyceridemic patients with lipoprotein lipase deﬁciency do not exhibit endothelial dysfunction.26 In addition, genetic variation in lipoprotein lipase is associated with coronary artery disease.27 However, there are several alternative explanations. Fenoﬁbrate may have had triglyceride-independent effects to improve vascular function. For example, the decrease in apolipoprotein B concentrations suggests that there was a reduction in potentially atherogenic choles- terol-containing particles. Also, changes in the number, density, or size of LDL particles could alter atherogenicity of LDL without changing LDL cholesterol concentrations. Fibrates are known to reduce LDL density and increase LDL particle size.28–30 In addition, fibrate have been shown to reduce inﬂammation, as evidenced by decreases in highly sensitive C-reactive protein.31,32 and inﬂammation may con- tribute to endothelial dysfunction. Finally, as the authors point out, it is possible that stimulation of PPAR-α receptors by fenoﬁbrate directly improves vascular smooth muscle function. It would be valuable to include normotriglyceride- demic subjects in future studies to explore the role of PPAR-α agonism.

Nonetheless, evidence from studies that use non-PPAR-α triglyceride-lowering drugs is consistent with the concept that reduction in TRLs, and thus LPL-mediated formation of free fatty acids, improves vascular function. For example, niacin has been shown to improve endothelium-dependent dilatation in patients with low-to-normal LDL.33 Although niacin increases HDL, it also substantially suppresses lipolysis and free fatty acid concentrations.34,35 More compelling data come from studies of omega-3 ﬁsh oil supplementation, in which there are improvements in vascular function in both hypercholesterolemic and hypertriglyceridemic subjects, without changes in HDL or LDL cholesterol.36–39 Fish oils have also been demonstrated to reduce circulating free fatty acids.40,41 It is certainly plausible that increased free fatty acids may cause vascular smooth muscle dysfunction, given that they increase endothelial layer permeability to proteins and oxidized lipoproteins and may also potentiate oxidant stress.

In conclusion, there are increasing data supporting a role for elevated TRLs in the pathophysiology of vascular disease. Some of the previous epidemiological studies may have underestimated the role of TRLs because they did not take into account the effects of lipoprotein lipase activity and free fatty acid formation. As demonstrated by Capell et al,22 treatment with PPAR-α agonists, such as fenoﬁbrate, improves vascular function in patients with high TRL levels, although the exact mechanism by which this occurs is still unproven. However, the weight of experimental evidence appears to support a role for lipoprotein lipase-mediated formation of free fatty acids in the vascular dysfunction associated with hypertriglyceridemia.

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