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Effect of ezetimibe on cholesterol absorption and lipoprotein composition in diabetes and metabolic syndrome

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Abstract

Ezetimibe exerts multiple favorable effects on the lipoprotein profile and reduces some inflammatory markers. Decreasing cholesterol synthesis with statin treatment can cause a compensatory increase in cholesterol absorption that reduces the efficacy of statin therapy, whereas addition of a cholesterol absorption inhibitor can improve outcomes. Recent evidence suggests a beneficial effect on atherosclerosis. In patients with diabetes, the effect of insulin resistance on low-density lipoprotein metabolism combined with the effect of hyperglycemia on cholesterol absorption may further diminish the favorable effects of statins. Further analysis is needed also to determine whether the stronger effects of ezetimibe seen in patients with diabetes are a consequence of an interaction of the drug with specific mechanisms.

Keywords: Ezetimibe; Insulin resistance; Lipoprotein metabolism; Diabetes; Metabolic syndrome

Recent studies have confirmed an effect of ezetimibe on atherosclerosis [1,2]. Whether this result is mediated only by its effect of cholesterol absorption is an area of active investigation. Inhibition of cholesterol synthesis by statins has been associated with a compensatory increase in intestinal cholesterol absorption. A crossover study, conducted on hyperlipidemic men receiving atorvastatin 40 mg/day vs placebo, shows that atorvastatin significantly increased intestinal mRNA levels of Niemann-Pick C1-like 1 protein (NPC1L1), as well as 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, low-density lipoprotein receptor (LDLR), proprotein convertase subtilisin/kexin type 9 (PCSK9), sterol regulatory element-binding protein-2 (SREBP-2), and hepatocyte nuclear factor 4alpha (HNF-4α) [3]. There was a positive correlation between the lipogenesis markers SREBP-2 and HNF-4α, and the expression of NPC1L1 at the intestinal level in hyperlipidemic men. Thus, when statin administration decreases cholesterol synthesis, the body adapts by increasing cholesterol absorption.

Abnormalities in cholesterol metabolism in type 2 diabetes include enhanced cholesterol synthesis and reduced cholesterol absorption. Also insulin resistance and obesity have been found to be associated with elevated cholesterol synthesis and low cholesterol absorption in cross-sectional studies [4–8]. Despite these observations, which are based mostly on indirect markers of cholesterol metabolism, diabetic dyslipidemia is typically characterized by increased very low density lipoprotein (VLDL) and reduced high-density lipoprotein (HDL), but surprisingly no change in low-density lipoprotein (LDL) cholesterol levels [9]. To explain this conundrum, it has been proposed that the increased hepatic VLDL lipids and apolipoprotein B (apoB) secretion characteristic of type 2 diabetes and metabolic syndrome are balanced by increased LDL fractional catabolism, at least in early type 2 diabetes, when subjects are hyperinsulinemic [10]. This effect is mediated in part by the insulin receptor, which influences LDL fractional catabolism by regulating LDLR protein levels. Insulin receptor knockdown suppresses hepatic LDLR expression via a pathway that involves mammalian target of rapamycin complex 1, hepatocyte nuclear factor 1-alpha and PCSK9. Although direct proof in humans is still lacking, it is intriguing to speculate that in the early phases

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of diabetes, which are characterized by mild insulin resistance, hyperinsulinemia is able to maintain normal LDLR expression and LDL catabolism, keeping total cholesterol in the physiological range [10]. This may explain the normal total cholesterol levels observed in early diabetes. On the contrary, in advanced disease, when chronic insulin resistance leads to beta cell failure and relative hypoinsulinemia, the insulin receptor/LDL receptor positive loop is lost, resulting in reduced LDLR expression and a lower LDL fractional catabolic rate (FCR) that may explain the hypercholesterolemia observed in patients with long-standing diabetes.

Experimental studies in control and streptozotocin diabetic rats that reveal another important aspect to consider: increased expression of NPC1L1 and reduced expression of ATP-binding cassette sub-family G members 5 and 8 (ABCG5 and ABCG8) are correlated with abnormally high chylomicron and VLDL levels [11].

The guidelines for cardiovascular prevention in subjects with diabetes recommend early statin treatment; however, decreasing cholesterol synthesis may provoke a compensatory increase in cholesterol absorption. The effects of insulin resistance on LDL metabolism combined with the effects of hyperglycemia on molecules mediating cholesterol absorption may diminish the favorable effects of statins in diabetic subjects.

These observations support the addition of ezetimibe to statin therapy in subjects with diabetes. Clinical data show that combination therapy with a statin plus ezetimibe has a positive effect on lipid profiles, and especially on apoB. Ruggenenti et al. found that adding ezetimibe to ongoing simvastatin therapy improved the pro-atherogenic lipoprotein profile in patients with type 2 diabetic who had failed to reach recommended lipid targets with statin therapy alone. LDL cholesterol (LDL-C) and total cholesterol and apoB significantly decreased by 30.9, 21.6, and 19.6%, respectively, in patients randomized to ezetimibe compared to placebo [12].

Another study compared the effect of ezetimibe on different lipoprotein classes and on apoB-100 kinetics in obese subjects. The effect of ezetimibe on apoB is independent of simvastatin, and is stronger with combination therapy. Both weight loss alone and weight loss plus ezetimibe resulted in significant reductions in VLDL apoB-100 concentrations (−13 and −19%, respectively) and secretion rates (−29 and −13%, respectively), without significant changes in the FCR of VLDL apoB-100 (+3 and +8%, respectively) [13]. In the LDL fraction, ezetimibe plus weight loss significantly decreased the plasma concentration of LDL apoB-100 with a significant increase in its FCR, compared to weight loss alone (Table 1).

Another important finding from this study was that addition of ezetimibe to the weight loss diet further decreased intrahepatic triglycerides (IHTG), in spite of similar changes in body weight (Fig. 1) and Homeostasis Model Assessment (HOMA) scores between groups. The HOMA score is a marker of hepatic insulin resistance, so the effect of ezetimibe on this marker is intriguing because it shows that treatment can influences insulin resistance. The same study also concluded that addition of ezetimibe to weight loss may reduce hepatic steatosis and inflammation. Clearly, we cannot exclude that the effect of Ezetimibe on HOMA is a consequence of the reduced hepatic steatosis.

A study in miniature pigs investigated the effects of ezetimibe and ezetimibe plus simvastatin treatment compared with control on apoB metabolism, showing that ezetimibe was efficacious at inhibiting absorption and decreasing plasma concentrations of phytosterols (Fig. 2) [14]. The combination of ezetimibe plus simvastatin decreased apoB-100 concentrations in both VLDL and LDL fractions by reducing VLDL production and enhancing LDL clearance via the LDLR. Ezetimibe inhibited cholesterol absorption

Table 1
Kinetic indices for apoB-100 before and after intervention in the weight loss and ezetimibe plus weight loss groups

	Weight loss ($n = 10$)		Ezetimibe plus weight loss ($n = 15$)	
	0	22 weeks	0	22 weeks
VLDL–apoB-100				
Concentration (mg/L)	142 ± 123	$123 \pm 19^{\dagger}$	134 ± 12	$109 \pm 11^{\dagger}$
Fractional catabolic rate (pools/day)	4.8 ± 1.1	3.8 ± 0.4	3.9 ± 0.4	4.2 ± 0.3
Production rate (mg/kg FFM/day)	41 ± 5	$29 \pm 7^{\dagger}$	38 ± 3	$32 \pm 4^{\dagger}$
IDL–apoB-100				
Concentration (mg/L)	76 ± 10	74 ± 12	82 ± 9	$65 \pm 9^{\S}$
Fractional catabolic rate (pools/day)	3.9 ± 0.7	3.6 ± 0.3	3.5 ± 0.4	$4.5 \pm 0.5^{\S}$
Production rate (mg/kg FFM/day)	20 ± 3	18 ± 2	20 ± 2	18 ± 2
LDL–apoB-100				
Concentration (mg/L)	957 ± 61	885 ± 36	952 ± 76	$774 \pm 62^{*\ddagger}$
Fractional catabolic rate (pools/day)	0.35 ± 0.03	0.34 ± 0.03	0.31 ± 0.02	$0.39 \pm 0.03^{*\ddagger}$
Production rate (mg/kg FFM/day)	26 ± 3	22 ± 2	22 ± 1	21 ± 2

Data are means ± SEM. $^{*}P < 0.01$, value significantly different from baseline value. $^{\dagger}P < 0.05$. $^{\ddagger}P < 0.05$, value significantly different using general linear modeling after adjustment for relative changes in the weight loss group. $^{\S}P = 0.06$, value different from baseline value.
VLDL, very low density lipoprotein; apoB, apolipoprotein B; FFM, free fat mass (vis a vis body composition); IDL, intermediate density lipoprotein; LDL, low density lipoprotein. (Reproduced with permission from Diabetes Care 2010 May;33(5):1134–9 [13].)