COMMENT ON XU ET AL.

Effects of Metformin on Metabolite Profiles and LDL Cholesterol in Patients With Type 2 Diabetes. Diabetes Care 2015;38:1858–1867

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In the task of alluding to the mode of action of metformin, Xu et al. (1) examined 131 fasting serum metabolites in three independent cross-sectional cohort studies. The authors found decreased concentrations of three metabolites (acyl-alkyl phosphatidylcholines [PCs]) in patients with type 2 diabetes treated with metformin compared with control groups not using glucose-lowering oral medication. The reduction of these metabolites was associated with lower plasma concentrations of LDL cholesterol, which was partially mediated by the three PCs. Statistical analyses suggested that the reduced PC concentrations were explained by metformin's effect on AMPK in the liver. Moreover, the metabolite variations were associated with 17 genes (including *FADS* genes, which function in fatty acid metabolism).

Xu et al. (1) are to be congratulated for their comprehensive study that brings substantial new knowledge to the enigmatic topic of metformin and its pleiotropic mode of action. However, in terms of LDL cholesterol reduction, we wish to draw attention to one mode of action that was not addressed in the study. The cholesterol-lowering effects of metformin have long been recognized (2). For some years now, we have also known that metformin represses intestinal bile acid absorption—an effect that likely arises from interaction with the bile acid transport system in the distal ileum (3). Reduced bile acid absorption leads to increased bile acid synthesis from cholesterol (4). This is largely exerted at the level of the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1) by feedback inhibition, which is partly mediated by the farnesoid X receptor (FXR) regulation of *CYP7A1* gene expression (4). Bile acid synthesis is also repressed by the gut hormone fibroblast growth factor 19, which is synthesized in ileal enterocytes in response to bile acid–induced FXR activation and released into the portal circulation (4). Naturally, interruption of the enterohepatic circulation by the removal of the distal ileum or by the administration of bile acid sequestrants enhances fecal bile acid excretion. Consequently, bile acid synthesis from cholesterol is increased, leading to an enhanced demand for cholesterol in the hepatocytes, which is achieved by LDL receptor upregulation. This increases uptake of cholesterol-rich lipoproteins, leading to a decrease in total cholesterol and LDL cholesterol. Bile acid sequestrants were the first lipid-altering drugs to show an ability to reduce the risk of coronary heart disease (5). Administration of the bile acid sequestrant cholestyramine demonstrated a 19% risk reduction of coronary heart disease death and/or nonfatal myocardial infarction compared with placebo (5). LDL cholesterol concentrations were reduced by 13% and total mortality was reduced by 7%. Considering these data, we find it is plausible that part of metformin's pleiotropic effects on lipids involves interruption of the enterohepatic circulation of bile acids, leading to increased bile acid synthesis, which eventually reduces circulating LDL cholesterol concentrations.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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