RESPONSE TO 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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We thank Sonne and Knop for their comments (1) on our article (2). They recalled that the induced AMPK pathway we investigated is not the only potential root of the observed decrease in LDL cholesterol (LDL-C) levels after metformin treatment. Sonne and Knop indicated the highly probable influence of the bile acid synthesis and the underlying mode of action (1). We fully agree with this comment.

However, we would like to clarify more precisely two points referred to by the authors. First, the statement referring to "decreased concentrations of three metabolites" when case subjects were compared with control subjects in our cross-sectional study (1) would be better described with the expression "lower concentration." The term "decreased" is appropriate when referring to our longitudinal results following the same person for 7 years (2), but it can be misleading when comparing groups of different individuals. Second, Sonne and Knop stated that "the cholesterol-lowering effects of metformin [had] long been recognized," citing a study by Giugliano et al. (3). However, the original article did not particularly report LDL-C levels, but total cholesterol and triglycerides (3). We thus wonder if the link between the studies can be drawn in such a straightforward manner. Additionally, the study by Giugliano et al. (3) is based on the investigation of 12 obese hypertensive women without diabetes; therefore, the underlying design is different from ours (2).

We appreciate that an additional mode of action was addressed (1). In fact, our analysis indicated that approximately 29% of the decrease in LDL-C can be explained by repressed FADS activity (2). Still, about 70% of the contribution to the reduction of LDL-C is unclear. The influence of metformin on the bile acid metabolism has been known since the 1970s (4). Indeed, AMPK, one of the targets of metformin, is an inhibitory regulator of the nuclear bile acid receptor farnesoid X receptor (FXR). FXR is a pleiotropic regulator of lipid and glucose metabolism and controls the synthesis and enterohepatic circulation of bile acid (5). In cultured hepatocytes and enterocytes, AMPK activation led to an inhibition of FXR transcriptional activity (5). Consequently, the impact of metformin on the FADS complex and bile acid might be linked by AMPK. Probably metformin's effect on blood lipid levels is due to not only the AMPK activation in hepatocytes but also its cross talk with other tissues. Napolitano et al. (6) investigated the enterohepatic flux of bile acid in multiple matrices of metformin-treated patients and observed poor correlations of four analyzed bile acids between feces and serum. This study indicates the complexity and diversity of metformin's pharmacological effects on bile acid in different tissues (6). However, the design of our population-based cohort study did not enable the investigation of multiple matrices, including feces (2). Additionally, bile acid was not included in our quantitative measurements of serum samples. More comprehensive insights into the mode of action could be better addressed in clinical intervention studies that include the examination of gut microbiota.

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