RESPONSE TO COMMENT ON GOLDFINE ET AL.

Targeting Inflammation Using Salsalate in Patients With Type 2 Diabetes: Effects on Flow-Mediated Dilation (TINSAL-FMD). Diabetes Care 2013;36:4132–4139

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In our study to target inflammation using salsalate in patients with type 2 diabetes, we demonstrate improvement in glycemia but no change in either flow-mediated, endothelium-dependent (FMD) or nitroglycerin-mediated, endothelium-independent dilation over 6 months in salsalate (3.5 g/day) compared with placebo-treated patients (1). It is important to note that no adverse cardiovascular safety signal for endothelial function was demonstrated. Our findings differ from Pierce and colleagues (2,3), who demonstrated improvement in vascular function and inflammation after 4 days of higher doses (4.5 g/day) of salsalate in overweight/obese persons without diabetes. Notably 12% of participants in that study withdrew for symptoms consistent with salicylism, as seen in other studies of higher dose salsalate (4). It is possible that the lower dose used in our study did not achieve adequate vascular effects. However, we evaluated optimal dosing based on safety, efficacy for glycemic lowering, and tolerability determined in a 3-month dose-ranging study (5). Moreover, initial improvements in vascular function seen over 4 days may not be durable.

There are multiple molecular pathways involved in inflammation. We previously demonstrated salsalate reduces nuclear factor κB activity in circulating mononuclear cells in humans (4), and showed anti-inflammatory effects in the current study as manifest by reduced circulating white blood cells and lymphocytes and increased adiponectin (1). However, this did not translate into improved endothelial function. A large proportion of our participants were on concomitant therapy with metformin and/or statin therapy, which could attenuate the vascular response to salsalate. Tests for heterogeneity of response when comparing subgroups on either statins or metformin alone compared with those not using either agent were not significant. The test for heterogeneity for FMD for those on both statins and metformin compared with neither agent was significant ($P = 0.043$). FMD was improved in participants not taking statins ($P = 0.048$) or taking neither statins nor metformin ($P = 0.017$) who received salsalate compared with placebo. However, tests of heterogeneity were no longer significant if accounting for multiple testing, and thus must be considered exploratory.

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

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