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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We read with interest the study by Goldfine et al. (1) in the recent issue of *Diabetes Care* that reported that 3 and 6 months of oral salsalate treatment, as part of the multicenter Targeting Inflammation Using Salsalate in Type 2 Diabetes (TINSAL-T2D) trial, had no effect on brachial artery flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (measurements of endothelium-dependent and -independent dilation, respectively) in patients with type 2 diabetes (T2D). The authors concluded that their findings suggest that *1*) salsalate does not inhibit vascular inflammation, *2*) inflammation does not cause endothelial dysfunction in patients with T2D, or *3*) the potential benefits of salsalate were masked by the unfavorable changes in serum lipids and urinary albumin.

These conclusions may all or partly be true but perhaps deserve further scrutiny. That salsalate does not inhibit vascular inflammation or that inflammation does not cause endothelial dysfunction in T2D is difficult to determine because no measure of vascular inflammation was assessed. Also, a substantial number of the patients were on statin therapy (69%) and antidiabetes therapy including metformin (92%). Importantly, statins are known to have antioxidant and anti-inflammatory actions and to increase endothelial cell nitric oxide synthase expression/activity. Metformin inhibits the key proinflammatory transcription factor nuclear factor-κB (2) and activates the master regulator of cell metabolism AMP-activated protein kinase (3)—both mechanisms by which salsalate likely mediates at least part of its beneficial vascular and metabolic effects (4,5). Therefore, it is not entirely surprising that salsalate had no added benefit in these optimally medicated patients with T2D. In this regard, it might be of interest for the authors to perform a subset analysis of the patients taking versus not taking metformin and/or statins to determine if salsalate had a differential effect in these subsets of patients. Last, whether the small change in LDL cholesterol and urinary albumin masked beneficial effects of salsalate seems unlikely, but these alterations certainly require further study.

As the authors characterized more than a decade ago, patients with T2D develop both microvascular endothelium-dependent and -independent dysfunction (6). Given that patients with T2D are at high risk for developing microvascular disease, determining whether salsalate improves microvascular endothelial function or prevents the development of microvascular comorbidity in T2D will require additional studies. Last, a technical issue related to the FMD technique used should be considered. Measuring the brachial artery peak diameter only at fixed time (e.g., 1 min after cuff release) may have underestimated the FMD% because peak dilation occurs earlier than 1 min after ischemia in many individuals.

Although at first glance the study by Goldfine et al. (1) appears to reduce enthusiasm for further use of salsalate on vascular end points, the study reemphasizes that chronic salsalate therapy is safe and can be tolerated in patients at high vascular risk. This is promising given that salsalate is inexpensive and generically available. Future studies might be directed at individuals who demonstrate endothelial dysfunction (e.g., obese/prediabetic, sedentary, aged) but are not eligible for statin or metformin therapy and are unable to sustain lifestyle behaviors to maintain preserved vascular function.

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

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