Response to Letter Regarding Article, “Statin Use and Adrenal Aldosterone Production in Hypertensive and Diabetic Subjects”

We thank Dr Campbell for his interest in our study,1 and the fair and helpful comments from the accompanying editorial by Andersson and Vasan, as well.2

We are in agreement with Dr Campbell that statins may influence adrenal steroidogenesis via a multitude of effects. Our study focused mainly on the regulation of aldosterone by using a series of complex physiological maneuvers that included manipulation of angiotensin II and potassium.

The subjects in our study were not taking antihypertensive therapy or were withdrawn of therapy, thus allowing investigation of their native physiology. In this context, our use of extreme sodium diets permitted the study of aldosterone when the renin-angiotensin system was maximally suppressed on high sodium and maximally stimulated on low sodium intake in the context of a fixed potassium diet. Therefore, all our assessments of aldosterone were conducted under conditions whereby the key secretagogues of aldosterone were both fixed to permit an isolated investigation of other influences on aldosterone secretion. In this context, we observed that statin use was consistently associated with lower aldosterone secretion as measured by serum concentrations at baseline, 24-hour urinary excretion, and following stimulation by angiotensin II. Importantly, the renin and potassium were not affected (as described in Table 1), suggesting that the reduction in aldosterone is not secondary to changes of classical regulatory factors. On the other hand, it is still unclear why renin did not increase when the aldosterone levels were lowered. Remarkably, a previous study using an aldosterone synthase inhibitor has demonstrated that moderate decreases in aldosterone are not sufficient to significantly upregulate renin.3

Dr Campbell cites the small study of 24 participants by Mol et al4 from 1989 as an example of how statins may lower cortisol and the cortisol response to adrenocorticotropic hormone. In principle, we agree that a more robust way to assess the influence of statins with lower aldosterone secretion as measured by serum concentrations at baseline, 24-hour urinary excretion, and following stimulation by angiotensin II. Importantly, the renin and potassium were not affected (as described in Table 1), suggesting that the reduction in aldosterone is not secondary to changes of classical regulatory factors. On the other hand, it is still unclear why renin did not increase when the aldosterone levels were lowered. Remarkably, a previous study using an aldosterone synthase inhibitor has demonstrated that moderate decreases in aldosterone are not sufficient to significantly upregulate renin.3

The influence of reduced cholesterol availability for adrenal steroidogenesis is an interesting concept included in our discussion. Future in vitro studies with mevalonate could provide insights into understanding the importance of adrenal 3-hydroxy-3-methylgluta- ryl coenzyme A in aldosterone steroidogenesis. Against being a key mechanism is the observation of normal corticosterone in fasciculata and glomerulosa cells (a precursor for aldosterone synthesis) in our ex vivo studies. From a clinical point of view, Sezer and colleagues demonstrated that very low low-density lipoprotein levels (the average of the statin group was 58±11.4 mg/dL) do not affect adrenal cortisol synthesis. It should also be noted that participants treated with statins in our 2 human intervention studies had significantly higher low-density lipoprotein levels than the ones reported by Sezer because they were not high-risk patients.

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Disclosures

None.

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