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Response to Letter from Campbell and colleagues

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We would like to thank Dr. Campbell for his interest in our study as well as the fair and helpful comments from the accompanying editorial by Andersson and Vasan [12]

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 using a series of complex physiologic maneuvers that included manipulation of angiotensin II and potassium.

The subjects in our study were not taking anti-hypertensive therapy or were withdrawn of therapy, thus allowing investigation of their native physiology. In this context, our use of

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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 of 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, 24h urinary excretion, and following stimulation by angiotensin II. Importantly, the renin and potassium were not affected (as described in Table 1), suggesting 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 prior study using an aldosterone synthase inhibitor have demonstrated that moderate decreases in aldosterone are not sufficient to significantly upregulate renin [3].

Dr. Campbell's cites the small study of 24 participants by Mol et al. from 1989 as an example of how statins may lower cortisol and the cortisol response to ACTH. In principle, we agree that a more robust way to assess the influence of statins on adrenal cortisol synthesis could involve ACTH stimulation; our study design did not include this physiologic maneuver and was more focused on manipulations to assess aldosterone, such as sodium balance, potassium balance, and angiotensin II infusion. However, it should be noted that in our study of >1,000 study visits and assessments, statin use did not influence morning cortisol levels. Further, a recent metanalysis with data from seven randomized studies showed no evidence of a cortisol-lowering effect with statins. Interestingly, they also showed a different effect of lipophilic versus hydrophilic statins in cortisol levels [4].

The influence of reduced cholesterol availability for adrenal steroidogenesis is an interest concept included in our discussion. Future *in vitro* studies with mevalonate could provide insights into understanding the importance of adrenal HMG-CoA 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 collagues demonstrated that very low LDL levels (the average of the statin group was 58+/− 11.4 mg/dl) does not effect adrenal steroid synthesis[5]. It should also be noted, that participants treated with statins in our two human interventions studies had significantly higher LDL levels that the ones reported by Sezer, since they were not high-risk patients.

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