Response to Letter to the Editor: "Methodological Issues Regarding Cortisol Secretion, Sensitivity, and Activity are Associated With Hypertension in Postmenopausal Eucortisolemic Women"

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To the Editor-in-Chief:

We read with interest the Letter to the Editor by Almasi-Hashiani and Monsournia about methodological issues regarding our previously published paper, in which we suggested a relation between cortisol secretion sensitivity and activity with either hypertension or the simultaneous presence of diabetes, hypertension, and fragility fractures in postmenopausal eucortisolemic women (1).

They raised the important question of the wide range of the odds ratio and 95% confidence limit related to the association between urinary free cortisol-to-urinary free cortisone ratio and either hypertension or the simultaneous presence of diabetes, hypertension and fragility fractures. As Almasi-Hashiani and Monsournia observed, this wide odds ratio is likely to be due to the small sample size. We certainly agree that the small sample size might have reduced the reliability of the results obtained. This limit of the study has been clearly discussed in our paper and prompted us to be very cautious in interpreting our findings.

Moreover, our data had been originally collected to assess the relation between cortisol secretion, peripheral activation and sensitivity, and bone fragility in diabetic patients and controls (2). In that previous study, no specific matching protocols have been used, and the nondiabetic subjects have been consecutively recruited on the basis of the same inclusion and exclusion criteria used for patients. In the second study (object of the Almasi-Hashiani and Monsournia criticisms), we simply re-analysed our dataset, comparing the cortisol "milieu" (ie, cortisol secretion, peripheral activation and sensitivity) between patients with hypertension and those without hypertension. Therefore, we are aware that the lack of a specific matching protocol is a limit of both studies. Furthermore, given that diabetes *per se* is characterized by an increased cortisol secretion (3), the original design of the study might have biased the results. However, the fact that the relationship between this cortisol "milieu" and hypertension seems to be present regardless of diabetes, age, and body mass index, renders these biases less likely.

In keeping with the idea that even in eucortisolemic patients, hypertension may be associated with cortisol "milieu," in the past few months three different groups obtained similar data. Indeed, Mazgelytė and colleagues found that hair cortisol concentration may be associated with the prevalence of major cardiovascular risk factors (4). In addition, Crawford and coauthors, analyzing prospective cohort and Mendelian randomization studies, suggested that morning plasma cortisol may be a cardiovascular risk factor (5). Finally, Haas and colleagues observed that higher urinary cortisol levels associate with increased cardiovascular risk (6).

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In summary, we agree with Almasi-Hashiani and Monsournia that the results of our study(ies) are affected by substantial sparse-data bias due to sparse data, as well as residual confounding and selection bias effects of matching variables. However, notwithstanding these limitations, we believe that multiple points of evidence point toward a possible causative effect of the individual cortisol "milieu" on cardiovascular disease, even in subjects without cortisol excess. These very early data suggest the need for larger studies assessing this possible causative association. These studies may consent 1) to verify the possibility that the assessment of the cortisol "milieu" could help in identifying the risk of cardiovascular disease in the individual subjects and 2) to evaluate whether strategies targeted at lowering cortisol action could be useful for their effects on cardiovascular disease (4).

Additional Information

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