Renal injury in extreme obesity: the important role of aldosterone


To the Editor: We read with interest the recent article by Serra et al.1 detailing a variety of glomerular lesions (increased mesangial matrix, mesangial cell proliferation, podocyte hypertrophy, and glomerulomegaly) in extremely obese patients without clinical signs of renal dysfunction. Despite using a broad array of clinical and biochemical variables in their regression models, only body mass index was found to be a significant predictor of glomerular lesions in multivariate analysis.

We believe that serum aldosterone, if included in the analysis, would have likely emerged as another important predictor of obesity-related renal damage. Obesity is frequently associated with elevated levels of aldosterone.2 In the obese state, oxidized fatty acids likely stimulate aldosteronogenesis;3 in vitro, human adipocytes secrete potent mineralocorticoid-releasing factors.4 Aldosterone is important in salt and water balance by acting on epithelial mineralocorticoid receptors, but its effects through mineralocorticoid receptors in nonepithelial tissues may be more important in the pathogenesis of chronic kidney disease. In animal models, unopposed aldosterone in the presence of high salt intake causes thomboctic and proliferative lesions in the glomeruli and renal vessels.5–7 These pathologic lesions occur independent of blood pressure, reflecting a direct, nonepithelial, profibrotic effect of aldosterone on the kidney.

The increased glomerulosclerosis in these hyperaldosterone models typically result in severe proteinuria, a distinctly different phenotype from Serra et al.’s extremely obese subjects whose clinical renal function was normal. The authors, however, argue that the early lesions found in this study are potential harbingers of future, overt kidney disease. If so, then the glomerular lesions described in this study will likely progress to the more sclerotic lesions typified in the seminal animal studies discussed above.

The role of aldosterone in obesity-related kidney injury becomes more important as the discussion shifts toward potential treatment options. Serra et al. admit that their study does not address whether bariatric surgery could reverse the renal lesions seen on biopsy, and the authors cite a study in which angiotensin-converting enzyme inhibitors and statins ameliorate podocyte damage in obese rats.8 In dogs fed a high-fat diet, the use of an aldosterone antagonist (compared to untreated controls) markedly attenuated obesity-induced glomerular hyperfiltration, sodium retention, and hypertension.9 Because it will not be possible to offer all extremely obese patients bariatric surgery, it may be beneficial to check these patients’ aldosterone levels and, if elevated, prescribe mineralocorticoid receptor blockers and salt restriction for renal protection. Alternatively, empiric treatment with mineralocorticoid receptor blockers and a low-salt diet may be undertaken even without aldosterone measurement, recognizing the possibility that mineralocorticoid receptor activation may also occur by elevated cortisol concentrations in obesity.10

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Response to ‘renal injury in extreme obesity: the important role of aldosterone’


We appreciate the comments of Dr Bomback and Dr Klemmer on the possible relationship between aldosterone and obesity-related renal lesions.1

Obesity is associated with elevated levels of several hormones including aldosterone, leptin, adiponectin, cortisol, renin, and angiotensin.2,3 Some of these hormones, such as leptin, have been associated with the production of renal lesions in animal models.4
Experimental evidence suggests that aldosterone could be responsible for thrombotic and proliferative lesions in the glomeruli and renal vessels. On the other hand, the administration of either spironolactone or angiotensin-converting enzyme inhibitors reduced renal damage in a rat model. Moreover, the administration of aldosterone reversed the renal protection provided by blockade of the renin-angiotensin-aldosterone system in another model. Therefore, significant experimental evidence exists that aldosterone could produce renal injury. Likewise, there is preliminary evidence stemming from the systematic review by Bomback et al. that the combination of aldosterone blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers could be useful in the control of patients with proteinuric chronic kidney disease. However, to our knowledge, no clinical studies have been conducted relating aldosterone to the renal lesions found in extremely obese (EO) patients. Such studies in obese and non-obese subjects would be highly welcome because, if they confirmed this relationship, the possibility of potential treatment options would be opened up.

The lack of these clinical-pathologic studies is probably due to the difficulty in obtaining renal tissue in the general population for ethical reasons. Nevertheless, it is possible to obtain renal tissue from EO patients during bariatric surgery. Obesity and extreme obesity are health problems of epidemic proportions and their prevention and treatment are extremely important. Some of these EO patients have microalbuminuria and could develop proteinuria and chronic kidney disease in the course of the disease. The great challenge is to discover new treatments to avoid obesity and/or once established, prevent the mechanisms of renal or other organ lesions induced by obesity and related diseases such as arterial hypertension. Meanwhile, we agree that the empiric use of aldosterone blockers and low-salt diet or the use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers in EO patients in whom bariatric surgery is delayed or not possible, could be an alternative treatment option.

In our article, we focused mainly on the description, for the first time, of the glomerular architecture in renal biopsies of EO patients with normal renal function. We did not attempt to study pathogenic or treatment aspects in depth. We centered exclusively on clinical-pathologic correlations and demonstrated that body mass index is an independent risk factor for glomerular lesions. Previous clinical-epidemiologic data had suggested the existence of a relationship between obesity and chronic kidney disease.