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COMMENTARY

Changes in aldosterone and obesity-related cardiometabolic risk factors with a 1-year weight loss intervention in normotensive overweight and obese young adults

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Aldosterone is classically regarded as a major sodium- and water-retaining hormone that counterbalances dehydration, hypotension and hypovolemia. When produced in excess, it causes primary aldosteronism, the most common endocrine cause of high blood pressure (HBP).[1] It may also have a role in increasing BP in the general population, as observed in the Framingham Offspring Study, where increased plasma aldosterone concentrations (PAC) within physiological range, and even more so the aldosterone:renin ratio, predicts the development of HBP in normotensive individuals.[2,3]

Of note, recent studies by Williams's group have indicated a relationship between aldosterone and adipose tissue deposition: a higher 24-h urinary aldosterone excretion and PAC after angiotensin (Ang) II infusion were found in overweight compared with lean normotensive subjects, who were exposed to a high sodium intake to remove the potentially confounding effect of sodium intake, a well-known determinant of aldosterone secretion.[4] This seminal observation suggested that the condition of overweight features inappropriate aldosterone secretion that could be related to increasing BP possibly because of an increased adrenocortical sensitivity to Ang II.

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This contention was thereafter proven in a substudy of the Primary Aldosteronism Prevalence in hYpertension (PAPY) Study:[1] by investigating a relatively large cohort of patients with primary (essential) HBP in whom all secondary causes were carefully excluded, we showed that PAC was directly related to BP.[5] More importantly, we demonstrated for the first time a direct relationship between PAC and body mass index (BMI) that was independent of plasma renin activity. This relationship was particularly strong among the overweight-obese patients, indicating that excess deposition of adipose tissue and excess aldosterone production are closely associated.

THE BASIS OF THE RELATIONSHIP BETWEEN ADIPOSE TISSUE AND THE SECRETION OF ALDOSTERONE

Sufficient evidence is now available to consider adipose tissue as a highly active endocrine organ that is involved in many physiological and pathological processes. Accordingly, several studies have highlighted the possibility that adipose tissue-derived factors can stimulate aldosterone secretion. Along this line, oxidized endogenous fatty acids and/or fat-derived factors (adipokines) have been proposed to constitute major stimuli for aldosterone secretion in overweight-obese subjects with HBP. Moreover, the adipokine collagen-like TNF α-related protein (CTRP)-1 was recently suggested to directly stimulate aldosterone secretion from human adrenocortical cells in vitro,[6] and the same may also apply to CTRP-3, another member of the family. Moreover, the finding of adiponectin receptor type 1 and 2 expression in the normal human adrenal cortex and in aldosterone-producing adenomas also indicates a potential modulatory role for this adipokine.[7] Therefore, in addition to some well-established mechanisms, including activation of the peroxisome proliferator-activated receptor, leptin, insulin, insulin resistance, and activation of the sympathetic nervous system, the direct stimulation of aldosterone secretion by adipokines ('adipotensins') can also increase aldosterone secretion in overweight-obese patients, in part through sensitization of adrenocortical cells to Ang II,[4,8] ultimately resulting in HBP and cardiovascular damage (Figure 1).

WHY IS THIS RELATIONSHIP IMPORTANT?

What makes these findings so crucially important is the dramatic increase in the prevalence of overweight/obesity currently ongoing worldwide. Additionally, in the presence of HBP (and often of dyslipidemias and impaired glucose tolerance with type 2 diabetes mellitus), overweight/obesity carries an excess risk of cardiovascular events. To emphasize the dreadful effects of this constellation of interrelated metabolic risk factors, the American Heart Association/National Heart, Lung, and Blood Institute[9] and other institutions[10] have coined the term 'metabolic syndrome (MS),' but intriguingly enough, the common underlying pathogenic denominator of MS remains unknown.

It is, however, worth remembering that almost 50 years ago, Conn himself noticed

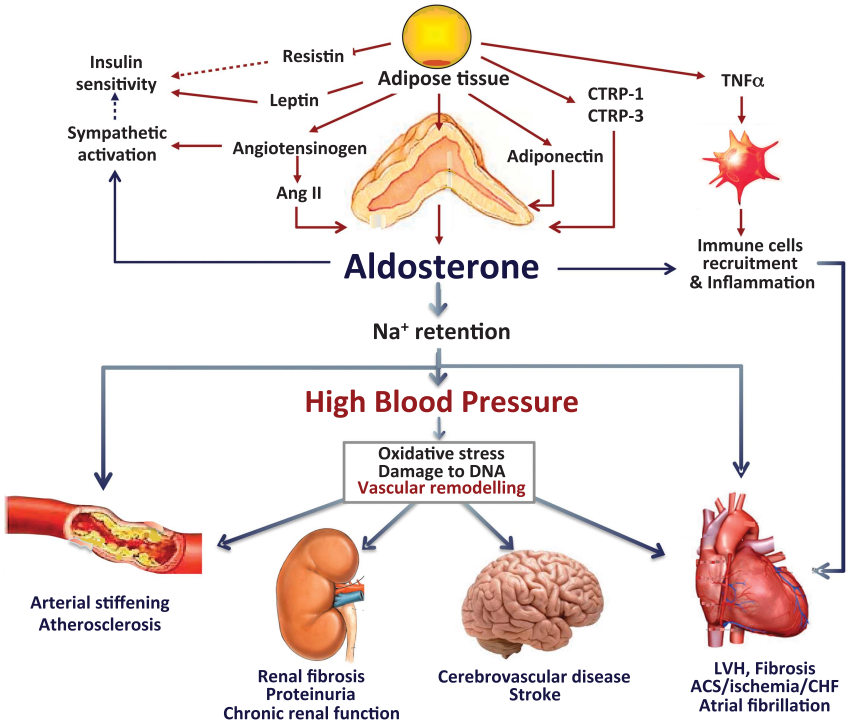

Figure 1 The cartoon illustrates the relationship between the adipose tissue as a metabolically active organ and aldosterone, and the key role of excess/inappropriate production of the hormone in the setting of high sodium (Na^+) intake in causing damage to the target organs of high blood pressure. ACS: acute coronary syndrome; CHF: cardiac heart failure; CTRP: collagen-like TNFα-related protein; LVH: left ventricular hypertrophy; TNFα: tumor necrosis factor α.

that more than 50% of a small number of patients with primary aldosteronism showed impaired glucose tolerance.[11] Various reports have since suggested that inappropriate aldosterone secretion can be key for inducing the metabolic alterations that are hallmarks of MS (reviewed in Sowers *et al.*[12]).

Clinically, the involvement of aldosterone in MS is also evidenced by the following: (i) compelling experimental and clinical evidence demonstrating that aldosterone drives damage to the target organs of HBP in the presence of excess sodium intake;[13] (ii) both aldosterone excess per se and MS are associated with increased cardiovascular morbidity and mortality.[14]

DOES WEIGHT LOSS REDUCE ALDOSTERONE AND CARDIOVASCULAR RISK?

Establishing a causal link between excess aldosterone, MS and an excess risk of cardiovascular events is clearly a challenging undertaking in that it would require carefully designed long-term prospective cohort studies. However, some interesting clues have been provided by the available intervention studies aimed at correcting overweight/obesity.

In this issue, Cooper *et al.*[15] report on their investigation of the relationships between weight loss, dietary sodium and vascular health in a community sample recruited for the Slow Adverse Vascular Effects of excess weight study (SAVE). This was a randomized-controlled trial in overweight/obese young adult participants (BMI $\geqslant 25$ and $<40\,kg\,m^{-2}$) in whom weight loss was achieved with diet and physical activity with or without dietary sodium intake, all implemented with a 1-year intervention.[15] After a measurement at baseline, body weight, PAC, 24-h sodium, potassium excretion and several obesity-related factors were measured again after 6, 12 and 24 months. Computed tomography was also used to measure subcutaneous fat, visceral fat and inter-muscular fat.

The intervention was effective in producing a small, albeit statistically significant, weight loss at 6 (-7%), 12 (-6%) and 24 months (-4%) (all $P<0.0001$). The weight loss was associated with decreases in C-reactive protein, leptin, insulin, homeostasis assessment of insulin resistance (HOMA-IR), heart rate and tonic cardiac sympathovagal balance, as well as increases in adiponectin (all $P<0.05$) in models adjusting for potential confounders (including baseline age, sex, race, intervention arm, time since baseline, and sodium and potassium excretion).

In all groups, the PAC also decreased with intervention, but not significantly. Of note, weight loss and reductions in thigh inter-muscular fat were associated with decreases in only the PAC in the subgroup ($n=98$) with MS.

Therefore, they concluded that favorable changes in obesity-related factors were associated with reductions in body weight in young subjects who had no risk factors other than excess weight. They also highlighted the possibility of lowering aldosterone and related risk factors with an intervention aimed at lowering body weight. Aldosterone reduction may therefore has an independent role in improving the cardiovascular risk profile during lifestyle modification, which might be important given the aforementioned role of aldosterone as a cardiometabolic risk factor. While of interest, the study has several limitations that the authors honestly acknowledged. Moreover, it raises some questions: for example, why were the lowering of aldosterone and its beneficial effects observed only in patients with MS? How do we know that the improved risk profile is from lowering aldosterone and not from just weight loss and decreasing salt intake?

The interpretation of why the PAC fell significantly and showed a relationship with the decrease of body weight only in those with MS is intriguing. The authors offered several potential explanations for the underlying mechanisms that remain speculative because the study was observational (descriptive) and not mechanistic in nature. Likewise, the obesity-related factors that were most influenced by aldosterone were unclear.

Above all, it must be noted that the intervention arms differed significantly for sodium intake. This was reflected in the significant differences in the changes in sodium excretion and serum aldosterone compared with baseline: in the low sodium/lifestyle arm, sodium excretion decreased by an average of 41.7 mmol per 24 h during the intervention. By comparison, in the control sodium/lifestyle arm, it decreased by only 12.4 mmol per 24 h. Concomitantly, the PAC was higher, albeit with only borderline significance, in the low sodium/lifestyle arm compared with the control sodium/lifestyle arm. Therefore, it is likely that the lowering effect of the body weight loss in the low sodium/lifestyle group on aldosterone production was minimized by the concurrent decrease in sodium intake, which has an opposite effect on aldosterone. The study design could have prevented the detection

of a relationship between weight loss and the decrease in the PAC when all groups were examined. Therefore, as for many other post hoc analyses of trials originally designed with a different aim, the results should be taken cautiously, as these types of studies are typically exposed to selection biases and serendipitous findings. Moreover, statistical adjustments do not always allow for compensating the untoward effects of a study design that was not originally set out to answer the question on the ground.

Finally, the 20% male and 15% African American representation in the study increased the sample size, and therefore the power of the study. However, it may have diluted the results given that the PAC differs according to race and gender, and moreover, varies throughout the menstrual cycle. As the authors acknowledged, without knowing the changes in any of the components of the renin–angiotensin system even with adjusted analyses, it is hard to determine the extent to which weight loss contributes to lowering aldosterone, and in turn, its pathophysiological role.

CONCLUSIONS AND PERSPECTIVES

Notwithstanding the limitations of their study, Cooper *et al.* should be commended for clearly showing that a 1-year intervention was effective not only in achieving a significant, albeit small, decrease in body weight, but more importantly, in blunting numerous obesity-related cardiometabolic risk factors. As weight loss was directly associated with the reduction in aldosterone levels in only patients with MS and not the overall cohort, it would appear that the role of inappropriate aldosterone secretion is peculiar to this group of patients in whom it may increase cardiovascular risk. Whether the changes in aldosterone and obesity-related cardiovascular risk factors can translate to a better long-term prognosis is worthy of further prospective interventional studies.

1 Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, Ganzaroli C, Giacchetti G, Letizia C, Maccario M, Mallamaci F, Mannelli M, Mattarello MJ, Moretti A, Palumbo G, Parenti G, Porteri E, Semplicini A, Rizzoni D, Rossi E, Boscaro M, Pessina AC, Mantero F. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol* 2006; **48**: 2293–2300.
2 Vasan RS, Evans JC, Larson MG, Wilson PW, Meigs JB, Rifai N, Benjamin EJ, Levy D. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med* 2004; **351**: 33–41.
3 Newton-Cheh C, Guo CY, Gona P, Larson MG, Benjamin EJ, Wang TJ, Kathiresan S, O'Donnell CJ, Musone SL, Camargo AL, Drake JA, Levy D, Hirschhorn JN, Vasan RS. Clinical and genetic correlates of aldosterone-to-renin ratio and relations to blood pressure in a community sample. *Hypertension* 2007; **49**: 846–856.
4 Bentley-Lewis R, Adler GK, Perlstein T, Seely EW, Hopkins PN, Williams GH, Garg R. Body mass index predicts aldosterone production in normotensive adults on a high-salt diet. *J Clin Endocrinol Metab* 2007; **92**: 4472–4475.
5 Rossi GP, Belfiore A, Bernini G, Fabris B, Caridi G, Ferri C, Giacchetti G, Letizia C, Maccario M, Mannelli M, Palumbo G, Patalano A, Rizzoni D, Rossi E, Pessina AC, Mantero F. Body mass index predicts plasma aldosterone concentrations in overweight-obese primary hypertensive patients. *J Clin Endocrinol Metab* 2008; **93**: 2566–2571.
6 Jeon JH, Kim KY, Kim JH, Baek A, Cho H, Lee YH, Kim JW, Kim D, Han SH, Lim JS, Kim KI, Yoon do Y, Kim SH, Oh GT, Kim E, Yang Y. A novel adipokine CTRP1 stimulates aldosterone production. *FASEB J* 2008; **22**: 1502–1511.
7 Rossi GP, Sticchi D, Giuliani L, Bernante P, Zavattiero S, Pessina AC, Nussdorfer GG. Adiponectin receptor expression in the human adrenal cortex and aldosterone-producing adenomas. *Int J Mol Med* 2006; **17**: 975–980.
8 Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A, Langenbach J, Willenberg HS, Barthel A, Hauner H, McCann SM, Scherbaum WA, Bornstein SR. Human adipocytes secrete mineralocorticoid-releasing factors. *Proc Natl Acad Sci USA* 2003; **100**: 14211–14216.
9 Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112**: 2735–2752.
10 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
11 Conn JW. Hypertension, the potassium ion and impaired carbohydrate tolerance. *N Engl J Med* 1965; **273**: 1135–1143.
12 Sowers JR, Whaley-Connell A, Epstein M. Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. *Ann Intern Med* 2009; **150**: 776–783.
13 Rossi GP, Sechi LA, Giacchetti G, Ronconi V, Strazzullo P, Funder JW. Primary aldosteronism: cardiovascular, renal and metabolic implications. *Trends Endocrinol Metab* 2008; **19**: 88–90.
14 Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 2004; **110**: 1245–1250.
15 Cooper JN, Fried L, Tepper P, Barinas-Mitchell E, Conroy MB, Evans RW, Mori Brooks M, Woodard GA, Sutton-Tyrrell K. Changes in serum aldosterone are associated with changes in obesity-related factors in normotensive overweight and obese young adults. *Hypertens Res* 2013; **36**: 895–901.