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Aldosterone, Hypertension, and Antihypertensive Therapy: Insights From a General Population

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Abstract

Objective: To investigate the relationships among aldosterone level, use of antihypertensive (anti-HTN) medications, clinical profile, and atrial natriuretic peptide (ANP) level in individuals with HTN.

Participants and Methods: In a community-based cohort, we analyzed aldosterone plasma levels based on the presence (n=477) or absence (n=1073) of HTN. In individuals with HTN, we evaluated circulating aldosterone levels according to the number of anti-HTN drugs used, analyzed the associated clinical characteristics, and determined the relationship to the counterregulatory cardiac hormone ANP. Data were collected from August 25, 1997, through September 5, 2000.

Results: Participants with HTN had higher serum aldosterone levels than those without HTN (6.4 vs 4.1 ng/dL [to convert to pmol/L, multiply by 27.74]; $P<.001$). When individuals with HTN were stratified according to the number of anti-HTN medications used, the increase in number of medications (0, 1, 2, and ≥3) was associated with higher aldosterone levels (4.8, 6.4, 7.10, and 7.9 ng/dL, respectively; $P=.002$), worse metabolic profile, and higher prevalence of cardiovascular, renal, and metabolic disease. In participants with HTN, ANP plasma levels were inversely related to aldosterone levels when the latter was divided into tertiles.

Conclusion: In this randomly selected general population cohort, aldosterone levels were higher in individuals with HTN compared with normotensive participants. Aldosterone levels increased with anti-HTN medication use. These findings also suggest a relative ANP deficiency with increasing aldosterone levels and anti-HTN drug use. These studies have pathophysiologic and therapeutic implications for targeting aldosterone in the clinical treatment of HTN.

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Aldosterone is a hormone that plays a fundamental role in intravascular volume and blood pressure (BP) homeostasis. Beyond its physiologic role and through activation of the mineralocorticoid receptor (MR), aldosterone may also exert actions leading to organ damage in the heart, kidneys, and vasculature.[1] Seminal studies by the Calhoun Laboratory have importantly advanced aldosterone as a key factor in hypertension (HTN), most importantly in resistant HTN.[2-4] Indeed, the successful use of the MR antagonist spironolactone in the PATHWAY-2 trial in individuals with resistant HTN led to the conclusion that aldosterone may be the predominant underlying pathophysiologic cause of resistant HTN through sodium retention.[5]

We recently reported in a general population study that plasma aldosterone levels, even within the reference range, are significantly associated with HTN as well as chronic kidney disease (CKD) and metabolic syndrome[6] and also predicted these diseases in the future.[7] The influence of aldosterone in early-stage HTN is also supported by Vasan et al,[8] who reported that increased aldosterone levels within the reference range are associated with new-onset HTN in participants without HTN.

Most recently, the American College of Cardiology and the American Heart Association (ACC/AHA) released the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.[9] In part, the new landmark recommendations were a product of the Systolic Blood Pressure Intervention Trial (SPRINT).[10] This seminal study validated the importance of optimizing anti-HTN therapy to achieve BP control (systolic BP [SBP] <120 mm Hg), improve survival, and reduce the onset of adverse cardiovascular (CV) outcomes in patients with HTN at high CV risk. The relevance of SPRINT to the general US population was recently supported by Bress et al,[11] who reported that a substantial percentage of US adults meets the eligibility criteria for SPRINT, supporting its generalizability to the general US population. Because the 2017 ACC/AHA guidelines propose more aggressive goals for treatment, a high priority is to better characterize the clinical phenotype of adults treated with 1 or more anti-HTN agents. The in-depth characterization could provide pathophysiologic and therapeutic insights, which may help optimize anti-HTN strategies. Furthermore, with the growing role of aldosterone as a therapeutic target as well as a biomarker in HTN, there is also a strong rationale to investigate the relationship between aldosterone levels and anti-HTN therapy in patients with HTN.

Hence, the present study used a well-characterized, randomly selected, adult, community-based cohort using the Rochester Epidemiology Project in Olmsted County, Minnesota.[12] We hypothesized that aldosterone levels would be increased in participants with HTN compared with those without a diagnosis of HTN. We also tested the hypothesis that aldosterone levels would be progressively higher with increasing number of anti-HTN drugs used. Last, based on previous studies, we hypothesized that in participants with HTN, plasma aldosterone levels would be characterized by an inverse relationship with the counter-regulatory hormone atrial natriuretic peptide (ANP).[6,13-15]

PATIENTS AND METHODS

Study Population

The Mayo Clinic Institutional Review Board approved this study, and the participants gave informed consent. Using the resources of the Rochester Epidemiology Project at Mayo Clinic, we analyzed a previously studied random sample of individuals from the general population of Olmsted County.[12] Specifically, 4203 residents were eligible for the study, and 2024 of these were enrolled. The design, selection criteria, and characteristics of this cohort have been previously described elsewhere.[16] A trained nurse abstractor reviewed the medical record for each participant and documented the clinical diagnosis of HTN, myocardial infarction (MI), coronary artery disease, or diabetes mellitus (DM). Each participant underwent an in-depth physical examination including measurement of BP, height, and weight. For the present study, 1550 individuals who underwent a visit between August 25, 1997, and September 5, 2000, were analyzed. All the participants had plasma aldosterone and ANP levels measured, and their use and number of drugs or nonuse of anti-HTN medications were carefully documented, with 1550 of the 2024 participants having both aldosterone and ANP levels available. Of the 1550 participants, 1073 were without a diagnosis of HTN and 477 had a diagnosis of HTN.

For anti-HTN therapy, we considered the following drugs: β-blockers (BBs), calcium channel blockers (including dihydropyridines and nondihydropyridines), vasodilators (including α_1-blockers, reserpine, and central α_2-agonists), angiotensin ll receptor blockers, angiotensin-converting enzyme inhibitors, and all classes of diuretics (thiazides, thiazides-like, loop diuretics, potassium-sparing, and MR antagonists). Lipid-lowering therapy was defined as the use of 1 or more of the following drugs: statins, fibrates, niacin, ezetimibe, and cholestyramine.

To better define associated phenotypes to aldosterone and HTN, body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) was defined using established criteria as previously described.[6] Obesity was defined as a BMI of 30 or greater. Waist circumference, measured at the top of the umbilicus, was expressed in centimeters, and central obesity was defined as waist circumference greater than 102 cm in men and greater than 88 cm in women. Hypertension was defined according to the use