Revisión

Hypertension in postmenopausal women. Role of androgens.

RODRIGO O. MARAÑÓN
Instituto de Fisiología de la Facultad de Medicina, Instituto Superior de Investigaciones Biológicas (INSIBIO).
Universidad Nacional de Tucumán y Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Tucumán.
(4000) San Miguel de Tucumán, Argentina.
E-mail

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Abstract

In Argentina, one in four women dies from cardiovascular disease (28%), being responsible for 46% of postmenopausal women's deaths worldwide. Hypertension (HTN) is the cardiovascular risk factor most related to mortality in this female population. From birth to menopause, women appear to be protected from cardiovascular events compared to age-matched men. This protection occurs most often during the fertile age of a woman, where estrogen would play an important protective role against cardiovascular events. Subsequently, during post-menopause, women equal and may exceed the prevalence of HTN and cardiovascular events. However, the cause of this difference between men and women still needs to be elucidated. Different theories highlight the protective role of estrogen; however, androgens may contribute to increased blood pressure after menopause. In this period, women would increase androgen levels by up to four-fold while reducing estrogen levels. The imbalance between androgens and estrogens would induce vascular, renal, cardiac, and brain functional and structural changes, which would contribute to the above. This review highlights the role of androgens as a possible causal factor for postmenopausal hypertension and discusses possible mechanisms that would participate in this process.
Key words: High blood pressure. Postmenopausal. Androgens.

INTRODUCTION

In Argentina, one in every four women dies due to cardiovascular disease (28%), being responsible for 46% of deaths in postmenopausal women in the world [1,2] . This scenario may worsen if it is taken into account that different estimations predict a significant increase in the female population in the future. Christensen et al, estimated that in developed countries, such as the United States and France, life expectancy will increase significantly. Thus, it is estimated that individuals born in year 2000 will live approximately 100 years [3]. Further, a study by Barton and Meyer projected an increase in both pre and postmenopausal female populations. However, the increase would be significantly greater for postmenopausal women, particularly the age group older than 80 years [4]. Consequently, it is expected for cardiovascular events in the female population to also increase.

DIFFERENCE IN GENDER AND HYPERTENSION

Hypertension (HTN) constitutes the risk factor most frequently associated to cardiovascular events [5]. From the point of view of gender, from birth and as age advances, the prevalence of HTN increases in men and women. Blood pressure is higher in men than in women until age 45, a period of life characterized by the appearance of menopause in women. From there, the prevalence of HTN is similar in both men and women until ages 50-55. At such time (postmenopausal age in women), blood pressure is higher in women than in men, particularly in those older than 75 years [6,7] . However, the mechanisms by which blood pressure changes with age in both genders are not completely clear.

There are different theories about the mechanism of gender difference in HTN. Growing evidence suggests that the decrease in estrogen levels and the

increase in androgen levels (estrogen/androgen relation) after menopause play a significant role in this process [8]. Experimental and clinical studies suggest that estrogens contribute to protection against HTN in the fertile period of women [9]. Estradiol would have genomic effects (modification in the synthesis of proteins and gene expression) and nongenomic effects (vasodilation by endothelial nitric oxide synthase (eNOS) activation), that may prevent the appearance of HTN and cardiovascular disease during such period [10]. However, during menopause and postmenopause, this protection disappears gradually, leaving women exposed to cardiovascular risk factors that lead to myocardial infarction, heart failure and stroke in the end [11].

HYPERTENSION IN POSTMENOPAUSAL WOMEN

In the last decade, different observational studies and large-scale clinical trials approached the effect of hormone replacement therapy (HRT) in postmenopausal women. For instance, Grady et al, presented a meta-analysis where they showed that HRT was associated to a third less of fatal cases of congestive heart disease [12]. Moreover, the Nurses' Health Study (NHS), performed in women with ages ranging from 30 to 55 years, showed a reduction in the general risk of congestive heart disease in women under hormonal treatment [13]. This study also suggested that short-term use presents a greater coronary benefit than long-term treatment [13].

On the contrary, the HERS I and II studies showed that hormone replacement therapy does not present any cardiovascular benefit in postmenopausal women; particularly to reduce or prevent HTN [14,15] . Likewise, other studies, including the Women's Health Initiative (WHI), showed that HRT not only did not yield any benefit, but even increased the incidence of thrombosis and cardiovascular diseases [16,17,18]. Currently, the most recent studies are showing a certain efficacy to control some cardiometabolic factors. Thus, in spite of current progress, the role of HRT on HTN and CV risk factors is still being investigated.

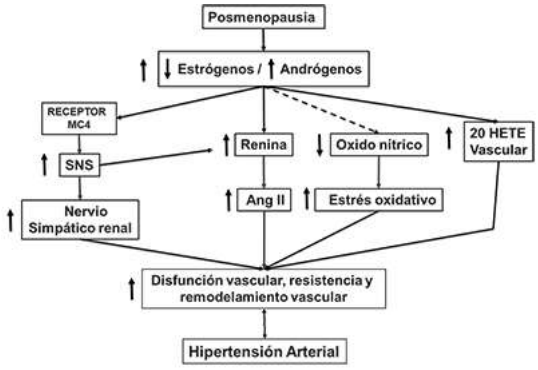
In the postmenopausal age, due to an imbalance between estrogens and androgens, women present a relative excess of androgens with deleterious effects on blood pressure during age *(Marañon RO, et al. 2013)* . From a physiological point of view, estradiol and testosterone decrease after menopause; but testosterone progressively increases until age 70, when the production of androgens is similar to premenopausal levels [19]. Thus, the origin of a relative excess of androgens in postmenopausal women and their role on blood pressure is being discussed.

In the postmenopausal period, women suffer an increase in androgens of up to four times the normal levels, which is accompanied by a reduction in estrogen levels. At this age, the organs that produce androgens in women are suprarenal glands and ovaries [20]. The evidence available shows that adrenal androgens start to decrease their levels at around age 30. At the time of postmenopause, their levels are half that of the fertile period (premenopause) [21]. Studies about the effect of dehydroepiandrosterone sulfate (one of the main adrenal androgens), show that low concentrations of this metabolite are associated to high mortality in postmenopausal women *(Davison SL, et al. 2005)* .

On the other hand, ovarian androgens start to decrease after adrenal androgens (around 40 years), reaching a 30% reduction in postmenopausal age *(Labrie F, et al. 1997)* . In spite of this reduction, androgens have been proposed as an alternative mechanism to develop hypertension in postmenopausal women or with hyperandrogenemia by another cause *(Hulley S, et al. 1998, 2002)*. Some authors hypothesized that, before the loss of the counterregulatory effect of estrogens, androgens would be free to exercise their deleterious cardiovascular effects more easily.

There are different theories about androgen action in postmenopausal women contributing to hypertension during old age. The increase in androgens would stimulate different systems contributing to the development and/or maintenance of postmenopausal hypertension [22]. Between the main mechanisms, the following stand out: increase in sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS) and endothelin system regulation, changes in arachidonic acid metabolites (20-HETE), increase in oxidative stress and metabolic syndrome/obesity [23,24,25]. These systems would increase their activity by an increase both in the levels and activity of androgens.

Postmenopausal women present a greater activity of the autonomic nervous system than premenopausal women and men at the same age [26]. During menopause, a bigger increase is observed in visceral fat, inducing a masculinizing body structure (**Figure 1**), behaving as an endocrine organ and releasing adipocytokines such as leptin, resistin, tumor necrosis factor alpha (TNFα) and interleukin 6 (IL6).



Leptin is considered a main factor of sympathetic nervous system activation. This would act activating the neurons of pro-opiomelanocortin, which in turn would activate the melanocortin ¾ receptor. Through such receptors, sympathetic nervous system activation would occur, accompanying increase in BP [27]. In experimental animals, it was observed that alpha- and beta-adrenergic receptors block in the sympathetic nervous system transitorily decreases blood pressure. Likewise, it was observed that renal denervation in these animals partially reduces blood pressure but does not normalize it *(Maranon RO, et al. 2014)*. Thus, these results suggest that sympathetic nervous activation, and particularly of the renal sympathetic nerve, contribute to postmenopausal hypertension.

Some studies have related the role of the renal sympathetic system with the renin-angiotensin-aldosterone system in blood pressure increase. In a study in our group, it was observed that the combination of renal denervation and angiotensin II receptor block in spontaneously hypertensive postmenopausal rats (SHR), was insufficient to reduce blood pressure to values below 140/90 mmHg [28]. This information suggests that in postmenopausal women, these

systems would act independently. On the other hand, the melanocortin ¾ receptor block, partly responsible for the sympathetic nervous system, would be capable of reducing blood pressure only in male experimental animals (SHR ~18 months of age); while it would have no effect on hypertensive females with the same age [29]. This, added to the increase of sympathetic nervous activity both in striated muscles and smooth muscles, prolongs for a longer time the vasoconstriction state that would foster the development and/or maintenance of postmenopausal hypertension. This evidence backs the possible existence of a gender difference in blood pressure regulation mechanisms, requiring further research.

Interestingly, one of the hypothesis that is against the previous one, suggests that it would be androgen deficiency, rather than hyperandrogenemia, that would enable structural changes in adipocytes. This fact would facilitate an increase in visceral fat due to increased lipid accumulation in adipocytes, which in turn, would cause cellular death followed by macrophage activation, production of cytokines and endothelial dysfunction [30]. NF-kB signaling pathway is possibly playing an important role in visceral adipocyte enlargement [31]. Thus, androgen deficiency would be one of the main determinants of HTN prevalence increase in elder men and in postmenopausal women, this would occur when the protective role of estrogens on fat ends [32].

Another alternative is that androgens may contribute with blood pressure elevation through 20-hydroxyeicosatetraenoic acid (20-HETE) [33]. In this case, the high levels of androgens would produce an increase in vascular 20-HETE, which in turn would produce more inflammation and oxidative stress. As a consequence, there would be an increase in renal vascular resistance and hypertension. In an animal model of hyperandrogenemia by polycystic ovary syndrome, it was observed that 20-HETE, through the CYP4A2 enzyme, contributes to the increase in blood pressure *(Dalmasso C, et al. 2016)*.

Similarly, in conditions of hyperandrogenemia, women develop metabolic syndrome with sympathetic nervous system activation, increase in renin-angiotensin activity and blood pressure elevation. Remarkably, renal denervation in these women reduces blood pressure; however, and in agreement with other studies, this procedure does not normalize it [34,35] . Therefore, future clinical studies are necessary to determine the mechanisms by which androgens contribute to postmenopausal hypertension.

CONCLUSIONS

The study of HTN in women is underestimated due to different reasons; one of the most important ones being the fact that in the past, in basic investigations and in many clinical trials, research is conducted on the male population or else, analysis was limited to the general population, not discriminating by gender. For this reason, more investigations are needed, to be able to understand the possible mechanisms contributing to postmenopausal HTN, since to this date, there is not enough data to make a personalized treatment according to the age and gender of patients. Further, there is no hypertension guideline available, whether American or European, that would propose personalized treatments according to the age of women.

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CONTACTENOS

Bulnes 1004 (C1176ABT) CABA, Argentina

+54 (11) 4866 5910

mesadirectiva@fac.org.ar