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HYPERTENSION AND HORMONAL STATUS

# Hypertension and Menopause

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## ABSTRACT

Hypertension is more common in postmenopausal females than males. As they move in postmenopausal state, a normal protection from cardiovascular (CV) disease is withdrawn and control of hypertension also becomes tougher despite being more sincere in blood pressure (BP) monitoring and treatment. They are more affected with nondipping in night, which reflects more target organ damage. Renin–angiotensin system activation may lead to postmenopausal hypertension though it is not the sole cause. Obesity is another causal factor as a component of metabolic syndrome, which also impacts outcome of antihypertensive therapy in postmenopausal females. Sympathetic activation increases BP, which is aggravated further by weight gain, increased leptin level, and age. Role of estrogen is not clear in normal protection of young females from CV risks or its low level in postmenopausal women with hypertension. Young girls with polycystic ovary syndrome have elevated serum androgens which are low after menopause but increases up to premenopausal level till 70 years of age and correlates with body mass index only in postmenopausal age. Increased serum testosterone correlates with risk of type 2 diabetes mellitus in postmenopausal females. Sympathetic activation with anxiety and depression may lead to hypertension which is established with metabolic syndrome also. Angiotensin-converting-enzyme inhibitors are used for BP for reducing anxiety and depression. Therefore, it needs different treatment approach for postmenopausal hypertension.

**Keywords:** Androgen, Anxiety, Depression, Diabetes, Estrogen, Hypertension, Menopause, Metabolic, Obesity, Renin-Angiotensin system.

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## INTRODUCTION

Aging in males and females can be identified by a rise in blood pressure (BP),[1-8] and the incidence of hypertension in postmenopausal women is greater than in males,[1-4] with 41% of postmenopausal females being hypertensive.[4] Globally, 25% of adult females become hypertensive,[5] and in the USA, greater than 75% of females over 60 years of age are hypertensive.[4,6,7] In trials involving the National Health and Nutrition Examination Survey (NHANES) IV (1999–2004) database, the proportion of subjects with uncontrolled BP was 50.8 ± 2.1% in males and 55.9 ± 1.5% in females, in spite of the fact that more females measured their BP in the last 6 months.[9] Moreover, a trial that compared the NHANES III cohort and the NHANES IV cohort concluded that hypertension was not much controlled in females than males; however, the therapy used to manage hypertension was same in males and females.[9] In addition, lesser fall of BP during night hours can be correlated with more target organ complications in males and females.[10-14] Therefore, nondipping in females is due to more target organ complications.[10,12] Postmenopausal females are more affected compared with males and premenopausal females in nocturnal nonreduction of BP.[10] Therefore, however, antihypertensive medications are not different in males and females, and females are more prone to have their BP assessments, hypertension is likely to be lesser managed in females. This can predict that females may not be as actively managed in hypertension.

## SIGNIFICANCE OF RENIN–ANGIOTENSIN SYSTEM IN HYPERTENSION IN WOMEN

Activation of the renin–angiotensin system (RAS) can be postulated as the process through which BP increases in aging postmenopausal females. In postmenopausal females, plasma renin activity is increased,[14,15] which shows the increase in RAS activity. Moreover, in postmenopausal women, due to hereditary reasons, RAS activation may lead to postmenopausal hypertension between the age group of 40 and 70 years; however, it is not seen in males.[16] Studies suggested that RAS activation is not the sole contributor in the postmenopausal BP increase.[16] For postmenopausal hypertension, it can be described as mediator.

## IMPACT OF OBESITY IN POSTMENOPAUSAL HYPERTENSION

Obesity may be another causal factor of hypertension in postmenopausal females.[17,18] Obesity is the integral part of the group of metabolic disorders called as the metabolic syndrome which contains insulin resistance, type 2 diabetes, dyslipidemia, and hyperleptinemia, all of which are known to cause hypertension.[17,18] The incidence

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of obesity is close to 40% in postmenopausal women.[19] Obesity is more prevalent and prone to increase after surgical menopause and in females who have been prescribed hormone replacement therapy within 12 months of amenorrhea.[20]

There are also incidences where females have not gained extra weight after menopause and the body fat has been redistributed, leading to a rise in abdominal fat compared with subcutaneous fat in the hips region.[21] Weight that assimilates in the abdomen is responsible for increased prevalence of cardiovascular (CV) disease than weight, i.e., assimilated in the lower region of body.[22] Rossi et al[22] concluded that decrease in endothelial dysfunction and inflammation seen due to antihypertensive therapy in postmenopausal females aged 47 to 60 years who had signs and symptoms of the metabolic disorder. Therefore, metabolic disorders may not cause only hypertension but may also affect the outcome of antihypertensive medications in postmenopausal females.

## SIGNIFICANCE OF SYMPATHETIC ACTIVATION IN POSTMENOPAUSAL HYPERTENSION

Weight gain, plasma leptin levels, and increased age are the causal factors for sympathetic activation.[23-26] Moreover, studies suggested[27] that the sympathetic nervous system has a role in increasing BP with increased weight. In addition, obesity can be correlated with increases in plasma leptin levels,[23,26] and infusion of leptin rises BP in animals.[23] Inhibition of the sympathetic nervous system may decrease hypertensive activity,[26] thereby indicating leptin in sympathetic activation.

Leptin has been hypothesized to enhance the sympathetic nervous system via activation of melanocortin 4 receptors in proopiomelanocortin neurons in the hypothalamus.[24,27] Inhibition of these receptors decreases BP in obese rats.[27] Such kind of studies suggested that obesity and increased leptin levels can lead to hypertension in pre- and postmenopausal females via activation of the sympathetic nervous system.

## IMPORTANCE OF ESTROGEN/ANDROGEN RATIOS IN HYPERTENSION IN WOMEN

Estrogen levels are controversial in the protection against hypertension in premenopausal females, and the effect of decreased estrogen levels on hypertension in postmenopausal women is also controversial. Olszanecka et al[28] evaluated ambulatory BP in normotensive and hypertensive females aged 40 to 60 years and concluded that there is no difference in BP in normotensive and hypertensive subjects irrespective of menopausal status. Coincidently, there have been no studies wherein ambulatory BP has been evaluated periodically over the perimenopausal phase in order to document any BP change with menopausal phase.

It is unclear whether the estrogen levels save young females from high BP or decreased estrogen levels favor endothelium-dependent, flow-mediated vasodilation hypertension in postmenopausal women. Studies concluded that decreased estrogen level leads to endothelial dysfunction irrespective of age, and is prevalent in population with high BP. Young females with polycystic ovary syndrome have increased levels of plasma androgens with normal plasma estradiol levels, which can be correlated with elevated risk of CV disease in pre- and postmenopausal periods.[28-30] Studies have concluded that serum androgens are low after menopause, but till 70 years of age, they are gradually increased to levels found in premenopausal women.[31] The ovary in postmenopausal females is a main contributor of androgens;[32,33] however, studies concluded that nonproductive tissues like kidney also produce androgen.[34] Moreover, in postmenopausal females, serum androgen levels increase with increase in body mass index (BMI); on the contrary, it has not been seen with premenopausal females.[35] In addition, with increases in BMI and obesity, androgen levels have also been decreased in males.[36]

Moreover, increased serum testosterone levels can be correlated with increased risk of type 2 diabetes in postmenopausal females, on the contrary, not seen in age-matched males.[37]

## SIGNIFICANCE OF ANXIETY AND DEPRESSION IN HYPERTENSION IN WOMEN

Anxiety and depression may be the risk factors for hypertension, and it has been seen that females who are hypertensive may have increased incidences of anxiety and depression. Depression and anxiety incidences occur at much increased rate in females than in males.[38] Depression and anxiety can be correlated with increased risk of CV disease and other metabolic disorders. For instance, patients with bipolar abnormalities have an added risk of hypertension.[39] Sympathetic activity can be upregulated with anxiety and chronic mental stress, which may lead to hypertension. This correlation has been established in patients with metabolic syndrome and hypertension.[40] Increased BP was also seen due to enhanced levels of anxiety in a small Spanish cohort.[41] Moreover, angiotensin-converting-enzyme inhibitors used for the management of hypertension have been seen to decrease the incidence of depression with anxiety.[42] The mechanisms pertaining to the cause of chronic anxiety and depression and its correlation to hypertension in postmenopausal females are not clear and should be studied further.

## CONCLUSION

Hypertension in postmenopausal females has many etiologies and risk factors. Females are much more compliant to the advice of health-care providers and stick to their pharmacotherapy. On the contrary, hypertension in this group is not very well-controlled compared with age-matched men, which suggests that different pathophysiologic mechanisms may be involved and different management approach is required compared with the strategies that are successful in men, for the management of hypertension in postmenopausal females.

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