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REVIEW

Gender Differences in Hypertension

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Abstract

Hypertension is the leading risk factor for global mortality and morbidity and remains the major preventable cause of cardiovascular diseases. Gender differences in risk factors and awareness, treatment, and control of hypertension have been well established in humans. There are significant differences in epidemiology and clinical characteristic of hypertension between men and women. Moreover, gender differences are linked with several specific types of hypertension, including postmenopausal hypertension, white coat hypertension, masked hypertension, and hypertensive disorders of pregnancy. Gender differences have been implicated in the prevalence and determinants of hypertension and prehypertension whereas the control rate is similar between men and women taking antihypertensive medication. Importantly, distinct roles of the angiotensin-converting enzyme 2/Apelin signaling, sex hormone, endothelin-1, and sympathetic nervous activity contribute to sex differences in blood pressure control. This review summarizes gender differences in clinical features and determinants of hypertension and the underlying mechanisms responsible for hypertension.

Keywords Hypertension · Gender difference · Renin-angiotensin system · Sex hormone · Endothelin-1 · Immune system

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACE2	Angiotensin-converting enzyme 2
ACEI	Angiotensin-converting enzyme inhibitor
AHA	American Heart Association
Ang-(1–7)	Angiotensin 1–7
AngII	Angiotensin II
ARB	Angiotensin receptor blocker
AT1	Angiotensin II type 1 receptor
AT2	Angiotensin II type 2 receptor
BP	Blood pressure
CCB	Calcium channel blockers
CVD	Cardiovascular diseases
DBP	Diastolic blood pressure
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ET-1	Endothelin-1
LIFE	The Losartan Intervention For Endpoint Reduction in Hypertension Study
MH	Masked hypertension
NO	Nitric oxide
NHANES	National Health and Nutrition Examination Survey
RAS	Renin-angiotensin system
SBP	Systolic blood pressure
SNA	Sympathetic nervous activity
WCH	White coat hypertension

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Introduction

Hypertension is a prominent risk factor for global mortality and morbidity and has been broadly associated with cardiovascular diseases (CVD) such as atherosclerosis, acute myocardial infarction, and cardiomyopathy [1, 2]. Blood pressure (BP) control rates remain poor worldwide and are far from satisfactory. Consequently, hypertension remains the major preventable cause of CVD and all-cause death globally.

Hypertension directly contributes to stroke, ischemic heart disease, and other CVD [1]. Meanwhile, hypertension indirectly aggravates heart failure and kidney dysfunction with gender differences at an early age around the world [2]. The prevalence, awareness, treatment, and control of hypertension are greatly different between men and women. Men have lower levels of hypertension awareness and a higher incidence of hypertension compared with age-matched women before the sixth decade of life [3]. According to the National Health and Nutrition Examination Survey (NHANES), there is a greater improvement in awareness and treatment of hypertension in younger adults, along with lower BP control rate among young adults, especially in young men [3]. Specific guidelines for hypertension treatment in women and men have not yet to be developed [4]. The major mechanisms responsible for hypertension play a different role in men and women, including the renin-angiotensin system (RAS), the sympathetic nervous activity (SNA), sex hormones, endothelin-1 (ET-1), and the immune system [4–6]. This review will focus on sex differences in clinical features and determinants of hypertension and the underlying mechanisms responsible for hypertension.

Gender Differences in Epidemiology of Hypertension

It is well established that prevalence of hypertension differs between men and women with advancing age [1, 3, 6]. In China, 23.2% of the adult population aged ≥ 18 years had hypertension and another 41.3% had prehypertension according to the Chinese Hypertension Guidelines [6]. The awareness, treatment, and control rates of hypertension were higher among women in China than men (51.9% vs. 42.5%, 46.6% vs. 35.6%, and 17.7% vs.13.2%, respectively), with no control rate difference between men and women taking antihypertensive drugs (37.0% vs. 38.0%). The weighted prevalence of hypertension was higher in men than in women (24.5% vs. 21.9%) and was more than two times higher in obese individuals compared with those of normal weight (44.5% vs. 15.4%) [6]. In the USA, men have higher incidence of hypertension until the age of 45 years, men and women have similar rate from the age of 46 to 64 years, and hypertension is more prevalent in women than men after 65 years old [7]. According to the Framingham Heart Study, prevalence of hypertension and drug treatment increased with advancing age, whereas BP control rates were markedly lower in older women with BP levels less than 140/90 mmHg. For ages younger than 60 years, 60 to 79, and 80 years and older, respectively, control rates were 38%, 36%, and 38% in men and 38%, 28%, and 23% in women [8]. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), 34.5% of men and 33.4% of women over the age of 20 were defined as hypertensive in the USA [7]. The data from the NHANES revealed that men had a much higher prevalence of prehypertension compared with women (45% vs. 27%) [3, 7]. A recently published report of 250,741 individuals (120,605 men and 130,136 women) from 13 countries demonstrated that the pooled prevalence of prehypertension was 40% among men vs. 33% among women [9]. 52.5% of men and 74.3% of women with hypertension are aware of their hypertensive condition, 36.1% of men and 62.1% of women are taking prescribed medications to reduce BP, but only 21.1% of all achieve target goals in a cross-sectional survey from the Southern Cone of Latin America [10]. Taken together, gender differences in the epidemiology of hypertension indicate distinct clinical characteristic of hypertension in both men and women.

Gender Differences in Clinical Characteristic of Hypertension

Arterial pressure shows a circadian rhythm performed by 24-h ambulatory blood pressure monitoring (ABPM) in healthy humans [11, 12]. Adolescent nocturnal systolic BP (SBP) was significantly lower in women in all cycles of their menstrual cycle than in men [11]. Diurnal SBP in men was significantly higher than in women in their follicular phase [11]. Notable gender differences are associated with the age-related progression of diurnal and nocturnal hypertension. Generally, mean values of SBP and frequency of nocturnal hypertension are lower in young women compared with age-matched men without observation in the elderly. In addition, women are more likely to reduce dipping patterns than age-matched men [12]. The absence of nocturnal dipping is associated with a greater left ventricular mass index in women with hypertension than in men [13]. Gender differences in clinical characteristic of hypertension are explained by the hemodynamic mechanism of BP disparate in women and men.

Gender Differences in the Treatment and Prognosis of Hypertension

European Society of Cardiology/European Society of Hypertension (ESC/ESH) recommended thiazide-diuretic, calcium channel blockers (CCB), angiotensin-converting enzyme (ACE) inhibitor (ACEI), or angiotensin receptor blocker (ARB) as first line of antihypertensive therapy [14]. Women with hypertension are more likely to be prescribed diuretics, whereas men with hypertension are inclined to take β-blockers, ACEI and CCB [15]. In the German Health Examination Surveys, younger women are more often prescribed β-adrenergic receptor blockers and less ACEI than

men. Women are less likely to be treated β-blockers, CCB, or ACEI than diuretics compared with men when it comes to antihypertensive monotherapy. Gender differences in side effects may be a possible explanation of these choices of antihypertensive drugs. Women treated with ACEI are more likely to cough and more susceptible to vasodilatation related to dihydropyridine CCB than men [16]. Both reduction of diastolic BP (DBP) levels and the control rate of hypertension were greater in women in a prospective study by investigating the effects of amlodipine monotherapy than in men [15]. In addition, the ARB plus hydrochlorothiazide combination resulted in much lower levels of BP in women than in men [15]. Although the number of women received antihypertensive treatment is more than that of men, the control rate of hypertension and BP target-achievement rate in women received antihypertensive treatment are found to be less than those of men. Importantly, significant differences in response to antihypertensive drugs exist between men and women [17]. In the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study, more women required hospitalization for angina in the losartan group than in the atenolol group, whereas no such difference appeared among the men [17]. Compared with atenolol-based treatment, losartan-based treatment resulted in fewer overall cardiovascular events and stroke, reduced total mortality, and less new-onset diabetes in women with hypertension. Moreover, women in the LIFE study had more adverse events but fewer serious antihypertensive drug-related adverse events than men [17], suggesting that antihypertensive drugs have gender-specific adverse profiles.

Gender Differences in Hypertension Guidelines

Hypertension is characterized by office SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg according to ESC/ESH Guidelines in 2018 [14]. Gender difference in hypertension is first reported in university students where men have consistently higher BP compared with women [7]. Recently, the majority of guidelines recommend similar type and dosage of drugs for women and men with hypertension in all age groups without detailed description about target goals and choice of antihypertensive drugs in two genders [7]. The JNC7 report did not mention antihypertensive therapy in postmenopausal women with hypertension and pregnancy-associated hypertension [18]. The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines in 2017 defined hypertension as at least 130/80 mmHg and recommended the antihypertensive treatment goals should be less than 130/80 mmHg for both men and women with various complications [19]. The 2017 ACC/AHA Guidelines focus on special issues related to gender differences in hypertension such as postmenopausal women with hypertension and pregnancy-associated hypertension [19]. However, it is not able to predict individual responsiveness to antihypertensive medication by gender [20]. The AHA Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women showed similar recommendations to prevent CVD between women and men [21]. Although the relationship of postmenopausal women with hypertension and pregnancy-associated hypertension, oral contraception, and hormone replacement therapy exist, the treatment of hypertension is not described in detail for men and women in the 2018 ESC/ESH Guidelines [14]. It is necessary to focus on gender differences to provide different antihypertensive treatment between men and women for hypertension guidelines in the world.

Postmenopausal Hypertension

Hypertension is the leading cause of morbidity and mortality in postmenopausal women. There is evidence that changes in estrogen/androgen ratios favoring increases in androgens, activation of the RAS, SNA and ET-1 systems, inflammation, increased vasoconstrictor eicosanoids, and anxiety and depression may be important in the pathogenesis of postmenopausal hypertension [22–24]. There is evidence that hypertension is less well controlled in aging women than in aging men, but the reasons for this gender difference are not clear. Estradiol is an antihypertensive sex hormone in the development of postmenopausal hypertension by promoting nitric oxide (NO) production and reducing angiotensin II (AngII) type 1 receptor (AT1) and ET1 receptor levels [24]. Transdermal estrogen replacement is associated with a slight reduction of mean night-time SBP in women with postmenopausal hypertension [25], suggesting beneficial effects of estrogen replacement therapy on BP regulation in postmenopausal women.

Pregnancy-Associated Hypertension

Pregnancy-associated hypertensive disorders are leading causes of maternal and fetal mortality. Since improving maternal and child health outcomes is a public health priority worldwide, the main aim of treatment of hypertension in pregnant women is to prevent complications during pregnancy, labor, and postpartum [14, 26, 27]. Thus, much attention is paid to the use and safety of antihypertensive drugs during pregnancy [28, 29]. However, there is no definite conclusion about the optimal BP threshold at which to initiate antihypertensive treatment and the target goals in most of guidelines on the management of pregnancy-associated hypertension [27]. There is controversy about antihypertensive benefits for mild-to-moderate pregnancy–associated hypertension based on the adverse outcomes of antihypertensive drugs, particularly for those that aggressively

lower BP. In addition, there is no evidence that antihypertensive treatment improves maternal or fetal outcomes for mild-to-moderate pregnancy-associated hypertension [28]. Although less-tight control is associated with a significantly higher frequency of severe maternal hypertension, less-tight control of maternal hypertension in pregnancy shows no significant difference in the risk of adverse perinatal outcomes compared with tight control [18]. Currently, methyldopa and labetalol are regarded as the first-line therapy for women with pre-pregnancy and pregnancy [14]. Sublingual nifedipine is frequently prescribed in pregnancy-associated hypertension by reducing the incidence of severe hypertension without an increase in adverse perinatal outcome [30]. In general, there is a less restricted target goal in women with hypertensive disorders of pregnancy. Women with a normal body mass index choose to discontinue the use or reduce the doses of antihypertensive medication in patients with mild-to-moderate pregnancy-associated hypertension.

Gender Differences in White Coat Hypertension and Masked Hypertension

The detection of white coat hypertension (WCH) and masked hypertension (MH) depends on both 24-h ABPM and office BP [31–33]. WCH is characterized by high office BP levels but normal BP by 24-h ABPM [32]. The prevalence of WCH is negatively correlated with age and waist circumference, whereas positively correlated with smoking and alcohol usage. Among the general public, WCH is more common among women [31]. It is generally regarded as a stress-related alarm reaction to the circumstances of clinical measurement [32]. MH is characterized by normal office BP but high BP levels by 24-h ABPM. The characteristics of MH are associated with relatively young age, male sex, stress, or increased physical activity during the daytime. It is reported that male is associated with increased prevalence of MH [33]. MH has been described in treated hypertensive patients and in children, indicating a precursor of sustained hypertension in youths [33]. Furthermore, the risk of developing sustained hypertension is higher in young men with MH than in young women. Meanwhile, the yearly rate of SBP increment is much higher in young men than age-matched young women [34]. These findings show gender difference in MH with significant influence factors such as growth pattern and sex hormones.

Roles of the RAS in Gender Differences in Hypertension

The RAS is one of the most crucial mechanisms known to be responsible for gender differences in development and control of hypertension [35–39]. There were lower levels of classical AngII-AT1-ACE axis activation and higher levels of activation of the non-classical ACE2-Ang-(1–7)-Mas axis in hypertensive female rats than in male [35]. Importantly, the AT2 receptor has a depressor influence on the response to chronic AngII infusion in female hypertensive rats but not in male (Table 1) [36]. AngII infusion contributes to higher BP levels in male mice compared with female mice. Notably, these sex differences were abolished in AT2 receptor knockout mice, indicating cardiovascular protective roles of AT2 in young female mice [37]. A kidney transplant study was performed to determine the role of the RAS in mediating the sex differences in hypertension in mice where the same-sex kidney transplant in C57Bl/6 mice had a greater pressor response to AngII infusion in male mice than in female [38]. Kidney transplant from male to female augmented the pressor response to AngII whereas transplanting female kidneys to male attenuated the pressor response to AngII. The pressor responses to AngII in female kidney transplanting into male were lower than male to male or male to female. Meanwhile, the levels of AT1 receptor were increased in female to male transplant, whereas decreased in male to female transplant [38], implicating regulatory roles of both sex chromosome and sex hormone in the AngII-mediated pressor response. ACE2 is a monocarboxylic peptidase which converts AngII into Ang-(1–7) [39, 40, 48]. Apelin is a second substrate for ACE2 as a cardiovascular protective peptide [48]. Both ACE2 and Apelin locate on the X chromosome in human and play a crucial role to BP control, exerting protective effects through modulating inflammation, fibrosis, and cardiovascular remodeling [39, 48]. ACE2 genetic variants may be the determinants of circulating Ang-(1–7) levels in women with hypertension. The rare alleles of ACE2 rs2074192 and rs2106809 were associated with reduced circulating Ang-(1–7) levels in female hypertensive patients (Table 1) [40]. ACE2 haplotype CAGC was associated with elevated circulating Ang-(1–7), whereas TAGT was associated with reduced circulating Ang-(1–7) levels in female hypertensive patients (Table 1) [40]. The analysis of single nucleotide polymorphisms of the ACE2/Apelin signaling may provide a new approach for recognizing the sex differences in hypertension.

Roles of Estrogens and Androgens in Gender Differences in Hypertension

It is well established that sex hormones play an important role in BP regulation. Both endogenous and exogenous estrogens have been shown to reduce BP levels in postmenopausal women with hypertension (Table 1) [42]. Ovariectomy operation promoted SBP levels in female rats which were reversed by estrogen replacement therapy with 17β-estradiol through promoting vasodilatation and enhancing vascular

Table 1 Gender differences in mechanisms responsible for hypertension

Associated mechanisms	Experimental models/population study	Gender differences in hypertension	References
AT2 receptor	Female rats with hypertension	Lower BP levels in female hypertensive rats than in male	Hilliard et al. 2011 [36]
ACE2	Patients with hypertension	Reduction of circulating Ang-(1–7) levels in hypertensive women with SNPs of ACE2 (rs2106809 and rs2074192) and ACE2 haplotype TAGT Enhancement of circulating Ang-(1–7) levels in hypertensive women with ACE2 haplotype CAGC	Chen et al. 2018 [40]
SNA	SHR	Lower BP levels in female SHR than in male	Maranon et al. 2014 [23]
Th17/Tregs	SHR	Higher Th17 cell and lower Tregs levels in female SHR than in male	Tipton et al. 2012 [41]
Estrogens	Postmenopausal women with hypertension	Lower BP levels in postmenopausal women with hypertension by endogenous and exogenous estrogens therapy	Reckelhoff 2001 [42]
	Female Sprague Dawley rats	Reduction of BP levels by estrogen replacement therapy with 17β-estradiol	Hernandez et al. 2000 [43]
Androgens	Hypertensive rats	Enhancement of BP levels in rats treated with testosterone	Reckelhoff et al. 2000 [44]
	SHR	Reduction of BP levels in hypertensive rats treated with castration	Dubey et al. 2002 [45]
ET-1	Population study	Higher levels of ET-1 in men than in age-matched women	Tostes et al. 2008 [46]
	Hypertensive rats	Higher levels of $ET\text{-}_{1A}$ in male hypertensive rats than in female	Intapad et al. 2015 [47]

BP, blood pressure; *ET-1*, endothelin-1; *Tregs*, T regulatory cells; *AT2*, angiotensin type 2; *ACE2*, angiotensin-converting enzyme 2; *SNP*, single nucleotide polymorphisms; *SNA*, sympathetic nervous activity; *SHR*, spontaneously hypertensive rats

conductance (Table 1) [43]. Furthermore, estrogens cause vasodilatation and reduce BP levels through increasing the activation of endothelial NO synthase/NO signaling. Administration of 17β-estradiol lowers BP levels in rats indirectly through inhibiting the synthesis of potent vasoconstrictors such as AngII and ET-1 [43]. Androgen supplements contribute to higher BP levels in female normotensive rats compared with male rats. Moreover, the association between testosterone and hypertension is supported by recent observation that castration attenuates development of hypertension in 3- or 5-week-aged spontaneously hypertensive rats (SHR) (Table 1) [45]. Chronic treatment with testosterone resulted in irreversible increases in BP levels in castrated male rats, normotensive female rats, and ovariectomized female hypertensive rats (Table 1) [44]. These observations indicate critical roles of sex hormones in gender differences in hypertension.

Roles of ET-1 in Gender Differences in Hypertension

ET-1-mediated vasoconstriction has been linked to the etiology of hypertension by increased ET_{1A} and/or reduced ET_{1B} activity through enhancement of vasodilatation of NO. The ET_{1A} receptor is higher in male hypertensive rats than in female (Table 1) [47]. Both ET_{1A} selective and dual $ET_{1A/B}$ antagonists decrease BP levels, whereas selective ET_{1B} antagonist increases BP in male hypertensive rats [49]. In addition, middle-aged and older men are under greater ET_{1A} receptor-mediated vasoconstrictor tone than age-matched women. Since the ET_{1A} receptor is the predominant receptor subtype in the vasculature, this sex difference in vasoconstrictor tone may be a mechanism contributing to sex difference in the prevalence of hypertension in middle-aged and older adults (Table 1) [46]. Estrogens suppress ET-1 expression, whereas testosterone promotes ET-1 release [50], suggesting the interactions among ET-1 and sex hormone in hypertension.

Roles of the SNA in Gender Differences in Hypertension

β-adrenergic receptor antagonists associated with SNA are common antihypertensive medications prescribed to men and women [5, 51]. Balance of the variability in SNA is mediated by vascular adrenergic responses in individuals. There were lower BP levels in both young and old female SHR pretreated with α1, β-adrenergic receptor blockade than in male (Table 1) [23]. Surprisingly, transduction of SNA into vasoconstriction is offset partially by opposing β-adrenergic vasodilatation in healthy young women [52]. The protective effect of the β-adrenergic receptors is lost in postmenopausal women and young men [52]. Both β-blockers and renal denervation attenuated the hypertension more in old female SHR than young female rats with hypertension [5, 23]. Intriguingly, renal denervation reduced BP levels in aged female SHR and caused a further reduction in BP levels by losartan treatment [5]. These data suggest that hypertension in old female SHR is in part due to activation of the SNA and that renal nerves contribute to hypertension in old females.

Roles of Immunoregulatory Cytokines in Gender Differences in Hypertension

Hypertension is considered as a state of low-grade inflammation by enhancing pro-inflammatory cytokines and facilitating infiltration of immune cells [53]. Administration of the immunosuppressant mycophenolate mofetil led to a decrease in BP levels in both male and female, with greater roles in female [54]. Women have a stronger responsive immune system because of incomplete inactivation of their XX chromosomes that host many genes related to the immune function regulation [55]. Sex differences have been reported in T cells in patients with hypertension. Activation of T cells in the kidney results in the development of hypertension in male. AngII infusion induces higher BP in male mice than female, whereas the sex differences disappear in T cell-deficient mice [53]. Importantly, adoptive transfer of male T cells into T cell-deficient mice exacerbates hypertension in male but not female recipient mice, indicating regulatory roles of sex of the host in susceptibility to immune modulation of hypertension [56]. Healthy women have higher levels of circulating cluster of differentiation (CD) 4–positive ($CD4^+$) T cells than men. Meanwhile, isolated $CD4^+$ T cells from women produce more interferon-γ and lower interleukin-17 levels than from men [53]. Sex differences in renal T cell subpopulations have been reported in SHR. Female SHR had more circulating $CD3^+$, $CD4^+$, and pro-inflammatory $CD3^+/CD4^+/ROR_\Gamma{}^+$ Th17 cells, whereas male had more immune-suppressive $CD3^+/CD4^+/Foxp3^+$ T regulatory cells (Table 1) [41]. Regardless, more clinical studies are needed to fully define T cell phenotype and function in both healthy and hypertensive men and women and improve the control rate of hypertension in a sex-dependent manner.

Conclusion

Hypertension is often termed the “silent killer” as a major risk factor for coronary artery disease and stroke and contributes significantly to cardiovascular and renal morbidity and mortality in both men and women. Gender differences exist in the prevalence, awareness, therapy, and prognosis of hypertension and underlying mechanisms responsible for hypertension. However, present hypertension guidelines rarely focus on the gender differences in

hypertension management. Enormous efforts have been made to understand the potential mechanisms responsible for hypertension in two genders. A thorough comprehension of gender differences in hypertension could provide optimal therapeutic agents. Targeting the ACE2/Apelin, estrogens, and ET-1 signaling represents novel therapeutic approaches against hypertension in both sexes, particularly among women. More strategies are required to further improve care of patients with hypertension across the world.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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