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Gender differences in hypertension awareness, diagnosis and treatment

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Abstract

Introduction: Hypertension is most important risk factor for cardiovascular disease (CD) and stroke, two of the leading causes of death in adults worldwide. Even though over last decade there has been improvement in increasing the awareness, treatment, and control of hypertension, undiagnosed and uncontrolled hypertension remain one of main public health challenges. In order to make progress in dealing with this problem it important to understand in which areas of the treatment strategy appropriate changes have not yet been implemented. First step to do this is to improve our understanding of the factors that affect the treatment and control of hypertension. International Guidelines for hypertension recommend the same hypertension management for both sexes, however studies reveal that there are actual differences in hypertension management.

Purpose of the study: The aim of this study was to conduct a paper review to provide most comprehensive contemporary estimates of sex differences in the awareness, treatment, and control of hypertension.

Material and method: A literature review was conducted in English language databases, based only on original articles, regarding awareness, control and treatment of hypertension, using key words: 'hypertension', 'sex-differences', 'hypertension treatment', 'gender gap', 'public health'.

Results and conclusions: Based on researched studies we can state that woman have higher awareness, treatment and control rates for hypertension than men worldwide [4,5,6,7,8,9,10]. This suggests that, the guidelines for the treatment and management of hypertension should be gender specific.

Keywords: Public health; sex difference; hypertension; cardiovascular disease.

Introduction: Hypertension is a major cause of premature death worldwide. According to World Health Organization (WHO; 2022) 46% of adults is unaware that they have hypertension and less than half of grownups (42%) is diagnosed and treated [1]. High blood pressure (BP) is the most important modifiable risk factor for cardiovascular disease which increases the mortality rate. Blood pressure lowering significantly reduces cardiovascular risk across various baseline blood pressure levels and comorbidities [2]. Despite considerable improvement in increasing the awareness, treatment, and control of hypertension, undiagnosed and uncontrolled hypertension remain one of the biggest public health challenges [1]. Therefore it is essential to ensure that diagnosis and appropriate treatment of hypertension is personalized to patients, in an effort to reduce cardiovascular disease and mortality.

In order to develop effective treatment strategies, it is crucial to identify factors that affect control of hypertension. To factors that are well known to affect BP belong sociodemographic factors, health status (diabetes mellitus, hyperlipidemia), health- related behavioral choices (smoking, drinking) and obesity [3]. However other studies suggest that the gender differences should be taken into consideration when planning effective treatment of hypertension. Thus, this paper review aims to provide comprehensive contemporary knowledge of sex differences in the awareness, treatment, and control of hypertension.

Methods

English language databases (PubMed, The Lancet, Springer) were searched for original studies regarding awareness, treatment, and control of hypertension separately for women and men worldwide. Additional following criteria were acquired: Meta- Analysis, Clinical trial, using keywords: hypertension, gender differences, sex differences. All recent (since 1997 to 2022) studies that met our criteria were studied in order to deliver most adequate and up-to-date paper review. Only studies meeting our criteria were taken into consideration.

Results

Sex differences in the awareness of hypertension

Awareness of hypertension was defined in studies as self-report of patients before any diagnosis of hypertension, therefore it has a great significance as precursor of starting treatment. According to Egam et al. (2010), a study representing a probability sample of the US civilian population, hypertension awareness increased with time in men but not women, however was greater in women than men [4]. Moreover the systematic review with meta-analyses, which included over 2 million individuals in China, states that women consistently had greater awareness of hypertension than men [5]. This findings are coherent with data from the Bangladesh Demographic and Health Survey (BDHS 2011), which found higher hypertension awareness and medication use among women, similar to a previous report from Bangladesh [6]. Data presented in research performed in Germany, state that men in general, especially younger men, tend to have lower awareness in hypertension than women [8]. Moreover 64% of Canadian men aged 18 to 34 years are not aware of their hypertension, compared with only 19% of Canadian women [9]. Only data from research based on nine hundred and fifty-nine participants over 39 years old, living in Porto, were incoherent with previous noted findings. This study reported that no gender differences were observed among hypertensives aware of their condition [24]. As presented in Table 1 majority of researched studies show that men are less likely to be aware of having hypertension [4,5,6,7,8,9].

Table 1. *Sex differences in awareness of hypertension based on researched publications.*

Study	*Female*	*Male*
	Awareness of hypertension	
US population, National Health and Nutrition Examination Survey (NHANES)- Egan et al. (2010)	Higher	Lower
China population – Redfern et al. (2019)	Higher	Lower
Bangladesh Demographic and Health Survey (BDHS 2011) – Rahman et al. (2017)	Higher	Lower
Germany- Sarganas et al. (2016)	Higher	Lower
Canada – Joffres et al. (1997)	Higher	Lower
Porto- Lunet et al.(2002)	No difference	No difference

Sex differences in control of hypertension

First of all, most studies assumed, that hypertension was considered as controlled if participants had a systolic BP of <140 mmHg and diastolic BP of <90mmHg.

Majority of reviewed studies states that women consistently had better control of their hypertension than men [4,5,7,8,10]. Moreover, other aspects of gender differences in control of hypertension are being raised. Rahman et al. (2017) states that medication use among women was higher, however working women were disadvantaged because of their low use of antihypertensive treatment (AHT), compared with non-working males. Bangladesh study findings substantiated the general consensus that while women are aware about having hypertension, this does not translate into adequate BP control. This sex-disaggregated analysis showed older females had poor BP control compared with older males (36 vs. 46%) and younger females (AOR 0.67). Furthermore, it was found that overweight males had better BP control than overweight females [6].

Positive findings published by Sarganas et al (2016), showed improvement of control of hypertension among the treated adults in all age- gender groups. Unfortunately, the magnitude of the improvement was only half as large in younger men compared with the other three age–gender groups (older men, younger women and older women). This study revealed a new gender gap in control of hypertension, among those treated for hypertension in age group 18–54 with 84.8% control among treated women but only 63.9% control among treated men. According to Redfern et al. (2019), the control of hypertension was better in women than men, but there were no sex differences in the control of hypertension among those receiving AHT [5]. Matching results presented Daugherty et al (2011), stating that men tended to have lower rates of hypertension control compared to women (41.2 vs. 45.7% respectively). A significant gender by age interaction was found with men aged 18–49 having 17% lower odds of hypertension control and men aged at least 65 having 12% higher odds of hypertension control compared to women of similar ages ($P < 0.001$) [22].

Hypertension treatment

In data presented by Rahman et al. (2017) women, had worst antihypertensive medication practice, despite the fact that they had higher awareness of hypertension. Moreover, women in Bangladesh not involved in any income generation or in the poorest/poorer wealth quintiles were less likely than their male peers to use AHT. Bangladesh Demographic and Health Survey (BDHS 2011) findings highlight a gender inequality in treatment affordability for expensive AHT [6].

On the other hand, Lunet et al. (2002) as well as Redfern et al. (2019), state that women consistently had greater treatment of their hypertension than men. This findings are coherent with a report from the US National Health and Nutrition Examination Survey (NHANES), as well as research performed in Germany, which revealed that younger men are considerably more likely than younger women to be untreated and uncontrolled [4, 8]. Moreover, results from study, which used data set from the Korean National Health and Nutrition Examination Survey of Seven

hundred eighty participants, show that 11,3% of men and 26,2% of women were receiving AHT [7]. Interestingly Kim et al. (2020) states that men after marriage improve their adherence to medical treatment regimens and BP tracking with family support. This might suggest, importance of introducing family education to young men at the time of hypertension diagnosis [7].

According to Redferen et al. (2019) the type of therapy, in terms of monotherapy vs polytherapy, was similar in both sexes. Differences in specific antihypertensive drug class usage are presented in Table 2. Variations became apparent only when comparing β- blockers in younger groups. In this group women used more β- blockers than men (60.8 vs. 42.3% respectively). Other exception was higher use of ACEI (Angiotensin Converting Enzyme Inhibitors) in men compared to women (53 vs. 37% P=0,000) [8]. One of the reasons why women are less often prescribed ACEIs and ARBs (angiotensin II receptor blockers) is the risk of pregnancy [11]. Physicians have to take this contraindication into consideration and discuss the risk or choose a safer drug class. In terms of beneficial effects, a meta-analysis examined the effects of BP lowering treatments in men and women and found only significant sex differences for stroke prevention, where CCBs (calcium channel blockers) seemed superior to ACEIs ($p = 0.05$) [15].

Zapater et al. (2004) performed bioequivalence study of enalapril formulations administered to healthy volunteers. They found no significant sex- differences in pharmacokinetic but gender differences were observed in pharmacodynamic. First of all, women had lower minimum ACE activity after administration of enalapril. Second, the inhibition of ACE activity in women was dependent on the plasma enalaprilat (active metabolite) concentration. For concentrations <5ng/ml plasma ACE inhibition was lower in women. Over 5 ng/ml the same level of ACE inhibition was obtained for men and women. The authors noted lower SBP (Systolic Blood Pressure) and ACE activity in women at all enalaprilat concentrations even at maximum inhibition of ACE activity [16].

Another group of antihypertensive medications, which are often prescribed to patients are thiazide diuretics (TD). Thoenes et al. (2010) report that TD are often choose for women, because of their beneficial effect on decreased renal excretion of calcium, bone density and reduction of fracture risk in postmenopausal women. Accordingly Lunet et al. (2002) revealed that, in case of monotherapy, the use of ACEI/ARB was more frequent in men and treatment with diuretics higher in women [25]. On the other hand, there are many studies showing that female sex is a risk factor for hyponatremia in TD users [18,19]. Cadeddu et al. (2016) found that women were five times more likely to be hospitalized for hyponatremia due to TD. Moreover Swedish study on spontaneously reported adverse drug reactions (ADR) for common antihypertensive drugs found that tremendous majority (86%) of the reports for TD induced hyponatremia were for women [20]. Medicals should keep in mind when prescribing TD, that women seem to be more prone to ADR. Thus, a gender- based criteria of pharmacological treatment could lead to better control of hypertension and therapeutic adherence.

Worth noting are reports regarding cytochrome 2D6 genetic polymorphism influence on β-blockers metabolism. Thürmann et al. (2006) examined the interaction between gender and adverse effects of β-blockers, by dividing this drug class into two groups: CYP 2D6- dependent (carvedilol, metoprolol, nebivolol, and propranolol) and CYP2D6-independent (atenolol, bisoprolol and sotalol). It was found that ADR associated with CYP2D6- dependent β-blockers was significantly more frequent in women than in men. But for CYP2D6-independent β-blockers there was no gender disparity. Interestingly drug interaction with other heart rate lowering drugs was also more frequent in women with CYP2D6-dependant β-blockers [21]. This field requires further studies, since pharmacogenetic factors are important determinants in pharmacological response to therapy.

On the other hand, meta-analysis performed on 82 high-quality studies reporting adherence to antihypertensive drugs measured by self-report or pharmacy refill prescription-based methods among men and women, did not provide convincing evidence that men and women differently adhere to AHT drug therapy. However, it was outlined that inconsistency between studies suggests that sex– adherence association need careful discussion before being judged absent [23].

Unfortunately despite the abundance of clinical trials for the treatment of hypertension, specific data for both genders separately is not easily obtained. This might be result of not performing gender specific analysis and in many of these studies women are underrepresented. Although several studies report minor sex-differences in hypertension treatment [8,15], the overall amount of sex-specific data is insufficient.

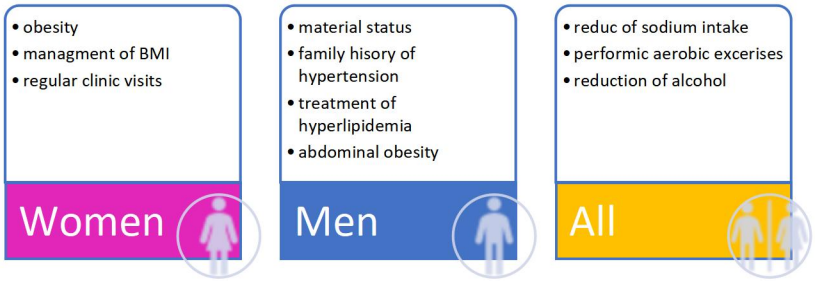
Table 2. *Antihypertensive treatment among adults treated in Germany 2008-2011 based on Sarganas et al. (2016).*

Age	*18-54 years*			*55-79 years*		
Drug class	Men %	Women %	Percentage points difference	Men %	Women %	Percentage points difference
B- blockers	42,3	60,8	18,5	54,9	54,2	0,7
ACEI	51,4	35,1	16,3	52,5	38,2	14,3

Other factors affecting hypertension

Several experimental studies and epidemiological data have suggested that the gender dissimilarities may be related to biological or pathophysiological factors, as well as disparities in health care or differences in the response to therapy [11]. Furthermore, many studies highlight sex-differences in the pharmacokinetics (PK) of cardiovascular drugs [12]. As presented in Figure 1, Kim et al. (2020) suggests that different factors affecting blood pressure should be considered for men and women. When it comes to reduction of sodium intake, there appears to be a gender dimorphism in salt- sensitive hypertension. After menopause women have been noted to become more sodium sensitive, suggesting a hormonal influence in salt handling [12,13,14]. This theory is supported by the reported benefits of salt restriction in older women and experimental animal models. Studies on salt sensitive rats, have shown a lower proportion of development of hypertension in female rats compared to male rats when put on a high-sodium diet [12,13]. Furthermore, in female rats, ovariectomy resulted in increased salt-sensitive hypertension [12]. However, it is important to remember that healthy diet by consuming less sodium and cholesterol should be recommended to both genders to improve hypertension control [7].

Figure 1. *Most important factors affecting blood pressure divided by sex category based on Kim et al. (2020).*



Conclusions

In conclusion, based on researched studies we can state that women have higher awareness, treatment and control rates for hypertension than men in Germany, United States, Bangladesh, China, Canada and Czech Republic [4,5,6,8,9, 10]. Therefore specific guidelines for hypertension treatment strategies different for men and women have yet to be developed.

One of the reasons, that hypertension is still one of major cause of death worldwide might be lack of gender specific data, hindering a comprehensive approach. With the advent of personalized medicine there is a common agreement that gender differences in pharmacotherapy should be studied systematically and gender should be included in covariate analyses and not only in post hoc analysis. To gain an in-depth understanding of hypertension, as well as its treatment and control, it is necessary to study the two genders separately. Although we focused on assessment gender differences in hypertension awareness, diagnosis and treatment, more research is needed into the other factors such as sex/gender differences in mechanisms responsible for hypertension, socioeconomic, psychometric, metabolic and different life style, to determine the best treatment options that will reduce the risk of hypertension and subsequent cardiovascular diseases in both genders.

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