Gender-specific therapeutic approach in arterial hypertension – Challenges ahead

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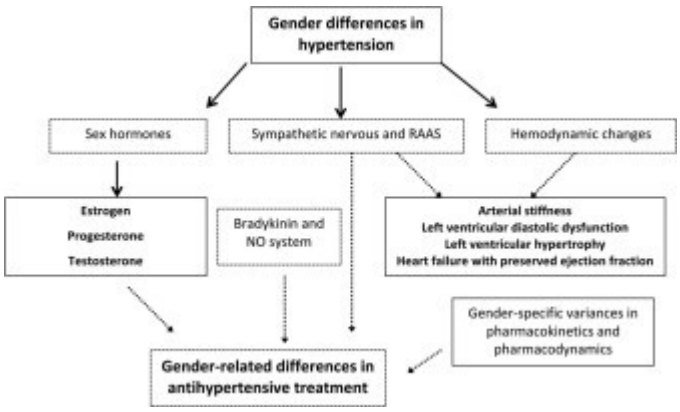
Abstract

Hypertension was thought to be more important cardiovascular risk factor in men than in women. However, studies showed that overall incidence of hypertension-related cardiovascular diseases is higher in women comparing with men and this is particularly valid in menopause when prevalence of hypertension and its complications sharply and suddenly rises. It was also noticed that the effect of various antihypertensive groups was different in women and men. Some medications are prescribed more often in women, but it does not necessary mean that these drugs are more effective in this gender. There are several important reasons that could explain gender-induced differences in blood pressure levels, blood pressure control and antihypertensive treatment. They involve sex hormones, the renin-angiotensin-aldosterone and sympathetic nervous system, and arterial stiffness. However, taking into account many observational studies and trials, there are no consistent data regarding the impact of gender on effect of antihypertensive medications. Longitudinal study focused on gender and current antihypertensive groups would significantly help to understand the impact of gender. This might change therapeutic approach and improve cost-effectiveness in antihypertensive therapy in both genders. A full understanding of the pathophysiological characteristics of variations between genders demands additional research.

This review article summarized the current knowledge regarding differences in the prevalence and awareness of arterial hypertension in women and men; alterations in pathophysiological mechanisms of hypertension between sexes; as well as the impact of sex on the effects of main antihypertensive groups of medications.

Graphical abstract



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Introduction

The cardiovascular risk in women is usually underestimated due to assurance that they are protected by hormones during reproductive period. Recent large epidemiological overview showed that women are under higher hypertension-related cardiovascular diseases than men [1]. Large study that included 61 585 men and women older than 55 years of age and followed at least 14 years showed that lifespan estimated risk of cardiovascular disease was 52.5% for men and 39.9% for women [2]. The reason for the difference in these statements lies in the fact that sex hormones have unique impact on development of hypertension and its complications in women and men in different period of their lives. Namely, estrogen and progesterone have protective effect in women during generative period, but after menopause the incidence of hypertension and hypertension-related cardiovascular diseases suddenly raises, reaches and even overtakes the incidence from men [3].

Awareness of hypertension and blood pressure (BP) control are also different among genders and varies during life. The awareness of hypertension and number of antihypertensive medications is higher in women [4,5]. Large meta-analysis from studies done in Chinese population showed that awareness, treatment among all and aware subjects, control among all and treated patients were low for both sexes, but more favorable in women than men [4]. The other study showed that the achievement of BP control was significantly higher in men, even though antihypertensive polytherapy was more prevalent among women [5]. The recent large study showed that women reported adverse effect in 6 out of 10 groups of antihypertensives [6]. Aldosterone antagonists was the only group with higher prevalence of adverse effects among men [6]. Investigations also showed that antihypertensive treatment prescribed to patients was strongly affected by sex [5,7,8]. The remaining question is if this therapeutic approach is justified from pathophysiological point of view and existing studies or not.

PubMed, Medline, OVID and EMBASE databases were searched for the studies published from January 1990 up to November 2018 in English language using the following keywords “arterial hypertension,” “gender”, “antihypertensive therapy”, “renin-angiotensin inhibitors”, “angiotensin receptor blockers”, “beta-blockers”, “calcium channel blockers”, “diuretics”, and “thiazide”.

The aim of this article is to provide an updated overview of pathophysiological differences in development of arterial hypertension and necessity for gender-specified antihypertensive treatment.

Section snippets

Prevalence of hypertension in both genders

The large French cross-sectional study that included 17,856 hypertensive patients in the period from 2000 to 2015 showed significant difference no prevalence of hypertension between sexes over 15 years (50% *vs.* 50%) [7]. The prevalence of uncontrolled hypertension significantly decreased over 15 years from 74.6 to 59.0% in men ($p < 0.001$) and from 60.7 to 51.6% in women ($p < 0.001$), but it was significantly higher in men [7]. However, the prevalence of patients with no antihypertensive

Pathophysiology of arterial hypertension

The most important roles in the sexual differences between genders have sex hormones, activation of sympathetic nervous and renin-angiotensin-aldosterone (RAAS) systems, and arterial stiffness [15]. The main gender-related pathophysiological differences are mainly ascribed to the RAAS and in the bradykinin and NO system [15].

Estrogen has the main protective vascular effect in premenopausal women. Estrogens play an important role in endothelial function on several levels: vascular, cardiomyocyte

Antihypertensive therapy

Although many studies showed significant difference in prescription of various antihypertensive groups in women or men, as well as more favorable effect of some antihypertensive groups in one sex, there is still no enough evidence to base antihypertensive therapy according to gender. Hormone differences and variation in comorbidities and risk factors between genders could partly justify gender-related antihypertensive therapy. However, guidelines do not recommend any difference in hypertension

Conclusion

It is time to involve the gender from the very beginning of the research to medical practice, but as the primary aim and not only as retrospective analysis. Existing studies regarding outcomes with respect to gender and antihypertensive therapy are variable, and it is difficult to conclude something about gender-specific antihypertensive therapy. It should be also emphasized that most of investigations evaluated the effects of more traditional antihypertensive medications. Follow-up study

Conflict of interest

None.

References (65)

- C. Ljungman et al.

  Gender differences in antihypertensive drug treatment: results from the Swedish Primary Care Cardiovascular Database (SPCCD)

  J. Am. Soc. Hypertens.

  (2014)
- Y. Nakamura et al.

  Estrogen receptors in atherosclerotic human aorta: inhibition of human vascular smooth muscle cell proliferation by estrogens

  Mol. Cell. Endocrinol.

  (2004)
- S. Miura et al.

  Hormone replacement therapy improves arterial stiffness in normotensive postmenopausal women

  Maturitas

  (2003)
- V. Regnault et al.

  Sex difference in cardiovascular risk: role of pulse pressure amplification

  J. Am. Coll. Cardiol.

  (2012)
- D.M. Rabi et al.

  Reporting on sex-based analysis in clinical trials of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker efficacy

  Can. J. Cardiol.

  (2008)
- B. Dahlof et al.

  Cardiovascular morbidity and mortality in the losartan intervention for end point reduction in hypertension study (LIFE): a randomized trial against atenolol

  Lancet

  (2002)

- B. Dahlof et al.

  Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial

  Lancet

  (2005)
- R.A. Kloner et al.

  Sex- and agerelated antihypertensive effects of amlodipine. The Amlodipine Cardiovascular Community Trial Study Group

  Am. J. Cardiol.

  (1996)
- C.M. Wright et al.

  Calcium channel blockers and breast cancer incidence: an updated systematic review and meta-analysis of the evidence

  Cancer Epidemiol.

  (2017)
- N. Townsend et al.

  Cardiovascular disease in Europe 2015: epidemiological update

  Eur. Heart J.

  (2015)
- N. Allen et al.

  Impact of blood pressure and blood pressure change during middle age on the remaining lifetime risk for cardiovascular disease: the cardiovascular lifetime risk pooling project

  Circulation

  (2012)
- L.A. Ramirez et al.

Sex differences in hypertension: where we have been and where we are going
Am. J. Hypertens.
(2018)

- A. Redfern et al.

Sex differences in the awareness, treatment, and control of hypertension in China: a systematic review with meta-analyses
Hypertens. Res.
(2018)

- Q. Gu et al.

Gender differences in hypertensive treatment, drug utilization patterns, and blood pressure control among US adults with hypertension: data from the National Health and Nutrition Examination Survey 1999-2004
Am. J. Hypertens.
(2008)

- D.M. Rydberg et al.

Sex differences in spontaneous reports on adverse drug events for common antihypertensive drugs
Eur. J. Clin. Pharmacol.
(2018)

- T. Deborde et al.

Sex differences in antihypertensive treatment in France among 17856 patients in a tertiary hypertension unit
J. Hypertens.
(2018)

- C. Ljungman et al.

Antihypertensive treatment and control according to gender, education, country of birth and psychiatric disorder: the Swedish primary Care cardiovascular Database (SPCCD)
J. Hum. Hypertens.
(2015)

- G. Sarganas et al.

The persisting gender gap in hypertension management and control in Germany: 1998 and 2008-2011
Hypertens. Res.
(2016)

- P. Van der Niepen et al.

Gender and hypertension management: a sub-analysis of the I-inSYST survey
Blood Press.
(2011)
- J.A. Staessen et al.

The epidemiology of the association between hypertension and menopause
J. Hum. Hypertens.
(1998)
- B. Everett et al.

Gender differences in hypertension and hypertension awareness among young adults
Biodemogr. Soc. Biol.
(2015)
- H.M. Choi et al.

Sex differences in hypertension prevalence and control: analysis of the 2010-2014 Korea National Health and Nutrition Examination Survey
PLoS One
(2017)
- EUGenMed Cardiovascular Clinical Study Group et al.

Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes
Eur. Heart J.
(2016)
- A. Iorga et al.

The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy
Biol. Sex Differ.
(2017)
- M. Hay

Sex, the brain and hypertension: brain oestrogen receptors and high blood pressure risk factors
Clin. Sci.
(2016)
- M. Barton et al.

Postmenopausal hypertension: mechanisms and therapy
Hypertension
(2009)

- L. Te Riet et al.

  Hypertension: renin-angiotensin-aldosterone system alterations

  Circ. Res.

  (2015)
- M. Canonico et al.

  Postmenopausal hormone therapy and risk of stroke: impact of the route of estrogen administration and type of progestogen

  Stroke

  (2016)
- E. Løkkegaard et al.

  Risk of stroke with various types of menopausal hormone therapies: a national cohort study

  Stroke

  (2017)
- M.R. Williams et al.

  Variations in endothelial function and arterial compliance during the menstrual cycle

  J. Clin. Endocrinol. Metab.

  (2001)
- L. Wu et al.

  Gender difference in the association between aminotransferase levels and hypertension in a Chinese elderly population

  Medicine (Baltimore)

  (2017)
- E. Gerdts et al.

  Gender differences in left ventricular structure and function during antihypertensive treatment: the Losartan Intervention for Endpoint Reduction in Hypertension Study

  Hypertension

  (2008)

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