Journal of Human Hypertension special issue on sex and gender differences in hypertension

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Running title: Sex and Gender Differences

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Hypertension remains one of the most important modifiable risk factors for cardiovascular disease and mortality worldwide[1]. Considerable differences exist between men and women relating to the pathophysiology, epidemiology and outcomes relating to this condition[2]. Understanding the means by which sex related biology and gender mediated psycho-socio-cultural characteristics influence blood pressure regulation and the development of hypertension is imperative to ensuring equitable evidence based management of this condition, and broadening our understanding of the mechanisms responsible[3].

In this special issue we provide a diverse collection of reviews and original articles aiming to enhance our knowledge of the role of sex and gender in hypertension. This aimed to capture the latest research relating to the mechanisms by which sex (i.e. sex hormones, chromosomal complement and sex-specific factors) and gender (sociocultural factors) interact to modulate the development of this condition, and the impact this has upon those with hypertension[3-5]. We are therefore pleased to incorporate a variety of topics into this special issue pertinent to hypertension pathophysiology such as sex-hormone mediated mechanisms[6], the impact of psychosocial gender[3], the effect of menopause[7], preclinical models[8] and hypertensive multi-organ damage[9-12]. Importantly, this special issue provides the scope to discuss underrepresented and underserved populations who may experience hypertension, including women[13,14], gender-diverse individuals[15], those with chromosomal aneuploidies[16], the young[17], and those living in low and middle income countries[18]. To translate findings into clinical practice we look at hypertension guidelines[13] and data from primary care[19].

A major strength of this special issue is that the articles included provide valuable insight into sex-dependent mechanisms evident in the development of hypertension. Kringeland *et al* demonstrate in a cohort of 48 year old individuals from the Hordaland Health study that elevated inflammatory biomarkers, high-sensitive C-reactive protein and a measure of T cell activation, neopterin, were associated with elevated blood pressure and incident hypertension in women. These findings suggest sex-specific influences differentially regulate the innate and adaptive immune responses, resulting in sex-dependent vascular inflammation and the development of hypertension[20].

The influences of dietary salt intake upon sex-dependent renal mechanisms is also explored. Ferreri *et al* show that the cytokine tumor necrosis factor-α (TNF-α), a product of thick ascending limb of Henle's loop (TAL) and regulator of the NaK2Cl− cotransporter type 2 (NKCC2), to be secreted in a sex-specific fashion in response to a dietary salt intervention[21]. NKCC2 mediates TAL salt handling, and dysregulation has been shown to elevate blood pressure in human and animal models[22]. Within

this analysis, elevated levels of TNF-α were demonstrated in females in response to salt intake, potentially limiting NKCC2 activity and mitigating salt-dependent increases in blood pressure. Such mechanisms may represent an interplay between inherited sex-specific immune responses, and psychosocial dietary behaviours relevant to gender. Another protein that interacts with salt handling in the TAL is uromodulin[23]. Algharably ate al. provide data on genetic variants of uromodulin and a range of physiological parameters in older women and men[24].

Moreover, sex-specific factors such as pregnancy undoubtedly influence cardiovascular risk in the female populations. Brown *et al*, show that women a history of preeclampsia have higher risk of cardiovascular events later in life in the Scottish Family Health Study[25]. This legacy effect of pre-eclampsia has significant implications with respect to the future cardiovascular risk in women, but also raises many questions regarding the underlying physiology responsible for such a pervasive influence upon cardiovascular disease development in later life[26].

Our special issue focusses on systemic hypertension but we couldn't resist and included a paper on pulmonary arterial hypertension[27]. This condition is not normally in the focus of "hypertensiologists" but being so much more prevalent in women than in men it not only fits nicely into this special issue but may also give us food for thought to better understand sex and gender differences in systemic hypertension. Indeed, in their paper Sless et al. provide insight into systemic vascular function in those with pulmonary arterial hypertension[27].

Taken together, the studies highlight the potential mechanisms by which sex-specific mediators may act across a variety of systems to regulate blood pressure and the development of hypertension. The editorial team and authors that contributed to this special issue urge those engaging in hypertension research to consider the influences of the sex and gender continuum in their work to ensure that it is not limited by traditional conformities.

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