Role of biological sex in cardiovascular disease: the case of hypertension and related target organ damage

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Recent data report a prevalence of hypertension of around 30–45% in the general population of high-income countries and between 20–40% in low-income countries. In fact, around the globe, 31.1% of the adult population (1.39 billion people) had hypertension in 2010.

Hypertension is a complex disease influenced by characteristics of the individual, such as age, biological sex, race, fat mass and genetic factors, have a major impact on physiological and pathological processes. Consequently, individuals can respond differently to the development and manifestation of disease, treatment, outcome and the recovery process. In fact, there are major differences in the function of the biological system of men and women, who do not differ only on the basis of their reproductive system. Sex chromosomes and sex hormones, together with other factors, interact in a complex manner, thereby leading to sex-specific protective or maladaptive mechanisms. In this context, studying the role and effects of biological sex is crucial for the identification of novel therapeutic targets, whose therapeutic exploitation will promote a personalized and improved treatment and care according to individual needs. The vast influence of biological sex is recognized in many diseases. Here, we focus on hypertension, due to its high prevalence and importance, since it is the primary risk factor for premature death and disability worldwide.

Figure 1. Biological sex, as well as other factors, influence the development of hypertension

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Hypertension is a complex disease influenced by characteristics of the individual, such as age, sex and sex hormones, race, body mass index (BMI), adipokines, genetic factors, and by environmental factors, lifestyle and dietary habits, such as salt intake (Figure 1). The prevalence of hypertension is higher in men than women at younger ages, but following menopause, blood pressure in women increases steeply, thereby affecting more women than men in elderly individuals. Consequently, the prevalence of hypertension is lower in women than men until 45 years of age, but it is much higher in women than men over 65 years of age. Furthermore, women are at greater risk of developing resistance to antihypertensive treatment than men.

Patients with hypertension and lack of blood pressure control have a high probability of developing target organ damage, such as cardiac hypertrophy; vascular alterations, including arterial stiffness; and renal damage. The development of these cardiovascular...
complications also differs significantly between men and women (Figure 2). Therefore, it is important to study and understand the sex-specific mechanisms involved in the development of cardiovascular diseases.

**Influence of body fat**

Interestingly, higher BMI is associated with an increased risk of hypertension development over time; however, one sex may be more vulnerable than the other. Data from the Framingham study revealed that overweight and obese women had a higher risk of developing hypertension compared with overweight and obese men.

In addition, women may have higher levels of body fat (adipose tissue) compared with men and greater risk of developing metabolic syndrome. Adipokines, such as leptin – a metabolic regulator and feedback signal of body fat to regulate appetite – and adiponectin – an anti-inflammatory hormone – are cytokines released by the adipose tissue. These hormones have gained attention due to their capacity to influence the inflammatory system with pro- and anti-inflammatory actions. Adipokine levels can be impaired in obesity and metabolic syndrome, thereby contributing to cardiovascular complications, including insulin resistance, diabetes, atherosclerosis and hypertension. Some evidence has shown that women can present with higher levels of adipokines and, interestingly, these adipokines may be associated with vascular and renal damage, arterial stiffness and lack of blood pressure control.

**Sex differences in cardiac hypertrophy**

Cardiac hypertrophy is the response of the heart to injury and overload and is a major risk factor for heart failure and sudden death. In the development of pressure overload-induced hypertrophy, distinct molecular processes are regulated between men and women. In particular, maladaptive remodelling occurs more frequently in men than women, which is associated with greater activation of pro-fibrotic and inflammatory mediators. Sex hormones, especially 17β-oestradiol (E2), play an important role in the development of cardiac hypertrophy and sex-specific responses. In particular, reduced E2 levels associated with menopause are expected to be a contributing factor to the higher vulnerability of post-menopausal women to develop hypertension. Along this line, in female animals, E2 confers protective effects on the heart under pathological conditions. However, the genetic composition of the model studied may lead to divergent effects. On the
other hand, in males, E2 leads to impaired contractile function of cardiomyocytes. Further animal studies have demonstrated major sex differences in the development of hypertension-induced cardiac hypertrophy, where males develop greater cardiac hypertrophy and dysfunction than females.

### Sex differences in arterial stiffness

Arterial stiffness is characterized by reduced capability of an artery to expand and contract in response to pressure changes. This process is intimately associated with hypertension and has emerged as an important predictor of adverse cardiovascular events and mortality. Arterial stiffness is mainly determined by age, sex and blood pressure. Importantly, markers of arterial stiffness may differ between men and women. Studies have demonstrated a higher prevalence of aortic stiffness in older women than men.

Sex hormones contribute to sex differences in vascular biology and to tissue and cellular differences resulting in sex-specific responses to various stimuli. In particular, E2 directly affects arterial wall remodelling by increasing elastin production and decreasing collagen deposition in human arteries. Along this line, the post-menopausal period is associated with increases in arterial stiffness and administration of hormonal therapy ameliorates arterial stiffness in post-menopausal women.

### Sex differences in renal dysfunction

Chronic kidney disease (CKD), defined by reduced estimated glomerular function rate and/or albuminuria levels, caused by hypertension. CKD is a worldwide health problem associated with high rates of morbidity and mortality. Compared with pre-menopausal women, CKD can be more severe in post-menopausal women or age-matched men, with higher progression rate and mortality risk. In most experimental models of CKD, males progress more rapidly than females.

Influence of sex hormones, sex differences in kidney anatomy, lifestyle, diet, lipid metabolism and blood pressure have been suggested to contribute to the sex-specific aspects of CKD, where females appear to be less vulnerable than males. In fact, sex hormones play an important role in biological mechanisms associated with variability in CKD prevalence and differences in CKD development between men and women.

### Importance of studying the role of biological sex

In order to perform research, it is necessary to define who will be studied. The goal of such research is to make generalizations beyond the given individuals studied to others with similar characteristics and conditions. To make such generalizations, the assumption is made that the responses of the individuals studied will be representative of the overall population considered. However, given that mechanisms of disease differ between men and women, how should this be addressed?

Here, we discuss two main ways. First, the individuals included in the research can be studied combining men and women together in the same group. However, some factors should be taken into account. When studying two or more groups with different subjects, the differences that could bias the results should be equally distributed between the groups. Therefore, there should be similar numbers of males and females in the group studied to avoid...
over- or under-representation of one or the other, which could lead to false positive or false negative data. Second, men and women could be studied separately to try to understand any given effects involved within each sex (Figure 3).

Several experimental and clinical studies have demonstrated the importance of understanding the role of sex and the underlying mechanisms in many diseases, highlighting that sex differences represent important biological phenomena that need further investigation. Considering medical practice, what would the application of this knowledge be? The number of deaths related to cardiovascular diseases in many cases differs significantly between men and women, thereby demonstrating the need for sex-specific research aimed at unravelling the complex interactions of sex and cardiovascular (patho)physiology, along with other factors. Consequently, a better understanding of the role of sex, not only in the cardiovascular field, but rather overall, may facilitate the identification of targets that respond to specific therapies, ultimately contributing to a more personalized medical care. Therefore, the elucidation of sex-specific disease mechanisms and therapeutic targets may contribute to the development of more efficient treatments for men and women.

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Georgios Kararigas has recently co-authored a review in Clinical Science covering how precision medicine can be achieved by the integration of biological sex into pharmacogenomics; see Gaignebet, L. and Kararigas, G. (2017) Clinical Science 131, 329–342, doi: https://doi.org/10.1042/cs20160379. The review is part of the journal’s Gender and Molecular Medicine Collection, covered on pages 38-43 of this issue of The Biochemist.