



Review

Sex-gender-related therapeutic approaches for cardiovascular complications associated with diabetes

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ABSTRACT

Diabetes is a chronic disease associated with micro- and macrovascular complications and is a well-established risk factor for cardiovascular disease. Cardiovascular complications associated with diabetes are among the most important causes of death in diabetic patients. Interestingly, several sex-gender differences have been reported to significantly impact in the pathophysiology of diabetes. In particular, sex-gender differences have been reported to affect diabetes epidemiology, risk factors, as well as cardiovascular complications associated with diabetes. This suggests that different therapeutic approaches are needed for managing diabetes-associated cardiovascular complications in men and women. In this review, we will discuss about the sex-gender differences that are known to impact on diabetes, mainly focusing on the cardiovascular complications associated with the disease. We will then discuss the therapeutic approaches for managing diabetes-associated cardiovascular complications and how differences in sex-gender can influence the existing therapeutic approaches.

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Abbreviations: ARBs, angiotensin II type 1 receptor blockers; BH4, tetrahydrobiopterin; BMI, body mass index; CABG, coronary artery bypass graft; EPCs, endothelial progenitor cells; ER α , estrogen receptor alpha; ER β , estrogen receptor beta; GLUT4, glucose transporter 4; HbA1c, glycated haemoglobin; HDL, lower high-density lipoprotein; HRT, hormone replacement therapy; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; iPS, induced pluripotent stem cells; MI, myocardial infarction; MRFTT, Multiple Risk Factor Intervention Trial; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; STEMI, ST-elevation MI; TZDs, thiazolidinediones.

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1. Introduction

Diabetes mellitus is a metabolic disease characterised by the inability of the body to maintain normal glucose homeostasis. Diabetes is a major threat to human health and is one of the most important chronic diseases contributing to significant morbidity and mortality worldwide [1,2]. According to the International Diabetes Federation statistics, 415 million adults have diabetes and the number of people diagnosed with diabetes is estimated to rise to more than 640 million by 2040 [3], indicating that diabetes (and its complications) is one of the most considerable health challenges in the world.

There are several different forms of diabetes [4–7], of which the most common are Type 1 diabetes, Type 2 diabetes and gestational diabetes [2,8]. Nonetheless, patients with diabetes have increased risk of developing a number of acute or chronic complications including diabetic nephropathy, retinopathy and neuropathy, as well as cardiovascular complications such as coronary artery disease, cardiomyopathy, stroke and peripheral artery disease (PAD) [9,10]. Cardiovascular complications are one of the most important causes of death among patients with diabetes [11,12].

Remarkably, there is an emerging awareness that gender has a significant impact in the pathophysiology of diabetes as well as in the cardiovascular complications associated with the disease. In this context, it is relevant to underlie that sex and gender have not the same meaning (for a detailed discussion see Marino et al. [13] and Franconi et al. [14]). In brief, “sex” refers to biological status of males and females, “gender” refers to the socially constructed roles that a given society considers appropriate for men and women. In the last years, gender has been considered more politically correct and it is becoming more commonly used in scientific publications. However, in medicine, it is almost impossible to properly distinguish between sex and gender as already discussed by Franconi et al. [14], thus we use sex-gender.

Importantly, sex-gender has a significant impact not only on the pathophysiology of diabetes and diabetes-associated cardiovascular complications, but also in the diseases outcome in response to drugs. Indeed, numerous sex-gender differences were found in risk factors, clinical manifestations, prognosis, therapeutics and outcomes in the setting of diabetes in general and diabetes-associated cardiovascular complications in particular [15–21], providing the basis for specific evidence-based interventions both for men and women. Indeed, it is relevant to recall that sex differences reported in animal models of Type 2 diabetes do not perfectly translate in humans [22], increasing the difficulties of studying new pharmacological approaches.

In this review we will mainly address sex-gender -specific aspects in cardiovascular complications associated with diabetes mellitus, also focusing on new therapeutic strategies for diabetes-associated cardiovascular complications.

2. Sex-gender differences in the epidemiology and risk factors associated with diabetes

2.1. Epidemiology

Some sex-gender differences have been reported for diabetes epidemiology: whereas Type 1 diabetes has a slight predominance in males [23,24], no clear evidence reports a sex-gender difference in the prevalence of Type 2 diabetes, although women show a higher incidence of impaired glucose tolerance (IGT), especially in elderly age [25], and impaired fasting glucose (IFG), a pre-diabetes condition, is more common in men [25,26].

Interestingly, in young age Type 2 diabetes seems to be more common in girls than in boys [27,28], and some reports indicate

that girls display higher insulin resistance than boys at birth and until adolescence [29–31]. Some pathological conditions, in particular mental diseases, may influence the onset of diabetes in a sex-specific manner. Overall, the incidence of diabetes is from two to four times higher in schizophrenic people [32,33], and a study shows that the global prevalence of diabetes in China is 20% and 27% in men and in women, respectively, where schizophrenic women have a 1.4 fold greater risk of antipsychotic-associated diabetes than males [34]. Moreover, Zhang et al. reported that diabetic and schizophrenic men have a worst cognitive outcome than non-diabetic ones, while the same is not observed in women [35]. In addition, diabetic men with schizophrenia display higher levels of glycated haemoglobin (HbA1c), and lower high-density lipoprotein (HDL) if compared with women [35].

A relationship between depression and diabetes has also been recognised since sixteen century by Thomas Willis who associated diabetes with melancholy (<http://www.diapedia.org/introduction-to-diabetes-mellitus/1104693411/thomas-willis>). Diabetic patients experience depression from 1.3 to 3 times as often as those without the disorder [36–38], have an increased risk of work loss [39], functional disability [40] and micro- and macrovascular complications [41,42], and a bad adherence to therapies diets and self-monitoring of blood glucose levels [43,44]. Moreover, depressed patients with diabetes die earlier than other people [45] and, as depression is more frequent in women than in men, mental illness associated with diabetes could be more relevant for women [46].

2.2. Risk factors

Sex-gender differences have been also reported for diabetes risk factors and cardiovascular complications [15,47] (Fig. 1). Additionally, all risk factors associated with cardiovascular diseases appear to be more active in diabetic females than in their male counterparts [17]. Some risk factors are predominantly male-related, such as being former smokers [48] or heavy alcohol drinkers [48,49], have increased systolic blood pressure [48], suffer from hypogonadism [50,51] (Fig. 1). Moreover, a positive correlation exists between gestational diabetes and low birth weight only in male neonates [52,53]. Interestingly, a recent Canadian study shows that women with a male foetus are more likely to develop gestational diabetes and metabolic changes, while women with gestational diabetes carrying a female baby display a higher risk to develop Type 2 diabetes after pregnancy [54].

Risk factors associated with women are represented by increased uric acid levels [48,55], low physical activity and obesity [48], polycystic ovarian syndrome [56], and gestational diabetes [57,58] (Fig. 1). Moreover, women suffer more from postprandial hyperglycaemia than men, leading to IGT, which in turn is associated with higher oxidative stress and a higher cardiovascular risk [59]. In addition, the risk of developing Type 2 diabetes after gestational diabetes is associated with an excessive weight gain during pregnancy, insulin therapy, increased levels of HbA1c and fasting blood glucose [60].

3. Sex-gender differences in cardiovascular complications associated with diabetes

Cardiovascular complications associated with diabetes represent one of the most important causes of death among diabetic patients [11,12], and several sex-gender differences have been reported about them. In particular, ischaemic complications such as PAD and myocardial infarction (MI) are major causes of morbidity and mortality in patients with diabetes [61].

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