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Review

Why We Need Sex-Gender Medicine: The Striking Example of Type 2 Diabetes

Giuseppe Seghieri [1], Flavia Franconi [2] and Ilaria Campesi [2,3,*]

[1] Agenzia Regionale Sanità della Toscana, 50141 Firenze, Italy
[2] Laboratorio Nazionale di Farmacologia e Medicina di Genere, Istituto Nazionale Biostrutture Biosistemi, 07100 Sassari, Italy
[3] Dipartimento di Scienze Biomediche, Università degli Studi di Sassari, 07100 Sassari, Italy
* Correspondence: icampesi@uniss.it

Abstract: Type 2 diabetes mellitus is a widespread and a chronic disease associated with micro- and macrovascular complications and is a well-established risk factor for cardiovascular disease, which are among the most important causes of death in diabetic patients. This disease is strongly affected by sex and gender: sex-gender differences have been reported to affect diabetes epidemiology and risk factors, as well as cardiovascular complications associated with diabetes. This suggests the need for different therapeutic approaches for the management of diabetes-associated complications in men and women. In this review, we describe the known sex-gender differences in diabetic men and women and discuss the therapeutic approaches for their management. The data reported in this review show that a sex-gender approach in medicine is mandatory to maximize the scientific rigor and value of the research. Sex-gender studies need interdisciplinarity and intersectionality aimed at offering the most appropriate care to each person.

Keywords: sex-gender differences; type 2 diabetes mellitus; therapy

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1. Introduction

Over the past 20–30 years, research has shown, from single cells to multiple complex biological systems, that biological sex and gender differences are numerous and involve all branches of the biomedical sciences. According to the Council of Europe [1], the term sex regards "*the different biological and physiological characteristics of males and females, such as reproductive organs, chromosomes or hormones*", whereas gender regards "*the socially constructed characteristics of women and men—such as norms, roles, and relationships of and between groups of women and men*". Nowadays it is clear that sex and gender interact forming Gordian node [2,3]; thus, it is very difficult to separate them [2–4].

It is important to recognize that sex differences apply to all vertebrates and humans and that sexual dimorphism varies in the species and strains of animals. Sex should, in fact, be considered in all cell studies, as it is now evident that primary cells other than males and females behave differently [5–11]. In diabetes research, as an example, it is very difficult to find an animal model suitable for studying gender differences in the pathology and its complications as different animal models show sexually dimorphic diabetic phenotypes [12].

Moreover, sex-gender differences are highly influenced by age: they, in fact, begin in the uterus. Fetal programming includes also a set of epigenetic changes in response to various environmental stimuli that can affect life and the health of the child even in adulthood [13–16], a phenomenon that was well known by diabetologists because David J Bakers hypothesized that chronic, degenerative conditions of adult health, such as cardiovascular diseases and type 2 diabetes, may be triggered by in utero events [17].

The lack of attention to the sex-gender variable is also found in some clinical studies: the erroneous assumption that men and women are equal has led to the underrepresentation of women in clinical studies or to considering the differences between men and women as normal [18]. A major reason for this shortcoming is that the overall gender-stratified sample size is often too small to produce valid results. Furthermore, despite well-recognized sex and gender differences in disease management, most management guidelines are not sex-gender specific [2,19,20].

In this context, it is important to stress that the pharmacological response is multifactorial and depends not only on the drug but also on patient-related factors, such as genetic and epigenetic factors, age, body composition and metabolism, use of concomitant drugs (including oral contraceptives), and exposure to environmental factors, as well as to socio-cultural factors [11,20–23]. All of this has a strong impact on pharmacokinetics and pharmacodynamics and on the onset of adverse drug reactions, which are more reported by women. They also take more drugs and botanical remedies and experience more interactions with an increased risk of adverse drug reactions [19,24–27].

An interesting and significant example of how sex-gender can influence pathophysiology and therapeutic response is provided by type 2 diabetes [4,28–31].

2. Type 2 Diabetes: A Sex-Gender Disease

Diabetes is one of the most common diseases, with a continuous worldwide rise in its incidence [32]. The toll paid by people with diabetes is the associated huge burden of cardiovascular diseases including coronary artery disease, ischemic stroke, or heart failure; they are going to suffer throughout their life with a reduced quality of life as well as a reduced life expectancy. In this context, an aspect that is emerging with ever greater clarity is that both the pathogenesis of diabetes as well as its cardiovascular complications are significantly sex-gender oriented. Sex, in fact, plays a significant role in determining the risk of developing diabetes, especially type 2 diabetes mellitus, which represents about 90% of all cases of diabetes. First, according to most epidemiological surveys, men are more at risk of diabetes, as compared to women, at least excluding the older strata of the population, where the women seem to be more represented [33]. A lot of evidence has been accrued, during the last decade, suggesting that the metabolic regulation of carbohydrates and lipids is different in women as compared to men [34]. Overall, the female sex is characterized by features that have a protective role against the development of diabetes such as reduced visceral disposition of adiposity, higher total body insulin sensitivity, and greater non-esterified fatty acids oxidation after exercise, with the only exception of the finding that women present greater plasma glucose value after 2-hr- oral glucose tolerance test (OGTT) [4,35]. It is reported that the one shield which protects women against metabolic derangements predisposing them to diabetes, as well as protecting them against its cardiovascular complications, is represented by the exposure to estrogens [36–39]. Estrogens in animal models impressively reduce whole-body adiposity, increase insulin sensitivity and improve overall glucose tolerance [40,41]. This protective action of estrogens, however, is lost with menopause [42], and due to this event, from this date females are being exposed to risk factors for cardiovascular diseases, including diabetes, even more than men.

Numerous studies have investigated the potential mechanisms that may underpin the sex-gender differences in type 2 diabetes mellitus [43–48]. Glycated hemoglobin (HbA1c) is more strongly associated with fasting plasma glucose in women than in men, and age, waist circumference, body max index, systolic and diastolic blood pressure, triglyceride levels, total cholesterol, low density lipoprotein, high density lipoprotein, fasting insulin, and proinsulin levels all predict type 2 diabetes mellitus better in women [45,48].

The impaired fasting glucose/impaired glucose tolerance occurs in a more severe endothelial dysfunction in women than men, including changes in markers of endothelial function (E-selectin and soluble intercellular adhesion molecule). In addition, fibrinolysis (plasminogen activator inhibitor-1) is more abnormal in premenopausal women with

type 2 diabetes than their male counterparts [43,44,49]. Moreover, hyperglycemia induces oxidative stress and upregulation of pro-inflammatory factors, promoting a vascular dysfunction [50]. Oxidative stress induces insulin resistance by altering the insulin-signaling pathway and the levels of adipokines nuclear factor kappa-B, tumor necrosis factor α, interleukin 1β plasma endotoxin, and toll-like receptor 4 are increased [50–53].

Metabolic pathways involved in the pathogenesis of diabetes seem to be, therefore, in part, sex determined; however, in this sex dimorphism, even if the effect of estrogens is well delineated, the additional role of other determinants, such as sex chromosomes, gut microbiome, prenatal conditioning events or sex-related epigenetic modifications, cannot be ruled out being the object of ongoing research [54–57].

3. Sex-Gender Differences in Diabetic Complications

As testified by metanalytical studies regarding large populations, women with diabetes have a significantly higher risk of coronary heart disease, stroke, ischemic stroke, or vascular dementia than men [4,54], with the only exclusion being peripheral arterial diseases [58]. All this means that diabetes is associated with a greater adjusted relative risk of cardiovascular events, especially coronary heart diseases and ischemic stroke in women (by ~40%) as compared to men [59,60]. Further proof of concept for this greater diabetes-driven facility of women comes from the recent finding that after hospitalization for diabetic foot, a diabetes complication overwhelmingly associated with male sex, women are more at risk of cardiovascular events such as ischemic stroke or myocardial infarction [61,62]. As compared to people without diabetes, moreover, women are more exposed not only to all complications of diabetes but also to other risk factors for cardiovascular diseases such as obesity, smoking, hypertension, or dyslipidemia. All this is of great importance since all these risk factors are frequently combined, all or in part, in the same woman with diabetes. In addition, interestingly, at diagnosis of diabetes women are on average more obese and have a higher number of either traditional or novel risk factors not at target, as compared to men [63–65]. In conclusion, the burden of diabetes and its macrovascular complications, as well as the relative greater impact of all risk factors for atherosclerosis, is greater among women, being only partly counterbalanced by a lesser absolute risk of diabetes or cardiovascular events, when compared to men [66]. Furthermore, a lot of effort has been made over time to shed light on the role of sex in female disadvantage given to diabetes. In this context, interestingly, recent studies have demonstrated that any causal effect of genetic liability to type 2 diabetes on the risk of coronary heart disease is not stronger for women than men [67], while the impairment in the metabolic control of diabetes, as expressed by each one unit increase in glycated hemoglobin, impacts to the same extent in men and women [68]. Sex-gender aspects, however, cannot be ruled out to explain this greater diabetes-associated risk among women. Inequalities in the treatment of diabetes and of associated vascular risk factors leading to a lesser percentage of women who reach the optimal target after treatment of diabetes [69] or differences in socioeconomic status, mainly disadvantaging women, may be additionally considered causes to explain the reason of this gender-oriented gap. In conclusion, women are more susceptible to cardiovascular complications of diabetes than men are, even if practically this is mitigated by a lesser absolute risk of both diabetes and atherosclerotic events among women. Sex biological, hormonal, and genetic differences associated with gender aspects such as inequalities in treatment or differences in socioeconomic status between men and women may explain and further modulate the extent of this gap. The main lesson for health caregivers is to tailor primary and secondary interventions in people with diabetes, keeping in mind the existence of such sex-gender differences in susceptibility to its vascular complications.

4. Microvascular Complications

The sex-gender impact of diabetes on microvascular complications is much less defined, as compared to what is evidenced for macrovascular complications. Regarding retinopathy, both in type 1 and in type 2 diabetes, its severity, as well as the evolution over

time, seems worse among males [70–72]. Studies concerning sex- gender differences in incidence or severity of diabetic nephropathy are more uncertain, with some suggesting men as more affected by renal complications, while others suggest that women are more predisposed to a worse prognosis for end-stage renal disease [73–75]. In this regard, it is interesting to note that women with type 2 diabetes are at greater risk of non-albuminuric renal failure, presumably due to this type of renal damage apparently being most associated with cardiovascular events [76]. There are, however, studies that do not find sex-gender differences in both the incidence and time course of diabetic nephropathy. Regarding diabetic neuropathy, both peripheral sensory-motor and autonomic diabetic neuropathy have been found to be more prevalent in men, even if the reports are conflicting [77–82], due also to the non-standardized methodology in the diagnosis of neuropathy for epidemiological purposes. Finally, it should be emphasized that no clear pathophysiological aspects have been identified to explain the sex-gender-related differences in diabetic microangiopathy, not unlike those suggested for macrovascular complications.

5. Drug Response

Until now the sex and gender influences on drug response have been neglected and the "one size fits all" model is still predominant both in research and in daily clinical practice [2,21,83]. Relevantly, the clinical trials of new antidiabetic drugs enrolled only 20–40% of women [18], and often, some of them have no statistical power to verify whether sex-gender may be related to response differences [84]. The low participation of women leads to reduced appropriateness in women because data are accumulating, pointing out the sex and gender differences in drug prescribing, the pharmacokinetics, the pharmacodynamics, and the efficacy and safety profile of multiple combinations of drugs [18,21].

Concerning diabetes, it should be noted that in diabetic individuals the pharmacokinetics and pharmacodynamics change. In particular, changes in blood flow in subcutaneous adipose tissue and muscle, gastric mobility, and acidity may altogether affect the absorption of drugs [18]. Type 2 diabetes mellitus-induced effects on oral absorption may prevail in women [21]. The gastroenteric diabetic alterations in fact can vary the ionization of weak acids and bases, therefore, changing absorption, as occurs with glipizide [85]. It should be considered, moreover, that healthy women have longer gastrointestinal emptying times and higher gastric pH than men [21]. The sex and gender differences observed in healthy individuals in subcutaneous adipose tissues and skeletal muscle (more fat and less muscle in women) together with blood flow variations could lead to altered subcutaneous and intramuscular absorption of insulin in a sex-specific way [85]. The non-enzymatic glycation of protein may involve drug-metabolizing enzymes altering biotransformation and drug transporters involved in drug elimination. Notably, alterations in pharmacokinetics are drug specific [18]. The obesity present in many diabetic individuals may participate in pharmacokinetic variation observed in diabetics [85]. The effect of diabetes on pharmacodynamics is less known but it cannot be underestimated that type 2 diabetes mellitus alters ions channels [86] increasing the risk of arrhythmias including the prolonging of the QT interval [87], which is longer in women than in men, and being a woman is a risk factor for iatrogenic QT long syndrome. Several recent reviews have brilliantly and exhaustively reported sex and gender differences in pharmacokinetics, pharmacodynamics, and safety profiles available for the different antidiabetics drug classes [18,24], which are summarized in Table 1.

Treatments with new synthetic antidiabetic drugs, namely, sodium-glucose-cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor (GLP-1R) agonists, decrease ischemic events and atherosclerotic cardiovascular disease [84,88]. SGLT2 inhibitors also have cardio-renal benefits even in non-diabetic patients. They reduce hospitalizations and mortality for patients with heart failure with reduced ejection fraction and prevention of progression of chronic kidney disease. However, trials with GLP-1R agonists for cardiovascular risk assessment enrolled only a few women (ranging from 30% with albiglutide (HARMONY) to 46% with dulaglutide (REWIND)) [88]. Trials with SGLT2 inhibitors

enrolled even fewer women (ranging from 29% empagliflozin (EMPA-REG-OUTCOME) to 37% with dapagliflozin (Declare-TIMI-58)) [88]. The number of women is still low in the second-generation trials. The absence of women in clinical trials leads to the lack of sex-gender-specific reporting rates. With SGLT2 inhibitors, urinary tract/genital infection dominated in women, while a gastrointestinal drugs effect prevailed in women treated with GLP-1R agonists [29]. In view of sex-gender differences that significantly impact pharmacokinetics and pharmacodynamics [21], research devoted to finding sex-gender differences in drug response is urgent. Still, it is also urgent to identify sex-gender differences, including the higher reporting rates of adverse events in women [3] which will impact pharmacovigilance results.

Table 1. Some sex-gender differences in antidiabetic drugs.

Drug	Differences	References
Insulin	fertile women require higher dose higher risk of hypoglycaemia in women	[24,89,90] [91]
Biguanides	higher reduction in HbA1c in men higher lactic acidosis in women higher treatment failure in women	[92] [93] [94]
Sulfonyureas	higher exposure in women higher weight loss in women lower end-stage kidney disease in men	[95] [92] [96]
Thiazolidinediones	higher exposure to pioglitazone in women higher risk of bone fractures in women	[95] [97,98]
GLP-1R agonists	higher prescription in young women better glycaemic control in men higher weight loss in women higher gastrointestinal adverse effects in women	[84] [84,99] [99] [99]
Alpha glucosidase inhibitors	more effective in older and non-obese women higher gastrointestinal adverse effects in men	[100] [101]
SGLT2 inhibitors	better response in men higher urinary infections in women higher ketoacidosis in women higher Fournier gangrene in men	[102] [103,104] [105,106] [107]

6. Conclusions

The data reported in this review show that a sex-gender approach in medicine is mandatory. To maximize the scientific rigor and value of the research, it is mandatory to include sex and gender in both pre-clinical and clinical research, to ensure health equity and to ameliorate the health and well-being of all citizens. Therefore, sex-gender studies need interdisciplinarity and intersectionality aimed at offering the most appropriate care to each person. Gender biases could be avoided by implementing greater scientific rigor of research, from preclinical to clinical practice, by making a concerted effort to ensure that sex-gender-specific analyses are included, to ensure health equity and appropriateness.

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