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Sex and diabetes

Sex differences in type 2 diabetes

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Summary

The influence of sex – considered to be the biological differences between women and men – and gender – considered to be sociologically constructed differences based on membership in one of the two sex categories – appears to be particularly important for noncommunicable diseases such as type 2 diabetes (T2D) and obesity. Many T2D risk factors are behavioural and greatly, but not only, influenced by gender-related determinants, making them modifiable factors. In this review, we focus on sex-related biological differences in the prevalence of diabetes and its biological risk factors, such as obesity, fat distribution, metabolic syndrome and glucose homoeostasis, with a particular interest in the influence of menopause and pregnancy. Globally, men have had a higher prevalence of T2D than women with regional, socioeconomic and age-related variations. Overall, women tend to be more protected from cardiometabolic diseases before menopause than men. However, hormonal variation over the course of life, particularly during menopause, modifies these risks. Similarly to T2D, there are differences in the prevalence of obesity between women and men that change during the lifespan. The link between obesity and T2D seems to be stronger in women compared to men. Various hormones have an impact on glycaemic levels and on body fat and their concentrations and effect on metabolic parameters can differ by sex. Understanding and acknowledging sex-related differences in T2D and its risk factors is important to improve health research, lead to better clinical care, more suitable preventive policies and programs for both women and men.

Keywords: Type 2 diabetes, sex, hormones, lifestyle

Introduction

According to the 10th edition of the International Diabetes Federation (IDF) Atlas [1], more than one in 10 adults were living with diabetes in 2021 worldwide. The estimated prevalence of diabetes in women is slightly lower than in men (10.2% and 10.8% respectively) [1]. In 2021, there were 17.7 million more men than women living with diabetes [1]. Important biological, lifestyle, environmental and socioeconomic differences between women and men influence the predisposition, clinical presentation and development of type 2 diabetes (T2D) [2]. To improve T2D care and prevention in both women and men it is important to better understand these differences.

Long, there has been a lack of attention on sex and gender in clinical research and guidelines, in which women remain largely underrepresented. Despite the increasing awareness of the importance of considering both sex and gender in health science, it is important to have a clear definition and conceptual model of both [3]. Table 1 provides concise definitions of the key concepts of sex, gender and gender norms.

This narrative review focuses on the population of women and men, because health research on sex and gender minorities – such as populations with variations in sexual development or gender diverse people – is scarce. We will mainly focus on sex-related biological differences between men and women. Due to limited space, gender-related sociocultural differences in T2D will be addressed in a separate article. We first assess how the prevalence of diabetes differs between women and men by using an intersectional approach, integrating geographic, ethnic and lifespan considerations. Then we review the biological risk factors, including sexual dimorphism in obesity, fat distribution, metabolic syndrome (MetS) and glucose homoeostasis, with a particular interest in the influence of hormones at menopause and a quick overview of the changes occurring during pregnancy.

Epidemiology

Considering differences in the prevalence of T2D between men and women, men have had a higher prevalence than women in the last 20 years (fig. 1) [1]. However, many regional, socioeconomic and age-related differences are observed. In two recent studies, sex differences ranged from almost no significant difference in adults with a low income in China [4] up to 10.1% in adults aged 50-59 years in Korea (men 19.0%; women 8.9%) [5]. A study from Germany reported that over a larger lifespan women aged 0 to 85 years (T2D population 2007 to 2010) had a higher prevalence than men did [6], as did women aged 25-65 years in another study from Sweden (1990 to 2009) [7]. However, recently, a shift has been observed with a higher increase in the prevalence of T2D in men compared to women. This observation is in line with the worldwide trend, where the global prevalence of diabetes between 1980 and 2021 increased from 4.3% to 10.8% for men and from 5.0% to 10.2% for women [1, 8]. Higher rates of T2D diagnoses in women from lower socioeconomic status (SES) groups were found in a systematic review and meta-analysis by Agardh et al. [9], showing a reduced gap among po-

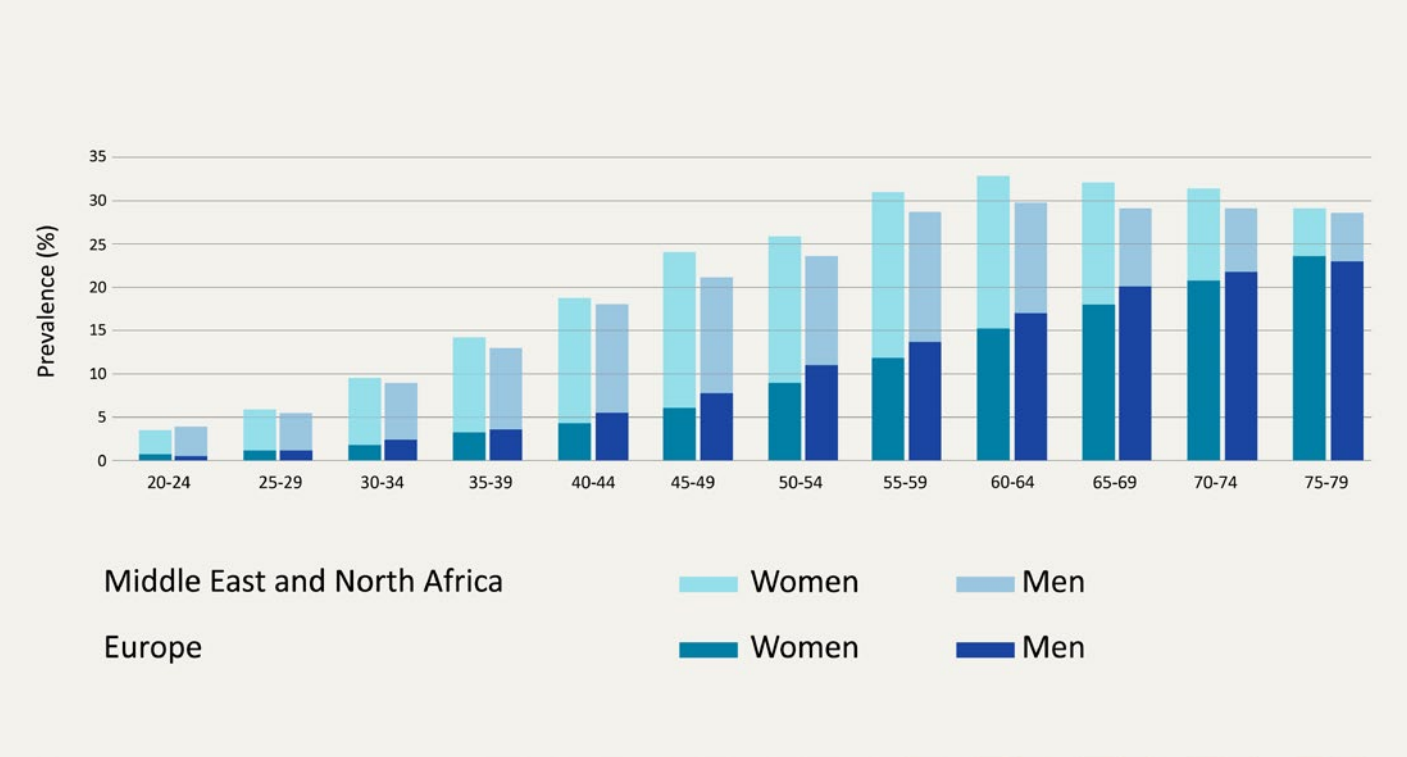

Figure 1: Prevalence (%) estimates of diabetes by age and sex in 2021 [1] with kind permission.

pulations with low SES. One hypothesis is that women in these groups are more prone to physical inactivity, psychosocial stress and obesity than women of higher SES and that this SES difference is more pronounced in women than in men. The prevalence of T2D also fluctuates across the lifespan. The literature review conducted by Huebschmann et al. [10] in 2019 showed that women have significantly higher rates of T2D in youth, whereas men have a significantly higher prevalence in midlife and the rates are similar between women and men in later life. The presence of unhealthy behaviours among young women, the stronger negative impact these behaviours have on them and the changes that occur during the perinatal period (women gaining on average 4-5 kg with each pregnancy) and after menopause could partly explain these observed differences [10].

Regarding the incidence of T2D, data comes almost entirely from high-income countries, making global trends imprecise. A recent systematic review by Magliano et al. [11] shows that in high-income countries, the incidence of T2D slowed from 2006 to 2014, with levelling trends and even declining trends in two thirds of the studied populations. Regarding the difference between women and men, the literature shows that, similar to the differences in prevalence, the incidence in women is slightly lower than in men and globally follows the same levelling or declining patterns as in men [11].

Biological differences between women and men in T2D risk factors

Obesity

For women and men, obesity, particularly abdominal obesity, is one of the strongest risk factors for developing a T2D. Weight is determined by individual behaviours, such as diet and physical activity, as well as by a variety of biological factors (fig. 2). In contrast to low income countries, obesity in Europe tends to be more frequent in men than in women [12], e.g., 12.3% and. 10.2% respectively in Switzerland [13]. Differences in prevalence are partially mediated by sociocultural factors (gender-related variables) and sex hormones (sex-related variables) [12]. Women have a higher body fat percentage than men and more often develop peripheral adiposity [14], whereas men more often develop abdominal obesity, which is more strongly associated with the risk of T2D and cardiovascular diseases (CVD) [15]. However, women in peri- and postmenopausal period have an increasing tendency towards developing abdominal obesity [12]. Aside from sex hormones, unequally distributed behavioural (diet and physical activity), psychological (coping with stress) and environmental (sociocultural norms) factors are also likely to contribute to differences in obesity prevalence between women and men [12]. For both women and men, as Body Mass Index (BMI) increases, the relative risk for T2D increases as well, though this association is stronger in women. At a BMI of 35 kg/m2, the relative risk increases 60.9-fold in women and 40-fold in men [16]. Nevertheless, men tend to develop diabetes at a lower average BMI than women do [17]. An increase in BMI is therefore a stronger predictor of T2D for women and women with T2D are generally more obese than men with T2D [2]. In the diabetes population, the prevalence of abdominal obesity is more than 70% in women compared with 40% in men. However, the determinant criteria are different between women and men, with a lower cut-off for women (for example using ATP-III criteria waist circumference [WC] >88cm) than for men (WC >102cm) [18]. This finding suggests that the association between abdominal obesity and T2D is stronger in women than in men [18]. Abdominal obesity is often approximated with WC – which by itself cannot differentiate between visceral and subcutaneous fat – using sex- and ethnicity-specific cut-off points [19]. Notably, visceral fat has been described as a better predictor for T2D in the Caucasian population [20]. A more precise estimation of visceral adiposity than by using WC can be obtained by measuring visceral fat with dual-energy X-ray absorptiometry, magnetic resonance imaging, computed tomography or the visceral adiposity index, a mathematical model using anthropometric and laboratory parameters. This could shed light on the sex-specific differences in visceral adiposity as a predictor for T2D [19].

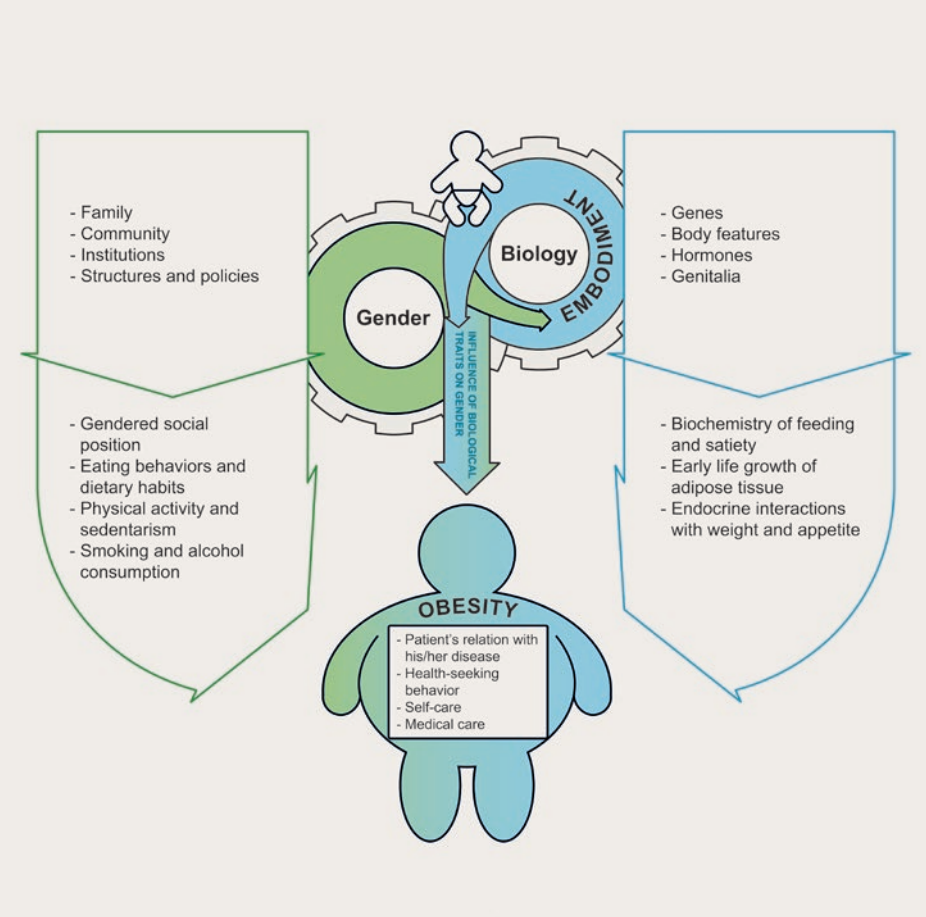

Figure 2: Obesity as an example of the interwoven interactions of gender and biology.

Metabolic syndrome (MetS)

The Metabolic syndrome (MetS) is a condition that includes the clustering of abdominal obesity, insulin resistance, dyslipidaemia and elevated blood pressure and is highly predictive of T2D [21]. Its prevalence seems to be higher in men than in women in high income countries [22], but lower in low and median income countries [23]. However, the existence of various definitions of MetS complicates comparisons between women and men worldwide, as well as across specific countries or ethnicities. The current literature describes the sex-specific differences in MetS as originating from two main factors [24]. The first factor is the variation in prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG is more prevalent in men and IGT is more prevalent in women [25]. Notably, because more recent guidelines do not include IGT tests for T2D screening, women tend to be underdiagnosed [24]. The second factor is the hormonal regulation of body weight and abdominal adiposity, for example the effects of oestrogen on body fat distribution [26]. With the start of menopause women see their risks for developing diseases coupled to MetS, such as obesity, CVD and T2D, rise dramatically [27].

Sex-specific risk of gestational diabetes

Changes that occur during pregnancy can represent risk factors for T2D. Gestational diabetes, which affects mostly insulin-resistant overweight or obese women, increases the risk of T2D, CVD and obesity for the mother, as well as representing a long-term risk for these conditions for the child [2, 28]. The prevalence of excessive gestational weight gain outside the recommended ranges is increasing [29] and studies have shown that high rates of gestational weight gain may increase women's risk of gestational diabetes and postpartum weight retention and consequently, of T2D [29]. The prevalence of gestational diabetes (GD) varies considerably, ranging from 1% to over 30% depending on the geographic region, ethnicity, screening methods and diagnostic criteria [30]. In Switzerland, the prevalence of GD is approximately 11 % [31]. Table 2 summarises risk factors and adverse health outcomes of GD.

Glucose homoeostasis

Sexual dimorphism in glucose homoeostasis has been described in the literature [32]. Investigators point out that premenopausal women are more insulin sensitive than men are even after adjustment for age and BMI. This advantage disappears in the population with T2D, where a similar extent of insulin resistance is observed in women and men [33]. This difference can be explained by enhanced glucose uptake by skeletal muscles in women and the protection that oestrogen furnishes against insulin resistance [32]. Furthermore, women seem to exhibit a greater insulin secretion capacity than men do, as shown by estimates of beta cell function following an oral glucose tolerance test or a standardised meal [34]. In people with T2D, impairment of beta cell function is similar in both sexes [32].

Hormones

Many hormones and binding proteins have an impact on glycaemia and body fat. Both their levels and their impact on these parameters can differ by sex [35].

Cortisol. Cortisol, in addition to its adrenal production, is also generated in adipose tissue through the conversion of inactive cortisone to active cortisol by the enzyme 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1), whose activity increases with increasing body weight [36]. Oestrogen attenuates 11betaHSD1's activity in the liver, kidney and testis, but upregulates its mRNA expression in preadipocytes in women [36]. High cortisol levels play an important role in increased insulin resistance, gluconeogenesis, accumulation of visceral adipose tissue, hypertension and dyslipidaemia. Some studies showed a slightly higher morning salivary cortisol in women, but most of these studies were not conclusive.

Testosterone. A systematic review and meta-analysis by Yao et al. [37] showed that men with lower levels of testosterone have a higher risk of developing T2D, whereas increased androgen levels augments insulin resistance in women, increasing the risk of T2D and CVD [27].

Sex hormone-binding globulin (SHBG). The synthesis of SHBG, which regulates free active testosterone, is inhibited by insulin. In a situation of hyperinsulinemia, lower SHBG contributes to higher androgen levels [18]. In the case of polycystic ovary syndrome this creates a vicious circle: higher insulin levels stimulate the synthesis of androgens in the ovaries and decrease SHBG, which then exacerbates hyperandrogenaemia and thereby insulin resistance. Results from a systematic review and meta-analysis by Ding et al. [27] also indicate that there is a stronger negative association between SHBG and T2D in women than in men. Regarding the patient characteristics in this study, women with T2D had significantly lower plasma levels of SHBG than controls, whereas men with T2D had only marginally lower levels.

Oestrogen. There are three types of oestrogen, the primary female sex hormone: oestrone (E1), oestriol (E3) and oestradiol (E2). The latter is the most potent and the principal circulating type in women during their reproductive life [38]. Oestrogen is synthesised in the ovaries in premenopausal women, as well as in adipose tissue in every human, through the conversion of testosterone by aromatase [35]. Obese women and men have higher aromatase levels and therefore elevated levels of oestrogen [39]. Oestrogen has a protective effect against T2D through various mechanisms. It enhances insulin sensitivity, lowers levels of liver fat, stimulates insulin synthesis and secretion, exerts protective effects on islets in women and by direct effects on the brain; it can also decrease food intake [2, 32-34]. During puberty, oestrogen also promotes gluteofemoral fat accumulation, resulting in women's gynoid shape [2]. Nonetheless, these advantages were shown to disappear after menopause with the loss of production of this hormone, resulting in decreased insulin sensitivity and more abdominal fat accumulation in postmenopausal women [2, 26]. Subsequently, decreased insulin resistance and reduced incidence of T2D were demonstrated in clinical trials of oestrogen replacement therapy in postmenopausal women [26]. Oestrogen deficiency could be considered a risk factor for T2D, as it affects glucose regulation and increases insulin resistance in men with congenital oestrogen deficiency, as well as in postmenopausal women [40].

Progesterone. In an article by Picard et al. [41], a clear correlation between non-fasting plasma glucose levels and progesterone levels was described in female mice, suggesting that increased progesterone levels are associated with hyperglycaemic states in rodents. Moreover, investigators have shown that progesterone accelerates the progression of diabetes in animal models [41]. Progestins, as used in oral contraception, are known to increase insulin resistance [42] and some of this effect depends on their androgenicity. However, new combinations such as estradiol valerate and dienogest have shown no effect on the carbohydrate metabolism [43].

Growth hormone (GH) and insulin-like growth factor 1 (IGF-1). The diabetogenic action of high doses of GH and IGF-1 has been well described, although IGF-1 has also been suggested to have beneficial effects on glucose homoeostasis due to its glucose-lowering and insulin-sensitising actions [44]. In healthy populations, women have higher mean GH levels and GH pulse amplitudes than men do, but there are no sex differences in serum IGF-I levels, possibly related to the impact of oestrogen on GH and IGF-1 production [45].

Key points

- Both sex, the biological differences between women and men, and gender, the sociologically constructed differences based on membership in one of the two sex categories, influence the prevalence of noncommunicable diseases such as obesity and type 2 diabetes (T2D).
- Many modifiable T2D risk factors are behavioural and greatly, but not only, influenced by gender-related determinants.
- There are differences in the prevalence of obesity and T2D between women and men that change during the lifespan.
- Pregnancy and menopause have a special impact with (abdominal) obesity and T2D increasing after the menopause.
- The link between obesity and T2D seems to be stronger in women than in men.
- Various hormones, such as sex hormones, but also cortisol, growth hormone and other hormones can impact glycaemic levels and body fat and their concentrations and effect on metabolic parameters can differ by sex.

Adipokines. Healthy men, compared with healthy women, tend to have lower circulating adiponectin levels, a hormone produced and secreted by adipocytes, which increases the insulin sensitivity of the liver and skeletal muscle [35]. This lower level could be partially explained with men being more prone to insulin resistance, which decreases adiponectin levels. Whether adiponectin is the cause or consequence of greater insulin resistance in general remains unclear.

Leptin, an adipokine produced in adipose tissue, has long been known as a key hormone in the control of food intake, but more recent studies showed that it is also critical for glycaemic control [46]. Leptin levels are generally higher in women, but it is not yet fully understood whether this is due to sex differences in fat mass or due to other factors, such as sex steroids [47]. There may also be opposing effects on the risk of CVD in the population with T2D, increased leptin levels being potentially protective in women but a risk factor in men [48, 49].

Conclusion

Numerous biological sex-related differences have a strong impact on the risk and pathophysiology of T2D. The differences in the prevalence of diabetes and obesity between men and women are mediated by both biological and psychosocial factors. Overall, women tend to be more protected from cardiometabolic diseases before menopause than men. However, hormonal variation over the course of life, particularly during menopause, modifies these risks. The link between obesity and T2D seems to be stronger in women compared to men. Hormones such as sex hormones, but also other hormones such as cortisol and GH have an impact on glycaemic levels and on body fat. Hormonal concentrations and their effect on metabolic parameters can differ by sex.

Sex-related factors alone are insufficient to explain the observed differences between men and women. Gender-related social determinants, although not mentioned in this article, also need to be considered as behavioural, environmental and psychosocial factors are potentially modifiable by adequate individual and structural interventions. The gathered knowledge will allow the building of gender- and sex-adapted clinical guidelines across the lifespan to better prevent, diagnose and treat T2D.

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