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Gender differences in glucose homeostasis and diabetes

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Abstract

Some aspects of glucose homeostasis are regulated differently in males and females. This review discusses the most fundamental gender differences in glucose homeostasis and diabetes. These include the prevalence of impaired fasting glucose and impaired glucose tolerance, the prevalence and incidence of type 2 and type 1 diabetes, and the sex-specific effects of testosterone and estrogen deficiency and excess. These gender-specific differences in glucose homeostasis represent a source of factors that should be studied to develop gender-based therapeutic avenues for diabetes.

Keywords

Gender differences; sex differences; diabetes; obesity; glucose homeostasis

Introduction

Increasing evidence suggests that sex and gender affect the pathophysiology, incidence, prevalence, symptoms and signs, course and response to therapy of many diseases. Sex differences in physiology and disease are of fundamental importance because they represent gender-related biological factors that might lead to better prevention and therapy. Between April 20th and 21st 2017, the American University in Washington DC hosted a symposium on “Sex Differences: from Neuroscience to the Clinic and Beyond.” This review summarizes a presentation I made at this meeting to discuss the most fundamental gender differences in glucose homeostasis and diabetes. These include the prevalence of impaired fasting glucose and impaired glucose tolerance, the prevalence and incidence of type 2 and type 1 diabetes and the sex-specific effects of testosterone and estrogen deficiency and excess in men and women.

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Gender differences in glucose homeostasis

There are considerable gender differences in the response to an oral glucose tolerance test (OGTT). In an Australian population, Sicree et al. reported that women have lower fasting plasma glucose (FPG), higher 2-hour plasma glucose following an OGTT (2-hour PG) and greater FPG-2-hour PG increment [1]. These differences are correlated to height and may to be due to smaller muscle mass and associated glucose uptake, for a fixed charge of 75g of glucose during the OGTT [1]. In fact, men and women have near identical HbA1c values, suggesting that in daily life the postprandial glucose excursions are similar in men and women and that the 2hPG may be a consequence of the fixed glucose load of the OGTT. Alternatively, gonadal hormones have been implicated in this gender difference in glucose homeostasis. Indeed, menopausal estrogen therapy decreases fasting glucose while impairing glucose tolerance [2, 3].

Insulin sensitivity also differs by sex. Compared to men of the same age, healthy women have lower skeletal muscle mass and higher adipose tissue mass, more circulating free fatty acids (FFA), and higher intramyocellular lipid content, all factors that could promote insulin resistance in women compared to men. Yet, women are as sensitive to insulin as men. In fact, women are even resistant to FFA-induced insulin resistance [4]. When matched for physical fitness and during a hyperinsulinemic, euglycemic clamp, the gold-standard to quantify systemic insulin action, insulin sensitivity is greater in women as a result of higher glucose disposal by skeletal muscles [5]. However, physical fitness is a critical parameter for female insulin sensitivity, and women with lower fitness than men exhibit insulin resistance [6]. Yet these same women exhibit comparable glucose disposal to men because of enhanced glucose effectiveness (the ability of glucose to promote its own disposal in an insulin-dependent manner) [6]. Women also tend to have enhanced postprandial insulin and C-peptide concentrations (despite similar plasma glucose) after a meal test [6]. In addition, the disposition index was higher in women than in men, reflecting greater insulin secretion for a given level of insulin action [6]. The mechanisms for facilitated glucose homeostasis in women compared to men are unclear, but could be due at least in part to the beneficial effect of a physiological window of circulating estrogens before menopause, as will be discussed below.

Gender differences in type 2 diabetes

The prevalence of pre-diabetic syndromes such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) is also sexually biased in all populations studied. Indeed, IFG is more prevalent in men while IGT is more prevalent in women [1, 2, 7, 8]. The reason for these differences in early dysglycemia is unknown, but could involve the effect of gonadal hormones. Indeed, menopausal hormone therapy with estrogens decreases fasting glucose while impairing glucose tolerance [2, 3]. The prevalence of type 2 diabetes is also characterized by a sex difference. Overall, the global diabetes prevalence is higher in men, but there are more women with diabetes than men [9]. The sex difference in the prevalence of diabetes is reversed depending upon the stage of reproductive life [9]; that is, there are more diabetic men before the age of puberty, while there are more diabetic women after the age of menopause and in older age. The combined effect of a greater number of elderly

women than men in most populations and the increasing prevalence of diabetes with age is the given explanation for this observation. Recent data from the National Health and Nutrition Examination Survey (NHANES) over two decades reveals that in 2011–2012, diabetes and prediabetes (including undiagnosed cases) affected almost half the adult US population and exhibited a sex bias [10]. When diabetes was not previously diagnosed, the authors used two definitions of diabetes corresponding to different subsets of data: The first included three criteria, combining the hemoglobin A_{1c} with FPG) and 2-hour PG; the second included the hemoglobin A_{1c} and the FPG only, without the 2-hour PG. During the 2011–2012 period, the authors report a significant increase in the prevalence of total diabetes (13.6% vs 11.4%) and a trend toward an increase in the prevalence of prediabetes (39.1% vs 33.8%) in men compared to women, only when the 2-hour PG was not used in the definition. This is an important observation because, as discussed above, more men show impaired FPG and more women show impaired glucose tolerance (assessed by 2-hour PG). Thus, the exclusion of the 2-hour PG values in the calculation of diabetes prevalence may have underestimated the prevalence of diabetes and prediabetes cases in women.

An important male predominance (75%) is also observed in ketosis-prone diabetes (also called idiopathic type 1 diabetes), a form of type 2 diabetes mostly encountered in non-Caucasian subjects and with a propensity to acute and phasic insulin dependence and diabetic ketoacidosis [11, 12]. In ketosis-prone diabetes, women are relatively protected unless they are in an anovulatory or hypoestrogenic state [11, 13].

Interestingly, in the Jackson Heart Study visceral adipose tissue is associated with increased FPG and type 2 diabetes in both sexes but a stronger association between visceral adipose tissue and alterations in glucose homeostasis is observed for women [14].

Gender difference in type 1 diabetes

There is also a gender difference in type 1 diabetes incidence. Type 1 diabetes is the only common autoimmune disease not characterized by a female predominance. In fact, T1D is characterized by a male predominance in Caucasians (ratio: 1:7) [15]. The pubertal period is associated with a decreased incidence of T1D in girls [16, 17] who retain stronger residual β -cell function than boys [18]. This suggests that female gonadal hormones transiently protect against T1D. Consistent with this possibility, serum levels of estradiol (E2), the main estrogen, and serum estrogenic activity are decreased in adolescents with T1D, suggesting that they are not protected by E2 [19]. In addition, E2 has been shown to protect rodent and human islet survival from multiple metabolic and pro-inflammatory injuries *in vivo* [20, 21]. In a recent study, a general E2 treatment prevented insulinitis and T1D in nonobese diabetic (NOD) mice by restoring the immunomodulatory functions of iNKT cells [22].

Menopause and type 2 diabetes in women

The diabetogenic effect of menopausal E2 deficiency in women can be considered a sexually dimorphic form of dysglycemia. The exact effect of menopause on dysglycemia in women, independent from aging, has been extensively reviewed [3]. The EPIC-InterAct study, a prospective study with a follow-up of over 10 years, concluded that early menopause (before

the age of 40) is associated with a greater risk of type 2 diabetes than menopause occurring after the age of 50 [23]. Similarly, an observational study in over 16,000 Chinese women reported that early menopausal age (before the age of 45) is associated with increased risk of diabetes compared to menopause starting at 50 years [24]. In addition, longitudinal studies in women with rapid and severe E2 deficiency from surgical ovariectomy reported an increased diabetes risk [25]. Thus, women with bilateral ovariectomy exhibited an increased risk of diabetes compared to women with natural menopause over a 9-year follow up [26]. The mechanisms for the effect of menopause on type 2 diabetes development have been reviewed recently and include alteration in insulin secretion, insulin sensitivity, and glucose effectiveness [3]. Therefore, the accumulated evidence argues for a role of menopausal E2 deficiency in the increased risk of type 2 diabetes in women. However, it should be emphasized that E2 favors glucose homeostasis within a physiological window. When circulating estrogens rise to supraphysiological concentrations [27], or when powerful synthetic estrogens like oral contraceptives are used [28], insulin resistance develops.

Testosterone deficiency and type 2 diabetes in men

Another area of sex difference in glucose homeostasis is the bi-directional modulation of diabetes risk by testosterone in males and females. Testosterone deficiency produces metabolic dysfunction and predisposes to diabetes in aging males, but in females increased circulating testosterone concentrations also predispose to metabolic dysfunction and dysglycemia. The impact of testosterone deficiency on the development of visceral obesity, insulin resistance and metabolic syndrome in men is well established [29–35]. The role of testosterone in predisposing to type 2 diabetes is more controversial. In most large population-based prospective studies, low testosterone levels predicted incident type 2 diabetes in older men [36, 37]. Consistent with the beneficial effect of endogenous testosterone in glucose homeostasis in men, large randomized control trials (over 200 subjects) that have assessed the effect of testosterone therapy (TRT) in patients with type 2 diabetes have observed an improvement in glycemic controls in patients randomized to testosterone [38, 39].

Subjects treated with androgen-depletion therapy (ADT) for prostate cancer exhibit primary testosterone deficiency, making it possible to determine the causative role of testosterone deficiency on incident diabetes. ADT suppresses testosterone production and produces severe cellular androgen deficiency with bilateral orchidectomy or the use of gonadotropin-releasing hormone (GnRH) analogues [40]. In a large population-based study of 70,000 men aged 66 years or older, diagnosed with prostate cancer and without prior diagnosis of diabetes, ADT with GnRH analogues was associated with a 44% increased risk of incident diabetes (34% increased risk with orchidectomy) compared to controls [41]. Similarly, an observational study of over 37,000 men with prostate cancer in the Veterans Healthcare Administration reported that ADT with GnRH analogues was associated with a 28% increased risk of incident type 2 diabetes (16% increased risk for orchidectomy) compared to controls [42]. Thus, severe testosterone deficiency is instrumental in predisposing to hyperglycemia and diabetes in these patients. The diabetogenic effect of androgen depletion in men involves the combination of insulin resistance and visceral adiposity associated with decreased β -cell function [35, 43, 44].

Testosterone excess and type 2 diabetes in women

The association between androgen excess and diabetes in women has been described for almost a century [45]. Bjorntorp and coworkers initially reported that low concentrations of Sex-Hormone Binding Globulin (SHBG), which increases free circulating testosterone, was a strong independent risk factor for the development of type 2 diabetes in women [46]. It was then reported that postmenopausal women with impaired glucose tolerance exhibited higher androgen activity than those with normal glucose tolerance, with androgen activity correlating with the degree of glucose intolerance [47, 48]. Higher levels of free testosterone and lower levels of SHBG have been repeatedly associated with glucose intolerance and insulin resistance in women [37, 49–52]. A meta-analysis of prospective and cross-sectional studies relating testosterone and SHBG with risk of type 2 diabetes concluded that increased testosterone concentrations are associated with increased risk of T2D in women [53]. In postmenopausal women, higher plasma levels of estradiol and testosterone were strongly and prospectively related to increased risk of developing T2D [54].

During hyperglycemic and euglycemic-hyperinsulinemic clamps, high testosterone levels produce insulin resistance by decreasing insulin-stimulated whole body glucose uptake in healthy pre- and post-menopausal women [37, 55–57].

Women with testosterone excess in the context of polycystic ovarian syndrome (PCOS) also exhibit pancreatic β -cell dysfunction. Some show higher basal insulin secretion and decreased post-prandial insulin secretory responses [58]. In other instances, women with testosterone excess were shown to exhibit inadequate acute insulin release to the degree of insulin resistance or an exaggerated acute insulin response to glucose [59]. These abnormalities were independent from insulin resistance and closely associated with testosterone excess [60]. In these hyperandrogenic women, a robust relationship between β -cell function and free testosterone was described, raising the possibility that excess testosterone leads to insulin hypersecretion in women [61]. Thus, women with testosterone excess exhibit β -cell hyperfunction, which may predispose to secondary β -cell failure and type 2 diabetes.

Conclusions

The role of sex and gender is a fundamental issue in medicine, and there are sex differences in glucose homeostasis, prediabetic syndromes, and type 1 and type 2 diabetes. Sex hormones play a role, at least partially, in these sex differences. Further characterization of these sex-specific differences in glucose homeostasis, insulin secretion and insulin action, as well as in the incidence and progression of diabetes, will provide a new source of factors that can be harnessed to prevent dysglycemia and inform clinical trials. This knowledge is essential to foster the development of relevant sex-based therapeutic avenues for diabetes.

Highlights

- In response to an oral glucose tolerance test, women have lower fasting plasma glucose and higher 2-hour plasma glucose than men.

- Impaired fasting glucose is more prevalent in men while impaired glucose tolerance is more prevalent in women
- Type 1 diabetes is the only common autoimmune disease not characterized by a female predominance and exhibits an increased incidence in boys after puberty.
- Estrogen deficiency and/or testosterone excess predisposes women to type 2 diabetes
- Testosterone deficiency predisposes men to type 2 diabetes

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