Epidemiology of Gender Differences in Diabetes and Obesity

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Abstract Some aspects of glucose homeostasis and energy balance are regulated differently in males and females. This review discusses the most fundamental gender differences in diabetes and obesity, including the prevalence of impaired fasting glucose and impaired glucose tolerance, the prevalence and incidence of type 2 and type 1 diabetes, as well as the prevalence of metabolic syndrome and obesity. These gender-specific differences in glucose homeostasis and energy balance represent a source of factors that should be studied to develop gender-based therapeutic avenues for diabetes.

Introduction

Epidemiology is defined as the study of the patterns, causes, and effects of health and disease in selected populations. It is central to public health and shapes policy decisions and evidence-based medicine by identifying risk factors for disease and targets for disease prevention. Increasing evidence suggests that sex and gender affect the pathophysiology, incidence, prevalence, 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. Some aspects of glucose homeostasis and energy balance are regulated differently in men and women. This chapter provides an overview of the most fundamental gender differences in diabetes and obesity. These include the prevalence of impaired fasting glucose and impaired glucose tolerance, the prevalence and incidence of type 2 and type 1 diabetes, as well as the prevalence of metabolic syndrome and obesity. These gender-specific differences in glucose homeostasis and energy balance represent a source of factors that may lead to the development of gender-based therapeutic avenues for metabolic disease.

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Gender Differences in Glucose Homeostasis

There are considerable gender differences in the response to an oral glucose challenge (glucose tolerance test, OGTT). Women have lower fasting plasma glucose (FPG) and higher plasma glucose 2 h following an OGTT (2-h PG) (Sicree et al. 2008). These differences are positively correlated to height and have been hypothesized to be secondary to smaller muscle mass and associated glucose uptake, for a fixed charge of 75 g of glucose during the OGTT in women (Sicree et al. 2008). In fact, men and women have almost identical HbA1c values, suggesting that chronic postprandial glucose excursions are similar in men and women and that the 2-h PG may be a consequence of the fixed glucose load during the OGTT. Alternatively, gonadal hormones may be responsible for this gender difference in glucose homeostasis. Indeed, menopausal estrogen therapy decreases FG while impairing glucose tolerance (Van Genugten et al. 2006; Mauvais-Jarvis et al. 2017).

Insulin sensitivity also differs by sex. Healthy women have lower skeletal muscle mass, higher adipose tissue mass, more circulating free fatty acids, and higher intramyocellular lipid content than men of the same age, all factors that should promote insulin resistance in women compared to men. Yet, women exhibit similar insulin sensitivity as men. Women are even resistant to free fatty acid-induced insulin resistance (Frias et al. 2001). When matched for physical fitness, during a hyperinsulinemic, euglycemic clamp, systemic insulin sensitivity is higher in women than men as a result of higher glucose disposal by skeletal muscles (Nuutila et al. 1995). However, it is important to keep in mind that physical fitness is a critical parameter for insulin sensitivity in women. Women with lower fitness than men exhibit insulin resistance (Basu et al. 2006). Yet, these same women exhibit comparable glucose disposal to men because of the enhanced ability of glucose to promote its own disposal in an insulin-dependent manner (glucose effectiveness) (Basu et al. 2006). Women also tend to have enhanced postprandial insulin and C-peptide concentrations (despite similar plasma glucose) after a meal test, suggesting increased insulin secretion compared to men (Basu et al. 2006). In fact, the disposition index is higher in women than in men, reflecting greater insulin secretion for a given level of insulin action (Basu et al. 2006). The mechanisms that facilitate glucose homeostasis in women compared to men are unclear, but the differences could be due at least in part to the beneficial effect of endogenous estradiol before menopause (Mauvais-Jarvis et al. 2017).

Gender Differences in Type 2 Diabetes

The prevalence of prediabetic syndromes such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) is also characterized by a sex difference in all populations studied. Indeed, IFG is male biased while IGT is more prevalent in women (Glumer et al. 2003; Sicree et al. 2008; Van Genugten et al. 2006; Williams

et al. 2003). The reason for these sex 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 (Van Genugten et al. 2006; Mauvais-Jarvis et al. 2017). The prevalence of type 2 diabetes is also characterized by a sex difference. Overall, the global prevalence of diabetes is higher in men, but there are more women with diabetes than men (Wild et al. 2004). This sex difference in diabetes prevalence is reversed depending upon the stage of reproductive life (Wild et al. 2004); that is, there are more diabetic men before the age of puberty, while there are more diabetic women after the age of menopause. 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 revealed that diabetes and prediabetes (including undiagnosed cases) affect almost half of the adult US population and exhibit a sex bias (Menke et al. 2015). 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} (HbA_{1c}) with FPG and 2-h PG; the second included the HbA_{1c} and FPG only, without the 2-h PG. From 2011 to 2012, the study reported a significant male predominance in the prevalence of total diabetes (13.6% vs 11.4%, men vs women) and a trend toward an increase in the prevalence of prediabetes (39.1% vs 33.8%, men vs women), only when the 2-h 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-h PG). Thus, the exclusion of the 2-h 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 (classified as idiopathic type 1 diabetes by the American Diabetes Association), a severe form of type 2 diabetes mostly encountered in non-Caucasian subjects and with a propensity to acute insulin dependence and diabetic ketoacidosis alternating with periods of remission (Mauvais-Jarvis et al. 2004; Umpierrez et al. 2006). In ketosis-prone diabetes, women are relatively protected unless they are in an anovulatory or hypoestrogenic state (Mauvais-Jarvis et al. 2004; Louet et al. 2008).

Gender Differences in Type 1 Diabetes

There is a gender difference in the incidence of type 1 diabetes (T1D). Interestingly, T1D is the only common autoimmune disease not characterized by a female predominance. In fact, T1D is even characterized by a male predominance in Caucasians (ratio, 1:7) (Gale and Gillespie 2001). The pubertal period is associated with a decreased incidence of T1D in girls (Blohme et al. 1992; Nystrom et al. 1992) who retain more robust residual β-cell function than boys (Samuelsson et al. 2013). This suggests that female gonadal hormones transiently protect against T1D. In fact,

serum levels of the main estrogen, estradiol (E2), and serum estrogen activity are decreased in adolescents with T1D, suggesting that these individuals could have lost the protective effect of E2 against T1D (Martinez et al. 2016). In addition, E2 has been shown to protect rodent and human islet survival from multiple metabolic and pro-inflammatory injuries in vivo (Tiano and Mauvais-Jarvis 2012; Mauvais-Jarvis 2016). In a recent preclinical study, E2 treatment prevented insulitis and T1D in nonobese diabetic (NOD) mice by restoring the immunomodulatory functions of iNKT cells (Gourdy et al. 2016).

Gender Differences in Metabolic Syndrome and Obesity

The global prevalence of obesity is higher in women than in men in all continents (Kelly et al. 2008). Interestingly, in recent decades, the prevalence of abdominal obesity has increased more in women than in men in the USA (Ford et al. 2004). Today, the prevalence of visceral obesity associated with metabolic syndrome is two to ten times higher in women in many countries around the world (Al-Lawati et al. 2003; Gu et al. 2005; Gupta et al. 2004). Using the data from the National Health and Nutrition Examination Survey (NHANES), a recent study reported that the prevalence of metabolic syndrome in 2012 was significantly higher in women than in men (35.6% vs 30.3%, respectively) (Aguilar et al. 2015). A previous study using the data from the NHANES for the years 1999–2006 (Mozumdar and Liguori 2011) previously reported a significant increase in incidence of metabolic syndrome among US women compared to men. A large increase in the prevalence of metabolic syndrome among women compared with men is a noteworthy finding also described in Chinese adults (17.8% vs 9.8%, respectively) (Gu et al. 2005) and Indian populations (39.9% vs 22.9%, respectively) (Gupta et al. 2004). Importantly, when the individual abnormalities of metabolic syndrome were analyzed, the prevalence of abdominal obesity was dramatically higher in women than in men in the adult population of the USA (58.0% vs 41.1%, respectively) (Mozumdar and Liguori 2011), India (44% vs 25.6%, respectively) (Gupta et al. 2004), and especially China (13.9% vs 1.7%, respectively) (Gu et al. 2005) and Oman (44.3% vs 4.7%, respectively) (Al-Lawati et al. 2003). This female predisposition to central adiposity was observed across all age groups and in both urban and rural areas (Gu et al. 2005).

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 may help to prevent dysglycemia and inform clinical trials. This knowledge is essential to foster the development of relevant sex-based therapeutic avenues for diabetes. The determinants of these sex differences in the development of the global epidemic of abdominal obesity represent an untapped source of factors that can be harnessed to develop relevant gender-based therapeutic avenues for metabolic syndrome.

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