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Review

Role of Estrogen in Type 1 and Type 2 Diabetes Mellitus: A Review of Clinical and Preclinical Data

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Key Messages

- Premenopausal women are protected from developing diabetes and its complications.
- Preclinical studies suggest that estrogen directly affects beta-cell health and function.

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ABSTRACT

The incidence and prevalence of diabetes mellitus, and the cardiovascular complications associated with this disease, are rapidly increasing worldwide. Individuals with diabetes have a higher mortality rate due to cardiovascular diseases and a reduced life expectancy compared to those without diabetes. This poses a significant economic burden on health-care systems worldwide, making the diabetes epidemic a global health crisis. Sex differences in the presentation and outcome of diabetes do exist. Premenopausal women are protected from developing diabetes and its cardiovascular complications relative to males and postmenopausal women. However, women with diabetes tend to have a higher mortality as a result of cardiovascular complications than age-matched men. Despite this evidence, preclinical and clinical research looking at sex as a biologic variable in metabolic disorders and their cardiovascular complications is very limited. The aim of this review is to highlight the current knowledge of the potential protective role of estrogens in humans as well as rodent models of diabetes mellitus, and the possible pathways by which this protection is conferred. We stress the importance of increasing knowledge of sex-specific differences to facilitate the development of more targeted prevention strategies.

Mots clés :
cellule bêta
maladie cardiovasculaire
diabète
œstrogène

RÉSUMÉ

L'incidence et la prévalence du diabète sucré et les complications cardiovasculaires associées à cette maladie ne cessent d'augmenter dans le monde. Les personnes diabétiques ont un taux de mortalité plus élevé en raison des maladies cardiovasculaires et une espérance de vie plus courte que les personnes non diabétiques. Pour les systèmes de soins de santé du monde entier, il s'agit d'un fardeau économique important, qui fait de l'épidémie du diabète une crise mondiale de la santé. Le tableau clinique et l'évolution du diabète montrent des différences entre les sexes. Par rapport aux hommes et aux femmes postménopausées, les femmes préménopausées sont à l'abri du diabète et de ses complications cardiovasculaires. Toutefois, du fait des complications cardiovasculaires, les femmes diabétiques présentent une mortalité plus élevée que les hommes appariés selon l'âge. En dépit de ces données scientifiques, la recherche préclinique et clinique, qui montre que le sexe est une variable biologique des perturbations métaboliques et de leurs complications cardiovasculaires, est très limitée. L'objectif de la présente étude est de présenter les connaissances actuelles sur le rôle protecteur potentiel des œstrogènes dans des modèles de diabète sucré chez les humains et chez les rongeurs, et les voies par lesquelles cette protection peut être obtenue. Nous insistons sur l'importance d'accroître les connaissances sur les différences liées au sexe pour faciliter l'élaboration de stratégies de prévention plus ciblées.

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Introduction

Diabetes mellitus is a group of metabolic disorders characterized by the presence of elevated blood glucose levels (hyperglycemia). The underlying characteristic of all forms of diabetes mellitus is the inability of pancreatic beta cells to produce/secrete sufficient quantities of insulin to regulate glucose levels. In type 1 diabetes mellitus (T1DM), the inability of regulating blood glucose levels results from the rapid destruction of pancreatic beta cells due to autoimmune processes, which leads to insulin deficiency. In type 2 diabetes mellitus (T2DM) hyperglycemia is the result of an insufficient insulin secretion combined with an impaired response to insulin (insulin resistance) in the hepatic, skeletal and/or adipose tissues. The early stages of T2DM are characterized by pancreatic beta-cell hyperfunction, which leads to dysfunction and, ultimately, apoptosis of the beta cells (1).

Diabetes mellitus is associated with the development of microvascular and macrovascular complications. Microvascular complications include diabetic nephropathy, neuropathy and retinopathy. Macrovascular complications include coronary artery disease, peripheral arterial disease and stroke (2). Atherosclerosis is the main underlying cause of macrovascular complications (2), and people with diabetes have a 2-fold increased risk of death (3) as well as a reduced life expectancy by up to 15 years (4,5) when compared to those without diabetes. Individuals with diabetes are also at a higher risk of developing blindness, renal failure, chronic neuropathic pain, below-knee amputations, cancer, depression, cognitive decline, cirrhosis, frailty and a significant increase in the risk of cardiovascular disease (CVD), even when controlling for other CV risk factors (6,7).

In the last few decades, as a result of changes in lifestyle and increased rates of obesity, there has been a dramatic increase in the incidence and prevalence of diabetes mellitus worldwide (8–10). The costs associated with the treatment of diabetes and its complications present a major burden on health-care systems around the world (11,12). Herein, we review the clinical data pertaining to sex differences in the prevalence of diabetes and its CV complications. In addition, we examine rodent models of diabetes and CV complications in which similar sex-specific differences have been observed. We discuss how these models have been used to highlight the protective role of estrogen and to suggest potential mechanism(s) by which this protection is conferred.

Sex Differences in Diabetes and Cardiovascular Complications

Sex differences in the pathophysiology of diabetes mellitus do exist and females have a protective advantage compared with males. Many studies have shown that there is a higher prevalence of T1DM in males than in females (13,14). Moreover, sexual dimorphism can also be observed in T2DM. Specifically, premenopausal women have a lower prevalence of T2DM when compared with men or postmenopausal women (15). This trend has been observed in many studies worldwide that show a persistent male predominance in the incidence of T2DM in the long-term follow up of patients (16–20). This evidence suggests a potential protective role of estrogens in the development of diabetes. This hypothesis is supported by 2 large, randomized, double-blind, placebo-controlled clinical trials, the Women's Health Initiative study and the Heart and Estrogen/Progesterin Replacement Study, which showed that women taking hormone replacement therapy, were less prone to develop diabetes than those of a placebo group (21,22).

Sex differences can also be observed in diabetes-associated CVDs, which represent the major cause of mortality and morbidity among patients with diabetes (23). Evidence shows that there is a 3- to 5-fold increased risk in coronary heart disease (CHD) in men without diabetes vs premenopausal females (24). Furthermore, women tend to develop CHD later than men, supporting a potential protective role of female sex hormones (25). However, when women are diagnosed with diabetes, this protective factor is erased, as shown by a recent meta-analysis concluding that women with diabetes have a 40% increased risk of developing CHD compared to men with diabetes (26). Consistent with these findings, a meta-analysis of prospective cohort studies showed that women with diabetes have about 50% greater risk of CHD than men with diabetes, even after consideration of other major cardiovascular risk factors (27). Another systematic review showed that the relative risk of stroke in women with diabetes was 27% higher than males with diabetes, after taking into account baseline and major cardiovascular risk factors (28). Similarly, a Japanese study showed that women with diabetes have a higher risk of a stroke event compared with males (29). A collaborative meta-analysis of 102 prospective studies worldwide showed similar outcomes in terms of the presence of diabetes in women and the risk of CVD (20).

The higher rate of CVD in women with diabetes results in a higher CV mortality compared with women or men without diabetes (30). A Canadian study showed that hospitalization and mortality risk due to CVD was significantly increased in women with diabetes vs those without diabetes. Strikingly, the mortality rate was 2-fold higher in women than men (31). Consistent with these data, 2 population-based studies in Sweden and Italy, respectively, highlighted that the survival rate after stroke or other CVDs was significantly lower in women with diabetes compared with men (32,33). It was previously thought that the sex-specific severity of diabetes-associated CV complications was a result of disparities in the management of diabetes between male and female patients; however, as treatment has become more equal between sexes, the greater risk of severe CVD in women has persisted (26). This finding supports a potential protective role of estrogens, because women tend to develop diabetes after menopause and have a higher risk of severe diabetes-associated CVD complications and consequent higher mortality rate compared to men with diabetes.

The current trends for diabetes and its cardiovascular complications predict a progressive increase in their prevalence, which will pose a significant economic and managerial burden in health-care systems worldwide (34). Further research needs to be carried out to increase our understanding of the role of sex in the development and progression of diabetes mellitus and its cardiovascular complications. This will facilitate the establishment of targeted strategies to more effectively prevent and manage these diseases.

Potential Role of Estrogen in Diabetes and Its Cardiovascular Complications

The increased CV risk in postmenopausal women may result from the reduction in circulating estrogen and the associated risk of increased body weight, which can result in the onset of insulin resistance (35). Insulin resistance causes beta cells to significantly hypersecrete insulin. Elevated circulating insulin concentrations can have deleterious effects on the vasculature, such as sodium and liquid retention, vasoconstriction, proliferation of smooth muscle cells and proinflammatory activity, which can induce high blood pressure as well as development of atherosclerosis (36,37). Hyperglycemia, high blood pressure and atherosclerosis represent predominant risk factors for CVDs, hence they pose a significant risk in postmenopausal women (36). The underlying mechanisms by which estrogens may confer protection against diabetes and its associated vascular complications have begun to be investigated in new rodent models of cardiometabolic disease (38).

Rodent Models of Sexual Dimorphism in Diabetes Mellitus

Rodent models of diabetes mellitus are very useful when it comes to delineating the pathogenesis of metabolic disorders. Many rodent models of diabetes and/or hyperglycemia present sexual dimorphism in terms of glucose regulation and associated complications that are similar to those observed in human patients (Table 1). To mimic menopause and to more clearly investigate the roles of ovarian hormones, ovariectomized rodents are commonly used as an experimental model (39).

To our knowledge, the only study to address sex-specific differences in the development of hyperglycemia-induced atherosclerosis involved the ApoE$^{-/-}$:Ins2$^{+/Akita}$ mouse model (38). This mouse strain shows sex dimorphism in glucose regulation with male mice developing chronic hyperglycemia and female mice being transiently hyperglycemic (38). Furthermore, atherosclerotic analysis showed that both male and female ApoE$^{-/-}$:Ins2$^{+/Akita}$ mice developed atherosclerosis; however, ovariectomized ApoE$^{-/-}$:Ins2$^{+/Akita}$ mice developed chronic hyperglycemia and showed signs of advanced atherosclerosis, similar to what was observed in male hyperglycemic ApoE$^{-/-}$:Ins2$^{+/Akita}$ mice (38). This suggests that the loss of estrogens contributes to the development of hyperglycemia and atherosclerosis, both significant risk factors for CVD.

Mechanisms of Estrogen Protection

The sex differences in glucose homeostasis observed in both humans and rodent models suggest a potential protective role of female sex hormones in the prevention of diabetes. The mechanisms by which this protection is conferred are still not clear.

Estradiol has been shown to increase insulin content and glucose-stimulated insulin secretion in isolated mouse pancreatic islets, suggesting an active role for this hormone in glucose homeostasis (40). It was shown that ovariectomized C57BL/6J mice have an altered glucose homeostasis characterized by impaired glycemia, reduced glucose tolerance, insulinemia and impaired insulin secretion when compared to females supplemented with estradiol (41). Another study in leptin-resistant female Zucker Diabetic Fatty Rats showed that fasting blood glucose levels were higher and glucose tolerance was impaired in an ovariectomized group as opposed to sham controls or ovariectomized females given estradiol treatment (42). Consistent with these observations, many other studies have highlighted the beneficial role of estradiol in glucose homeostasis (43–45).

Pancreatic beta cells express all 3 major estrogen receptors (ERs) ER-alpha, ER-beta and the G protein-coupled estrogen receptor, and there is evidence suggesting a role for each of these receptors in the maintenance and enhancement of beta-cell function (46–48). A study conducted in mice lacking either ER-alpha or ER-beta showed that beta-cell survival was significantly impaired in both models when compared with controls (49). The same study also showed that female mice lacking G protein-coupled estrogen receptor lost their protection against streptozotocin-induced beta-cell apoptosis (49).

Oxidative stress has been implicated as a mechanism by which hyperglycemia may promote beta-cell dysfunction. However, antioxidant therapies have failed to significantly protect beta cells from apoptosis (50,51). The role of endoplasmic reticulum (ER) stress in beta-cell dysfunction is currently being investigated as an alternative pathway by which elevated concentrations of glucose may damage beta cells. The ER is an organelle in the cytoplasm of the cell whose function is to synthesize, properly fold and deliver proteins to the location of interest. Pancreatic beta cells have a complex, well-developed ER because they need to synthesize and secrete large quantities of insulin in response to the physiologic needs of glucose regulation (52). However, in situations of chronic hyperglycemia and/or insulin resistance, the demand of insulin is significantly increased and, as a result, the folding capacity of the ER is also increased. When the functional folding capacity of the ER is exceeded, unfolded proteins accumulate and induce a condition known as ER stress (53,54). The accumulated misfolded proteins trigger the unfolded protein response, which is an adaptive mechanism aimed at restoring homeostasis within the ER (55). The unfolded protein response activates the expression of ER-resident protein chaperones that function to increase the protein folding capacity of the cell. If the ER homeostasis cannot be restored, apoptotic mechanisms are triggered (56,57).

An in vitro study conducted using the INS-1 cell line showed that elevated concentrations of glucose can induce the expression of ER stress markers, but treatment of these cells with estradiol can significantly reduce stress marker expression (58). Furthermore, estradiol protected cells from apoptosis when challenged with an ER stress inducer, thapsigargin, in the presence of high glucose

Table 1
Rodent models of sexual dimorphism with diabetes and/or hyperglycemia

Rodent model	Type of diabetes	Main features
ZDF rats, TALLYHO/JngJ mice	Polygenic	• Males develop chronic hyperglycemia, females remain normoglycemic (63,64)
OLETF rats	Polygenic	• Males develop chronic hyperglycemia, females remain normoglycemic • Females increase beta-cell mass after partial pancreatectomy • This compensatory effect is lost after ovariectomy and restored by estradiol replacement (65,66)
NZO mice	Polygenic	• Males and females develop obesity when given a high-fat diet • Males develop chronic hyperglycemia, females remain normoglycemic unless ovariectomized • Male diabetic mice have an impaired cardiac function compared with normoglycemic females (67,68)
Wfs1 knockout mouse (Wfs1$^{-/-}$)	Monogenic	• Hyperglycemia is less severe in female Wfs1$^{-/-}$ compared with age-matched males • This phenotype is similar to that in humans with mutations in the Wfs1 gene (69,70)
Ins2$^{+/Akita}$ mouse, ApoE$^{-/-}$:Ins2$^{+/Akita}$ mouse	Monogenic	• Point mutation in one allele of the Ins2 gene (C96Y), which impairs formation of functional insulin • Female Ins2$^{+/Akita}$ mice develop less severe hyperglycemia compared with males • Female ApoE$^{-/-}$:Ins2$^{+/Akita}$ mice are only transiently hyperglycemic (by 10 weeks they become normoglycemic); ovariectomy eliminates normalization of blood glucose levels (38,71)
STZ-injected rodents	Chemically induced hyperglycemia	• STZ is a naturally occurring alkylating antineoplastic agent that is selectively toxic to pancreatic beta cells • Female rodents are more resistant to the toxic effects of STZ (higher concentrations and/or more frequent injections are required to induce diabetes in females) (43,72,73)
Alloxan-injected rodents	Chemically induced hyperglycemia	• Alloxan is a toxic analogue of glucose that has been used to selectively eliminate pancreatic beta cells • Administration of estrogen in male rats protects against alloxan-induced hyperglycemia (74)

Apo, apolipoprotein; *Ins*, insulin; *NZO*, New Zealand Obese; *OLETF*, Otsuka Long-Evans Tokushima Fatty (rats); *STZ*, streptozotocin; *Wfs*, Wolfram syndrome; *ZDF*, Zucker Diabetic Fatty (rats).

concentration (58). The results of the study suggested that all 3 estrogen receptors play a role in signalling (58). Another study using INS-1 cells and isolated murine pancreatic islets demonstrated that estradiol protects beta cells from apoptosis when exposed to high levels of glucose (59). Ovariectomized rats treated with glucosamine, a supplement that in high doses can cause ER stress, had significantly reduced levels of insulin in their pancreatic islets as well as increased glucosamine-induced beta-cell apoptosis when compared with nonovariectomized controls. This supports a protective role for estrogens against beta-cell ER stress (60). Similarly, improved beta-cell function and health was observed in ovariectomized females and male hyperglycemic $Ins2^{+/Akita}$ mice receiving estrogen treatment (61).

Accumulating evidence is highlighting the importance of ER homeostasis in the maintenance and function of healthy beta cells. Given the systemic effects of estrogens and the multifaceted nature of intracellular hormone signalling, it is of high importance to conduct further research that can identify how sex hormones can affect relevant pathways and mechanisms that regulate beta-cell health.

Conclusions

Despite the strong evidence for sexual dimorphism in diseases, such as diabetes, and its cardiovascular complications in humans as well as animal models, these differences remain poorly studied and represent a critical research gap. Moreover, preclinical studies are still predominantly conducted using male animal models and male-derived cell lines, resulting in an accumulation of incomplete, sex-biased data (62). It is, therefore, critical to address this gap in both clinical and preclinical research conducted in these fields so we may gain better understanding of sex differences in diabetes-associated cardiometabolic diseases and the impact of menopause, aging and hormone replacement therapies on health outcomes. This may lead to more targeted, effective and sex-specific management and prevention of cardiometabolic diseases.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

MDP and GHW wrote and edited the manuscript.

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