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A Review on 17-β estradiol a Potent Therapeutic Factor of Diabetic Cardiomyopathy

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Abstract

Type 2 diabetes causes structural and functional changes in the myocardium, which is called cardiomyopathy. Diabetic cardiomyopathy (DCM) is a distinct primary disorder process, independent of coronary artery disease, which leads to heart failure in diabetic patients. Also, DCM is a multifaceted disorder that is one of the leading causes of death in elderly and postmenopausal women. Menopause is associated with decreased and stopped ovarian function, which reduces and stops the production of ovarian hormones, especially estrogen. Moreover, menopause is associated with an increased risk of cardiovascular diseases. Sex steroids such as 17-β estradiol have a variety of protective effects on many tissues in the body, including the cardiovascular system. In this article, the concept of DCM, the underlying molecular signaling pathway, and, finally, the role of 17-β estradiol as one of the most important estrogens in moderating DCM are discussed to provide a theoretical basis for in-depth study.

Keywords: 17-β estradiol, Diabetes, Cardiomyopathy, Menopause

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Introduction

The prevalence of weight gain, diabetes, and hypertension is increasing worldwide due to diet and lifestyle changes (1). Furthermore, Obesity, type 2 diabetes, and metabolic syndrome are the main causes of the prevalence of cardiovascular disorders so obese and diabetic patients have different types of heart disorders such as congestive heart failure, hypertrophy, fibrosis, and cardiomyopathy. Cardiac dysfunction in diabetic patients was first reported in the early 1970s (2). If a diabetic patient has cardiomyopathy and has no symptoms of hypertension or coronary heart disease, it is considered DCM (1). A variety of mechanisms are involved in the pathogenesis of DCM. Changes in the metabolism and structure of cardiomyocytes, along with increased inflammation and dysfunction of intracellular organs such as the endoplasmic reticulum, which have been shown mainly in research, are considered to be the primary mechanisms involved in DCM (3). Today, gender is considered one of the main factors in the outcomes of patients with cardiovascular disorders (4). Both clinical and laboratory studies suggested that these cardiovascular disorders such as cardiomyopathy are gender-sensitive and less common in premenopausal women but increase after menopause, possibly due to lower levels of female sex steroids, including estrogen. In cardiomyopathy, vascular endothelial cells and cardiomyocytes are the two main components of cardiovascular disorders and the leading cause of death in patients (4,5). But, various studies had also expressed the different cardiovascular protective effects of estrogen (5-7). In this article, we discuss the common evidence for the protective effects of estrogen in DCM.

Estrogen and its receptors

Estrogens as 18-carbon steroids are mainly produced in the ovaries and may also be locally synthesized in the other tissues such as fat cells, bone, breast, brain, and adrenal cortex due to the presence of cytochrome P450 aromatase, which converts testosterone to estradiol (6). Also, estrogens as sex steroids are able to affect many organs beyond their reproductive function. Estrogen has three forms: 17-β estradiol, estriol and estrone (8). Among them, 17-β estradiol is functionally the most potent. The secretion of 17-β estradiol is pulsatile and concentrated during the reproductive years (100-600 pg/ml), but after menopause, its serum concentration decreases rapidly to similar or lower levels than men in the same age (5 to 20 pg/ml) (4). 17-β estradiol has three known receptors in the body: estrogen receptor α (ERα), estrogen receptor β (ERβ), and G-protein-coupled estrogen receptor (GPER) (9). ERα and ERβ, the so-called classical ERs, are nuclear hormone receptors that act largely as ligand-activated transcription factors (genomic pathways) (10). Both classical ERs can activate and regulate cell survival, growth, and metabolism by modulating the expression of various genes (11). Unlike the classical ERs, the third known estrogen receptor, GPER, is a G protein-coupled receptor that predominantly induces rapid, non-genomic estrogen signaling (non-genomic pathways) (12). They are expressed in various tissues and various studies have shown that all three receptors are expressed in the heart and activation of each of them has a variety of effects (6). GPER is involved in activating the mechanisms of production of secondary messengers into the cell, activating protein kinase signaling cascades, and regulating cyclic adenosine monophosphate (cAMP), all of which lead to indirect regulation of gene expression (13). Today, extensive research has been done on 17-β estradiol, all of which have shown that 17-β estradiol has metabolic and anti-inflammatory protective effects in many tissues of the body, including the heart tissue (14-16).

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Anti-inflammatory effects of 17-β estradiol in DCM

Studies showed that diabetes is associated with increased inflammation in the body (17), which plays an important role in the onset and progression of cardiovascular disorders (18,19). There is also a direct link between high cholesterol levels in diabetes and increased inflammation in the arteries (20,21). In 2018, it was shown that 17-β estradiol-mediated GPER was able to reduce inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α (TNF-α) and increase the anti-inflammatory cytokine interleukin-10 in diabetic hearts (6). Further studies have shown that reducing inflammation caused by GPER can affect the cardiovascular function and reduce blood pressure, reduce cardiovascular risk indexes, and atherogenic markers in diabetes (22,23). Also, studies on selective estrogen receptor modulators (SERMs) showed their anti-inflammatory effects (24,25). For example, both tamoxifen and raloxifene as SERMs can reduce cardiac inflammation and decrease the atherogenic index in diabetic conditions, all of which lead to increased and improved cardiovascular function in diabetic conditions (25). All of these results emphasize that 17-β estradiol, selective receptor agonists, and even SERMs improve heart function by reducing inflammation, which is a major cause of DCM.

Anti–endoplasmic reticulum stress effects of 17-β estradiol in DCM

The endoplasmic reticulum(ER) is one of the most important organs in the human body, and its dysfunction is seen in many diseases, including obesity, diabetes, and cardiovascular disorders (26,27)**.** When the misfolded or unfolded proteins accumulate in the ERand induce endoplasmic reticulum stress (ERS), a homeostatic signaling network called the unfolded protein response (UPR) begins, which restores homeostasis in the endoplasmic reticulum (28). Various factors and conditions such as oxidative stress, excessive fat accumulation, and inflammation lead to ER dysfunction and thus induce ERS (29). The ERS itself exacerbates cellular disorders, resulting in cell death (29). One of the causes of vascular endothelial cell disorders in diabetics is the increased ESR caused by hyperglycemia, which leads to the destruction of endothelial cells and consequently to hypertension (30). It has been shown that 17-β estradiol can reduce ERS and improve endothelial cell function by reducing oxidative stress and phosphorylation and activation of Janus Kinase (JNK) and Phosphoinositide 3-kinase (PI3 Kinase–Akt) signaling pathways and thus counteract hypertension (31,32). Also, various studies using antagonists of all three estrogen receptors have shown that all three estrogen receptors are mediators of this protective action (33-35). In addition, it is proven that gender differences also affect diabetes-induced cardiovascular disorders through changes in calcium signaling (36-38). 17-β estradiol is a major regulator of calcium signaling in many cells in the body, including cardiomyocytes, possibly reducing the damage caused by ischemic heart disease and DCM (7,39,40).

Cardio-metabolic protective effects of 17-β estradiol in DCM

There are metabolic changes in the heart of both diabetic and menopausal subjects that indicate the role of sex steroids, including 17-β estradiol, in regulating cardiac metabolism in diabetes (41). Ongoing studies show that 17-β estradiol plays an essential role in controlling energy balance and glucose homeostasis through various mechanisms (4). These metabolic changes include decreased glucose uptake and increased lipid uptake, which ultimately reduce cardiac efficiency (42). Studies reported that diabetic hearts lose 70% of their efficiency due to the accumulation of more fat in the circulation and the presence of insulin resistance in the cardiomyocytes (43).

New studies showed that all three estrogen receptors work on the body and heart metabolism through different mechanisms. To date, data suggested that ERα is involved in

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the central effects of 17-β estradiol on energy expenditure, insulin resistance, and metabolic regulation (4). ERα and its specific agonists can increase glucose uptake into the heart, and the deletion of ERα in the cardiomyocytes alters the expression of sex-dependent metabolic genes in cardiomyocytes (44). Interestingly, a study reported the regulation of peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) expression by ERα, and this may provide one of the underlying molecular mechanisms behind 17-β estradiol-mediated regulation of glucose metabolism in cardiomyocytes (45). There is little information on the role of ERβ in the metabolic regulation of the heart (4). A study reported that ERβ regulates mitochondrial IV respiratory complex activity in the heart of mice (46). It has been shown that 17-β estradiol may be able to reduce obesity and insulin resistance through GPER, thereby improving the metabolic status of the heart in DCM (6). For example, it has recently been found that stimulation of the GPER reduces glycogen content in diabetic hearts by increasing the enzyme hexokinase 2 (HK II), which is primarily responsible for cardiac metabolism (41). Also, it has been shown that lowering cardiac glycogen content is associated with improved function and increased efficiency of diabetic hearts (41). Overall, the cardiac metabolic beneficial effects of 17-β estradiol are mediated by ERα and GPER, which may mediate the protective effects of 17-β estradiol in premenopausal women.

Conclusion

Female sex hormones, especially 17-β estradiol, exert their effects on the body through various mediators and activation of various signaling pathways. This review article provides information on the protective effects of 17-β estradiol against DCM inflammation, endoplasmic reticulum stress, and metabolic changes that may be key mediators in the treatment of DCM (Figure 1). It is clear that DCM, due to its complexity and increased mortality of diabetic patients, is so important and 17-β estradiol and its receptor agonists may be acceptable therapeutic targets against it. Future studies should examine in more detail the functional mechanisms of 17-β estradiol and even other female sex steroids.

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Conflict of Interest

The authors declare no conflict of interest.

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