Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus

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Abstract
Heart failure with preserved ejection fraction (HFpEF) constitutes approximately 50% of heart failure patients. The prevalence of diabetes mellitus in HFpEF is high at 30-40%. The paper provides a systematic review of the pathophysiological features underlying HFpEF in diabetes mellitus. The importance of mechanisms other than left ventricular diastolic dysfunction underlying this important condition is emphasised. Thus, ventricular-arterial coupling & vascular dysfunction together with chronotropic incompetence & cardiovascular reserve dysfunction play an important role. The various morphologic and molecular features occurring in the myocardium and vasculature in diabetes secondary to hyperglycaemia and other metabolic disturbances are also discussed. These include microangiopathy, myocardial fibrosis, increased oxidative stress, impaired calcium homeostasis, activation of the cardiac renin-angiotensin system, autonomic neuropathy, endothelial dysfunction, re-expression of foetal gene response as well as stem cell involvement. Nonetheless, a lot is still unknown and further studies are needed to establish the underlying pathophysiological mechanisms with the hope that novel pharmacotherapies targeting this disease will be developed. In the meantime, cardiometabolic factors, including hyperglycaemia, hypertension and dyslipidaemia should be targeted and aggressively treated.

Background
In the past decade, there has been increasing interest in patients with signs and symptoms of heart failure (HF) despite a normal or near-normal left ventricular (LV) systolic function, for which the term “heart failure with preserved ejection fraction” (HFpEF) has been introduced. HFpEF constitutes approximately 50% of HF patients [1]. The Cardiovascular Health Study [2] suggests that it may be even commoner amongst patients with heart failure in the community and in women.

In the past, HFpEF was referred to as “diastolic heart failure” as opposed to “systolic heart failure” which relates to HF with reduced ejection fraction (HFrEF). However, there is now increasing emphasis on abandoning the terms diastolic/systolic HF since mechanisms other than diastolic dysfunction may contribute to HFpEF and an element of diastolic dysfunction exists in most cases of HFrEF [3]. The term ‘heart failure with preserved systolic function’ has also been used by some authors but the term HFpEF is preferable since parameters of systolic function other than EF may be abnormal. The problem with the present terminology and diagnostic criteria is that HFpEF cannot be diagnosed in subjects with low EF, even if diastolic dysfunction exists. The differentiation between HFpEF from HFrEF is not only of academic interest but is also useful in clinical practice since medications used in the treatment of HFrEF have been disappointing in HFpEF. This observation also suggests that HFpEF is a separate pathophysiological entity [4]. Nonetheless, others argue that HFpEF and HFrEF are not separate entities but rather form part of one HF spectrum [5].

The prevalence of diabetes mellitus (DM), especially type 2 DM, is steadily increasing [6]. Although DM is a well-known risk factor for atherosclerosis and for coronary artery disease (CAD), its role in development of HF is less established. Nevertheless, the prevalence of DM in HF is approximately 20-35% [7] and is somewhat higher in patients with HFpEF, at 30-40% [8]. HFpEF and type 2 DM commonly coexist. Both conditions are associated with hypertension, obesity and old age [1], all of which promote the occurrence of HF. However, irrespective of underlying cardiovascular disease, DM has a crucial role in HFpEF as demonstrated in the CHARM study whereby the relative risk of cardiovascular death or HF hospitalization conferred by DM was significantly greater in patients with HFpEF compared with those with HFrEF [9]. The prevalence of HFpEF may be high even in asymptomatic and well-controlled diabetic subjects [10,11]. Despite the increased prevalence and poor outcome, pathophysiological features underlying HFpEF in DM remain uncertain, and will therefore be addressed hereunder.

Methods
A systematic review of the published literature was performed using Medline and Embase as computerized databases. The search included all published papers up to 21st May, 2011. The terms “heart failure with preserved ejection fraction”, “heart failure with normal ejection fraction” and “diabetes mellitus” were used.

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fraction” and “diastolic dysfunction” in association with “diabetes mellitus”, were utilised in the search strategy.

1. Physiological Abnormalities associated with HFrEF in Diabetes

Four sets of guidelines have been published for the diagnosis of HFrEF [5,12-14]. They all require the simultaneous and obligatory presence of signs and/or symptoms of HF, normal LV ejection fraction, and evidence of diastolic LV dysfunction or of surrogate markers of the latter, e.g. LV hypertrophy, left atrial enlargement, atrial fibrillation, or elevated plasma natriuretic peptide levels. Although evidence of diastolic dysfunction forms an integral part in the diagnostic algorithms of HFrEF, this does not mean that it represents the sole contributor to disease pathophysiology. It is being increasingly recognized that other mechanisms play important roles, mainly resting and exercise-exacerbated systolic dysfunction [14-19], impaired ventricular-vascular coupling [17,18,20,21], abnormal exercise-induced and flow-mediated vasodilation [15-17,22], chronotropic incompetence [15,17,18,23], and pulmonary arterial hypertension [24,25]. The risk factors for progression to HFrEF are variable according to the underlying diseases [26]. However, many of the mechanisms above-mentioned are thought to play a role in the pathophysiology of HFrEF in DM.

1A. Left Ventricular Diastolic Dysfunction

LV diastolic dysfunction has been suggested as the first manifestation of diabetic heart disease in both type 1 and type 2 DM patients [27,28] (Figure 1). In the Strong Heart Study [30], which investigated the effect of DM on LV filling pattern in normotensive and hypertensive individuals, type 2 DM was associated with an impaired relaxation pattern independently of age, blood pressure (BP), LV mass and LV systolic function. The combination of DM and hypertension resulted in more severe abnormal LV relaxation than groups with either condition alone, suggesting a synergistic deleterious effect when both conditions were present. Moreover, abnormal relaxation in DM subjects was associated with higher fasting glucose and glycated haemoglobin (HbA1c) levels. The impact of poor glycaemic control on development of HF was also demonstrated in a registry of 49,000 DM individuals whereby each 1% increase in HbA1c was associated with an 8% increased risk of HF [31].

The mechanical processes of diastole can be divided into active relaxation and passive compliance, both of which can be affected. In the absence of endocardial/pericardial disease, diastolic dysfunction results from increased myocardial stiffness that is determined by the extracellular matrix and the cardiomyocytes. In addition, both compartments influence each other via matricellular proteins. The actual contribution of LV relaxation and compliance to the development of HFrEF in DM is still unclear. In a study by Takeda et al [26] on 544 Japanese DM patients with ejection fraction (EF) ≥50%, female sex, high body mass index, low haemoglobin, and low diastolic wall strain (DWS) were independently associated with the prevalence of HFrEF. A low DWS indicates impairment of LV compliance [32]. On the other hand, the decrease in E velocity, an index of LV relaxation, was not independently associated with HFrEF. This was a cross-sectional one and thus subject to various limitations, including survival bias and inability to assess cause and effect. Nonetheless, the impaired LV compliance noted is known to be associated with increased collagen accumulation and enhanced collagen cross-linking [33]. In DM, there is increased myocardial deposition of collagen and advanced glycation end-products (AGEs) which promote cross-linking [34]. Willemsen et al [35] have shown that DM HF patients had higher tissue AGEs and poorer exercise capacity than those without DM. Also, tissue AGEs correlate with mean E’ in DM, suggesting a close relationship between tissue AGEs, diastolic function, and exercise capacity independent of EF.

The findings of Takeda et al [26] contrast with those of van Heerebeek et al [36]. The latter used LV endomyocardial biopsy samples from 64 patients (26 diabetic), to compare myocardial fibrosis, AGE deposition, and cardiomyocyte resting tension (Fpassive) of isolated cardiomyocytes between DM and non-DM HFrEF patients and between DM and non-DM HFrEF patients. All patients had been hospitalized for worsening HF and none had CAD. It was shown that DM HFrEF patients had increased LV myocardial stiffness (assessed by radial LV stiffness modulus) in comparison to non-DM patients with HFrEF. Furthermore, the increased diastolic LV stiffness was related more to cardiomyocyte Fpassive and less to AGE deposition. On the other hand, in DM HFrEF patients, the higher diastolic LV stiffness was related to both AGE deposition and interstitial fibrosis. The authors suggest that the high cardiomyocyte Fpassive is probably secondary to a phosphorylation deficit of myofilamentary or cytoskeletal proteins [37,38]. High Fpassive was accompanied by Z-line widening, suggesting that Z-line widening results from altered elastic properties of cytoskeletal proteins that pull at and open up adjacent Z lines. Also, Fpassive rose progressively from HFrEF to HFrEF in non-DM to HFrEF in DM, and this rise was paralleled by an increase in cardiomyocyte diameter and a shift from eccentric to concentric LV remodeling. All of the HFrEF DM patients had type 2 DM and fasting hyperinsulinaemia. They thus suggest that the excess cardiomyocyte hypertrophy in DM HFrEF is probably secondary to insulin resistance since hyperinsulinaemia is known to stimulate prohypertrophic signaling in insulin-responsive tissues e.g. the myocardium [39].

The population studied by van Heerebeek et al showed different clinical characteristics to those observed in epidemiological studies. Thus, as suggested by Connelly et al [40], one should not conclude that fibrosis does not contribute to HFrEF in DM. Animal studies suggest that fibrosis contributes to this syndrome [41], while human studies have shown that collagen volume fraction is increased approximately 2-fold in both DM and non-DM subjects with HFrEF [42]. It seems that both fibrosis and cardiomyocyte Fpassive are linked attributes to HFrEF in DM though the relative contribution of each remains under debate. Undoubtedly, research into new treatment strategies should include both antifibrotic and antihypertrophic strategies [40].
1B. Ventricular-arterial Coupling & Vascular Dysfunction

EF is preserved in HFpEF, but EF is more accurately regarded as a measure of ventricular-arterial coupling than contractility alone [41]. Ventricular-arterial coupling can be expressed as the ratio of arterial elastance to end-systolic elastance [43]. Elastance is a measure of stiffness. Arterial elastance is determined by peripheral vascular resistance, total arterial compliance, impedance, and systolic and diastolic time intervals [44] and therefore represents the arterial afterload on the LV. In healthy subjects, ventricular-arterial coupling maintains this ratio within narrow limits, so as to optimise the energy efficiency of the myocardium.

However, ageing, hypertension, and DM lead to ventricular and vascular stiffening, with consequent HFpEF [8,45], the latter leading to greater BP lability with amplified BP changes for any alteration in preload/afterload [46]. Thus, although ventricular-arterial coupling appears beneficial in maintaining optimal cardiovascular performance [47,48], ultimately it results in adverse cardiovascular effects, including increased sensitivity to volume shifts and decreased exercise capacity [49]. Ventricular-arterial coupling may be particularly relevant in DM. The brachial-ankle pulse wave velocity (baPWV), an indirect surrogate of vascular compliance, is increased in DM subjects as compared with normal subjects [50].

Figure 1. Left Ventricular Diastolic Dysfunction

Doppler evidence of left ventricular diastolic dysfunction: (A) Mitral inflow pattern showing reversed E/A ratio; (B) Tissue Doppler evidence indicating diastolic dysfunction.
Similarly, in the Digitalis Investigation Group (DIG) ancillary study, a higher pulse pressure was noted in HFrEF patients with DM compared to non-DM patients [51]. Increased arterial stiffness in DM is probably secondary to AGEs; this could have contributed to the increased risk of adverse cardiovascular outcomes in DM HFrEF patients [51].

Nonetheless, the role of ventricular-arterial coupling in DM patients with HFrEF is still controversial. In the study by Takeda et al [26], there was no difference in baPWV between DM subjects without HF and DM subjects with HF while Poulsen et al [52] have shown that valvulo-arterial impedance (p=0.027) and summed stress score, an indicator of myocardial ischaemia (p<0.001), are independent predictors of grade 2 diastolic dysfunction in type 2 DM, though only summed stress score (p<0.001) was a predictor of left atrial dilation. Taken together, these results suggest that ventricular-arterial coupling might play a role in the development of HFrEF in DM.

Systemic vasorelaxation with exercise is attenuated in HFrEF [15-17], promoting impaired delivery of blood flow to skeletal muscle. Vascular dysfunction in HFrEF may be partly secondary to endothelial dysfunction, as suggested by Borlaug et al [17] whereby impaired flow-mediated vasodilation was noted in HFrEF compared with healthy age-matched controls. Endothelial dysfunction is a common finding in DM, as discussed below.

1C. Chronotropic Incompetence & Cardiovascular Reserve Dysfunction
Various studies have highlighted the importance of abnormalities in cardiovascular reserve function with exercise stress in HFrEF [15-20,23], explaining why most patients with HFrEF complain of symptoms only on exertion. Normal exercise reserve function is determined by diastolic reserve, systolic reserve and chronotropic reserve. Abnormalities in each of these components have been identified in HFrEF, including subjects with DM.

Diastolic reserve is reduced in HFrEF such that patients display blunted increases in preload volume with exertion, despite marked elevations in filling pressure. In a comprehensive study using upright bicycle exercise testing with simultaneous right heart catheterization and serial radionuclide ventriculography [53], cardiac index, stroke volume index, and LV end-diastolic volume (LVEDV) at rest did not differ between HFrEF patients, some of whom were diabetic, and control subjects but were lower in patients with HFrEF at peak exercise. This resulted in markedly lower peak oxygen consumption. The authors suggest that this is secondary to impaired LV filling and failure to use the Frank-Starling mechanism properly [48]. An impaired chronotropic response was also reported. This is probably related to downstream deficits in β-adrenergic stimulation since there is a similar increase in plasma catecholamines with exercise in HFrEF and healthy controls [15]. This is possibly secondary to autonomic dysfunction, a common co-morbidity in DM, since baroreflex sensitivity is reduced and heart rate recovery impaired in HFrEF [15,54].

In a study by Borlaug et al [15], HFrEF patients, most of whom were diabetic, showed a lower increase in heart rate, lower decrease in systemic vascular resistance index, and lower increase in cardiac index during exercise when compared with controls while LVEDV increased similarly in both groups. These findings suggest that in HFrEF both the chronotropic and vasodilatory reserves are diminished [15]. The latter would result in reduced diastolic reserve. In another study by Westermann et al [55], a decrease in LVEDV and stroke volume were noted in HFrEF patients (17% diabetic) during pacing at 120 beats/min; this was interpreted as manifestation of increased LV stiffness. However, during handgrip, a more physiologic form of exercise, there was no change in LVEDV. In view of these contradictory results, further studies are needed to understand the haemodynamic response to exercise in HFrEF.

With respect to systolic reserve, blunted increases occur in EF, contractility, and longitudinal systolic shortening velocities during exercise [15-19]. It has been suggested that myocardial ischaemia (epicardial/microvascular coronary disease or vascular rarefaction), impaired β-adrenergic signalling [56], myocardial energetics [18,57], and abnormal calcium handling [58] play a role in systolic and diastolic reserve dysfunction in HFrEF. These pathological changes have been noted in DM (discussed below).

2. Pathophysiological Mechanisms underlying HFrEF in Diabetes
Various morphologic changes occur in the diabetic heart leading to the abnormal physiological findings described above. These include increased extracellular collagen deposition, interstitial fibrosis, myocyte hypertrophy and intramyocardial microangiopathy. These changes are probably secondary to altered myocardial glucose and free fatty acid metabolism (FFA) in DM as outlined below and in Figure 2.

2A. Hyperglycaemia
The hallmark of type 2 DM is insulin resistance with impaired myocardial glucose use and increased turnover of FFAs, leading to myocardial lipotoxicity, uncoupling of mitochondrial oxidative phosphorylation and disturbed contraction/relaxation coupling [59]. In type 1 DM, even though no hyperinsulinaemia is usually present, hyperglycaemia secondary to β-cell failure leads to numerous adverse cellular effects including down-regulation of sarcoplasmic reticulum calcium ATPase (SERCA) expression and activity, decreased Na+/K+-ATPase function and decreased myocardial flow reserve, leading to both LV systolic and diastolic dysfunction [60]. Furthermore, diminished C-peptide levels in type 1 DM may adversely affect cardiac endothelial function [61,62], probably through diminished nitric oxide release [63].

Glycaemic control has been reported to improve diastolic dysfunction [64] and to reduce LV mass [65] over a 6-12 month period. It is important to note that good glycaemic control may also be a marker of improved metabolic control including free fatty acid concentration.
2B. Lipotoxicity
Diabetic subjects exhibit increased myocardial fat [66] and this is associated with diastolic dysfunction [67]. In both type 1 and type 2 diabetes, the myocardium is increasingly dependent on fatty acid rather than glucose metabolism for its energy requirements [68]. Since fatty acid metabolism requires more oxygen for energy production, it may lead to relative hypoxia. This may predispose to diastolic dysfunction [68] as ventricular relaxation is an energy-dependent process. Furthermore, intermediates of fat metabolism, such as ceramide might be toxic, inducing cell apoptosis [69].

2C. Hyperinsulinaemia
HFpEF is not only associated with diabetes but also with the metabolic syndrome [70] and with impaired glucose tolerance [71], suggesting that insulin resistance and/or hyperinsulinaemia might be implicated. Nichols et al [72] reported that insulin use was associated with both prevalent and incident HF. In the Uppsala Longitudinal Study of Adult Men, baseline fasting proinsulin and insulin resistance predicted future HF [73].
Cardiomyocyte-selective insulin receptor knockout mice show reduced cardiac and cardiomyocyte size [74]. In humans, insulin levels have been associated with LV relative wall thickness [75].

Figure 2. Pathophysiological Mechanisms
Pathophysiological mechanisms underlying HFpEF in diabetes mellitus (RAS: renin-angiotensin system)
Insulin is a growth factor to many cell types, including the cardiomyocyte. The signaling pathways mediating the metabolic and growth factor properties of insulin are different. Crucially, insulin resistance seems to affect only the metabolic, but not the growth factor, effects of insulin. Therefore hyperinsulinaemia in subjects with type 2 DM or the metabolic syndrome exposes them to exaggerated growth factor-like effects.

2D. Advanced glycation endproducts (AGEs)
Chronic hyperglycemia leads to non-enzymatic glycation of matrix proteins in the vascular wall and myocardium, producing AGEs. AGEs stimulate collagen production and cross-linkage, leading to increasing LV diastolic stiffness and diminished compliance of the blood vessels [76]. AGEs increase oxidative stress and pro-inflammatory cytokine release while AGE receptor activation induces pro-fibrotic signaling and impairs calcium homeostasis [77,78]. Increased serum AGEs are associated with LV diastolic stiffness, endothelial dysfunction, impaired vascular compliance and reduced NO bioavailability, in both type 1 and 2 DM patients [77,78].

2E. Impaired calcium homeostasis
Calcium handling by the cardiomyocyte is important in both systole and diastole. Membrane depolarization results in the release of calcium from the sarcomplasmic reticulum (SR) into the cytosol (through ryanodine receptors), where it binds troponin C to start the contractile process. During diastole, calcium is taken up by the SR through activation of the SR calcium+ pump (SERCA2a), the sarcolemmal Na+-Ca2+ exchanger, and the sarcolemmal Ca2+ ATPase.

In both type 1 and 2 DM, disturbed cardiomyocyte calcium handling results from reduced activity of calcium handling proteins, such as SERCA2a, ryanodine receptor, Na2+/-Ca2+ exchanger and sarcolemmal Ca2+ ATPase. This leads to impaired excitation-contraction coupling and LV systolic and diastolic dysfunction [59,79].

2F. Myocardial Oxidative Stress
Hyperglycaemia induces oxidative stress via several mechanisms, mainly glucose auto-oxidation, formation of AGES, activation of the polyol pathway and increased levels of FFAs and leptin [80]. Cardiovascular sources of reactive oxygen species (ROS) production include xanthine oxidoreductase, nicotinamide adenine dinucleotide 3-phosphate (NAD(P)H) oxidase, mitochondrial oxidases and uncoupled nitric oxide (NO) synthases [80,81]. Increased generation of ROS leads to cardiac injury and endothelial dysfunction, by direct oxidative cellular damage and by diminished NO bioavailability [81].

2G. Myocardial Fibrosis
Increased collagen deposition occurs in the diabetic myocardium, as evidenced by abnormal increased backscatter on echocardiography [82]. Hyperglycaemia, oxidative stress and elevated aldosterone and angiotensin II levels lead to increased expression of collagen type I and downregulation of collagen-degrading matrix metalloproteinases [82].

2H. Left Ventricular Hypertrophy
LV hypertrophy is commoner in diabetic subjects, independently of BP and other factors [83,84]. This can be mediated through hyperinsulinaemia and/or insulin resistance (see above). Various adipokines may also be implicated. These include resistin [85] (a cytokine released by adipose tissue macrophages) and leptin [86] (a marker of fat mass), both of which are increased in type 2 diabetes and the metabolic syndrome.

2I. Endothelial dysfunction
Altered insulin signaling, glyco- and lipotoxicity, and AGES accumulation, all factors that occur in DM, lead to endothelial dysfunction [87]. This results in dysregulation of vascular permeability, inflammatory responses, vascular remodelling and atherosclerosis, with consequent increased arterial stiffness, BP and pulse pressure [88,89]. The increase in afterload results in increased resting myocardial oxygen requirements and in myocardial hypertrophy which ultimately leads to LV diastolic dysfunction [90].

2J. Microangiopathy
Diabetic patients exhibit microangiopathy that is characterized by abnormal capillary permeability, microaneurysm formation, subendothelial matrix deposition, and fibrosis surrounding arterioles [91]. This impairs oxygen delivery to myocardial cells. Interestingly, coronary blood flow reserve is reduced in DM even in the absence of obstructive CAD [92,93]. Thus, myocardial ischaemia may play a role in diastolic dysfunction in DM in the absence of significant CAD since myocardial relaxation is an energy-dependent process. This can be further exacerbated by dependence on fatty acids as an energy substrate, mitochondrial uncoupling (see above) and LV hypertrophy that increases the diffusion distance between blood in the microcirculation and parts of the myocardium.

2K. Neurohormonal Regulation
Hyperglycaemia and hyperinsulinaemia activate the cardiac renin-angiotensin system (RAS) by increasing the expression of angiotensinogen, angiotensin II, and angiotensin II type 1 receptor. This contributes to diastolic dysfunction via hypertension and impaired myocardial relaxation [94-96]. Myocardial RAS activation has been demonstrated in streptozocin-induced diabetic rats [97].

2L. Autonomic Neuropathy
Diabetic autonomic neuropathy affects both the sympathetic and parasympathetic nervous system; this has been associated with impaired systolic and diastolic function [98]. In transgenic mice, an increased expression of the β1-receptor results in enhanced apoptosis, fibrosis, hypertrophy, and impaired myocardial function [99].
2M. The Foetal Gene Programme

This entails the expression of genes normally expressed in foetal/early neonatal life. Re-expression of the foetal gene programme might be an adaptive response in the failing heart. It leads to upregulation of the β-myosin heavy chain (β-MyHC) gene and down-regulation of the fast contracting isofom, α-MyHC [100]. These changes may be adaptive: β-MHC would allow cardiac muscle to work more efficiently when chronically overloaded because it contracts and relaxes more slowly than α-MHC [101]. However, it may predispose to diastolic dysfunction as demonstrated in alloxan-induced diabetic rats [102].

2N. Stem Cell involvement

LV dysfunction in DM might be a stem cell disease. Rota et al [103] have shown that enhanced oxidative stress in DM can affect cardiac progenitor cell function leading to defective myocyte formation, premature myocardial aging and HF. It has been suggested that the p66shc gene is responsible for promoting the senescent phenotype [103].

2O. Other Myocardial Changes in Diabetes

Other changes at the molecular level include altered protein kinase C metabolism resulting in endothelial dysfunction, increased leukocyte adhesion, increased albumin permeability, and impaired fibrinolysis [104,105]; impaired myocardial NO bioavailability resulting in increased LV diastolic stiffness [106]; and impaired myocardial cGMP synthesis leading to impaired protein kinase G (PKG) activity. PKG has anti-hypertrophic, anti-remodeling and anti-inflammatory actions [107]. Downregulation of NO-mediated cGMP-PKG signalling, probably induced by vascular inflammation and oxidative stress, could account for the high Fpassive of hypertrophied cardiomyocyte observed in DM HfPEF patients [108].

Conclusion

Although various studies have been performed to unravel the pathophysiology of HfPEF in diabetic patients, a lot is still unknown. The key issue is that diabetic individuals are at increased risk of HF, particularly HfPEF with associated poor prognosis. Therapeutic options for HfPEF are still controversial. Thus, currently, cardiometabolic prevention, focusing on dyslipidaemia, hypertension and hyperglycaemia, should form the cornerstone in the management of DM patients. Undoubtedly, further studies are needed to establish the pathophysiological mechanisms underlying HfPEF in DM with the hope that novel pharmacotherapies targeting this disease will be developed.

Competing Interests

The authors declare that they have no competing interests.

Authors’ Contributions

All authors were involved in literature review, drafting the manuscript and revising it critically for important intellectual content. Furthermore, all have approved the final version to be published.

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