Heart failure, diabetes and the thiazolidinediones: an unfolding story

Samy I McFarlane[1†] & Fadi A El-Atat[2]

[†]Author for correspondence
[1†]SUNY-Downstate and Kings County Hospital Centers, Division of Endocrinology, Diabetes and Hypertension, 450 Clarkson Avenue, Box 50, Brooklyn, NY, 11203, USA
Tel: +1 718 270 3711
Fax: +1 718 270 6358
[2]SUNY-Downstate and Kings County Hospital Centers, Division of Cardiovascular Medicine, 450 Clarkson Avenue, Box 50 Brooklyn, NY, 11203, USA

"This unfolding story reminds us of the restrictions placed on the use of β-blockers in patients with heart failure..."

Thiazolidinediones (TZDs) have emerged as major therapeutic tools in patients with Type 2 diabetes [1]. Besides their potent hypoglycemic and insulin-sensitizing properties, these agents also possess several beneficial cardiovascular effects [2]. These include improved endothelial function and reduced inflammation and thrombosis. Despite the cautious recommendations on their use in patients with heart failure (HF) [3], accumulating evidence indicates that these agents might improve cardiac functions including regulation of left ventricular (LV) remodeling and improvement of LV function [4,5]. This unfolding story reminds us of the restrictions placed on the use of β-blockers in patients with HF, until randomized controlled trials demonstrated that in HF patients, including those with diabetes, the use of β-blocking agents actually improved symptoms as well as survival [6].

Heart failure in people with diabetes mellitus

The Framingham study established diabetes mellitus (DM) as an independent risk factor for the development of HF [7]. Furthermore, patients with HF and DM have higher mortality rates than nondiabetic patients with HF [8]. The increased predisposition to HF in the insulin-resistant state of DM is multifaceted [9,10]. In this state, there is accelerated development of atherosclerosis, myocardial infarction (MI) and ischemic HF [2,3]. Also, there is a higher prevalence of hypertension, dyslipidemia, progressive renal disease and LV hypertrophy, which further contributes to the development of HF, including ischemic HF [2,9]. Furthermore, DM and HF share multiple neurohormonal pathways, including an enhanced sympathetic nervous system (SNS) and activation of the rennin–angiotensin system (RAS), together with the oxidative, prothrombotic and proinflammatory state associated with generalized endothelial dysfunction [1,2,9]. In addition, DM exerts direct deleterious effects on cardiac structure and both systolic and diastolic functions, leading to what is now recognized as an entity, diabetic cardiomyopathy [10].

Beneficial effects of TZDs on cardiac parameters (Box 1)

Effects on LV remodeling & neurohormonal regulation

There is evidence from animal studies that TZDs reduce cardiac hypertrophy [4,11], inhibit LV remodeling [9,12,13] and even improve LV systolic function in failing hearts [9] through multiple mechanisms, including insulin sensitization, alleviation of RAS/SNS activation [14] and suppression of the expression of proinflammatory cytokine genes such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, as well as inducible nitric oxide synthase (iNOS) and matrix metalloproteinase (MMP)-9, with a role for nuclear factor (NF)-κB [4,5,15,16].

LV hypertrophy is an important risk factor for coronary heart disease (CHD) and CHD mortality, and plays a key role in diastolic dysfunction. Hyperinsulinemia contributes to this hypertrophy directly by acting through insulin-like growth factor (IGF) receptors and indirectly through coexisting hypertension. Experimental studies have shown that TZDs, through their insulin-sensitizing effect, help alleviate this hypertrophy [11]. In addition, following MI, there are a number of factors that further depress LV function, including: LV dilatation; hypertrophy and fibrosis of the noninfarcted myocardial tissue; and an alteration of LV geometry, otherwise referred to as LV remodelling. Several neurohormonal and chemical pathways are incriminated in this remodeling, including, TNF-α, IL-1β, iNOS and MMP-9. TZDs have been shown *in vitro* and *in vivo* to suppress the expression of these genes, subsequently inhibiting or regulating LV remodeling and ultimately preserving and even improving LV function [4,5,14,16]. Although small clinical trials revealed only a neutral effect of TZDs on cardiac structure and function [2,3], ongoing large randomized clinical trials are expected to clarify the effects of TZDs on LV remodeling and hypertrophy [3,101].

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Direct effects of TZDs on vasculature & afterload

The insulin-resistant state of diabetes and obesity is characterized by abnormal vascular reactivity [17]. This is secondary to disturbed balance between vasoconstrictors and vasodilators in the insulin-resistant state. This state is a prothrombotic, proinflammatory one with major oxidative stress [17]. TZDs, via suppression of inflammation, oxidative stress and thrombosis, restore the balance between vasodilators and vasoconstrictors, leading to improved vascular reactivity and reduction in afterload and peripheral resistance, a particularly desirable effect in patients with HF. This, in addition to inhibition of vascular smooth muscle cell (VSMC) proliferation and migration, help alleviate the atherogenic propensity of the insulin-resistant state, again with a beneficial effect on the state of HF, including ischemic HF. Further details about these vascular effects of TZDs have been discussed in our previous article [2].

Ischemia & reperfusion-induced cardiac injury

Animal studies suggest a beneficial cardiac effect of TZDs after ischemia and reperfusion injury. This is believed to be mediated by inhibiting Jun NH-terminal kinase/activating protein-1 in the heart, leading to reduction in MI size and improvement of contractile performance [18,19].

Myocardial glucose energy metabolism

In the insulin-resistant state of diabetes, there is almost a total shift in myocardial energy metabolism toward fatty acids (FAs) with a subsequent increase in oxygen consumption, worsening of contractile function and predisposition to arrhythmias [20]. This is particularly detrimental after acute MI. TZDs counteract these abnormalities by correcting the myocardial insulin resistance, thus restoring myocardial glucose metabolism [20,21].

Established & controversial side effects

Fluid retention, peripheral edema & HF

Clinical trials have shown an increased incidence over a range of 2–5% of fluid retention, peripheral edema and increased plasma volume with the use of TZDs [1,5,22]. Higher percentages have been reported with the concomitant use of insulin. This is believed to be the result of an increased endothelial permeability and is less likely due to alteration of renal hemodynamics [23]. Such fluid retention may be of concern in patients with HF [24–26]. However, there have not been any published randomized clinical trials on TZDs in patients with HF. In addition, only few cases of HF linked to TZDs have been reported [24–26]. Clinical trials revealed a new-onset HF incidence of less than 1% with the use of TZDs, similar to the incidence in placebo-treated patients [26]. This figure reaches 2–3% with the concomitant use of insulin [3]. Further, epidemiologic studies have shown an increased risk of HF with the use of TZDs, with hazard ratios ranging from 1.2 to 1.6 [3]. Authors of these studies concluded that the risk of HF attributable to TZD use is in itself, small. In addition, recently, a small 2-year observational study of 111 patients with baseline HF, New York Heart Association (NYHA) Classes I–III concluded that fluid retention was related to concomitant insulin use and female sex but not to baseline severity of HF [22]. As such, the authors suggested that despite the risk for fluid retention, TZDs could be used in patients with stable HF as long as they are monitored for development of HF [22]. Of note is that while the TZD-induced fluid retention is partially refractory to diuretic therapy, it responds promptly to dose lowering or discontinuation of the TZD [1,4,22].

Weight gain

Weight gain is a common side effect of most hypoglycemic agents, including TZDs [3]. However, unlike other agents, TZDs are believed to favorably relocate the excess visceral fat to the subcutaneous compartment, where it is less biologically active [27]. Further, weight gain resulting from the use of these agents is avoidable through appropriate dietary modifications.

Recommendations for TZD use in HF

Currently, cautious recommendations regulate the use of TZDs in people with HF. In diabetic individuals with stable NYHA Class I and II, LV ejection fraction < 45% or people with at least one other risk factor for HF, if a TZD is chosen, it is recommended to be started with a low dose. Subsequently, close monitoring for signs and symptoms of HF is necessary while gradually titrating the dose [3,4,28].

Box 1. Beneficial effects of thiazolidinediones on cardiac functions.

Reduced cardiac hypertrophy
Inhibition of left ventricular remodeling
Improved left ventricular systolic function in the failing heart
Decreased afterload
Decreased peripheral vascular resistance

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Affiliations

Samy I McFarlane, MD, MPH, FACP, Associate Professor of Medicine, Interim Chief, SUNY-Downstate and Kings County Hospital Centers, Division of Endocrinology, Diabetes and Hypertension, 450 Clarkson Avenue, Box 50, Brooklyn, NY, 11203, USA
Tel.: +1 718 270 3711
Fax: +1 718 270 6358

Fadi A El-Atat, MD, Senior Fellow SUNY-Downstate and Kings County Hospital Centers, Division of Cardiovascular Medicine, 450 Clarkson Avenue, Box 50 Brooklyn, NY, 11203, USA