An overview of the beneficial cardiovascular effects of thiazolidinediones

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Cardiovascular disease is a major cause of morbidity and mortality in people with diabetes and those with the metabolic syndrome. With the rising prevalence of these disorders that is now reaching epidemic proportions around the globe, cardiovascular disease is also expected to rise substantially. Although lifestyle and dietary interventions are the first-line approaches in the management of diabetes and the metabolic syndrome, pharmacotherapy is almost always necessary to achieve optimal control of glycemia, elevated blood pressure, microalbuminuria, dyslipidemia and other associated cardiovascular disease risk factors. Therapeutic agents that have beneficial cardiovascular effects are attractive choices in treating these high-risk patients. Thiazolidinediones have recently gained momentum due to an increase in interest in their insulin-sensitizing, pleiotrophic effects and their potential to reduce the risk of cardiovascular disease in people with diabetes and reduce diabetes itself. In this article, the beneficial cardiovascular effects of thiazolidinediones in people with insulin resistance and diabetes shall be reviewed, highlighting their anti-atherosclerotic and anti-inflammatory role together with their potential effects on dyslipidemia, visceral obesity, hypertension and microalbuminuria.

Diabetes is estimated to affect around 17 million adults, and the metabolic syndrome of an even higher number, reaching 25 million adults in the USA [1,2]. Cardiovascular disease (CVD) is a significant macrovascular complication and the leading cause of death in people with diabetes, accounting for up to 80% of deaths in this population [3]. Control of CVD risk factors such as hypertension, dyslipidemia and hyperglycemia is largely suboptimal. For example, in a study by the authors' group only 5% of diabetic patients achieved metabolic control as recommended by the American Diabetes Association guidelines [4]. Therefore, agents with the potential to reduce the risk of CVD in people with diabetes seem to be the logical option in curbing the rising epidemic of the disease. Not surprisingly, increasing attention is being paid to such agents. Among these agents, thiazolidinediones (TZDs) seem to have a myriad of beneficial cardiovascular effects in addition to improving insulin resistance and glycemic control (**Box 1**) [5].

The mechanism of action of TZDs involves binding to the peroxisome proliferator-activated receptor-γ (PPAR-γ), a transcription factor that regulates the expression of specific genes, especially in fat cells, but also in other tissues [6]. It is likely that TZDs act primarily on adipose tissue where PPAR-γ is predominantly expressed. TZDs have been shown to interfere with the expression and release of mediators of insulin resistance originating in adipose tissue such as free fatty acids (FFAs), adipocytokines such as tumor necrosis factor (TNF)-α, resistin and adiponectin, by a method which results in a net improvement of insulin sensitivity in muscle and liver [6].

Direct effects of TZDs on atherosclerosis: effects on vasculature

Vascular effects of TZD

The insulin-resistant state of diabetes and obesity is characterized by abnormal vascular reactivity, namely an abnormal vasodilatory response to ischemia, exercise, carbon dioxide and thermal challenges [7]. The basal vascular tone and arterial blood flow are, however, preserved. The abnormal vasodilatory response is secondary to disturbed balance between vasoconstrictors and vasodilators in the insulin-resistant state [8]. This state is prothrombotic and proinflammatory with major oxidative stress [9]. There is a surge of reactive oxygen species (ROS), $p47^{phox}$ (an essential protein which converts molecular oxygen to the superoxide radical), FFAs, TNF-α, interleukin (IL)-6 and hypercoagulable platelets which constitute the source for thromboxane (TX)A, norepinephrine (NE) and serotonin, thus completing the myriad of vasoconstrictors [9]. These vasoconstrictors in turn contribute to the decreased levels and action of vasodilators by reducing the synthesis and release of nitric oxide (NO) and enhancing the degradation

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Box 1. Metabolic and cardiovascular effects of thiazolidinediones.

- Decreased levels of proinsulin and insulin
- Decreased free fatty acids
- Decreased diastolic blood pressure
- Decreased stress-related elevation of blood pressure
- Decreased microalbuminuria
- Decreased plasminogen activator inhibitor (PAI)-1 levels
- Inhibition of vascular smooth muscle cell proliferation
- Reduction of carotid artery intimal–medial thickness
- Improved endothelial function
- Reduction of inflammatory mediators:
  C-reactive protein (CRP)
  Monocyte chemoattractant protein (MCP)-1
  Matrix metalloproteinase (MMP)-9
  Tumor necrosis factor-α and free fatty acid levels

of prostacyclin, a scenario characteristic of the insulin-resistant state [10]. TZDs help restore the vasodilatory response in this population through improving endothelial and vascular smooth muscle cell (VSMC) function (**Box 1**) [11–14]. Their anti-inflammatory effect is manifested by reduction of C-reactive protein (CRP), monocyte chemoattractant protein (MCP)-1, matrix metalloproteinase (MMP)-9, TNF-α and FFA levels (**Box 1**) [13,14]. They are also responsible for suppressing the surge of ROS [14]. Further, they restore the vasodilatory effect of insulin by improving insulin sensitivity [15].

Plasminogen activator inhibitor (PAI)-1 levels are generally elevated in diabetes- and insulin-resistant states [16]. PAI-1 is the main inhibitor of endogenous intravascular fibrinolysis and elevated PAI-1 levels correlate with atherogenicity [17]. In addition to exercise and weight loss, TZDs reduce PAI-1 levels and activity, an effect that remained significant even after addition of sulfonylurea therapy [18].

Moreover, VSMC proliferation and migration in response to vascular injury is an essential step in the formation of atheroma [19]. TZDs have been shown to inhibit VSMC migration and proliferation both *in vitro* and *in vivo* with reduction in early in-stent restenosis [20]. More recently, in humans, rosiglitazone significantly reduced in-stent restenosis in diabetic patients up to 6 months after coronary stenting [21].

Further support for the beneficial effect of TZDs on halting the progression of atherosclerosis comes from studies on carotid intimal–medial thickness (IMT), as measured by B-mode ultrasonography. Carotid IMT correlated with CVD and stroke [22]. The use of troglitazone resulted in a significant reduction in carotid IMT at 3 months and this effect was maintained for 6 months [23]. Other studies using rosiglitazone and pioglitazone obtained similar results, reduction in carotid IMT consistent with inhibition of early atherosclerotic process by PPAR-γ activation [24–26].

In a nutshell, TZDs – via suppression of inflammation, oxidative stress and thrombosis – restore the balance between vasodilators and vasoconstrictors, leading to improved vascular reactivity. This, in addition to inhibition of VSMC proliferation and migration, helps alleviate the atherogenic propensity of the insulin-resistant state.

Indirect effects of TZDs on atherosclerosis: effects on CVD risk factors

Traditional CVD risk factors that aggregate in patients with diabetes and the metabolic syndrome include insulin resistance/hyperinsulinemia, hypertension, visceral obesity, increased triglycerides, reduced high-density lipoprotein (HDL) and microalbuminuria, among others [27] (**Box 2**). TZDs seem to exert beneficial effects on these risk factors, which might help to reduce the burden of CVD in these particularly vulnerable populations.

Insulin resistance/dysglycemia

Insulin resistance, through alteration of multiple neurochemical and hormonal mediators including FFAs, seems to play a pivotal role in the elevated CVD risk in people with diabetes and the metabolic syndrome [2]. TZDs, potent and selective agonists of PPAR-γ, have been shown to improve insulin sensitivity at the level of adipose tissue, skeletal muscle and liver [15]. They also reduce FFA levels, attenuating the role of these pathological messengers in the insulin-resistant state [28,29].

In addition, TZDs have been shown to preserve α-cell function, likely prevent α-cell apoptosis and maintain α-cell and plasma insulin levels, all contributing to better glycemic control with beneficial cardiovascular effects [30–32]. Furthermore, TZDs have been shown to at least moderate several of the plethora of maladaptive cardiovascular and metabolic responses associated with the insulin-resistant state, including dyslipidemia, hypertension, microalbuminuria and visceral obesity [5].

Box 2. Metabolic and cardiovascular effects of thiazolidinediones.

- Hypertension
- Insulin resistance/ hyperinsulinemia
- Central obesity
- Sedentary lifestyle
- Cigarette smoking
- Dyslipidemia:
  - Increased triglycerides
  - Low high-density lipoprotein
  - Small dense low-density lipoprotein
- Increased inflammation
- Procoagulant state
- Absence of nocturnal decrease in blood pressure and heart rate
- Left ventricular hypertrophy
- Microalbuminuria

Dyslipidemia

People with insulin resistance and those who have developed overt diabetes have a characteristic atherogenic lipid profile with reduced HDL-cholesterol, elevated triglycerides and predominance of small dense low-density lipoprotein (LDL) cholesterol particles [33].

TZDs have been demonstrated to increase HDL and reduce triglyceride levels [34]. In addition, although there was an initial elevation of LDL levels following 8 weeks of treatment with these agents, an accompanying alteration in the size of these particles in favor of the those that are light, buoyant and less atherogenic, was noted [35]. Furthermore, after long-term treatment with these agents to 100 weeks, LDL levels were lower than baseline [34]. Meta-analysis of randomized controlled trials in patients with diabetes comparing the CVD effects of TZDs, namely pioglitazone and rosiglitazone, showed that although both of these TZDs had similar effects on glycemic control and body weight, pioglitazone had a more favorable effect on lipid profile particularly in reducing fasting triglycerides levels [36].

Visceral obesity

Obesity, particularly android or visceral, seems to be the niche for inflammatory processes predominating the insulin-resistant state [9]. In fact, it is an independent predictor of cardiovascular morbidity and mortality [37]. TZDs seem to relocate fat deposition from intra-abdominal to subcutaneous tissues where fat is less atherogenic [37,38].

Hypertension

People with insulin resistance or diabetes are twice as likely to develop hypertension compared with those with normal insulin sensitivity [39]. Further, hypertension seems to contribute synergistically to the elevated CVD risk in people with diabetes [40]. As a result, particular attention has been focused on aggressive blood pressure (BP) control, with the recommended BP levels currently less than 130/80 mmHg in people with diabetes and the metabolic syndrome [41].

TZDs have been demonstrated to result in a modest but significant reduction in diastolic BP in people with diabetes [42], leading to attenuation of CVD risk in these individuals [40,43]. Furthermore, TZDs appear to reduce stress-related systolic (S)BP elevation in patients with diabetes and insulin resistance [44]. This effect, which is likely related to the overall reduction in vascular resistance with TZDs, has been demonstrated in a study of Type 2 diabetic patients randomized to troglitazone versus glyburide, a sulfonylurea, in which troglitazone showed a significant reduction in SBP response to mental arithmetic test provided at 6 months of treatment [44]. In this study troglitazone also significantly reduced BP at baseline compared with glyburide, highlighting the overall beneficial effects of TZDs on BP [42,44].

Microalbuminuria

Microalbuminuria is an early marker for diabetic nephropathy as well as an indicator of generalized endothelial dysfunction and inflammation accompanying the insulin-resistant state [45,46]. In fact, microalbuminuria is now considered an integral component of the metabolic syndrome and an established predictor of CVD morbidity and mortality in people with diabetes [2]. In this light, reduction of microalbuminuria is recommended as a therapeutic goal to reduce the overall CVD risk [47]. TZDs have been shown to reduce microalbuminuria above and beyond the effect of controlling hyperglycemia, highlighting the importance of the cardiovascular protective effects of these agents [48].

TZDs in the prevention of Type 2 diabetes

Aside from dietary and lifestyle interventions, several pharmacological agents have been examined in randomized controlled trials for the prevention of Type 2 diabetes [49]. Among these agents, troglitazone, a TZD that was examined in the Troglitazone in the Prevention of Diabetes (TRIPOD) study [50]. It has also been shown to delay or prevent the onset of Type 2 diabetes compared with placebo in a group of 133 high-risk Hispanic women with a history of gestational diabetes

Highlights

- Cardiovascular disease (CVD) is a major cause of morbidity and the leading cause of death in people with diabetes.
- The prevalence of diabetes mellitus and the metabolic syndrome is of epidemic proportions worldwide. Thus, CVD is projected to rise substantially.
- Lifestyle and dietary interventions are the first-line approaches in the management of diabetes and the metabolic syndrome
- However, pharmacotherapy is frequently inevitable to achieve optimal control of glycemia, elevated blood pressure, microalbuminuria, dyslipidemia and other associated CVD risk factors in people with diabetes.
- The use of agents that have beneficial cardiovascular effects is gaining momentum in treating these high-risk patients.
- Thiazolidinediones (TZDs) are prominent among these agents.
- The mechanism of action of TZDs involves binding to the peroxisome proliferator-activated receptor (PPAR)-γ, especially in fat cells.
- TZDs act primarily on adipose tissue.
- TZDs have been shown to interfere with the expression and release of mediators of insulin resistance in a net improvement of insulin sensitivity.
- TZDs help restore the equilibrium between vasodilators and vasoconstrictors in the vasculature.
- TZDs were demonstrated to have potent insulin-sensitizing, anti-atherosclerotic and anti-inflammatory effects.
- Further, TZDs provide favorable potent effects on dysglycemia, dyslipidemia, visceral obesity, hypertension and microalbuminuria.
- Hence, TZDs have a strong potential to reduce the risk of CVD in people with diabetes.
- TZDs may also reduce diabetes itself.

followed for 30 months. Prevention of diabetes by troglitazone was proportional to the reduction in plasma insulin level after 3 months of treatment [50]. These results are consistent with the notion that TZDs prevent diabetes by ameliorating insulin resistance.

Currently, rosiglitazone is being investigated in a large multicenter trial, along with the angiotensin-converting enzyme (ACE) inhibitor, ramipril, in a 2 × 2 design, with the primary end point being the development of diabetes in patients with impaired glucose tolerance, defined as 2 h glucose value of 140–199 mg/dl (7.8–11.0 mmol/l), after the administration of 75 g of glucose load [51]. This study will also examine the various cardiovascular endpoints using rosiglitazone and/or ramipril [51].

Clinical utility of TZDs in treatment of Type 2 diabetes

Insulin resistance is a major contributor to increased CVD in patients with Type 2 diabetes and the metabolic syndrome (**Box 2**) [27], and usually precedes the development of Type 2 diabetes [52]. Therefore, therapeutic agents that treat insulin resistance appear to be the logical options in the initial management of Type 2 diabetes [53]. Among these agents, biguanides and TZDs are the two pharmacological classes currently available. While TZDs work primarily by increased muscle glucose uptake [15], biguanides such as metformin mainly decrease hepatic glucose output [54]. TZDs appear to have a stronger effect in terms reducing insulin resistance [53]. For example, in a study comparing the effects of troglitazone and metformin on insulin requirements in patients with Type 2 diabetes [55], troglitazone decreased insulin requirements by 57% compared with a 31% decrease with metformin [55]. Side effect profile and contraindications of each of these two classes of drugs however, must be taken into an account. While metformin causes an initial modest weight loss, TZD is associated with initial weight gain of an average of 2 to 3kg in the first year of treatment [53]. Weight gain associated with TZDs, is usually related to increased fluid retention and increased subcutaneous adiposity [53]. This fluid retention associated with the use of TZD, is a likely explanation for the mild non-significant anemia associated with these agents [56,57]. Furthermore, fluid retention can cause exacerbation of congestive heart failure (CHF). Therefore, TZDs are not recommended in patients with advanced, class III and IV New York Heart Association CHF [58].

While metformin is contraindicated in kidney disease (serum creatinine > 1mg/dl in women or > 1.5mg/dl in men) [54], TZD are contraindicated in significant liver disease defined as alanine aminotransferase (ALT) three folds higher than

the upper limit of normal. Further, monitoring of ALT in patients treated with TZD is recommended at baseline every 2 months for the first 12 months and periodically thereafter [56,59]. If ALT increased to more than three times the upper limit of normal, it should be rechecked. If it remains elevated, it should be discontinued [59].

Expert opinion

TZDs, potent and selective PPAR-γ agonists, through their insulin-sensitizing actions and a constellation of pleotrophic cardiovascular effects, have the potential for reducing CVD risk in people with diabetes and the metabolic syndrome, a particularly high-risk population. These beneficial effects include reduction in diastolic BP and microalbuminuria, modification of lipid profile and body fat distribution, in addition to direct vascular effects. Remarkable among the latter are the anti-inflammatory, antioxidant effects, contributing to improved endothelial function and ultimately slowing the progression of atherosclerosis. Hence, when lifestyle/behavior modification, diet and exercise fail to achieve optimal control of dysglycemia and other cardiovascular and metabolic abnormalities associated with the insulin-resistant state, addition of TZDs, seem to and help achieve better glycemic control and exert potent beneficial cardiovascular effects in the population. Furthermore, TZDs have the potential for prevention of Type 2 diabetes in high-risk populations, an effect that is currently being evaluated in a large randomized controlled trial.

Outlook

Our understanding of the crucial role of nontraditional cardiovascular risk factors such as inflammation, in the pathogenesis of cardiovascular disease in diabetes is rapidly expanding. Hence, the use of agents such as TZDs will gain more support in the future, since these agents have pleotrophic effects including anti-inflammatory and anti-atherosclerotic in addition to their insulin-sensitizing and hypoglycemic properties.

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- • **Very thorough review of the maladaptive cardiovascular and metabolic responses to obesity in the metabolic syndrome. Elaborates on the inflammatory, prothrombotic, insulin-resistant, dysglycemic, dyslipidemic mechanisms in the insulin-resistant state of people with diabetes or the metabolic syndrome.**
- • **Smoothly yet thoroughly describes the role of various vasodilators and vasoconstrictors in vascular reactivity, which is impaired in people with diabetes. Further, it pinpoints the beneficial effects of TZDs in restoring the vascular reactivity in these individuals through a better equilibrium between vasodilators and vasoconstrictors.**

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