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# Pioglitazone and Endothelial Dysfunction: Pleiotropic Effects and Possible Therapeutic Implications

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**Abstract**
The vascular endothelium has a central role in the modulation of vascular tone with associated antioxidant, anti-inflammatory, pro-fibrinolytic, anti-adhesive, and anticoagulant effects. This is primarily accomplished by the timely release of endothelial autacoids. On the other hand, endothelial dysfunction (ED) provoked by insulin resistance has been linked with reduced nitric oxide bioavailability, increased production of reactive oxygen species, and alterations of endothelial regeneration. Pioglitazone is classified as an insulin-sensitizing, anti-hyperglycemic agent. The mechanism of action associated with pioglitazone includes the activation of peroxisome proliferator-activated receptorgamma with stable improvement in glycemic control in diabetic patients. Today, it is known that apart from the beneficial effects on glucose homeostasis, pioglitazone exerts several pleiotropic effects, including the improvement of ED. Thus, the aim of this article was to summarize the current knowledge related to signaling mechanisms of the pioglitazone-induced improvement or reversal of ED. The relevant clinical studies and possible therapeutic implications connected to pioglitazone-related action on the endothelium were analyzed too.

**Keywords:**
Pioglitazone • Endothelial dysfunction • Diabetes • Nitric oxide • PPARγ

**Introduction**
Thiazolidinediones, as an insulin-sensitizing group of drugs, have been shown to exert beneficial effects on the cardiovascular system independently of their action on glucose and insulin sensitivity. They have been demonstrated to be effective alone or in combination with a sulfonylurea, metformin, or insulin. The peroxisome proliferatoractivated receptor-gamma (PPARγ) agonist, pioglitazone, belongs to the insulin-sensitizing group of drugs, which is used in the treatment of type 2 diabetes mellitus (T2DM). Insulin resistance and hyperglycemia contribute to the development and progression of atherosclerosis within a complex milieu of interrelated risk factors, which include hypertension, dyslipidemia, chronic subclinical inflammation, ED, and abnormalities in coagulation and fibrinolysis. Insulin resistance is typically present for some years before diagnosis, manifested as diminished stimulation of glucose transport in muscle and adipose tissue and inadequate suppression of glucose production in the liver in response to insulin. Although PPARγ activation plays an important role in glucose metabolism by enhancing insulin sensitization, the activation of quoted ligand-activated transcription factor inhibits adhesion cascades and detrimental vascular inflammatory events with a distinctive role in regulating the physiology and expression of endothelial NO-synthase (eNOS), thus resulting in enhanced generation of vascular (nitric oxide) NO. Knowing that NO is the most important endothelium-derived relaxing autacoid and that there is a positive correlation among insulin and the up-regulation of eNOS, the additional mechanisms related to the activation of PPARγ may be significant for cardiovascular disorders linked with diabetes mellitus, too. Accordingly, even though pioglitazone is known to exert renoprotective effects in diabetic nephropathy at doses that normalize glycemia, it has also been reported that at low doses that do not normalize glycemia, pioglitazone administration in Zucker diabetic fatty rats was associated with the normalization of the renal levels of connective tissue growth factor and fibronectin, tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), and monocyte chemotactic protein-1, megalin, the proliferating cell nuclear antigen/caspase-3 ratio, vascular endothelial growth factor (VEGF), and the ratio between endothelial and inducible NOS. The beneficial effects of short-term, low-dosage pioglitazone on ED in regards to increasing adiponectin expression and decreasing low-grade inflammation in T2DM patients were reported as well. These and other similar findings have led to the hypothesis that pioglitazone could exert vasculoprotective effects that are independent of its metabolic action involving the activation of PPARγ

**Conclusions**
Having in mind the serious vascular complications associated with T2DM, an appropriate prevention and treatment of this pathological condition should be a paramount. Accordingly, the widely accepted diagnostic and preventive model of the metabolic response of an individual patient to a meal is the oral glucose tolerance test, which is also a reliable experimental technique to evaluate the modification related to post-prandial glycemia of endothelial stress systemic markers. PPARγ activation improves insulin sensitivity, decreases inflammation, plasma levels of free fatty acids, and blood pressure, so indirectly leading to the inhibition of atherogenesis, improvement of ED, and reduction of cardiovascular events. Pioglitazone is an insulin-sensitizing, anti-hyperglycemic agent which stimulates PPARγ, yet the vasculoprotective effects seem not to be directly associated to the activation of this nuclear receptor. Nevertheless, positive correlations are currently well documented considering the improvement of different markers related to ED and pioglitazone administration.

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