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Potential Role of Oral Thiazolidinedione Therapy in Preserving β-Cell Function in Type 2 Diabetes Mellitus

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Abstract

Worsening glycaemic control in type 2 diabetes mellitus relates to a decline in β-cell function, associated with impaired negative feedback regulation of insulin release. Insulin resistance, the 'traditional' cornerstone defect of type 2 diabetes, leads to an array of adverse effects on β cells, including hypertrophy, apoptosis and those caused by lipotoxicity and glucotoxicity. In particular, increased levels of free fatty acids and their metabolites are thought to diminish both insulin synthesis and glucose-stimulated insulin secretion.

Thiazolidinediones are synthetic peroxisome proliferator-activated receptor-γ agonists that decrease insulin resistance but, as *in vitro* and *in vivo* studies suggest, may have direct beneficial effects on pancreatic β cells. Troglitazone, for example, demonstrated improvements in insulin secretory capacity in isolated pancreatic islets from Wistar rats and a hamster β-cell line. *In vivo* studies reveal thiazolidinediones promote β-cell survival and regranulation as well as maintenance of β-cell mass and reduction in amyloid deposition.

Clinical evidence for thiazolidinediones is largely derived from comparative trials, mainly against sulfonylureas and metformin. Data at 2 years from a number of trials are now available and establish the positive effects of thiazolidinediones on glycaemic control. Empirical evidence showing decreases in fasting plasma insulin levels with pioglitazone and rosiglitazone indicate thiazolidinediones also improve insulin sensitivity. A possible effect of thiazolidinediones on normalising asynchronous insulin secretion, as assessed in a short-term placebo-controlled study, is less established. However, recent and ongoing clinical studies are focusing attention on verifying animal and other data, which support the notion that thiazolidinediones have beneficial effects on β-cell function. These clinical studies have shown thiazolidinediones capable of preventing or delaying the development of type 2 diabetes in a high-risk population; restoring the first-phase insulin response; and improving secretory responses to oscillations in plasma glucose levels. Many of these effects appear to be independent of improvements in insulin sensitivity. Other research efforts are examining the potential cardiovascular protective effects of thiazolidinediones. Available data imply thiazolidi-

nediones are associated with cardiovascular risk reduction, although results from large, clinical outcome trials, currently in progress, are still needed.

Improved understanding of the role that declining β-cell function has in the development of type 2 diabetes has drawn attention to the need for hypoglycaemic agents that can address this process. Emerging evidence suggests thiazolidinediones offer specific benefits for preventing or delaying the decline in β-cell function and, thereby, a substrate for early intervention efforts aimed at lowering the worldwide burden of type 2 diabetes.

Current treatment modalities for type 2 diabetes mellitus tend to focus on managing hyperglycaemia. However, recent clinical research indicates that focusing on glycaemia is inadequate to address the substantial morbidity and mortality associated with diabetes.[1] Rather, there is growing evidence that early intervention targeting the insulin resistance and increased secretory demand that are associated with pancreatic β-cell failure, can delay progression or even prevent type 2 diabetes for relatively long periods of time.[2]

The peroxisome proliferator-activated receptor (PPAR)-γ is a nuclear receptor that is expressed in several tissues including adipose, muscle, liver, vascular and the β cell, and is involved in regulation of glucose and lipid metabolism. In addition to roles in adipocyte differentiation and function (in particular, a key regulatory role in adipogenesis in the adipose tissue[3,4]), PPAR-γ regulates cell proliferation and differentiation, and inflammatory responses. Natural ligands of PPAR-γ include products of arachidonic acid and linoleic acid metabolism. The thiazolidinediones (glitazones) are synthetic PPAR-γ agonists that have been shown not only to decrease insulin resistance, but also to exert substantial effects on the integrity and functioning of the β cell.[5]

This review provides an overview of the pathogenesis of type 2 diabetes, particularly the central position of β-cell failure and the factors that contribute to it. It then discusses the possible role of oral thiazolidinedione therapy in preserving or improving β-cell function, and associated benefits, as suggested by clinical trial data. Searches of Medline and abstracts from recent scientific meetings on diabetes were undertaken to identify relevant references.

1. β-Cell Failure in Type 2 Diabetes Mellitus

1.1 Epidemiology

β-Cell function has been shown to decline with increasing duration of diabetes, notwithstanding the use of a number of existing therapies. The UKPDS (UK Prospective Diabetes Study), a 20-year trial, showed that glycaemic control (glycosylated haemoglobin [HbA_{1c}] <7%) gradually deteriorated over time, even in patients receiving intensive sulfonylurea or insulin treatment.[1] This deterioration in glycaemic control was shown to be due to progressive β-cell failure.[6] The Skaraborg Hypertension and Diabetes Project, a Swedish community-based surveillance of 376 primary care patients with type 2 diabetes, found HbA_{1c} levels to increase over time in association with a corresponding decline in β-cell function.[7] An HbA_{1c} level ≥6.5% was associated with impairment of β-cell function (homeostasis model assessment [HOMA] index 19.5 vs 45.8) and longer duration of diabetes (10.6 vs 6.4 years), irrespective of age and gender. These associations are likely to be causal, since β-cell function in patients with type 2 diabetes is diminished, as reflected in a marked decrease in the acute insulin response to an oral or intravenous glucose challenge, irrespective of the degree of insulin resistance.[8]

1.2 Pathophysiology

Under normal conditions, glucose regulation relies on a negative feedback loop between the liver and peripheral tissues and the insulin-secreting β cells in the pancreatic islets. As insulin resistance

(an attenuated responsiveness of cells to insulin) develops, the β cell adapts by increasing secretion of insulin to prevent fasting hyperglycaemia.[9] The increased demand for insulin results in β-cell hypertrophy, a gradual decline in secretory capacity and, as a result, fasting hyperglycaemia. Hypertrophied β cells are more prone to apoptosis, producing impaired functioning of the total population of β cells.[10] Cell apoptosis markedly increases in rate as impaired glucose tolerance (IGT) progresses to frank diabetes.[11] Progressive loss of β-cell function and mass results in a sustained imbalance between insulin supply and demand and, eventually, type 2 diabetes;[9] it also leads to alterations in pulsed and oscillatory insulin secretion, and in conversion of proinsulin to insulin.[8,9]

Other features of insulin resistance include increased exposure of the β cells to free fatty acids (FFAs) ['lipotoxicity'], increased production and deposition of islet-amyloid polypeptide (IAPP; amylin) and 'glucose toxicity'.[9]

2. Key Pathophysiological Factors Driving β-Cell Dysfunction

2.1 Current Theory of β-Cell Failure

Insulin resistance is the major driver of impaired insulin secretion in type 2 diabetes. The insulin secretion defect arises from β-cell dysfunction, which is correlated with the degree of fasting hyperglycaemia.[1] As UKPDS 33 has confirmed, the progression through IGT to frank type 2 diabetes results from a gradual deterioration in β-cell function in the presence of insulin resistance.[1,8]

Insulin resistance is an inherited trait involving an insulin receptor signalling defect, with a wide spectrum of response to an imposed nutrient load.[12] Progression to diabetes proceeds through hyperinsulinaemia in the presence of normoglycaemia, to hyperglycaemia with hyperinsulinaemia, and ultimately to β-cell failure signified by marked hyperglycaemia and hypoinsulinaemia.[12] Studies using animal models highlight the genetic differences in insulin secretory capacity, related to β-cell neogenesis, which determines the extent of this progression.[12]

2.2 Glucose Toxicity

The term 'glucose toxicity' refers to the desensitisation of β-cells to glucose in the presence of increased blood glucose levels, which has been clearly demonstrated in experimental studies.[13-16] Cell replication rate and apoptosis rates are held to be dependent on the concentration of blood glucose in one model based on *in vitro* data.[17] It is proposed in this model that below normal glucose levels the rate of β-cell death exceeds the replication rate but, as levels increase, the rate of replication becomes greater than the rate of death, causing cell mass to increase and glucose levels to return to the normal range. However, if levels continue to rise, the rate of β-cell death will exceed the replication rate, exacerbating the situation further.

Chronic hyperglycaemia appears to result in depletion of insulin secretory granules from β cells ('degranulation'), so that a subsequent glucose stimulus prompts less release of insulin. In frank type 2 diabetes β-cell function deteriorates further in response to glucose stimuli, as UKPDS 26[6] and the Belfast Diet Study[18] have shown, and reduction in glucose levels permits β-cell regranulation and partially restores insulin responses. Adding support to this, Diani et al.[19] found that pioglitazone preserves pancreatic islet structure in murine models of type 2 diabetes. Pioglitazone-treated mice exhibited significantly greater β-cell granulation, as well as evidence of reduced β-cell stress and significantly higher levels of pancreatic insulin.[19]

2.3 Lipotoxicity

FFAs sustain basal insulin secretion by the β cell in the fasted state, and potentiate the acute release of insulin in response to a glucose load.[20] However, prolonged exposure to high levels of FFAs impairs β-cell function[20-23] and FFAs are considered crucially important in the development of type 2 diabetes.[4]

Studies of the pathogenesis of type 2 diabetes in an obese Zucker diabetic fatty (ZDF) rat model

indicate that high levels of FFAs (hyperlipacidaemia) persist despite hyperinsulinaemia, suggesting resistance to insulin-mediated antilipolysis.[23] Sensitivity of the β cells to hyperlipacidaemia results in the complete loss of glucose-stimulated insulin secretion (GSIS) observed in the presence of high levels of FFAs.[23] Unused FFAs in islets of the ZDF rat are esterified, resulting in excessive FFA deposition over time,[24] associated with nitric oxide (NO)-mediated apoptosis of β cells.[25]

Increased FFA levels diminish both insulin synthesis and GSIS by way of a glucose-FFA cycle,[22] and also exert a proapoptotic effect on β cells in isolated human islets.[26] In nondiabetic individuals with a genetic predisposition to type 2 diabetes, a sustained increase in plasma FFA levels has recently been shown to impair postprandial insulin secretion and GSIS.[27] This research indicates that lipotoxicity is strongly implicated in progressive β-cell failure.

Physicochemical properties of individual FFAs appear critical in conferring an increased insulinotropic effect.[4,28,29] In particular, the malonyl coenzyme A (CoA)/long-chain acyl-CoA pathway appears to underlie Ca^{2+}-independent augmentation of insulin release by glucose and other nutrients.[30]

2.4 Islet Amyloid

Amylin is a normal secretory product of the β cell and is found in insulin secretory granules.[31] Islet amyloid, a polymer that is toxic to β cells, is formed by deposition of amylin in the form of fibrils. Formation of the polymer within the islet creates lesions that impair insulin secretion and absorption.[31] The presence of islet amyloid is associated with loss of β-cell mass in type 2 diabetes; it has been claimed that up to 90% of patients with type 2 diabetes have islet amyloid deposits[17] and that the degree of amyloidosis correlates with the duration and severity of diabetes.[32]

2.5 Insulin Processing Dysfunction

β Cells of patients with type 2 diabetes are further dysfunctional in their processing of insulin, secreting increased amounts of proinsulin compared with normal individuals – reflecting increased demand for insulin in the presence of β-cell dysfunction.[33] In a controlled study, the ratio of basal proinsulin to total immunoreactive insulin (IRI) in patients with type 2 diabetes was approximately double that in nondiabetic individuals of similar age and adiposity.[33] More recently, the Mexico City Diabetes Study demonstrated that a high proinsulin **:** specific insulin ratio predicts progression to type 2 diabetes irrespective of glucose tolerance.[34] Furthermore, the Insulin Resistance Atherosclerosis Study found that low acute insulin response and high fasting glucose levels were associated with a disproportionate increase in proinsulin levels in patients with newly diagnosed type 2 diabetes.[35]

2.6 Islet Progenitor Cells

The development of mature functioning pancreatic islet cells is initiated in undifferentiated precursor or progenitor cells, which subsequently differentiate to form mature islets. Islet progenitor cell populations are expanded in rodents with insulin resistance and the number of progenitor cells falls with the onset of islet atrophy.[36]

3. Putative Evidence for the Potential of Thiazolidinediones to Arrest Progression of Type 2 Diabetes Mellitus

3.1 Experimental Evidence

In normal human islet cells (α, β and δ), PPAR-γ is highly expressed at the level of both messenger RNA (mRNA) and protein, supporting the concept of a direct influence of PPAR-γ agonists such as thiazolidinediones on the islet β cell.[3] This is consistent with observations that thiazolidinedione treatment improves islet morphology and β-cell function, restoring the β-cell response to an oscillatory glucose infusion in animal models of obesity,[37] as discussed in sections 3.1.1 and 3.1.2.

3.1.1 In Vitro Studies

Insulin Resistance and Lipotoxicity

The proinflammatory cytokine tumour necrosis factor (TNF)-α is implicated in the development of

insulin resistance associated with obesity in insulin-sensitive peripheral cells such as those of skeletal muscle, liver and adipose tissue.[38-43] TNFα directly interferes with insulin receptor signalling by inducing phosphorylation of insulin receptor substrate-1, blocking the biological actions of insulin.[39,41]

It has now been shown in isolated islets from Sprague-Dawley rats that TNFα induces insulin resistance in β cells themselves, an effect which is mediated by a functional β-cell insulin receptor.[44] This insulin resistance of the β cell appears to be a major determinant of β-cell failure and the inability of β cells to compensate for increased insulin demand in the development of type 2 diabetes.[44]

TNFα appears to exert its effects by a markedly different mechanism than that observed in insulin-sensitive cells in peripheral tissues, namely a specific defect in the upstream signalling pathway. Within the islets, TNFα activates macrophages, resulting in release of interleukin-1, induction of expression of the inducible isoform of NO synthase within β cells, and overproduction of the free radical NO.[44] NO then interferes with insulin signalling associated with β-cell growth and proliferation, producing global inhibition of metabolism.

According to the 'lipotoxicity hypothesis', β-cell dysfunction in adipogenic type 2 diabetes is the result of excessive accumulation of fat in the pancreatic islets. In obese ZDF rats, the over-accumulation of fat reflects a mutation in the leptin receptor, which blocks the normal triglyceride-lowering action of leptin on islets.[45] This leads to lipotoxicity through exaggerated production of NO, by means of the mechanism outlined earlier in this section.

However, in isolated islets from obese *fa/fa* (leptin-deficient) ZDF rats, addition of troglitazone halved triglyceride content, doubled insulin secretion stimulated by arginine and produced a greater than 30-fold increase in that stimulated by glucose.[37] This is consistent with the ability of thiazolidinediones to prevent TNFα-induced inhibition of insulin signalling by islets.

In the same animal model *ex vivo*, hyperglycaemia was observed to occur in parallel with net β-cell apoptosis.[46] It appears that β-cell proliferation initially compensates for the loss of β cells while plasma glucose is modestly elevated, but ultimately fails. Rosiglitazone treatment was found to maintain β-cell proliferation, and to produce a 5-fold attenuation in the net rise in β-cell death, preventing the loss of β-cell mass.[46]

Excessive β-cell apoptosis is associated with excessive accumulation of intracellular triglycerides.[25] It was recently shown that pioglitazone treatment of *db/db* mice reduced the triglyceride content of islets by 58%, suggesting that pioglitazone prevents β-cell damage by mitigating lipotoxicity.[47]

Moreover, in the rat β-cell line INS-1, which expresses PPAR-γ, troglitazone ameliorated lipotoxicity due to FFAs (palmitic, oleic and linoleic acids – all PPAR-γ ligands), resulting in decreased basal insulin secretion and the recovery of GSIS.[4] According to the researchers, these findings indicate that the thiazolidinedione has greater affinity for PPAR-γ than these FFAs. The thiazolidinedione may act via the ATP-sensitive potassium channel (K_{ATP})-dependent signalling pathway.[4]

In isolated human pancreatic islets, expression of PPAR-γ was markedly and time-dependently reduced by exposure to progressively higher concentrations of FFA.[48,49] The presence of FFAs also produced a deleterious cytostatic effect, inhibiting GSIS by 80%, as well as reducing islet insulin content by 75% and reducing insulin mRNA expression. However, incubation with rosiglitazone prevented FFA-induced down-regulation of PPAR-γ and insulin mRNA expression, and GSIS inhibition.[49]

In the same model, high concentrations of FFAs produced an almost 3-fold increase in rates of islet cell death, in association with significant increases in activity of the protease enzymes caspase 3 (apopain) and caspase 9, key mediators of apoptosis.[50] Incubation with rosiglitazone at a concentration of 15 μg/mL attenuated islet cell death and normalised caspase activity levels.[50]

Insulin Secretory Capacity

In addition to enhancing insulin synthesis, thiazolidinediones have shown direct effects on β-cell

function. Troglitazone exerted a dual direct effect on GSIS by β cells, in both isolated pancreatic islets from male Wistar rats and a hamster β-cell line (HIT cells): the drug stimulated insulin release at low doses and inhibited release at high doses.[51] In HIT cells, troglitazone produced increases in glucose uptake in parallel with enhanced insulin secretory capacity. Troglitazone stimulated glucose uptake and subsequent insulin secretory capacity by modulating glucose transport activity – probably by altering intrinsic activity, rather than numbers, of the glucose transporter GLUT-2.[51]

Proinsulin Secretion

Since GSIS was also enhanced by troglitazone in rat INS-1 cells,[4] this suggests that thiazolidinedione treatment may cause the cell to secrete less pre-proinsulin or proinsulin, and more insulin of high quality. Indeed, Prigeon et al.[52] and other groups[53-55] have reported thiazolidinediones to lower the ratio of proinsulin to IRI (proinsulin **:** IRI) in patients with type 2 diabetes (see section 3.2.5). Similarly, in the MIN6 insulinoma cell line, overexpression of PPAR-γ in β cells was found to suppress glucose-induced proinsulin synthesis and insulin release, an inhibitory effect augmented by pretreatment with pioglitazone.[56]

3.1.2 In Vivo Animal Models

In animal models *in vivo*, thiazolidinediones have been shown to optimise islet endocrine cell distribution and to ameliorate islet degranulation.

In the normal rat, troglitazone stimulated pancreatic growth not only by reducing insulin resistance and improving glucose metabolism, but also by suppressing fibrosis of the islets.[57] Pancreatic weight decreases with age, and this effect is reduced or prevented by thiazolidinediones principally by stimulating pancreatic hyperplasia.[57]

The insulin-sensitising properties of thiazolidinediones appear to be beneficial in promoting islet survival and function. In a streptozocin-induced diabetic rat model troglitazone prolonged the functional survival of transplanted islets compared with control and glimepiride-treated animals.[58] These findings may indicate potential for thiazolidinediones in patients undergoing islet transplantation.

The insulin content of granules in cells is determined by the balance between insulin synthesis and secretion.[59] C57BL/KsJ *db/db* mice are unable to adapt to sustained hyperglycaemia, resulting in islet degeneration and atrophy. In these animals troglitazone increased insulin synthesis, thereby promoting regranulation of β cells.[59] Troglitazone also normalised the distribution of endocrine cells in the islet, decreasing the proportion of islets containing exocrine (α- and γ-) cells and relocating them peripherally – even at late stages of the disease.[59] Thus, troglitazone ameliorated the degeneration process of the islet and restored the granulation status of β cells, not only by decreasing plasma glucose but also apparently by a direct effect on the pancreas.[59]

In the same model, pioglitazone treatment prevented the loss of β-cell mass, as determined by immunohistochemical staining, and restored insulin content as well as insulin secretory capacity.[60] However, nateglinide treatment had no effect on these parameters. Glucose-induced insulin secretion was restored to almost 3-fold that of control animals.[60] Similar results were reported by Diani et al.[19] in this and two other murine models of type 2 diabetes: the C57BL/6J *ob/ob* mouse, which is obese, hyperinsulinaemic and hyperglycaemic; and the obese KKA(y) mouse, which exhibits early-onset hyperinsulinaemia and hyperglycaemia. All three models exhibit similar islet and β-cell pathology, and pioglitazone treatment resulted in preservation of islet and β-cell architecture and granulation, in association with significant increases in insulin content, independently of the reduction in plasma insulin levels.[19]

Islet Progenitor Cells

The decline in progenitor cells can be prevented by activation of PPAR-γ. Thus, thiazolidinediones have been shown to increase β-cell mass.[36] In contrast, in Goto-Kakisaki rats, a non-obese model of type 2 diabetes, gliclazide failed to induce a β-cytotrophic effect.[61]

Amyloid Deposition

In non-diabetic human IAPP (hIAPP) transgenic mice, long-term treatment (12 months) with rosiglitazone or metformin, but not glibenclamide, de-

creased islet area, β-cell area, and prevalence and severity of amyloid.[62] The effect of rosiglitazone on amyloid prevalence remained statistically significant after adjustment for the ratio of abdominal to subcutaneous fat.

3.2 Clinical Evidence

The aim of therapeutic intervention in type 2 diabetes is to reduce glucose levels in three ways: (i) by improving β-cell function so that insulin secretion is improved; (ii) by reducing hepatic glucose production; and (iii) by improving uptake of glucose in peripheral tissues.[63]

3.2.1 Glycaemic Control

The coefficient of failure for HbA_{1c} is a measure of disease progression.[64] Two 1-year randomised double-blind studies were conducted in patients with type 2 diabetes uncontrolled by diet alone, treated with pioglitazone up to 45mg versus gliclazide up to 320 mg/day or metformin 850mg up to three times daily, in the respective studies. The coefficient of failure for HbA_{1c} with pioglitazone was 0.057% per year, significantly lower than with either gliclazide or metformin (0.853% and 0.291%, respectively), indicating more sustained long-term glycaemic control with pioglitazone.[65]

More recently, data from 2-year extension trials of pioglitazone as add-on therapy (to gliclazide or metformin, which were also used as comparators) have become available.[66-70] These data consistently reveal a sustained, positive effect of thiazolidinedione treatment on glycaemic control, as shown by reductions in HbA_{1c} and markers for insulin sensitivity. In one multicentre, randomised, double-blind trial, pioglitazone (up to 45 mg once daily; n = 270) was compared with gliclazide (up to 160mg twice daily; n = 297) in type 2 diabetes patients who completed the original 1-year study and had an HbA_{1c} ≤9%.[70] Kaplan-Meier curves show that more patients 'failed' (HbA_{1c} ≥8% at any time after 24 weeks) in the gliclazide compared with pioglitazone group, and the separation between groups increased during the study.

Various mechanisms to explain these findings have been advanced, including a lessened demand on the β cell with thiazolidinedione therapy.[67] However, it is difficult to differentiate potential direct effects of thiazolidinediones with those related to gluco- or lipotoxicity. Indeed, recent studies associate recovery of β-cell function with a reduction in plasma FFA and FFA metabolites within pancreatic islets.[71] Lupi et al.[49] showed that rosiglitazone was able to prevent downregulation of PPAR-γ_2 and insulin mRNA expression in human islets caused by FFA exposure, providing a more detailed explanation of how thiazolidinediones might positively influence GSIS in β cells.

3.2.2 Reduction in Insulin Levels

Fasting plasma insulin (FPI) levels are frequently measured in clinical trials of diabetes as an indicator of insulin sensitivity. Decreases in FPI levels have been reported in the vast majority of trials performed with pioglitazone, mirroring a decreased secretory demand on β cells. In patients taking pioglitazone 30–45 mg/day reductions in FPI have been in the range of 10.7–31.8 pmol/L with monotherapy.[72-75] When pioglitazone 30 mg/day was administered in combination with metformin a mean FPI reduction of 36.2 pmol/L resulted.[76]

Similar to the trials evaluating pioglitazone, the majority of studies that have assessed the impact of rosiglitazone on FPI have found significant reductions compared with baseline levels. The mean rosiglitazone-induced reduction in FPI ranged from 6.6 to 27.2 pmol/L.[77-80] As with pioglitazone, the addition of metformin to rosiglitazone resulted in even greater reductions in FPI (−31.1 pmol/L).[81] Data on the effect of troglitazone on FPI is more limited, but shows a similar pattern to pioglitazone and rosiglitazone. Troglitazone monotherapy (200–800 mg/day) resulted in reductions of FPI of 18–30 pmol/L,[52,82] while the addition of troglitazone to patients already receiving maximal doses of sulfonylureas and metformin led to a 19 pmol/L decrease in FPI.[83]

3.2.3 Pulsatility of Insulin Release

While the insulin-sensitising effect of thiazolidinediones is well established, less is known about their influence on insulin secretion. It now appears that thiazolidinediones normalise the asynchronous

Table I. Ratios of basal and acute response proinsulin (PI) to immunoreactive insulin (IRI) in patients with type 2 diabetes mellitus versus healthy individuals[33]

	Basal PI : IRI ratio	Acute PI response : acute IRI response ratio
Patients with diabetes	0.29	0.08
Healthy individuals	0.13	0.02

insulin secretion that characterises β-cell failure. In a placebo-controlled study in patients with type 2 diabetes, 3 months' treatment with rosiglitazone was shown to increase the ability of an oscillatory glucose infusion to programme high-frequency pulsatile insulin secretion, despite the absence of any direct action on β-cell secretory capacity. The investigators postulated that the improvement in β-cell function could be related to a reduction in glucotoxicity due to the improved glycaemic control and/or improved insulin sensitivity seen with thiazolidinediones.[84] This could indicate an increased ability of β cells to detect and respond to fluctuations in glucose levels within the physiological range after thiazolidinedione treatment.

3.2.4 β-Cell Function

As a class effect, thiazolidinediones consistently improve basal β-cell function, as measured by the HOMA model.[31,73] In the TRIPOD (TRoglitazone In the Prevention Of Diabetes) study, troglitazone prevented β-cell failure and prevented or delayed type 2 diabetes in a population of high-risk patients (Hispanic women with prior gestational diabetes).[2,9] There was a >50% reduction in the incidence of type 2 diabetes in these women,[2] accounted for by the reversal of insulin resistance and reduction in secretory demands on the β cell.

Further evidence that thiazolidinediones exert beneficial effects on the β cell derive from a study in which 2 months' treatment with pioglitazone restored the first-phase insulin response (a measure of β-cell function) on an intravenous glucose tolerance test (IVGTT), in both patients with IGT and with frank type 2 diabetes.[85]

Similar results were reported in a randomised 6-month study of rosiglitazone versus insulin in patients with type 2 diabetes, using a frequently sampled IVGTT.[86] At study end, the acute insulin response to glucose was significantly increased with rosiglitazone, with no effect of insulin apparent.

In a double-blind study in patients with IGT, insulin secretory responses to oscillations in plasma glucose were improved by troglitazone compared with baseline as well as with placebo.[87] Thus, in addition to increasing insulin sensitivity, troglitazone improved the impaired β-cell response to glucose typical of IGT.

Moreover, troglitazone significantly increased the glucose : insulin ratio, as well as meal-stimulated C-peptide levels, compared with a non-thiazolidinedione control group, providing indirect evidence of a recovery of β-cell function.[88]

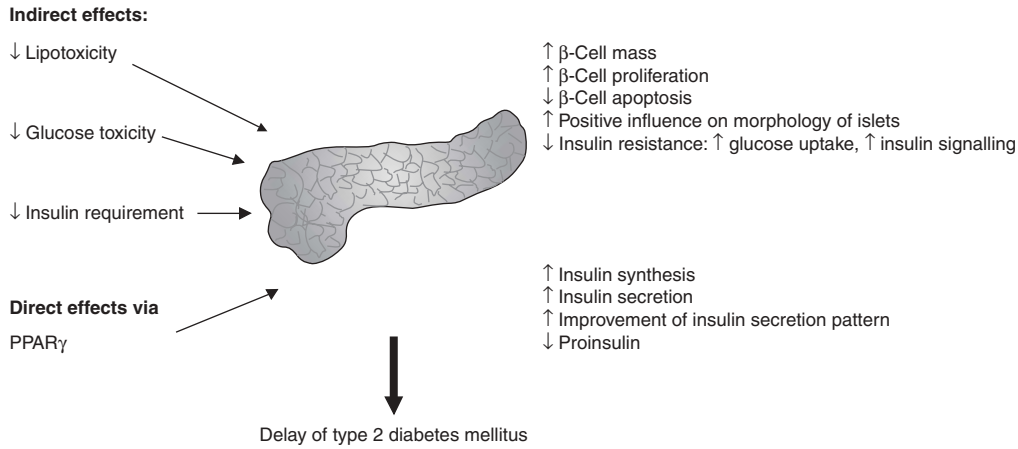

Fig. 1. Mechanism of action of thiazolidinediones on the pancreatic β-cell. **PPAR** = peroxisome proliferator-activated receptor.

It should be noted, as highlighted in section 2.2.3, that these improvements in β-cell function may be related to the reduction in glucotoxicity associated with thiazolidinedione treatment.

Data from ongoing studies using pioglitazone and rosiglitazone have also been published in abstract form.[71,89-91] These demonstrate a beneficial effect of both agents on recovery or improvement of β-cell function as well as, in one trial,[90] β-cell mass. As suggested previously, the recovery of pancreatic β-cell function may be mediated by reductions in FFA and FFA metabolites within the β cell (see section 2.3).[71] Another study found that a decrease in intramyocellular triglyceride, noted with pioglitazone but not metformin, was not accompanied by an increase in muscle succinate dehydrogenase activity. This suggests that beneficial effects in terms of improved insulin sensitivity, β-cell function and β-cell mass resulted from a redistribution of fat rather than increased fat oxidation.[90]

Overall, it appears that thiazolidinediones can promote recovery of β-cell function independently of the amelioration of insulin sensitivity.

Figure 1 summarises the effects of thiazolidinediones on the pancreatic β cell.

3.2.5 Proinsulin Secretion

In patients with type 2 diabetes the ratio of proinsulin to IRI is elevated relative to healthy individuals, indicating disproportionate proinsulinaemia, which is inversely correlated with β-cell function (table I).[33,35] As a class effect, thiazolidinediones have been consistently shown to significantly and dose-dependently reduce proinsulin levels and the proinsulin **:** IRI ratio, indicating an improvement in β-cell function, compared with glibenclamide, gliclazide or placebo (table II).[52-54,92]

3.2.6 Potential Cardiovascular Protective Effects

Maintaining the importance of positively influencing clinical endpoints in the treatment of type 2 diabetes is essential. Although preliminary, evidence is gradually accumulating that indicates thiazolidinedione therapy has cardiovascular protective effects.[55,89,93-97]

Koro et al.,[55] using a case control study, identified 229 index cases (matched to 1374 controls) of myocardial infarction (MI) hospitalisations among type 2 diabetic patients from a managed care database to model the odds of MI. Compared with insulin monotherapy, thiazolidinedione use was associated with a 49% reduction in the risk of MI (95% CI 0.27, 0.95).[55] Hence, the effectiveness of thiazolidinedione for reducing cardiovascular outcomes is potentially appreciable. The awaited results of large, clinical outcome trials such as PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events)[98] and RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) will provide further data on the effects of thiazolidinediones on macrovascular outcomes.

Although the mechanism(s) for these effects is unclear at present, endpoints based around biochemical cardiovascular markers and, in particular, endothelial function are being assessed.

4. Conclusions

Type 2 diabetes is now acknowledged to involve dual defects: insulin resistance and β-cell dysfunc-

Table II. Effects of various thiazolidinediones (TZDs) on the ratio of proinsulin (PI) to immunoreactive insulin (IRI)[52,53,92]

TZD	Baseline PI : IRI	PI : IRI change from baseline	PI : IRI difference (comparator)
Pioglitazone 40mg (mean values)	0.291	−0.044	−0.041 (gliclazide 30mg)
Pioglitazone[a] (mean values)	ND	−0.057	−0.061 (placebo)
Rosiglitazone 2mg (median values)[b]	0.267; 0.293	−0.017; 0.019	−0.053 (placebo); −0.046 (glibenclamide[a])
Rosiglitazone 4mg (median values)[b]	0.278; 0.282	−0.037; −0.044	−0.081 (placebo); −0.062 (glibenclamide[a])
Troglitazone 200–800mg (mean values)	0.387	−0.057	NA

a Dose not specified.

b Two values from two studies.

NA = not applicable.

tion. As a result, altered conversion of proinsulin to insulin, and qualitative and quantitative changes in GSIS occur. Accordingly, successful management now relies on a shift in therapeutic focus from hyperglycaemia to arresting the progressive loss of β-cell function before frank diabetes develops. The thiazolidinediones have been shown to exert clear benefit in preserving β-cell mass and function in animal models and in patients with IGT or type 2 diabetes, and early intervention with these agents affords great promise in addressing the global epidemic of diabetes.

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