

New Approach in The Treatment of T2DM and Metabolic Syndrome (Focus on a Novel Insulin Sensitizer)

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ABSTRACT

Peroxisome Proliferator-Activate Receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily. The three PPARs (α , β/δ , and γ) are distributed differently in the different organs. PPAR α is most common in the liver; but also found in kidney, gut, skeletal muscle and adipose tissue, while PPAR β/δ , is fairly ubiquitous; it may be found in body tissues and brain (for myelination process and lipid metabolism in the brain). PPAR γ has 3 isoforms, such as PPAR γ_1 , PPAR γ_2 , and PPAR γ_3 .

The syndrome-X was firstly coined by Reaven in 1988 and then to be provided in 1999 by the name : the metabolic syndrome-X.¹ This metabolic syndrome represents a “Cluster” of metabolic disorders and cardiovascular risk factors which has been collected and summarized by the author and such a cluster includes: insulin resistance/hyperinsulinemia, central obesity, glucose intolerance/DM, atherogenic dyslipidemia (\uparrow TG, \downarrow HDL-cholesterol, \uparrow Apo-B, \uparrow small dense LDL), hypertension, prothrombotic state (\uparrow PAI-1, \uparrow F-VII, \uparrow fibrinogen, \uparrow vWF, \uparrow adhesion molecules), endothelial dysfunction, hyperuricemia, and increased hsC-RP and cytokines. The metabolic syndrome-X may lead to the development of T2DM and coronary heart disease (CHD); insulin resistance plays pivotal roles in the progression of such a syndrome and cardiovascular diseases.

Improvement of Insulin Resistance, therefore, is most likely to reduce the high cardiovascular event rate in T2DM. It has been generally accepted that Insulin Resistance (detected by HOMA-R) and Acute Insulin Response = AIR (by HOMA-B) are both usually present in T2DM.

The Thiazolidinedions (TZDs) are Insulin Sensitizers (e.g Rosiglitazone = ROS, Pioglitazone = PIO) introduced into clinical practice in 1997; clinical evidence data showed that TZDs improved both HOMA-R, and HOMA-B.

PPAR γ can be activated by TZDs and it appears to be fundamental to the pathophysiology of diabetes mellitus i.e \uparrow GLUT-4, \uparrow glucokinase, \downarrow PEPCK, \uparrow GLUT-4, and decreases

production by fat cell of several mediators that may cause insulin resistance, such as TNF α and resistin. PPAR γ also mediates increased production of Adiponectin and the insulin signaling intermediate PI3K, and both actions lead to increase insulin sensitivity.

A “dual PPAR γ –PPAR α agonists” (e.g PIO, but ROS poorly activate PPAR α) might lower glucose and modulate lipids. Thus, PIO, as a stronger “dual PPAR γ –PPAR α agonists”, shows an important therapeutic pathway in diabetes mellitus and cardiovascular diseases, even in metabolic syndrome.

Current evidence suggests a close relationship between activation of PPAR γ and restoration of insulin sensitivity by reductions in TNF α and FFAs, and the enhancement of insulin stimulation of PI3-K Pathway and also \uparrow adiponectin & \downarrow resistin.

Key words: PPAR γ , TNF α , insulin resistance, metabolic syndrome, type 2 diabetes mellitus

INTRODUCTION

Peroxisome Proliferator-Activated Receptors (PPARs) are involved in the regulatory response processes of lipid and glucose metabolisms, adipocyte differentiation, inflammatory response.¹ The three PPARs (α , β/δ , and $\gamma_1, \gamma_2, \gamma_3$) are found differently in many organs. PPAR α is most common in the liver, but also found in adipose tissue, skeletal muscle, kidney and gut, while PPAR β/δ is found in several tissues and brain. PPAR γ_1 is found in adipose tissue, skeletal muscle, etc; PPAR γ_2 is found mainly in adipose tissue, while PPAR γ_3 is distributed in adipose tissue, macrophages, and colon epithelium.

Insulin resistance followed by compensatory hyperinsulinemia may lead to the development of Insulin Resistance Syndrome or Syndrome-X which represents a cluster of metabolic disorders and cardiovascular risk factors. In 1999, Reaven renamed these abnormalities as the Metabolic Syndrome-X. By collecting several recent literatures, such a syndrome can be extended until 9 components and will be shortly described below.²

In clinical practice point of view, oral hypoglycemic agents (OHAs) can be categorized into 5 groups, such as : 1). Insulin secretagogues (sulphonylureas and non-sulphonylureas), 2). Insulin sensitizers (troglitazone–withdrawn, rosiglitazone FDA May 1999, and pioglitazone FDA July 1999, and darglitazone), 3). Biguanides, 4). Alpha-glucosidase inhibitors (acarbose, voglibose, etc), and 5). Alpha-amylase inhibitors (tendamistane, etc).

The impairment of glucose uptake in the peripheral tissues (liver, muscle, and adipose tissue) caused by insulin resistance (can be detected by HOMA-R) and impaired acute insulin response = AIR (by HOMA-B) with compensatory hyperinsulinemia, both belong to type 2 diabetes mellitus (T2DM). Thus, insulin resistance may be assessed as a culprit of the progression of T2DM, the metabolic syndrome-X and cardiovascular diseases.

The PPARs can be activated by several agonists, such as, natural (UFAs, SAFAs, and Eicosanoids) or synthetic agonists (analogues of PGJ2, LB4 and LD4, Fibrates, NSAIDs, as well as Thiazolidinedions = TZDs). PPAR γ appears to be associated with increased or decreased degrees of insulin sensitivity. PPAR γ_2 is associated with improved insulin sensitivity, lower BMI, high HDL levels and a reduced risk of developing T2DM.³ PPAR α appears to be associated with lipid and lipoprotein metabolisms.

Pioglitazone (PIO) binds with high affinity to PPAR γ_1 and PPAR γ_2 and has comparable activity at PPAR γ to Rosiglitazone (ROS). Pioglitazone also binds to PPAR α (dual PPAR γ - PPAR α agonist) but compared with ROS, PIO is a stronger activator of PPAR α .⁴ PPAR γ is expressed mainly in adipose tissue, where it promotes glucose uptake, adipogenesis, and lipogenesis.

Stimulation of PPAR γ alters transcription of several genes responsible for the restoration of insulin sensitivity, notably transport proteins (GLUT-4 \rightarrow increased glucose uptake), and enzymes, such as FATP and aP2 for increased fatty acids uptake, and LPL & Acyl-Co synthase for adipocyte differentiation & lipogenesis.⁵

Hence, PPAR γ agonists, PPAR α agonists, and “dual PPAR γ - PPAR α agonists” (e.g. Pioglitazone) are most likely of great benefits in the new approach of the treatment of type-2 diabetes mellitus (T2DM), the metabolic syndrome-X, and CVDs.

The aim of this paper is to give a basic knowledge on PPARs in connection with new insights into the therapy of T2DM and the associated complications of metabolic/insulin syndrome (cardiovascular diseases, etc).

THE METABOLIC – INSULIN RESISTANCE SYNDROME

This syndrome represents a cluster of metabolic disorders and cardiovascular risk factors which is initiated by the existence of insulin resistance. In 1999, Reaven renamed it the metabolic syndrome–X which more complete than the previous one and consists of 9 (nine) components as mentioned below :⁶

1. Insulin resistance/hyperinsulinemia
2. Central obesity
3. Glucose intolerance/diabetes mellitus
4. Atherogenic dyslipidemia
 - Increase in Plasma Triglyceride
 - Decrease in Plasma HDL-Cholesterol
 - Increase in Apoprotein-B
 - Increase in Small Dense LDL (Type B pattern)
5. Hypertension
6. Prothrombotic state
 - Increasing in PAI-1
 - Increase in F-VII
 - Increase in Plasma Fibrinogen
7. Endothelial dysfunction
 - Increase in Urinary Albumin Excretion
8. Hyperuricemia
9. Inflammatory response (C-RP and Cytokines)

A particular individual may have as few as 2 or 3 components of the syndrome to as many as all of the 9-components. This syndrome can be recognized long before it has any clinical manifestations. Numerous studies have shown that the metabolic syndrome precedes the development of type-2 diabetes mellitus (T2DM) by many years depends on the life style of the individuals. In the San Antonio heart study, it was associated with as much as a 13-fold increased risk for the development of T2DM.⁷ Similarly, it precedes the development of coronary heart disease (CHD) and in several epidemiologic studies conferred a 2 to 3 –fold risk for CHD.

Insulin-receptor (IR) signaling involves two major pathways :

1. The P13-K Pathway (Phosphatidyl Inositol 3,4,5 Phosphate-Kinase)
2. The MAPK Pathway (Mitogen-Activated Protein Kinase)⁸

It should not be forgotten that each pathway could (under certain circumstances) activate the other. Thus, PKB/Akt may activate Raf Kinase, and conversely. Thus, the two pathways can be schematically drawn below.

The MAPK pathway (atherogenic = “villain pathway”) : IR \rightarrow SHS \rightarrow Grb2 \rightarrow m SOS \rightarrow Ras \rightarrow Raf \rightarrow MEK \rightarrow MAPK \rightarrow gene expression/mitogenic (atherogenic).

The PI3-K pathway (atheroprotective = “hero pathway”): IR → IRS proteins → divided into 2 pathways:

1. IR → Grb2 → m SOS → Ras → Raf ⇌ mitogenic (atherogenic)
2. IR → p85 → p110 → PI3 Kinase → PDK1 (PDK2) → AKT/PKB → glucose transport, glycogen synthesis, protein synthesis, anti-lipolysis, anti-apoptosis → metabolic (atheroprotective).

Initially, the activated IR will binds SHC and IRS molecules and these interact with downstream substrates. The PI3-K Pathway leads to a large variety of biological actions after IR activation.

The aggravated insulin resistance of T2DM is primarily of a postreceptor nature insulin receptor tyrosine kinase (IRTK) activity in patients could be inhibited because of elevation in Tyr phosphatase activity (Kasari et al 1994) or enhanced Ser/Thr phosphorylation of the receptor that impairs its Tyr kinase activity.^{9,10} Ser/Thr phosphorylation of the IR occurs in response to the treatment of cells with insulin, or with activators of PKC or the cAMP-dependent protein kinase.^{11,12} Accordingly, downstream signaling cascade would be decreased in proportion to the defect in IRTK activity; apparently, however, when compared with the reductions in Tyr phosphorylation of the IR and IRS-1, PI3-K is more severely reduced in T2DM.¹³ The effects of Pioglitazone (PIO) on selected target genes affecting glucose including the restoration of insulin sensitivity (thus, PIO opposes insulin resistance), such as (modified) :

1. Increases GLUTs expression (↑Glucose Uptake)
2. Activates Glucokinase (↑ Glucose Uptake)
3. Activates Insulin Receptor Tyrosine Phosphorylation = IRTK (↑ Insulin Signaling)
4. Activates IRS-1 Tyrosine phosphorylation (↑ Insulin Signaling)
5. Stimulates IRS-2 Expression (↑ Insulin signaling)
6. Activates PI3-Kinase (↑ Insulin Signaling)
7. Suppresses PEPCK (↓Gluconeogenesis)¹⁴

People with insulin resistance show reduced insulin stimulation of PI3-Kinase Pathway in skeletal muscle. In rats, PIO treatment reversed the deficiency in insulin stimulation of PI3-Kinase as well as reducing their hyperglycemia and hyperinsulinemia.¹⁵ In addition, it was recently shown that the important of alternate docking protein for PI3-Kinase, IRS-2, is a target gene for PIO.¹⁴

PPAR γ AND PPAR α AS THERAPEUTIC TARGETS IN TYPE-2DM (FOCUS ON THE ROLES OF A NOVEL INSULIN SENSITIZER)

Lines of evidence suggest that PPARs are involved in the regulatory processes of glucose and lipid

metabolism, adipocyte differentiation, and inflammatory response.

The thiazolidinediones (TZDs) are insulin sensitizer introduced in clinical practice in 1997. The first agent on the market was troglitazone (TRO), which was later withdrawn when an association with hepatotoxicity was substantiated. The hepatotoxicity problem with TRO may have been due to the structure if its alpha tocopherol side-chain that when metabolized may result in oxidative stress in the liver.¹⁶ Neither PIO (a novel insulin sensitizer) nor ROS has this oxygen atom, and therefore, liver damage is not a class effect for TZDs. Nonetheless, PIO and ROS are not recommended for use in patients with serum ALT over 2.5 times the upper limit of normal.

PPAR γ AGONISTS

Stimulating PPAR γ is now a recognized mechanism to improve insulin sensitivity, although it may not be the only mechanism through which TZDs improve glycemic control.

Mechanism of action of a TZDs in an adipocyte can be summarized TZDs bind to PPAR γ , which exists as a heterodimer with the RXR (retinoid X receptor).⁴ Ligand binding will release repressors, and exposing the active site of the receptors which binds with a specific DNA nucleotide sequence PPRE (PPAR-response element). Co-activators and RNA polymerase are recruited to initiate transcription of mRNA for the genes that carry PPRE in their promoter region. The mRNA is translated into the enzymes (Acyl-CoA synthase and LPL), and transporter proteins (GLUT-4, FATP = fatty acid transporter proteins, and aP2 = adipocyte fatty acid binding protein). Both enzymes and transporters will bring about the biological effects of TZDs in the cell. These enzyme (LPL and Acyl-CoA synthase) are responsible adipocyte differentiation and lipogenesis, whereas transporter (GLUT-4, FTAP, aP2) an for increased glucose uptake and increased fatty acid uptake into adipocytes.⁵

Stimulation of PPAR γ may alter transcription several genes that are also sensitive to insulin, notably all enzymes and transporters mentioned above.

The TZDs may improve insulin sensitivity and glucose metabolism in several ways.

1. The antihyperglycemic effect is partly due to increase in new adipocyte lipogenesis, which decreases circulating FFAs, and decreases lipid levels in liver and muscle. This alters the glucose-fatty acids cycle (Randle cycle) so as to favour glucose utilization by muscle.⁵ Staels (2001) explained that the improvement in insulin sensitivity may be also

due to the differentiation of pre-adipocytes into adipocytes and apoptosis of terminally differentiated, fat-loaded, insulin-resistant adipocytes; this in turn leads to a greater proportion of smaller adipocytes that are more insulin-sensitive. The normal amounts of adipose tissue are important to maintain normal insulin sensitivity. Lipoatrophic patients have no adipose tissue and they are severely insulin-resistant.²

2. Stimulation of PPAR γ in an adipocyte may decrease or increase the production of several mediators which alter insulin sensitivity, such as⁵ :
 - increased production of TNF α and resistin (insulin resistance)
 - increased production of adiponectin (insulin sensitive)
 - increased insulin signaling intermediate PI3-K (insulin sensitive)
 - increased production of FATP (\uparrow fatty acid uptake)²
3. Decreased FFAs may improve peripheral insulin sensitivity (HOMA-R) and β -cell function (HOMA-B). Possible mechanism: the fatty acids are diverted away from the muscle and to the adipocyte, which prevents the inhibition of glucose oxidation by fatty acids in the muscle. This process can be described as a release of the Randle cycle effects by the fatty acids.
4. Numerous tissues express PPAR γ , including the pancreatic β -cell, and preliminary evidence in diabetic animals suggests that chronic treatment with PPAR γ agonists can improve β -cell morphology and insulin content.

DUAL PPAR γ -PPAR α AGONISTS

PPAR α which is strongly expressed in muscle and liver mediates increased oxidation of fatty acids through increased transcription of Acyl-CoA synthase, Acyl-CoA oxidase and thiolase. Stimulation of PPAR α by Fibrates accounts for much of the lipid lowering capability of Fibrates. Thus, a “dual PPAR γ - PPAR α agonist“ might lower both glucose and lipids.

Transactivation assays of Kimura¹⁷ revealed that Pioglitazone (PIO) and Rosiglitazone (ROS) caused a maximal activation of the PPAR γ and PPAR α , and this transactivation is due to direct binding. Kimura¹⁷ noted that ROS appears to show a different lipid profiles than PIO. While PIO is known to activate both PPAR γ and PPAR α at therapeutic concentrations, this is not the case with ROS. Such a difference may be caused by metabolites of PIO which have may account for the greater beneficial effect of PIO on plasma lipid profile than occurs with ROS.¹⁸

PPAR γ AND PPAR α : ATHEROSCLEROSIS AND INFLAMMATORY RESPONSE

Both PPAR γ and PPAR α are expressed in endothelial cells, in macrophages, and in the vascular wall: 1). Both PPARs regulated a number of inflammatory cytokines and prostaglandins in these cells and influence chemokines and ET-1 production in endothelial cell. 2). PPAR activation leads to a lowering of the recruitment and adherence of circulating monocytes and lymphocytes to the endothelial cell, and hence, a diminished inflammatory response may pursue.² 3). The conversion of macrophages to foam cells involves internalization of oxLDL particles. This internalization does not occur through the LDL receptor but rather through lipid transporter such as CD 36, SR-A, and others. Combination treatment of 15d-PG γ_2 and the RXR agonist LG 100268 caused induction of macrophage markers and increased expression of CD36 and uptake of oxLDL.¹⁹ The induction of CD 36 expression suggests the possibility of an oxLDL- PPAR γ -CD 36 positive feedback loop. However, it is important to point out that this induction of CD 36 expression required the combination of a PPAR γ agonist and an RXR agonist; treatment with a PPAR γ agonist alone could not induce CD 36. Thus, it is possible that RXR agonists contribute to foam cell formation through activation of other signaling pathways. 4). PPARs activate SR-B1 receptor and ABCA1 transporter, leading to increased cholesterol efflux.¹ 5). PPARs suppress tissue factor and MMP9 expression which involve in thrombosis and plaque stability respectively.¹ 6). Patients with coronary artery disease also responded favorably to Fenofibrate treatment, showing reduced plasma levels of IL-6, Fibrinogen, and C-RP, possibly through negative regulation of NF-kB and AP-1 by PPAR α .^{20,1} 7). Ishibashi et al²¹ demonstrated that PPAR γ activation with Pioglitazone (PIO) prevented coronary arteriosclerosis, possibly by its anti-inflammatory effects (down regulation of CCR2 in circulating monocytes). Inhibition of the CCR2-mediated inflammation may represent novel anti-inflammatory actions of PIO beyond improvement of metabolic state. 8). Recently, Shiomi et al²² reported that PIO improved LV remodeling and functions in mice with post-MI heart failure. This effect was associated with an attenuated LV expression of inflammatory cytokines and chemokines. Hence, PIO has promise as preventive and therapeutic drug for heart failure.

CLINICAL EFFICACY AND SAFETY PROFILE OF PPARs – AGONISTS (FOCUS ON A NOVEL PPARs-AGONISTS)

This topic will be described systematically and shortly in a sequential number:

- I. Thiazolidinediones, such as Pioglitazone (PIO), are synthetic ligands for PPARs. Lines of evidence noted that PIO can be categorized as a “dual PPAR γ -PPAR α agonist”.^{5,17}
- II. PIO binds with high affinity to PPAR γ 1 and PPAR γ 2, and as mentioned above also binds to PPAR α but compared with Rosiglitazone (ROS), PIO is stronger activator of PPAR α .⁴ Hence, this effect may result in the greater therapeutic beneficial effect of PIO on plasma lipid profile than occurs with ROS.¹⁸
- III. ROS and PIO have been recognized by FDA in May 1999 and July 1999, respectively. The next PPAR-agonist, darglitazone, is still on investigation. PIO restores insulin sensitivity and glucose homeostasis in several ways as mentioned below:^{14,23}
 1. Increasing GLUTs and glucose uptake
 2. Enhancing Insulin Signaling and insulin sensitivity (\uparrow IRTK, \uparrow IRS-2 Expression, \uparrow PI3-K)
 3. Increasing post receptor effect/insulin sensitivity (\downarrow TNF α , \downarrow FFAs, \downarrow Resistin, \uparrow Adiponectin). TNF α inhibits IRTK activity and subsequent phosphorylation of the IRSs.
 4. Reducing hepatic glucose production/gluconeogenesis (\downarrow FFAs, \downarrow PEPCK = phospho enol pyruvate carboxy kinase).
 5. Remodeling adipose tissue PIO is an efficient promoter of adipocyte differentiation in vitro and in vivo.^{24,25} PIO increased adipose tissue glucose utilization and lipogenic capacity as well as modulated gene expression. PIO may also induced increased mRNA for insulin receptors an total cellular insulin receptors numbers in adipose cells. In addition, PIO (via PPAR γ stimulation) inhibits calcium-influx through L-type calcium channels. This may result in relaxation and inhibition of cell proliferation of SMC.²⁶
- IV. PIO is metabolized in the liver to form 5 primary metabolites (M-I, M-II, M-IV, M-V, and M-VI); of these M-VI is further metabolized to M-III and, to lesser extent, M-V is metabolized to form M-VI.²⁷ Three of these metabolites (M-III, M-IV, and to a lesser extent M-II) have anti-hyperglycemic potency about 40-60% of that of PIO. The triglyceride lowering potency of M-II was nearly twice that of the parent compound, while the potencies of M-III and M-IV were slightly less than those of PIO. PIO

is extensively bound to plasma protein (esp. albumin). The active metabolites, M-III and M-IV are also highly protein bound.

V. Pharmacokinetic in Special Cases

- Hepatic and/or renal insufficiency, elderly, drug-interaction. The hepatotoxicity problems (f.e. Troglitazone) may be due to the structure of its alpha tocopherol side-chain that when metabolized may result in oxidative stress in the liver.²⁸ Both PIO and ROS have not such a side-chain, and therefore liver damage is not a class effect of these TZDs. Nonetheless, PIO is not recommended for use in patients with serum ALT over 2.5 times the upper limit of normal,²⁹ liver function test should be performed every 2 months, and then longer thereafter.

Patients with Renal Insufficiency: No dosage adjustment is needed in renal impairment: subjects whose creatinine clearance between 4.3 and 120 ml/mm.³⁰

Elderly patients : No clinically significant changes in pharma-cokinetics were found in healthy elderly people (aged over 65 years). Hence, the same once-daily dose regimen may be used as in the non-elderly.²⁷

Interaction of PIO with co-administered drugs (Warfarin, Phenprocoumon, Glipizide, Metformin, Digoxine) were not reported; thus, PIO has low potential for drug interactions.³¹

- Monotherapy and combined trials. PIO improves glycemic control in T2DM with once daily dose of 15, 30, or 45 mg for 26 weeks: mean decreased in AIC – 1.60% (but – 2.55% for the 45 mg treated group), in FPG – 65.3 mg/dl.³² There were consistent significant decreases in triglycerides and HDL-Cholesterol, but not in total Cholesterol and LDL-Cholesterol.

In an open trial of the 16 weeks combined therapy (PIO plus Sulphonylurea), resulted in : β -cell preservation markers, Homeostasis Model Assesment Insulin Resistance (HOMA-R) and β -cell function (HOMA-B) in combined treated group (HOMA-R improved by 30.1%, HOMA-B by 38.4%) were significantly superior to placebo plus Sulphonylurea.

Combination with Metformin (MET) plus PIO 30mg, after 16 weeks of treatment had reduced AIC by 0.83%, FPG by 37.7mg/dl.²⁹ In a long-term open extension to this study from week 16 to week 40, AIC and FPG of combined treated patients showed a continued improvement (decrease in AIC-1.70%, in FPG-156.5mg/dl).

It is hoped that the effects of PIO on DM, insulin resistance, and dyslipidemia will result in a reduction of cardiovascular complications in these patients (metabolic syndrome). Comparison of the effect of TZDs on lipid profiles reveals that PIO is most effective in its ability to decrease Triglyceride and increase HDL-Cholesterol. PIO also appears to affect favorably LDL-cholesterol composition. Although the overall levels of LDL-Cholesterol do not change during PIO therapy, levels of VLDL were significantly decreased as were those of Small, Dense LDL in a study of 6-months PIO therapy.³³

VI. Adverse Events

1. During PIO treatment there was a small decrease in Hemoglobin and Hematocrit which was dose dependent but which was secondary hemodilution.²⁹ The Hemodilution tended to occur in the first months of treatment and then stabilized and was not considered clinically relevant.³⁴ No effects on other cellular components of blood suggestive of toxic effect on bone marrow occurred.
2. There was slightly higher levels of CPK (creatin phosphokinase) and LDH (lactic dehydrogenase) with PIO than placebo (albeit within the normal range), which may represent improve muscle metabolism due to improved glycemic control.³⁴
3. In many clinical trials, PIO had no effect on systolic blood pressure, although there was a trend towards reduction of diastolic blood pressure.³⁴
4. Analysis of echocardiography results showed no effects on cardiac conduction or evidence of cardiac hypertrophy. There was no excess of cardiovascular adverse events (including CHF) in placebo control trials or any increasing incidence of such events with 2 years of PIO treatment. Wayman et al³⁵ demonstrated that various chemically distinct ligands of PPAR γ (including ROS, PIO, as well as 15d-PG γ 2 and PGE $_1$) cause substantial reduction of myocardial infarct size in the rat.
5. The incidence of oedema reported in clinical trials was greater in the PIO treated groups than in the placebo groups;³⁶ in monotherapy the incidence of oedema 3.2% (placebo 0.7%), and in combination with Metformin 6.0% (placebo 2.5%), combined with Sulphonylurea = SU 5.9% (SU plus placebo 2.1%, combined with insulin 15.3% (Insulin plus placebo 7.5%). In general, the oedema was mild or moderate and usually did not require cessation of therapy.

Sometimes the oedema resolved despite continued therapy. Its occurrence was not correlated with weight gain or extent of hemodilution. The mechanism has not yet been elucidated but is thought to be either via pre-capillary vasodilation (similar to that seen with calcium antagonists) or anti-natriuretic effect.³⁷

6. Another adverse reaction that is common to the TZDs is weight gain.^{37,38} It occurs most rapidly during the first few months of treatment and plateaus at about 5% of body weight.³⁴ In combination trial, there was a smaller weight gain when PIO was taken with Metformin than with SU.³⁸ Most probably, such a weight gain was associated with improved glycemic control.^{34,39}
7. However, body composition analysis of a Study of 25 T2DM who were naïve to therapy, received either PIO 45 mg or Placebo for 18 weeks, revealed that the weight increases were due to increase in subcutaneous fat with a decrease in intra abdominal fat (mean increase in weight in PIO was 2.8 kg). By contrast, Placebo treated patients suffered a slight increase in abdominal fat and a decrease in subcutaneous fat. There was a small increase in total body water. These results indicate that, while PIO increases body weight, this does not increase cardiovascular risk and in fact may be beneficial by virtue of the reduction in abnormal fat, which is a known cardiovascular risk factor; this phenomenon can be called “PPAR γ – Paradox”.²⁹

CONCLUSION

PIO as a stronger “dual PPAR γ - PPAR α agonist” than ROS may have multiple effects that improve insulin resistance and lipid profiles, and anti-inflammation. Hence, this novel insulin sensitizer may play a pivotal role in the new approach in the treatment of diabetes mellitus and/or metabolic insulin syndrome and cardiovascular diseases.

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