REVIEW ARTICLE

DRUG THERAPY

Thiazolidinediones

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Insulin resistance both precedes and predicts type 2 diabetes mellitus.[1] Although exercise and weight loss ameliorate insulin resistance and may in some cases prevent or delay onset of the disease,[2] therapy that combats insulin resistance in those who fail to change their lifestyle is needed. Current pharmacologic approaches are unsatisfactory in improving such consequences of insulin resistance as hyperglycemia, diabetic dyslipidemia, abnormal coagulation and fibrinolysis, and hypertension,[3] each of which may require the use of at least one medication. Thus, the development of drugs targeted to reverse insulin resistance is important. The insulin-sensitizing thiazolidinediones, which are selective ligands of the nuclear transcription factor peroxisome-proliferator–activated receptor γ (PPARγ),[4] are the first drugs to address the basic problem of insulin resistance in patients with type 2 diabetes. Furthermore, this class of agents may have a role in treating patients with nondiabetic insulin-resistant conditions. This review briefly describes the current understanding of the mechanisms of action of thiazolidinediones and focuses on their use as hypoglycemic therapies in patients with type 2 diabetes.

The Superfamily of Peroxisome-Proliferator–Activated Receptors

The peroxisome-proliferator–activated receptors (PPARs) are a subfamily of the 48-member nuclear-receptor superfamily[5] and regulate gene expression in response to ligand binding.[6,7] Various fatty acids serve as endogenous ligands for PPARs, whereas some members of the superfamily (farnesoid X receptors) bind bile acids and others (liver X receptors) bind oxysterols.[5] Three PPARs, designated PPARα, PPARδ (also known as PPARβ), and PPARγ, have been identified to date.

After ligand binding, PPARs undergo specific conformational changes that allow for the recruitment of one coactivator protein or more.[8] Ligands differ in their ability to interact with coactivators, which explains the various biologic responses observed.[6,7,9-11] PPARs regulate gene transcription by two mechanisms (Fig. 1). Transactivation is DNA-dependent and involves binding to PPAR response elements of target genes and heterodimerization with the retinoid X receptor.[8] A second mechanism, transrepression, may explain the antiinflammatory actions of PPARs. It involves interfering with other transcription-factor pathways in a DNA-independent way.[9]

PPARα is expressed predominantly in the liver, heart, and muscle, as well as in the vascular wall.[7] Fibrates such as fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil act as full or partial PPARα agonists. In general, PPARα activation enhances free fatty acid oxidation, controls expression of multiple genes regulating lipoprotein concentrations, and has antiinflammatory effects (Fig. 2). PPARα agonists prevent or retard atherosclerosis in mice and humans.[12-14]

PPARδ is expressed in many tissues, with the highest expression in the skin, brain, and adipose tissue. In mice in which PPARδ is ablated (PPARδ null mice),[15] these tissues display alterations such as delayed wound closure and diminished myelination.

PPARγ is expressed most abundantly in adipose tissue but is also found in pancreatic beta cells, vascular endothelium, and macrophages.[8,16] Its expression is low in tissues that express predominantly PPARα, such as the liver, the heart, and skeletal muscle. The discovery of PPARγ as the target for thiazolidinediones was followed by large-scale clinical trials of several agents.[17-27] In January 1997, the first thiazolidinedione, troglitazone, was approved as a glucose-lowering therapy for patients in the United States with type 2 diabetes. Troglitazone was subsequently withdrawn from the market, in March 2000, because of hepatotoxicity. The two currently available PPARγ agonists, rosiglitazone and pioglitazone, were approved in the United States in 1999.

MECHANISM OF ACTION OF THIAZOLIDINEDIONES

INSULIN SENSITIVITY AND SECRETION

Thiazolidinediones consistently lower fasting and postprandial glucose concentrations as well as free fatty acid concentrations in clinical studies.[28-31] Insulin concentrations also decrease in most studies.[28-31] Such changes indicate that thiazolidinediones act as insulin sensitizers, which has been confirmed by direct measurements in in vivo studies in humans. For example, treatment of nondiabetic subjects or those with type 2 diabetes for three to six months with troglitazone, rosiglitazone, or pioglitazone increases insulin-stimulated glucose uptake in peripheral tissues.[28,30,32-34] In similar studies, thiazolidinediones increase hepatic insulin sensitivity (the ability of insulin to suppress endogenous glucose production) and insulin sensitivity in adipose tissue (measured from the ability of insulin to suppress free fatty acid concentrations).[30] In addition, insulin secretory responses, even after adjustment for an improvement in insulin sensitivity, have increased in subjects with impaired glucose tolerance[35] and type 2 diabetes.[36] Somewhat paradoxically, these improvements are generally accompanied by weight gain and an increase in the subcutaneous adipose-tissue mass.[30,32,33,37,38]

ENHANCEMENT OF INSULIN SENSITIVITY

PPARγ is essential for normal adipocyte differentiation and proliferation as well as fatty acid uptake and storage. Thiazolidinediones increase the number of small adipocytes and the subcutaneous adipose-tissue mass in studies in animal models.[11,32,39] These observations, plus the high level of PPARγ expression in adipose tissue, have led to the hypothesis that thiazolidinediones exert their insulin-sensitizing actions either directly (the "fatty acid steal" hypothesis) or indirectly, by means of altered adipokine release, modulating insulin sensitivity outside adipose tissue. According to the "fatty acid steal" hypothesis, thiazolidinediones promote fatty acid uptake and storage in adipose tissue. In this way, they increase adipose-tissue mass and spare other insulin-sensitive tissues such as skeletal muscle and the liver, and possibly pancreatic beta cells, from the harmful metabolic effects of high concentrations of free fatty acids. Thiazolidinediones thus keep fat where it belongs.

In a manner consistent with that hypothesis, thiazolidinediones lower circulating free fatty acid concentrations and triglyceride content in the liver, but not in skeletal muscle, in patients with type 2 diabetes[31,37,40-42] and lipodystrophy.[43] Metformin increases insulin sensitivity in the liver without changing its fat content in patients with type 2 diabetes,[42] and thiazolidinediones can lower fasting insulin concentrations without increasing subcutaneous fat mass in patients with lipodystrophy.[43]

In mice, targeted deletion of PPARγ in adipose tissue does not induce insulin resistance in muscle,[44] whereas muscle-specific PPARγ deletion does cause such resistance.[45] Insulin resistance in muscle is unresponsive to thiazolidinediones, implying that these agents sensitize by directly stimulating muscle PPARγ receptors.[45] Hepatic insulin resistance in mice lacking PPARγ in adipose tissue can be reversed with thiazolidinediones.[44] These data suggest that the insulin-sensitizing effects of thiazolidinediones in the liver and muscle of mice are not mediated by PPARγ receptors in adipose tissue in cases in which adipose tissue is unable to respond to these agents normally. However, the lipoatrophy that accompanies tissue-specific PPARγ deletion may make the action of PPARγ agonists abnormally dependent on PPARγ expression in other tissues. For example, rosiglitazone is able to reverse hypertriglyceridemia, hyperglycemia, and hyperinsulinemia in normal mice, whereas the drug is ineffective in lipoatrophic mice.[46] Taken together, data from knockout-mouse models support the idea that adipose tissue is the most important site for thiazolidinedione action if there are normal amounts of adipose tissue.

INDIRECT EFFECTS IN ADIPOSE TISSUE

Although thiazolidinediones may enhance insulin sensitivity by keeping fat where it belongs, indirect effects may also be involved. Gene-expression pro-

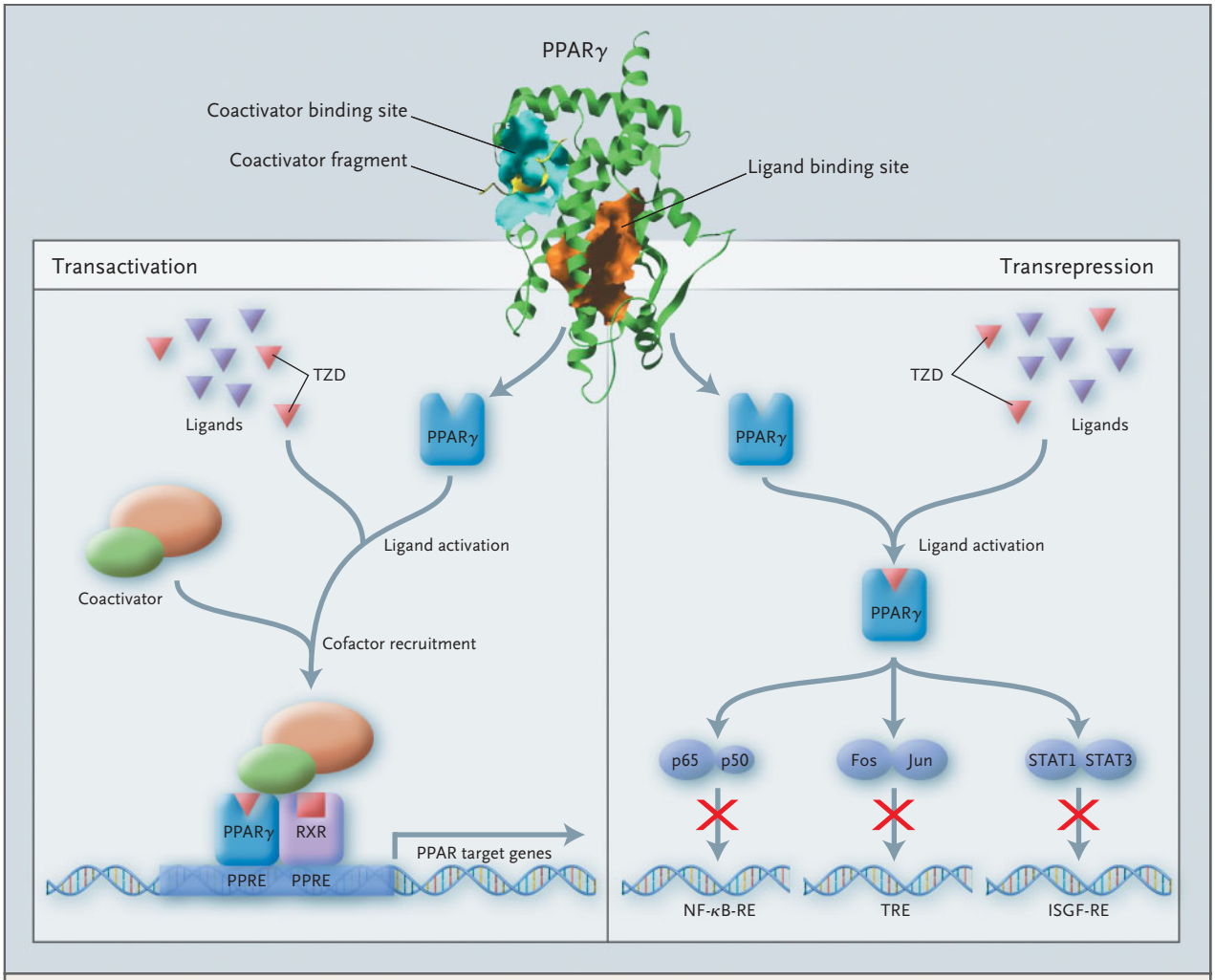

Figure 1. Molecular Mechanisms of Biologic Responses of Thiazolidinediones.

Peroxisome-proliferator–activated receptor γ (PPARγ) is a transcription factor activated by thiazolidinediones (TZDs). In transactivation, which is DNA-dependent, PPARγ forms a heterodimer with the retinoid X receptor (RXR) and recognizes specific DNA response elements called PPAR response elements (PPRE) in the promoter region of target genes. This results ultimately in transcription of PPARγ target genes. After ligand binding, PPARs undergo conformational changes, which lead to recruitment of cofactor proteins and coactivators. The coactivators interact with nuclear receptors in a ligand-dependent way and influence the set of genes transcribed. In transrepression, PPARs can repress gene transcription by negatively interfering with other signal-transduction pathways, such as the nuclear factor-κB (NF-κB) signaling pathway, in a DNA-binding–independent manner. STAT denotes signal transducers and activators of transcription, ISGF-RE interferon-stimulated gene factor responsive element, and TRE TPA responsive element, where TPA is a phorbol ester.

filing studies using oligonucleotide microarrays in differentiated 3T3-L1 adipocytes have indicated that rosiglitazone and pioglitazone each regulate the expression of more than 100 genes and that these genes are not identical, although they cluster together.[10] A small fraction of the established PPARγ target genes that also seem to be regulated in human adipose tissue in vitro are shown in Figure 2.[47-49] Various adipokines, such as adiponectin,[50,51] tumor necrosis factor α,[52] resistin,[53] and 11β-hydroxysteroid dehydrogenase 1, the enzyme that produces cortisol locally in adipose tissue,[11,54] are among the genes that are regulated by PPARγ agonists in rodents. Of these, adiponectin increases insulin sensitivity, and tumor necrosis factor α, resistin, and 11β-hydroxysteroid dehydrogenase 1[55] induce insulin resistance in rodents.

Adiponectin, an adipocytokine produced exclu-

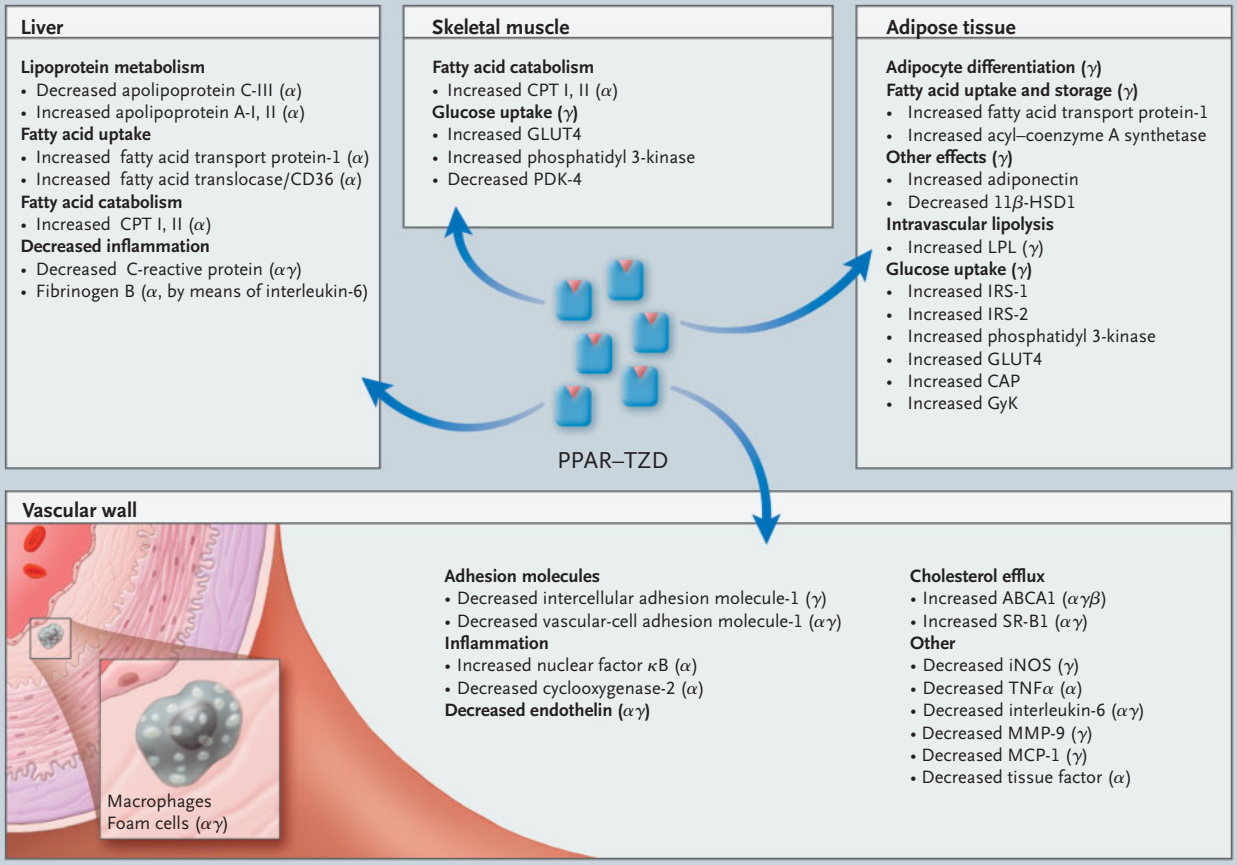

Figure 2. Molecular Targets of PPARγ and PPARα Action.

PPARα is expressed mainly in the liver, in skeletal muscle, in the heart (not shown), and in the endothelial cells and smooth-muscle cells of the vascular wall. It regulates genes that influence lipoprotein metabolism and fatty acid uptake and oxidation as well as production of inflammatory markers. PPARγ is expressed mainly in adipose tissue, where it regulates genes involved in adipocyte differentiation, fatty acid uptake and storage, and glucose uptake. It also stimulates intravascular lipolysis. CPT denotes carnitine palmitoyl transferase, α regulation of the gene by PPARα agonists, γ regulation of the gene by PPARγ agonists, β regulation of the gene by PPARβ (PPARδ) agonists, GLUT4 insulin-sensitive glucose transporter, PDK-4 pyruvate dehydrogenase kinase 4, HSD1 hydroxysteroid dehydrogenase type 1, LPL lipoprotein lipase, IRS insulin-receptor substrate, CAP Cbl–associated protein, GyK glycerol kinase, ABCA1 ATP-binding cassette A1, SR scavenger receptor, iNOS inducible nitric oxide synthase, TNF-α tumor necrosis factor α, MMP-9 matrix metalloproteinase 9, MCP-1 monocyte chemoattractant protein 1, and TZD thiazolidinedione.

sively by adipose tissue, has both insulin-sensitizing and antiatherogenic properties in mice.[50,51] PPARγ agonists increase adiponectin expression in vitro in adipose tissue.[56] Adiponectin levels are low in patients with obesity and type 2 diabetes,[57-62] as well as in patients with lipodystrophy.[63-66] In vivo treatment with thiazolidinediones[31,56,59-61,67,68] markedly increases circulating concentrations of adiponectin, the most abundantly expressed gene transcript in human adipose tissue.[69] It is unclear whether adiponectin increases hepatic insulin sensitivity in humans as it does in mice, although plasma adiponectin concentrations correlate with liver fat content both before and after thiazolidinedione treatment in patients with type 2 diabetes.[31,42]

In the liver and in adipose tissue, 11β-hydroxysteroid dehydrogenase 1 catalyzes the interconversion of cortisone to cortisol.[70] A full-blown metabolic syndrome characterized by obesity and the accumulation of visceral fat, as well as increased concentrations of cortisol in the portal vein but not of systemic cortisol, develops in mice that overex-

press 11β-hydroxysteroid dehydrogenase 1 in adipose tissue.[55] Thiazolidinediones down-regulate 11β-hydroxysteroid dehydrogenase 1 expression in adipose tissue[54] and might thereby alleviate features of the metabolic syndrome. However, no data on the effects of thiazolidinediones on 11β-hydroxysteroid dehydrogenase 1 activity or expression in humans are available.

The many effects of thiazolidinediones in various tissues make it impossible to define the exact mechanisms underlying their insulin-sensitizing effects in vivo in humans. Data suggest that multiple mechanisms are probably involved (Fig. 3). One mechanism includes stimulation of free fatty acid storage in adipose tissue, sparing other tissues such as the liver, skeletal muscle, and possibly beta cells from lipotoxicity.[71] These drugs may also have indirect insulin-sensitizing effects, especially in the liver by means of the secretion of adiponectin from adipose tissue.

CLINICAL EFFICACY OF THIAZOLIDINEDIONES IN HUMANS

EFFECTS IN PATIENTS WITH TYPE 2 DIABETES

Rosiglitazone and pioglitazone are currently approved in most countries for the treatment of hyperglycemia in patients with type 2 diabetes, either as monotherapy or in combination with sulfonylureas or metformin. In the United States, both drugs have also been approved for use in combination with insulin, provided certain precautions are followed.

HYPOGLYCEMIC EFFECTS

Placebo-controlled studies suggest that both pioglitazone and rosiglitazone are moderately effective in achieving glycemic control (Table 1). At maximal doses, these two drugs seem to decrease glycosylated hemoglobin values on average by 1 to 1.5 percent. Thus, in a typical patient with type 2 diabetes, one may expect glycosylated hemoglobin to decrease from a value of 8.5 percent to a value of 7 percent (normal range, 4 to 6 percent). Pioglitazone and rosiglitazone decrease glycosylated hemoglobin values more than the weakest hypoglycemic drugs (e.g., nateglinide and α-glucosidase inhibitors) but slightly less than full doses of glimepiride (4 to 6 mg), glyburide (glibenclamide, 10 to 15 mg), or metformin (2 to 2.5 g).[72-74] Whether thiazolidinediones are used as monotherapy or are added to existing therapies does not seem to affect their hypoglycemic efficacy. No data are available on patient characteristics that can predict a good treatment response, and no data are available to support long-term maintenance of glycemic control with rosiglitazone or pioglitazone as compared with other existing therapies. Ongoing studies may be useful, such as the A Diabetes Outcome Progression Trial (ADOPT), which involves patients with type 2 diabetes who have not previously received treatment and who have been randomly assigned to receive rosiglitazone, glyburide, or metformin monotherapy.[75]

EFFECTS ON LIPIDS

There are no head-to-head double-blind studies comparing the effects of pioglitazone and rosiglitazone on serum lipids and lipoproteins. However, low-density lipoprotein (LDL) cholesterol levels have consistently remained unchanged when monotherapy with pioglitazone or combination therapy with pioglitazone and sulfonylurea, metformin, or insulin has been used. In contrast, increases in LDL cholesterol levels, ranging from 8 to 16 percent, have been noted in studies of rosiglitazone (Fig. 4). High-density lipoprotein (HDL) cholesterol levels have increased by approximately 10 percent with both drugs.

The effects of thiazolidinediones on triglycerides have been somewhat more variable. Decreases in triglyceride levels have been observed more often with pioglitazone than with rosiglitazone (Fig. 4). The only direct comparison of rosiglitazone and pioglitazone in an open-label trial, in 127 patients previously treated with troglitazone, supports the idea that the two agents have similar effects on glycemia and body weight.[76] The same study showed that pioglitazone is more effective than rosiglitazone in regard to LDL cholesterol and serum triglyceride levels. The difference between the effects of the drugs on lipids cannot be attributed to differences in their effects on serum free fatty acid concentrations, which decreased by similar amounts, approximately 20 to 30 percent.[30,33] Pioglitazone seems to act like a partial PPARα agonist in vitro, whereas rosiglitazone seems to be a pure PPARγ agonist.[77]

Data on mechanisms underlying the effects of the thiazolidinediones on lipids in humans are virtually nonexistent. For example, there are no data to characterize the effects of thiazolidinediones on the production and removal of lipoprotein parti-

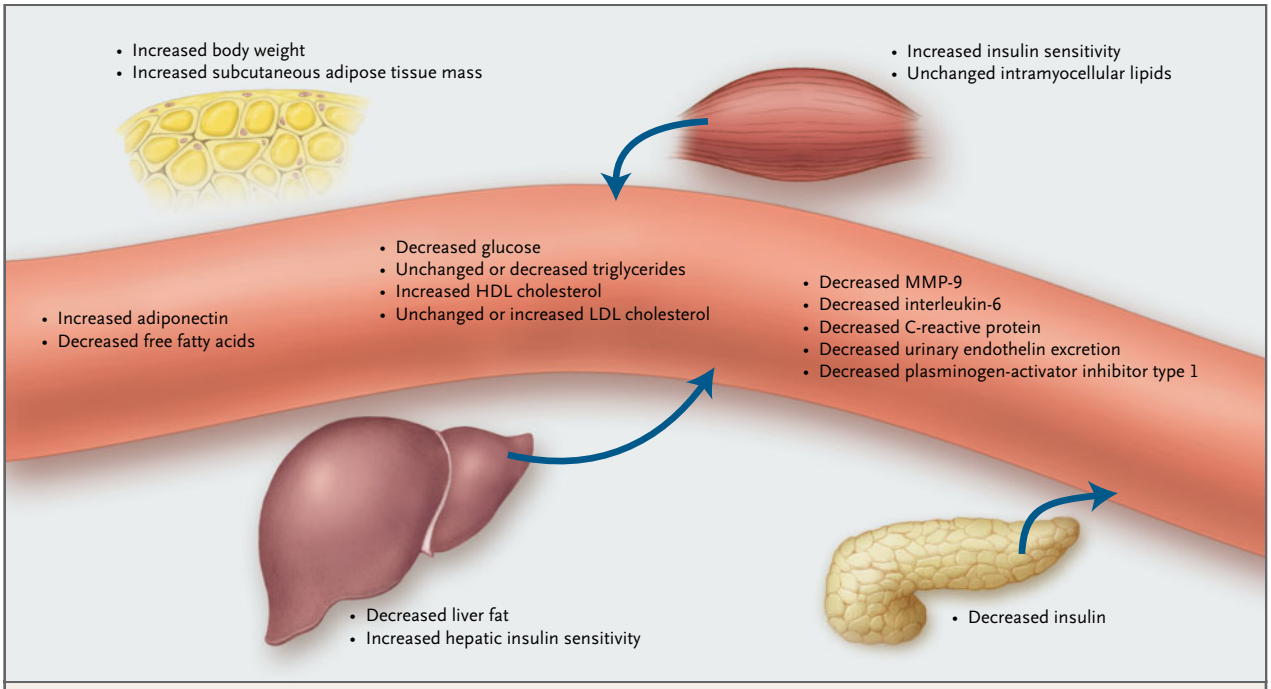

Figure 3. Mechanism of Action of Thiazolidinediones in Vivo in Humans.

Thiazolidinediones may keep fat where it belongs — that is, they may increase lipogenesis in adipose tissue, which decreases serum free fatty acid concentrations and increases subcutaneous adipose tissue mass and body weight. Adipose tissue expression and serum concentrations of adiponectin also increase, which, together with the lowering of serum free fatty acid levels, could contribute to increased hepatic insulin sensitivity, the lowering of hepatic fat content, and the inhibition of hepatic glucose production. The latter decreases plasma glucose concentrations. Serum insulin concentrations decrease as a consequence of enhanced insulin sensitivity and clearance. Thiazolidinediones have also been shown to decrease circulating or urinary markers of cardiovascular risk and vascular inflammation such as plasminogen-activator inhibitor type 1, C-reactive protein, matrix metalloproteinase 9 (MMP-9), and urinary endothelin excretion. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

cles containing apolipoprotein A-I or apolipoprotein B. The cause of the increase in HDL and LDL cholesterol levels during rosiglitazone treatment is therefore unknown. The effects of rosiglitazone or pioglitzone on the size of LDL particles have not been studied in a double-blind, placebo-controlled trial. Rat and mouse models are not ideal for the study of human lipoprotein metabolism, because impaired clearance is the principal defect responsible for hypertriglyceridemia in these models, rather than overproduction of very-low-density lipoproteins, which is the case in humans.[78]

EFFECTS OF THIAZOLIDINEDIONES ON CONDITIONS CHARACTERIZED BY INSULIN RESISTANCE

Type 2 diabetes is currently the only approved indication for therapy with thiazolidinediones. However, thiazolidinediones have been tested as experimental therapies with variable success in other insulin-resistant conditions, such as nonalcoholic fatty liver disease,[79] polycystic ovary syndrome,[80] and lipodystrophies.[81]

NONALCOHOLIC FATTY LIVER DISEASE

Type 2 diabetes is strongly associated with nonalcoholic fatty liver disease, a spectrum of liver damage that ranges from benign hepatic steatosis to potentially fatal cirrhosis.[79] According to the third National Health and Nutrition Examination Survey, 6.4 million adults in the United States have nonalcoholic fatty liver disease.[82] It is the most common cause of levels of elevated levels of liver enzymes,[82] and elevated alanine aminotransferase levels predict type 2 diabetes independently of obesity.[83] Hepatic steatosis is associated with increased hepatic insulin resistance in humans[84] and correlates with insulin requirements during insulin therapy in patients with type 2 diabetes.[85]

Table 1. Comparative Effects of Maximal Doses of Rosiglitazone (8 mg) and Pioglitazone (30 to 45 mg) on Glycemic Control as Measured by Absolute Change in Glycosylated Hemoglobin as Compared with Placebo or Control Group (Metformin, Sulfonylurea, or Insulin Alone or in Combination).

Type of Therapy	Study	No. of Patients	Duration of Study	Decrease in Glycosylated Hemoglobin	Weight Gain*
			wk	%	*kg*
Pioglitazone					
Monotherapy	Aronoff et al.[17]	155	26	1.6	4.1
	Scherbaum and Göke[18]	162	26	0.7	1.9
	Rosenblatt et al.[19]	197	23	1.4	3.2
Combination therapy					
Metformin	Einhorn et al.[20]	328	16	0.8	2.3
Sulfonylurea	Kipnes et al.[21]	376	16	1.3	3.7
Insulin	Rosenstock et al.[22]	358	16	1.0	3.7
Rosiglitazone					
Monotherapy	Lebovitz et al.[23]	327	26	1.5	4.5
Combination therapy					
Metformin	Fonseca et al.[24]	223	26	1.2	3.1
	Gomez-Perez et al.[25]	70	26	1.5	3.3
Sulfonylurea	Vongthavaravat et al.[26]	348	26	1.2	—
Insulin	Raskin et al.[27]	207	26	1.3	4.4

* A dash indicates no data.

In several recent studies, thiazolidinediones have been shown to reduce fat accumulation in the liver in patients with type 2 diabetes[37,40-42] and in patients with lipodystrophy associated with the use of highly active antiretroviral therapy.[43] It is consistent with such findings that liver enzymes, which have been extensively monitored because of fear of hepatotoxicity, seem to decrease rather than increase during treatment with pioglitazone and rosiglitazone.[40,43]

Nonalcoholic steatohepatitis represents an advanced stage within the spectrum of nonalcoholic fatty liver disease and is defined histologically by the presence of steatosis along with areas of necrosis and inflammation. Recent studies have suggested that thiazolidinediones not only decrease liver fat content but also induce improvements in liver histology.[86,87]

POLYCYSTIC OVARY SYNDROME

The polycystic ovary syndrome is a disorder of unknown cause affecting approximately 4 percent of women of reproductive age.[88] Women with the polycystic ovary syndrome are frequently insulin resistant and at increased risk for type 2 diabetes.[89] The hyperinsulinemia accompanying insulin resistance is thought to contribute to hyperandrogenism in patients with the polycystic ovary syndrome.[80,90] Interventions that reduce insulin levels, such as weight loss and medications (e.g., metformin, diazoxide, or somatostatin analogues), decrease hyperandrogenism and reduce insulin resistance.[91] A large-scale placebo-controlled trial including 410 women showed that troglitazone treatment was associated with significant improvements in ovulatory function, hirsutism, hyperandrogenemia, and insulin resistance.[92] Similar data were recently reported in a small placebo-controlled study in which women underwent randomization to rosiglitazone and placebo or to rosiglitazone and clomiphene. Overall, 56 percent of women previously resistant to clomiphene ovulated: 33 percent of those who were treated with rosiglitazone alone and 77 percent of those who were treated with combination therapy.[93] Although metformin is considered safe for women who become pregnant, rosiglitazone and pioglitazone are classified as pregnancy category C owing to experimental evidence of growth retardation in mid-to-late gestation in animal models. Agents in category C have had toxic effects in studies in animal

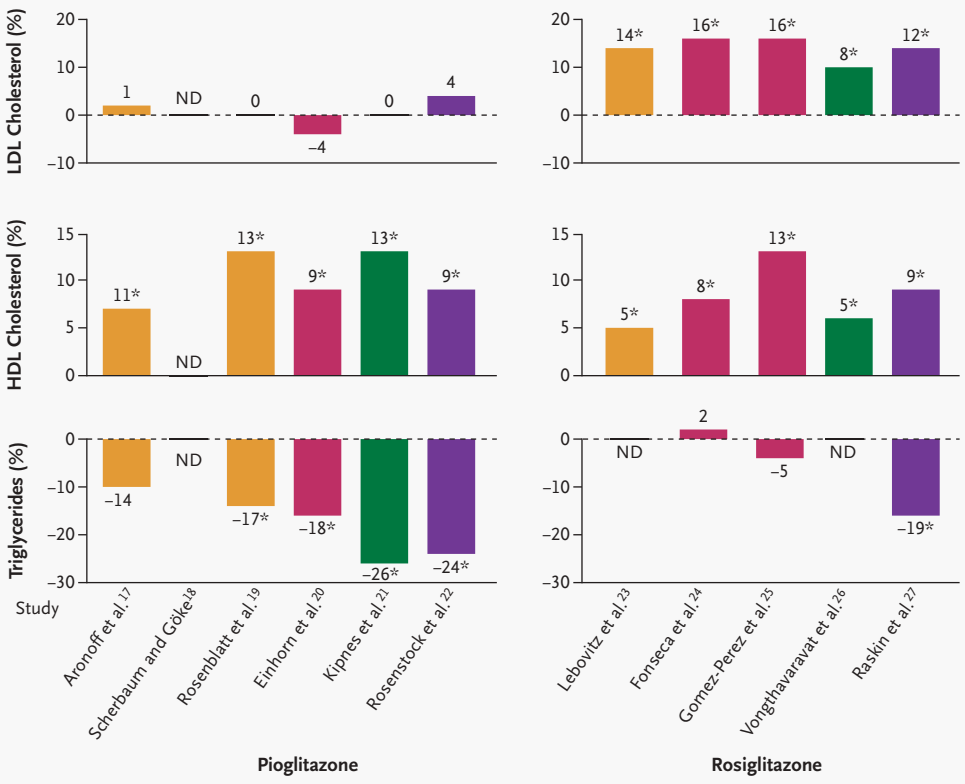

Figure 4. Comparative Effects of Maximal Doses of Rosiglitazone (8 mg) and Pioglitazone (30 to 45 mg) on Serum Lipids and Lipoproteins in Randomized, Controlled Trials.

All changes are shown as percent changes relative to the change in the placebo group (i.e., percent change from baseline with pioglitazone or rosiglitazone minus percent change with placebo from baseline). Asterisks indicate P≤0.05. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, and ND no data. Yellow bars indicate monotherapy, red bars combination therapy with metformin, green bars combination therapy with sulfonylurea, and purple bars combination therapy with insulin.

models, but the results of studies in humans are inadequate; the agents should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Polycystic ovary syndrome is not an approved indication for the use of thiazolidinediones.

LIPODYSTROPHIES

By far the most common form of lipodystrophy is that associated with use of highly active antiretroviral therapy in patients with human immunodeficiency virus (HIV) disease. At least one lipodystrophy-related symptom develops after 12 to 18 months in approximately half of patients treated with highly active antiretroviral therapy.[94] Lipodystrophy, especially facial lipoatrophy, can be disfiguring and stigmatizing. There is no pharmacologic therapy for lipoatrophy, which is invariably accompanied by marked insulin resistance. Thiazolidinediones would seem to be an ideal therapy for insulin resistance and lipoatrophy associated with highly active antiretroviral therapy, because the drugs increase both insulin sensitivity and subcutaneous fat mass. However, in the only placebo-controlled trial in which patients with lipodystrophy associated with highly active antiretroviral therapy were treated (rosiglitazone, 8 mg per day for six months), there was no evidence of an increase in adiposity or body weight,[43] in contrast to studies in patients with type 2 diabetes.[30,32] In rare forms of human lipodystrophy, treatment with troglitazone for six months was reported to decrease glycosylated hemoglobin values and triglyceride levels and to induce a slight increase (2.4 percent) in subcutaneous fat.[95]

EFFECTS OF THIAZOLIDINEDIONES ON MARKERS OF CARDIOVASCULAR RISK

Cardiovascular disease is the leading cause of death worldwide and a major complication of type 2 diabetes.[96] In contrast to insulin, sulfonylureas, and metformin, all of which were shown in the United Kingdom Prospective Diabetes Study to be of benefit, or at least safe,[97,98] only data on markers of cardiovascular risk are currently available for thiazolidinediones.

BODY COMPOSITION AND BLOOD PRESSURE

Thiazolidinediones lead to an increase in body weight of 2 to 3 kg for every 1 percent decrease in glycosylated hemoglobin values (Table 1). The magnitude of the increase is similar during monotherapy and combination therapy with insulin[99] or metformin[20,24,25] in type 2 diabetes. The increase in body weight has been attributed to expansion of the subcutaneous fat depot, and in some patients to edema, whereas the mass of visceral fat remains unchanged[37] or decreases.[32] The clinical significance of these changes for patients with cardiovascular disease remains to be established. Systematic reviews of the literature have found no notable benefits of thiazolidinediones in regard to blood pressure.[100]

PLASMA AND URINARY MARKERS

Both pioglitazone and rosiglitazone may decrease the risk of cardiovascular disease by reducing glucose, insulin, and free fatty acid concentrations and by increasing HDL cholesterol levels. The significance of the increase in LDL cholesterol levels observed during rosiglitazone treatment is unclear, because of a lack of data on the effect of the drug on the size of LDL particles.

Circulating concentrations of adiponectin are low in patients with insulin-resistant conditions and are increased by thiazolidinediones. Circulating concentrations are also low in patients with coronary artery disease.[57,101]

Few data are available regarding the effects of thiazolidinediones on other markers of cardiovascular risk. One double-blind, placebo-controlled study showed that in patients with type 2 diabetes, rosiglitazone monotherapy was associated with a decrease in the ratio of urinary albumin to creatinine.[23] Another placebo-controlled study showed that rosiglitazone decreased plasma levels of plasminogen-activator inhibitor type 1 in cases of lipodystrophy associated with the use of highly active antiretroviral therapy in HIV-positive patients.[102] Other reports suggest that rosiglitazone decreases serum concentrations of the matrix-degrading MMP-9 (matrix metalloproteinase 9), C-reactive protein, and interleukin-6 (Fig. 3).[103,104]

VASCULAR FUNCTION AND DISEASE

Two double-blind, placebo-controlled studies have examined the effects of troglitazone on endothelium-dependent and -independent vasodilatation in humans. One study showed that eight weeks of troglitazone therapy had no effect on vascular function in patients with obesity,[34] whereas the other showed improvements in flow-mediated vasodilatation in a subgroup of patients in whom type 2 diabetes had been newly diagnosed.[105] A placebo-controlled study showed reduced progression of the intima–media thickness of the common carotid artery in patients with type 2 diabetes who were treated with rosiglitazone.[106] There are no data on the effects of thiazolidinediones on cardiovascular events in patients with insulin-resistant conditions. Two studies, the Prospective Pioglitazone Clinical Trial in Macrovascular Events and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes trial, are currently investigating the effects of pioglitazone and rosiglitazone on cardiovascular events in patients with type 2 diabetes.[107]

SAFETY AND TOLERABILITY OF THIAZOLIDINEDIONES

WEIGHT GAIN, FLUID RETENTION, AND ANEMIA

The use of thiazolidinediones is associated with weight gain (Table 1), and a subgroup of patients have fluid retention and plasma volume expansion, which lead to peripheral edema. Edema has been reported in 4 to 6 percent of patients undergoing treatment with thiazolidinediones as compared with 1 to 2 percent of those receiving placebo or other hypoglycemic therapies. The increase in body weight and edema has been associated with an increase in the incidence of heart failure in patients being treated with thiazolidinediones and insulin. The Food and Drug Administration has included a warning in the prescription information for rosiglitazone (Avandia) and pioglitazone (Actos). The European Agency for the Evaluation of Me-

dicinal Products considers insulin therapy a contraindication to the use of thiazolidinediones. According to the agency, the frequency of congestive heart failure was 2.5 times as great with combination therapy with insulin and thiazolidinediones as with insulin alone, although the reason was not clear. The use of thiazolidinediones is also associated with slight decreases in the hemoglobin level and hematocrit, probably without clinical consequence.[100]

HEPATOTOXICITY

The idiosyncratic liver toxicity observed with troglitazone does not seem to be a class effect. In 13 double-blind studies, 1.91 percent of 2510 patients, 0.26 percent of 1526 patients, and 0.17 percent of 3503 patients receiving troglitazone, pioglitazone, and rosiglitazone had alanine aminotransferase values that were more than three times the upper limit of the reference range.[108] Alanine aminotransferase levels more than 10 times the upper limit of normal were observed in 0.68 percent of patients undergoing treatment with troglitazone as compared with none taking rosiglitazone and pioglitazone.

INSULIN SENSITIZATION BEYOND THIAZOLIDINEDIONES

The lipid-lowering and cardioprotective effects of PPARα agonists, such as fenofibrate[14] and gemfibrozil,[13] and the glucose-lowering effects of thiazolidinediones have led to a search for dual PPAR agonists (compounds with the combined effects of PPARα and PPARγ). Amelioration of insulin sensitivity in humans by means of interventions such as weight loss leads to the correction of abnormalities in both glucose and lipid metabolism. Therefore, dual PPAR agonists might be closer to true insulin sensitizers than are pure PPARγ agonists, which have only questionable effects on lipid metabolism. Studies in animal models suggest that this is the case.[109] According to the Food, Drug, and Cosmetic Act report of new drug applications, as many as eight dual PPAR agonists are currently under clinical development, including two in phase 3 trials.

Another approach to improving the metabolic profile of thiazolidinediones has been to identify selective PPAR modulators that act like partial agonists or antagonists of pure PPARγ agonists.[110] Examples of selective modulators that have been developed include tamoxifen and raloxifene, which act like antagonists in the breast but like estradiol in the bone.[111] Studies in animal models suggest that, unlike the thiazolidinedione full agonists, nonthiazolidinedione selective PPAR modulators have retained metabolic efficacy regarding the lowering of glucose and insulin concentrations but have counteracted weight gain and the expansion of subcutaneous adipose depots.[10] Clinical development of these agents has not yet begun. Finally, tyrosine-based nonthiazolidinedione PPARγ agonists, which are more potent than thiazolidinediones, have also been developed to surmount some of the problems of thiazolidinediones.[112]

CONCLUSIONS

The epidemic of type 2 diabetes has created a large need for new hypoglycemic therapies, but very few agents have been introduced during the past 20 years. The thiazolidinediones represent a potentially important new group of drugs with a mechanism of action differing from and perhaps complementary to existing therapies. Thiazolidinediones, unlike metformin or sulfonylureas, decrease hepatic fat content and increase insulin sensitivity in muscle. These properties would seem to make the drugs particularly useful in patients with insulin-resistant type 2 diabetes, but no data are currently available to help identify the patients who would respond best to these drugs. Although thiazolidinediones lower glucose concentrations and increase insulin sensitivity, their nonglycemic effects on body weight, lipids, and blood pressure have been a disappointment, implying that this class of medications will not reduce the need to treat dyslipidemia and hypertension with separate therapies.

Since cardiovascular disease is a major burden in patients with type 2 diabetes, data about the effects of thiazolidinediones on cardiovascular disease are urgently needed. Until such data are available, one might conclude that although the study of PPARs has greatly expanded our understanding of the biology of adipose tissue, currently available thiazolidinediones are no more than moderately effective and expensive alternatives to existing hypoglycemic therapies.

REFERENCES

1. Yki-Järvinen H. Pathogenesis of non-insulin-dependent diabetes mellitus. Lancet 1994;343:91-5.
2. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
3. Yki-Järvinen H. Insulin resistance in type 2 diabetes. In: Pickup JC, Williams G, eds. Textbook of diabetes. 3rd ed. Oxford, England: Blackwell, 2003:22.1-22.19.
4. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). J Biol Chem 1995;270:12953-6.
5. Chawla A, Repa JJ, Evans RM, Mangelsdorf DJ. Nuclear receptors and lipid physiology: opening the X-files. Science 2001;294:1866-70.
6. Berger J, Moller DE. The mechanisms of action of PPARs. Annu Rev Med 2002;53:409-35.
7. Barbier O, Torra IP, Duguay Y, et al. Pleiotropic actions of peroxisome proliferator-activated receptors in lipid metabolism and atherosclerosis. Arterioscler Thromb Vasc Biol 2002;22:717-26.
8. Willson TM, Lambert MH, Kliewer SA. Peroxisome proliferator-activated receptor gamma and metabolic disease. Annu Rev Biochem 2001;70:341-67.
9. Chinetti G, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. Inflamm Res 2000;49:497-505.
10. Berger JP, Petro AE, Macnaul KL, et al. Distinct properties and advantages of a novel peroxisome proliferator-activated protein [gamma] selective modulator. Mol Endocrinol 2003;17:662-76.
11. Picard F, Auwerx J. PPAR(gamma) and glucose homeostasis. Annu Rev Nutr 2002;22:167-97.
12. Duez H, Chao YS, Hernandez M, et al. Reduction of atherosclerosis by the peroxisome proliferator-activated receptor alpha agonist fenofibrate in mice. J Biol Chem 2002;277:48051-7.
13. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999;341:410-8.
14. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet 2001;357:905-10. [Erratum, Lancet 2001;357:1890.]
15. Michalik L, Desvergne B, Wahli W. Peroxisome proliferator-activated receptors beta/delta: emerging roles for a previously neglected third family member. Curr Opin Lipidol 2003;14:129-35.
16. Dubois M, Pattou F, Kerr-Conte J, et al. Expression of peroxisome proliferator-activated receptor gamma (PPARgamma) in normal human pancreatic islet cells. Diabetologia 2000;43:1165-9.
17. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. Diabetes Care 2000;23:1605-11.
18. Scherbaum WA, Göke B. Metabolic efficacy and safety of once-daily pioglitazone monotherapy in patients with type 2 diabetes: a double-blind, placebo-controlled study. Horm Metab Res 2002;34:589-95.
19. Rosenblatt S, Miskin B, Glazer NB, Prince MJ, Robertson KE. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. Coron Artery Dis 2001;12:413-23.
20. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. Clin Ther 2000;22:1395-409.
21. Kipnes MS, Krosnick A, Rendell MS, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. Am J Med 2001;111:10-7.
22. Rosenstock J, Einhorn D, Hershon K, Glazer NB, Yu S. Efficacy and safety of pioglitazone in type 2 diabetes: a randomised, placebo-controlled study in patients receiving stable insulin therapy. Int J Clin Pract 2002;56:251-7.
23. Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. J Clin Endocrinol Metab 2001;86:280-8. [Errata, J Clin Endocrinol Metab 2001;86:1659, 2002;87:iv.]
24. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA 2000;283:1695-702. [Erratum, JAMA 2000;284:1384.]
25. Gomez-Perez FJ, Fanghanel-Salmon G, Antonio Barbosa J, et al. Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. Diabetes Metab Res Rev 2002;18:127-34.
26. Vongthavaravat V, Wajchenberg BL, Waitman JN, et al. An international study of the effects of rosiglitazone plus sulphonylurea in patients with type 2 diabetes. Curr Med Res Opin 2002;18:456-61.
27. Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. Diabetes Care 2001;24:1226-32.
28. Nolan JJ, Ludvik B, Beerdsen P, Joyce M, Olefsky J. Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. N Engl J Med 1994;331:1188-93.
29. Suter SL, Nolan JJ, Wallace P, Gumbiner B, Olefsky JM. Metabolic effects of new oral hypoglycemic agent CS-045 in NIDDM subjects. Diabetes Care 1992;15:193-203.
30. Miyazaki Y, Glass L, Triplitt C, et al. Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in Type 2 diabetic patients. Diabetologia 2001;44:2210-9.
31. Bajaj M, Suraamornkul S, Piper P, et al. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. J Clin Endocrinol Metab 2004;89:200-6.
32. Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002;87:2784-91.
33. Miyazaki Y, Mahankali A, Matsuda M, et al. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. Diabetes Care 2001;24:710-9.
34. Tack CJ, Ong MK, Lutterman JA, Smits P. Insulin-induced vasodilatation and endothelial function in obesity/insulin resistance: effects of troglitazone. Diabetologia 1998;41:569-76.
35. Cavaghan MK, Ehrmann DA, Byrne MM, Polonsky KS. Treatment with the oral antidiabetic agent troglitazone improves beta cell responses to glucose in subjects with impaired glucose tolerance. J Clin Invest 1997;100:530-7.
36. Miyazaki Y, Matsuda M, DeFronzo RA. Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. Diabetes Care 2002;25:517-23.
37. Carey DG, Cowin GJ, Galloway GJ, et al. Effect of rosiglitazone on insulin sensitivity and body composition in type 2 diabetic patients. Obes Res 2002;10:1008-15. [Erratum, Obes Res 2002;10:following table of contents.]
38. Adams M, Montague CT, Prins JB, et al. Activators of peroxisome proliferator-activated receptor gamma have depot-specific effects on human preadipocyte differentiation. J Clin Invest 1997;100:3149-53.
39. Okuno A, Tamemoto H, Tobe K, et al. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. J Clin Invest 1998;101:1354-61.
40. Mayerson AB, Hundal RS, Dufour S, et al. The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skele-

tal muscle triglyceride content in patients with type 2 diabetes. Diabetes 2002;51:797-802.
41. Bajaj M, Suraamornkul S, Pratipanawatr T, et al. Pioglitazone reduces hepatic fat content and augments splanchnic glucose uptake in patients with type 2 diabetes. Diabetes 2003;52:1364-70.
42. Tiikkainen M, Häkkinen A-M, Korsheninnikova E, Nyman T, Mäkimattila S, Yki-Järvinen H. Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes 2004;53:2169-76.
43. Sutinen J, Häkkinen A-M, Westerbacka J, et al. Rosiglitazone in the treatment of HAART-associated lipodystrophy — a randomized double-blind placebo-controlled study. Antivir Ther 2003;8:199-207.
44. He W, Barak Y, Hevener A, et al. Adipose-specific peroxisome proliferator-activated receptor gamma knockout causes insulin resistance in fat and liver but not in muscle. Proc Natl Acad Sci U S A 2003;100:15712-7.
45. Hevener AL, He W, Barak Y, et al. Muscle-specific Pparg deletion causes insulin resistance. Nat Med 2003;9:1491-7.
46. Gavrilova O, Haluzik M, Matsusue K, et al. Liver peroxisome proliferator-activated receptor gamma contributes to hepatic steatosis, triglyceride clearance, and regulation of body fat mass. J Biol Chem 2003;278:34268-76.
47. Guan HP, Li Y, Jensen MV, Newgard CB, Steppan CM, Lazar MA. A futile metabolic cycle activated in adipocytes by antidiabetic agents. Nat Med 2002;8:1122-8.
48. Rieusset J, Auwerx J, Vidal H. Regulation of gene expression by activation of the peroxisome proliferator-activated receptor gamma with rosiglitazone (BRL 49653) in human adipocytes. Biochem Biophys Res Commun 1999;265:265-71.
49. Smith U, Gogg S, Johansson A, Olausson T, Rotter V, Svalstedt B. Thiazolidinediones (PPARgamma agonists) but not PPARalpha agonists increase IRS-2 gene expression in 3T3-L1 and human adipocytes. FASEB J 2001;15:215-20.
50. Maeda N, Shimomura I, Kishida K, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 2002;8:731-7.
51. Matsuda M, Shimomura I, Sata M, et al. Role of adiponectin in preventing vascular stenosis: the missing link of adipo-vascular axis. J Biol Chem 2002;277:37487-91.
52. Peraldi P, Spiegelman B. TNF-alpha and insulin resistance: summary and future prospects. Mol Cell Biochem 1998;182:169-75.
53. Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. Nature 2001;409:307-12.
54. Berger J, Tanen M, Elbrecht A, et al. Peroxisome proliferator-activated receptor-gamma ligands inhibit adipocyte 11beta-hydroxysteroid dehydrogenase type 1 expression and activity. J Biol Chem 2001;276:12629-35.
55. Masuzaki H, Paterson J, Shinyama H, et al. A transgenic model of visceral obesity and the metabolic syndrome. Science 2001;294:2166-70.
56. Maeda N, Takahashi M, Funahashi T, et al. PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes 2001;50:2094-9.
57. Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.
58. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.
59. Hirose H, Kawai T, Yamamoto Y, et al. Effects of pioglitazone on metabolic parameters, body fat distribution, and serum adiponectin levels in Japanese male patients with type 2 diabetes. Metabolism 2002;51:314-7.
60. Phillips SA, Ciaraldi TP, Kong AP, et al. Modulation of circulating and adipose tissue adiponectin levels by antidiabetic therapy. Diabetes 2003;52:667-74.
61. Yu JG, Javorschi S, Hevener AL, et al. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. Diabetes 2002;51:2968-74.
62. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.
63. Haque WA, Shimomura I, Matsuzawa Y, Garg A. Serum adiponectin and leptin levels in patients with lipodystrophies. J Clin Endocrinol Metab 2002;87:2395.
64. Mynarcik DC, Combs T, McNurlan MA, Scherer PE, Komaroff E, Gelato MC. Adiponectin and leptin levels in HIV-infected subjects with insulin resistance and body fat redistribution. J Acquir Immune Defic Syndr 2002;31:514-20.
65. Addy CL, Gavrila A, Tsiodras S, Brodovicz K, Karchmer AW, Mantzoros CS. Hypoadiponectinemia is associated with insulin resistance, hypertriglyceridemia, and fat redistribution in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy. J Clin Endocrinol Metab 2003;88:627-36.
66. Sutinen J, Korsheninnikova E, Funahashi T, Matsuzawa Y, Nyman T, Yki-Järvinen H. Circulating concentration of adiponectin and its expression in subcutaneous adipose tissue in patients with highly active antiretroviral therapy-associated lipodystrophy. J Clin Endocrinol Metab 2003;88:1907-10.
67. Yang WS, Jeng CY, Wu TJ, et al. Synthetic peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetic patients. Diabetes Care 2002;25:376-80.
68. Combs TP, Wagner JA, Berger J, et al. Induction of adipocyte complement-related protein of 30 kilodaltons by PPARgamma agonists: a potential mechanism of insulin sensitization. Endocrinology 2002;143:998-1007.
69. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Commun 1996;221:286-9.
70. Walker BR. How will we know if 11beta-hydroxysteroid dehydrogenases are important in common diseases. Clin Endocrinol (Oxf) 2000;52:401-2.
71. Unger RH. Lipid overload and overflow: metabolic trauma and the metabolic syndrome. Trends Endocrinol Metab 2003;14:398-403.
72. Gale EA. Lessons from the glitazones: a story of drug development. Lancet 2001;357:1870-5.
73. Nathan DM. Initial management of glycemia in type 2 diabetes mellitus. N Engl J Med 2002;347:1342-9.
74. DeFronzo RA, Goodman AM, Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1995;333:541-9.
75. Viberti G, Kahn SE, Greene DA, et al. A Diabetes Outcome Progression Trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care 2002;25:1737-43.
76. Khan MA, St Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. Diabetes Care 2002;25:708-11.
77. Sakamoto J, Kimura H, Moriyama S, et al. Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. Biochem Biophys Res Commun 2000;278:704-11.
78. Malmström R, Packard CJ, Caslake M, et al. Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM. Diabetologia 1997;40:454-62.
79. Clark JM, Brancati FL, Diehl AM. Nonalcoholic fatty liver disease. Gastroenterology 2002;122:1649-57.
80. Franks S, Gilling-Smith C, Watson H, Willis D. Insulin action in the normal and polycystic ovary. Endocrinol Metab Clin North Am 1999;28:361-78.
81. Reitman ML, Arioglu E, Gavrilova O, Taylor SI. Lipoatrophy revisited. Trends Endocrinol Metab 2000;11:410-6.
82. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated amino-

transferase levels in the United States. Am J Gastroenterol 2003;98:960-7.
83. Vozarova B, Stefan N, Lindsay RS, et al. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 2002;51:1889-95.
84. Seppälä-Lindroos A, Vehkavaara S, Häkkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metab 2002;87:3023-8.
85. Ryysy L, Häkkinen AM, Goto T, et al. Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulin absorption are associated with insulin requirements during insulin therapy in type 2 diabetic patients. Diabetes 2000;49:749-58.
86. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Oliver D, Bacon BR. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. Hepatology 2003;38:1008-17.
87. Promrat K, Lutchman G, Uwaifo GI, et al. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology 2004;39:188-96.
88. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998;83:3078-82.
89. Solomon CG. The epidemiology of polycystic ovary syndrome: prevalence and associated disease risks. Endocrinol Metab Clin North Am 1999;28:247-63.
90. Nestler JE, Powers LP, Matt DW, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab 1991;72:83-9.
91. Iuorno MJ, Nestler JE. Insulin-lowering drugs in polycystic ovary syndrome. Obstet Gynecol Clin North Am 2001;28:153-64.
92. Azziz R, Ehrmann D, Legro RS, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. J Clin Endocrinol Metab 2001;86:1626-32.
93. Ghazeeri G, Kutteh WH, Bryer-Ash M, Haas D, Ke RW. Effect of rosiglitazone on spontaneous and clomiphene citrate-induced ovulation in women with polycystic ovary syndrome. Fertil Steril 2003;79:562-6.
94. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet 2000;356:1423-30.
95. Arioglu E, Duncan-Morin J, Sebring N, et al. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. Ann Intern Med 2000;133:263-74.
96. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.
97. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-52. [Erratum, Lancet 1999;354:602.]
98. *Idem*. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65. [Erratum, Lancet 1998;352:1557.]
99. Yki-Järvinen H. Combination therapies with insulin in type 2 diabetes. Diabetes Care 2001;24:758-67.
100. Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J. Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation. Health Technol Assess 2004;8(13):1-91.
101. Kumada M, Kihara S, Sumitsuji S, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;23:85-9.
102. Yki-Järvinen H, Sutinen J, Silveira A, et al. Regulation of plasma PAI-1 concentrations in HAART-associated lipodystrophy during rosiglitazone therapy. Arterioscler Thromb Vasc Biol 2003;23:688-94.
103. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 2002;106:679-84.
104. Marx N, Froehlich J, Siam L, et al. Antidiabetic PPAR gamma-activator rosiglitazone reduces MMP-9 serum levels in type 2 diabetic patients with coronary artery disease. Arterioscler Thromb Vasc Biol 2003;23:283-8.
105. Caballero AE, Saouaf R, Lim SC, et al. The effects of troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late type 2 diabetes: a placebo-controlled randomized clinical trial. Metabolism 2003;52:173-80.
106. Sidhu JS, Kaposzta Z, Markus HS, Kaski JC. Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery disease patients without diabetes mellitus. Arterioscler Thromb Vasc Biol 2004;24:930-4.
107. Charbonnel B, Dormandy JA, Erdmann E, Massi-Benedetti M. The PROactive study: preliminary baseline characteristics in 1843 patients. Diabetologia 2002;45:A107. abstract.
108. Lebovitz HE, Kreider M, Freed MI. Evaluation of liver function in type 2 diabetic patients during clinical trials: evidence that rosiglitazone does not cause hepatic dysfunction. Diabetes Care 2002;25:815-21.
109. Ljung B, Bamberg K, Dahllof B, et al. AZ 242, a novel PPARalpha/gamma agonist with beneficial effects on insulin resistance and carbohydrate and lipid metabolism in ob/ob mice and obese Zucker rats. J Lipid Res 2002;43:1855-63.
110. Katzenellenbogen JA, O'Malley BW, Katzenellenbogen BS. Tripartite steroid hormone receptor pharmacology: interaction with multiple effector sites as a basis for the cell- and promoter-specific action of these hormones. Mol Endocrinol 1996;10:119-31.
111. Riggs BL, Hartmann LC. Selective estrogen-receptor modulators — mechanisms of action and application to clinical practice. N Engl J Med 2003;348:618-29. [Erratum, N Engl J Med 2003;348:1192.]
112. Henke BR, Blanchard SG, Brackeen MF, et al. N-(2-benzoylphenyl)-L-tyrosine PPARgamma agonists. 1. Discovery of a novel series of potent antihyperglycemic and antihyperlipidemic agents. J Med Chem 1998;41:5020-36.