R E V I E W

Concomitant therapy with pioglitazone and insulin for the treatment of type 2 diabetes

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Abstract: To prevent hyperinsulinemia, which may cause atherosclerosis, thiazolidinediones (TZDs), also known as insulin sensitizers, are often added to the therapeutic regimen of patients with type 2 diabetes who are receiving insulin. The combination of insulin with pioglitazone, a TZD, reduces glycated hemoglobin (HbA_{1c}) by 0.6%–2.1%. The higher the HbA_{1c} baseline the larger the therapeutic reduction of HbA_{1c}. This combination therapy has been shown to be beneficial even in lean Japanese patients with diabetes. It should be noted that such combination therapy is much more useful when the main clinical aim is lowering not postprandial, but fasting and nocturnal glycemia. The glycemic-lowering effects of pioglitazone alone occur slowly, whereas the addition of insulin to pioglitazone often shows a dramatic glucose-lowering effect. Thus, such combination therapy increases the possibility of frequent hypoglycemia within 1 to 2 months of combining the drugs. Severe hypoglycemia in patients using this therapy is rare. Patients treated with combination therapy who show a predominant reduction of glycemia often have severe edema; in 10%–20% of patients, combination therapy leads to drug-related congestive heart failure (CHF). However, this phenomenon is usually weakened if low doses of pioglitazone which are added to insulin therapy (ie, 15 mg/day or even 7.5 mg/day for women). It is well known that pioglitazone has an anti-atherosclerotic effect, although it is unclear if hyperinsulinemia induces atherogenic changes, either directly or indirectly, by the promotion of obesity. Until now, we have not confirmed whether the anti-atherosclerotic effects of pioglitazone exceed the supposed disadvantageous action of insulin when used in combination therapy. The addition of pioglitazone tends to reduce daily insulin dosages, but study findings have not been consistent. Improvement of lipid profiles has also been weak with this combination therapy. Long-term trials are needed before any conclusions can be reached concerning atherogenic effects of treatment for type 2 diabetes. Combination therapy of even small doses of pioglitazone with insulin should be primarily used for patients who achieve insufficient reduction in glycemia with insulin monotherapy.

Keywords: pioglitazone, glycemia, insulin monotherapy, hyperinsulinemia, diabetes

Introduction

Pioglitazone was developed after troglitazone was removed from the market because of hepatotoxicity. In Japan, pioglitazone is the only thiazolidinedione (TZD) available, as rosiglitazone has not been approved for commercial use. The TZDs, also called glitazones, affect a group of nuclear receptors known as the peroxisome proliferator-activated receptors (PPAR) and subsequently enhance the effects of insulin[1,2] through a decrease in insulin resistance, without stimulating insulin release. Although some of the activity mechanisms of TZDs have been revealed, the metabolic parameters of TZDs in the body have not been fully elucidated. None of the favorable effects of

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TZDs on: tumor necrosis factor-α; adiponectin; free fatty acids; adipocyte size; or fat distribution are directly linked to glucose metabolism.

Because the main action of pioglitazone, as with other TZDs, is the reconstitution of fatty tissue, its effects on glycemia occur slowly.[3] Generally, patients require nearly 6 months of therapy before the maximum glucose-lowering effect is obtained.[3,4] Furthermore, about 50% of patients receiving pioglitazone monotherapy are "non-responders," defined as a reduction in glycosolated hemoglobin (HbA$_{1c}$) < 0.7%. In many cases, an early reduction in free fatty acids (FFA) may predict subsequent decreases in blood glucose levels;[4] however, because FFA values are easily influenced by eating, it is not always helpful to use this measurement as the only parameter for assessing potential decreases in blood glucose levels that will occur with TZDs. Generally, pioglitazone monotherapy reduces HbA$_{1c}$ levels by around 1.0%. This means that the recent key word "target of treatment," defined as an HbA$_{1c}$ of < 7.0%, can be attained when this drug is used for patients with an HbA$_{1c}$ < 8.0%. However, it is less likely to be successful in patients with an HbA$_{1c}$ ≥ 8.0%.

Unlike Western populations, Japanese patients with type 2 diabetes are more likely to be lean and primarily experience insulin deficiency. Thus, in general, sulfonylureas are relatively effective, and have been the primary therapeutic choice for Japanese patients with diabetes. In this population, sulfonylureas plus pioglitazone have also been shown to be effective. The indication for TZD treatment is suggested by a high score on the homeostasis model assessment-insulin resistance (HOMA-IR) factor, which is calculated from fasting plasma glucose, multiplied by fasting insulin concentration. A high HOMA-IR score implies that hyperinsulinemia is advantageous for TZD to exert its effects. Based on our experience, hyperinsulinemia induced endogenous insulin,[5] and/or exogenous insulin or sulfonylureas, contributes to successful pioglitazone action. The addition of pioglitazone to insulin is also widely used in lean Japanese patients with type 2 diabetes. In most lean Japanese patients with diabetes, the addition of metformin has been shown to be less effective for glucose reduction than the addition of pioglitazone.

Patients with type 2 diabetes who have inadequate responses to oral diabetic agents usually progress to insulin therapy. Recent advances in basal-supported oral therapy (BOT) have made it easy to start insulin without withdrawing oral drugs. In this therapy, other than with pioglitazone, drugs that have been used so far are usually not replaced by insulin. The addition of a small dosage of pioglitazone together with

insulin has been shown to be effective; however, there are few studies to support this. In contrast to monotherapy with glitazone, the combination therapy of glitazone and insulin often shows a rapid and large lowering effect in plasma glucose within 1 to 2 months of starting treatment. Insulin may be one of the best combination partners for pioglitazone. Because the addition of ≥30 mg pioglitazone frequently induces severe hypoglycemic events, a low starting dose of pioglitazone (15 mg/day) when added to insulin has been recommended in Japan. In cases in which insulin is added to pioglitazone therapy, the dose of pioglitazone should be decreased beforehand. There is still a need for additional data to clarify which insulin is best, that is, rapid type or once daily glargine, for combination with pioglitazone. Moreover, we have to clarify the treatment target. For example, glycemia should not be assessed only by HbA$_{1c}$, but by nocturnal glycemia and postprandial glycemia levels as well. In addition, the reduction of glycemic excursions should be regarded as an independent target of glycemia-lowering therapy.

Recently, it was shown that hyperglycemia itself induces oxidative stress that may result in apoptosis of β-cells. The need to continually increase glucose-lowering therapy reflects the progressive nature of diabetes. However, many Japanese doctors still hesitate using insulin in patients with hyperinsulinemia. Currently, patients with type 2 diabetes treated with insulin are more likely to have insulin deficiency due to a longer duration of disease in Japan.

The electronic search of scientific and medical journals (cross referencing terms of combination, pioglitazone, and insulin) yielded 1161 publications, of which only 7 studied the efficacy of a combination therapy of pioglitazone and insulin, in patients with type 2 diabetes. At present, there are few potentially relevant evidence-based publications therefore we incorporated all 7 studies into this review (Table 1).

Efficacy of the pioglitazone-insulin combination therapy
Glycemic control

Previous studies of pioglitazone with insulin therapy reported reductions in HbA$_{1c}$ ranging from 0.6% to 2.1% (Table 1). Rosenstock and colleagues[6] compared the effects of once-daily pioglitazone (15 or 30 mg) to placebo, in combination with insulin, in 566 patients (71%–75% were Caucasian) with type 2 diabetes receiving stable insulin regimens for ≥30 days who still had an HbA$_{1c}$ level ≥ 8.0%. At the end of a 16-week treatment patients receiving pioglitazone, 15 or 30 mg, showed statistically significant decreases in HbA$_{1c}$

Table 1 Summary of clinical studies evaluating the effects of combination therapy

Authors	No. of cases	Female (%)	Age (years)	BMI	Design	Combination	Follow up	Reduction	
								FPG (mg/dl)	HbA1c (%)
Rosenstock[6]	566	52.7	30–75 (range)	33.2–34.3	V	Pio 15 mg Pio 30 mg	16 weeks	−34.5 −48.0	−1.0 −1.3
Mattoo[20]	263	56.7	58.8 (mean)	31.8–32.5	BBT	Pio 30 mg	6 months	−26.1	−0.69
Ratz[17]	281	40	56 (mean)	29.5	BI	Pio 30 mg	18 weeks	−31	−0.64
Davidson[7]	690	45.4	56.3–56.6 (mean)	33.2	V	Pio 30 mg Pio 45 mg	24 weeks	−31.9 −45.8	−1.17 −1.46
Asnani[16]	20	—	18–75 (range)	—	R	Pio 30 mg	4 months		−1.6
Berhanu[21]	222	—	18–80 (range)	—	V	Pio 45 mg (titrated) (metformin involved)	20 weeks	−8.6 (insulin dose reduction study)	−1.6
Fernandez[9]	30	—	—	—	MDII	Pio 45 mg (titrated) (CSII involved)	36 weeks	−67	−2.1

Abbreviations: V, various insulin products; BBT, basal bolus treatment; BI, biphasic insulin twice a day; R, rapid alone; MDII, multiple daily insulin injection; BMI, body mass index; FPG, fasting plasma glucose; Hb1c, glycosolated hemoglobin.

levels as compared to baseline (−1.0% and −1.3% respectively; $P < 0.0001$). In that study, subjects were obese (BMI 33.2–34.3) and had plasma C-peptide levels > 0.7 µg/L. Davidson and colleagues[7] observed that patients receiving pioglitazone (45 mg) showed decreases in HbA_{1c} levels of 1.46%, whereas 1.17% in comparison with a group treated with 30 mg of pioglitazone. 64% of participants were Caucasian with 25% being African American. In that study,[7] individuals with higher baseline HbA_{1c} levels experienced a greater reduction in HbA_{1c} levels from baseline; which was also shown in a previous study of rosiglitazone.[8]

The most prominent glucose-lowering effect was described by Fernandez,[9] who showed a reduction in mean HbA_{1c} levels of 2.1% over 36 weeks of treatment in 30 Mexican-American patients; a control group was given a placebo. However, this study involved a combination therapy with pioglitazone plus continuous subcutaneous insulin infusion in 40% of participants. Furthermore, the relatively long-term period of study must be noted. As mentioned above, TZDs act slowly on glycemia as compared to sulfonylureas. This means that at least 6 months of therapy are needed to confirm the efficacy of TZDs; if efficacy is determined using HbA_{1c} levels, which change within 1 to 2 months after glycemic changes.[3] Thus, in short-term clinical studies, we may underestimate the glucose-lowering effect of TZDs if HbA_{1c} level is the only tool used to assess efficacy.

A link between the elevation of free fatty acid (FFA) levels and increasing insulin resistance during the night has been reported.[10,11] The stimulation effect of TZDs on insulin-induced FFA use was also reported.[12] We have speculated that pioglitazone lowers both FFA and glucose levels in the early morning.[3] Pioglitazone also decreases the nocturnal hepatic output of glucose, resulting in lower fasting plasma glucose (FPG) levels.[13] Japanese patients taking pioglitazone had relatively lower FPG and 1,5-anhydroglucitol (1,5-AG) levels compared to HbA_{1c} levels.[3] FPG is thought to reflect mainly nocturnal plasma glucose levels, whereas 1,5-AG, which is decreased by hyperglycemia, reflects mainly post-prandial glycemia.[14,15] HbA_{1c} is an indicator of overall daily glycemia. Generally, a 1% change in HbA_{1c} corresponds to 21 mg/dL in FPG. As shown in Table 1, nearly all studies had greater decreases in FPG than those suggested by the decreases in HbA_{1c}.

The relationship between HbA_{1c} and FPG is useful when trying to select the appropriate insulin to use in combination with TZDs. With pioglitazone, intensive insulin therapy using glargine as a basal insulin,[9] or a rapid-acting insulin[16] has been reported. However, in many trials, the type of insulin used is not fully described, and different trials have used different products. Patients using biphasic insulin aspart 30/70 (BIAsp 30) injected twice daily and showed a greater reduction in FPG as compared to HbA_{1c} (Ratz and colleagues,

Table 1).[17] Nevertheless, FPG targets were not achieved even though HbA_{1c} targets were reached. Because the portion of insulin aspart in BIAsp 30 acts to lower postprandial glucose,[18] it is likely that greater glycemic reductions could have been achieved if the insulin doses had been increased.[19] By the end of this trial, the mean BIAsp 30 dose was 0.5 U/kg in the plus pioglitazone therapy group and 0.7 U/kg in the monotherapy group (without oral diabetic agents).

Lipid profiles

Generally, pioglitazone in combination with insulin therapy significantly increases high-density lipoprotein cholesterol (HDL) and decreases triglycerides and FFA levels.[20,21] Because triglycerides frequently decrease in parallel with glycemic improvement, a reduction in triglyceride level, with combination therapy, may not depend primarily on the actions of these agents. However, it should be noted that unlike pioglitazone, rosiglitazone has been shown to increase or have a neutral effect on triglycerides.[22,23]

LDL levels are not usually influenced by pioglitazone, however, LDL particle subfractions change to favorable lipid forms. At a given LDL level, smaller LDL particles have been associated with greater cardiovascular risk than larger LDL particles.[24] Pioglitazone shifts LDL particle concentrations from small to large and increases the mean LDL particle size.[7,21] The addition of other TZDs combined with insulin has been reported to cause significant increases in LDL.[8,25,26]

Further trials with similar glycemic endpoints are needed to compare the effects of various antidiabetic regimens on lipid profiles.

Pleiotropic effects on atherosclerosis

Amelioration of vascular dysfunction and reduction in inflammatory biomarkers is not thought to be attributed solely to glycemic control or improvement in dyslipemia.[9] TZDs have been shown to result in improved cardiovascular outcomes or atherosclerotic biomarkers through various mechanisms in diabetic patients.[31] In contrast, insulin has been suggested to have atherogenic actions, especially at high blood concentrations. In combining pioglitazone with insulin therapy, it is thought that the anti-atherogenic actions of pioglitazone may exceed the negative effects of insulin in the development of atherosclerosis.[9,20] Recently, intensive insulin therapy alone has been found to reduce levels of a circulating inflammatory biomarker, highly sensitive C-reactive protein (hsCRP), as well as the formation of reactive oxygen and nitrogen species and macrophages, thus minimizing the inflammatory response.[32–34] This means that not insulin itself, but rather acute glycemic fluctuations caused by inadequate insulin therapy, may induce vascular dysfunction. Glycemic excursions have been regarded as an independent risk factor for promoting atherosclerotic changes.[35,36] Because pioglitazone does not stimulate insulin release, it is an antidiabetic drug that does not easily induce glucose fluctuations.

Pioglitazone in combination with insulin (n = 142) decreased plasminogen activator inhibitor-1 (PAI-1) (−5.10 U/mL; $P < 0.001$) and hCRP (−1.47 mg/L; $P < 0.05$) compared to placebo plus insulin (n = 147) in patients with type 2 diabetes mellitus.[20] Ethnicity was not described. Both indicators increased in the placebo group. Ratz and colleagues[17] also reported a decrease in PAI-1 levels in the subgroup of patients in which the marker was measured in their study. PAI-1 is a risk factor for progress of thrombosis.

The addition of pioglitazone to insulin restored endothelial function,[16] as assessed by flow mediated dilatation (FMD) and nitroglycerine-induced dilatation (NID) in patients with type 2 diabetes. FMD significantly improved from 10.1% ± 4.0% to 14.6% ± 6.2% ($P = 0.036$). NID showed a trend toward improvement from 13.3% ± 8.0% to 18.9% ± 5.4% ($P = 0.056$). Vascular reactivity, as assessed by changes in forearm blood flow (FBF) also improved.[9] These data provide support, and possible mechanistic insight, into the cardioprotective results of the PROactive study.[37] PRO active was a prospective, randomized, controlled trial to compare outcomes (mortality, myocardial infarction, and stroke) between pioglitazone and placebo, in 5238 patients with type 2 diabetes, who had cardiovascular disease.

Insulin dose reduction

Although there are some exceptions in protocol designs of insulin dose adjustment, many studies[7,9,20,21,38] report that pioglitazone combined with insulin lead to a reduction in insulin dosage together with better glycemic control compared to the baseline. In the hyperinsulinemic clamp study, pioglitazone demonstrated a 50% increment in insulin-mediated glucose disposal.[9] Insulin dose reductions from baseline were 4.5–6.9 U/day for pioglitazone 30 mg/day and 7.3–12 U/day for pioglitazone 45 mg/day. These reductions were about 10% from baseline, which is less than 12%–13% reductions seen with troglitazone.[8,26,39] However, in many studies, insulin dosage was not the primary endpoint and was only reduced to prevent hypoglycemia. Thus, it is impossible to simply compare the results of studies of insulin dose reduction. Further head-to-head comparison studies are needed to clarify the differences effects of various TZDs.

In terms of insulin, there is a lack of evidence concerning whether biphasic insulin or glargine (or long-acting analogue insulin) should be added to pioglitazone.

In the subanalysis of the PROactive study, addition of pioglitazone to insulin resulted in not only insulin dose reduction but success in insulin withdrawal in about 10% of patients receiving insulin.[40] Thus, insulin dose reduction by adding pioglitazone may be beneficial both for the prevention of hypoglycemia and of the promotion of atherosclerotic changes induced by hyperinsulinemia.

Safety
Hypoglycemia
Although pioglitazone monotherapy is slow to show efficacy, its addition to insulin often causes rapid glucose-lowering effects. Hypoglycemia usually occurs in the first week or weeks after starting combination therapy.[38] The frequency of hypoglycemia generally is not related to BMI, as it is pioglitazone alone. Rather, hypoglycemia with combination therapy is attributable to longer duration of diabetes.[7] Almost all hypoglycemic events were considered mild without deep coma,[21,41] and most were self-treated with caloric intake or could be easily avoided by an appropriate reduction in daily insulin dosage. A total of 15% of patients receiving 30 mg of pioglitazone with insulin reported hypoglycemia.[6] The group was composed of 188 mainly Caucasian patients with a BMI of 34.3. However, until now hypoglycemic events have been recorded based on data from questionnaires. The use of a continuous glucose monitoring system will allow us to track hypoglycemia in patients who may be unaware of its occurrence.

Treatment doses should not be lowered or discontinued immediately just because of hypoglycemia, because the hypoglycemia itself indicates that therapy is lowering blood glucose levels. In Japan, pioglitazone 15 mg/day is usually added to insulin therapy to avoid hypoglycemia; a dose of 7.5 mg/day is used in women. In the case of moderate to severe hypoglycemia, a dose of 7.5 mg every other day may be used.

Edema and congestive heart failure (CHF)
Plausible mechanisms for the increase in mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[42] in which the majority of patients were treated with rosiglitazone and insulin, include a significant weight gain.[43] Weight gain can be attributed to water retention and/or increase in body fat.

Edema is usually dominant, and severe, in patients who respond to TZDs therapy. The overall occurrence of edema in combination therapy has been shown to be 10% to 20%.[21] According to the manufacturer's report, TZDs caused fluid retention in 2%–5% of patients receiving monotherapy; this increases to 5%–15% among patients receiving concomitant insulin therapy.[38] However, these incidences may be influenced by differences in the characteristics of the study populations, including whether participants have a high risk of macrovascular disease.

Edema from TZDs occurs in the lower limbs as well as the face; it can also occur in one ankle only.[44] These symptoms are different from that the edema that usually accompanies CHF.

Recent meta-analysis of three randomized controlled trials showed an odds ratio (OR) of 2.1 (95% CI 1.08–4.08; $P = 0.03$) for the risk of CHF with TZDs compared with placebo.[45] Another meta-analysis[46] also confirmed that patients given TZDs had increased risk for the development of CHF (relative risk [RR] 1.72, 95% Cl 1.21–2.42, $P = 0.002$). The results showed no heterogeneity of effects across studies, which indicated a class effect for TZDs. It is also well-known that insulin can cause water retention in the body through activating epithelial sodium channels in the collecting tubules.[47,48] Thus, edema from TZDs is both dose-dependent, and greater, when these agents are used in combination with insulin[6,8,20,21] than when they are used alone. CHF occurs in approximately 1.0% of patients receiving pioglitazone.[6,49] The US Food and Drug Administration-approved prescribing information for pioglitazone shows that 1.1% of patients treated with pioglitazone plus insulin develop CHF compared with no patients in the group receiving insulin alone. Therefore, TZDs should be used with caution in patients with diabetes who are predisposed to heart failure, as well as in the elderly or in those receiving insulin.[50] Some studies have reported that pulmonary edema develops after treatment with TZDs.[51,52] Older age, longer duration of diabetes, and the use of high doses of insulin (82, 140 and 740 U/day) appear to be risk factors for the development of pulmonary edema.[38]

Edema or fluid retention can cause CHF. However, only in a minority of edema cases induced by TZD treatment are associated with CHF. Furthermore, fluid retention following the use of TZDs is not accompanied by decreased left ventricular dysfunction.[53,54] Pioglitazone induces elevation of plasma brain natriuretic peptide (BNP) level.[55] In most cases, BNP increases slightly, or moderately, (to <70–100 pg/mL)[56] which is the value that suggests the presence of CHF. Recently, "vascular leak syndrome" has been noted after treatment with TZDs. Although the mechanisms of this phenomenon are not clear, an enhancement in endothelially-mediated vasodilatation[57] or an increase in vascular permeability through augmentation of vascular endothelial growth factor[58,59] are suggested causes.

Further studies are required to establish the safety of glitazone and insulin in combination to treat patients with diabetes and CHF and/or cardiovascular events.[60,61]

Patients receiving TZDs, including pioglitazone, show remarkable weight increases of about 5 kg.[62,63] The weight gain occurs during the first weeks of treatment and tend to stabilize thereafter. In some cases, increases in body weight still continue up to two to three years. Weight gain has also been observed with TZDs in combination with insulin,[6] and was strongly correlated with decreases in HbA$_{1c}$ levels (r = 0.8844; P = 0.002). The reason TZDs cause weight gain may be related to increases in total body fluid volume caused by edema. However, other causes may also contribute to weight gain, including increased fat accumulation and redistribution.[38]

Adipogenesis and increases in body fat

Treatment with TZDs often causes an increase in body fat. Unlike in Western countries, most patients with diabetes in Japan are not obese. Weight gain can be seen mainly in patients with obesity and correlates with the drug's effectiveness in lowering glycemia. Stimulation of PPARγ is supposed to increase feeding and adipogenic efficiency; however, details regarding these effects remain unclear. Troglitazone was reported to lower plasma leptin levels and increase hunger in humans.[64]

Many studies[65–67] have now shown that TZDs increase the amount of subcutaneous fat, whereas the amount of visceral fat is unchanged. These differential effects may be related to the observation that PPARγ are more highly expressed in subcutaneous than omental preadipocytes.[68] It is also known that the differentiating capacity of subcutaneous adipocyte precursor cells is higher than that of visceral fat precursor cells.

The addition of TZDs to insulin is likely to augment the fat-accumulating effect of each agent. For rosiglitazone and insulin combination therapy, body weight was shown to increase significantly, but the waist-to-hip ratio did not change.[8] Weight gain was more common in patients treated with BIAsp 30 plus pioglitazone (8% of patients) than in those treated with BIAsp 30 monotherapy (3%) or glibenclamide plus pioglitazone (2%).[17]

The negative effects of weight gain on glycemic control and metabolism on a long-term basis have not been extensively investigated. Obesity may induce secondary failure of TZD therapy. Although the frequency of secondary failure is thought to be relatively less than that seen with sulphonylurea, a significant re-elevation of HbA$_{1c}$ has been observed 56 weeks after starting pioglitazone therapy in a Japanese phase II study (unpublished data). Losing dietary therapy should be followed closely in patients being treated with TZDs.

Liver injury

The combination of pioglitazone with insulin does not significantly alter the relationship between pioglitazone treatment and liver damage in patients with type 2 diabetes. In a multicenter study, no patient in the pioglitazone 15 mg plus insulin group had an alanine aminotransferase (ALT) level >3 × the upper limit of normal.[6] In contrast to troglitazone, pioglitazone has no potential hepatotoxicity in patients with type 2 diabetes, including those treated with insulin.[38]

Bone fracture

Bone fracture risk with rosiglitazone has emerged in A Diabetes Octcome Progression Trial (ADOPT).[69] Recent meta-analysis showed that long-term TZDs, including pioglitazone, use doubles (OR 2.23, 95% CI 1.65–3.01; P < 0.001) the risk of fractures among women with type 2 diabetes.[70] TZDs exposure was also associated with significant change in bone mineral density at the lumbar region of the spine and the hip.[70] TZDs increased adiposity of bone marrow, decreasing osteoblast activity, and increased bone resorption.[71,72] The meta analysis involved around 45,000 participants, thus, the number of patients involved undergoing combination therapy was high. The study suggested a long-term effect of the drug, which may not be avoided by slow-dose titration. Whether combination therapy with insulin increases the risk of fractures is still unclear and will require further long-term study.

New regimen, basal supported oral therapy (BOT)

Success in attaining strict glycemic control in newly diagnosed diabetes will influence long-term outcomes.[73] In fact, aging and hyperglycemia are major causes of oxidant stress, which stimulates apoptosis of pancreatic β-cells. Because β-cells have weak regenerative potential it is important to reduce hyperglycemia as early as possible after diabetes is diagnosed. Insufficient achievement of glycemic control can induce glycemic fluctuations and further development of diabetic complications.

It has been reported that insulin monotherapy for patients with type 2 diabetes does not lead to HbA$_{1c}$ levels < 7.0%, especially when used for long periods. The reason for this lack of change in HbA$_{1c}$ levels may be related to the factors discussed

above. There is yet no set algorithm on how to add oral anti-diabetic agents to insulin monotherapy in patients with type 2 diabetes. Although, the addition of TZDs to patients who have failed to respond to insulin monotherapy may be beneficial, as in those patients who have strong insulin resistance; metformin or glimepiride are the most frequently chosen agents, probably in an effort to avoid adverse effects, such as weight gain. It was reported that patients who had oral antidiabetic drugs added to their insulin therapy were less likely to attain glycemic control than those treated with insulin monotherapy.[74] The effectiveness and safety of adding pioglitazone to patients in whom combination therapy with insulin, sulfonylureas, and metformin have failed has not been evaluated.

Alternatively, insulin therapy for patients for whom oral agents have failed, called basal supported oral therapy (BOT), has gained increasing support because of its ease of use and safety.[75] It should be noted, however, that a consensus on its algorithm has not been reached, and the definition of this therapy remains unclear. The addition of insulin to a monotherapy drug may be even included in this therapy. In a recent consensus algorithm[76] reported by the ADA and EASD, only the combination of metformin plus insulin is recommended in Tier 1 therapy. Use of pioglitazone in the BOT regimen has not been assessed.

In the BOT regimen, if a long-acting analogue insulin is chosen for insulin treatment, management of postprandial hyperglycemia may be insufficient. The algorithm recommended by the ADA and EASD lacks data regarding postprandial hyperglycemia except for the glucagon-like peptide-1 (GLP-1) analogue used in Tier 2 therapy. Unlike in the United States, α-glucosidase inhibitors (α-GI) are frequently used in Japan. Combination therapy of α-GI and insulin is beneficial to prevent glucose excursions and/or hypoglycemia. The addition of glinides to insulin is also useful. Pioglitazone may be a good partner for these drugs to prevent postprandial hyperglycemia. However, additional studies are needed to support the addition of pioglitazone to rapid, ultra rapid analogue or mixed type insulin.

Conclusions

The combination of pioglitazone with insulin may enhance glycemic control beyond the level achieved by insulin alone. It may also help to reduce insulin dosages in patients already receiving insulin. From a safety perspective, pioglitazone should be started at a low dose in patients already receiving insulin, or be reduced to a lower dose in patients who are already receiving pioglitazone who are going to start insulin therapy. If frequent hypoglycemia and/or edema occur with

the additional of pioglitazone, the drug can be withdrawn and started again at a lower dose or once every other day after 3 to 4 months. If CHF occurs, pioglitazone should be stopped. Mild CHF and edema are usually manageable by reducing the dose of pioglitazone and/or adding a diuretic. Monitoring of plasma BNP may be useful to predict the occurrence CHF, because many patients with diabetes have asymptomatic cardiac failure. Patients should also be told to avoid dietary salt if they experience edema and should be instructed to follow a low-calorie diet. Despite the need for prudence, combination therapy with pioglitazone and insulin should be considered for the patients with poor glycemic control.

Disclosures

The authors report no conflicts of interest in this work.

References

1. Willson TM, Lambert MH, Kliewer SA. Peroxisome proliferator-activated receptorgamma and metabolic disease. *Annu Rev Biochem*. 2001;70:341–367.
2. Stumvoll M, Haring HU. Glitazones: clinical effects and molecular mechanism. *Ann Med*. 2002;34(3):217–224.
3. Yamanouchi T, Sakai T, Igarashi K, Ichiyanagi K, Watanabe H Kawasaki T. Comparison of metaboric effects of pioglitazone, metformin, and glimepiride over 1 year in Japanese patients with newly diagnosed type 2 diabetes. *Diabet Med*. 2005;22(8):980–985.
4. Tan M, Johns D, Gálvez GG, et al; for the GLAD Study Group. Effects of pioglitazone and glimepiride on glycemic control and insulin sensitivity in Mexican patients with type 2 diabetes mellitus: a multicenter, randomized, double-blind, parallel-group trial. *Clin Ther*. 2004;26(5):680–693.
5. Pfützner A, Forst T. Pioglitazone-an antidiabetic drug with the potential to reduce cardiovascular mortality. *Expert Opin Pharmacother*. 2006;7(4):463–476.
6. Rosenstock J, Einhorn D, Hershon K, Glazer NB, Yu S; the Pioglitazone 014 Study Group. Efficacy and safety of pioglitazone in type 2 diabetes: A randomized, placebo-controlled study in patients receiving stable insulin therapy. *Int J Clin Pract*. 2002;56(4):251–257.
7. Davidson JA, Perez A, Zhang J; The Pioglitazone 343 Study Group. Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: results of a double-blind, multicentre, randomized study. *Diabetes Obes Metab*. 2006;8(2):164–174.
8. Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J; Rosiglitazone Clinical Trials Study Group. A randomized trial of rosiglitazone therapy in patient with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care*. 2001;24(7):1226–1232.
9. Fernandez M, Triplitt C, Wajcberg E, et al. Addition of pioglitazone and ramipril to intensive insulin therapy in type 2 diabetic patients improves vascular dysfunction by different mechanisms. *Diabetes Care*. 2008;31(1):121–127.
10. Reaven GM, Hollenbeck C, Jeng CY, Wu MS, Chen YD. Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM. *Diabets*. 1988;37(8):1020–1024.
11. Boden G, Chen X, Urbain JL. Evidence for a circadian rhythm of insulin sensitivity in patients with NIDDM caused by cyclic changes in hepatic glucose production. *Diabetes*. 1996;45(8):1044–1050.
12. Oakes ND, Thalen PG, Jacinto SM, Ljung B. Thiazolidinediones increase plasma-adipose tissue FFA exchange capacity and enhance insulin-mediated control of systemic FFA availability. *Diabetes*. 2001;50(5):1158–1165.

13. 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(4):710–719.

14. Kishimoto M, Yamasaki Y, Kubota M, et al. 1,5-Anhydro-D-glucitol evaluates daily glycemic excursions in well-controlled NIDDM. *Diabetes Care*. 1995;18(8):1156–1159.

15. Yamanouchi T, Inoue T, Ogata E, et al. Post-load glucose measurements in oral glucose tolerance tests correlate well with 1,5-anhydroglucitol, an indicator of overall glycemic state, in subjects with impaired glucose tolerance. *Clin Sci*. 2001;101(3):227–233.

16. Asnani S, Kunhiraman B, Jawa A, Akers D, Lumpkin D, Fonseca V. Pioglitazone restores endothelial function in patients with type 2 diabetes treated with insulin. *Metab Syndr Relat Disord*. 2006;4(3):179–184.

17. Ratz I, Stranks S, Filipczak R, et al. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: An 18-week, randomized, open-label study. *Clin Ther*. 2005;27(9):1432–1443.

18. Hermanson K, Colombo M, Storgaard H, et al. Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. *Diabetes Care*. 2002;25(5):883–888.

19. Raskin P, Allen E, Hollander P, et al; for the INITIATE Study Group. Initiating insulin therapy in type 2 diabetes: A comparison of biphasic and basal insulin analogs. *Diabetes Care*. 2005;28(2):260–265.

20. Mattoo V, Eckland D, Widel M, et al. Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: results of a six-month, randomized, double-blind, prospective, multicenter, parallel-group study. *Clin Ther*. 2005;27(5):554–567.

21. Berhanu P, Perez A, Yu S. Effect of pioglitazone in combination with insulin therapy on glycemic control, insulin dose requirement and lipid profile with type 2 diabetes previously poorly controlled with combination therapy. *Diabetes Obes Metab*. 2007;9(4):512–520.

22. Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dislipidemia. *Diabetes Care*. 2005;28(7):1547–1554.

23. Buse JB, Tan MH, Prince MJ, Erickson PP. The effects of oral anti-hyperglycemic medications on serum lipid profiles in patients with type 2 diabetes. *Diabetes Obes Metab*. 2004;6(2):133–156.

24. Lamarche B, St Pierre AC, Ruel IL, Cantin B. A prospective, population-based study of low density lipoprotein particle size as a risk factor for ischemic heart disease in men. *Can J Cardiol*. 2001;17(8):859–865.

25. Buse JB, Gumbiner B, Mathias NP, et al. for the Troglitazone insulin study group. Troglitazone use in insulin-treated type 2 diabetic patients. *Diabetes Care*. 1998;21(9):1455–1461.

26. Strowig SM, Aviles-Santa ML, Raskin P. Comparison of insulin mono-therapy and combination therapy with insulin and metformin or insulin and troglitazone in type 2 diabetes. *Diabetes Care*. 2002;25(10):1691–1698.

27. Natali A, Baldeweg S, Toschi E, et al. Vascular effects of improving metabolic control with metformin/rosiglitazone in type 2 diabetes. *Diabetes Care*. 2004;27(6):1349–1357.

28. Pfützner A, Marx N, Lubben G, et al. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the Pioneer Study. *J Am Coll Cardiol*. 2005:45(12):1925–1931.

29. Wajcberg E, Stiwijilkamol A, Musi N, DeFronzo R, Cersosimo E. Relationshiop between vascular reactivity and lipids in Mexican Ameri-can with T2DM treated with pioglitazone. *J Clin Endoclinol Metab*. 2007;92(4):1256–1262.

30. Hohberg C, Pfütznen A, Forst T, et al. Successful switch from insulin therapy to treatment with pioglitazone in type 2 diabetes with residual β-cell function: results from the PioSwitch Study. *Diabetes Obes Metab*. 2009;11(5):464–471.

31. Potenza MA, Addabbo F, Montagnani M. Vascular actions of insulin with implications for endothelial dysfunction. *Am J Physiol Endocrinol Metab*. 2009;297(3):E568–E577.

32. Dandona P, Ajada A, Mohanty P, et al. Insulin inhibits intra-nuclear factor κB and stimulates IκB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab*. 2001;86(7):3257–3265.

33. Evans JL, Goldfine IA, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endcr Rev*. 2002;23(5):599–622.

34. Van den Berghe G. How dose blood glucose control with insulin saves lives in intensive care? *J Clin Invest*. 2004;114(9):1187–1195.

35. International Diabetes Federation: Guideline for management of postmeal glucose. 2007 Available from: www.idf.org.

36. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*. 2008;57(5): 1349–1354.

37. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROactive pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366(9493):1279–1289.

38. Scheen AJ. Combined thiazolidinedione-insulin therapy. Should we be concerned about safety? *Drug Safety*. 2004;27(12):841–856.

39. Schwartz S, Raskin P, Fonseca V, Graveline JF. Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. Troglitazone and Exogenous Insulin Study Group. *N Engl J Med*. 1998;338(13):861–866.

40. Scheen A, Charbonnel B, Belgium L, France N. Reduced insulin requirements and improved glycemic control with pioglitazone in insulin-treated patients with type 2 diabetes: results from PROactive. ADA 66th Scientific Sessions 2006;561-P.

41. Cryer PE, Davis SN. Hypoglycemia in diabetes. *Diabetes Care*. 2003;26(6):1902–1912.

42. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545–2559.

43. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA diabetes trials. *Diabetes Care*. 2009;32(1):187–192.

44. Bell DSH. Unilateral edema due to a thiazolidinediones [letter]. *Diabetes Care*. 2003;26(9):2700.

45. Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure. *Diabetes Care*. 2007;30(8):2148–2153.

46. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. *Lancet*. 2007;370(9593):1129–1136.

47. DeFronzo RA. The effect of insulin on renal sodium metabolism: a review with clinical implications. *Diabetologia*. 1981;21(3):165–171.

48. Muscelli E, Natali A, Bianchi S, et al. Effect of insulin on renal sodium and uric acid handling in essential hypertension. *Am J Hypertens*. 1996;9(8):746–752.

49. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs. glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes. The PERISCOPE randomized control trial. *JAMA*. 2008;299(13):1561–1573.

50. Delea TE, Edelsberg JS, Hagiwara M, et al. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. *Diabetes Care*. 2003;26(11):2983–2989.

51. Kermani A, Garg A. Thiazolidinedione-associated congestive heart fail-ure and pulmonary edema. *Mayo Clin Proc*. 2003;78(9):1088–1091.

52. Cheng AY, Fantus IG. Thiazolidinedione-induced congestive heart failure. *Ann Pharmacother*. 2004;38(5):817–820.

53. Ghazzi MN, Perez JE, Antonucci TK, et al; the Troglitazone Study Group. Cardiac and glycemic benefits of troglitazone treatment in NIDDM. *Diabetes*. 1997;46(3):433–439.

54. St John Sutlon M, Rendall M, Dandona P, et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2002;25(11):2058–2064.

55. Ogawa S, Takeuchi K, Ito S. Plasma BNP levels in the treatment of type 2 diabetes with pioglitazone. *J Clin Endocrinol Metab*. 2003;88(8):3993–3996.

56. Shirabe S, Sasamoto K, Araki A, et al. BNP elevation following 12-week pioglitazone treatment in patients with type 2 diabetes. *Diabetologia*. 2009;52(Suppl 1):S335.

57. Niemeyer NV, Janney LM. Thiazolidinedione-induced edema. *Pharmacotherapy*. 2002;22(7):924–929.

58. Fukunaga Y, Itoh H, Doi K, et al. Thiazolidinediones, peroxisome proliferator-activated receptor-gamma agonists, regulate endothelial cell growth and secretions of vasoactive peptides. *Atherosclerosis*. 2001;158(1):113–119.

59. Emoto M, Anno T, Sato Y, et al. Troglitazone treatment increases plasma vascular endothelial growth factor in diabetic patients and its mRNA in 3T3-L1 adiposities. *Diabetes*. 2001;50(5):1166–1170.

60. Duan SZ, Usher MG, Mortensen RM. Peroxisome proliferator-activated receptor-gamma-mediated effects in the vasculature. *Circ Res*. 2008;102(3):283–294.

61. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes. The PERISCOPE Randomized Controlled Trial. *JAMA*. 2008;299(13):1561–1573.

62. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351(11): 1106–1118.

63. Chilcott J, Tappenden P, Lloyd JM, et al. A systematic review of the clinical effectiveness of pioglitazone in the treatment of type 2 diabetes mellitus. *Clin Ther*. 2001;23(11):1792–1823.

64. Shimizu H, Tsuchiya T, Sato N, et al. Troglitazone reduces plasma leptin concentrations but increases hunger in NIDDM patients. *Diabetes Care*. 1998;21(9):1470–1474.

65. 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(6):2784–2791.

66. Shadid S, Jensen MD. Effects of pioglitazone versus diet and exercise on metabolic health and fat distribution in upper body obesity. *Diabetes Care*. 2003;26(11):3148–3152.

67. Larsen TM, Toubro S, Astrup A. PPAR gamma agonists in the treatment of type II diabetes: is increased fatness commensurate with long-term efficacy? *Int J Obes Relat Metab Disord*. 2003;27(2):147–161.

68. Sewter CP, Blows F, Vidal-Puig A, et al. Regional differences in the response of human pre-adipocytes to PPAR gamma and RXR alpha agonists. *Diabetes*. 2002;51(3):718–723.

69. Kahn SE, Haffner SM, Heise MA, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy [erratum in *N Engl J Med*. 2007;356:1387–1388]. *N Engl J Med*. 2006;355(23):2427–2443.

70. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidin-ediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ*. 2009;180(1):32–39.

71. Schwartz AV, Sellmeyer DE, Vittinghoff E, et al. Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab*. 2006;91(9):3349–3354.

72. Wan Y, Chong LW, Evans RM. PPAR-gamma regulates osteoclasto-genesis in mice. *Nat Med*. 2007;13(12):1496–1503.

73. Retnakaran R, Drucker D. Intensive insulin therapy in newly diagnosed type 2 diabetes. *Lancet*. 2008;371(9626):1725–1726.

74. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among US adults diagnosed with type 2 diabetes: A preliminary report. *Diabetes Care*. 2004;27(1):17–20.

75. Bretzel RG, Nuber U, Landgraf W, et al. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. *Lancet*. 2008;371(9618):1073–1084.

76. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32(1):193–203.