Targeting the pathophysiology of type 2 diabetes: rationale for combination therapy with pioglitazone and exenatide

Stanley Schwartz
University of Pennsylvania, Philadelphia, PA, USA

ABSTRACT

Objective: The objectives of this article are to review the pathophysiology of type 2 diabetes mellitus (T2DM), present the rationale for a pathophysiologically based treatment approach for patients with T2DM and discuss the role of the therapeutic combination of pioglitazone and exenatide in the management of T2DM.

Methods: References were identified from searches of the PubMed database that were conducted in May 2007, October 2007 and March 2008 and updates to product labeling that occurred between May 2007 and December 2007. Information was selected for inclusion on the basis of its relevance to the pathophysiology of T2DM or the clinical use of thiazolidinediones or exenatide. Discussion of other anti-diabetic treatment strategies is not included.

Results: T2DM results from a combination of insulin resistance and beta-cell dysfunction. The combination of a thiazolidinedione and an incretin mimetic offers a combination of characteristics (e.g., glycemic control, reduced insulin resistance, decreased weight, potential cardiovascular benefits, beta-cell preservation) that addresses many of the pathophysiologic underpinnings of T2DM. A recent small placebo-controlled study assessed the effects of exenatide used with a thiazolidinedione (TZD; pioglitazone or rosiglitazone) with or without metformin. Exenatide demonstrated a greater incidence of glycosylated hemoglobin (HbA1c) < 7%; greater reductions in fasting blood glucose, postprandial plasma glucose and body weight; and improved beta-cell function versus the TZD/placebo group. However, exenatide was associated with a high dropout rate, and the 16-week duration of treatment in this study precluded evaluation of the long-term effects of the exenatide/pioglitazone combination. Furthermore, exenatide/pioglitazone has not been compared with any other anti-diabetic combination in a head-to-head clinical study.

Conclusions: Dual effects on insulin sensitivity (TZD) and insulin secretion (exenatide) make the TZD/exenatide combination a rational treatment option for patients who do not attain glycemic control with a single agent. Studies undertaken to evaluate the effects on cardiovascular outcomes and the potential for prevention of T2DM with impaired glucose tolerance may reveal additional advantages of this combination approach.

Introduction

Diabetes is a chronic illness characterized by hyperglycemia that carries with it a high incidence of microvascular and macrovascular complications. The prevalence of type 2 diabetes mellitus (T2DM) is expected to increase as the population ages and as the prevalence of risk factors such as obesity and the metabolic syndrome continues to rise. Aggressive glycemic control has been shown to significantly reduce the risk of microvascular complications of T2DM, with a trend toward reduction in macrovascular complications in the United Kingdom Prospective Diabetes Study. Results from the recent Veterans Administration
Diabetes Trial (VADT) showed that while aggressive glucose control did not significantly lower the risk of cardiovascular events relative to standard therapy in the overall study population, there was a possible protective effect in those with a shorter duration of diabetes\(^5\). However, recent results from the ADVANCE (Action in Diabetes and Vascular Disease) and ACCORD (Action to Control Cardiovascular Risk in Diabetics) studies failed to demonstrate macrovascular benefits in patients undergoing intensive glycemic control\(^3,4\). Thus, improved glucose control in and of itself may not reduce macrovascular disease in a cause-and-effect manner in patients with T2DM\(^6\). The objectives of this article are to review the pathophysiology of T2DM, present the rationale for a pathophysiologically based treatment approach for patients with T2DM and discuss the role of new therapeutic combinations in providing aggressive glucose control, thus minimizing the risk of hypoglycemia and potentially preserving beta-cell function and improving cardiovascular (CV) outcomes in patients with T2DM.

**Methods**

This review encompasses literature selected from searches of the PubMed database that were conducted in May 2007, October 2007 and March 2008 and updates to product labeling that occurred between May 2007 and December 2007. The following terms were employed in the searches: \textit{pioglitazone and type 2 diabetes}, \textit{rosiglitazone and type 2 diabetes}, \textit{exenatide and type 2 diabetes}, \textit{PPAR-gamma and type 2 diabetes}, \textit{GLP-1 and type 2 diabetes} and \textit{pathophysiology and type 2 diabetes}. Searches were limited to articles published in English from 1995 to 2008. Results of these searches were reviewed and references were selected for inclusion on the basis of relevance to the pathophysiology of T2DM or the clinical use of thiazolidinediones or exenatide. Reference lists of the selected articles were then examined for additional references of relevance that were not identified during the initial searches.

**Pathophysiology of type 2 diabetes mellitus**

T2DM is a disease with a strong genetic component, as suggested by differences in incidence among ethnic groups, aggregation in families and concordance rates in twin studies\(^7\). Environmental factors, such as stress, diet and amount of exercise, also play a role. The interaction of these genetic and environmental factors leads to insulin resistance, abnormal beta-cell function and, ultimately, the development of T2DM when compensatory increases in insulin secretion can no longer keep plasma glucose levels within normal limits\(^8\).

**Insulin resistance**

Insulin resistance is defined as impairment in the ability to respond to insulin. The mechanisms by which obesity and diabetes are inter-related involve the release by visceral adipose tissue of increased quantities of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other tissue factors and a reduction in adiponectin; these combined factors promote insulin resistance\(^9\) and lower insulin secretion through impaired beta-cell function in individuals susceptible to diabetes\(^9\). These same factors are associated with endothelial dysfunction and inflammatory changes in endothelium that further exacerbate the atherosclerotic process associated with obesity, insulin resistance, the metabolic syndrome and diabetes.

**Abnormal islet-cell function**

In the non-diabetic person, a reduction in glucagon secretion and an increase in insulin secretion occur after glucose ingestion; these changes are necessary to maintain glucose levels within normal ranges\(^10\). The endocrine response to glucose ingestion may be similar in patients with pre-diabetes or T2DM, but the increase in insulin may not be sufficient to maintain normal glucose levels. Hyperglycemia results in T2DM when pancreatic beta cells are unable to release enough insulin to compensate for increased peripheral insulin resistance; this reaction is likely due to genetic abnormalities and often is exacerbated by other events, such as changes in beta-cell function induced by the presence of non-esterified fatty acids (e.g., lipotoxicity)\(^9\), or by glucotoxicity. Abnormal islet-cell function is typified by loss of first-phase insulin secretion, reduced incretin effects and concurrent increased glucagon output by pancreatic alpha cells\(^11\). Table 1 summarizes the types and functions of hormones involved in glucose regulation.

**Loss of first-phase insulin response and postprandial hyperglycemia**

Early on in beta-cell dysfunction, loss of first-phase insulin response leads to postprandial hyperglycemia, which is the earliest detectable glycemic abnormality in most patients with T2DM\(^12\) and those with pre-diabetes\(^13\); it correlates more closely with glycosylated hemoglobin (HbA\(_1c\)) than with fasting plasma...
glucose (FPG) levels. This is one of the reasons that some have suggested that the American Diabetes Association (ADA) re-evaluate the thresholds for the diagnosis of diabetes. In the United Kingdom Prospective Diabetes Study, HbA1c levels remained above target levels even when patients had achieved target FPG levels. This finding seemed counter-intuitive until a separate study that analyzed the glyemic profiles of 290 consecutive clinic patients with T2DM reported that, at HbA1c levels approaching the ADA-recommended treatment goal of 7.0%, postprandial plasma glucose (PPG) accounted for a disproportionate amount of the individual’s glyemic burden – as much as 75%. These results underscored the importance of targeting both PPG and FPG as part of the T2DM treatment strategy.

Postprandial hyperglycemia independently predicts a person’s risk for CV disease or mortality, possibly in relation to the increased incidence of hypertension (odds ratio, 1.36) in patients with elevated PPG. People with normal FPG but elevated PPG levels are at greater risk for excessive CV mortality, whereas the predictive ability of an elevated FPG level for higher risk is largely dependent on the presence of elevated PPG. PPG excursions also have been associated with an increase in carotid intima-media thickness (CIMT), a validated surrogate marker for atherosclerosis, as well as with the release of a cascade of other atherogenic events. Decreasing PPG levels have been shown to reduce inflammatory markers and to have a beneficial effect on oxidative stress and endothelial function.

Given these considerations, it seems that antihyperglycemic strategies should continue to include efforts to maintain PPG levels below those recommended by the ADA (peak level < 180 mg/dL), especially if these levels can be achieved without causing hypoglycemia.

**Diminished incretin hormone effect**

The principle that gastrointestinally derived hormones affect the body’s insulin response to glucose challenge was demonstrated in 1986 by a differential insulin response to intravenous versus oral glucose administration, despite nearly identical levels of glycemia. The hormones responsible for this effect, known as incretins, are essential to normal glucose metabolism and are closely involved with the control of glucose after a meal.

Of the incretin hormones that have been identified, glucagon-like peptide 1 (GLP-1) exhibits features that have prompted clinical interest in this hormone as a therapeutic target in diabetes. The actions of GLP-1 include release of glucose-dependent insulin, glucose-dependent suppression of glucagon secretion, a slowed rate of gastric emptying, promotion of satiety and preservation of beta-cell health (Table 1). Pioglitazone and exenatide treatment for type 2 diabetes, especially if these levels can be achieved without causing hypoglycemia.

**Table 1. Hormones involved in glucose regulation**

<table>
<thead>
<tr>
<th>Pancreas</th>
<th>Intestine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell type: hormone</strong></td>
<td><strong>Cell type: hormone</strong></td>
</tr>
<tr>
<td>Alpha cells: glucagon</td>
<td>L cells: glucagon-like peptide 1</td>
</tr>
<tr>
<td>Stimulates breakdown of stored liver glycogen</td>
<td>Enhances glucose-dependent insulin secretion</td>
</tr>
<tr>
<td>Promotes hepatic glucose output</td>
<td>Decreases glucose-dependent glucagon secretion</td>
</tr>
<tr>
<td>Beta cells: insulin</td>
<td>Reduces PPG levels</td>
</tr>
<tr>
<td>Affects glucose metabolism and nutrient storage</td>
<td>Slows gastric emptying</td>
</tr>
<tr>
<td>Promotes uptake of glucose by cells</td>
<td>Promotes satiety/reduces food intake → reduces body weight</td>
</tr>
<tr>
<td>Suppresses PPG levels</td>
<td>Promotes beta-cell health</td>
</tr>
<tr>
<td>Promotes protein and fat synthesis</td>
<td></td>
</tr>
<tr>
<td>Promotes use of glucose for energy</td>
<td></td>
</tr>
<tr>
<td>Beta cells: amylin</td>
<td></td>
</tr>
<tr>
<td>Suppresses PPG levels through several mechanisms</td>
<td></td>
</tr>
<tr>
<td>Decreases glucagon secretion</td>
<td></td>
</tr>
<tr>
<td>Slows gastric emptying</td>
<td></td>
</tr>
<tr>
<td>Promotes satiety/reduces food intake → reduces body weight</td>
<td></td>
</tr>
<tr>
<td>PPG = postprandial plasma glucose</td>
<td></td>
</tr>
</tbody>
</table>

been shown to reduce hepatic glucose production indirectly by increasing the body’s ratio of insulin to glucagon\textsuperscript{23}. GLP-1 has the potential to normalize fasting plasma glucose (FPG) in patients with T2DM when given intravenously\textsuperscript{24} or subcutaneously\textsuperscript{25}. In experimental models of diabetes, GLP-1 receptor activation promoted beta-cell proliferation, inhibited beta-cell apoptosis and increased functional islet-cell mass, which led to delay of diabetes onset in mice\textsuperscript{21,26}. Further, GLP-1 receptors play a crucial role in cardiac function, as demonstrated by reduced resting heart rate and elevated left ventricular (LV) end-diastolic pressure in mice with genetic deletion of GLP-1\textsuperscript{27}.

**Overview of T2DM treatment goals**

The pathophysiology of T2DM provides a logical construct for successful treatment. Principles emphasized include treating insulin resistance and abnormal islet-cell function, avoiding hypoglycemia, reducing weight, minimizing weight gain, preserving beta-cell function and reducing CV risk factors and CV outcomes. Combination therapy is increasingly considered the optimal way to achieve as many of these goals as possible. Long-term micro-/macrovascular outcomes data are not yet available for exenatide, and the macrovascular outcomes data forTZDs are controversial. However, the combination of a TZD (such as pioglitazone) and an incretin mimetic (such as exenatide) offers a blend of characteristics (e.g., glycemic control, decreased weight, potential CV benefits, beta-cell preservation) that may be very useful for many patients in the management of T2DM. Ideally, the clinical characteristics of each agent used should be matched to the clinical characteristics of the patient who is being treated. Table 2 provides an overview of currently available non-insulin therapies from a clinical perspective, along with information on expected efficacy, patient selection and special concerns\textsuperscript{28}.

**Thiazolidinediones**

At present, the TZD class of drugs contains pioglitazone and rosiglitazone. However, differences exist within the class because individual peroxisome proliferator–activated receptor (PPAR\textsuperscript{–}\gamma) agonists have differential effects on gene transcription\textsuperscript{29,30} and thus have some differing effects. Examples of these differences include the effects of pioglitazone and rosiglitazone on lipid profiles\textsuperscript{31} and on the incidence of CV events\textsuperscript{32–34}. Nevertheless, both of these drugs are ligands of PPAR\textsuperscript{–}\gamma, which, when activated, alters the transcription of several genes related to carbohydrate and lipid metabolism\textsuperscript{35,36}. This alteration has the effect of increasing insulin sensitivity in muscle, fat and peripheral tissue\textsuperscript{36}. PPAR\textsuperscript{–}\gamma activation also reduces lipolysis\textsuperscript{37} and enhances adipocyte differentiation\textsuperscript{36}, providing further beneficial effect. In clinical trials of patients with T2DM, TZDs have been shown to improve beta-cell function as assessed by indirect measures, such as Homeostasis Model Assessment (HOMA)\textsuperscript{38–40}, to have anti-inflammatory and lipid-lowering effects\textsuperscript{31,41–44}, to exhibit an anti-atherogenic effect as measured by CIMT\textsuperscript{45} and IVUS\textsuperscript{46}, to improve vascular parameters\textsuperscript{47} and to decrease fatty liver effects\textsuperscript{48}.

**Enhancers of the incretin effect**

Exogenously administered GLP-1 normalizes glucose-dependent insulin and glucagon responses, reduces appetite and slows the rate of gastric emptying\textsuperscript{21}. Exogenous GLP-1 infusion also improves endothelial function (but not insulin resistance) in patients with T2DM\textsuperscript{49} and LV function in non-diabetic patients with heart failure (HF) and has been shown to decrease postprandial triglyceride and non-esterified fatty acid levels in non-diabetic subjects\textsuperscript{50,51}. Recombinant GLP-1 has been shown in animal models to increase myocardial glucose uptake, to improve LV function\textsuperscript{52,53} and to have antihypertensive effects\textsuperscript{54}; its infusion may improve myocardial function in patients with T2DM and HF\textsuperscript{55}.

Because GLP-1 has a short half-life (\(\approx 2\) min), two relatively new treatment approaches were developed to enhance its actions. Incretin mimetics (exenatide) are injected agents that mimic the action of GLP-1 and increase GLP-1–like effects by overcoming the short half-life of natural GLP-1 because they are not degraded by dipeptidyl peptidase 4 (DPP-4). The DPP-4 inhibitors are oral agents that slow the inactivation of GLP-1 by blocking the actions of DPP-4\textsuperscript{21}. They have been shown to promote glucose regulation alone and in combination with pioglitazone and to have a weight-neutral effect\textsuperscript{56–58}. At present, only sitagliptin is approved for use in the United States; three others – vildagliptin, saxagliptin and alogliptin – are currently in clinical trials. Two-year safety data on sitagliptin, presented in abstract form, suggest that it is very well tolerated as monotherapy or when given in combination with pioglitazone, metformin or sulfonylurea therapy\textsuperscript{59}. Prescribing information for sitagliptin cites nasopharyngitis as the only adverse event occurring in \(\geq 5\%\) of patients treated with sitagliptin monotherapy and more commonly than in patients receiving placebo. Incidences of upper respiratory tract infection, headache and hypoglycemia with sitagliptin were \(\geq 5\%\).
and higher than placebo in some studies evaluating sitagliptin used in combination with other oral anti-diabetic agents (OADs)\textsuperscript{60}.

### Overview of pioglitazone and exenatide

**Pioglitazone**

Pioglitazone and rosiglitazone have comparable glycemic efficacy (a meta-analysis found reductions in HbA\textsubscript{1c} of about 1–1.5% with each\textsuperscript{61}); however, pioglitazone monotherapy (30 mg once daily) reduces PPG levels, which may help to reduce the risk of macrovascular events in patients with T2DM\textsuperscript{62}, and had a greater effect on PPG level (final dose, 45 mg once daily) when compared with rosiglitazone (final dose, 4 mg twice daily; mean change from baseline [mmol/min/L], −605.3 vs. −493.8\textsuperscript{63}). In a large ($N=802$) head-to-head study comparing the effects of these agents on triglycerides in patients with T2DM and dyslipidemia, pioglitazone (final dose, 45 mg once daily) significantly...
reduced triglycerides from baseline, whereas rosiglitazone (final dose, 4 mg twice daily) significantly increased triglycerides. Other benefits specific to pioglitazone included significant reduction in LDL particle concentration, only a modest increase in non-HDL cholesterol and no significant effect on apolipoprotein B. Rosiglitazone was associated with a significant increase in LDL particle concentration and apolipoprotein B from baseline, as well as an increase in non-HDL cholesterol that was significantly greater than that for pioglitazone (Table 3). In a second study in a similar patient population (COMPLEMENT; N = 305), a significant reduction in triglycerides was observed when rosiglitazone was replaced with open-label pioglitazone (30 mg once daily) while a stable regimen of other lipid-lowering therapies was maintained. Pioglitazone produces these beneficial changes independent of its antihyperglycemic effects. In a small crossover study (N = 17) of pioglitazone and rosiglitazone in patients with T2DM, pioglitazone (final dose, 45 mg once daily) significantly reduced fasting total cholesterol (p = 0.031), fasting triglycerides (TGs) (p < 0.037) and postprandial TGs (p < 0.017) relative to rosiglitazone (final dose, 4 mg twice daily). Thus, it appears that, despite glycemic benefits similar to rosiglitazone, pioglitazone may provide greater lipid advantages.

To assess CV outcomes, pioglitazone was studied in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive). Of patients with T2DM enrolled in PROactive, a double-blind, placebo-controlled, secondary CV event prevention study of pioglitazone, about half had a history of myocardial infarction (MI) and 20% had a history of stroke. Addition of pioglitazone (final dose, 45 mg once daily) to patients’ existing treatment regimens significantly lowered the composite end point of death (all-cause), nonfatal MI and stroke compared with placebo during the 3-year study (p = 0.027). No significant difference was noted between the pioglitazone and placebo groups in terms of the study’s primary end point—a broad composite of all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries and amputation above the ankle. However, the evidence for benefit in secondary prevention among high-risk groups with previous stroke or MI is strong. Although statistical significance was not reached for the primary study end point, the results for secondary outcome measures support the clinical consensus that pioglitazone is likely to confer CV benefits rather than worsen CV health.

In a subsequent report on the subset of patients in PROActive with previous stroke (pioglitazone, n = 486; placebo, n = 498), the trend toward benefit in terms of the primary end point was more robust (Figure 1) and the benefit for reduction of recurrent stroke (fatal and nonfatal) was highly significant (47% reduction; p = 0.0085). Pioglitazone also reduced the rate of recurrent fatal or nonfatal MI by 28% (p = 0.045) and of acute coronary syndrome by 37% (p = 0.035) in a subgroup of patients from PROactive with previous MI (pioglitazone, n = 1230; placebo, n = 1215).

Pioglitazone produces significant reductions in levels of C-reactive protein [CRP], a marker of inflammation and predictor of cardiovascular events, and increases plasma levels of adiponectin, an adipokine believed to promote insulin sensitivity. It significantly attenuates renal effects of diabetes (through reduction of the microalbumin:creatinine ratio), decreases carotid artery stiffness and reduces or slows the progression of CIMT independent of its antihyperglycemic

---

**Table 3. Effects of pioglitazone and rosiglitazone on lipid profiles in a head-to-head clinical trial**

<table>
<thead>
<tr>
<th>Primary end point</th>
<th>Pioglitazone HCl (N = 369)</th>
<th>Rosiglitazone* (N = 366)</th>
<th>p-value (between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>−12.0 †</td>
<td>14.9 †</td>
<td>≤ 0.005</td>
</tr>
<tr>
<td>Secondary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>−0.7% †</td>
<td>−0.6% †</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>14.9% †</td>
<td>7.8% †</td>
<td>≤ 0.005</td>
</tr>
<tr>
<td>Non–HDL-C, mg/dL</td>
<td>3.6</td>
<td>25.7</td>
<td>≤ 0.005</td>
</tr>
<tr>
<td>LDL-C</td>
<td>15.7% †</td>
<td>23.3% †</td>
<td>≤ 0.005</td>
</tr>
<tr>
<td>LDL particle conc, nmol/L</td>
<td>−50.5 ‡</td>
<td>110.5 †</td>
<td>≤ 0.005</td>
</tr>
<tr>
<td>LDL particle size, nm</td>
<td>0.5 †</td>
<td>0.3 †</td>
<td>0.005</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>−0.2 ‡</td>
<td>10.6 †</td>
<td>≤ 0.005</td>
</tr>
</tbody>
</table>

*Mean ± SD; †p < 0.001 versus baseline; ‡p < 0.05 versus baseline; NS versus baseline

Apo B = apolipoprotein B; HbA1C = glycosylated hemoglobin; HCl = hydrochloride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NS = not significant

Data from Goldberg et al.31
The CV safety of diabetes treatment is of major importance. Recently, results of several hypothesis-generating meta-analyses based on clinical or observational data have suggested that rosiglitazone, but not pioglitazone, is associated with a significantly increased risk of MI and death from CV causes compared with placebo or other treatment regimens. Data from an unplanned interim analysis of an ongoing non-inferiority trial of rosiglitazone (4–8 mg/day) added to metformin or sulfonylurea versus metformin plus sulfonylurea in 4447 patients with T2DM were inconclusive regarding these risks because the short mean follow-up period (3.75 years) limited the power to detect treatment differences. A retrospective cohort analysis in 29,911 patients with T2DM found that hospitalization for MI, after adjustment for baseline population differences, was 22% less frequent in patients treated with pioglitazone than in patients treated with rosiglitazone. Although it was recognized that results of meta-analyses do not offer conclusive evidence of an increased CV event rate in patients treated with rosiglitazone, the US Food and Drug Administration (FDA) recently added a black box warning to the rosiglitazone label to raise awareness of the potential increase in CV events.

Based on data from a meta-analysis conducted by GlaxoSmithKline, similar restrictions have been added in the European Union and Canada on the use of rosiglitazone, but not pioglitazone. In fact, the FDA added data showing the potential cardiovascular benefits of pioglitazone by placing the individual end points of the primary composite end point of the PROactive trial (all except leg artery revascularization, which shows no benefit with pioglitazone) in the current product insert for pioglitazone. Thus, although pioglitazone and rosiglitazone impart comparable glycemic effects, superior benefits of pioglitazone on lipid parameters, surrogate markers of cardiovascular disease (i.e., CIMT, IVUS) and possibly cardiovascular outcomes may establish pioglitazone as the preferred TZD for treatment of T2DM.

**Edema and congestive heart failure**

Because of treatment-related fluid retention, concerns have been raised about HF among patients treated with TZDs. This result may be due to effects of these agents...
on the renal system, resulting in increased total body renin, sodium and water rather than reflecting a primary detrimental effect on the heart. In animal models, TZDs appear to directly affect sodium exchange in the distal collecting duct of the nephron and to increase sodium absorption; this reaction represents the probable mechanism for TZD-associated edema and fluid retention. However, because edema (5% monotherapy; up to 15–16% combined with insulin) and congestive HF (CHF) (<1.0% monotherapy, up to 3% combined with insulin) are observed with rosiglitazone and pioglitazone, a distinct black box warning for CHF was added recently to both product inserts.

The incidence of CHF was about 1% in pioglitazone clinical trials. In the high-risk population enrolled in PROactive, heart failure requiring hospitalization occurred in 7.5% of patients receiving pioglitazone and 5.2% receiving placebo. However, HF-related mortality rates were similar with pioglitazone and with placebo. Patients with CHF who remained on pioglitazone showed the same significant decrease in the secondary composite CV end point as those without CHF. However, a recent meta-analysis of 20,191 patients who received TZDs found that, although CHF was a class effect across TZDs, the relative risk of cardiovascular death was not increased with either agent (relative risk = 0.93, 0.67–1.29, p = 0.68).

Edema and CHF can be addressed clinically through sodium-restricted diets for patients who are starting TZDs and by appropriate patient selection. Pioglitazone may be considered for use in patients with New York Heart Association Class I/II HF with appropriate screening and introduction of a salt-restricted diet, use of a low starting dose and monitoring to detect excessive weight gain, new-onset pedal edema or dysnea.

Risk of fracture

An increased risk of fracture in women recently has been identified as a possible class effect of TZDs. Data from the ADOPT (A Diabetes Outcome Progression Trial) study of rosiglitazone showed an overall increase in the incidence of fractures in female patients receiving rosiglitazone (2.74/100 patient-years), compared with those receiving metformin (1.54/100 patient-years) or glyburide (1.29/100 patient-years). The majority of fractures were noted in the humerus, hand and foot, which are different from sites associated with fractures due to postmenopausal osteoporosis. A subsequent review of the pioglitazone clinical trial database conducted by Takeda revealed an overall fracture risk of 1.9/100 patient-years in women who received pioglitazone compared with 1.1/100 patient-years in women who received a comparator. The majority of fractures occurred in the distal upper limb (forearm, wrist, hand) or distal lower limb (tibia, fibula, ankle, foot). None of these results have come from studies specifically designed to evaluate the effects of TZDs on bone metabolism or risk of fracture, and, therefore, the results should be interpreted with caution. Two studies currently are under way to evaluate the effects of pioglitazone and rosiglitazone on bone metabolism in women with type 2 diabetes, information from these trials may provide greater insight into the use of TZDs in these patients. In the interim, providers should consider the potential risk of fracture when considering initiation of TZD treatment in women and make efforts to assess and maintain bone health in accordance with current standards of care while patients are on treatment.

Weight gain

Weight gain has been identified as a class effect of the TZDs; several reviews suggest that an average weight gain of 3–4 kg occurs over the first 6 months of TZD treatment, with a decrease in the rate of weight gain thereafter. Factors that may contribute to TZD-induced weight gain include increased adipocyte differentiation and fluid retention. TZD-induced weight gain is accompanied by increases in plasma volume; therefore, careful monitoring for signs of volume overload, such as edema, is suggested, particularly in patients who experience rapid changes in weight while on TZD therapy. Weight gain is more pronounced when TZDs are combined with sulfonylureas or insulin, whereas, in combination with metformin, TZD-associated weight changes may be reduced or even absent. Therefore, the combination of TZDs with anti-diabetic agents that are weight neutral or that promote weight loss, such as incretin mimetics, may represent an important future direction for therapy.

Enhancers of incretin effect: exenatide

As was previously discussed, natural GLP-1 is problematic as a therapeutic agent because it is quickly degraded by DPP-4 and has a half-life of less than 2 min. Exenatide is a naturally occurring incretin mimic derived from a Southwestern reptile (Heloderma suspectum). It is injected subcutaneously (SC) and has actions similar to those of human GLP-1; however, it is resistant to DPP-4 degradation, resulting in a longer duration of action that allows once- or twice-daily administration.

Exenatide (10 μg SC twice daily) was compared with basal insulin (glargine) and premixed insulin aspart in two open-label studies enrolling patients with T2DM whose condition was suboptimally controlled with...
OADs. Although exenatide provided similar benefit in lowering HbA1c levels compared with either insulin treatment, exenatide was associated with a substantially higher incidence of gastrointestinal adverse events and withdrawals\(^{104,105}\). Furthermore, only 21.6% and 8.6% of the insulin glargine and exenatide groups, respectively, in one study achieved the target FPG (<100 mg/dL)\(^{105}\). Exenatide was associated with weight loss, whereas patients receiving both insulin treatments gained weight\(^{104,105}\). Significant reductions in PPG and FPG with exenatide are supported by additional trials in patients with T2DM\(^{106–108}\). Results from a recent clinical trial showed that a long-acting version of exenatide (exenatide long-acting release [LAR]) produces similar reductions in PPG, greater decreases in HbA1c and FPG, greater weight loss and one-half the incidence of nausea reported with exenatide; however, this formulation is in phase 3 development and is not yet commercially available\(^{109}\).

In general, treatment with exenatide has been shown to lower HbA1c in patients whose condition is not controlled by OADs, to decrease weight, to improve some CV risk factors and to possibly restore first-phase insulin secretion along with a low risk of hypoglycemia\(^{107,108,110–113}\). When added to existing sulfonylurea therapy, exenatide (10 µg SC twice daily) has been shown to provide additional benefit for patients with poorly controlled T2DM. After 30 weeks of treatment, HbA1c levels declined by 0.86% in the group treated with exenatide (\(n = 129\)) but increased by 0.12% in the group given placebo (\(n = 123\))\(^{113}\). Those patients treated with exenatide experienced progressive weight loss throughout the 30-week study and lost 1.6 kg body weight by study end; those who received placebo lost 0.6 kg during the study\(^{113}\). Exenatide also was studied in combination with metformin in patients with T2DM that was poorly controlled with metformin alone\(^{107}\). HbA1c levels decreased by 0.8% in patients treated with exenatide 10 µg twice daily (\(n = 84\)) and increased by 0.1% in those given placebo (\(n = 77\))\(^{107}\). Forty-six percent of those who received exenatide achieved HbA1c < 7% compared with 13% of those given placebo\(^{107}\). Baseline body weight was on average 100 kg in the study; after 30 weeks, those treated with exenatide had lost 2.8 kg compared with a weight loss of 0.3 kg in those who received placebo (\(p \leq 0.001\)). Weight loss with exenatide in combination with metformin was progressive throughout the trial and was dose dependent and independent of baseline body mass index\(^{107}\).

In a small subset of patients who underwent a standard meal challenge, PPG was significantly (\(p = 0.004\)) lower in the exenatide-treated group (\(n = 16\)) than in the placebo group (\(n = 13\)). This change was accompanied by a rise in plasma insulin response, with a shift toward earlier insulin response in exenatide-treated patients\(^{107}\). In a third 30-week study, exenatide was added to existing OAD therapy with metformin plus a sulfonylurea for the treatment of patients with poorly controlled T2DM\(^{108}\). As was reported in the other studies, treatment with exenatide SC 10 µg twice daily produced additional benefit likely secondary to reduced HbA1c levels (−0.8%), progressive weight loss (−1.6 kg) and improved control of postprandial hyperglycemia\(^{108}\).

In all of these studies, nausea, generally mild to moderate in nature, was the adverse effect most commonly associated with exenatide treatment. In an 18-month follow-up report (\(N = 314\)), the incidence of nausea peaked early in treatment (by Week 10) and stabilized at between 14% and 20% after 30 weeks\(^{111}\), consistent with the results of earlier studies\(^{107,113}\). Nausea led to treatment discontinuation in 3.6% of patients during 18 months of treatment\(^{111}\). Only one case of severe hypoglycemia was reported in 30 weeks of treatment\(^{108}\), and four cases occurred during 18 months of treatment, all in patients receiving exenatide in combination with metformin plus a sulfonylurea\(^{111}\).

Although no studies have looked at nausea in detail, it is believed that most treatment-related nausea is an indirect effect of normalized gastric emptying. Patients can prevent or abate symptoms by administering the drug close to the time of initiation of food intake, and by stopping eating when they feel full. In addition, titration of exenatide from 5 µg to 10 µg (SC twice daily) may help to minimize nausea.

Two-year data for exenatide confirm that decreased HbA1c levels, weight loss and improved beta-cell function are sustained over time\(^{114}\). Additional data with results after 3 years of treatment with exenatide (10 µg SC twice daily) in combination with metformin or a sulfonylurea show sustained reductions in HbA1c levels (−1.1%), FPG levels (−23.5 mg/dL) and body weight (−5.3 kg) (all, \(p < 0.0001\) vs. baseline). Weight loss after 3 years was about double that observed after 30 weeks of treatment (\(p < 0.0001\))\(^{115}\). In the same cohort of patients, CV risk factors improved after 3.5 years of exenatide treatment. Decreases of 12% in TG, 5% in total cholesterol and 6% in low-density lipoprotein cholesterol, and a 24% increase in HDL-C were observed. In addition, patients’ systolic and diastolic blood pressures declined by 2% and 4%, respectively\(^{116}\).

**Combination therapy: pioglitazone and exenatide**

Pioglitazone and exenatide have complementary mechanisms of action and effects. Pioglitazone reduces
insulin resistance, improves lipid profiles and beta-cell function, confers little or no risk of hypoglycemia and has beneficial effects on CV risk factors and fatty liver disease; common adverse effects include fluid retention and modest weight gain, which can be minimized through appropriate dietary restrictions. Exenatide enhances glucose-dependent insulin secretion, inhibits glucose-dependent glucagon secretion, slows gastric emptying, reduces food intake, decreases weight, may improve beta-cell function and confers little or no risk of hypoglycemia. The most commonly associated adverse effect is nausea, which can be minimized to a marked degree by delaying the titration from the 5-μg to the 10-μg dose. Thus, the patient with T2DM with significant risk of CV disease, who may wish to avoid weight gain and hypoglycemia or who may be at undue risk as a result of it, may be an ideal candidate for combination therapy with pioglitazone and exenatide. However, this combination of treatment has not been evaluated for effects on CV outcomes.

One recently published clinical trial assessed the effects of combination therapy with a TZD (pioglitazone or rosiglitazone) and exenatide in patients with T2DM. Patients (N = 233) in this 16-week double-blind, placebo-controlled, parallel-group trial did not achieve their HbA1c goal while receiving treatment with a TZD with (79%) or without (21%) metformin. They were randomly assigned to receive exenatide (10μg SC twice daily) or placebo in addition to their prior treatment. At study end, 62% of those receiving the TZD/exenatide combination versus 16% in the TZD/placebo group achieved HbA1c < 7% – the primary end point (Figure 2); in addition, larger reductions in FPG and PPG levels were observed in the TZD/exenatide group than in the TZD/placebo group (Figure 3). Those patients who received the TZD/exenatide combination also exhibited a significant reduction in body weight (−1.5 kg), obviating the weight gain observed when a TZD is used alone. HOMA of beta-cell function increased by 19% for those receiving the active combination and decreased by 6% for those in the placebo group; however, HOMA for insulin sensitivity increased in both groups (23% and 10%, respectively). Nausea was reported more frequently in the exenatide group than in the placebo group (40% vs. 15%, respectively). No difference in incidence of hypoglycemia was noted between the two groups. Limitations of the study included a small sample size, lack of implementation of lifestyle modifications (e.g., diet, exercise) and a higher dropout rate caused by adverse effects in the exenatide group versus the placebo group (16% vs. 2%, respectively). Furthermore, the relatively short duration of treatment precluded evaluation of the long-term effects of the exenatide/pioglitazone combination on beta-cell function, body weight, glucose control and CV safety.

**Conclusion**

The goals of therapy for T2DM include controlling hyperglycemia (FPG and PPG), helping patients to achieve ADA treatment goals, preventing disease progression, preserving beta-cell function and mass, avoiding hypoglycemia and ultimately reducing micro- and macrovascular complications of the disease. Used in combination in a single clinical trial, TZDs and exenatide provided better overall glucose control, improved control of FPG and PPG, enhanced beta-cell function and reduced weight gain compared with TZD therapy.
with or without metformin. Though not proven, this result suggests that the addition of exenatide to pioglitazone may improve outcomes without an undue risk of hypoglycemia for patients with T2DM who require more intensive therapy to get to goal but may not require or may not be ready to accept insulin treatment. This combination also may help to mitigate the underlying causes of T2DM by improving and sustaining beta-cell function through dual effects on insulin sensitivity (pioglitazone) and insulin secretion (exenatide).

Additional goals of weight loss and reduction of CV risk should be considered when therapy is selected. The benefits of exenatide with regard to weight loss have been shown in clinical trials, as have the effects of pioglitazone on modifying markers of CV disease, such as lipid profiles and CIMT. Finally, because the prevalence of T2DM is expected to increase among older and younger members of the population, it is obligatory to think in terms of preventing T2DM with earlier intervention for patients with impaired glucose tolerance/impaired fasting glycemia or those who have metabolic syndrome. Redefining T2DM as FPG > 100 mg/dL may represent an initial step toward earlier treatment in at-risk individuals.

Our current understanding of the pathophysiology of T2DM suggests that therapies that reduce insulin resistance and improve beta-cell function may prevent and/or alter the natural history of diabetes. In fact, several interventions already have been shown to have benefits in this regard. In patients with IGT/IFG, lifestyle interventions have reduced progression to T2DM by 58% and metformin and acarbose reduced progression by 31% and 25%, respectively. Results from the recent ACT NOW study showed a significant reduction (81%; p < 0.00001) in progression to diabetes in patients with IGT treated with pioglitazone (incidence, 1.5%/year) versus placebo (incidence, 6.8%/year) over a mean follow-up of 2.6 years. Given the actions of the exenatide and pioglitazone combination described previously, this combination may emerge in the future as a treatment option for preventing the progression or delaying the onset of T2DM. This area of research should be a matter of priority, as should comparison of this combination to other anti-diabetic combinations in head-to-head clinical trials.

Limitations

The goal of this review was to describe the pathophysiologic rationale and potential clinical utility of exenatide/pioglitazone combination therapy for T2DM. Thus, the article does not represent a comprehensive review of combination strategies to treat T2DM. The content was based solely on published literature relevant to this combination; important factors such as adherence to therapy and cost/benefit relationships are not addressed because there are no published studies to support their discussion. Furthermore, the author acknowledges that clinical data supporting use of the exenatide/pioglitazone combination are limited to one study and that future research may identify other promising anti-diabetic drug combinations.

Acknowledgements

Declaration of interest: Financial support for editorial services was provided by Takeda Pharmaceuticals North America. S.S. has served on Advisory Boards for Lilly, Takeda and Amylin, and is a member of the speakers bureaus for Lilly, Takeda, Amylin, sanofi-aventis and Merck. Editorial assistance for preparation of this manuscript was provided by Scientific Connexions, Inc, Newtown, PA, USA.

References

35. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA 2002;287:360-72
45. Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006;296:2572-81
66. Wilcox R, Bousser MG, Betteridge D, for the PROactive Investigators. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events (04). Stroke 2007;38:865-73
84. Avandia [prescribing information]. Research Triangle Park (NC): GlaxoSmithKline; August 2007
88. ACTOS [prescribing information]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; September 2007


118. The DREAM Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. Lancet 2006;368:1096-105


CrossRef links are available in the online published version of this paper: http://www.cmrojournal.com

Paper CMRO-4647_4, Accepted for publication: 6 August 2008

Published Online: 30 September 2008
doi:10.1185/03007990802390795