TZDs in Combination With Incretins: Synergy in Diabetes Treatment

Using these agents in tandem targets the pathophysiology of type 2 diabetes and may be particularly useful in stress-induced diabetes and surgery.

BY STANLEY SCHWARTZ, MD

Intensive glycemic control significantly reduces the risk of microvascular complications associated with type 2 diabetes,[1-4] and data from the UKPDS (United Kingdom Prospective Diabetes Study) revealed a trend toward a reduction in macrovascular complications.[1] Long-term follow-up of the UKPDS cohort[5] confirms later reduction of cardiovascular events especially in the metformin-treated patients. This is not unlike the delayed benefits in reduced cardiovascular outcomes seen in the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) study population 12 years after the study was completed.[6] The recent VADT (Veterans Administration Diabetes Trial) showed that aggressive glucose control did not significantly lower the risk of cardiovascular events versus standard therapy in the overall study population, although there was likely a protective effect in those who had a shorter duration of diabetes or had earlier atherosclerotic disease (coronary artery calcium score <100).[7]

The ADVANCE (Action in Diabetes and Vascular Disease) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) studies failed to demonstrate macrovascular benefits in patients undergoing intensive glycemic control.[3,4] Use of sulfonylureas may have obviated any benefit of achieving A1C levels of 6.5% in ADVANCE, based on greater risk of mortality with sulfonylureas as seen in a study by Simpson et al.[8] Additionally, failure of achieving benefit by aiming for A1C <6.0% in ACCORD is likely due to a failure of the *process* of control in these patients, which resulted in an average weight gain of 20 lbs and a three- to fourfold increase in hypoglycemia. It is unknown at this time whether improved glucose control to ≤6.5% in and of itself can reduce macrovascular disease.[9] It seems wise, however, based on the pathophysiology of hyperglycemia and its association with increased cardiovascular risk,[10] that the current goal advocated by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the American Association of Clinical Endocrinologists for achieving the lowest A1C possible without undue risk of hypoglycemia—and I would add without undue weight gain—still seems appropriate. In fact, the ADA is dedicated to testing this philosophy by committing research dollars to Defronzo's Banting Lecture (www.diabetesconnect.com) proposal for the use of pioglitazone, metformin, and exenatide (Byetta, Eli Lilly and Amylin) versus its own guideline,[11] which still includes sulfonylureas.

In this vein, I review the pathophysiology of type 2 diabetes and present the rationale for a pathophysiologically based treatment approach for patients with type 2 diabetes, discussing the role of new therapeutic combinations. Some aspects of this review appeared in *Current Medical Research and Opinions* (2008;24:3009–3022).

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Type 2 diabetes is a strongly genetic disease, with inheritance of genes related to insulin resistance and abnormal beta-cell function, with an additional role played by environmental factors, such as poor diet and inactivity.[12,13] In obese individuals, visceral adipose tissue releases increased amounts of nonesterified fatty acids, glycerol, hormones, proinflammatory cytokines and other tissue factors, and a reduction in adiponectin. This cascade of events combines to further promote insulin resistance[14] and reduce insulin secretion through impaired beta-cell function in diabetes-susceptible individuals.[14] These factors are also associated with endothelial dysfunction and inflamma-

tion, starting and exacerbating the atherosclerotic process associated with obesity, insulin resistance, metabolic syndrome, and diabetes.

Abnormal islet-cell function. In a person without diabetes, a reduction in glucagon secretion and an increase in insulin secretion occur after the ingestion of glucose, therefore maintaining normal glucose levels.[15] Among individuals with type 2 diabetes, hyperglycemia results when pancreatic beta-cells cannot release enough insulin to compensate for increased peripheral insulin resistance. Abnormal islet-cell function is typified by loss of first-phase insulin secretion, reduced incretin effects, and increased glucagon output by pancreatic alpha-cells.[16]

Loss of first-phase insulin response and postprandial hyperglycemia. The earliest detectable glycemic abnormality in most patients with type 2 diabetes[17] and prediabetes[18] is the loss of first-phase insulin response that can lead to postprandial hyperglycemia and late postprandial hypoglycemia in some patients, well before they develop overt diabetes. Postprandial hyperglycemia correlates more closely with A1C than with fasting plasma glucose (FPG).[14] It has been argued, therefore, that the ADA reevaluate the thresholds for the diagnosis of diabetes.[19] UKPDS patients' A1C levels remained above target even when the target FPG was achieved. An analysis of the glycemic profiles of 290 consecutive clinic type 2 diabetes patients[20] revealed that with A1C levels approaching the ADA goal of 7.0%, postprandial plasma glucose (PPG) accounted for as much as 75% of the individual's glycemic burden.[20] Thus, both PPG and FPG must be targeted as part of a diabetes treatment strategy.

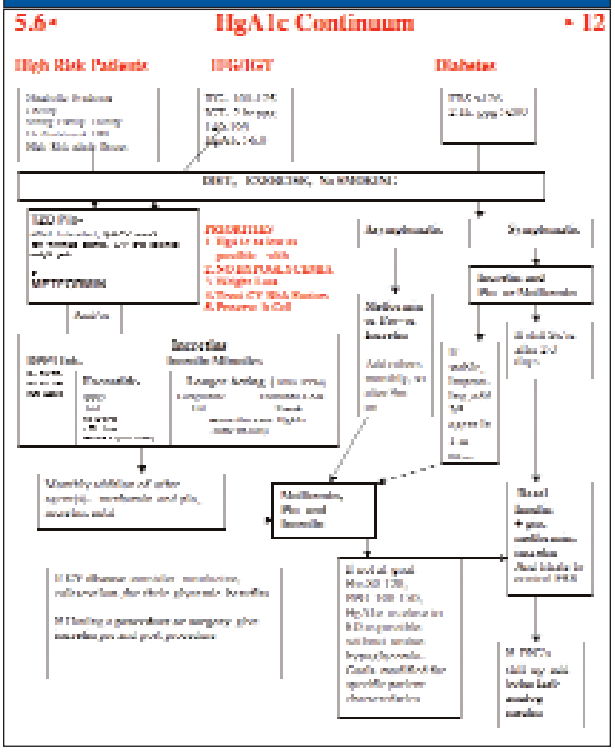
TABLE 1. PATHOPHYSIOLOGICAL RATIONALE FOR THE MANAGEMENT OF HYPERGLYCEMIA: A SUGGESTED TREATMENT APPROACH FOR THE TREATMENT OF TYPE 2 DIABETES ON THE BASIS OF ALIGNMENT OF DRUG AND PATIENT CHARACTERISTICS

CHF = congestive heart failure; Cr = creatinine; CV = cardiovascular; DPP-4 = dipeptidyl peptidase; FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NYHA = New York Heart Association; PPG = postprandial plasma glucose; RD = renal disease. Table was created by Stanley Schwartz, for the University of Pennsylvania Health System Disease Management Program, under the auspices of David Horowitz, MD (adapted with permission).

Diminished incretin hormone effect. Incretin hormones affect the body's insulin response to glucose challenge, and as such are essential to normal glucose metabolism and are linked with PPG control.[21,22] As beta-cell dysfunction becomes evident, there is a reduction in the incretin effect (augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, in particular glucagon-like peptide [GLP]-1) both in reduction of GLP-1 levels as well as response to GLP-1 by the at-risk beta cell.[23]

GLP-1 has garnered clinical interest as a therapeutic target in diabetes. GLP-1's actions include the release of glucose-dependent insulin, glucose-dependent suppression of glucagon secretion, a slowed rate of gastric emptying, promotion of satiety, and beta-cell health preservation.[24,25] The glucose-dependent effects of GLP-1 on glucagon secretion and insulin release imply minimal risk of hypoglycemia when GLP-1 is administered exogenously. GLP-1 can indirectly reduce hepatic glucose production

TABLE 2. PATIENTS AT HIGH RISK FOR DIABETES AND HYPERGLYCEMIA OF IFG/IGT



by increasing the body's ratio of insulin to glucagon,[26] and it has the potential to normalize FPG in diabetes patients when given intravenously[27] or subcutaneously.[28] In experimental models, GLP-1 receptor activation promoted beta-cell proliferation, inhibited beta-cell apoptosis, and increased functional islet-cell mass.[24,29]

DIABETES TREATMENT GOALS

Principles emphasized in the treatment of type 2 diabetes include treating insulin resistance and abnormal islet-cell function, avoiding hypoglycemia, reducing weight, minimizing weight gain, preserving beta-cell function, and reducing cardiovascular risk factors and cardiovascular outcomes.

Combination therapy seems to be the most optimal way to achieve these goals. We believe the combination of a thiazolidinedione (TZD) and an incretin offers a blend of characteristics that may be quite useful in the management of type 2 diabetes. Specifically, macrovascular outcomes are likely beneficial with pioglitazone treatment[30] and may accrue for incretins, although long-term micro- and macrovascular outcomes data are not yet available.

In deciding therapy, one should match the clinical characteristics of an individual patient to the therapeutic characteristics of the agents used in diabetes treatment. Table 1 is a proposed guideline that gives an overview of currently available noninsulin therapies from a clinical perspective, along with information on expected efficacy, patient selection, and special concerns,[31] and Table 2 shows how the principles might be applied.

TZDs

Available TZDs are pioglitazone (Actos, Takeda) and rosiglitazone (Avandia, GlaxoSmithKline). Both agents are ligands of peroxisome proliferator-activated receptor (PPAR)-gamma and increase insulin sensitivity in muscle, fat, and peripheral tissue. In clinical trials of patients with type 2 diabetes, TZDs improve beta-cell function,[32-34] improve glycemic control,[34] have antiinflammatory effects,[35] and decrease fatty liver.[36] Side effects of edema and congestive heart failure can be minimized by appropriate patient selection and avoidance of undue salt intake. Weight gain can be prevented by caloric control or prevented/treated with exenatide coadministration.[37]

Pioglitazone and rosiglitazone have comparable glycemic efficacy;[38] however, pioglitazone monotherapy reduces PPG levels, which may help to reduce the risk of macrovascular events in type 2 diabetes patients[39] and had a greater effect on PPG level when compared with rosiglitazone.[40,41] Presumably, because individual PPAR agonists have differential effects on gene transcription,[41,42] the two agents have different effects with regard to lipid profiles (that is not "covered up" with statin therapy)[38,43] and cardiovascular events[44-46] (Table 3). Pioglitazone, although failing a wide primary endpoint that included elective decisions for leg amputation and coronary artery bypass grafting (CABG), reduced a hard endpoint composite outcome of death, myocardial infaction (MI), and stroke by 16% over 3 years, reduced cardiovascular outcomes in patients with prior MIs,[30] and reduced subsequent strokes by 47% in those who had prior strokes.[30] This is remarkable considering the length of time needed to show cardiovascular outcome reduction in Steno-2,[47] UKPDS,[1] and the DCCT/EDIC trials.[6] The results are supported by a lack of progression of atherosclerotic changes versus glimiperide in carotid and coronary vascular studies.[48,49] Worry about an increase in adverse cardiovascular outcomes in meta-analyses of rosiglitazone[46] resulted in a black-box warning[50] and has led to removal of rosiglitazone from the most recent EASD/ADA consensus guideline.[51] The clinical consensus is that pioglitazone is likely to confer cardiovascular benefits rather than worsen cardiovascular health.[52-54]

Weight gain has been identified as a TZD class effect; several reviews suggest that an average weight gain of 3

TABLE 3. EFFECTS OF PIOGLITAZONE AND ROSIGLITAZONE ON LIPID PROFILES IN A HEAD-TO-HEAD CLINICAL TRIAL[38]

	Pioglitazone	Rosiglitazone*	*P* value
	(N = 369)	(N = 366)	(between groups)
Primary endpoint			
Triglycerides	−12.0†	14.9†	≤.005
Secondary endpoint			
A1C	−0.7%†	−0.6%†	NS
HDL cholesterol	14.9%‡	7.8%‡	≤.005
Non-HDL cholesterol, mg/dL	3.6	25.7	≤.005
LDL cholesterol	15.7%†	23.3%†	≤.005
LDL particle concentration, nmol/L	−50.5‡	110.5†	≤.005
LDL particle size, nmol/L	0.5†	0.3†	≤.005
Apo B, mg/dL	−0.2‖	10.6†	≤.005

Apo B = apolipoprotein.
**Mean ± SD.*
† P≤.001 vs baseline; ‡ ≤.05 versus baseline; ‖ NS vs baseline.
Data from Goldberg et al.[38]

to 4 kg occurs over the first 6 months of treatment, with a decrease in the rate of weight gain thereafter.[55,56] Weight gain is more pronounced when TZDs are combined with sulfonylureas or insulin,[57] whereas in combination with metformin[58,59] or exenatide[60] (see later), TZD-associated weight changes may be reduced or even absent. The combination of TZDs with antidiabetic agents that are weight neutral or that promote weight loss—such as incretins—may represent an important future direction for therapy.

Incretins

Exogenously administered GLP-1 normalizes glucose-dependent insulin and glucagon responses, reduces appetite, and slows the rate of gastric emptying.[24] Incretins have been shown to decrease postprandial triglyceride and nonesterified fatty acid levels in nondiabetic individuals.[61,62] Both incretins might also be expected to resolve late postprandial hypoglycemia in patients because of their beneficial effects on improving first-phase insulin release.[62] Incretins also improve endothelial function in patients with type 2 diabetes[63] and left ventricular function in nondiabetic patients with heart failure.[64] Moreover, in patients undergoing CABG, perioperative use of GLP-1 achieved better glycemic control and comparable hemodynamic recovery without the requirements for high-dose insulin or inotropes.[65] GLP-1 reduced wall motion abnormalities in MI patients undergoing cardiac catheterization and coronary stenting.[66]

Exenatide. Exenatide is a naturally occurring incretin mimetic derived from a Southwestern reptile. It is injected subcutaneously 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.[24] Exenatide was compared with basal insulin (glargine) and premixed insulin aspart in two open-label studies enrolling patients with type 2 diabetes who were suboptimally controlled with oral antidiabetic agents (OADs). Exenatide had a similar benefit for lowering A1C levels compared with insulin; however, it was associated with weight loss compared with weight gain and no undue hypoglycemia in absence of secreatogogue, albeit a substantially higher incidence of gastrointestinal (GI) adverse events and withdrawals.[67,68] Significant reductions in PPG and FPG with exenatide are supported by additional trials in patients with type 2 diabetes.[69-71]

Exenatide has been shown to decrease weight, improve some cardiovascular risk factors, and possibly restore first-phase insulin secretion with a low risk of hypoglycemia.[70-75] When added to existing sulfonylurea, exenatide provides additional benefit,[75] and exenatide-treated patients also lost 1.6 kg by study end versus 0.6 kg in placebo patients.[75] Exenatide was studied in combination with metformin in patients poorly controlled with that agent alone,[70] A1C decreased by 0.8% in exenatide patients versus an increase of 0.1% in placebo patients,[70] and 46% of those who received exenatide achieved A1C ≤7% versus 13% of placebo-assigned patients.[70]

In all trials, mild-to-moderate nausea was the most common adverse effect associated with exenatide. In an 18-month follow-up report of 314 patients, the incidence of nausea peaked by week 10 of treatment and stabilized after 30 weeks, consistent with earlier studies.[70,75] Although no studies have looked at nausea in detail, it is believed that most treatment-related nausea can be prevented or abated by administering the drug close to the time of starting food intake and by patients stopping eating when they feel full. Delay in titration of exenatide from 5 µg to 10 µg (subcutaneously twice/day) may help to minimize nausea.

Two-year data for exenatide confirm that decreased A1C, weight loss, and improved beta-cell function are sustained over time.[76] Additional data from 3-year treatment with exenatide plus metformin or a sulfonylurea show sustained reductions in A1C, FPG, and body weight (all $P<.0001$ vs baseline). Cardiovascular risk factors also improved after 3.5 years of exenatide treatment among the same group.[77]

DPP-4 inhibitors. DPP-4 inhibitors are oral agents that slow the inactivation of GLP-1 by blocking the actions of DPP-4.[24] They promote glucoregulation alone and in combination with pioglitazone and have a weight-neutral effect.[78-80] Sitagliptin (Januvia, Merck) is the only such agent currently available in the United States, three others are in clinical trials, (vildagliptin [Galvus, Novartis], saxagliptin [Onglyza, Bristol Myers Squibb], and alogliptin [Takeda]).

Sitagliptin was well-tolerated at doses of 100 mg once daily, either as monotherapy, or in combination with metformin or pioglitazone, without significant hypoglycemia or weight gain in phase 3 trials.[81-83] Safety data on sitagliptin suggest that it is well tolerated as monotherapy or in combination with pioglitazone, metformin, or sulfonylurea.[84,85] There appears to be no undue adverse events associated with the agent, specifically no undue GI side effects and no safety signals have been reported to the Food and Drug Administration in the past 2 years. A small crossover design study comparing exenatide to sitagliptin for 2 weeks on a drug and then switching to the other for 2 weeks showed double the reduction in PPG and glucagons with exenatide compared to sitagliptin, decreased gastric emptying with exenatide, and no change was noted with sitagliptin.[86]

COMBINATION THERAPY: PIOGLITAZONE AND INCRETINS

Pioglitazone and incretin mimetics 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, improves fatty liver disease, has beneficial effects on cardiovascular risk factors and likely reduces cardiovascular adverse outcomes. The common adverse effects of fluid retention and modest weight gain can be minimized through appropriate dietary restrictions.

Incretin mimetics enhance glucose-dependent insulin secretion, inhibit glucose-dependent glucagon secretion, may improve beta-cell function, and confer little or no risk of hypoglycemia. DPP-4 inhibitors are weight neutral, and exenatide slows gastric emptying, reduces food intake, and decreases weight. Type 2 diabetes patients with significant risk of CVD, who want to avoid weight gain and hypoglycemia or who may be at undue risk as a result of it, may be ideal candidates for pioglitazone and incretin mimetic combination therapy. The combination has not been evaluated for effects on cardiovascular outcomes.

A recently published clinical trial assessed the effects of combination therapy with a TZD (pioglitazone or rosiglitazone) and exenatide in type 2 diabetes patients.[60] Patients (N = 233) in this 16-week double-blind, placebo-controlled, parallel-group trial did not achieve A1C goal with a TZD with (79%) or without (21%) metformin.[60] They were randomized to exenatide or placebo in addition to their prior treatment. At study end, 62% of those receiving the TZD-plus-exenatide combination versus 16% in the TZD-plus-placebo group achieved A1C <7%—the primary end point. Larger reductions in FPG and PPG were observed in the TZD plus exenatide group versus the TZD-plus-placebo group.[60] Patients who received the TZD plus exenatide combination also exhibited a significant reduction in body weight. Homeostasis model assessment (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).[60] 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 cardiovascular safety.

In patients with type 2 diabetes who had inadequate

glycemic control (A1C 7%–10%), the addition of 100 mg/day sitagliptin to metformin or pioglitazone monotherapy for 24 weeks improved glycemic control compared with monotherapy plus placebo, with 47% and 45% of patients achieving A1C <7%, respectively.[87,88] Compared with patients on either monotherapy, the addition of sitagliptin enhanced the fasting serum proinsulin:insulin ratio, indicating improved processing of proinsulin to insulin by beta-cells. Addition of sitagliptin to metformin slightly improved the lipid profile but no effect was observed when sitagliptin was added to pioglitazone. Importantly, the addition of sitagliptin to either therapy did not alter weight control compared to addition of placebo.

STRESS-INDUCED DIABETES

Stress-induced diabetes may be a special case for the benefit of combination therapy with pioglitazone and an incretin mimetic. The stress of surgery and other acute and chronic illnesses confers increases in stress-associated hormones including glucagon and endogenous corticosteroids. Moreover, among patients that require exogenous steroids perioperatively or chronically, in the genetically susceptible patient, stress-induced hyperglycemia into diabetic ranges can result, and glucose levels in patients with known type 2 diabetes can be exacerbated. It is generally accepted that most of the patients with stress/steroid-related hyperglycemia require insulin therapy to control hyperglycemia and its associated fluid/electrolyte complications and perhaps to reduce perioperative, postoperative, and chronic morbidity engendered by hyperglycemia. In an effort to control hyperglycemia using intensive insulin protocols, however, there is an increase in the utilization of resources, and patients may be at a greater risk of hypoglycemia and for an increase of in-hospital complications, described as a *j-point effect*.[89-91]

Steroid diabetes has superficially been associated only with its well-known increase in insulin resistance. In this regard, the benefit of having a TZD (pioglitazone) on board, perioperatively or with chronic steroid therapy, seems obvious.

Not everyone exposed to stress or exogenous steroids has hyperglycemia, however. This has led to the concept that steroid-related hyperglycemia may have more to do with beta-cell dysfunction in people genetically susceptible to their effect and this gene(s) may be related to the mechanism of increased insulin secretion by incretins. Diabetes-associated TCF7L2 polymorphisms are associated with lower incretin-mediated insulin secretion.[92] PDX-1—a transcription factor necessary for insulin secretion in beta-cells, is necessary for GLP-1 effects in mice.[93] Glucocorticoids suppress PDX-1 expression, an islet-specific insulin secretion enhancer,[94] and the reduction in insulin secretion by glucocorticosteroids in mice is reversed with GLP-1.[95]

Thus, incretin therapy, both by mitigating the effect of steroids on decreased insulin secretion and by decreasing glucagon secretion, pathophysiologically may be an ideal therapy for the treatment of steroid and/or stress diabetes alone or in combination with pioglitazone. Postoperative short-term GLP-1 infusion was used to reduce glucose concentrations in patients with type 2 diabetes after major surgery,[96] and glycemic benefits were noted.[97]

We have observed clinically that we can prevent the need for insulin therapy by administering incretins postoperatively in about 30% of patients undergoing neurosurgical (even in those given exogenous steroids) and other operations. In CABG and other cardiac surgery procedures, we have decreased the need for insulin in some patients, and the incretin mimetics allow earlier reduction and withdrawal of insulin. Practically speaking, in the stress- or steroid-induced diabetes patient, a DPP-4 inhibitor equals about 20 units of insulin and exenatide equals about 40 units of insulin. These guidelines may help us determine which patients—with no prior history of diabetes mellitus or with chronic steroid diabetes—can likely come off insulin and which, particularly after insulin drip therapy postcardiac surgery, can be expected to require insulin at home or be taken off insulin after insulin drip protocols and discharged with incretin therapy without insulin. Thus by decreasing the need for insulin among a significant number of patients, one might expect decreased resource utilization and decreased hypoglycemia as well as the potential for other favorable measures of inpatient and outpatient outcomes in these patients.

SUMMARY AND FUTURE DIRECTIONS

The goals of therapy for type 2 diabetes patients include controlling hyperglycemia, helping patients 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. We believe that, used in combination, pioglitazone plus incretins have the greatest likelihood of providing overall glucose control, improving control of FPG and PPG, enhancing beta-cell function, and controlling weight (with or without metformin). We do not routinely use secretagogues due to their association with hypoglycemia, weight gain, exhaustion of beta-cell function, short-term efficacy, and possibly increase in cardiovascular events. (We note

the removal of chlorpropamide and glyburide from the newest EASD/ADA guideline.) The combination of a TZD and an incretin may also help to mitigate the underlying causes of type 2 diabetes by improving and sustaining beta-cell function through dual effects on insulin sensitivity and insulin secretion. Additionally, we see a very promising role for incretins in the management of patients undergoing surgery who could benefit from treatment that may off-set increases in stress-associated hormones that occur with interventions and acute illnesses. This area of research should be a matter of priority. ■

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