Insulin Sensitizers for Type 1 and Type 2 Diabetes

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Introduction

Numerous studies presented at the 60th Scientific Sessions of the American Diabetes Association examined the use of insulin sensitizers for diabetes.

Metformin

Use of Metformin in the Pediatric Population

A number of fascinating reports discussed treatment with metformin. Jones and colleagues[1] studied 82 children with type 2 diabetes aged 10 to 16 years who had an average HbA1c of 8.6%, fasting glucose of 182 mg/dL, and weighing 92 kg. Results of this study showed that metformin at a dose of 500-1000 mg twice daily lowered fasting glucose levels by 43 mg/dL in 40 patients. Patients in the control group (n = 30) experienced an average 21 mg/dL increase in blood glucose levels. Metformin treatment did not produce a change in body weight, suggesting that it should be used in the treatment of pediatric type 2 diabetes. In another fascinating study of pediatric diabetes, Walravens and colleagues[2] studied 80 teenagers with poorly controlled type 1 diabetes, with mean HbA1c of 9.6%, despite treatment with > 1 unit insulin/kg body weight. Metformin 500 mg twice daily was given to half of these patients. Assessment at 3 months showed that compared with placebo, metformin decreased HbA1c (9.4%vs 8.7%), decreased mean blood glucose (224 vs 190 mg/dL), and decreased body weight (70 vs 64 kg).

Glycemic Effect of Metformin Extended-Release Formulation

In adults with type 2 diabetes, Brazg and colleagues[3] studied an extended-release (XR) formulation of metformin administered once daily in 742 patients with type 2 diabetes whose HbA1c was at 8.3% using diet and exercise. Treatment with metformin XR decreased HbA1c by 0.6%, 0.7%, 1.0%, and 1.0% using 500 mg, 1000 mg, 1500 mg, and 2000 mg respectively, and by 1.2% at a dose of 1000 mg twice daily. Fasting blood glucose decreased by 23, 27, 36, 37, and 41 mg/dL, respectively. Gastrointestinal side effects were similar with the extended-release and the immediate-release (IR) formulations. In another study, Fujioka and colleagues[4] studied 217 patients being treated with metformin IR 500 mg twice daily. Patients either continued taking this regimen or were changed over to XR at doses of 1000 mg or 1500 mg daily. HbA1c was 7.0% at baseline, and at 24 weeks was increased 0.1% in IR patients and 0.3% and 0.1% in the patients taking 1000 mg and 1500 mg XR, respectively. Fasting glucose increased 14mg/dL in the IR group and 12 mg/dL and 8 mg/dL in the patients taking 1000 mg and 1500 mg XR, respectively.

Combining Metformin with Glyburide

The effect of a combination regimen of metformin and glyburide was studied by a number of investigators. Donovan and colleagues[5] randomized 806 patients with type 2 diabetes to placebo, glyburide 2.5 mg, metformin 500 mg, and 2 combination formulations of metformin/glyburide (250 mg/1.25 mg or 500 mg/2.5 mg). After 20 weeks, fasting glucose changed from baseline levels of 175-179 mg/dL to 182, 143, 154, 137, and 137 mg/dL in the respective treatment groups. Doses were then titrated up to 4 doses per day over an 8-week period. In the respective treatment groups HbA1c decreased 1.3%, 0. %, 1.7%, and 1.7% with 2 doses per day

and 1.1%, 1.2%, 1.9%, and 2.2% with four.[6] Comparing the different agents in the same study based on initial HbA1c levels, Garber and colleagues[7] reported greater HbA1c-lowering efficacy of combination glyburide/metformin compared with either agent alone, although this reached significance only when baseline HbA1c levels exceeded 9%, a level at which one would not expect monotherapy to be fully effective. Whether the initial use of combination tablets will give the same duration of glycemic control as the usual approach of starting with 1 agent can only be addressed by long-term studies. Hypoglycemia was more frequent with the high-dose combination than with either monotherapy or with the low dose combination, suggesting that the lower dose is be preferable for initial use.[8]

Guidelines for Metformin Use are Often Poorly Followed

It is noteworthy that guidelines for metformin use are often not properly followed. Calabrese and colleagues[9] conducted a retrospective evaluation of 263 hospital admissions to the University of Pittsburgh Medical Center during which at least 1 dose of metformin was administered. An elevated serum creatinine was present or developed during 32 admissions but metformin was appropriately discontinued in only 8 of these patients. Concomitant administration of iodinated contrast agents occurred during 97 admissions.

Cardiovascular Effect of Metformin is Independent of the Antihyperglycemic Effect

The cardiac benefits of metformin monotherapy in the United Kingdom Prospective Diabetes Study exceeded those for insulin and sulfonylureas. Ruggiero-Lopez and colleagues[10] reported that methylglyoxal, a reactive dicarbonyl that leads to the formation of advanced glycation end products is cleared more rapidly in patients taking metformin by formation of a stable product, triazepinone. They suggested that metformin acts to clear methylglyoxal independent of its antihyperglycemic effect, and that this may contribute to the prevention of chronic diabetic complications.

Non-TZD PPAR-gamma Agonists Join TZDs in the Fight on Insulin Resistance

The thiazolidinediones (TZD) are agonists of the peroxisome proliferator-activated receptor-gamma (PPAR-gamma). Approaches to treatment with these and several new non-TZD PPAR-gamma agonists were reported at the 60th Scientific Sessions.

The Effect of TZDs is Mediated by Adipocytes

In a study of the mechanism of action of TZDs, Eckel and colleagues[11] reported that the decrease in insulin receptor substrate-1 (IRS-1) expression in myocytes incubated with the cytokine co-culture with adipocytes and tumor necrosis factor-alpha (TNF-alpha) was reversed by troglitazone. In the absence of adipocytes troglitazone had no effect. This complex experiment supports the hypotheses that TZDs have a direct action on the adipocyte and that these agents may reverse effects of cytokines on insulin resistance. Yokoyama and colleagues[12] reported that cardiac and skeletal muscle glucose utilization, as well as whole-body glucose uptake, was decreased in 26 patients with type 2 diabetes; these parameters were increased by treatment with TGZ. This effect was accompanied by a fall in circulating free fatty acid levels. Mahankali and colleagues[13] reported an increase in insulin sensitivity of 33% to 39%, an increase in glycogen formation, and a fall in free fatty acid levels during glucose clamp studies in 8 patients with type 2 diabetes who were treated with 45 mg daily of pioglitazone for 4 months. Fasting glucose decreased from 174 mg/dL to 147 mg/dL and HbA1c decreased from 7.8% to 6.6%. Indirectly addressing the mechanism of pioglitazone action, Mathisen and Brockley[14] observed that body weight gain in a total of 2319 patients treated with pioglitazone correlated with an improvement in HbA1c, suggesting that an increase in adipocyte mass is directly related to the mechanism of action of this agent.

The Effect of Combination Therapy on Glycemic Control

Strowig and colleagues[15] reported on the glycemic effects of the combination of TGZ 600 mg daily, metformin 2 g daily, and insulin (triple therapy), compared with either oral agent alone in combination with insulin (double therapy) in a 16-week study of 21 patients with type 2 diabetes. HbA1c decreased from 6.7% with double therapy to 6.0% with triple therapy, suggesting that this is a promising approach for optimizing glycemic control. The same investigators conducted a 16-week study[16] comparing insulin, insulin plus metformin, and insulin plus TGZ in 69 patients initially treated with insulin alone. HbA1c decreased from 8.7% to 7.1%, from 8.9% to 7.2%, and from 8.5% to 6.4%, respectively, suggesting possible modest greater effect of TGZ. A study by Kim and colleagues[17] compared the efficacy of adding TGZ 600 mg daily or metformin 850 mg 3 times daily to an existing regimen of glyburide 10 mg twice daily in 22 patients with type 2 diabetes having an HbA1c higher than 8.5%. Clamp studies showed an improvement in glucose uptake of 44% with TGZ and 20% with metformin. Free fatty acids decreased from 0.58 to 0.44 mEq/L in the TGZ group, compared with an increase from 0.44 to 0.48 mEq/L in the metformin group. TGZ reduced HbA1c from 8.6% to 7.0%, whereas metformin caused a reduction from 9.2% to 7.6%, suggesting overall clinical similarity despite somewhat different mechanisms of action

Ovalle and Bell[18] compared C-peptide-glucose ratios before and after the addition of TGZ to a failing double-therapy regimen of metformin and sulfonylurea in 28 patients with those in a group of 26 patients treated with addition of metformin to a sulfonylurea. C-peptide increased from 3.2 to 4.2 with addition of TGZ and from 4.8 to 5.0 with metformin. The C-peptide-glucose ratio increased from 1.9 to 3.1 in the former group while remaining unchanged at 3.4 in latter group. Using a different approach, Porter and colleagues[19] analyzed 947 patients treated with rosiglitazone either added to glyburide or compared with placebo. Whereas the proinsulin to insulin ratio decreased with rosiglitazone in a dose-dependent fashion, it increased with either placebo or with glyburide alone, suggesting improvement in beta-cell function.

TZDs is Effective in Previously Untreated Type 2 Patients

To assess the efficacy of rosiglitazone monotherapy in previously untreated patients with type 2 diabetes, Grunberger and colleagues[20] analyzed 2090 patients enrolled in 3 multicenter double-blind studies of rosiglitazone monotherapy. Between 32% and 62% of patients failed to show a decrease of at least 0.7% in HbA1c, although 59% to 86% achieved HbA1c levels ≤ 8% during the 26- to 52-week study. Brockley and Schneider[21] analyzed a related important question -- what is the initial glycemic response in patients treated with pioglitazone? An analysis of 3 trials of pioglitazone monotherapy in 595 patients showed 10 mg/dL and 19 mg/dL decreases in blood glucose at 2 weeks and 11 mg/dL and 31 mg/dL decreases at 4 weeks with 15 mg and 30 mg pioglitazone, respectively. In an additional analysis, Schneider and colleagues[22] observed that for untreated patients whose fasting glucose exceeded 280 mg/dL, daily treatment with pioglitazone 7.5 mg, 15 mg, 30 mg, and 45 mg for 26 weeks decreased fasting glucose by 30, 48, 33, and 71 mg/dL. For those whose fasting glucose was ≤ 280 mg/dL, however, the respective decreases were 9, 17, 25, and 43 mg/dL. At the same time, patients in the placebo group having a fasting glucose under 280 mg/dL showed an increase of in fasting blood glucose of 23 mg/dL, whereas those with a fasting glucose over 280mg/dL showed a decrease in fasting blood glucose of 5 mg/L.

Nonglycemic Effects of TZDs

Another fascinating area of investigation is the nonglycemic effects of TZD. Chu and colleagues[23] reported that 22 patients treated with glyburide 10 mg twice daily showed a 35% fall in C-reactive protein with the addition of metformin 850 mg 3 times a day without changes in low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, or LDL size. Those randomized to TGZ 600 mg daily, however, had a 1.34% increase in

LDL size, 11% increase in HDL cholesterol, 21% fall in triglycerides, and 60% fall in C-reactive protein, suggesting greater beneficial effect on cardiovascular risk-factors. Similarly, Shaffer and colleagues[24] reported 9% to 10% decreases in serum triglycerides and 12% to 19% increases in HDL cholesterol with pioglitazone 15mg to 45 mg daily. Owen and colleagues[25] reported that in studies of 1181 patients treated with rosiglitazone at recommended doses, rosiglitazone decreased gamma-glutamyltransferase levels 6% to 14% compared with controls. The investigators suggested that an increase in this serum enzyme is a marker for increased visceral and hepatic fat, supporting the benefit of rosiglitazone in promoting increases in subcutaneous adipose tissue while decreasing these potentially-harmful abdominal fat deposits. Bakris and colleagues[26] conducted a study to assess the effect of TZDs on blood pressure. In this study, 203 patients were randomized to receive either rosiglitazone or glyburide. Compared with patients in the glyburide group, those in the rosiglitazone group experienced a 3 to 4 mm Hg mean decreased in blood pressure at weeks 28 and 52 of the study. Crandall and colleagues[27] reported decreased thrombogenicity with TGZ, and Aljada and colleagues[28,29] reported on the anti-inflammatory and antiatherosclerotic effects of TGZ on monocytes. Oka and colleagues[30] reported that TGZ increased vascular endothelial growth factor, which also has antiatherosclerotic potential, although this requires consideration of the potential adverse effects on retinopathy.

TZDs Alter the Metabolism of Glucocorticoids

Davidson and colleagues[31] reviewed the management of glycemia in patients treated with glucocorticoids, a common cause of hyperglycemia in hospitalized patients. Of 25,309 admissions to their hospital in 1998, 6631 persons received doses equivalent to at least 50 mg prednisone daily. A sample of 100 patients from this group showed that 19% had preexisting diabetes with glucose levels ≥ 200 mg/dL. Management of hyperglycemia was unsuccessful in 67% of these patients. Furthermore, 26% of the 81% of the glucocorticoid-treated patients who did not have previously recognized diabetes did not undergo glucose testing. Fifty-two percent of those not known to have diabetes who had their glucose measured had diabetes-range glucose levels, and 77% required glycemic treatment, however only 20% of these achieved glucose levels <200 mg/dL. Therefore, better approaches to treatment are clearly required.

The thiazolidinediones (TZDs) may be useful in this regard. Studies by Ishida,[32] Ishii,[33] Willi,[34] and Morita[35] reported the benefit of both TGZ and pioglitazone on glycemic control in patients undergoing corticosteroid therapy and made the interesting additional observation that TGZ increases glucocorticoid metabolism in a way that is similar to the way it increases the metabolism of oral steroid contraceptives. Hence, the beneficial effect of TGZ on glycemic control could be mediated by a decrease in the desired steroid action. Further studies with currently used TZDs are required to assess the time course, efficacy, and potential adverse effects of these agents in patients requiring steroid treatment.

Non-TZD PPAR-gamma Agonists

The effect of treatment with a new L-tyrosine-based non-TZD PPAR-gamma agonist, GI262570, was assessed by a number of investigators. In vitro GI262570 was more efficacious than TZDs at inducing or stabilizing transcriptionally-relevant receptor complexes of PPAR-gamma with the retinoid X receptor (RXR).[36] O'Connor-Semmes and colleagues[37] reported dose-related decreases in glucose, insulin, and triglycerides before and 2 weeks after treatment with GI262570 in 35 patients with type 2 diabetes. Fiedorek and colleagues[38] treated 376 patients with type 2 diabetes for 12 weeks with 1 mg, 2 mg, 5 mg, or 10 mg GI262570 daily. Treatment decreased fasting glucose by 8, 28, 48, and 66 mg/dL, respectively from a baseline of 201-208 mg/dL, This compares with an increase of 22 mg/dL with placebo. HbA1c was 7.8% to 8.1% at baseline and increased 1.1% with placebo and 0.7% and 0.3% with 1-mg and 2-mg doses; HbA1c decreased 0.3% and 0.7% with the 5- and 10-mg doses. Wilson and colleagues[39] reported that treatment with GI262570 produced beneficial

changes in lipids, as shown by 44% and 53% falls in triglycerides and 12% and 15% increases in HDL cholesterol with the 5- and 10-mg doses, respectively.

In a combination clinical study, Raz and colleagues[40] treated 385 patients with type 2 diabetes who were inadequately controlled on glyburide 15 g daily with GI262570 at doses of 0, 1, 2, 5, or 10 mg daily for 12 weeks. Fasting glucose levels decreased within 2 to 4 weeks in 85% of patients receiving 5 mg or 10 mg daily. Patients experienced a decrease in HbA1c of at least 0.7% from baseline levels of 9.6% to 10.0% -- falling, on average, 0.7%, 0.5%, 1.9%, and 2.1% in the 1-, 2-, 5-, and 10-mg groups at 12 weeks. Dose-related weight gain, peripheral edema, and decreases in hemoglobin were similar to that reported with the TZDs. In the same study, Edwards and colleagues[41] reported that triglycerides decreased 32% and 40% and HDL-cholesterol increased 21% and 23% with the 5- and 10-mg doses, respectively, at 12 weeks.

New TZD and TZD-like Compounds in Development

A number of other TZD and TZD-like agents are being developed, including a TZD with a long half-life (NIP-221), which appears to be similar in potency to rosiglitazone.[42] Other new TZDs are CS-011[43] and CI-1037/CS-011,[44] a TZD-linked to a non-TZD, and CLX-0921, which appears to cause less fluid retention.[45,46] The isooxazolidinedione, PNU-182716 (JTT-501) produced less weight gain than pioglitazone or rosiglitazone in rodent models,[47] and may prove beneficial for this reason.

Non-PPAR agents affecting glycemia were also studied. Juang and colleagues[48] reported no effect of treatment with 400 mg chromium trinicotinate twice daily in 15 patients with impaired glucose tolerance in a 4-month placebo-controlled trial.[48] Caiapo, an extract of white sweet potatoes, was given in doses of 2 g and 4 g daily for 6 weeks to 18 men with type 2 diabetes. Treatment produced an improvement in insulin sensitivity and glucose tolerance.[49] Interestingly, Kusano and colleagues[50] reported that daily administration of white-skinned sweet potato to the obese Zucker fatty rat (100 mg/kg body weight) produced an effect similar to that of troglitazone 50 mg/kg/daily. Finally, masoprocol, which lowers glucose levels in rodent type 2 diabetes models, was found to act by inhibiting hepatic glucose-6-phospatase.[51]

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