ROLE OF THIAZOLIDINEDIONES IN THE MANAGEMENT OF TYPE 2 DIABETES: FOCUS ON ETHNIC MINORITY POPULATIONS

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Persons from ethnic minority populations in the United States suffer disproportionately more from type 2 diabetes and its complications than do Caucasians. Genetic and acquired factors likely contribute to the ethnic disparities of type 2 diabetes. The pathophysiologic hallmarks consist of insulin resistance, progressive pancreatic β-cell dysfunction, and excessive hepatic glucose production. The ideal treatment for type 2 diabetes should correct insulin resistance and β-cell dysfunction; and normalize hepatic glucose output; and prevent, delay, or reverse diabetic complications. The discovery of a new class of drugs, thiazolidinediones, has provided an effective tool to correct key underlying defects in type 2 diabetes. Thiazolidinediones improve insulin sensitivity and have beneficial effects on pancreatic β-cell function and hepatic glucose production. Furthermore, their potent insulin-sensitization effect predicts that treatment with thiazolidinediones will improve cardiovascular risk factors, including lipid profile, fibrinolysis, endothelial function, and atheroinflammatory markers. These benefits are expected to be particularly important among ethnic minority patients who tend to have greater insulin resistance than do Caucasians. (*Ethn Dis*. 2006;16:51–57)

Key Words: Thiazolidinediones, Diabetes

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INTRODUCTION

More than 150 million people worldwide have diabetes, the prevalence of which is increasing so rapidly that the number of adults with diabetes in the world will rise to 300 million in the year 2025.[1] Data from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that the number of prevalent cases of adults with diagnosed type 2 diabetes increased from 8.1 million in 1988–1994 to 10.3 million in 1999–2000.[2] The latter number increased to 13.3 million in 2002,[3] and it is projected to keep increasing during the next decade.

Epidemiologic studies have reported that compared to Caucasians, the prevalence of diabetes is higher in Native Americans, Hispanics, Asian-Americans, African Americans, and Pacific Islanders.[4] Recent surveys indicate further increases in diabetes prevalence among ethnic minorities.[5] Asian Americans are approximately twice as likely to develop diabetes as Whites, even though they are less obese.[6]

RISK FACTORS FOR INCREASED TYPE 2 DIABETES IN MINORITY POPULATIONS

"Westernization" superimposed on a "thrifty" genotype has been proposed as an explanation for the higher prevalence of type 2 diabetes in ethic minority groups.[7] Although genetic factors may influence the development of diabetes in some minority groups, the increase in prevalence of diabetes observed in migrant populations happens immediately and does not wait several generations. This observation suggests that environmental factors play a major role in the pathogenesis of ethnic disparities in diabetes prevalence.[8–11]

Specific environmental and lifestyle factors that promote diabetes risk include obesity,[12–16] a known risk factor for insulin resistance and metabolic syndrome.[17–19] The effect of adipose tissue distribution and resultant insulin resistance is particularly striking among Asian populations.[20,21] Other risk factors include physical inactivity, which is quite prevalent among minority populations,[22] and dietary practices that promote insulin resistance.[23,24]

The prevalence of several of the diabetic complications is also higher among some ethnic minorities compared to Caucasians.[4,25–27] Asian patients with diabetes appear to be at a lower risk of lower-extremity amputation than Caucasians and other populations.[28] Diabetes-related mortality also has been reported to be higher in African Americans compared with their European-American counterparts.[29]

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

The development of type 2 diabetes is characterized by progression from normal glucose tolerance to impaired glucose tolerance to diabetes. Insulin resistance and impaired insulin secretion

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are demonstrable at every stage of this transition.[30–32] Both insulin resistance and insulin secretory dysfunction play pathogenic roles during the development of type 2 diabetes and are targets for concurrent therapeutic interventions.[30] Insulin resistance is a hallmark of the metabolic syndrome–a cluster of abnormalities that includes dyslipidemia, hypertension, obesity, and defects in coagulation, inflammation, and fibrinolysis.[33–35] Several studies have reported greater insulin resistance among ethnic minority subjects compared to Caucasians.[36,37]

The final common pathway responsible for the development of type 2 diabetes is the failure of the pancreatic β-cell to compensate for insulin resistance.[32,38,39] The exact mechanisms underlying β-cell dysfunction are not well understood.

GOALS OF THERAPY

The therapeutic goals in type 2 diabetes are alleviation of symptoms through normalization or near-normalization of fasting and postprandial blood glucose levels and prevention of acute and long-term complications. Prospective randomized clinical trials[40–42] have shown that improved glycemic control decreases the rates of retinopathy, nephropathy, and neuropathy. In these trials, treatment regimens that reduced average hemoglobin A1C to ≤7% were associated with the best outcomes.[43,44]

Nonpharmacologic Therapy

Nonpharmacologic treatment modalities such as reduced caloric intake and physical activity constitute the foundation of diabetes management.[45–48] Clinical studies have demonstrated a consistently beneficial effect of exercise on carbohydrate metabolism by enhancing insulin sensitivity, cardiovascular risk factors, muscular strength, and sense of well-being.[47] Initial physical activity recommendations should be modest, based on the patient's willingness and ability, gradually increasing the duration and frequency to 30–45 minutes of moderate aerobic activity 3–5 days per week, when possible. Greater activity levels of at least one hour per day of moderate (walking) or 30 minutes per day of vigorous (jogging) activity may be needed to achieve sustained metabolic benefits.[48]

Pharmacologic Therapy

According to data from the Centers for Disease Control and Prevention, in 2002, 11.0 million adults with diabetes reported taking some type of medication for their diabetes,[3] with comparable rates of medication use among Caucasians (77.7%), African Americans (87.9%), and Hispanics (78.7%). Of the adults taking diabetes medications, 7.4 million reported taking only oral agents, 2.0 million reported taking only insulin, and 1.6 million reported taking both insulin and oral medications.

The oral antidiabetic agents include sulfonylureas (tolbutamide, chlorpropamide, glyburide, glipizide, and glimepiride), benzoic acid derivatives (repaglinide), D-phenylalanine derivatives (nateglinide), α-glucosidase inhibitors (acarbose and miglitol), biguanides (metformin), and thiazolidinediones (rosiglitazone and pioglitazone).[49–51]

Sulfonylureas, repaglinide, and nateglinide act as insulin secretagogues by binding to and closing ATP-dependent potassium channels on pancreatic β-cells. These drugs can be used as monotherapy for type 2 diabetes, or in combination with other agents.[49,52] The β-glucosidase inhibitors work by inhibiting the absorption of carbohydrate from the gut.[53] Metformin, the only biguanide currently available in the United States, exerts its glucose-lowering effect primarily by reducing hepatic glucose production and, to a lesser extent, by increasing muscle glucose utilization.[54–56] Notably, metformin therapy was associated with a 39% reduction in the risk of myocardial infarction in the United Kingdom Prospective Diabetes Study (UKPDS).[52]

Data from clinical studies indicate no ethnic differences in the glycemic response to sulfonylurea, metformin, or insulin therapy among Caucasians and minority populations.[57] Of interest, in the Veterans Affairs Cooperative Study of intensive insulin therapy for type 2 diabetes, response rates (indicated by decrements in HbA1C level) were greater in African Americans than in non-African Americans.[58]

THIAZOLIDINEDIONES

Effects on Insulin Resistance

The thiazolidinediones (TZDs) enhance insulin sensitivity mainly at the level of muscle and adipose tissue, with some effect in the liver, resulting in increased insulin-dependent glucose disposal.[59] The TZDs' binding to a nuclear receptor—peroxisome proliferator-activated receptor γ (PPARγ)—enhances the expression and transcription of multiple genes that encode proteins, which modulates glucose and lipid metabolism.[59] Activation of PPARγ receptors promotes differentiation of adipocytes and induction of lipogenic and glucoregulatory proteins. The TZD treatment improves insulin-stimulated glucose disposal as well as other components of the metabolic syndorme.[55,59–61] The TZDs also induce the lipoprotein lipase, thereby increasing triglyceride uptake into fat and reducing circulating free fatty acids

(FFAs).[59,60] The TZD therapy leads to a reduction in circulating triglycerides levels, modest increases in high-density lipoprotein (HDL) levels, decrease in blood pressure, reduction in plasminogen activator inhibitor (PAI)-1 levels, and attenuation of microalbuminuria.[55,59–61]

African-American, Hispanic, and Asian subjects have been reported to have higher rates of insulin resistance compared to non-Hispanic White subjects.[62,63] In the San Antonio Heart Study, Hispanic Americans had a greater constellation of metabolic syndrome markers compared with non-Hispanic White subjects.[63] Treatment with TZDs appears to improve insulin resistance and glycemic control across all ethnic groups. Osei et al[64] compared the effects of treatment with 4 mg or 8 mg daily doses of rosiglitazone in African-American and non-African-American patients with type 2 diabetes. Compared to non-African Americans, African-American patients experienced a greater magnitude of HbA1C reduction in response to rosiglitazone therapy. The differences persisted after adjustment for baseline HbA1C levels, sex, body mass index, and prior form of therapy: the changes in HbA1C levels were −1.89% (95% confidence interval [CI] −2.59 to −1.20) for African Americans compared to −1.29 (95% CI −1.46 to −1.12) in non-African Americans. Similarly, TZDs have been shown to be safe and highly effective in prospective and randomized trials in Hispanics and other minority populations.[65,66]

Effects on β-Cell Function

The UKPDS data indicated that pancreatic β-cell function is significantly depleted at the time of diagnosis of type 2 diabetes. Progressive deterioration of β-cell function predicts failure of sulfonylureas and metformin to maintain glycemic control. The pathophysiology of progressive β-cell failure in patients with type 2 diabetes is not well understood, but factors such as glucose toxicity, lipotoxicity, and insulin resistance within the β-cells have been suggested.

Recent data indicate that β-cell function improves significantly following treatment with TZDs.[16,17] The TZDs enhance the responsiveness and efficiency of β-cells, presumably by decreasing glucose and FFA levels, both of which have deleterious effects on insulin secretion.[30,67] Preliminary data also suggest that TZDs prolong β-cell survival[68] through multiple mechanisms, including amelioration of insulin resistance, reduction in circulating FFA levels, and correction of lipotoxicity. Using the homeostasis model assessment method to assess insulin sensitivity and β-cell function, treatment with rosiglitazone at a dose of 8 mg/day in patients with type 2 diabetes reduced insulin resistance by 33% and improved β-cell function by 65%;[69] similar results have been reported with combination therapy with sulfonylurea and metformin.[70,71]

Effects on Glucose Tolerance and Glycemic Control

The TZDs reduce fasting and postprandial glucose levels and HbA1C initially through actions on insulin sensitivity and later by pancreatic rejuvenation and increased β-cell regranulation.[56] This reduction occurs in a dose-related manner with both monotherapy and combination therapy.[69,72,73] Controlled clinical trials assessing the efficacy of rosiglitazone[72,74] and pioglitazone[75] as a single therapeutic agent in type 2 diabetes showed an average decrease of fasting plasma glucose levels by ≈45–60 mg/dL and HbA1C by ≈1%–2%.[72,74,76] Larger decreases in HbA1C from baseline were observed in obese and drug-naive subjects and in patients with higher baseline HbA1C values.[69,72,73] The TZDs are indicated as monotherapy or as combination therapy with sulfonylureas, metformin, or insulin.[76]

A recent European study compared metabolic control in drug-naive type 2 diabetes patients given either pioglitazone or metformin for one year.[77] A total of 1199 patients with poorly controlled type 2 diabetes mellitus (HbA1C 7.5%–11%) were randomized to receive either pioglitazone (≤45 mg/day) or metformin (≤850 mg three times daily). Treatment with either TZD or metformin resulted in comparable reductions in HbA1C levels from baseline to week 52 (−1.4% and −1.5%).

The most clinically relevant side effects of the TZD class are weight gain, fluid retention, and peripheral edema. Although improved glycemic control accounts for some weight gain, most of it occurs from a net increase in fat.[78,79] Some patients taking TZDs experience fluid retention that may contribute to weight gain, peripheral edema, and reduction of hemoglobin values from hemodilution. Fluid retention is caused by increased permeability of capillaries.[79] Dependent edema can be lessened by removal of concurrent medications that promote edema formation (eg, dihydropyridine calcium channel blockers, nonsteroidal anti-inflammatory agents), empiric use of loop diuretics, or reduction in the dose of TZD. Because the increase in plasma volume may worsen subclinical heart failure, these agents are not recommended in patients with NYHA class III or IV congestive heart failure.

The incidence of elevated liver enzyme levels in diabetic patients treated with TZDs are similar to the placebo.[80] Although no cases of acute liver failure or severe liver dysfunction have been reported with the use of rosiglitazone or pioglitazone, the FDA has recommended monitoring liver function at baseline before initiating TZD therapy. The incidence of side effects is similar with the use of rosiglitazone and pioglitazone[76] and among different ethnic groups.[81,82]

Effect on Macrovascular Disease

Macrovascular complications (coronary artery disease, stroke, and periph-

eral vascular disease) are increased two- to five-fold in patients with diabetes.[51,83] Many such patients have had the insulin resistance syndrome for years before the diagnosis of type 2 diabetes. People with the metabolic syndrome are at increased risk for developing diabetes and cardiovascular disease[83,84] as well as increased risk of death from cardiovascular disease and all causes.[85] The unadjusted and age-adjusted prevalence of the metabolic syndrome among US adults were 21.8% and 23.7%, respectively.[86] The prevalence differed little among men (24.0%) and women (23.4%). It was highest among Mexican Americans (31.9%) and lowest among Whites (23.8%), African Americans (21.6%), and people reporting an ''other'' race or ethnicity (20.3%). African-American and Mexican-American women had approximately a 57% and 26% higher prevalence of metabolic syndrome than men, respectively.

Dysregulation of FFA metabolism plays a central role in the development of the insulin resistance syndrome and its relation to the risk of cardiovascular disease.[87,88] Thiazolidinedione therapy is associated with a decrease in circulating FFA levels.[55,59,60] Relationship between PPARγ ligands (such as the thiazolidinediones) and atherosclerosis is not fully understood. The PPARγ is involved in differentiation and uptake of oxidized LDL by macrophages, which suggests that they may help regulate gene expression during atherogenesis. Insulin-resistant subjects also have a defect in insulin-stimulated nitric oxide production and impaired endothelial-mediated vasodilatation, which parallels their defect in glucose transport.

The TZDs improve blood pressure in patients with diabetes. Rosiglitazone treatment (8 mg/daily for 16 weeks) in nondiabetic, hypertensive patients significantly reduced mean systolic and diastolic blood pressure.[89] Changes on blood pressure were closely correlated with enhanced insulin sensitivity and improvement on cardiovascular risk factors (triglycerides, PAI-1, and C-reactive protein).[90] In addition, the TZDs exert a number of antiatherogenic effects on the vascular wall, including modulating smooth muscle proliferation and migration, reducing cytokine production and macrophage activation, and suppressing matrix metalloproteinase production in macrophages.[91] Furthermore, the use of TZDs frequently results in improvement in lipid profile. High-density lipoprotein (HDL) cholesterol concentrations increase with TZD therapy, and triglyceride concentrations frequently fall.[55,92] The effect on low-density lipoprotein (LDL) cholesterol concentrations is more variable,[92,93] and recent reports suggest that TZDs may result in a rise in LDL cholesterol concentrations due to a shift from small, dense to large, buoyant low-density lipoprotein particles, which are less atherogenic.[93]

COMBINATION THERAPY

The UKPDS study showed that type 2 diabetes is a progressive disease that requires multiple therapies to achieve glycemic target levels in the long term.[46] After three years, ≈50% of patients could attain the therapeutic goal of HbA1C <7% with monotherapy. By nine years, this number declines to ≈25%. Numerous studies have shown the additive glucose-lowering effect of the combination of an insulin-sensitizing agent and an insulin secretagogue.[49,52,55,71,73,83,93] Combination therapy involving drugs with distinct mechanisms of action will not only improve glycemic control but also result in lower overall drug dosing in some settings and minimize adverse effects.[49,50,94,95]

The most popular combinations are sulfonylureas and metformin, metformin and TZD, and sulfonylurea and TZD. No evidence suggests that a specific combination is any more effective in lowering glucose levels or more effective in preventing complications than another. Since HbA1C reduction is the overriding goal in all patients, the precise combination used may not be as important as the glucose levels achieved. To facilitate compliance with combination treatment, fixed combination tablets containing glyburide and metformin, glipizide and metformin, and rosiglitazone and metformin have recently become available.[96,97] Patients with severe type 2 diabetes who are not acutely ill and are not ketotic may be treated with double or triple oral therapy.[95]

The introduction of the TZD class of antidiabetic agents provides a unique opportunity to concurrently ameliorate insulin resistance and β-cell dysfunction and reduce macrovascular risk factors for patients with type 2 diabetes.

CONCLUSION

Peripheral insulin resistance and β-cell dysfunction constitute key defects underlying the pathophysiology of type 2 diabetes. Insulin resistance is a risk factor for macrovascular disease. The therapeutic goals in type 2 diabetes are alleviation of symptoms through normalization or near-normalization of fasting and postprandial blood glucose levels and prevention of acute and long-term complications. In terms of glycemic effect alone, no compelling reason exists to favor one antidiabetic agent (sulfonylurea, metformin, or TZD) over another. However, because metformin is the only drug associated with weight loss, or at least weight neutrality, it has become the most widely prescribed

single antihyperglycemic drug and is generally regarded as the best first-line agent, at least in the obese patient without contraindications for its use.[50] The introduction of the TZD class of antidiabetic agents provides a unique opportunity to concurrently ameliorate insulin resistance and β-cell dysfunction and reduce macrovascular risk factors for patients with type 2 diabetes. Combination therapy involving agents with distinct mechanisms of action will not only improve glycemic control but also result in lower overall drug dosing in some settings and minimize adverse effects.

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