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Target Audience

This educational activity is designed for primary care physicians, internal medicine specialists, endocrinologists, diabetologists, cardiologists, and other healthcare professionals involved in the care and management of patients with type 2 diabetes, insulin resistance, and cardiovascular disease.

Learning Objectives

With information from the latest evidence-based studies, participants should be able to:

- Identify patients with insulin resistance, type 2 diabetes, and/or cardiovascular disease
- Select the most appropriate therapeutic regimen for patients with type 2 diabetes and its macrovascular and microvascular complications
- Identify risk factors for cardiovascular disease in patients with type 2 diabetes and select an appropriate therapeutic regimen

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Some of the drug treatments discussed in this issue may note uses not approved by the Food and Drug Administration. Articles containing such uses will be noted at the end of the article.

Additional PPS Staff Disclosures

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Addition of Exenatide to Thiazolidinedione Therapy Improves Glycemic Control and Reduces Body Weight in Patients With Type 2 Diabetes

Exenatide, the first in a new class of anti-hyperglycemic agents called incretin mimetics, is approved for treating type 2 diabetes in combination with metformin, a sulfonylurea, metformin plus a sulfonylurea, or a thiazolidinedione (TZD). However, there are few data regarding the efficacy of combining exenatide with a TZD. The combination could be effective because exenatide and TZDs exert complementary actions that target β -cell dysfunction and insulin resistance—the primary pathophysiologic defects in hyperglycemia of type 2 diabetes.

Zinman and colleagues tested the effects of this combination in patients with type 2 diabetes. Conducted at 49 sites in Canada, Spain, and the United States, this randomized, double-blind trial involved 233 patients with type 2 diabetes that was suboptimally controlled with TZD treatment. Patients were randomized to receive either exenatide (10 μ g; twice-daily subcutaneous abdominal injections) (n=121) or placebo (n=112) added to a TZD (with or without metformin) for 16 weeks. Patients were required to be on stable doses of a TZD (rosiglitazone ≥ 4 mg/d or pioglitazone ≥ 30 mg/d). The mean \pm standard error (SE) baseline glycated hemoglobin (A1C) level was $7.9\% \pm 0.1\%$. The primary outcome was change from baseline in A1C level. Other outcomes included fasting serum glucose level, body weight, self-monitored blood glucose level, and adverse events.

After 16 weeks, A1C levels decreased by a mean (\pm SE) of $0.89\% (\pm 0.09\%)$ in the exenatide group but increased by mean of $0.09\% (\pm 0.10\%)$ in the placebo group. The mean between-group difference in A1C levels was -0.98% (95% confidence interval [CI], -1.21% to -0.74% ; $P < 0.001$). An A1C level of $\leq 7\%$ was achieved by signifi-

cantly more patients treated with exenatide than those treated with placebo ($P < 0.001$). Baseline oral antihyperglycemic treatment (TZD alone vs TZD plus metformin) did not affect A1C levels ($P = 0.87$ for interaction).

After 16 weeks, mean \pm SE fasting serum glucose level decreased in the exenatide group (-28.6 ± 3.96 mg/dL) but increased in the placebo group (1.80 ± 3.78 mg/dL). The mean between-group difference in fasting serum glucose level was -30.4 mg/dL (CI, -40.0 to -21.1 mg/dL; $P < 0.001$). Self-monitored blood glucose profiles for the exenatide group were significantly lower at each measurement throughout the day at week 16 compared with baseline measurements ($P < 0.001$). In contrast, there were no changes in self-monitored blood glucose measurements between baseline and week 16 in the placebo group. Furthermore, exenatide treatment blunted postprandial glucose excursions.

Homeostasis model assessment (HOMA) of β -cell function increased by 19% from baseline in the exenatide group but decreased by 6% in the placebo group ($P = 0.005$). HOMA of insulin sensitivity at 16 weeks increased by 23% from baseline in the exenatide group and by 10% in the placebo group, with no significant difference between the 2 groups ($P = 0.20$).

Exenatide treatment was associated with a decrease in mean \pm SE body weight (-1.75 ± 0.25 kg), whereas placebo treatment was associated with essentially no change in body weight (-0.24 ± 0.26 kg) ($P < 0.001$). At week 16, the mean difference in body weight reduction between the 2 groups was -1.51 kg (CI, -2.15 to -0.88 kg; $P < 0.001$).

Discontinuation of treatment because of adverse events occurred in 16% of patients in the exenatide group and 2% of patients in the

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placebo group. Significantly more patients in the exenatide group than in the placebo group experienced nausea (40% vs 15%) and vomiting (13% vs 1%). The incidence of treatment-emergent edema was similar in the exenatide and placebo groups (6% vs 8%). The overall incidence of hypoglycemia, defined as symptoms or a self-monitored glucose <60 mg/dL, was also low and similar between the exenatide and placebo groups (11% vs 7%). No severe episodes of hypoglycemia were reported in either treatment group.

This study had several limitations. First, combinations with TZDs and sulfonylureas were not tested. Second, trial duration was relatively short. Third, the completion rate was low; only 71% and 86% of patients in the

exenatide and placebo groups, respectively, completed the study.

These results demonstrate that adding exenatide to TZDs in patients with type 2 diabetes that was suboptimally controlled with TZD therapy modestly improves glycemic control and reduces body weight but elicits more nausea and vomiting. This combination offers the potential for disease modification with a low risk for hypoglycemia and minimal weight gain.

Zinman B et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med.* 2007;146:477-485.

COMMENTARY

THOMAS A. BUCHANAN, MD, Professor of Medicine, Obstetrics and Gynecology, and Physiology and Biophysics at the Keck School of Medicine of the University of Southern California, Los Angeles, California.

This 16-week study by Zinman et al demonstrates that exenatide lowers glucose and A1C levels in patients with type 2 diabetes whose A1C levels remained between 7% to 10% despite treatment with a mid-range dose of a thiazolidinedione (TZD) with or without metformin. Given the different mechanisms of action of exenatide compared with TZDs, the results are not unexpected. The ~1% reduction in final A1C compared with placebo is potentially important, and the effect was associated with weight loss of ~1.5 kg on average, suggesting a clinical approach to mitigation of the weight gain associated with TZD treatment. On the downside, treatment was discontinued by twice as many people in the exenatide group as compared to the placebo group (29% vs 14%). The study provides clinicians with another option for at least short-term glycemic control in type 2 diabetes with the added benefit of modest weight loss but the complication of nausea and vomiting. The real question is whether the combination of GLP-1 based therapy and TZDs can stabilize or even reverse the progressive β -cell dysfunction that characterizes type 2 diabetes over the long term. A positive answer to that question would be a real advance in diabetes management, but it awaits longer and more mechanistically oriented studies.

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Disparities in Insulin Resistance and Risk Factors for Type 2 Diabetes and Cardiovascular Disease in Moderately Obese Individuals

Heterogeneity in metabolic abnormalities in moderately obese individuals has not been addressed in previous studies examining the relationship between obesity and morbidity and mortality. As such, McLaughlin et al assessed whether risk factors for type 2 diabetes and cardiovascular disease (CVD) vary among moderately obese individuals based on insulin sensitivity.

This cross-sectional analysis included 211 apparently healthy, moderately obese (body mass index [BMI], 30.0-34.9 kg/m²) adults who volunteered for weight loss studies at Stanford University, Stanford, California. Main outcome measures included insulin-mediated glucose uptake as quantified by the insulin suppression test and metabolic risk factors for type 2 diabetes and CVD.

The study population was stratified into tertiles based on differences in insulin action. Tertiles 1, 2, and 3 had mean steady-state plasma glucose concentrations of 81 mg/dL, 166 mg/dL, and 247 mg/dL, respectively ($P < 0.001$ for trend). Compared with the most insulin-sensitive third (tertile 1), the most insulin-resistant third of the population (tertile 3) demonstrated significantly higher systolic and diastolic blood pressure, higher fasting and 2-hour oral glucose load concentrations, higher plasma triglyceride concentrations, lower plasma high-density lipoprotein (HDL) cholesterol concentrations, and more prevalent impaired glucose tolerance (IGT) ($P < 0.001$ for trend for each risk factor). The most clinically relevant finding was the striking difference in IGT between tertiles 1 and 3 (2% vs 47%). Most of the values for the risk factors in

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Disparities in Insulin Resistance and Risk Factors for Type 2 Diabetes and Cardiovascular Disease in Moderately Obese Individuals

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tertile 3 were also significantly different from those in tertile 2. There were no significant differences between the groups with regard to total and low-density lipoprotein cholesterol concentrations.

Risk factors for developing type 2 diabetes or CVD assessed in this study included hypertension, hypertriglyceridemia (≥ 150 mg/dL), low HDL cholesterol (men, < 40 mg/dL; women, < 50 mg/dL), impaired fasting glucose (≥ 100 mg/dL), and IGT (2-hour level ≥ 140 mg/dL). All 5 risk factors were significantly greater when comparing tertile 3 with tertile 1 (ranging from adjusted odds ratios of 3.0 to 54.8).

Limitations of this analysis were inclusion of mostly white individuals, use of a volunteer sample, selection of apparently healthy individuals,

and lack of quantification of the development of diabetes.

This study revealed substantial disparities in insulin resistance and risk factors for type 2 diabetes and CVD in apparently healthy, moderately obese individuals. Therefore, not all obese individuals are at equal risk of developing diabetes or CVD. In light of these findings, the study investigators suggest that intensive therapeutic interventions should target the insulin-resistant subset of this population.

McLaughlin T et al. Heterogeneity in the prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus in obese individuals: effect of differences in insulin sensitivity. *Arch Intern Med.* 2007;167:642-648.

Traditional Obesity Threshold Might Be Too High for Non-European Populations

Body mass index (BMI) is commonly used to measure risk for type 2 diabetes and cardiovascular disease (CVD). However, because the obesity threshold (BMI > 30 kg/m²) was derived from samples that were predominantly white and of European descent, the appropriateness of applying this cut point in non-European populations is unclear. South Asian and Chinese individuals, for example, face an increased risk of type 2 diabetes, hypertension, and dyslipidemia at BMIs below the traditional threshold for obesity.

To define obesity cut points in different ethnic groups, Razak and associates assessed the metabolic risk associated with BMI in a cross-sectional study of 1,078 randomly sampled subjects from 4 ethnic groups (289 South Asians, 281 Chinese, 207 Aboriginals, and 301 Europeans) from 4 regions in Canada.

Principal components factor analysis was used to establish latent factors associated with 14 cardiometabolic markers (fasting glucose, 2-hour glucose, A1C, fasting insulin, 2-hour insulin, homeostasis model assessment insulin resistance, low-density cholesterol, high-density cholesterol, fasting triglycerides, 2-hour triglycerides, free fatty acids, 2-hour free fatty acids, systolic blood pressure, and diastolic pressure).

Three primary latent factors emerged: lipid metabolism, glucose metabolism, and blood pressure, and BMI cut points were identified where the degree of abnormality in these measures in the non-European groups approximated that found in Europeans with a BMI of 30 kg/m². For each of these latent factors, the main effect of ethnicity was highly significant ($P < 0.001$).

Compared with the BMI cut point of 30.0 kg/m² in Europeans, a similar glucose factor distribution was noted at corresponding BMI cut points of 21.0 kg/m² in South Asians, 20.6 kg/m² in Chinese, and 21.8 kg/m² in Aboriginals. A similar lipid factor distribution to Europeans with a BMI of 30.0 kg/m² occurred at a BMI of 22.5 kg/m² in South Asians, 25.9 kg/m² in Chinese, and 26.1 kg/m² in Aboriginals. Cut points for the elevation in the blood pressure factor occurred in South Asians at a BMI of 28.8 kg/m² and in Chinese at a BMI of 25.3 kg/m² compared with a BMI of 30.0 kg/m² in Europeans. No cut point for the elevation in the blood pressure factor was derived for Aboriginals, whose blood pressure values were substantially lower.

These data support the contention that "normal ranges" for obesity using BMI cut points derived in European populations are inappropriately high when applied to other ethnic populations such as South Asians, Chinese, and Aboriginals. They also suggest that cut points vary by risk factor. Among non-Europeans compared with Europeans, the cut point for obesity based on glucose and lipid factors is lower by approximately 6 kg/m². The study investigators suggest that revisions may be necessary for BMI thresholds among non-Europeans. Additional research is needed to determine if individuals from these ethnic groups who exceed these lower BMI cut points are at increased risk of CVD.

Razak F et al. Defining obesity cut points in a multiethnic population. *Circulation.* 2007;115:2111-2118.

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