

The following abstracts—from medical journals containing recent literature on diabetes—were selected for their relevance to this conference and to a managed care perspective.

The Diabetes Prevention Program

The goal of this study is to determine whether intense lifestyle management, pharmacological therapy, or both is effective in preventing the development of Type 2 diabetes. Recruitment for the Diabetes Prevention Program started in 1996 and will eventually include 4000 patients at high risk for diabetes due to impaired glucose tolerance, family history of diabetes, minority race, history of gestational diabetes and other factors. Twenty-five centers are recruiting patients and the follow up will range from 3 to 6 years. Patients will be randomized to undergo lifestyle modification with dietary changes and physical activity to promote weight loss, oral therapy with metformin and/or troglitazone, or placebo. Both drug groups and the placebo group will receive standard lifestyle modification instructions. The primary outcome measure of the study will be the development of diabetes. Secondary outcomes will focus on cardiovascular disease and its risk factors and changes in glycemia; insulin secretion and sensitivity; obesity; physical activity and nutrient intake; quality of life; and occurrence of adverse events.

Fujimoto WY for the Diabetes Prevention Program Research Group. A National Multicenter Study to Learn Whether Type II Diabetes Can Be Prevented: The Diabetes Prevention Program. *Clinical Diabetes* 1997;15:13-17.

Diabetes in a Managed Care System

The author reviewed studies analyzing several primary managed care strategies and their effects on diabetes care and outcomes. This article finds that although managed care organizations have the potential to provide excellent care for diabetics, little evidence exists that they have improved either the quality or the cost effectiveness of diabetes care. The author makes several recommendations for improving the managed care approach to diabetes. (1) The diabetes community should work with managed care organizations to develop methods-of-care delivery that improve outcomes and cost effectiveness. (2) The roles of primary care physicians, specialists, nutritionists and other members of the diabetes care team must be clearly defined and coordinated. (3) Existing data must be assembled to document the cost effectiveness of diabetes care and data must be organized in a format that appeals to managed care organizations. (4) Diabetes care research must be conducted at academic centers and funded with help from the federal government and managed care organizations. (5) The responsibility for organizing, coordinating, and overseeing the funding of the diabetes care effort should be assigned to an arm of the federal government.

Quickel KE Diabetes in a Managed Care System. *Ann Intern Med* 1996;124:160-163.

Cardiac and Glycemic Benefits of Troglitazone

A 48-week study involving 154 Type 2 diabetes patients receiving either troglitazone or glyburide titrated to achieve glycemic control was conducted to determine whether there was cardiac mass increase or cardiac function impairment associated with troglitazone therapy. Echocardiographs for each patient were conducted at baseline, 12, 24, 26, and 48 weeks. Researchers found the left ventricular mass index was no different between patients receiving troglitazone and those receiving glyburide, demonstrating the safety of troglitazone. A statistically significant increase in stroke volume index and significant decreases in cardiac index, diastolic pressure, and estimated peripheral resistance were observed in the troglitazone-treated patients. The authors propose several possible mechanisms of action for these beneficial effects. The enhanced cardiac output and stroke volume may be the result of decreased peripheral resistance. Troglitazone also produced long-term benefits in glycemic control as measured by both hemoglobin A_{1c} levels and C-peptide levels. In addition, troglitazone-treated patients showed lower triglyceride levels and higher levels of high-density lipoprotein cholesterol. The authors concluded that troglitazone therapy appears to have favorable cardiovascular effects.

Ghazzi MN, Perez JE, Antonucci TK, et al. Cardiac and glycemic benefits of troglitazone treatment in NIDDM *Diabetes* 1997;46:433-439.

Preventing Complications in Type 2 Diabetics

The objective of this ongoing study is to determine whether improved blood glucose control in Type 2 diabetics will prevent complications, and whether any specific therapy is advantageous or disadvantageous. Of 3867 patients, 1138 will receive conventional therapy consisting mainly of dietary changes and 2729 will be randomized to intensive therapy with sulfonylurea or insulin. In addition, of 753 obese patients, 411 will be randomized to conventional therapy and 342 will receive metformin. The median study duration is expected to be 11 years and complete results will be reported in 1998. To date, 2287 patients have completed 6 years of therapy. In the first arm of the study, intensive therapy with sulfonylurea and insulin produced improved glucose control compared to conventional therapy during the first year but fasting plasma glucose levels increased in all patient groups during the next 5 years and was associated with progressive beta-cell function loss. Glycohemoglobin was 8% in the conventionally treated patients and 7.1% in the intensively treated patients after 6 years. In the obese patients, metformin improved glucose control to the same extent as intensive sulfonylurea or insulin therapy and did not increase body weight or induce hypoglycemia. There has been a high incidence of diabetes complications in the study patients.

Turner R, Cull C, Holman R, for the United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 16 Overview of 6 years' therapy of type II diabetes: A progressive disease. *Diabetes* 1995;44:1249-1258

Intensive Insulin Therapy for Type 2 Diabetes

Researchers aimed to determine whether intensive insulin therapy with multiple daily injections could better prevent microvascular complications in Type 2 diabetics. A total of 110 patients were randomized to either standard insulin therapy or the intensive program and were followed for 6 years. The progression of retinopathy, nephropathy, and neuropathy were evaluated every 6 months throughout the study. Among patients with no baseline retinopathy, development of retinopathy occurred in 7.7% of the multiple injection group compared to 32% of the standard therapy group. Among patients who had baseline retinopathy, 19.2% taking multiple insulin injections showed progression compared with 44% among the standard therapy group. Nephropathy developed in 7.7% of intensive therapy patients and 28% of the standard therapy patients and progressed among those with baseline nephropathy in 11.5% and 32%, respectively. After the 6-year study period, there was significant improvement in nerve conduction velocities among multiple-injection patients and significant deterioration among those taking standard therapy. The authors reported that the glycemic threshold needed to prevent the onset and progression of these microvascular complications included glycohemoglobin of less than 6.5%, fasting blood glucose of less than 110 mg/dL, and 2-hour, postprandial blood glucose concentrations of less than 180 mg/dL. They concluded that intensive glycemic control through multiple daily insulin injections can accomplish these goals in Type 2 diabetics.

Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;28:103-117.

Quality of Diabetes Care in an HMO

Researchers evaluated the quality of care given to 384 diabetic members of a large health maintenance organization (HMO) in California and compared it to the care standards recommended by the American Diabetes Association. The retrospective analysis covered care during a 1-year period and documented follow up and measures of glycemic and lipid control. Results show that 21% of HMO patients had fewer physician visits than recommended, glycosolated hemoglobin levels were not documented at all in 56% of the patients, and 39% of those with a hemoglobin test showed a value of over 10%. In addition, fasting plasma glucose levels were not measured in 65% of the patients despite the recommendation that this be done four to six times annually. Foot examinations were not documented for 94% of the patients and urine protein measurements were not conducted in 52%. The authors conclude that diabetes management was inadequate and the lack of preventive care demonstrated is likely to lead to an increased risk of acute and chronic diabetes complications, which will create a greater burden on the healthcare system.

Peters AL, Legorreta AP, Ossorio RC. Quality of outpatient care provided to diabetic patients: A health maintenance organization experience. *Diabetes Care* 1996;19:601-606.

Maximal-Dose Sulfonylurea and Symptomatic Type 2 Patients

This study evaluated the efficacy of 10 mg bid glyburide in 55 patients with polyuria, polydipsia, nocturia, involuntary weight loss, and blood glucose concentrations greater than 300 mg/dL. Retrospective data for 30 patients and prospective data for 25 patients was available for analysis and data were collected at baseline, 1 week, and 4 months after starting sulfonylurea treatment. Patients responded rapidly with blood glucose levels falling from an average of 456 mg/dL to 202 mg/dL after 1 week and to 120 mg/dL after 4 months. Glycated hemoglobin levels dropped from 18.1% to 8.1% after 4 months. Most patients experienced symptomatic improvement within 3 days with this very experimental treatment. After 4 months, 11 patients were being managed with diet therapy alone, 29 with submaximal sulfonylurea therapy, 6 remained on maximal dose sulfonylurea therapy, and 3 required insulin. The remaining 6 patients were lost to follow up. The researchers concluded that maximal-dose sulfonylurea therapy is effective in severely symptomatic Type 2 diabetes patients.

Peters AL, Davidson MB. Maximal dose glyburide therapy in markedly symptomatic patients with type 2 diabetes: A new use for an old friend. *J Clin Endocrinol Metab* 1996;81:2423-2427

Thiazolidinediones and Insulin Resistance

Since insulin resistance is an almost universal feature of Type 2 diabetes, researchers speculate that enhancement of insulin action may be an effective pharmacologic approach to diabetes management. Thiazolidinediones reduce insulin resistance by increasing insulin-dependent glucose disposal and reducing hepatic glucose output. Clinical trials with these drugs have shown they are effective. The mechanism of action of these agents is not clear but transcriptional changes in tissue culture cells that produce enhanced insulin action have been observed. This regulation of gene expression appears to be mediated by the interactions of thiazolidinediones with peroxisome proliferator-activated receptors. The authors cite several animal models in which troglitazone restored the hyperglycemia-induced reduction of phosphorylation and prevented the glucose-induced inhibition of insulin receptor tyrosine phosphorylation. Furthermore, the rapid onset of this effect on receptor phosphorylation suggests that it may be mechanistically distinct from the transcriptional effects. A better understanding of the mechanism of action of these drugs should lead to the development of even more effective treatments for diabetes and may contribute to a better understanding of the underlying molecular abnormalities of Type 2 diabetes mellitus.

Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and Type II diabetes. *Diabetes* 1996;45:1661-1669.

Troglitazone and Metabolic Control

The effects of troglitazone were studied in 330 Type 2 diabetes patients in a randomized, placebo-controlled trial including doses of 200 mg, 400 mg, 600 mg, or 800 mg once daily for 12 weeks; or 200 mg or 400 mg twice daily for 12 weeks. All patients had discontinued oral hypoglycemic agents at least 3 weeks prior to study entry or had been previously treated with diet therapy alone. During treatment, glycohemoglobin rose from 7.2% to 8% in placebo patients but remained unchanged in those taking any troglitazone dose. After 12 weeks of therapy, troglitazone patients demonstrated significantly lower glycohemoglobin levels with a mean of 7% to 7.4% and fasting plasma glucose concentrations were 9.2 mmol/L to 11 mmol/L compared to 12.9 mmol/L for placebo. All doses of troglitazone were found to be equally effective. Troglitazone was also found to lower fasting plasma insulin concentrations by 12% to 26% compared to placebo. Insulin sensitivity was greater after troglitazone treatment and serum triglyceride and nonesterified fatty acid concentrations were significantly lower. High-density lipoprotein cholesterol (HDL-C) was higher with the 600-mg and 800-mg daily troglitazone doses and low-density lipoprotein cholesterol (LDL-C) increased at the 400-mg and 600-mg doses. However, the LDL-C to HDL-C ratio did not change during treatment. Although there were no adverse effects associated with troglitazone treatment, a tendency toward reduced neutrophil counts was observed in patients taking the highest doses.

Kumar S, Boulton AJM, Beck-Nielsen H, et al. Troglitazone, an insulin action enhancer, improves metabolic control in NIDDM patients. *Diabetologia* 1996;39:701-709

CME QUESTIONS: TEST #0397S10

Long Island Jewish Medical Center and Johns Hopkins University School of Medicine are accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Long Island Jewish Medical Center, the Long Island Campus for the Albert Einstein College of Medicine, designates this continuing medical education activity for 1.0 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. This CME activity was planned and produced in accordance with the ACCME Essentials and Standards for Commercial Support.

Instructions

After reading this Special Report, select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is 1 hour. CME credits are distributed on a yearly basis.

1. **New recommendations for the diagnosis of diabetes include a fasting blood glucose concentration of:**
 - a) 110 mg/dL
 - b) 126 mg/dL
 - c) 140 mg/dL
 - d) 180 mg/dL
 - e) over 200 mg/dL
2. **According to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, people younger than 45 should be tested more frequently if they:**
 - a) are dyslipidemic and obese
 - b) are women with a history of gestational diabetes and have had given birth to babies weighing 9 lbs or more
 - c) are hypertensive or have first-degree relatives with diagnosed diabetes
 - d) all of the above
 - e) a and c only
3. **The approximate prevalence of diabetics in the United States is:**
 - a) 20 million
 - b) 60 million
 - c) 12 million
 - d) 16 million
 - e) 25 million
4. **The desired maintenance hemoglobin A_{1c} level in order to minimize complications in Type 2 diabetics is:**
 - a) 12%
 - b) 5%
 - c) 9%
 - d) 8.3%
 - e) 7%
5. **Patients diagnosed with impaired glucose tolerance are at risk for:**
 - a) hypertension
 - b) obesity
 - c) dyslipidemia
 - d) Type 2 diabetes
 - e) all of the above
6. **The underlying abnormality associated with Type 2 diabetes is:**
 - a) hyperglycemia
 - b) hyperinsulinemia
 - c) decreased hepatic glucose production
 - d) a and b
 - e) b and c
7. **Therapy with diet and exercise alone is effective in normalizing blood sugars in what percent of the diabetic patient population?**
 - a) 5% of patients
 - b) 30% of patients
 - c) 60% of patients
 - d) 95% of patients
 - e) none of the patients

(CME QUESTIONS CONTINUED ON PAGE S44)

<p>CME TEST FORM AJMC Test #0397S10S</p> <p>New and Emerging Therapies in the Treatment of Type 2 Diabetes</p> <p><i>Application for 1 Credit Hour of AMA Category I</i></p> <p>(Test valid through November 30, 1998. No credit will be given after this date.)</p>	<p>Please circle your answers:</p> <p>1. a b c d e 2. a b c d e 3. a b c d e 4. a b c d e 5. a b c d e 6. a b c d e 7. a b c d e 8. a b c d e 9. a b c d e 10. a b c d e</p>	<p>(PLEASE PRINT CLEARLY)</p> <p>Name _____</p> <p>Address _____</p> <p>City _____</p> <p>State/ZIP _____</p> <p>Phone # _____</p> <p>Please enclose a check for \$10, payable to American Medical Publishing, and mail with this form to:</p> <p style="text-align: center;">The AJMC CME Test American Medical Publishing 1816 Englishtown Road, Suite 101 Old Bridge, NJ 08857</p>
---	--	--

PROGRAM EVALUATION

Long Island Jewish Medical Center and Johns Hopkins University School of Medicine would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CME test form. We thank you for your evaluation, which is most helpful.

On the whole, how do you rate the information presented in the article?

excellent good fair poor

Is the information presented useful in your practice?

yes no

Comments:

Do you have recommendations to improve this program?

yes no

Comments:

Were any portions of this program unsatisfactory or inappropriate?

yes no

If so, which?

Do you find the information presented in these articles to be fair, objective, and balanced?

yes no

Is there subject matter you would like included in the future?

yes no

Comments:

In your opinion, were the authors biased in their discussion of any commercial product or service?

yes no

Comments:

Program Evaluation

Physician Name

Address

City, State, ZIP

Specialty

(CME QUESTIONS CONTINUED FROM PREVIOUS PAGE)

8. Today's therapeutic approach to Type 2 diabetes is marked by:

- a) more prolonged and accountable efforts with stringent diet and exercise
- b) more frequent and higher therapeutic doses of insulin
- c) more frequent testing and genetic counseling
- d) earlier, more aggressive intervention that includes both lifestyle changes and medications
- e) none of the above

9. Effective combination therapies for Type 2 diabetics not adequately controlled with one agent are:

- a) a sulfonylurea and insulin
- b) troglitazone or metformin and insulin
- c) troglitazone and a sulfonylurea
- d) b and c
- e) none of the above

10. The primary goal in Type 2 diabetes treatment is to enable the patient to:

- a) discontinue insulin therapy
- b) discontinue oral therapy
- c) require only one oral agent
- d) maintain control with diet and exercise
- e) achieve control with any combination of means needed