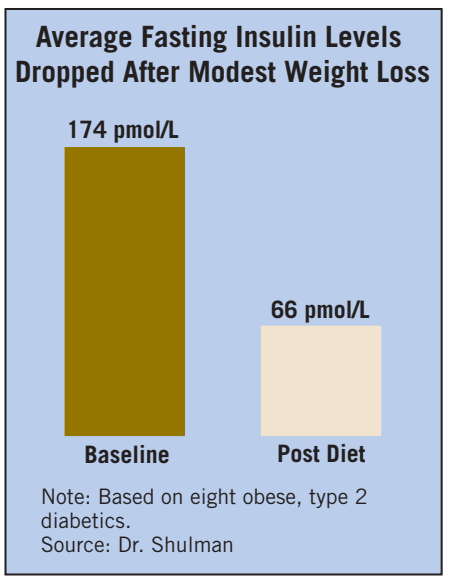
Modest Weight Loss Benefits Type 2 Diabetic Patients

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — A relatively modest amount of weight loss can normalize fasting plasma glucose and greatly improve insulin sensitivity in people with type 2 diabetes, according to a study reported by Dr. Gerald I. Shulman at the Third World Congress on Insulin Resistance Syndrome.

Eight obese patients with type 2 diabetes achieved these significant improvements after losing an average of just 8 kg (17.6 pounds), equivalent to about 8% of their body weight, said Dr. Shulman of Yale University, New Haven, Conn. Dr. Kitt Falk Petersen was the lead author of the recently published study (Diabetes 2005;54:603-8).



These results have important clinical implications for patients with poorly controlled type 2 diabetes in that a modest weight loss is a psychologically easier goal than achieving normal body weight.

The diabetic patients enrolled in the study began with an average weight of 86 kg and an average body mass index of 30 kg/m^2. Their fasting glucose averaged 8.8 mmol/L; their fasting insulin averaged 174 pmol/L.

The study diet was a liquid diet formula with 50% carbohydrate, 43% protein, 3% fat, and 12 g of dietary fiber, which was supplemented with raw fruit and vegetables to about 1,200 kcal/day. The patients continued this diet until they achieved euglycemia, which took between 3 and 12 weeks. They were stabilized on an isocaloric diet for 4 weeks before the final metabolic measurements were taken.

Following the diet, the patients weighed an average of 78 kg and had an average BMI of 27.5. Their fasting glucose averaged 6.4 mmol/L, and their fasting insulin averaged 66 pmol/L. All these values represented statistically significant decreases from baseline.

In addition, the patients achieved a marked improvement in glucose responsiveness as measured by a fourfold increase in the glucose infusion rate required to maintain euglycemia during a hyperinsulinemic-euglycemic clamp.

By measuring hepatic glucose metabolism with deuterated glucose, the investigators determined that the weight reduction improved hepatic insulin sensitivity but had no effects on peripheral insulin sensitivity. ■

Rosiglitazone Reduces CRP And Carotid Atherosclerosis

BY MITCHEL L. ZOLER
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DALLAS — Treatment with rosiglitazone was linked with markedly reduced serum levels of C-reactive protein and regression of carotid atherosclerosis in a study with about 70 patients with type 2 diabetes. In contrast, treatment with metformin was unable to produce either of these effects.

These findings "point to potential superior efficacy of thiazolidinediones over metformin for cardiovascular outcomes, but direct studies are needed," Dr. Allen J. Taylor said at the annual scientific sessions of the American Heart Association.

"The data are consistent with the biologically plausible hypothesis of a direct antiatherosclerotic effect of rosiglitazone," said Dr. Taylor, chief of cardiology services and professor of medicine at Walter Reed Army Medical Center in Washington.

The study, done at Walter Reed, had no commercial sponsorship.

The researchers enrolled patients with type 2 diabetes and a hemoglobin A_{1c} level of more than 7% despite treatment with diet or a sulfonylurea drug. Patients were randomized to treatment on an open-label basis to either 4 mg rosiglitazone (Avandia) daily or 850 mg metformin (Glucophage) twice daily. The randomization was stratified to assign patients with similar levels of statin use to both treatment groups.

The primary end point was the change in serum levels of C-reactive protein (CRP) after 24 weeks of treatment. In the rosiglitazone group, serum CRP fell by about half after the first 2 weeks of treatment, from an average of 6 mg/L at baseline to a mean of 3 mg/L. The CRP level continued to gradually drop during subsequent treatment, and after 24 weeks, was at an average of 2 mg/L in 37 evaluable patients.

Every time CRP levels were measured, after 2, 4, 16, and 24 weeks of treatment, the reductions were significantly different, compared with baseline.

In contrast, metformin produced no significant drop in CRP at any of the measured times in 38 evaluable patients.

The secondary end point was a change in the ultrasound measurement of carotid intimal medial thickness after 24 weeks of treatment, compared with baseline levels.

In the rosiglitazone group, the mean carotid intimal media thickness regressed by an average of 0.069 mm in 35 evaluable patients, an indicator of reduced atherosclerosis. The average change in 38 patients treated with metformin was atherosclerosis progression of 0.011 mm. The difference between the rosiglitazone and metformin groups was statistically significant.

An exploratory analysis indicated a modest statistical link between the change in serum CRP and the change in carotid intimal medial thickness, Dr. Taylor said.

Neither drug had an effect on serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides. ■

Surrogate Tests of Insulin Resistance Deemed More Practical

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Surrogate measures of insulin resistance, while not nearly as reliable, may be far more practical for routine clinical use than the hyperinsulinemic-euglycemic clamp and the insulin suppression test, which can take 3 hours or more.

At the Third World Congress on Insulin Resistance Syndrome, Dr. Sun H. Kim, of Stanford (Calif.) University, discussed available surrogate tests. Other speakers at the congress discussed two new instrumental measures likely to become available soon.

One problem with using any measure of insulin resistance is its continuous distribution in the general population. There is no absolute criterion by which to classify individuals as insulin resistant or insulin sensitive. Dr. Kim follows the general practice of defining individuals who fall in the upper tertile of insulin resistance as having insulin resistance syndrome.

Available surrogate measures fall into three categories—routine measures, additional measures, and calculated measures.

The routine measures include fasting glucose and components of the lipid panel, especially HDL cholesterol and triglycerides.

Compared with the steady-state plasma glucose level (SSGL) derived from an insulin suppression test, fasting glucose has a correlation coefficient of just 0.38 and HDL has a correlation coefficient of just –0.41.

Triglyceride level is a somewhat better predictor of SSGL, with a correlation coefficient of 0.60.

Further, these three routine measures have an additional complication—their correlation coefficients vary depending on the patient's level of obesity.

The additional measures include fasting plasma insulin and the area under the curve for insulin in a 2-hour oral glucose tolerance test (OGTT). Fasting plasma insulin has a fairly good correlation with SSGL—0.61—but it, too, varies with the patient's obesity.

Among the routine and additional measures, the area under the curve of insulin in an OGTT has the highest correlation with SSGL (0.79), and that correlation does not vary depending on the patient's level of obesity.

The calculated measures include the ratio between triglycerides and HDL cholesterol, the homeostasis model assessment of insulin resistance (HOMA-IR), and the quantitative insulin sensitivity check index (QUICKI).

A triglyceride to HDL ratio above 3 predicts SSGL with a correlation coefficient of 0.61, and this varies only modestly with obesity. This is likely to be the most frequently used measure in clinical practice. HOMA-IR and QUICKI make use of fasting insulin and fasting glucose levels. Both correlate well with insulin sensitivity, but not much better than fasting insulin alone.

The two new instrumental measures, however, promise to provide more sensitive and specific measures of insulin sensitivity.

The deuterated-glucose disposal test (^{2}H-GDT) involves an overnight fast followed by a challenge with deuterated glucose, which is not radioactive. Blood samples are taken at baseline and hourly for 4 hours for the measurement of heavy water (^2H_2O) production, the result of glucose metabolism. In laboratory studies, this test exhibits a correlation coefficient of 0.95, when compared with the hyperinsulinemic-euglycemic clamp.

Deuterated water is measured with an isotope ratio mass spectrometer, a large instrument that costs about $250,000. But Dr. Marc Hellerstein of the University of California, Berkeley, hopes to be able to employ a smaller, less expensive laser spectrometer that would have the additional advantage of a high throughput.

The second instrumental measure is a ^{13}C-glucose breath test called the Diatest. A fasting patient consumes nonradioactive ^{13}C-glucose, after which $^{13}CO_2$ in the patient's expired breath is measured for 90 minutes by either an isotope ratio mass spectrometer or by nondispersive infrared spectroscopy, similar to tests for *Helicobacter pylori*.

According to Dr. Richard Z. Lewanczuk of the University of Alberta, Edmonton, human studies have demonstrated that the breath test has a sensitivity of 78% and a specificity of 96%, compared with standard measures. The Food and Drug Administration recently approved this technique for use in clinical trials in the United States.

Dr. Lewanczuk disclosed that he is a major stockholder in Isotechnika Diagnostics, the company that hopes to market the ^{13}C-glucose breath test. Dr. Hellerstein is a consultant and adviser for KineMed, which hopes to market the ^{2}H-GDT test. Dr. Kim stated that she has no potential conflicts of interest. ■