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Nutrition, lipids, and alternative medicine

ZACHARY T. BLOOMGARDEN, MD

This is the second of seven reports on the American Diabetes Association (ADA) 60th Scientific Sessions held in San Antonio, TX, in June 2000. It covers topics related to nutrition, lipid levels, and alternative medicine in diabetes.

Dietary Carbohydrate and Fat
At a symposium discussing the roles of dietary fat and carbohydrate in the etiology and management of diabetes, Frank Hu, Boston, MA, pointed out that the prevalence of obesity in the U.S. has increased by ~50% over the past decade, despite a decrease in reported fat intake. Although this must be interpreted with caution, it suggests that high-carbohydrate diets cannot be regarded as inherently protective.

There are variations in the effects of various dietary fats. Saturated fats, as derived from meat and dairy products and from palm oil, tend to increase both LDL and HDL cholesterol levels. Trans fatty acids increase LDL cholesterol and triglyceride, decrease HDL cholesterol, and interfere with insulin response. Monounsaturated fats decrease LDL cholesterol and increase HDL cholesterol with improved insulin sensitivity. Fish oils containing omega-3 (n-3) fatty acids, may block arrhythmias and fatty acids, may block arrhythmias and reduce HDL cholesterol with improved insulin sensitivity. Fish oils containing omega-3 (n-3) fatty acids, may block arrhythmias and lower CHD risk as well as a study in women in Iowa and among Seventh Day Adventists. Hu pointed out that these findings “contradict the conventional wisdom that high fat increases the risk.” More than 11 studies have been done showing that fish consumption decreases the risk of coronary heart disease (CHD), with a decrease in diabetes risk as well in the NHS. Greater dietary intake of α-linoleic acid, as found in green vegetables or soy or canola oil, was also associated with decreased CHD risk in this study.

Similarly, rather than attempting to assess the relationship between diabetes and CHD risk and total carbohydrate intake, it is important to determine the effects of different types of carbohydrate. One approach is the glycemic index, which was first proposed by Jenkins and Jenkins (1). Foods such as potatoes and many breads may increase blood glucose levels more than equivalent caloric quantities of glucose and are therefore considered to have a high glycemic index; pasta, however, has a low glycemic index. Part of the biological explanation for differing glycemic indexes of foods may relate to whether a given starch is made up of less rapidly digested straight chain carbohydrate (the amyloses) or more rapidly digested branched chain carbohydrate (the amylpectins).

A refinement of the glycemic index is the glycemic load, which is calculated as the sum of the product of glycemic index and the quantity of carbohydrate of the various components of the diet. Glycemic load is strongly associated with higher triglyceride and lower HDL cholesterol levels and with increased CHD risk, both in general populations and among individuals with diabetes. Glycemic load may also be associated with increased risk of diabetes. Intake of vegetables, fruits, and cereal fiber and the related magnesium intake are associated with a decrease in diabetes risk. Whole grains are associated with a decrease in CHD risk, whereas refined grains are associated with an increase.

The glycemic index should not be used in isolation. Caloric density of foods and overall nutrient content should be considered. Hu suggested that “good carbohydrate” includes whole grains, pasta, fruits, and vegetables, particularly legumes, whereas “good fats” include liquid vegetable oils, nuts, avocados, and fish oils. While this may seem evident, the U.S. Recommended Dietary Allowance “Food Pyramid” does not distinguish various types of carbohydrate and fats. Hu advocated modifying this to encourage a decrease in consumption of red meat, processed meats, potatoes, refined grains, and high-fat dairy products.

Barbara Howard, Washington, DC, reviewed a number of longitudinal studies showing that the percentage of fat in the diet shows some predictive power for development of diabetes, but she agreed that type of fat rather than total fat is important, with polyunsaturated fats most strongly associated with decrease in diabetes risk. She described a controlled trial of 162 individuals randomized to a 38% fat diet either high in saturated fats or high in monounsaturated fats, the former worsening and the latter improving insulin sensitivity after 3 months (2). Administration of an n-3 fatty acid supplement had no effect.

Nutrition, Insulin Resistance, and Lipids
Gerald Shulman, New Haven, CT, discussed dietary regulation of insulin resistance. He noted that offspring of patients with type 2 diabetes show a trimodal distribution of insulin sensitivity, with the lowest

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.

Abbreviations: ADA, American Diabetes Association; apo, apolipoprotein; CHD, coronary heart disease; CVD, cardiovascular disease; IMT, intima-media thickness; LPL, lipoprotein lipase; NHS, Nurses Health Study; VA-HIT, Veterans Affairs–HDL Intervention Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
quartile appearing to show prediabetic levels. In this group, free fatty acids and, even more, intramyocellular triglycerides have a strong negative correlation with insulin sensitivity. He reviewed studies that suggest that high dietary fat levels lead to a decrease in muscle and adipocyte GLUT4 glucose transport, presumably contributing to the development of insulin resistance.

Marc Hellerstein, Berkley, CA, discussed the metabolic effects of dietary carbohydrate, asking whether humans convert excess carbohydrate to fat. All tissues have the capacity for de novo lipogenesis, but indirect calorimetry studies show little evidence of this. Surplus dietary carbohydrate can be stored as glycogen, converted to fat, or directly oxidized. Use of mass spectrometry and stable naturally occurring isotopically labeled tracers in a study of individuals who had recently quit smoking showed that despite an increase in food intake from 3,000 to 4,200 calories, de novo lipogenesis was quantitatively unimportant. As carbohydrate intake increased, the respiratory quotient increased from 0.84 to 0.95, suggesting virtually complete conversion to dietary carbohydrate as the fuel source, with dietary fat being minimally metabolized. Hellerstein concluded that under these circumstances, carbohydrate is oxidized rather than being converted to fat, but at the price of developing insulin resistance, which in turn spares fat from being utilized. On eucaloric high-carbohydrate diets, triglyceride levels rise by ~50%, both among normal and mildly hypertriglyceridemic individuals. This is accompanied by decreases in HDL and LDL cholesterol, but there is no fall in apolipoprotein (apo) B levels, so LDL density decreases. Clearance of both VLDL and chylomicrons decreases. Again, there is little de novo lipogenesis.

Nutrition to Control Weight and Lipid Levels

Abhimanu Garg of the University of Texas reviewed studies showing similar weight loss with a number of diets, suggesting that “calories are calories... whether you reduce calories from fats or carbohydrate.” High-fiber diets improve mean glucose levels significantly, suggesting this to be an important component of choice of carbohydrate for patients with diabetes. Soluble fiber inhibits bile acid reabsorption, part of the mechanism of cholesterol lowering, delays carbohydrate absorption, and has a variety of other effects. Although there is heterogeneity, dietary cholesterol is proportional to plasma cholesterol levels. Phytosterols can inhibit cholesterol absorption, as with plant sitosterols, which can reduce LDL cholesterol by 10–14%, offering another dietary approach. Asked about the high-protein diets advocated for weight loss, Garg commented that they are associated with high LDL cholesterol levels, hypercalcuiuria, and ketosis, all of which may have adverse effects, although there is a paucity of available data.

In his discussion of studies of various nutrition interventions, Ernst Schaefer of Tufts University stated that he wished he knew what the proper diet was. “There is certainly,” he said, “consensus on the fact that we need to decrease animal fat, decrease sugar, and increase our activity level.” Populations consuming high-fat diets have high rates of heart disease, as in Russia, Scotland, and Northern Ireland, for example, where there is high consumption of lard and tallow. In 20 countries studied, there was a correlation of intake of butter, dairy product, eggs, meat, and poultry with heart disease, while intake of grains was inversely correlated. Sugars and syrups had very high correlation (3). “The emphasis to change the fat,” Schaefer said, has however led many manufacturers to increase the sugar content of foods, which tends to raise triglyceride and reduce HDL levels.

The Oslo Diet Heart Study randomized patients to a diet low in saturated fat and high in polyunsaturated fat, thus reducing cholesterol and heart disease rates. The Los Angeles Veterans Affairs Study of patients in a residential facility gave two-thirds of fat either as vegetable oil or as animal fat, with a 31% decrease in cardiovascular disease (CVD) in the former group (4). The Finnish Mental Hospital Study of both men and women randomized to butter and whole milk versus soybean oil margarine and fat-free milk showed a 15% reduction in cholesterol and a large reduction in heart disease (5). Other studies show benefits of canola oil, which is rich in α-linoleic acid. In the U.S., the use of soybean oil rather than lard and tallow has been associated with a decrease in heart disease, an experience also reported in Poland and Czechoslovakia.

Schaefer noted that olive oil is expensive and is low in polyunsaturated fat, which has been best shown to reduce heart disease, so he considered soybean and canola oil to be the best dietary oils. Schaefer wondered whether the benefit of the Mediterranean diet was in wine and fish consumption and stressed that there is no evidence that monounsaturated fat consumption per se will decrease heart disease levels. Studies of administration of fish oil have similarly shown decreases in heart disease levels. Vitamin E was shown not to have benefit in the HOPE (Heart Outcomes Prevention Evaluation) (6) and GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico) (7) trials, with the latter study showing decreased cardiovascular event rates with administration of n-3 polyunsaturated fatty acid supplements (1 g daily).

In addition to LDL <130—ideally <100—triglyceride levels <175–200 and HDL >35–38 mg/dl are important goals for primary prevention, and remnant particles should be considered as well. Lipoprotein(a) is also important as a risk factor. Obesity drives these abnormalities to the greatest extent. Schaefer did not argue with Garg about the similarity of fat and carbohydrate calories, but he pointed out that fat has much higher caloric density, which will be expected to lead to greater degrees of overweight, recalling Kelley West’s data that dietary fat is correlated with the prevalence of diabetes. Schaefer reviewed a number of studies showing adverse effects of increased fat intake. “The question,” Schaefer asked Garg, “is ‘Do we pour on lots of olive oil?’ Intervention studies have shown that overfeeding with a high-fat diet increases body weight and causes dyslipidemia, whereas high-carbohydrate and low-fat diets tend to reduce weight by reducing caloric consumption, although meta-analysis shows that the degree of weight loss attained by such diets is not great. “What happens in the real world,” Schaefer suggested, is that counseling does not always lead to change in behavior, so he emphasized the role of the food industry in changing the content of foods. “I think we can encourage people,” he said, “to consume foods of plant origin. In America, most [sugars] are empty calories.”

Lipoproteins

At a separate symposium at the ADA meeting, Ronald Krauss, Berkley, CA, described two major pathways of LDL particle production. With normal VLDL, the action of lipoprotein lipase (LPL) leads to production of large LDL particles. However, altered VLDL particles contain apoCIII, which inhibits LPL, as well as apoB. These VLDLs have longer residence in plasma, allowing formation of VLDL remnants, which are metabolized by hepatic lipase to small, dense LDL particles and by cholesterol
ester transfer protein to intermediate-density lipoproteins, removing cholesterol from HDL particles. Thus, patients with hypertriglyceridemia tend also to have LDL particles of decreased size and low HDL cholesterol levels, whereas those with normal triglyceride levels tend to have large LDL and normal HDL. This bimodal LDL population distribution leads to two separate phenotypes, with those with pattern B having higher triglyceride and lower HDL, a pattern similar to that seen in type 2 diabetes and associated with insulin resistance and hypertension.

Genetic susceptibility accounts for 40–50% of the variation in LDL size, with linkage demonstrated to the hepatic lipase gene, which is responsible for conversion of HDL to LDL (8). Environmental factors include male sex, menopausal status, abdominal adiposity, and higher levels of dietary carbohydrate, with studies of diets high in simple carbohydrate showing a shift from pattern A to pattern B. There is a great deal of evidence that small, dense LDL particles are atherogenic, and pattern B shows a threefold increase in CHD risk (9). Moreover, there is an interaction between low HDL, high LDL, and pattern B, with a fivefold increase in risk in individuals with all three risk factors. Similarly, hyperinsulinemia and high apoB levels interact with pattern B in increasing CHD risk (10).

Some studies suggest that change in LDL density with lipid treatment is of greater importance than reduction in LDL levels themselves (11). Small, dense LDL has increased susceptibility to oxidation and may bind more tightly to arterial proteoglycans, thus leading to longer arterial wall residence and greater macrophage uptake, potentiating the atherosclerotic process. LDL size tends to increase with treatment with nicotinic acid, with gemfibrozil, and with thiazolidinediones (12), suggesting additional benefits of these agents.

John Brunzell, Seattle, WA, began a debate on whether HDL and triglycerides are appropriate therapeutic targets for patients with diabetes, suggesting that this is “quite an important issue that we really don’t have the answer to yet. Everyone would agree that a decrease in LDL cholesterol is a goal…HDL is also a risk factor. Should we be trying to decrease triglyceride? There is quite a bit of disagreement.” He suggested that hypertriglyceridemia is a marker of other conditions, most generally of the insulin resistance syndrome, with small LDL particles as the more specific risk factor. There are a number of conditions in which diabetes is associated with hypertriglyceridemia, including untreated diabetes, diabetic nephropathy—both with uremia and with nephrotic syndrome—and type 2 diabetes in general. Untreated hyperglycemia is associated with decreased adipose tissue LPL and increased hepatic VLDL synthesis. Insulin treatment, even without restoring perfect control, corrects this.

In type 1 diabetes, one of the major risk factors for CVD is nephropathy. The Diabetes Control and Complications Trial showed that intensive diabetes treatment prevents nephropathy and its progression and that it decreases triglyceride, decreases LDL cholesterol, and increases HDL. Brunzell noted that the subset of patients with type 1 diabetes who have excessive weight gain with intensive treatment, who typically have a family history of type 2 diabetes, develop a central obesity/insulin resistance syndrome. In type 2 diabetes, central obesity/insulin resistance is the major cause of hypertriglyceridemia. This is seen in a variety of insulin-resistant states, including 20–25% of the “so-called normal population,” and leads to increased VLDL production.

Brunzell suggested that increased hepatic lipase is the major cause of the dyslipidemia, which includes small, dense LDL, decreased HDL, and small VLDL and intermediate-density lipoproteins. Studies of familial combined hyperlipidemia show a twofold increase in risk of CVD over rates in familial hypertriglyceridemia and in spouses. At 20-year follow-up, CVD in women before age 65 and in men before age 55 is much more common in the former syndrome, again suggesting that “not all hypertriglyceridemia is the same.” Familial hypertriglyceridemia is due to an increase in VLDL production rather than to an increase in hepatic lipase.

In insulin-resistant individuals, assessment of patients with combined familial hyperlipidemia shows that intensive lipid-lowering treatment decreases progression of CHD, with the decrease in LDL most strongly predictive and the increase in HDL next most likely. Triglyceride lowering per se is not associated with a decrease in CHD. If hepatic lipase activity decreases, small, dense LDL levels decrease, and this is a more important risk factor than total LDL. Potential mechanisms of atherogenesis by small, dense LDL include increased penetration of arterial wall, increased uptake by macrophages, and increased glycation. Insulin-resistant individuals with familial combined hyperlipidemia can be treated with fibrates, with a decrease in VLDL cholesterol and an increase in LDL size and decrease in average buoyancy. Overall, small, dense LDL levels do not decrease with fibrate treatment, however, suggesting that nicotinic acid may be the better therapeutic agent.

Steven Haffner, San Antonio, TX, presented an epidemiological approach to therapy, suggesting that HDL and triglyceride should be secondary targets of treatment. Although CVD has decreased in the U.S. in individuals without diabetes, rates have increased among individuals with diabetes. There is overwhelming biological data that LDL treatment is important over a wide range of LDL levels, with the best treatment available for this lipid component. The data for HDL treatment are mixed, and Haffner termed “the data for triglyceride a little bit more complicated.” He noted that most studies do not show great abnormality of triglyceride in diabetes. Diabetic women have relatively greater lowering of HDL and of LDL size than do men. If triglyceride is “adjusted” statistically for HDL, the risk contribution decreases. Insulin is a risk factor, and in nondiabetic populations, adjustment for insulin eliminates the risk contribution of triglycerides.

Observational studies that support triglyceride as a risk factor for CHD show that the risk is greatest with high LDL (or high apoB) and low HDL, suggesting an interaction. It may be then that statin treatment alone can be adequate with sufficient LDL and apoB reduction. All studies show that individuals with diabetes have at least as great a response to statins as do those without diabetes, with an almost linear relationship between the achieved LDL and the CVD event rate. The Helsinki Heart Study (13) and Veterans Affairs–HDL Intervention Trial (VA-HIT) (14) showed similar reduction of risk in diabetic and nondiabetic groups treated with gemfibrozil, a fibric acid derivative. Haffner’s recommendations for triglyceride treatment included glycemic treatment in uncontrolled patients and recognition of the triglyceride-lowering effect of statins, which is particularly seen with hypertriglyceridemia. He suggested that fibrate treatment at present should not in general be considered primary. For patients with LDL <130 mg/dl and HDL <40 mg/dl, as in the VA-HIT, fibrates may be useful as primary treatment, with an HDL goal of 45 and triglyceride goal of 200 mg/dl.
Ongoing studies that include patients with diabetes are addressing LDL goals of 100 and 75 mg/dl and the comparison of benefits of fibrates, statins, and a combination of the two.

Abstracts on Dyslipidemia
A number of studies presented at the ADA meeting addressed aspects of dyslipidemia in diabetes, with interesting information about triglyceride abnormalities. Haffner and Stern (abstract 82) compared 238 individuals who developed diabetes over an 8-year follow-up with 2,495 in whom diabetes did not develop. At baseline, triglyceride levels were 171 and 134 mg/dl, HDL cholesterol 45 and 53 mg/dl, and systolic blood pressure 119 and 114 mmHg, respectively. HDL fell and blood pressure rose similarly in both groups, suggesting these to be mediated by factors other than those causing diabetes. However, triglyceride levels rose 62 mg/dl in the individuals developing diabetes versus 20 mg/dl in those not developing diabetes, suggesting a more important effect of glycemia.

Agular et al. (abstract 1103) compared the prevalence of coronary insufficiency and carotid artery stenosis in 35 patients with type 2 diabetes and familial hypertriglyceridemia and 46 patients with diabetes alone. Fasting blood glucose was 174 vs. 160 mg/dl, triglyceride 1,262 vs. 125 mg/dl, and cholesterol 283 vs. 185 mg/dl, but carotid intima-media thickness (IMT) was similar in both groups. Jenkins et al. (abstract 1112) and Lyons et al. (abstract 1117 and 1118) reported a nuclear magnetic resonance–determined lipoprotein subclass profile of >800 patients with type 1 diabetes from the Diabetes Control and Complications Trial follow-up study. Lower HDL and higher LDL cholesterol were found than with standard lipoprotein determinations, without interference by glycemia or lipoprotein glycation. Patients with HbA1c >10% had 40 and 64% higher total and VLDL triglyceride, 43% higher small LDL, and 18% higher LDL cholesterol than did patients with HbA1c <7.0%. Patients with retinopathy and nephropathy had similar patterns of dyslipidemia. Lewis et al. (abstract 50) compared lipid profiles of 14 kidney-pancreas transplant recipients who had portal anastomosis of the pancreas graft vein with 21 who had had systemic anastomosis. Triglyceride levels were 29 and 53% higher with a trend to lower HDL cholesterol levels in the former group, despite 38% lower fasting insulin levels.

Several studies addressed the significance of postprandial triglyceride abnormalities. Tuck et al. (abstract 56) studied postprandial lipid levels in 76 patients with diabetes with and 47 age- and sex-matched patients without coronary artery disease. They found no significant difference in triglyceride or retinyl palmitate levels before and during 10 h after a high-fat meal. Teno et al. (abstract 611), however, found that patients with normal fasting triglyceride levels showed carotid IMT of 0.73 mm with normal postprandial triglyceride but 0.86 mm with elevated (>2.3 mmol/l) postload triglyceride levels, similar to the level of 0.85 mm in patients with high fasting triglyceride levels. Patients with fasting hypertriglyceridemia showed a correlation between fasting triglyceride and carotid IMT.

Georgopoulos et al. (abstract 335) studied a polymorphism of threonine for alanine at codon 54 of the fatty acid binding protein 2 gene, for which 108 and 31 patients were heterozygous and homozygous in a group of 287 diabetic patients. Fasting triglyceride levels were 2.7 and 3.8 mmol/l in these two groups, but 2.0 mmol/l in those showing the normal pattern. In a substudy, postprandial triglyceride levels were elevated in the homozygotic subjects as well, suggesting that in type 2 diabetes, increased intestinal input of triglyceride can lead to fasting and postprandial hypertriglyceridaemia. This has not been shown in studies of nondiabetic individuals with the polymorphism.

A number of studies addressed aspects of lipid treatment. Cook et al. (abstract 1109) reported that among 204 patients with type 2 diabetes not treated for dyslipidemia, HbA1c had decreased from 9.3 to 8.1%, but total and LDL cholesterol were 210 and 140 mg/dl without change after 12 months of treatment. For the 103 patients whose HbA1c decreased (from 10.6 to 7.5%), LDL decreased by only 2.6 mg/dl. Thus, improved glucose control is not sufficient to manage dyslipidemia in patients with type 2 diabetes, suggesting that pharmacological therapy to lower LDL should be initiated upon detection of abnormalities in such populations.

Cull et al. (abstract 1110) reported the relationship of mean lipid levels to the U.K. Prospective Diabetes Study’s predefined clinical outcomes for the 3,847 patients in the study. For each 1 mmol/l decrease in LDL cholesterol, there was an 18% decrease, and for each 1 mmol/l increase in HDL cholesterol, there was a 50% decrease in “any diabetes related end points.” Diabetes-related death decreased 24 and 70%, and all-cause mortality decreased 12 and 40%, respectively.

Hedrick et al. (abstract 566) studied in vitro effects of lisofylline, which inhibits formation of lipid peroxides, which occur under conditions of hyperglycemia and activation of leukocyte-type 12-lipoxygenase. Monocyte adhesion to human aortic endothelial cells was stimulated by incubation with elevated levels of glucose or lipoygenase products, with lisofylline inhibiting this and potentially having a role in prevention of diabetes-induced atherosclerosis. Pravastatin may have an anti-inflammatory effect in addition to its cholesterol-lowering effect, as it has been shown to inhibit thrombin-induced interleukin-8 mRNA expression via the inhibition of p44/p42 mitogen-activated protein kinase in human aortic endothelial cells.

Takata et al. (abstract 609) reported that both high glucose and thrombin increased phosphorylation of this mitogen-activated protein kinase, with pravastatin blocking these effects.

Bandinelli et al. (abstract 1105) and Pucci et al. (abstract 1121) reported that the transcapillary albumin escape rate decreased from 8.9 to 7.7%/h and 7.6%/h after 6 and 12 months of therapy with atorvastatin (40 mg daily) in 22 patients with primary hypercholesterolemia, without change in insulin sensitivity. They also reported that tissue plasminogen activator was 7.3 in control subjects vs. 9.4 ng/ml in patients, decreasing to 7.7 ng/ml at 6 months, whereas plasminogen activator inhibitor 1 was 19.4 ng/ml in control subjects vs. 28.9 ng/ml in patients, decreasing to 19.6 ng/ml at 6 months. This suggested an effect of statin treatment on vascular permeability and fibrinolysis.

Kim et al. (abstract 578) reported that lipoprotein(a) concentrations were 25, 23, and 40 mg/dl for patients in the first, second, and third tertile of carotid IMT, suggesting a relationship to atherosclerosis in patients with diabetes. Kesala et al. (abstract 1114) treated 20 diabetic patients with niacin and with Niaspan at mean doses of 2,462 and 2,453 mg daily. There was a similar fall in LDL cholesterol from 131 to 90 and 93 mg/dl, a rise in HDL cholesterol from 35 to 61 and 59 mg/dl, and a fall in lipoprotein(a) from 43 to 14 and 12 mg/dl, with HbA1c falling from 7.4 to 6.3 and 6.4%, suggesting that with aggressive glycemic treatment, these are useful agents for patients with diabetes.
Alternative Medicine in Diabetes
In a study presented at the meeting, Wang et al. (abstract 291) administered chromium picolinate in an insulin-resistant rat model. Fasting insulin was 31% lower with improved glucose disposal during a 30-min insulin tolerance test and decreased glucose and insulin after an intraperitoneal glucose bolus, suggesting enhanced insulin sensitivity and glucose disposal. However, Juang et al. (abstract 455) treated seven individuals with impaired glucose tolerance and 2-h postprandial plasma glucose, showing improved insulin sensitivity. Kusano et al. (abstract 1282) reported a similar insulin-sensitizing antidiabetic effect of this agent to that of troglitazone in obese Zucker fatty rats. They reported regrualnization of pancreatic islet β-cells with both agents, and only troglitazone was associated with weight gain. Luo and Chuang (abstract 468) administered masoprolate, a lipoxynase inhibitor isolated from the creosote bush, to mice with diabetes, showing inhibition of hepatic microsomal glucose-6-phosphatase, a potential mechanism of the agent's glucose-lowering activity.

References