Aspects of Type 2 Diabetes and Related Insulin-Resistant States

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This is the fourth in a series of articles on presentations at the American Diabetes Association Annual Meeting, San Diego, California, 10–14 June 2005.

Exercise, diet, and lifestyle modification

Addressing the debate over aerobic versus anaerobic exercise, Sigal et al. (abstract 371) reported results of the Diabetes Aerobic and Resistance Exercise (DARE) clinical trial of 251 previously inactive persons with type 2 diabetes exercising at local YMCAs, supervised by personal trainers. Both aerobic and resistance training improved HbA1c (A1C) similarly. Both aerobic and resistance training improved HbA1c (A1C) similarly. Similarly, Snitker et al. (abstract 1094) found that among 80 Amish persons, who habitually engage in physical exercise, the time spent in moderate to vigorous activity correlated directly with the degree of insulin sensitivity. Cheng et al. (abstract 1015) studied 738 adults with and 6,376 persons without diabetes in the National Health and Nutrition Examination Surveys 1999–2002, reporting that C-reactive protein (CRP) levels were 31% higher in sedentary persons than in those who had high levels of physical activity, adjusting for age, sex, ethnicity, diabetes duration, BMI, energy intake, smoking, and alcohol consumption. Diabetes was associated with 35% higher CRP, independently of the effect of physical inactivity. Park et al. (abstract 164) reported 7% lower knee extensor strength per unit muscle mass in 485 persons with diabetes compared with 2,133 without diabetes at mean age 74 years, with follow-up examination 3 years later in ~70% showing greater loss of strength in the diabetic group.

Two studies analyzed effects of exercise in persons with type 1 diabetes. McMahon et al. (abstract 107) studied nine adolescents with type 1 diabetes with and without afternoon exercise, showing a 41% increase in the infusion rate of glucose required to maintain euglycemia while the subjects were sleeping, so that 6–7 h following exercise, for 4 h from the onset of sleep, the infused glucose requirement was proportional to the amount of exercise. Tsalkian et al. (abstract 260) studied 50 type 1 diabetic 11- to 17-year-old children with vigorous predinner exercise (60 min at a heart rate of 140 bpm), showing a fall in glucose levels from ~160 to 110 mg/dl following exercise, with glucose levels remaining ~25 mg/dl below those on a sedentary day and with 48 vs. 28% having a blood glucose <60 mg/dl. Hypoglycemia occurred infrequently on the sedentary night if the prebedtime snack glucose exceeded 130 mg/dl, but this was not protective following exercise. There may, then, be sustained increase in glucose requirement following exercise in type 1 diabetes, increasing the risk of nocturnal hypoglycemia, suggesting the need to reduce insulin dosages and/or increase nutrient intake not only in the immediate postexercise period but for as long as 10 h thereafter.

In the Diabetes Prevention Program (DPP) (abstract 1037), diabetes incidence decreased from 11, 11, and 10 cases per 100 person-years at ages 25–44, 45–59, and >59 years with placebo to 6, 5, and 3 cases per 100 person-years with the lifestyle intervention, suggesting particular benefit with greater age. Weight loss with the lifestyle intervention in the three age-groups was 4, 5, and 6 kg, and participants exercised 4, 6, and 19 metabolic equivalent (MET) hours/week, respectively. Analysis of electrocardiograms performed in the DPP (abstract 1003) showed that estimates of sympathetic and parasympathetic modulation of heart rate showed improvement only in the intensive lifestyle intervention. Higher heart rate was associated with greater risk of diabetes, and the heart rate declined 5 bpm in the lifestyle intervention versus 2 bpm with placebo and with metformin. Ramachandran et al. (abstract 366) randomized 531 Asian-Indian persons with impaired glucose tolerance (IGT) age 35–55 years to control, lifestyle, metformin, and lifestyle plus metformin for 30 months, with diabetes developing in 49.6, 35, 39.8, and 34.7%, respectively, suggesting that the benefit of lifestyle modification exceeds that of metformin and that there is no additive effect of combining the two approaches.

A number of additional studies analyzed aspects of diet related to diabetes. Song et al. (abstract 1016) analyzed alcohol consumption among 38,018 women, age ≥43 years, without a history of coronary heart disease, stroke, cancer, or dia-

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Abbreviations: CRP, C-reactive protein; d4T, dideoxyinosine/stavudine; DPP, Diabetes Prevention Program; GDM, gestational diabetes mellitus; HAART, highly active antiretroviral therapy; HCC, Hepatocellular carcinoma; HCV, hepatitis C virus; HOMA, homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; IGT, impaired glucose tolerance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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beverages in the Women's Health Study over 8.9 years of follow-up, showing decreases in risk of type 2 diabetes of 16, 28, 36, and 57% for women consuming 0.01–6.0, 6.1–12, 12.1–24, and ≥24 g/day, respectively, regardless of type of alcoholic beverage and controlling for age, BMI, total calorie intake, smoking, physical activity, postmenopausal hormone use, family history of diabetes, and dietary factors, including glycemic load, total fat, fiber, magnesium, and caffeine intake. Pereira et al. (abstracts 1056 and 1057) followed 28,812 postmenopausal women without diabetes, heart disease, and cancer for 11 years. Compared with women not drinking coffee, those drinking more than five cups daily of decaffeinated and regular coffee had 34 and 17% lower likelihoods of developing diabetes, respectively, adjusting for age, baseline BMI, waist-to-hip ratio, estrogen use, education, cigarette smoking, physical activity level, and intake of alcohol, total calories, fatty acids, cereal fiber, tea, milk, and soda. Compared with women not drinking sugar-sweetened beverages, the study showed that those consuming at least seven such beverages weekly had a 1.7-fold increased risk of developing diabetes, while compared with those drinking no fruit juice, 3.5–6.5 servings, and ≥7 servings weekly were associated with 24 and 38% increases in diabetes risk. Fowler et al. (abstract 1058) studied the relationship between soft drink consumption and weight gain, reporting that of those with baseline BMI <25 kg/m², drinking less than one-half can/day, one-half to less than can/day, one to less than two cans/day, and two or more cans/day of regular soda were associated with 26, 30, 33, and 47% likelihood of becoming overweight after 7–8 years. The respective risks associated with drinking diet soda were, however, even greater, at 37, 38, 55, and 57% increases in the risk of developing obesity, with risk increased 1.4-fold per can of diet soda consumed per day, suggesting that consumption of diet soda may not be a useful weight control strategy.

McMillan et al. (abstract 36) compared a low-fat/55% carbohydrate diet, a low-fat/55% carbohydrate low–glycemic index diet, a 25% protein/45% carbohydrate diet, and a 25% protein/45% carbohydrate low–glycemic index diet in 129 overweight persons (116 completers) without diabetes. After 12 weeks, weight loss was greater with the second and third diets in women, but not in men, and reductions in glycemic index but not in carbohydrate in both men and women lowered LDL cholesterol. Atkinson et al. (abstract 1766) fed 11 nondiabetic women on 4 different days a 25% protein/45% carbohydrate versus a low-fat/55% carbohydrate series of meals, with either low– or high–glycemic index carbohydrates, creating glycemic loads of 43, 84, 65, and 116. The respective incremental areas under the glucose curve were 196, 230, 223, and 315, suggesting physiologic validity to the concept of glycemic load. Furthermore, high-protein diets appeared to produce greater satiety. Manders et al. (abstract 7) administered a standard carbohydrate load with or without a casein protein hydrolysate containing additional leucine and phenylalanine to 10 patients with type 2 diabetes, showing tripling of insulin response and a 28% lowering of postload glycemia, associated with 13% greater glucose disposal based on labeled glucose turnover studies.

Heilbronn et al. (abstract 34) and Frisard et al. (abstract 35) compared 45 healthy overweight nonobese persons on a control diet with three dietary interventions, a 25% calorie restriction diet, a 12.5% calorie restriction with a 12.5% increase in energy expenditure by exercise, or a low-calorie diet until 15% weight reduction was achieved, followed by maintenance. Body weight decreased 10, 10, and 14% with the respective interventions; fasting insulin decreased 30, 17, and 11%; insulin sensitivity increased 40, 79, and 70%; intramuscular lipid was not affected; and intrahepatic lipid decreased 37, 28, and 40%, suggesting that it may be possible to specifically design interventions to optimize improvement in insulin sensitivity.

Maynard et al. (abstract 1767) placed 30 children with BMI >95th percentile on a low–glycemic load diet and exercise program, showing a 23% decrease in triglyceride-to-HDL ratio and a 19% decrease in CRP in those randomized to a 3-g daily long-chain ω-3 fatty acid supplement. Winzell et al. (abstract 39) studied an insulin-resistant mouse model treated with linoleic acid for 8 weeks, showing that rather than being beneficial, insulin sensitivity and adiponectin levels decreased with these agents; they noted that the term “linoleic acid” actually refers to a group of polyunsaturated fatty acids, suggesting that various fatty acids may play different roles in insulin sensitivity. Vitamin D may be related to type 2 diabetes as well, with Pittas et al. (abstract 1772) reporting that of 81,680 women without history of diabetes, cardiovascular disease, or cancer followed for 20 years in the Nurses’ Health Study, adjusting for age, BMI, hypertension, family history of diabetes, smoking, physical activity, caffeine, and alcohol intake, those in the highest versus lowest quintiles of vitamin D intake had a 28% lower risk of developing type 2 diabetes.

Pharmacologic approaches to weight loss were explored in several presentations at the meeting. Aronne et al. (abstract 1821) treated 148 persons with BMI 29–43 kg/m² with 10 mg sibutramine daily, with 95 achieving >5% weight loss (mean 8.3 kg) randomized to low-calorie diet using meal replacement therapy with versus without continued sibutramine, leading to 2.5-kg further weight loss vs. 2.8-kg weight gain. Long et al. (abstract 1822) and Fennoy et al. (abstract 1824) randomized 498 obese (mean BMI 36.1 kg/m²) adolescents ages 12–16 to 10 mg sibutramine daily versus placebo, showing 38, 23, and 39% vs. 82, 13, and 6% having respective weight loss <5, 5–10, and ≥10%, with expected improvement in blood pressure, triglyceride, and HDL cholesterol levels. Yatrus and Bridges (abstract 1830) reported that 54 obese diabetic persons treated with orlistat and monthly nutritional counseling showed reduction in A1C with the treatment. Given the evidence that obesity may be a state of low growth hormone function, Kim et al. (abstract 1834) administered growth hormone versus placebo to 16 vs. 8 obese type 2 diabetic patients for 12 weeks, showing increased insulin sensitivity and decreased visceral fat, triglyceride, free fatty acid, fibrinogen, and plasminogen activator inhibitor-1 levels. Albert et al.(abstract 1823) randomized 40 obese persons to growth hormone versus placebo, showing decreased body fat assessed by dual-energy X-ray absorptiometry. Wittwer et al. (abstract 1835) administered AOD9604, a modified growth hormone peptide fragment, or placebo, 1, 20 and 30 mg/day orally for 12 weeks, with greatest weight loss at the 1-mg dose, at 2.6 vs. 0.8 kg with placebo. Kok et al. (abstract 1843) reported that administration of the dopamine 2 receptor agonist bromocriptine versus placebo to 18 healthy obese premenopausal women led to a 5% increase in resting energy expenditure, with reduction in fasting insulin suggesting improvement in insulin sensitivity. Addressing an important risk factor for weight gain, Ader et al. (abstract 1848) administered olanzapine, risperidone, or placebo to normal dogs for 6 weeks, showing increased food
intake and fat mass with olanzapine. Fountaine et al. (abstract 1849) reported a 23% increase in food intake in 21 healthy persons receiving olanzapine 5 and then 10 mg daily versus placebo for 12 days. Rosenstock et al. (abstract 46) administered a controlled release formulation of topiramate to 111 persons with type 2 diabetes, showing that the mean BMI of 38 kg/m² decreased 5.8 vs. 2.3% with placebo, with a fall in A1C from baseline of 0.9 vs. 0.4%.

André Scheen (Liege, Belgium) gave the results of the Rimonabant In Obesity (RIO)-Diabetes study. Rimonabant is a selective CB1 receptor endocannabinoid blocker, having central action in decreasing food intake and showing evidence of action at the adipocyte in skeletal muscle, in the liver, and in the gastrointestinal tract, all further improving metabolic parameters. A total of 6,627 persons have been enrolled in four rimonabant phase III clinical development trials. RIO-Diabetes was a study of 5 vs. 20 mg rimonabant vs. placebo in 1,045 persons with diabetes who underwent a 2-week single-blind placebo period followed by 4 weeks of placebo versus 5 mg rimonabant, with the active treatment group then treated with 5 or 20 mg daily for a total of 52 weeks. Admission A1C was 6–10% (mean 7.3%), with the primary end point the change in body weight at 1 year and secondary end points A1C, lipids, waist circumference, metabolic syndrome, and safety. Totals of 348, 358, and 339 subjects were treated with placebo, 5 mg, and 20 mg daily. Approximately 60% had hypertension and 55% dyslipidemia, 66% received metformin and 33% sulfonylureas, and 79% had metabolic syndrome. Body weight decreased 1.4, 2.3, and 5.3 kg, and waist circumference decreased 1.9, 2.9, and 5.2 cm in the respective groups. Of patients, 14.5 vs. 21.7 vs. 49.4% lost ≥5% of initial weight and 2, 6.2, and 16.4% lost ≥10% of initial weight. At 1 year, the A1C was 7.3, 7.2, and 6.7%, with multivariate analysis suggesting that approximately half of the decrease in the 20-mg group was due to weight loss and half due to direct metabolic effect of CB1 receptor blockade at the level of the adipocyte, skeletal muscle, or liver. HDL cholesterol was 45 mg/dl at baseline and increased 7.1 vs. 9.2 vs. 13.4% at 1 year with 0, 5, and 20 mg. Their analysis suggested that more than half of the improvement was not attributable to weight loss. The triglyceride level increased 7.3 with placebo while decreasing 1.3 and 9.1% with active treatment. Compared with the placebo group, in which the prevalence of metabolic syndrome decreased 7.6%, in the 20-mg group, metabolic syndrome decreased 18.9%. There were some safety issues, with nausea experienced by 3.7 vs. 12.1% of the placebo versus 20-mg groups, self-reported hypoglycemia occurring in ~1 vs. 5%, and anxiety in 2.8 vs. 5%. Of treated patients, 5.5, 7.8, and 15% discontinued the drug because of adverse events.

**Oral agent treatment**

Fan et al. (abstract 1000) reviewed diabetes treatment patterns in national samples of 1,215 persons with diabetes in 1988–1994 and of 758 such persons in 1999–2002. The frequencies of diet and insulin treatment alone decreased from 27 to 19% and from 24 to 14%, while the frequencies of oral agent treatment alone increased from 45 to 57% and that of oral agents in combination with insulin increased from 3 to 10%. Rates of achieving A1C <7% decreased from 44 to 40% in those age ≥65 years and increased from 40 to 44% in those age 45–64 years, while among those age <45 years, only 16% in either time period achieved A1C <7%. Koro et al. (abstract 999) analyzed pharmacotherapy change in response to elevated A1C in a dataset of 9,335 persons receiving oral antidiabetic monotherapy. Among patients with at least one A1C >7%, those with A1C 7–10% had pharmacotherapy change in a median of 372 days and those with A1C >10% had pharmacotherapy change in a median of 160 days. With two elevated A1C test results, median times from the second test were 275 and 70 days, respectively, suggesting considerable room for improvement of diabetes treatment in the community.

**Sulfonylurea treatment.** Several studies addressed aspects of metformin and sulfonylurea treatment. Holman et al. (abstract 596) examined β-cell function and insulin sensitivity using the homeostasis model assessment (HOMA2) model in 1,741 U.K. Prospective Diabetes Study patients at the time of diagnosis of diabetes and after 1 year of therapy. β-Cell function increased 36% with sulfonylurea versus 11% with metformin, while insulin sensitivity decreased 4% versus increasing 10% with the respective therapies. Gottschalk et al. (abstract 264) compared glimepiride (mean 3.8 mg daily) versus metformin (mean 1,408 mg daily) in 263 children age 9–17 years with type 2 diabetes whose baseline A1C was 8.5%, showing 12-week A1C falls of 0.7 vs. 0.9%, with weight gain of 2.2 vs. 0.7 kg. Gerich et al. (abstract 266) randomized 428 type 2 diabetic persons with mean A1C 8.4%, not previously receiving pharmacologic treatment, to metformin plus either 120 mg nateglinide three times daily or 1.25–20 mg glyburide daily; both groups showed similar 2-year decreases in A1C of 1.5%, with 8 vs. 18% experiencing hypoglycemia. The A1C nadir occurred at 28 weeks, and A1C subsequently increased by ~0.3%/year in both groups. Girman et al. (abstract 994) reported the effect of adding a sulfonylurea to metformin in 2,220 persons with median age 63 years, A1C 8.8%, diabetes duration 3.8 years, and BMI 31.4 kg/m². A1C worsened before addition of the sulfonylurea, improved immediately after, and began worsening again 6 months after sulfonylurea initiation, particularly with higher initial A1C, younger age, and female sex. By 4 years, 85% of patients were predicted to have A1C ≥8.0%, although analysis of physician behavior suggested that only 34% would be given additional therapy. Nybäck-Nakell et al. (abstract 454) studied 23 type 2 diabetic persons treated with insulin and sulfonylurea for 7–24 years, 13 of whom were also treated with metformin. To ascertain whether there was long-term benefit from sulfonylurea, the agents were discontinued, with glucose control worsening in 77%. The duration of diabetes and of sulfonylurea treatment correlated with ongoing sulfonylurea benefit, without predictive effect of weight, BMI, waist-to-hip ratio, insulin requirement, baseline A1C, fasting glucose, C-peptide, or serum triglycerides.

**Metformin treatment.** Ehrich et al. (abstract 457) studied outcome of treatment of 1,833 persons who had developed heart failure among 12,272 new users of oral antidiabetic agents in the Saskatchewan Health database in 1991–1996, 208 of whom received metformin monotherapy, 773 sulfonylurea monotherapy, and 852 combination therapy. Over 2.5 years of follow-up, those receiving metformin monotherapy and combination therapy had 70 and 61% the mortality of those receiving sulfonylurea monotherapy, respectively, suggesting that it may be an ill-founded concept that there is a contraindication to metformin use among patients with heart failure due to concerns over lactic acidosis. In another
analysis using the same database, Bowker et al. (abstract 521) studied 10,309 persons receiving metformin or sulfonylurea followed for a mean of 5.4 years, finding the latter to have a 30% increase in cancer-related mortality. Insulin use was associated with a 90% increase, suggesting either a protective effect of metformin or a deleterious effect of sulfonylurea and insulin. Aguilar et al. (abstract 607) reported improvement in weight, blood pressure, HDL cholesterol, and endothelial vascular reactivity in 31 nondiabetic relatives of persons with type 2 diabetes treated with 850 mg metformin twice daily for 90 days. Analysis of the effect of metformin in the DPP (abstract 1004) showed evidence of increase in insulin secretion along with weight loss, explaining the decrease in diabetes development in comparison to the placebo group.

New pharmacological approaches to type 2 diabetes

A number of additional approaches to treatment of type 2 diabetes were explored. Yoshida et al. (abstract 472) studied CS-917, an orally administered inhibitor of fructose 1,6-bisphosphatase, a rate-limiting enzyme of gluconeogenesis, reporting dose-dependent glucose lowering in overnight-fasted normal cynomolgus monkeys and in Goto-Kakizaki rats. Van Poelje et al. (abstract 503) reported reduction in glucose from 305 to 166 mg/dl with use of this agent over 30 days in a rat type 2 diabetes model. Kumeda et al. (abstract 473) and Yamamoto et al. (abstract 474) reported that SGL0010, an orally active inhibitor of proximal renal tubular sodium-dependent glucose cotransporters, results in dose-dependent glycosuria, which had glucose-lowering effect in type 1 and type 2 diabetic models, with less potential to cause hypoglycemia than glyburide. Fye et al. (abstract 522) reported that the glucokinase activators PSN105 and PSN010 lowered glucose levels in animal models of type 2 diabetes. Song et al. (abstract 526) performed a meta-analysis of treatment of persons with type 2 diabetes with oral magnesium, reporting nine randomized controlled trials lasting 4–24 weeks with 392 total participants, showing A1C reduced 0.3% and fasting glucose 5 mg/dl. Shankar et al. (abstract 535) administered acarbose versus placebo to 196 persons with early type 2 diabetes, characterized by glucose level fasting <140 and at 2 h on glucose tolerance testing ≤200 mg/dl, reporting lowering of postprandial glucose and A1C but no reduction in progression from fasting glucose ≤140 to >140 mg/dl or from ≤126 to >126 mg/dl, leading the authors to suggest that β-cell failure, as shown by fasting hyperglycemia, is not improved by lowering postprandial glucose levels. Satoh et al. (abstract 647) administered the α-glucosidase inhibitor voglibose versus placebo to 12 vs. 12 persons with type 2 diabetes, the former showing lowering of fasting glucose, C-peptide, HOMA of insulin resistance (HOMA-IR), apolipoprotein B, apolipoprotein E, and triglycerides, despite similar improvement of BMI and A1C. Voglibose also decreased soluble intercellular adhesion molecule-1 and CRP, suggesting an anti-inflammatory effect.

Balkan et al. (abstract 618) administered PTP-3848, an inhibitor of the negative insulin signaling regulator protein tyrosine phosphatase 1B, orally to C57 mice, which develop insulin resistance on a high-fat diet. Fatty acid synthase decreased with an increase in carnitine palmitoyltransferase 1 and circulating ketone levels. Weight gain was prevented, with no decline in adiponectin or increase in insulin levels. Sayo et al. (abstract 604) examined the effect of the antibody to tumor necrosis factor α infliximab in patients with rheumatoid arthritis, showing increase in insulin sensitivity and in adiponectin levels. Several studies suggested benefit of chromium picolinate. Martin et al. (abstract 1778) randomized 27 type 2 diabetic persons treated with 5 mg glipizide GITS daily to placebo versus chromium 1 mg picolinate daily for 6 months, showing a decrease in A1C of 0.4 vs. 1.2% and weight gain of 2.2 vs. 0.9 kg with a 2.7-fold greater increase in abdominal fat and with evidence of insulin-sensitizing effect of chromium treatment. Albarracin et al. (abstract 1784) randomized 368 type 2 diabetic persons to 600 mg chromium picolinate plus 2 mg biotin daily versus placebo for 90 days, showing a 0.5, 0.7, 1.2, 1.8, and 2.0% lower A1C among those with baseline A1C 7–7.9, 8–8.9, 9–9.9, 10–10.9, and ≥11.0%, respectively. The decrease in LDL cholesterol among those with baseline cholesterol >200 mg/dl was 22 vs. 8 mg/dl.

Gestational diabetes mellitus

At a symposium addressing the use of metformin in pregnancy, Clifford Bailey (Birmingham, U.K.) discussed cellular and metabolic actions and pharmacology of metformin. Metformin is now the most used agent in the treatment of type 2 diabetes worldwide. In medieval Europe, Galega officinalis (French lilac, goatsrue, or professor-weed) was used as a treatment for diabetes, as well for increasing milk production by farm animals. In 1850, it was found to be rich in guanidine. Guanidine was found in 1918 to lower glucose levels, with subsequent recognition that biguanides have glucose-lowering effects. In 1957, metformin and phenformin were introduced, with phenformin withdrawn in 1977 because of concern about risk of lactic acidosis, and metformin was introduced in the U.S. in 1995.

Metformin crosses the placenta with somewhat higher concentrations in fetal than maternal blood, but there are low concentrations in breast milk.

Metformin counters insulin resistance by insulin-dependent and -independent mechanisms, lowering basal insulin levels, and not causing hypoglycemia when administered alone. Its antihyperglycemic effect appears mainly to reflect hepatic action, although there also is a muscle effect. Interestingly, the agent increases anaerobic metabolism in the gastrointestinal tract, increasing lactate production. At the cellular level, metformin alters membrane surface electrical charges, affecting membrane fluidity and plasticity. It acts on the β-subunit of the insulin receptor to increase tyrosine phosphorylation and increases glucose transporter movement to the cell membrane both via its effects at the insulin receptor and independently, may increase glucose metabolism mitochondrial effects, and may have effects on AMP kinase, although Bailey expressed skepticism as to the importance of this mechanism.

Clinically, metformin improves insulin resistance, reduces insulin levels, decreases the degree of abdominal obesity, decreases glucose levels, has modest triglyceride- and LDL cholesterol–lowering and HDL-raising effects, is antithrombotic, modestly decreasing plasminogen activator inhibitor-1 and lessening platelet aggregation, decreases advanced glycation endproduct levels, and increases endothelial and endothelium-indepen-
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dent blood flow. Of great importance is the favorable effect on weight with this treatment. The U.K. Prospective Diabetes Study showed metformin to be associated with reduced frequency of myocardial infarction and with decreased diabetes-related mortality.

Pregnancy is an insulin-resistant state. Among pregnant women not developing gestational diabetes mellitus (GDM), insulin secretion increases. GDM is associated with particularly severe insulin resistance and with failure of insulin levels to increase appropriately, so that metformin might offer a logical approach to treatment. In toxicology studies in rats, at dosage levels equivalent to 20 times the upper dose in humans, adverse fetal outcomes were not found, with normal growth of neonatal rats and without teratogenic effect. If one does consider use of this agent during pregnancy, care should be taken to avoid patients at risk of renal insufficiency, so that caution is needed with preeclampsia, with liver disease, alcohol abuse, or cardiac or respiratory predisposition to hypoxia, with gastrointestinal pathology, or with impairment of vitamin B12 and folate absorption. Despite these caveats, however, the agent has intriguing potential as a therapy to prevent GDM in susceptible women. Furthermore, if the agent can be safely used during pregnancy, one might anticipate improvement in glycemic control with combined metformin-insulin treatment among women with GDM requiring insulin.

Gerald Briggs (Long Beach, CA) discussed approaches to determining whether metformin might have teratogenic actions. He reviewed potential causes of structural defects, noting that 40% are of unknown cause, 8% are due to a monogenic abnormality, 6% to a chromosomal abnormality, as in Down's syndrome, and 8% environmental, with causes including infections, maternal illness (the vast majority diabetes), and chemicals including pharmaceutical agents. Approximately 40% of defects are felt to reflect an interaction between multiple gene variants and environmental factors. Structural defects are seen at birth in 2–3% of infants and at 1 year in 5–6%, with rates increased four- to sevenfold among children of women having preexisting diabetes. In addition to structural defects, agents may cause developmental toxicity, leading to embryonic or fetal death, to growth retardation or restriction, or to functional or behavioral abnormality. As an example, atenolol causes severe intrauterine growth retardation during the second trimester, although it is not a teratogen. Angiotensin II–directed agents cause renal failure in the human fetus, with the consequent oligohydramnios reducing blood flow to the topmost portion of the skull during the third trimester, resulting in bone defects. Drugs may, then, exhibit a number of reproductive and developmental toxicities, including effects on fertility, parturition, lactation, and development. "We can't really say," Briggs explained, "that a drug is safe . . . We can say that it is low risk." Metformin has low molecular weight, negligible protein binding, and is not metabolized. Although its plasma half-life is 6.2 h, the erythrocyte half-life exceeds 16 h, which Briggs characterized as "[being] there for a long time."

Criteria for establishing human developmental toxicity include epidemiologic studies, assessing outcome of pregnancies with exposure during critical times of fetal development. Case reports are important, as rare exposures may lead to rare defects, as was seen in the unusual development defects associated with thalidomide use. For many drugs, the only data are from animal studies. Addressing the question of whether metformin causes developmental toxicity in animals, Briggs noted that in rabbits there is no evidence of structural defects at doses up to two- to sixfold maximal human dose (based on plasma levels or, less optimally, on dose per unit body surface area). Embryotoxicity has, however, been found in rats at doses somewhat over threefold the maximal human level, suggesting that there may be moderate risk, although there are many variables from one species to another, with characteristics of the human placenta possibly differing from those of experimental animals.

There is somewhat mixed human data. One study found more preeclampsia and increased perinatal mortality with metformin, although without clear evidence that metformin was causally related (1). In analysis of studies comprising 152 women with PCOS, type 2 diabetes, and GDM, of whom 11 were treated only during the first trimester, and 141 received metformin throughout pregnancy, there were 21 spontaneous abortions, less than the number expected, and the only birth defect found was one case of chondrodysplasia (2–4). Biggs concluded that there is no evidence of growth retardation, fetal or perinatal mortality, or structural, functional, or behavioral deficits, which he contrasted with the strong evidence of toxicity from insufficient treatment of maternal diabetes. In women with GDM, then, there may be low risk with metformin. One must, of course, realize that the absence of evidence of risk is not evidence of the absence of risk, and given Bailey's warning of the potential for lactate accumulation with preeclampsia-induced renal insufficiency, the use of this agent will require extremely careful monitoring.

Charles Glueck (Cincinnati, OH) discussed the use of metformin in the first trimester and in the prevention of GDM, noting that the prevalence of GDM has greatly increased over the past decade. More than half of women with GDM develop type 2 diabetes within 5 years, and perhaps 70% within 10 years, in association with birth defects and abnormal childhood growth and glucose regulation, leading to a "cross-generational cycle of GDM." Administration of metformin to women with PCOS reduces GDM and fetal macrosomia, promotes ovulation, protects against first trimester miscarriage, is not teratogenic, probably reduces preeclampsia and eclampsia, and promotes normal infant growth and development. In a study of women with PCOS who became pregnant without metformin treatment, only 32% had live births, while during a subsequent pregnancy with metformin treatment, 85% had live births. A similar study reported 58 vs. 11% fetal loss, although both studies are limited by the use of historical controls (5). In a study comparing 97 pregnancies with 126 infants exposed to metformin throughout gestation for maternal PCOS treatment with 252 healthy control subjects, GDM occurred less often, in 7.6 vs. 15.9%, and preeclampsia occurred comparably in 5.3 vs. 3.6%. Birth weight and length were slightly decreased, perhaps related to the prevention of macrosomia, and at 3, 6, 9, 12, 18, and 36 months, there was no difference in growth or in motor or social development (6). Birth defects occurred in 1.4% of offspring of metformin-treated women, below the national average of ~4.5%. Glueck interpreted these findings to indicate that metformin "radically reduces [the] likelihood of first trimester miscarriage," perhaps via effects on prothrombotic state. A study of 40 women treated with metformin versus placebo later in pregnancy showed reduction in GDM from 31 to 13%, and preeclampsia rates of 5 vs. 23%
Glueck showed further data that lactation appears to be more successful when metformin is used and that its presence in breast milk does not appear to be clinically significant, without effect on infant height, weight, or development at 3 and 6 months. He concluded that that gestational use of metformin, which he gave in doses up to 2.5 g daily, is beneficial for pregnancy and has no adverse effect on the infant.

Janet Rowan (Aukland, New Zealand) further addressed the use of metformin for type 2 diabetes during pregnancy and for GDM. Most of her patients are of Polynesian ethnicity and are severely obese. The number of women with GDM seen in her clinic in 2000, 2001, 2002, 2003, and 2004 was 169, 193, 294, 370, and 348, respectively, which she believes indicates a real change in incidence rather than a referral bias. More than 25% of her patients with GDM, she noted, have IGT or type 2 diabetes 6 weeks postpartum. Compliance with insulin is a problem in her clinic, and she noted a study finding cord insulin levels more than twice as great in offspring of women with GDM versus control subjects, suggesting that insulin treatment as typically employed may be ineffective, with increased fetal insulin associated with increased risk of childhood obesity and a 10-fold increase in risk of IGT at age 6 years. Of siblings born to women with GDM during only one of two pregnancies, the second is more likely to be overweight and to develop diabetes (8). Thus, the use of metformin may be particularly appropriate during pregnancy, with potential benefit for offspring. In a retrospective study of 50 women treated with metformin, 68 with sulfonylurea, and 42 with insulin during pregnancy, preclampsia occurred in 32, 7, and 10% and stillbirths in 4, 0, and 1%, respectively, but weight was greater in the metformin-treated group at 31, 23, and 25 kg/m². Rowan noted the implication that retrospective studies may be misleading, as “we’re actually using the metformin in our highest risk women.” She concluded that metformin appears to be a logical treatment for pregnancy-related diabetes and described the Metformin in GDM randomized controlled trial currently in progress of 750 women receiving insulin versus metformin, with results to be ready in 2006.

Research presentations at the ADA meeting addressed further aspects of GDM. Eriksson and Cederberg (abstract 152) studied whether oxidative stress plays a role in the teratogenicity of diabetic pregnancy by administering high doses of α-tocopherol and ascorbate to nondiabetic and streptozotocin-induced diabetic pregnant rats. Malformation rates were reduced from 29 to 19% and fetal resorption from 38 to 26%.

Zhang et al. (abstract 1912) assessed the relationship between prepregnancy physical activity and GDM among 19,462 participants in the Nurses’ Health Study without previous diabetes who reported at least one pregnancy from 1990 to 1998, 1,192 of whom developed GDM. Adjusting for BMI, women in the top 40th percentile of physical activity had a GDM risk ~20% lower than those reporting less activity. Climbing 10–14 and ≥15 flights of stairs daily was associated with 21 and 58% reductions in GDM rate. Hedderson et al. (abstract 1914) compared 114 women who had had GDM with 95 control subjects. Compared with women whose weight did not change, those with weight gain of 0.39–1.62 kg/year and 1.8–8.4 kg/year in the 6 years before pregnancy had 50 and 150% increases in likelihood of GDM, respectively. Di Cianni et al. (abstract 156) studied 166 women who had had GDM and 98 control women 16 months after delivery, with similar age and BMI, showing 61% higher HOMA-IR, correlating with CRP, with high fasting glucose in 8 vs. 0%, low HDL in 37 vs. 17%, hypertriglyceridemia in 10 vs. 2%, and abdominal obesity in 34 vs. 18%. Hypertension was not more prevalent, present in 5 vs. 7%, but metabolic syndrome prevalence was 9% vs. 1%. Montoro et al. (abstract 1913) found that HOMA-IR during the third trimester of pregnancy showed a significant, although only modestly strong (r = 0.47), correlation with insulin sensitivity directly measured with a euglycemic clamp. Finally, in an important warning of the need for improved glycemic control of women with pre-GDM, Al-Ahga et al. (abstract 154) analyzed 260 singleton pregnancies of type 1 diabetic women, finding week 13 A1C values of 6.3, 6.9, and 7.1% in women whose infants’ birth weight was <4, 4–4.5, and >4.5 kg, respectively, suggesting the need to optimize glycemic control before the end of the first trimester.

Diabetes in specific disease states

**Diabetes in HIV-infected patients.** Colleen M. Hadigan (Boston, MA) noted that HIV has an important overlap with insulin resistance and with diabetes. In a study of 1,278 HIV-infected men and control subjects in 1999, the prevalence of diabetes was 5% among control subjects and 6% among persons with HIV not receiving highly active antiretroviral therapy (HAART), but 14% among patients receiving HAART, a 4.6-fold increase in risk (9). In a follow-up study, the diabetes incidence based on fasting glucose ≥126 mg/dl increased 4.11-fold among persons with HIV receiving HAART and 1.64-fold among HIV-positive men not receiving this therapy, with particular risk for those treated with ritonavir and those whose CD4 count was <300/mm³. Among women, 2.8 vs. 1.2% of patients with HIV receiving versus not receiving antiretroviral treatment and 1.4% of control subjects had diabetes in one study, with BMI an additional strong diabetes predictor (10). Persons with HIV and hepatitis C virus (HCV) coinfection had a 3.7-fold increase in diabetes risk over those with HIV alone (11). There is increased risk of CVD with increasing duration of HAART, with diabetes a strong predictive factor; those with diabetes have a 2.38-fold increase in myocardial infarction risk (12).

There are a number of potential mechanisms of the association of HIV with insulin resistance and diabetes, with direct antiretroviral drug toxicity an important component. Insulin sensitivity is markedly reduced by a single dose of indinavir (13), and there are specific effects of protease inhibitors on the GLUT4 transporter (14) and of nucleoside reverse transcriptase inhibitors on mitochondrial function. Lipodystrophy is a crucial aspect of the association of HAART with insulin resistance, leading to relative preponderance of visceral fat, to hepatic steatosis, and to fat deposition at other “ectopic” sites. In the fatless mouse animal model, diabetes and insulin resistance develop, responding to transplantation of subcutaneous fat (15). Using positron emission tomography imaging to assess muscle, liver, and subcutaneous fat, subcutaneous fat is almost completely absent and visceral fat increased in persons with HIV lipodystrophy, with decreased glucose uptake into muscle. Visceral adipose tissue area correlates inversely with whole-body glucose disposal in these persons. The protease inhibitor nelfinavir increases adipocyte lipolysis in vitro (16). Persons with lipodystrophy have decreased insulin sensitivity and increased circulating tumor necrosis factor α levels (17). This and other inflammatory adipocyte secretory products can be shown to...
decrease lipid synthesis in cultured adipocytes (18). There is increased basal lipolysis in vivo in HIV-infected persons and particular increase in those receiving protease inhibitors (19). HIV-infected persons have decreased peroxisome proliferator–activated receptor γ, sterol regulatory element–binding protein 1c, and other adipogenic markers (20), and Hadigan noted that patients treated with didoxynosine/stavudine (d4T) for an 80-week period have decreased subcutaneous fat. In a study comparing glucose tolerance of 75 HIV-infected persons with age-, weight-, and sex-matched persons from the Framingham cohort, ~35 vs. 5% had IGT and 7 vs. 0% diabetes, although among those with HIV without lipodystrophy, other than low HDL, there was no evidence of insulin resistance (21). Comparing HIV-infected persons with versus without lipodystrophy, the former have ~50% reduction in plasma adiponectin and in adipose tissue adiponectin mRNA levels, correlating with insulin resistance and with increased cytokine levels (22). In persons manifesting insulin resistance with HAART, regimens limiting use of protease inhibitors and thymidine analogs improve lipodystrophy, with use of abacavir rather than d4T and azathioprine leading to increased limb fat, although such an approach has not been shown to improve insulin sensitivity (23). New antiretroviral agents may have better toxicity profiles.

Certainly, use of diet and exercise are appropriate, and there is growing evidence that insulin sensitizers may be beneficial in these patients. A trial of metformin (500 mg twice daily) in 25 HIV-infected persons with waist-to-hip ratio >0.9 and fasting insulin >15 μU/ml showed improved insulin response to oral glucose and decreased weight, waist circumference, and diastolic blood pressure, although no improvement was seen in lipid levels (24). Subcutaneous fat on cross-sectional computed tomography scanning increases with rosiglitazone, with increased adiponectin and decreased free fatty acid levels (25), and a study of 108 persons with HIV and lipodystrophy treated with rosiglitazone versus placebo that failed to show a difference in limb fat found that concurrent d4T/azathioprine use decreased limb fat and interfered with the effect of rosiglitazone (26). Thus, diabetes and insulin resistance are more prevalent in persons with HIV, direct and indirect effects of antiretroviral agents contribute, and a number of therapeutic strategies exist to improve insulin sensitivity and modify cardiovascular risk. Recognition and management of diabetes and insulin resistance in HIV is increasingly important.

**Diabetes and liver disease.** James Lewis (Washington, DC) reviewed a number of diabetes-related issues encountered in the treatment of persons with liver disease. Cirrhosis may impact the treatment of diabetes, with sulfonylurea associated with greater likelihood of hypoglycemia, metformin with increased risk of lactic acidosis, difficulties in medication compliance among persons with encephalopathy, diarrhea leading to electrolyte abnormality associated with acarbose, and issues of fluid retention with thiazolidinedione treatment. Contaminated glucose monitors have been associated with hepatitis B epidemics (27).

Liver disease may be caused by medications for diabetes, notably that which was seen with troglitazone (and some hepatologists question the long-term safety of statins). Acute liver failure rates are increased in persons with diabetes, whose cumulative risk of acute liver failure is 2.31 per 10,000 person-years vs. 1.44 in nondiabetic persons (28). Another study reported acute liver failure rates of 0.15, 0.08, 0.12, and 0.10 per 1,000 person-years with insulin, sulfonylureas, metformin, and troglitazone, respectively (29). There is no evidence, however, that glyceremic medications other than troglitazone cause chronic liver disease or cirrhosis, and exposure to other diabetes treatment without evidence of acute injury has not been found to lead to subsequent increased risk of liver disease. Diabetes may occur in the setting of liver disease treatment with steroids, interferon, lactulose, or calcineurin inhibitors such as tacrolimus or cyclosporine.

It is difficult to determine the causal effect of specific agents in persons who may have coincident liver disease of other etiologies, including viral hepatitis, other drugs, such as statins, cholestatic disorders, and underlying nonalcoholic steatohepatitis (NASH)-related end-stage liver disease. An important association is that between diabetes and HCV. There is two- to fourfold increase in diabetes in persons with HCV, particularly among persons with cirrhosis, with some evidence that HCV can cause diabetes and that diabetes can increase the risk of contracting HCV. Genotype 2a HCV is disproportionately represented among persons with type 2 diabetes (30), and genotype 3 is associated with steatohepatitis and insulin resistance, while hepatitis B is not as strongly associated with diabetes (31). Among 9,841 adults in the National Health and Nutrition Examination Survey, 8.4% had type 2 diabetes and 2.1% HCV, with greater than a coincident finding of the two appearing together (32). HCV may cause β-cell dysfunction, with evidence of HCV-positive islet cell staining (33) in infected persons, and insulin sensitivity may worsen with progression of hepatic fibrosis. Curing hepatitis C reduces the likelihood of developing diabetes and may improve glycemia in persons who have developed diabetes. Furthermore, markers of insulin resistance may be associated with HCV progression, with evidence that fatty infiltration and fibrosis correlate with leptin levels (34).

Posttransplant diabetes is becoming more common, with ~16% of liver transplantation patients having preexisting diabetes, and with new-onset diabetes after transplantation seen in 7–28% of studies, averaging ~15%. The incidence of posttransplantation diabetes is tripled among persons with HCV, with tacrolimus, cyclosporin, and steroids additional risk factors increasing the likelihood of diabetes. Implications for liver transplantation are of the need to minimize steroid dosages, with changing tacrolimus to cyclosporine, treating HCV, and striving for close glycemic control further considerations (35), although Lewis emphasized the need for prospective trials of these approaches. Certainly, persons with posttransplant diabetes have worse outcome (36). Hepatocellular carcinoma (HCC) is the leading cancer worldwide, with HCC risk tripling among persons with diabetes (37).

There is a complex relationship between the liver and metabolic syndrome, with NASH the most common liver disease in Lewis’s population, and increasing appreciation that nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome (38). Eighty-five to 90% of persons with NAFLD have metabolic syndrome, while the risk of NAFLD triples among those who have metabolic syndrome (39). Diabetes or IGT develop in 23% of persons with NAFLD after 3 years of follow-up (40).

Although there is thought to be a relationship between hemochromatosis and diabetes (41), Lewis noted that it is uncertain how often this is clinically relevant, with diabetes rarely resolving after treat-
ment with phlebotomy. Furthermore, meta-analysis has not confirmed that genetic mutations causing hemochromatosis are associated with diabetes (42), although the study may not have been adequately powered, and a coincident mitochondrial defect may lessen weight gain in persons with these mutations, decreasing the likelihood of diabetes. Lewis concluded that associations have been established for HCV, cirrhosis, NAFLD, liver transplantation, cholestathiasis, and drug-induced injury and that associations are possible with HCC and with idiopathic acute liver failure.

A number of studies presented at the ADA meeting addressed aspects of the relationship between diabetes and liver disorders. Wallace et al. (abstract 1010) measured insulin sensitivity, intra-abdominal and subcutaneous fat, and liver function in 163 nondiabetic persons without clinical evidence of liver disease. Lean insulin-sensitive, lean insulin-resistant, and obese insulin-resistant persons had mean γ-glutamyltransferase of 10, 15, and 16 units/l, showing significant correlation with insulin sensitivity on multivariate analysis, while aspartate aminotransferase was 18, 19, and 20 units/l and alanine transaminase 11, 12, and 13 units/l, respectively, and transaminase levels correlating with waist-to-hip ratio but not with insulin sensitivity. Hanley et al. (abstract 165) followed 652 persons in the Insulin Resistance Atherosclerosis Study having neither diabetes nor metabolic syndrome at baseline examination. After 5.2 years, both alanine aminotransferase and alkaline phosphatase were associated with the number of metabolic syndrome disorders at follow-up and with risk of development of the syndrome, without effect of adjustment for ethnicity, sex, or alcohol ingestion, suggesting a role of NASH in development of metabolic syndrome.

Belfort et al. (abstract 79 and 600) administered 45 mg pioglitazone daily versus placebo to 18 vs. 14 persons with NASH and IGT or type 2 diabetes, showing improved transaminase levels in all patients, with a 50% decrease in hepatic fat on magnetic resonance spectroscopy. Both treated patients and control subjects showed decreased inflammation/necrosis on biopsy, but steatosis improved only with pioglitazone.

**Malignancy and prostatic hypertrophy.** Lipscombe et al. (abstract 159) addressed the question of whether hyperinsulinemia is a risk factor for breast cancer by analyzing rates of prior breast cancer in women with newly diagnosed diabetes, whose insulin levels were presumably highest before diabetes onset. Comparing 82,390 women with new diabetes and 411,950 age-matched women without diabetes from the Ontario, Canada, dataset, 3.7 vs. 2.7% had breast cancer, diagnosed 7.9 years previously, with a 13% increase in risk adjusting for age, income, and number of primary care visits. Donnelly et al. (abstract 160) compared 1,276 persons with type 2 diabetes hospitalized with cancer in 1993–2001 with 2,452 age-, diabetes duration-, and sex-matched diabetic persons without cancer, finding that 42% of those with cancer versus 47% without cancer had received metformin, those with cancer having approximately two-thirds as much long-term treatment (>1,800 days, >30 prescriptions filled), suggesting a protective effect of insulin-sensitizing medication.

Van Den Eeden et al. (abstract 1014) studied 84,170 persons, 10,629 with diabetes, in the California Men’s Health Study, showing the latter to have a 19% lower likelihood of benign prostatic hyperplasia although a 26% greater likelihood of reporting lower urinary tract symptoms, suggesting prostatic obstruction to be a less common cause of urinary symptoms among men with diabetes, implying a need for different treatment approaches.

**References**


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Perspectives on the News


