

## CLINICAL PERSPECTIVE

# Pharmacologic Approaches to the Prevention of Type 2 Diabetes in High Risk Pediatric Patients

MICHAEL FREEMARK

*Division of Pediatric Endocrinology and Diabetes, Duke University Medical Center, Durham, North Carolina 27710*

The past generation has witnessed a surge in the number of children, adolescents, and young adults with type 2 diabetes (1-3). In most cases the illness begins with excess weight gain, insulin resistance, and dyslipidemia and progresses through a stage of fasting or postprandial hyperglycemia [impaired glucose tolerance (IGT)] before the emergence of clinical symptoms (4). IGT, dyslipidemia, and overt type 2 diabetes predispose to hepatic steatosis and microvascular and macrovascular complications, which may arise early in the course of the illness (5-9). The threat of vascular and hepatic complications makes the prevention of type 2 diabetes of paramount importance.

Recent studies delineate risk factors for the development of type 2 diabetes in children and young adults. Chief among these are poorly defined genetic factors, ethnic background, and obesity (1-3). Rates of type 2 diabetes increase with age, as puberty is associated with a decline in insulin sensitivity (1-4). In the prodromal state, the risk of diabetes is highest among obese patients with severe insulin resistance and fasting or postprandial hyperglycemia. Emerging evidence suggests that lifestyle intervention and pharmacotherapy may reduce the rates of development of type 2 diabetes in subjects at highest risk (see below). This manuscript summarizes current views of the pathogenesis of type 2 diabetes in children and adolescents and discusses potential roles for pharmacological agents in the prevention of diabetes in high risk subjects.

### *Factors predisposing to the development of type 2 diabetes in children and young adults (1-4, 10-14)*

The risk of development of type 2 diabetes in childhood is determined in part by genetic and familial factors (Table 1). For example, a family history of type 2 diabetes in a first degree relative increases the risk for development of the disease, and type 2 diabetes is more common among children of Latino, Native American, Pacific Islander, or African-American descent than among Caucasian children. In some populations, the illness occurs more commonly in girls than in boys (1-3).

Abbreviations: ACE, Angiotensin-converting enzyme; BMI, body mass index; FFA, free fatty acid; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; UCP-2, uncoupling protein-2; VLDL, very low density lipoprotein.

The development of type 2 diabetes in subjects at risk is determined by the interplay of environmental and genetic factors, with nutrition playing a predominant role. The central role of obesity in the development of type 2 diabetes in adults is well established. For example, in a prospective 16-yr study (14) of nearly 85,000 female nurses, the most important determinant of diabetes risk was body mass index (BMI); at the highest levels of BMI, the relative risk of developing diabetes was increased nearly 40-fold. In comparison, the relative risk of type 2 diabetes was 1.3- to 1.5-fold higher among smokers and those with the lowest levels of exercise, whereas ingestion of saturated fats, high glycemic foods, and little or no fiber increased the risk 2-fold.

Among adults with increased BMI, the best predictor of diabetes and other metabolic complications is the quantity of abdominal, or visceral, fat (15). Whether this is true in children as well as adults is currently unclear. Caprio and her colleagues (16, 17) reported that the amount of visceral fat in obese adolescent girls correlated directly with basal and glucose-stimulated insulinemia and negatively with insulin sensitivity. Similar findings are reported in obese Hispanic children (aged 8-13 yr) with a family history of type 2 diabetes (18). Other investigators found that visceral fat in prepubertal African-American and Caucasian children was associated with elevated triglyceride and insulin concentrations, but not with insulin sensitivity (19, 20). Independent of visceral fat accumulation, insulin resistance was more common among African-American children than Caucasian children (19).

That obesity beginning in childhood contributes to the development of type 2 diabetes in adolescence and adulthood is suggested by four lines of evidence. First, insulin sensitivity in prepubertal and pubertal children correlates inversely with BMI and percentage body fat (21-23). Second, severe obesity is associated with high rates (21-25%) of glucose intolerance in prepubertal children and adolescents as well as increased rates (4%) of unsuspected type 2 diabetes in teenagers (23). Third, the absolute level of BMI and its rate of increase in childhood correlate with subsequent development of the cardinal features of the metabolic syndrome (obesity, hypertension, hyperinsulinemia, and dyslipidemia), which, in combination, increase exponentially the risks of developing type 2 diabetes and cardiovascular disease (24, 25). Finally, obesity and hyperinsulinemia in Finnish (26), African-American (23), and Pima Indian (27, 28) children

**TABLE 1.** Factors that predispose to the development of IGT or type 2 diabetes in children, adolescents, and young adults (1–4, 10–14)

---

|  |
|--|
| 1. Age (adults > adolescents > prepubertal children)                 |
| 2. Obesity   |
| 3. Family history of type 2 diabetes                                 |
| 4. History of maternal gestational diabetes                          |
| 5. Ethnicity   |
| 6. Low birth weight  |
| 7. Gender (females > males) <sup>a</sup>                             |
| 8. Polycystic ovary syndrome   |
| 9. Smoking <sup>b</sup>  |
| 10. Dietary factors <sup>b</sup> (other than excess caloric intake): |
| Low fiber intake increases risk                                      |
| High trans-fatty acids and saturated fat may increase risk           |
| Polyunsaturated fat and long-chain n-3 fatty acids may be protective |
| ? Role of glycemic load  |
| 11. Pregnancy  |

---

<sup>a</sup> In some populations.<sup>b</sup> Examined only in studies in adults.

predict the development of type 2 diabetes in adolescence and adulthood.

Powerful support for a link between adolescent weight gain and fat deposition and adult-onset diabetes is provided by two additional investigations. Among more than 23,000 pregnant women who delivered in New York state between 1994 and 1998, the risk of developing gestational diabetes was increased 3.1-fold in those at the highest quartile for prepregnancy BMI and 1.8-fold for those at the lowest quartile for height (29). And in a long-term study in young adult Pima Indians (30), BMI increased progressively for 10–25 yr before the development of type 2 diabetes and peaked at or immediately after diagnosis. In sum, excess weight gain beginning in childhood or adolescence increases the risk of glucose intolerance and type 2 diabetes.

Yet aberrations in metabolic function may result from nutritional imbalance imposed during fetal as well as postnatal life. For example, intrauterine growth retardation predisposes to the development of glucose intolerance and other features of the metabolic syndrome in adulthood (29, 31–33). Some have argued that the predisposition of low birth weight children to diabetes reflects their exaggerated fat deposition and linear catch-up growth during childhood (34). This theory, however, does not comport with the New York pregnancy study (29), which found a strong inverse correlation between birth weight and the development of gestational diabetes even after adjustment for prepregnancy BMI.

Children born large for gestational age are also at increased risk for obesity and development of gestational diabetes and type 2 diabetes in adulthood. As high birth weight is often a consequence of subclinical or overt diabetes in the pregnant mother, the predisposition of high birth weight children to subsequent diabetes is explained in large part by genetic factors as well as intrauterine exposure to the diabetic environment (35, 36). Accelerated weight gain and linear growth in childhood and adolescence, which are common in infants of diabetic mothers, play important contributory roles (37).

### *Pathogenesis of glucose intolerance and type 2 diabetes in obesity*

How does nutrient imbalance facilitate the development of glucose intolerance and type 2 diabetes in children at risk? Although our understanding in this area remains incomplete, we know from longitudinal studies in Pima Indians and other high risk groups that the development of type 2 diabetes in obese children begins in most cases with a prolonged period of insulin resistance (23, 27, 28, 38–41). However, insulin resistance alone is not sufficient for the development of glucose intolerance; the progression to diabetes requires  $\beta$ -cell dysfunction and a defective insulin secretory response to glucose.

Emerging evidence suggests a central role for disordered fat metabolism and storage in the development of insulin resistance and glucose intolerance in obese subjects (reviewed in Refs. 42–43a) (Fig. 1). Visceral obesity is accompanied by increases in fasting and postprandial free fatty acid (FFA) concentrations. Because the magnitude of release of FFA from adipose tissue is proportional to fat mass, the free fatty acidemia of obesity is related at least in part to exaggerated fat stores. Other factors contributing to increased plasma FFA include 1) increased sensitivity of the visceral fat depot to the lipolytic effects of catecholamines and reduced sensitivity to the antilipolytic effects of insulin; 2) reduction in insulin-dependent adipose tissue lipoprotein lipase, the rate-limiting enzyme in triglyceride clearance and FFA delivery to the adipocyte; and 3) blunting of insulin-dependent FFA esterification in adipose tissue.

Excess FFA released into plasma are diverted to nonadipose tissues, including liver, skeletal muscle, heart, and pancreatic  $\beta$ -cells. The uptake of visceral FFA from the portal blood leads to hepatic triglyceride accumulation (fatty liver), exaggerated very low density lipoprotein (VLDL) production, and secondarily, a reduction in plasma high density lipoprotein (HDL) concentrations (42). Increases in VLDL production and secretion increase plasma VLDL concentrations, which when hydrolyzed provide a continuing source of FFA. The accumulation of cytosolic triglyceride reduces hepatic insulin sensitivity, which blunts the suppressive effect of the hormone on hepatic VLDL synthesis and secretion and thereby potentiates the vicious cycle. The reduction in hepatic insulin sensitivity also reduces hepatic glucose utilization and augments hepatic glucose production, evoking an increase in circulating glucose concentrations (44, 45).

The rise in glucose concentrations is potentiated by resistance to insulin and IGF-I action in skeletal muscle (46, 47). The uptake of fatty acids by skeletal muscle promotes the accumulation of triglycerides within and between skeletal myocytes (48). In obese adolescents, the amount of muscle triglyceride deposition varies with visceral fat mass (48). The accumulation of lipid in skeletal muscle, which may reflect a defect in myocyte fatty acid oxidation and/or an increase in myocellular lipogenesis, is accompanied by insulin resistance and decreased myocellular glucose uptake.

The loss of insulin sensitivity in peripheral target tissues reduces insulin extraction from the circulation and triggers a compensatory rise in pancreatic insulin secretion. The resulting increase in plasma insulin concentrations maintains

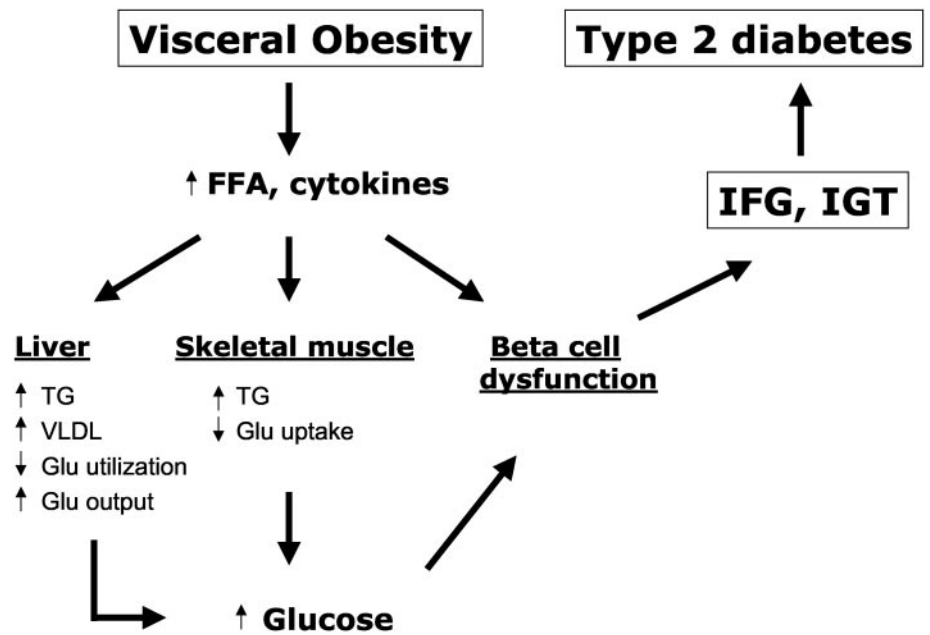


FIG. 1. Pathogenesis of glucose intolerance in obese individuals. TG, Triglycerides; glu, glucose.

total body glucose disposal in the early phases of the disease. At this stage, the insulin resistance and hyperinsulinemia appear to be reversible.

The downhill slide from insulin resistance to irreversible glucose intolerance and type 2 diabetes accelerates with the emergence of  $\beta$ -cell dysfunction, reflected initially as loss of first phase insulin secretion. The loss of  $\beta$ -cell function is induced by the combination of chronic free fatty acidemia and hyperglycemia (42, 43). Chronic elevations of FFA and glucose inhibit insulin production and glucose-dependent insulin secretion from pancreatic  $\beta$ -cells. Possible mechanisms for lipotoxicity and glucotoxicity include reductions in  $\beta$ -cell glucose transporter 2 and glucokinase expression, inhibition of insulin biosynthesis, alterations in ATP-sensitive potassium channels, and accelerated  $\beta$ -cell apoptosis. A unifying link in the pathogenesis of  $\beta$ -cell dysfunction may be induction of uncoupling protein-2 (UCP-2) by FFA (49–52). Induction of UCP-2 expression reduces cytosolic ATP levels and thereby inhibits glucose-dependent insulin secretion. Conversely, targeted deletion of UCP-2 in mice induces hyperinsulinemia and hypoglycemia. These observations suggest that chronic free fatty acidemia may inhibit  $\beta$ -cell insulin secretion through induction of UCP-2.

In obese subjects at risk for diabetes, progressive loss of  $\beta$ -cell function in a milieu of peripheral insulin resistance raises fasting and postprandial glucose concentrations. The consequent reductions in insulin secretion and  $\beta$ -cell mass cause progressive deterioration in glucose tolerance and, eventually, type 2 diabetes.

#### Roles of adipocyte cytokines, growth factors, and genes

Tissue sensitivity to insulin is modulated by cytokines and hormones produced by adipocytes and skeletal myocytes. IL-6 is overexpressed in adipose depots of obese and diabetic subjects, and plasma levels correlate inversely with insulin sensitivity (52a, 52b). Likewise, TNF $\alpha$  is overexpressed in adipose tissue and muscle in patients with visceral obesity

and type 2 diabetes (53). In 3T3-L1 preadipocytes, TNF $\alpha$  down-regulates expression of the insulin-dependent glucose transporter GLUT4 and several insulin-signaling proteins, including the insulin receptor, insulin receptor substrate 1, and protein kinase B and inhibits insulin-stimulated glucose uptake (54). Conversely, targeted deletion of TNF $\alpha$  in mice improves insulin sensitivity in adipose tissue (55). However, immunoneutralization of circulating TNF $\alpha$  in adults with long-standing type 2 diabetes had no effect on insulin sensitivity or glycemic control (56). Thus, the role of TNF $\alpha$  in the pathogenesis of human insulin resistance remains unclear.

TNF $\alpha$  may reduce insulin sensitivity indirectly through inhibition of expression of the adipocyte hormone adiponectin (57). Serum adiponectin levels (58, 58a) are inversely related to BMI, visceral fat mass, hepatic lipid content, and the homeostasis model assessment insulin resistance index (HOMA-IR). In rodents, adiponectin decreases postprandial free fatty acid levels and stimulates myocellular fatty acid oxidation, thereby increasing hepatic and skeletal muscle insulin sensitivity and reducing hepatic glucose output (59). Consequently, down-regulation of adiponectin production and secretion in obesity may contribute to systemic insulin resistance and increase the risk of development of type 2 diabetes (60).

The discovery of resistin was postulated to provide a critical link between obesity and insulin resistance. Resistin is an adipocyte protein that antagonizes the effects of insulin on glucose homeostasis. Stepan *et al.* (61) demonstrated increases in plasma resistin concentrations in obese mice and improved insulin action after immunoneutralization of circulating resistin. Subsequent investigations, however, found reduced expression of resistin in obese mice and very low or undetectable levels of expression of resistin in human adipose tissue. Moreover, resistin expression in human fat did not correlate with BMI or measures of insulin sensitivity (62–64). Nevertheless, very recent studies report elevated serum resistin concentrations in type 2 diabetic and obese

nondiabetic patients (65, 66). Clearly more work is required to clarify the role of resistin in the pathogenesis of human glucose intolerance.

Obese individuals with insulin resistance have high circulating levels of the adipocyte hormone leptin. In leptin-deficient humans and mice, the administration of leptin reduces food intake, stimulates energy expenditure through sympathetic activation, induces myocellular and white adipose tissue fatty acid oxidation, and increases insulin sensitivity (67–70). Yet food intake is normal or increased in human obesity, insulin sensitivity is reduced, and the oxidative response of skeletal muscle to leptin is blunted (71). These observations suggest that obesity is associated with resistance to leptin action. Leptin resistance may aggravate metabolic dysfunction because mutations or deletions of the leptin receptor cause obesity, insulin resistance, hypertriglyceridemia, and glucose intolerance in humans and mice (67).

Genetic variability in the response to adipocyte hormones and growth factors may influence the risk of developing the metabolic syndrome or type 2 diabetes. A Pro<sup>12</sup>Ala polymorphism in the peroxisomal proliferator-activated receptor  $\gamma$ 2 gene is associated in some studies with increased insulin sensitivity in humans (72, 73), and mice with targeted deletions of peroxisomal proliferator-activated receptor  $\gamma$ 2 develop lipodystrophy and hepatic insulin resistance (74). Conversely, adipose tissue overexpression of 11 $\beta$ -hydroxysteroid dehydrogenase type 1, which amplifies glucocorticoid signaling by converting inactive cortisone to biologically active cortisol, induces adiposity, dyslipidemia, and tissue resistance to insulin and leptin (75). Intense interest is now focused on identification of polymorphisms in these and other adipocyte genes in obese and diabetic subjects.

Nevertheless, familial trends in diabetes risk might be transmitted across generations by environmental as well as genetic cues (Fig. 2). For example, marked increases in BMI in pubertal and young adult women predispose to glucose intolerance and overt diabetes during pregnancy. Gestational diabetes promotes fetal overgrowth, and children born large for gestational age in diabetic pregnancies are themselves at higher risk of childhood obesity and type 2 diabetes (29–33, 35–37). Though this vicious cycle of glucose intolerance has been demonstrated most convincingly in PIMA Indians, we are likely to witness in the not too distant future a surge in the incidence of gestational diabetes in other high risk groups.

Rapid childhood growth and accelerated fat deposition may contribute to diabetes risk in subjects born at low birth weight (76) as well as those born large for gestational age. However, obesity does not account for diabetes risk in all low birth weight infants. Rather, fetal and perinatal malnutrition may reduce islet vascularity and decrease  $\beta$ -cell mass, limit the growth and function of skeletal muscle, and cause premature activation of the hypothalamic-pituitary-adrenal axis (77, 78). Diabetes in this case results from loss of  $\beta$ -cell secretory capacity and skeletal muscle resistance to insulin action (79).

## A vicious cycle of glucose intolerance in high risk populations

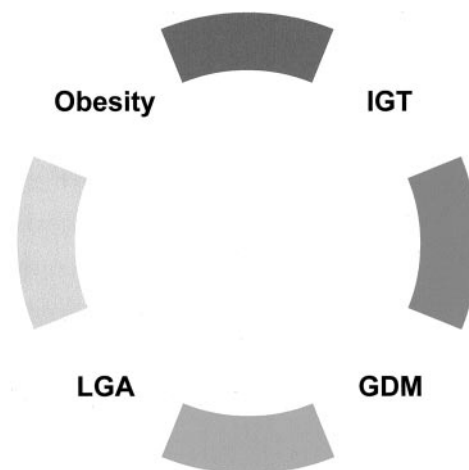


FIG. 2. Obesity predisposes to glucose intolerance in adolescents and to gestational diabetes (GDM) in young women of child-bearing age. Fetal overgrowth [large for gestational age (LGA)], which is common in women with gestational diabetes, in turn predisposes to obesity in childhood and adolescence.

### Pharmacological approaches to the prevention of type 2 diabetes in high risk patients

How can we intervene to prevent the development or progression of obesity and type 2 diabetes in populations at risk? It is clear from numerous investigations that intensive lifestyle intervention through diet and exercise can increase insulin sensitivity, reduce fasting and postprandial glucose and free fatty acid concentrations, reduce plasma low density lipoprotein and triglyceride concentrations, increase plasma HDL levels, and reduce the risk of developing type 2 diabetes in adults (80–82). Thus, diet and exercise represent the foundation of care for all obese individuals and are critical components of any approach to therapy. Unfortunately, the long-term success of lifestyle intervention alone has been disappointing, and rates of type 2 diabetes in children and adults continue to increase despite widespread recognition of the dangers of dietary indiscretion and a sedentary existence. This has stimulated interest in potential pharmacological approaches to diabetes prevention.

### Metformin in the treatment of insulin resistance or IGT

In deliberating an approach to pharmacological prevention of glucose intolerance in obese adolescents, my colleagues and I hypothesized that the biguanide metformin might prove a useful therapeutic modality. Through activation of hepatic AMP protein kinase (83), metformin reduces hepatic glucose and VLDL production, lowers fasting glucose and insulin levels in diabetic and nondiabetic adults, and increases insulin sensitivity (84–87). Serum cholesterol and triglyceride concentrations are reduced in some cases. Metformin may also protect  $\beta$ -cells against the lipotoxic effects of fatty acids (88).

Metformin has two properties that we thought would

prove advantageous in obese adolescents. First, initial studies in diabetic and nondiabetic adults showed that metformin caused little or no weight gain, and recent studies suggest that metformin may reduce food intake and body fat mass (89–91). Second, the drug is generally well tolerated, although as many as 25–50% of patients may have mild and self-limited gastrointestinal complaints.

We hypothesized that metformin would reduce glucose, insulin, and lipid levels and facilitate weight control in obese adolescents predisposed to the development of type 2 diabetes (92). To test this hypothesis, we selected a study population based on factors known to increase the risk of progression from IGT to type 2 diabetes in adults. These included an increased BMI (38.7–41.5 kg/m<sup>2</sup>), fasting hyperinsulinemia (28.0–31.5 μU/ml), and a family history of type 2 diabetes in a first or second degree family member. We excluded patients with fasting glucose exceeding 100 mg%, postprandial hyperglycemia, or elevated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>); thus, the patients did not have IGT or impaired fasting glucose (IFG). We also excluded patients with polycystic ovary syndrome and other disorders that might be accompanied by glucose intolerance. Subjects were randomly assigned to a placebo group or a group that received metformin (500 mg twice daily) for a total of 6 months. Both patients and investigators were blinded, and no dietary restrictions were provided or enforced.

Metformin caused a progressive decline in fasting blood glucose, from 84.9 mg/100 ml at baseline to 75.1 mg/100 ml at the end of the 6-month trial. In contrast, glucose levels in the placebo group rose from 77.5 to 82.5 (Fig. 3). The reduction in plasma glucose in the metformin group was accompanied by a reduction in fasting insulin concentrations, from 31.5 to 19.3 μU/ml. In contrast, fasting insulin levels in the placebo group did not change (Fig. 2). Insulin sensitivity, as assessed by fasting insulin to glucose ratios and by the QUICKI and HOMA-IR methods, was increased in the metformin group, although no changes were observed when insulin sensitivity was estimated using the Minimal Model. We found no effect of metformin on HbA<sub>1c</sub>, serum lipids, or serum lactate, and the medication was generally well tolerated by the majority of subjects. There were no episodes of vomiting or lactic acidosis.

As predicted, metformin caused a decline of 0.12 SD in BMI during the study, amounting to a mean decrease of 0.5 kg/m<sup>2</sup> or –1.3% from baseline. In contrast, BMI rose 0.23 SD, or 2.3% from baseline, in the placebo group ( $P < 0.02$ ). Metformin also reduced serum leptin concentrations in girls, suggesting a reduction in fat mass.

The results of this study must be interpreted cautiously, because the study group contained only 29 patients (18 girls and 11 boys), and the subjects treated with metformin had a mean BMI (41.5 ± 0.9 kg/m<sup>2</sup>) greater than that of placebo-treated subjects (38.7 ± 1.3 kg/m<sup>2</sup>;  $P < 0.05$ ). Nevertheless, the benefits of metformin in subjects at risk for type 2 diabetes have been confirmed in two subsequent investigations.

The first was a double-blind, placebo-controlled study in 24 obese (BMI, 40.8–41.2), hyperinsulinemic (fasting insulin 37–43 μU/ml), nondiabetic adolescents (93). The family histories of the study patients were not reported. In combination with a low calorie diet (1500–1800 calorie/d for girls and boys, respectively), metformin reduced weight by 6.5%; diet alone caused a 3.8% weight loss. Patients treated with metformin had greater decline in body fat (–6% vs. –2.7% in the placebo group), a decrease in plasma leptin levels, a 50% decrease in plasma insulin concentrations, and increased insulin sensitivity as determined by fasting and 2 h glucose and insulin levels. Plasma cholesterol and triglyceride levels also declined by 22% and 39%, respectively. These findings suggested that metformin and diet may act synergistically to limit weight gain and increase glucose tolerance.

The second was the recently completed Diabetes Prevention Program (82), which showed directly that metformin may delay or prevent the onset of type 2 diabetes in adults (age, ≥25 yr) with IGT. This randomized multicenter trial enrolled 3234 subjects with fasting glucose concentrations ranging from 95–125 mg/100 ml and 2 h glucose levels from 140–199 mg/100 ml. BMI was at least 24 in all participants except Asians, in whom it was at least 22. Participants were randomly assigned to one of three interventions. These included a placebo group who received standard lifestyle recommendations; a group treated with metformin 850 mg once or twice/d and given standard lifestyle recommendations;

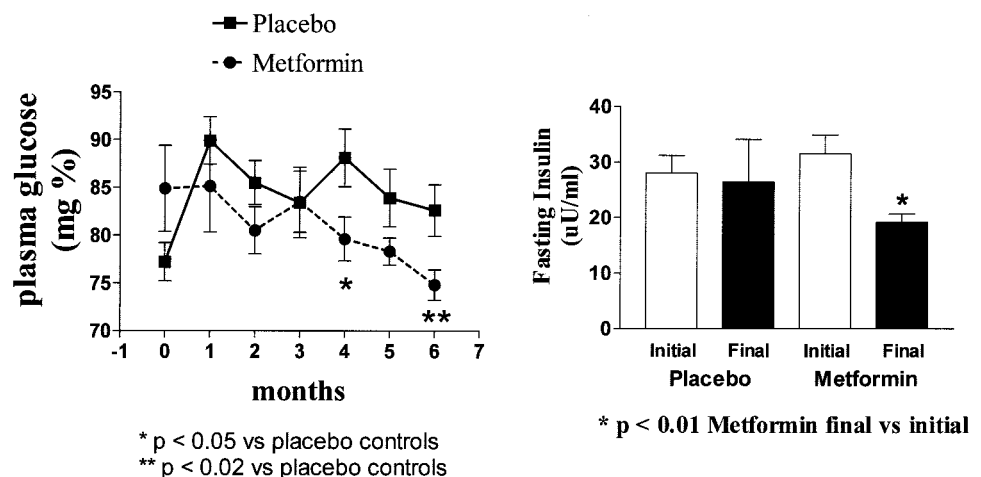


FIG. 3. Effects of metformin on fasting glucose and insulin levels in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes mellitus. Adapted from the report by Freemark and Bursey (89).

and a group treated with an intensive program of lifestyle modification.

Patients in the intensive lifestyle group were encouraged to follow a low calorie/low fat diet, to reduce weight by at least 7% from baseline, and to engage in moderately strenuous physical activity for at least 150 min/wk. In the lifestyle arm, subjects met with a case manager 16 times during the first 6 months and monthly thereafter. Month-long group courses on exercise and weight loss were offered every 3 months, and two supervised exercise sessions were offered each week. Incentives were provided to those in the intensive lifestyle program, including free exercise tapes and equipment, free enrollment in exercise facilities, free low calorie foods, and home visits.

The study lasted 1.8–4.6 yr. Daily energy and fat intake decreased only in the group randomized to intensive lifestyle modification. Nevertheless, patients in the metformin group also lost weight, although not as much as those in the intensive lifestyle group. In both groups, weight loss was most significant in the first 6–12 months of the study.

The changes in body weight were accompanied by reductions in the rates of progression from IGT to type 2 diabetes (Fig. 4). The 3-yr cumulative incidence of diabetes in the group overall was 28.9% in the placebo group, 21.7% in the metformin-treated group, and 14.4% in the intensive lifestyle group. Overall, therefore, intensive lifestyle intervention was more effective than metformin.

However, certain subgroups responded preferentially to the various interventions. Metformin was as effective as lifestyle change in subjects with BMI exceeding 34.9 and in those with highest fasting glucose concentrations (Fig. 4); these subgroups are at greatest risk for progression to type 2 diabetes. Metformin was also as effective as lifestyle intervention in younger adults aged 25–44 yr. On the other hand, treatment effects did not vary according to gender, race, or ethnic group.

In addition to reducing the risk of development of type 2 diabetes, intensive lifestyle intervention and metformin had favorable, albeit small, effects on blood pressure and serum lipids. Systolic and diastolic blood pressures were reduced by 1.1 and 3.3 mm Hg, respectively, in the metformin and intensive lifestyle groups, whereas total cholesterol, low den-

sity lipoproteins, and triglyceride concentrations declined by 5 and 8, 4.0 and 4.3, and 6 and 23 mg/100 ml, respectively, and HDL levels increased slightly (0.5 and 0.8 mg/100 ml, respectively).

The major effects of lifestyle intervention and metformin were exerted within the first 12–18 months of the study. After the first year, fasting blood glucose concentrations, HbA<sub>1c</sub> concentrations, and rates of diabetes increased in both the intensive lifestyle and metformin groups, and the slopes of the intervention and treatment curves after the first year appeared to parallel the slope of the placebo group. This finding suggests that the interventions may delay, rather than truly prevent, the development of type 2 diabetes.

The study raises additional important issues. For example, the rates of type 2 diabetes in adults remained high even in the intensive lifestyle and metformin groups and increased in parallel with time. Would the combination of metformin and intensive lifestyle intervention provide even greater benefit than either intervention alone? Can we define subgroups that respond preferentially to one or more forms of therapy? Would the responses of adolescents to lifestyle intervention or metformin be comparable to those of adults? Given the time requirements, expense, and difficulty of lifestyle intervention, what are its true costs? Would less intensive intervention prove effective? Finally, what are the long-term safety, efficacy, and costs of metformin? These issues require clarification and additional study.

#### Other medications that may reduce the risk of type 2 diabetes

There is reason to believe that other medications, in combination with diet and exercise, may reduce the risk of type 2 diabetes. For example, the thiazolidinediones increase insulin sensitivity, in part through induction of adiponectin and suppression of TNF $\alpha$  expression (94, 95). Treatment of diabetic adults with a thiazolidinedione reduces blood glucose concentrations and serum lipid levels, which may decrease the risk of cardiovascular complications.

The potential benefits of thiazolidinediones in preventing type 2 diabetes were demonstrated in the TRIPOD study (96), in which obese Hispanic women (BMI, 30) with previous gestational diabetes were randomized to receive placebo (n = 122) or troglitazone (400 mg daily; n = 114). Insulin sensitivity was lower, and fasting and glucose-stimulated insulin concentrations were slightly higher at baseline in the patients randomized to the placebo group. All subjects received dietary advice and exercise counseling and were followed for a mean of 30 months. The study showed a decrease in the rate of progression to type 2 diabetes in the patients treated with troglitazone (placebo, 12.1%/yr; troglitazone, 5.4%/yr). Those women with the greatest increase in insulin sensitivity and the greatest decline in glucose-stimulated insulin output during the first 3 months of treatment had the lowest risk of subsequently developing type 2 diabetes. Diabetes risk in the two groups did not appear to vary according to changes in BMI.

Posttrial testing was conducted among women who remained diabetes-free throughout the blinded trial. Eight months after discontinuing the study medication, 15% of the

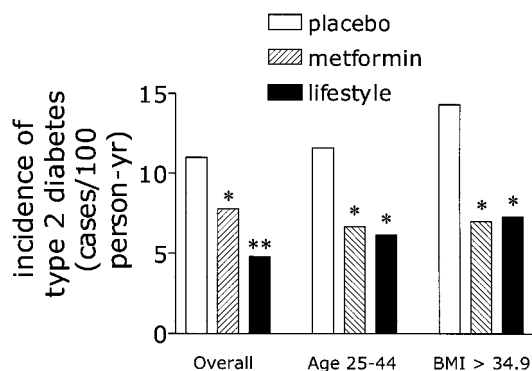


FIG. 4. Effects of metformin and intensive lifestyle intervention on the rate of development of type 2 diabetes in adults with IGT. \*, Significantly different from placebo; \*\*, significantly different from metformin or placebo. Adapted from the Diabetes Prevention Program (79).

placebo group had developed type 2 diabetes, compared with only 2.3% of the troglitazone-treated group. Moreover, insulin sensitivity and the acute insulin secretory response to glucose were 30–35% lower in placebo-treated than in troglitazone-treated patients. This observation suggested that troglitazone may have preserved  $\beta$ -cell function in study subjects.

There are potential concerns about the use of thiazolidinediones in the prevention of type 2 diabetes in obese children. First, the drugs commonly cause weight gain, although this appears to result from the accumulation of sc, rather than visceral, fat (97). Second, there is little or no information regarding the toxicity of the thiazolidinediones in pediatric patients. Troglitazone was removed recently from the commercial market after the development of severe hepatotoxicity in a subset of adult patients. Although hepatotoxicity with the newer thiazolidinediones appears to be quite rare in adults, the potential for hepatotoxicity in obese adolescents, who commonly have nonalcoholic steatohepatitis, is unknown. Finally in adults, thiazolidinediones may cause edema and anemia.

The  $\alpha$ -glucosidase inhibitor acarbose may reduce the progression to type 2 diabetes by limiting gastrointestinal absorption of carbohydrate. Evidence for this was provided by the recently completed STOP-NIDDM trial (98), which found a 25–36% reduction in type 2 diabetes in obese adults (age, 40–70 yr; BMI, 25–40) with IGT. Postprandial glucose and insulin concentrations were reduced, and weight declined slightly in patients treated with acarbose (100 mg, three times daily). Unfortunately, the gastrointestinal side-effects of the drug, which include flatulence and diarrhea, limit its potential appeal for adolescents and young adults.

Finally, a *post hoc* analysis of the HOPE study showed a 40% reduction in newly diagnosed diabetes in patients treated with the angiotensin-converting enzyme (ACE) inhibitor Ramipril (Aventis Pharmaceuticals, Kansas City, MO). In addition, a *post hoc* analysis of the West of Scotland Coronary Prevention Study (100) revealed 25% reduction in the incidence of newly developed diabetes in patients treated with Pravastatin (Bristol-Myers Squibb, Princeton, NJ). These findings are interesting, given the possibility that a single drug could reduce both cardiovascular and diabetic risks. Nevertheless, the benefits of Ramipril or Pravastatin must be confirmed in a study in which diabetes is a primary outcome measure.

*Synopsis: balancing lifestyle intervention and pharmacology in the prevention of type 2 diabetes in high risk pediatric patients*

The collective evidence suggests that the recent surge in type 2 diabetes in adolescents is related at least in part to increases in the prevalence of obesity among populations at risk for the disease. Therefore, preventive measures among pediatric patients should focus first on obese subjects with a family history of type 2 diabetes.

There are unfortunately no firm guidelines that permit us to distinguish safe or low risk obesity from dangerous or high risk obesity in pediatric patients. The recent report by Sinha *et al.* (23) documents high rates of glucose intolerance and

unsuspected type 2 diabetes among obese subjects with BMI above the 95th percentile for age and gender. Consequently, subjects with BMI exceeding the 95th percentile for age and gender must be considered at risk (7–9, 21–23). Nevertheless, some (particularly prepubertal) obese patients may have no apparent defects in insulin production or action and display no evidence of fasting hyperglycemia or glucose intolerance (101).

Glucose tolerance in obese patients is assessed best using a standard oral glucose tolerance test (102), which is reproducible and reliable in obese adolescents (23). Those with IGT (2 h glucose, 140–199 mg/100 ml) or IFG (fasting glucose, 111–125 mg/100 ml) are at greatest risk of developing type 2 diabetes (23). Such patients require immediate intervention to prevent further deterioration in blood glucose control.

In adults with IGT, intensive lifestyle intervention (80–82) has been shown in long-term studies to significantly reduce (by 31–58%) the rate of development of type 2 diabetes. In theory, intensive lifestyle intervention should also benefit pediatric patients who are at high risk for developing type 2 diabetes. However, lifestyle intervention is difficult, time-consuming, and, in many cases of childhood obesity, ineffective. Treatment failure may exacerbate insulin resistance, dyslipidemia, and glucose intolerance, leading to irreversible  $\beta$ -cell dysfunction and overt type 2 diabetes. Insulin resistance, dyslipidemia, and glucose intolerance in adolescents may also predispose to steatohepatitis and the development of arterial fatty plaques (4–9).

The physician is thus faced with a difficult dilemma: failure to correct defects in insulin sensitivity and glucose tolerance in an obese patient at risk for diabetes may have irreversible adverse consequences. Yet the efficacy of traditional lifestyle approaches has not yet been demonstrated in children.

Recent investigations suggest that pharmacological agents may complement the effects of lifestyle intervention and reduce the risk of type 2 diabetes in selected patients. Metformin, troglitazone, and acarbose reduce the risk of development of type 2 diabetes in adults with IGT (82, 96, 98), and metformin limits weight gain and reduces fasting glucose, insulin, and lipid levels in obese, insulin-resistant adolescents (92, 93), at least in the short term. Preliminary studies suggest that metformin may also be useful in the management of hepatic steatosis associated with insulin resistance (103). Metformin is well tolerated in the majority of children and adolescents with type 2 diabetes (104–108), insulin resistance (92, 93), and the polycystic ovary syndrome (109, 110), and life-threatening complications are extraordinarily rare in patients with normal cardiac, renal, gastrointestinal, and hepatic function (85, 86). Yet the long-term safety and efficacy of pharmacological agents in children at risk for type 2 diabetes and the metabolic syndrome are unknown.

In the opinion of the author, consideration should be given to the use of metformin in adolescents at highest risk for the development of type 2 diabetes; these include obese patients with IGT or IFG. Before initiation of drug therapy, such children should undergo a trial of intensive lifestyle intervention. If 6–12 months of lifestyle intervention proves unsuccessful despite a good-faith effort on the part of the patient, a trial of metformin is justifiable. A good faith effort

means that the patient has attempted to follow a low fat/low calorie diet recommended by a dietary counselor and has increased his or her energy expenditure through regular exercise. Unsuccessful means that the elevations of fasting or postprandial glucose persist or worsen despite lifestyle intervention.

After institution of metformin therapy, lifestyle intervention should be maintained, and the patient should be monitored closely for the development of adverse drug effects. Gastrointestinal complications can generally be prevented by taking the medication with food; persistent complaints can be reversed in many cases by reducing the dose of the medication. The drug should be discontinued if liver function tests exceed twice the upper limits of normal range. Mild hepatic dysfunction can often be reversed with intensification of diet and exercise; the drug can then be restarted, beginning at a lower dose and increasing gradually as needed. A multivitamin should be administered daily to prevent the unusual development of B12 deficiency.

Metformin should not be administered to patients with renal, cardiac, hepatic, or gastrointestinal disease and should be discontinued before radiological studies using contrast reagents. Concurrent use of alcohol is contraindicated.

In contrast to children with IGT or IFG, obese children with normal fasting and 2 h (or postprandial) glucose concentrations should be managed with lifestyle intervention alone. The use of metformin or other pharmacological agents in such children must at this time be considered experimental.

Once initiated, how long should pharmacotherapy be maintained? It currently is not possible to provide firm or uniform guidelines on this matter, and therapy must be individualized. A trial off metformin may be warranted if glucose tolerance is normalized, particularly if there has been a decline in BMI z-score. If IGT persists despite compliance with the medical/pharmacological regimen, it may be necessary to intensify lifestyle intervention and/or to increase the dose of medication. If glucose tolerance declines or the patient develops overt diabetes, he/she may require the addition of another pharmacological agent.

As noted previously, other pharmacological agents, such as thiazolidinediones, acarbose, ACE inhibitors, and statins, may prove useful in the prevention of type 2 diabetes, at least in adults. However, no studies have demonstrated their safety or efficacy in children with IFG or IGT, so their use in pediatric patients for diabetes prevention must await further investigation. Studies of the rates of development of diabetes in hypertensive or dyslipidemic adolescents treated with ACE inhibitors or statins may be of particular interest.

#### *Implications and thoughts for the future*

I would like to conclude with some thoughts about type 2 diabetes and the future of pediatric endocrinology.

It is clear now from our collective experience, from innumerable investigations, and from the results of the Bogalusa Heart Study (5, 22), the Minneapolis Children's Blood Pressure Study (24), and the Pathobiological Determinants of Atherosclerosis in Youth Study (7, 8) that type 2 diabetes and cardiovascular disease commence in childhood and may be entrained during intrauterine life. The progression of disease

from childhood to adulthood is often silent; by the time of diagnosis, many adults with type 2 diabetes already have microvascular and macrovascular complications (111–114). Intergenerational cycles and social/cultural factors perpetuate familial and ethnic patterns of chronic illness. These facts underscore the central importance of reproductive and pediatric medicine in the prevention of adult disease.

The prevalence of type 2 diabetes in the U.S. may increase as much as 65% during the next 50 yr (115), and if societal trends in obesity are not controlled, we can expect further increases in the prevalence of childhood disease and gestational diabetes. Such changes will place enormous burdens on the medical, financial, and social communities.

As pediatric endocrinologists caring for individual patients, we must aggressively manage hyperglycemia, dyslipidemia, and hypertension to prevent long-term complications. However, we must also define more precisely the metabolic, genetic, and lifestyle factors that increase the risk of chronic metabolic and cardiovascular disease and identify, at an early age, those families and children at highest risk. We will then, in collaboration with representatives of the lay community, be able to implement individual and societal measures that will prevent chronic illness.

#### **Acknowledgments**

Received July 5, 2002. Accepted September 26, 2002.

Address all correspondence and requests for reprints to: Dr. Michael Freemark, Box 3080, Department of Pediatrics, Duke University Medical Center, Durham, North Carolina 27710. E-mail: freem001@mc.duke.edu.

#### **References**

- Rosenbloom AL, Joe JR, Young RS, Winter WE 1999 Emerging epidemic of type 2 diabetes in youth. *Diabetes Care* 22:345–354
- Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GLA, Saaddine J, Gregg EW, Williamson DF, Narayan KMV 2000 Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 136:664–672
- Ludwig DS, Ebbeling CB 2001 Type 2 diabetes in children: primary care and public health considerations. *JAMA* 286:1427–1430
- Caprio S 2002 Insulin resistance in childhood obesity. *J Pediatr Endocrinol Metab* 15(Suppl 1):487–492
- Berenson GS, Srinivasan SR 2001 Emergence of obesity and cardiovascular risk for coronary artery disease: the Bogalusa Heart Study. *Prev Cardiol* 4:116–121
- Tounian P, Aggoun Y, Dubern B, Varille V, Guy-Grand B, Sidi D, Girardet JP, Bonnet D 2001 Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet* 358:1400–1404
- McGill Jr HC, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP 2000. Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr* 72:1307S–1315S
- McGill Jr HC, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, Malcom GT, Tracy RE, Oalman MC, Strong JP 2000 Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arterioscler Thromb Vasc Biol* 20:1998–2004
- Dean H, Flett B, Natural history of type 2 diabetes diagnosed in childhood: long term followup in young adult years [Abstract 99-OR]. Proc 62nd Annual Meeting of the American Diabetes Association, San Francisco, CA, 2002
- Lindhal B, Weinehall L, Asplund K, Hallmans G 1999 Screening for impaired glucose tolerance. Results from a population-based study of 21, 057 individuals. *Diabetes Care* 22:1988–1992
- Paris RM, Bedno SA, Krauss MR, Keep LW, Rubertone MV 2001 Weighing in on type 2 diabetes in the military: characteristics of US military personnel at entry who develop type 2 diabetes. *Diabetes Care* 24:1894–1898
- Hu FB, van Dam RM, Liu S 2001 Diet and risk of type 2 diabetes: the role of fat and carbohydrate. *Diabetologia* 44:805–817
- Legro RS, Kunselman AR, Dodson WC, Dunaif A 1999 Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance

- in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 84:165–169
14. **Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC** Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345:790–797
  15. **Ronnemaa T, Koskenvuo M, Marniemi J, Koivunen T, Sajantila A, Rissanen A, Kaitsaari M, Bouchard C, Kaprio J** 1997 Glucose metabolism in identical twins discordant for obesity: the critical role of visceral fat. *J Clin Endocrinol Metab* 82:383–387
  16. **Caprio S, Hyman LD, Limb C, McCarthy S, Lange R, Sherwin RS, Shulman G, Tamborlane WV** 1995. Central adiposity and its metabolic correlates in obese adolescent girls. *Am J Physiol* E118–E126
  17. **Caprio S** 1999 Relationship between abdominal visceral fat and metabolic risk factors in obese adolescents. *Am J Hum Biol* 11:259–266
  18. **Cruz ML, Bergman RN, Goran MI** 2002 Unique effect of visceral fat on insulin sensitivity in obese Hispanic children with a family history of type 2 diabetes. *Diabetes Care* 25:1631–1636
  19. **Gower BA, Nagy TR, Goran MI** 1999 Visceral fat, insulin sensitivity, and lipids in prepubertal children. *Diabetes* 48:1515–1521
  20. **Goran MI, Bergman RN, Gower BA** 2001. Influence of total vs. visceral fat on insulin action and secretion in African American and white children. *Obesity Res* 9:423–431
  21. **Arslanian S, Suprasongsin C** 1996 Insulin sensitivity, lipids and body composition in childhood: is “syndrome X” present? *J Clin Endocrinol Metab* 81:1058–1062
  22. **Srinivasan ST, Myers L, Berenson GS** 1999 Temporal association between obesity and hyperinsulinemia in children, adolescents and young adults: The Bogalusa Heart Study. *Metab Clin Exp* 48:928–934
  23. **Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, Savoye M, Rieger V, Taksali S, Barbetta G, Sherwin RS, Caprio S** 2002 Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 346:802–810
  24. **Sinaiko AR, Donahue RP, Jacobs Jr DR, Prineas RJ** 1999 Relation of weight and rate of increase in weight during childhood and adolescence to body size, blood pressure, fasting insulin and lipids in young adults: The Minneapolis Children’s Blood Pressure Study. *Circulation* 99:1471–1476
  25. **Srinivasan SR, Myers L, Berenson GS** 2002 Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: The Bogalusa Heart Study. *Diabetes* 51:204–209
  26. **Vanhala MJ, Vanhala PT, Keinanen-Kiukaanniemi SM, Kumpusalo EA, Takala JK** 1999 Relative weight gain and obesity as a child predict metabolic syndrome as an adult. *Int J Obes* 23:656–659
  27. **Pettitt DJ, Moll PP, Knowler WC, Mott DM, Nelson RG, Saad MF, Bennett PH, Kottke BA** 1993 Insulinemia in children at low and high risk of NIDDM. *Diabetes Care* 16:608–615
  28. **McCance DR, Pettitt DJ, Hanson RL, Jacobsson TH, Bennett PH, Knowler WC** 1994 Glucose, insulin concentrations and obesity in childhood and adolescence as predictors of NIDDM. *Diabetologia* 37:617–623
  29. **Innes KE, Byers TE, Marshall JA, Baron A, Orleans M, Hamman RF** 2002 Association of a woman’s own birth weight with subsequent risk for gestational diabetes. *JAMA* 287:2534–2541
  30. **Looker HC, Knowler WC, Hanson RL** 2001 Changes in BMI and weight before and after the development of type 2 diabetes. *Diabetes Care* 24:1917–1922
  31. **Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW, Hennekens CH, Speizer FE, Manson JE** 1999 Birthweight and the risk for type 2 diabetes mellitus in adult women. *Ann Intern Med* 130:278–284
  32. **Dabelea D, Pettitt DJ, Hanson R, Imperatore G, Bennett P, Knowler W** 1999 Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. *Diabetes Care* 22:944–950
  33. **Egeland GM, Skjaerven R, Irgens LM** 2000 Birth characteristics of women who develop gestational diabetes: population study. *Br Med J* 321:546–547
  34. **Lucas A, Fewtrell M, Cole T** 1999 Fetal origins of adult disease: the hypothesis revisited. *Br Med J* 319:245–249
  35. **Pettitt DJ, Bennett PH, Saad MF, Charles MA, Nelson RG** 1991 Abnormal glucose tolerance during pregnancy in Pima Indian women: long-term effects on offspring. *Diabetes* 40:126–130
  36. **Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, Knowler WC** 2000 Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 49:2208–2211
  37. **Silverman B, Rizzo T, Cho N, Metzger B** 1998 Long-term effects of the intrauterine environment. *Diabetes Care* 21:B142–B149
  38. **Eriksson J, Franssila-Kallunki A, Ekstrand A, et al.** 1989 Early metabolic defects in persons at increased risk for non-insulin dependent diabetes mellitus. *N Engl J Med* 321:337–343
  39. **Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR** 1990 Slow glucose removal rate and hyperinsulinemia precede the development of type 2 diabetes in the offspring of diabetic parents. *Ann Intern Med* 113:909–915
  40. **Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR** 1992 Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet* 340:925–929
  41. **Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C** 1993 Insulin resistance and insulin secretory dysfunction as precursors of non-insulin dependent diabetes mellitus: prospective studies of Pima Indians. *N Engl J Med* 329:1988–1992
  42. **Lewis GF, Carpentier A, Adeli K, Giacca A** 2002 Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev* 23:201–229
  43. **Poitout V, Robertson RP** 2002 Minireview: secondary  $\beta$  cell failure in type 2 diabetes: a convergence of glucotoxicity and lipotoxicity. *Endocrinology* 143:339–342
  - 43a. **Boden G, Shulman GI** 2002 Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and  $\beta$  cell dysfunction. *Eur J Clin Invest* 32(Suppl 3):14–23
  44. **Weyer C, Bogardus C, Pratley RE** 1999 Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes* 48:2197–2203
  45. **Paquot N, Scheen AJ, Dirlwanger M, Lefebvre PJ, Tappy L** 2002 Hepatic insulin resistance in obese non-diabetic subjects and in type 2 diabetic subjects. *Obes Res* 10:129–134
  46. **Pratipanawatr T, Pratipanawatr W, Rosen C, Berria R, Bajaj M, Cusi K, Mandarino L, Kashyap S, Belfort R, DeFronzo RA** 2002 Effect of IGF-I on FFA and glucose metabolism in control and type 2 diabetic subjects. *Am J Physiol* 282:E1360–E1368
  47. **Mauvais-Jarvis F, Kulkarni RN, Kahn CR** 2002 Knockout models are useful tools to dissect the pathophysiology and genetics of insulin resistance. *Clin Endocrinol (Oxf)* 57:1–9
  48. **Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma YZ, Savoye M, Rothman DL, Shulman GI, Caprio S** 2002 Assessment of skeletal muscle triglyceride content by (1)H nuclear magnetic resonance spectroscopy in lean and obese adolescents: relationships to insulin sensitivity, total body fat, and central adiposity. *Diabetes* 51:1022–1027
  49. **Fleury C, Neverova M, Collins S, Raimbault S, Champigny O, Levi-Meyrueis C, Bouillaud F, Seldin MF, Surwit RS, Ricquier D, Warden CH** 1997 Uncoupling protein-2: a novel gene linked to obesity and hyperinsulinemia. *Nat Genet* 15:269–272
  50. **Lameloise N, Muzzin P, Prentki M, Assimacopoulos-Jeannet F** 2001 Uncoupling protein-2: a possible link between fatty acid excess and impaired glucose-induced insulin secretion? *Diabetes* 50:803–809
  51. **Zhang CY, Baffy G, Perret P, Krauss S, Peroni O, Grujic D, Hagen T, Vidal-Puig AJ, Boss O, Kim YB, Zheng XX, Wheeler MB, Shulman GI, Chan CB, Lowell BB** 2001 Uncoupling protein-2 negatively regulates insulin secretion and is a major link between obesity,  $\beta$  cell dysfunction and type 2 diabetes. *Cell* 105:745–755
  52. **Chan CB, De Leo D, Joseph JW, McQuaid TS, Ha XF, Xu F, Tsumihara RG, Pennefather PS, Salapatek AM, Wheeler MB** 2001 Increased uncoupling protein-2 levels in  $\beta$  cells are associated with impaired glucose-stimulated insulin secretion: mechanism of action. *Diabetes* 50:1302–1310
  - 52a. **Bastard JP, Maachi M, Van Nhieu JT, Jardel C, Bruckert E, Grimaldi A, Robert JJ, Capeau J, Hainque B** 2002 Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both *in vivo* and *in vitro*. *J Clin Endocrinol Metab* 87:2084–2089
  - 52b. **Vojarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE** 2001 Circulating interleukin-6 in relation to adiposity, insulin action and insulin secretion. *Obes Res* 9:414–417
  53. **Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM** 1995 Increased adipose tissue expression of tumor necrosis factor- $\alpha$  in human obesity and insulin resistance. *J Clin Invest* 95:2409–2415
  54. **Ruan H, Hacohen N, Golub TR, Van Parijs L, Lodish HF** 2002 Tumor necrosis factor- $\alpha$  suppresses adipocyte-specific genes and activates expression of pre-adipocyte genes in 3T3-L1 adipocytes: nuclear factor- $\kappa$ B activation by TNF- $\alpha$  is obligatory. *Diabetes* 51:1319–1336
  55. **Ventre J, Doeberer T, Wu M, MacNaul K, Stevens K, Pasparakis M, Kollias G, Moller DE** 1997 Targeted disruption of the tumor necrosis factor- $\alpha$  gene: metabolic consequences in obese and nonobese mice. *Diabetes* 46:1526–1531
  56. **Ofei F, Hurel S, Newkirk J, Sopwith M, Taylor R** 1996 Effects of an engineered human anti-TNF- $\alpha$  antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. *Diabetes* 45:881–885
  57. **Fasshauer M, Klein J, Neumann S, Eszlinger M** 2002 Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. *Biochem Biophys Res Commun* 290:1084–1089
  58. **Paschke R, Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA** 2001 Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 86:1930–1935
  - 58a. **Stefan N, Bunt JC, Selbe AD, Funahashi T, Matsuzawa Y, Tataranni PA** 2002 Plasma adiponectin concentrations in children: relationships with obesity and insulinemia. *J Clin Endocrinol Metab* 87:4652–4656
  59. **Berg AH, Combs TP, Scherer PE** 2002 ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. *Trends Endocrinol Metab* 13:84–89
  60. **Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T,**

- Matsuzawa Y 2002 Diet induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 17:17
61. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA 2001 The hormone resistin links obesity to diabetes. *Nature* 409:307-312
  62. Way JM, Gorgun CZ, Tong Q, Uysal KT, Brown KK, Harrington WW, Oliver Jr WR, Willson TM, Kliewer SA, Hotamisligil GS 2001 Adipose tissue resistin expression is severely suppressed in obesity and stimulated by peroxisome proliferator-activated receptor  $\gamma$  agonists. *J Biol Chem* 276:25651-25653
  63. Janke J, Engeli S, Gorzelnik K, Luft FC, Sharma AM 2002 Resistin gene expression in human adipocytes is not related to insulin resistance. *Obes Res* 10:1-5
  64. Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, Considine RV, O'Rahilly S 2001 Resistin/Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor- $\gamma$  action in humans. *Diabetes* 50:2199-2202
  65. Degawa-Yamauchi M, Bovenkerk JE, Zhu Q, Considine RV, Serum resistin is significantly elevated in obese humans [Abstract 1660-P]. Proc 62nd Annual Meeting of the American Diabetes Association, San Francisco, CA, 2002
  66. McTernan PG, McTernan CL, Valsamakis G, Chetty R, Fisher FM, Lauer M, Barnett AH, Kumar S, Characterization of resistin expression and secretion in human adipose tissue [Abstract 1229-P]. Proc 62nd Annual Meeting of the American Diabetes Association, San Francisco, CA, 2002
  67. Jequier E 2002 Leptin signaling, adiposity, and energy balance. *Ann NY Acad Sci* 967:379-388
  68. Unger RH, Zhou YT, Orci L 1999 Regulation of fatty acid homeostasis in cells: novel role of leptin. *Proc Natl Acad Sci USA* 96:2327-2332
  69. Ebihara K, Ogawa Y, Masuzaki H, Shintani M, Miyanaga F, Aizawa-Abe M, Hayashi T, Hosoda K, Inoue G, Yoshimasa Y, Gavrilova O, Reitman ML, Nakao K 2001 Transgenic overexpression of leptin rescues insulin resistance and diabetes in a mouse model of lipotrophic diabetes. *Diabetes* 50:1440-1448
  70. Oral EA, Simha V, Ruiz E, Andrew A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, Gordon P, Garg A 2002 Leptin replacement therapy for lipodystrophy. *N Engl J Med* 346:570-578
  71. Steinberg GR, Parolin ML, Heigenhauser GJ, Dyck DJ 2002 Leptin increases fatty acid oxidation in lean but not obese human skeletal muscle: evidence of peripheral leptin resistance. *Am J Physiol* 283:E187-E192
  72. Hara K, Kubota N, Tobe K, Terauchi Y, Miki H, Komeda K, Tamemoto H, Yamauchi T, Hagura R, Ito C, Akanuma Y, Kadowaki T 2000 The role of PPAR $\gamma$  as a thrifty gene both in mice and humans. *Br J Nutr* 84(Suppl 2): S235-S239
  73. Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES 2000 The common PPAR $\gamma$  Pro<sup>12</sup>Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 26:76-80
  74. Koutnikova H, Cock T-A, Auwerx J, PPAR $\gamma$ 2 controls adipose tissue development in vivo [Abstract OR-17-1]. Program of the 84th Annual Meeting of The Endocrine Society, San Francisco, CA, 2002
  75. Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, Flier JS 2001 A transgenic model of visceral obesity and the metabolic syndrome. *Science* 294:2166-2170
  76. Forsen T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D 2000 The fetal and childhood growth of persons who develop type 2 diabetes. *Ann Intern Med* 133:176-182
  77. Phillips DIW 1998 Birth weight and the future development of diabetes: a review of the evidence. *Diabetes Care* 21(Suppl 2):B150-B155
  78. Lesage J, Blondeau B, Grino M, Breant B, Dupouy JP 2001 Maternal undernutrition during late gestation induces fetal overexposure to glucocorticoids and intrauterine growth retardation and disturbs the hypothalamo-pituitary adrenal axis in the newborn rat. *Endocrinology* 142:1692-1702
  79. Jensen CB, Storgaard H, Dela F, Holst JJ, Madsbad S, Vaag AA 2002 Early differential defects of insulin secretion and action in 19 year old Caucasian men who had low birth weight. *Diabetes* 51:1271-1280
  80. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV 1997 The Da Qing IGT and Diabetes Study: effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. *Diabetes Care* 20:537-544
  81. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukkaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M 2001 Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343-1350
  82. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM 2002 Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, and presentation by Kahn S, 62nd Annual Meeting of the American Diabetes Association, San Francisco, CA, 2002
  83. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE 2001 Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest* 108:1167-1174
  84. Cusi K, Consoli A, DeFronzo RA 1996 Metabolic effects of metformin in non-insulin dependent diabetes mellitus. *J Clin Endocrinol Metab* 81:4059-4067
  85. Bailey CJ, Turner RC 1996 Metformin. *N Engl J Med* 334:574-579
  86. DeFronzo RA 1999 Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 131:281-303
  87. Song S, Andrikopoulos S, Filippis C, Thorburn AW, Khan D, Proietto J 2001 Mechanism of fat-induced hepatic gluconeogenesis: effect of metformin. *Am J Physiol* 281:E275-E282
  88. Lupi R, Del Guerra S, Fierabracci V, Marselli L, Novelli M, Patane G, Boggi U, Mosca F, Piro S, Del Prato S, Marchetti P 2002 Lipotoxicity in human pancreatic islets and the protective effect of metformin. *Diabetes* 51(Suppl 1):S134-S137
  89. Fontbonne A, Charles MA, Juhan-Vague I, Bard JM, Andre P, Isnard F, Cohen JM, Grandmottet P, Vague P, Safar ME, Eschwege E 1996 The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. BIGPRO Study Group. *Diabetes Care* 19:920-926
  90. Paoiliso G, Amato L, Eccellente R, Gambardella A, Tagliamonte MR, Varrichio G, Carella C, Giugliano D, D'Onofrio F 1998. Effect of metformin on food intake in obese subjects. *Eur J Clin Invest* 28:441-446
  91. Glueck CJ, Fontaine RN, Wang P, Subbiah MTR, Weber K, Illig E, Streicher P, Sieve-Smith L, Tracy TM, Lang JE, McCullough P 2001 Metformin reduces weight, centripetal obesity, insulin, leptin and low density lipoprotein cholesterol in nondiabetic, morbidly obese subjects with body mass index greater than 30. *Metabolism* 50:856-861
  92. Freemark M, Bursey D 2001 The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. *Pediatrics* 107:e55
  93. Kay JP, Alemzadeh R, Langley G, D'Angelo L, Smith P, Holshouser S 2001 Beneficial effects of metformin in normoglycemic morbidly obese adolescents. *Metabolism* 50:1457-1461
  94. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I, Matsuzawa Y 2001 PPAR $\gamma$  ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50:2094-2099
  95. Peraldi P, Xie M, Speigelman BM 1997 Thiazolidinediones block tumor necrosis factor- $\alpha$ -induced inhibition of insulin signaling. *J Clin Invest* 100: 1863-1869
  96. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP 2002 Preservation of pancreatic  $\beta$ -cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2796-2803
  97. Nakamura T, Funahashi T, Yamashita S, Nishida M, Nishida Y, Takahashi M, Hotta K, Kuriyama H, Kihara S, Ohuchi N, Nishimura T, Kishino BI, Ishikawa K, Kawamoto T, Tokunaga K, Nakagawa C, Mineo I, Watanabe F, Tarui S, Matsuzawa Y 2001 Thiazolidinedione derivative improves fat distribution and multiple risk factors in subjects with visceral fat accumulation: double-blind placebo-controlled trial. *Diabetes Res Clin Pract* 54:181-190
  98. Chiasson J-L, Josse R, Gomis R, Hanefeld M, Karasik A, Laakso M 2002 Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. *Lancet* 359:2072-2077
  99. Yusuf S, Gerstein H, Hoogwerf B, Pogue J, Bosch J, Wolfenbutter BHR, Zinman B 2001 Ramipril and the development of diabetes. *JAMA* 286:1882-1885
  100. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A 2001 Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 103:357-362
  101. Sims EAH 2001 Are there persons who are obese, but metabolically healthy? *Metabolism* 50:1499-1504
  102. American Diabetes Association 2002 Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 25:5-20
  103. Youssef W, McCullough AJ 2002 Diabetes mellitus, obesity, and hepatic steatosis. *Semin Gastrointest Dis* 13:17-30
  104. Silverstein JH, Rosenbloom AL 2000 Treatment of type 2 diabetes mellitus in children and adolescents. *J Pediatr Endocrinol Metab* 13(Suppl 6):1403-1409
  105. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ 2002 Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 25:89-94
  106. Castells S 2002 Management of hyperglycemia in minority children with type 2 diabetes mellitus. *J Pediatr Endocrinol Metab* 15(Suppl 1):531-540
  107. Rosenbloom AL 2002 Increasing incidence of type 2 diabetes in children and adolescents: treatment considerations. *Paediatr Drugs* 4:209-221
  108. Zuhri-Yafi MI, Brosnan PG, Hardin DS 2002 Treatment of type 2 diabetes mellitus in children and adolescents. *J Pediatr Endocrinol Metab* 15(Suppl 1):541-546

109. **Glueck CJ, Wang P, Fontaine R, Tracy T, Sieve-Smith LN** 2001 Metformin to restore normal menses in oligo-amenorrheic teenage girls with polycystic ovary syndrome (PCOS). *J Adolesc Health* 29:160–169
110. **Arslanian SA, Lewy V, Danadian K, Saad R** 2002 Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. *J Clin Endocrinol Metab* 87:1555–1559
111. **Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A** 1999 Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care* 22: 920–924
112. **Bonora E, Kiechl S, Oberhollenzer F, Egger G, Bonadonna RC, Muggeo M, Willeit J** 2000 Impaired glucose tolerance, type II diabetes mellitus and carotid atherosclerosis: prospective results from the Bruneck Study. *Diabetologia* 43:156–164
113. **Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L** 2001 Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689
114. **Arad Y, Newstein D, Cadet F, Roth M, Guerci AD** 2001 Association of multiple risk factors and insulin resistance with increased prevalence of asymptomatic coronary artery disease by an electron-beam computed tomographic study. *Arterioscler Thromb Vasc Biol* 21:2051–2058
115. **Boyle JP, Honeycutt AA, Narayan KMV, Hoerger TJ, Geiss LS, Chen H, Thompson TJ** 2001 Projection of diabetes burden through 2050. *Diabetes Care* 24:1936–1940