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Insulin Resistance Syndrome in Children

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The insulin resistance syndrome (syndrome X, metabolic syndrome) has become the major health problem of our times. Associated obesity, dyslipidemia, atherosclerosis, hypertension, and type 2 diabetes conspire to shorten life spans, while hyperandrogenism with polycystic ovarian syndrome affect the quality of life and fertility of increasing numbers of women. Whereas a growing number of single genetic diseases affecting satiety or energy metabolism have been found to produce the clinical phenotype, strong familial occurrences, especially in racially prone groups such as those from the Indian subcontinent, or individuals of African, Hispanic, and American Indian descents, together with emerging genetic findings, are revealing the polygenetic nature of the syndrome. However, the strong lifestyle factors of excessive carbohydrate and fat consumption and lack of exercise are important keys to the phenotypic expression of the syndrome. The natural history includes small for gestational age birth weight, excessive weight gains during childhood, premature pubarche, an allergic diathesis, acanthosis nigricans, striae compounded by gynecomastia, hypertriglyceridemia, hepatic steatosis, premature atherosclerosis, hypertension, polycystic ovarian syndrome, and focal glomerulonephritis appearing increasingly through adolescence into adulthood. Type 2 diabetes, which develops because of an inherent and/or an acquired failure of an insulin compensatory response, is increasingly seen from early puberty onward, as is atheromatous disease leading to coronary heart disease and stroke. A predisposition to certain cancers and Alzheimer's disease is also now recognized. The looming tragedy from growing numbers of individuals affected by obesity/insulin resistance syndrome requires urgent public health approaches directed at their early identification and intervention during childhood. Such measures include educating the public on the topic, limiting the consumption of sucrose-containing drinks and foods with high carbohydrate and fat contents, and promoting exercise programs in our nation's homes and schools. (*J Clin Endocrinol Metab* 89: 2526–2539, 2004)

REAVEN (1) FIRST DESCRIBED syndrome X to comprise central obesity, hyperinsulinemia, hyperuricemia, hypertriglyceridemia, and a propensity to coronary heart disease (CHD) and stroke. The insulin resistance syndrome (IRS) has since been expanded from this core phenotype to become increasingly recognized by physicians, especially in the highly prone racial groups. A recent American College of Endocrinology position statement on IRS indicated that one in three or four U.S. adults have IRS, and 90% of diabetics are insulin resistant (IR), whereas one in 10 women have polycystic ovarian syndrome (PCOS).

The purpose of this review is to summarize the natural history of IRS, especially as it impacts children. We argue herein that attention must be urgently given to the children who are becoming more obese and more IR with time. In them, effective public health measures must be found to identify those affected as early as possible and treat them, if we are to prevent the burgeoning associated morbidities and mortalities that accumulate with their passage into adulthood.

Abbreviations: AGRP, Agouti-related peptide; AIR, acute insulin response; ALT, alanine aminotransferase; AN, acanthosis nigricans; BMI, body mass index; CBG, corticosteroid-binding globulin; CHD, coronary heart disease; CoA, coenzyme A; CRP, C-reactive protein; DI, disposition index; FA, fatty acid; FFA, free fatty acid; FSIVGTT, frequently sampled iv glucose tolerance test; GLUT4, glucose transporter 4; HDL, high-density lipoprotein; 11βHSD1, 11β-hydroxysteroid dehydrogenase type 1; IFNγ, interferon-γ; IGFBP-1, IGF-binding protein-1; IGT, impaired glucose tolerance; IR, insulin resistant, insulin resistance; IRS, insulin resistance syndrome; LDL, low-density lipoprotein; MC4R, melanocortin 4 receptor; NPY, neuropeptide Y; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor-1; PCOS, polycystic ovarian syndrome; POMC, proopiomelanocortin; PPAR, peroxisomal proliferator-activated receptor; SERPINS, serine protease inhibitors; SGA, small for gestational age; Si, insulin sensitivity; TG, triglycerides; Th1, T helper cell type 1; Vit-BP, vitamin D-binding protein; VLDL, very LDL.

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U.S. epidemiology of obesity and type 2 diabetes

The increasing prevalence of obesity in the U.S. is alarming, with 34% of the adult population being overweight]body mass index (BMI) ranging from 25–29.9 kg/m^2[, and another 27% are obese (BMI, $\geq$30 kg/m^2) (2). Thus, more than 45 million Americans are obese, a 74% increase in prevalence rates from 1991. Over the same time, diabetes rates have increased by 61% to affect at least 16 million (7.7%) Americans. Adults with a BMI greater than 40 have been found to be 7.4 times more likely to develop diabetes, 6.4 times more likely to have hypertension, and 1.9 times more likely to have hypercholesterolemia and to have increased death rates from all cancers combined that are 52% higher for men and 62% higher for women than those with BMIs less than 24.9 kg/m^2 (3, 4).

The prevalence of childhood obesity continues to increase at a rapid rate as well. Thirteen to 14% of children aged 6–11 yr and adolescents aged 12–19 yr were reported to be overweight in National Health and Nutrition Examination Survey IV (5). Data from 1999–2001 indicate continued increases to 15.5% of 12- to 19-yr-olds and 15.3% of

6- to 11-yr-olds. BMIs in excess of 28 kg/m^2 are associated with a 3- to 4-fold increase in risk of hypertension, dyslipidemia, and diabetes and a 2-fold increase in incident death rates (6). A prospective study found a significantly increased incidence of obesity-related morbidities over 5 yr of follow-up, when the BMI exceeded 27.5 kg/m^2 (7). The likelihood that an obese child will become an obese adult increases with age and the severity of obesity, whereas modest weight reductions of 5–10% significantly decrease the risk of complications of IR (8). Thus, a major effort to control childhood obesity must be mounted at all levels of health care delivery.

Insulin resistance (IR) alone is responsible for 46.8%, 6.2%, and 12.5% of the annual CHD events in type 2 diabetics, nontype 2 diabetics, and in the total U.S. population, respectively. The annual total cost of IR-attributable events in the U.S. was estimated to be $12.5 billion in 1999, of which $6.6 billion were direct medical costs. The annual cost of diabetes in medical expenditures and lost productivity climbed from $98 billion in 1997 to $132 billion in 2002. The direct medical costs of diabetes more than doubled in that time, from $44 billion in 1997 to $91.8 billion in 2002 (9). As mentioned, most diabetics have underlying IRS.

However, recent studies suggest that type 2 diabetes can be prevented. When 522 obese Finns with impaired glucose tolerance (IGT) were randomized to receive an intensive exercise and diet program, there was a 58% reduction in their progression to diabetes over a mean of 3.2 yr (10). The Diabetes Prevention Program trial (11), which involved 3234 subjects with IGT, showed a 58% reduction in progression to diabetes in the lifestyle group treatment group and a 31% decrease with metformin treatment from placebo-treated controls. Metformin was more effective in younger subjects (11). In the Troglitazone in the Prevention of Diabetes study of 235 Hispanic women with a history of gestational diabetes, a 56% reduction in progression to diabetes was observed after a median follow-up of 30 months (12). Metformin is a safe and effective agent to improve IR in pediatric patients (13–15, 28). It follows that as IRS is the constant precursor of type 2 diabetes, and IRS begins in childhood, then the earlier an intervention can be initiated in the natural history of the disease, the more effective it will be.

Definitions

IR is defined as an impaired ability of plasma insulin at usual concentrations to adequately promote peripheral glucose disposal, suppress hepatic glucose, and inhibit very low density lipoprotein (VLDL) output, but it can be inferred on strong clinical evidence and confirmed by insulin and glucose measurements made by fasting insulin/glucose screening, oral glucose tolerance tests (OGTT), the minimal model frequently sampled iv glucose tolerance test (FSIVGTT), and insulin/glucose clamp studies.

Biochemical definitions

Fasting levels of insulin greater than 15 μU/ml, or insulin peak (post-OGTT) levels of more than 150 μU/ml and/or more than 75 μU/ml at 120 min of OGTT are hyperinsulinemic levels, which infer IR (16).

Insulin sensitivity from OGTT can also be assessed by

TABLE 1. Methods of measuring insulin resistance from OGTT

Indices from OGTT	Formulae	Ref.
Fasting levels of insulin or insulin peak (post-OGTT)	≥15 mU/ml and/or peak ≥150 mU/ml are hyperinsulinemic levels	20
HOMA	$\frac{\text{Glu 0 min (mmol/liter)} \times \text{Ins 0 min } (\mu\text{U/ml})}{22.5}$	21
QUICKI	$\frac{1}{\log(\text{Ins 0 min}) + \log(\text{Glu 0 min})}$	22
Belfiore	$\frac{2}{(\text{AUC insulin} \times \text{AUC glucose}) + 1}$	23
Cederholm	$75{,}000 + (\text{Glu 0 min} - \text{2-h Glu}) \times 0.19 \times \text{BW}$ $120 \times \log(\text{mean Ins}) \times \text{mean Glu}$	24
Gutt	$\frac{75{,}000 + (\text{Glu 0 min} - \text{2-h Glu}) \times 0.19 \times \text{BW}}{120 \times \log([\text{Ins 0 min} + \text{2-h Ins}]/2) \times [\text{Glu 0 min} + \text{2-h Glu}]/2}$	19
Matsuda	$\frac{10{,}000}{\sqrt{(\text{Ins 0 min} \times \text{Glu 0 min}) \times (\text{mean Glu} \times \text{mean Ins})}}$	25
Stumvoll	$0.22 - 0.0032 \times \text{BMI} - 0.0000645 \times \text{2-h Ins} - 0.0037 \times \text{1.5-h Glucose}$	26
Soonthornpun	[1.9/6 × body weight (kg) × fasting glucose + 520 − 1.9/18 × BW × AUC glu − urinary glucose 1.8] ÷ [AUC ins × BW]	27
McAuley	Exp[2.63–0.28 ln (insulin mU/liter) − 0.31 ln (triglycerides mmol/liter)	28
Oral Glucose Insulin Sensitivity index (OGIS)	Table for calculation is available online (http://www.ladseb.pd.cnr.it/bioing/ogis/home.html)	29

Glu, Glucose; Ins, insulin; AUC, area under the curve; BMI, body mass index.

numerous indexes (Table 1). Such approaches are simple, albeit insensitive, have been validated for epidemiological studies (17, 18), and correlate with the indexes of insulin sensitivity obtained from glucose clamp studies and minimal model analysis (19).

The minimal model FSIVGTT is a more accurate method of quantifying insulin sensitivity (Si), acute insulin response (AIR) and disposition indexes (DI) (30). The AIR characterizes the first phase of insulin secretion that is a marker of early β-cell compensation (30). In nonobese children, the normal AIR range was recently reported by Gower *et al.* (31) to be 747 ± 122 μU/ml in Caucasians, 1210 ± 116 μU/ml in African-Americans, and 938 ± 38 μU/ml in Hispanic children at Tanner stages 1–3.

IR indexes (Si), calculated from IVGTT of 2×10^{-4} min^{-1}/(μIU/ml) or less, typically occur in the presence of IR, where values of 5×10^{-4} min^{-1}/(μIU/ml) or more are normal in adults and children (32). Si was reported to be in the range of $6.57 \pm 0.45 \times 10^{-4}$ min^{-1}/(μIU/ml) in prepubertal children, $4.63 \pm 0.86 \times 10^{-4}$ min^{-1}/(μIU/ml) in postpubertal adolescents, and $2.92 \pm 0.45 \times 10^{-4}$ min^{-1}/(μIU/ml) in pubertal children (33). Gower *et al.* (31) reported that IR in children at developmental Tanner stages 1–3 is different between races: Caucasian children, $6.3 \pm 0.6 \times 10^{-4}$ min^{-1}/(μIU/ml); African American children, $4.1 \pm 0.6 \times 10^{-4}$ min^{-1}/(μIU/ml); and Hispanic children, $4.5 \pm 0.5 \times 10^{-4}$ min^{-1}/(μIU/ml).

The DI characterizes the relationship of insulin secretion to the degree of IR. The DI calculated by (AIR × Si) describes the hyperbolic relationship between insulin secretion (AIR) and Si from FSIVGTT, which is sensitive to detect even latent β-cell defects. Gower *et al.* (31) reported DI from AIR (minutes^{-1}) to be in the range of 0.29 ± 0.07 in Caucasian, 0.45 ± 0.07 in African-American, and 0.35 ± 0.05 in Hispanic children at Tanner stages 1–3.

Hyperglycemic and euglycemic-hyperinsulinemic clamp studies are well established for assessing β-cell function and Si, but these are relatively invasive procedures that are difficult to perform. Well accepted normal values for children with any of the described methods are still needed.

Clinical definitions

The clinical phenotype of IRS includes centrally biased obesity; characteristic skin involvements]acanthosis nigricans (AN), skin tags, striae, acne, hirsutism, and frontal balding[; an allergic diathesis, especially as manifest by asthma; hypertension; an atherogenic dyslipidemia]increased VLDL with raised triglycerides (TG) and reduced levels of the protective high density lipoprotein (HDL) cholesterol[; early atherosclerosis, tall stature and pseudoacromegaly (with suppressed GH levels); focal segmental glomerulosclerosis; hepatic steatosis; and adrenal and ovarian hyperandrogenism (Table 2). Importantly, IR is not infrequent in the absence of obesity, whereas even considerably obese persons can be insulin sensitive.

Obese patients thus represent heterogeneous subgroups of metabolic and phenotypical expressions of IR, whereas individuals with the same BMI can have very different degrees of IR and metabolic (insulin) compensation. However, most individuals with BMIs more than 35–40 kg/m^2 are IR. Children with BMIs higher than the 85th percentile for age and gender are classified as overweight, whereas those that are higher than the 95th percentile are designated obese (34). Adolescents and adults with BMIs of 25 kg/m^2 or more are at risk for adiposity-related morbidity, whereas those with BMI greater than 30 kg/m^2 are obese according to the World Health Organization panel.

Pathogenesis

Nature vs. nurture. The dramatic rise in obesity-associated IRS reflects environmental increased availability and consumption of food with high carbohydrate and fat contents together with decreased physical activities. Genetic predispositions to obesity favor selection of metabolically advantaged (energy thrifty) traits resulting in an enhanced ability to store excess calories in tissues as fat and to spare protein breakdown for gluconeogenesis, favoring survival in times of hunger. Genotypic factors influence the ability to use food energy efficiently through mechanisms of intraabdominal fat distribution, resting metabolic rate, changes in energy expenditure, body composition to overfeeding, feeding behavior (includ-

TABLE 2. Features of IRS

Features of IRS	Pediatric features of IRS
AN skin tags	Positive family histories of diabetes, obesity, hypertension, CHD, and/or stroke
Striae: white	History of maternal gestational diabetes
Centrally biased obesity	SGA (mostly) or LGA (less often)
Hirsutism, ovarian hyperandrogenism and infertility	Asthma/allergic rhinitis
Dyslipidemia (↑ TG, ↓ HDL)	Premature pubarche
Premature atherosclerosis	Red (new) and white (old) striae, from adrenarche onward
Hypertension	Obesity appears or worsens at adrenarche
Hyperuracemia/gout	Decreasing resting energy expenditure
Allergies/asthma	Low resting fat to carbohydrate oxidation rates
Fatty liver (NASH)	AN
Chronic pancreatitis	Tall stature/pseudoacromegaly
Focal glomerulosclerosis	Hirsutism/PCOS with adolescence
Glucose intolerance	Adipomastia/gynecomastia
Type 2 diabetes	Acute pancreatitis
Increased cancer risk	Premature atherosclerosis
Increased Alzheimer's disease	Hypertension/glomerulonephritis
	Type 2 diabetes

ing food preferences), adipose tissue lipoprotein lipase activity, and the basal rate of lipolysis.

Genetic IR. The pathogenesis of IR is multifactorial (Table 3). Thus, several molecular pathways in energy homeostasis, lipid metabolism, insulin receptor signaling pathway, cytokines, hormone-binding proteins including those that are serine protease inhibitors (SERPINS), and other protease regulators are responsible for the development of IR, obesity, or lipodystrophy (Fig. 1). In the energy homeostasis pathway, uncoupling proteins, leptin-proopiomelanocortin (POMC), ghrelin-neuropeptide Y (NPY), and sympathetic nervous system regulation pathways have proved to be important. In the insulin-signaling pathway, mutations in insulin receptors, development of insulin receptor autoantibodies, and defects in plasma cell membrane glycoprotein-1 and glucose transporter 4 (GLUT4) molecules are reported. In the lipid homeostasis pathway, adipocyte-derived hormones, leptin, adiponectin, resistin, peroxisomal proliferator-activated receptor-γ (PPARγ), and PPARα are variously involved, as are lipoprotein lipase and genes responsible for adipose tissue formation. Increased availability of free fatty acids (FFAs) to muscle provokes IR. Proteases contributing to the development of diabetes are represented by CAPN 10 and prohormone convertase deficiencies.

Heterozygosity for recessive mutations. The concurrence of several heterozygosities for the mutations described above can have additive adverse effects. This is evident by the additive effects of heterozygosity for mutations of the leptin and leptin receptor genes in mice. Human heterozygotes for the LEPR mutation, have plasma leptin concentrations intermediate between wild-type and homozygous affected levels (35). Heterozygotes for the Bardet-Biedl syndrome have increased frequencies of obesity, renal disease, hypertension, and type 2 diabetes, consistent with haploinsufficiency for the responsible gene (36). Heterozygosity for inactivating mutations of the melanocortin 4 receptor (MC4R) similarly results in obesity in both mice and humans (37).

Acquired IR. Insulin receptor antibodies, Cushing's syndrome, glucocorticoid steroid therapy, acromegaly, hyperparathyroidism, and exogenous obesity can all produce IR

TABLE 3A. Genetics of IRS

Insulin receptor pathway defects	Fat cell defects − lipid homeostasis pathway	Hypothalamic level defects Leptin-POMC-MCR4 pathway	Miscellaneous
Type A syndrome mutation in the insulin receptor	Congenital generalized lipodystrophy (mutations in 11q13, BSCL2, AGPAT2 gene on 9q34)	POMC mutations MC4R mutations MC3R mutations	Proteases − CALP10 Impaired processing of prohormones prohormone convertase deficiency (PC1) Estrogen receptor mutations
Leprechaunism	Dunnigan's syndrome (lamin mutation)	Leptin mutations	
Rabson-Mendenhall syndrome	Kobberling's syndrome (mutation in the PPAR-γ gene)	Leptin receptor gene mutation, ghrelin polymorphisms, neuropeptide Y5 receptor polymorphisms, cocaine- and amphetamine-regulated transcript polymorphisms, cholecystokinin A receptor polymorphisms	
Polymorphism in plasma cell membrane glycoprotein-1 (PC-1)	Allelic variation in PPARγ influence body fat mass by effects on adipocyte; polymorphisms of PPARα gene can lead to higher triglyceride and insulin levels; polymorphism of the lipoprotein lipase gene was both linked and associated with insulin resistance; polymorphism of UCP1, UCP2, UCP3 genes; polymorphism of β_2- and β_3-adrenergic receptors	Single-gene defects leading to disruption of hypothalamic pathways of energy regulation Prader-Willi syndrome (15q11.2–q12, uniparental maternal disomy), Alström syndrome (ALMS1 gene mutants in the hypothalamus might lead to hyperphagia followed by obesity and insulin resistance), Bardet-Biedl syndrome, Cohen syndrome, Beckwick-Weidermann syndrome, Biemond syndrome II, choroideremia with deafness	

TABLE 3B. Acquired IR

Acquired IR pathway defects	Acquired fat cell defects	Acquired miscellaneous
Type B immune-mediated insulin resistance	Lipodystrophy associated with HIV protease inhibitors; acquired generalized lipodystrophy-Lawrence syndrome is caused by antibodies against adipocyte-membrane antigens Barraquer-Simons' syndrome (partial acquired cephalothoracic lipodystrophy) have accelerated complement activation and a serum IgG, called C3 nephritic factor, that is thought to cause lysis of adipose tissue expressing adipsin	Excess counterregulatory hormones; glucocorticoids, catecholamines, PTH, GH, placental lactogen in case of stress, infection, pregnancy, starvation, uremia, cirrhosis, ketoacidosis, aging, inactivity

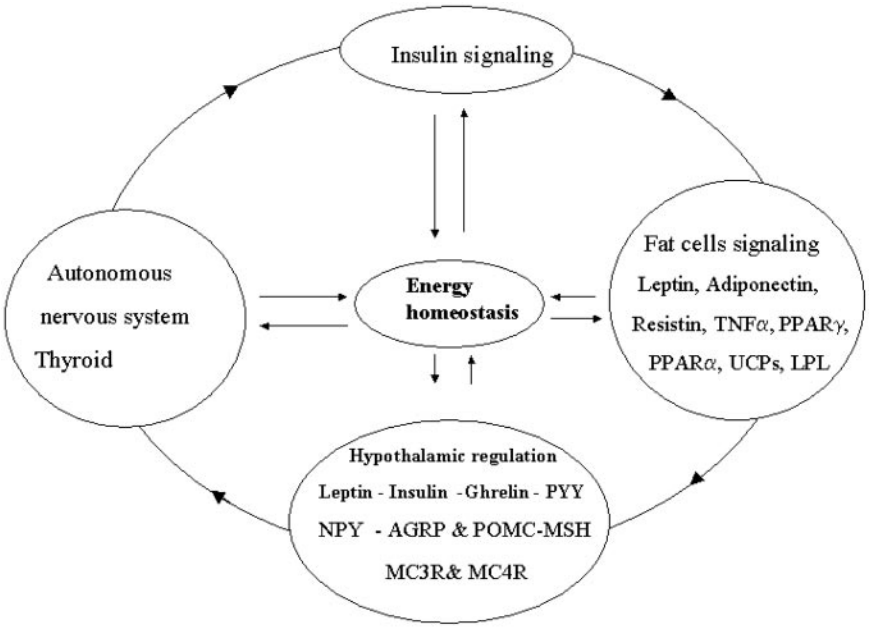

FIG. 1. Pathways of energy homeostasis.

(Table 3B). In practice, however, steroid-induced IR in a person who happens to be genetically prone to IR is the most commonly encountered, especially when the obese child also has IR-associated asthma. We find this a frequent occurrence in our clinical practices. GH therapy can provoke transient IR also, but this therapeutic issue needs further study. In the small for gestational age (SGA) disorders without catch-up growth, such as the Russell-Silver syndrome, IR may develop even before GH is given.

Birth weight and length. A continuum of increased risk of adulthood diseases, such as cardiovascular diseases, type 2 diabetes, and hypertension, based upon SGA at birth is now established (38). In our African American and Hispanic IR patients, moderate SGA has been startlingly common. Experimental utero-placental insufficiency in rats to provoke intrauterine growth retardation induced an impaired oxidative phosphorylation in skeletal muscle with a diminished uptake of glucose (39). In humans, the risk of IR is particularly apparent when an SGA newborn undergoes rapid postnatal weight gains to obesity. The Early Bird Study suggested that IR at 5 yr was related not to birth weight, but, rather, to weight catch-up growth, especially in girls (40). Such growth patterns following fetal growth restraint are associated with maternal-uterine factors such as primiparity, smoking, restrictions in the maternal diet, maternal IRS, and gestational diabetes. Alternatively, if an inherited IR state was manifested *in utero*, then diminished fetal growth with SGA might be anticipated, because insulin is a powerful prenatal GH. In many of the families we have studied in whom we have documented members with IRS, some 50% of the siblings also develop IRS, and these subjects tend to have been SGA compared with those who do not.

Curiously, large for gestational age children are at risk of IR as well. A U-shaped relation between birth weight and fasting insulin was shown in Pima Indian children with both low and high birth weights (41). The same U-shaped relation between birth weight, BMI, and fat mass was demonstrated recently in adolescents (42).

Gestational diabetes *per se* significantly increases the subsequent risk of obesity and type 2 diabetes (43), with the children of mothers with type 1 diabetes being more predisposed to type 2 diabetes as adults compared with children born to fathers with type 1 diabetes (44).

IR, leptin resistance, ghrelin, and satiety

The insulin/leptin-arcuate nucleus of the hypothalamus axis regulates energy homeostasis through control of appetite and energy expenditure. Both hormones rise in direct proportion to adipose mass; they cross the blood-brain barrier and have receptors in the arcuate nucleus. Leptin acts on POMC expression and αMSH release. αMSH, in turn, interacts with MC3/4R to reduce food intake and increase energy expenditure by activating the sympathetic nervous system. Leptin down-regulates anabolic NPY, agouti-related peptide (AGRP), orexins, and melanin-concentrating hormone in the hypothalamus. The central melanocortin system is a key mediator of the catabolic effects of insulin in the brain. Gastric secretion of ghrelin is increased by fasting and increases pituitary GH release, thereby stimulating lipolysis to provide energy substrates. Ghrelin stimulates NPY-AGRP to antagonize αMSH. The resultant lack of anorexic pressure on MC4Rs results in increased feeding behavior and energy efficiency (with reduced fat oxidation) to store energy as fat. Conversely, in the fed state, insulin and leptin levels are increased, which increases the synthesis and processing of hypothalamic POMC to its component peptides, including αMSH, which, together with its colocalized neuromodulator cocaine/amphetamine-regulated transcript, acts at the MC4R to decrease appetite. Insulin and leptin also directly inhibit NPY-AGRP, further limiting feeding and providing for unantagonized MC4R occupancy. Therefore, ghrelin,

insulin, and leptin represent afferent hormonal links between peripheral energy metabolism and central feeding behavior and tie together the gut, pancreas, adipocyte, hypothalamus, and pituitary to form a coordinated growth and energy regulatory system (45, 46). Genetic defects at many of these steps have been described.

Natural history of the clinical IRS

The natural history of IRS begins in childhood, from the interplay of genetic and environmental factors (Fig. 2 and 3). Although it is generally unclear whether a primarily genetically encoded state of IR and/or satiety disorder appears first, IR results in hyperinsulinism and precocious development of atherosclerosis and type 2 diabetes (47). A contemporary diet from early childhood replete with large amounts of saturated fats and excess carbohydrates is probably important to the development of hyperinsulinemia and obesity. The epidemic of obesity and diabetes follows U.S. commercially driven drink and food sources, with consumption of large amounts of sodas and fruit juices, and foods with a high glycemic index. Dietary carbohydrates (and fats) induce hyperinsulinism, a reduction in fatty acid (FA) oxidation, and hypertryglyceridemia. Diets rich in saturated FAs add a strong insulinotropic effect. In children, obesity and IR precede the development of hyperinsulinism. The hyperinsulinemia can thus be seen a compensatory mechanism for the preexisting, genetically programmed IR, which represents a mechanism for protection against the development of IGT and diabetes.

Insulin hypersecretion (especially portal) leads to increased FA synthesis, especially in the liver and adipose tissue. A compensatory increase in glucose oxidation and increased malonyl coenzyme A (CoA) signaling in the face abundant FAs direct an FA diversion away from β-oxidation to compensatory increases in long-chain CoA and TG synthesis in the liver. TG in the blood is a marker of intracellular hepatic long-chain CoA accumulation and increased VLDL synthesis. Normally appetite can be suppressed by both leptin and insulin; however, diets high in fat stimulate appetite directly. The liver, in turn, becomes insensitive to compensatory leptin signaling to increase β-oxidation, which is blocked in IR because of high levels of malonyl CoA. Elevated levels of malonyl CoA block FA β oxidation, leading to TG accumulation in muscle and liver, with impaired serine phosphorylation of insulin receptor substrate-1, decreased GLUT4 translocation, and thereby decreased glucose oxidation. In the islets, these events lead to activation of caspases and increased ceramide levels inducing apoptosis of β-cells. Type 2 diabetes thus results when there is insufficient insulin secretion to counter preexisting IR. This is consistent with the United Kingdom Prospective Diabetes Study findings of progressive deterioration of β-cell function over time in both obese and nonobese patients with type 2 diabetes (48).

In experimental rats and human patients, IR is correlated with total muscle TG, as measured in biopsy samples, especially when intramyocellular fat is the measured variable. Also, tight positive correlations were found between the TG content of skeletal muscle, liver, and whole pancreas and variables such as the plasma insulin concentration, β-cell function, and IR in a variety of rat models with very different fat contents (49).

Loss of first phase insulin response to predict development of diabetes

Children affected by IRS are usually hyperinsulinemic individuals in whom carbohydrates can induce a delayed, but excessive, rise in insulin secretion. This may cause an

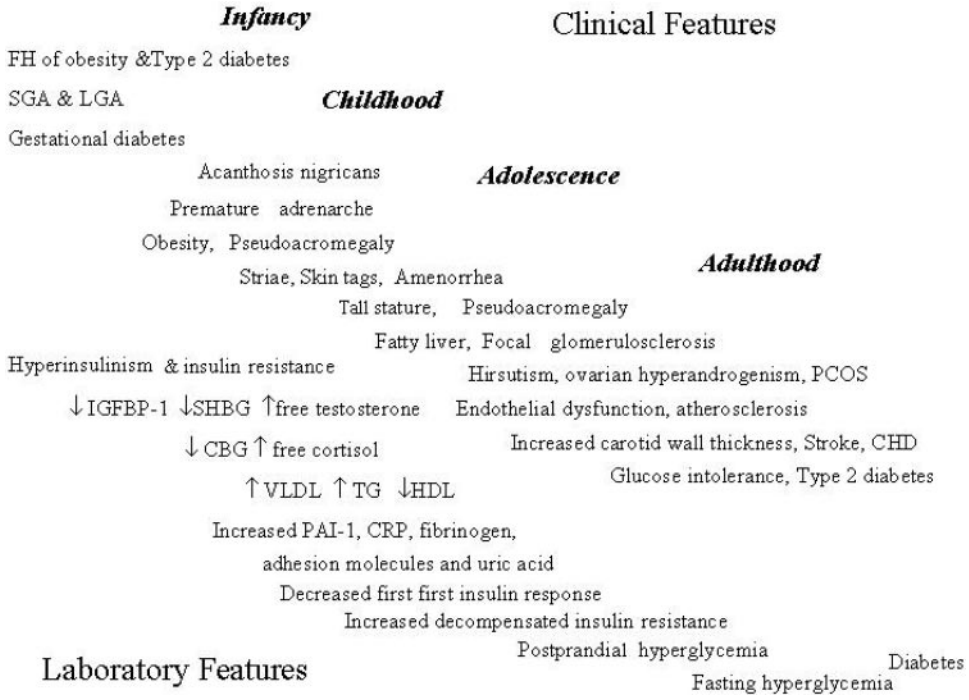

FIG. 2. Clinical and laboratory features of IRS with natural history.

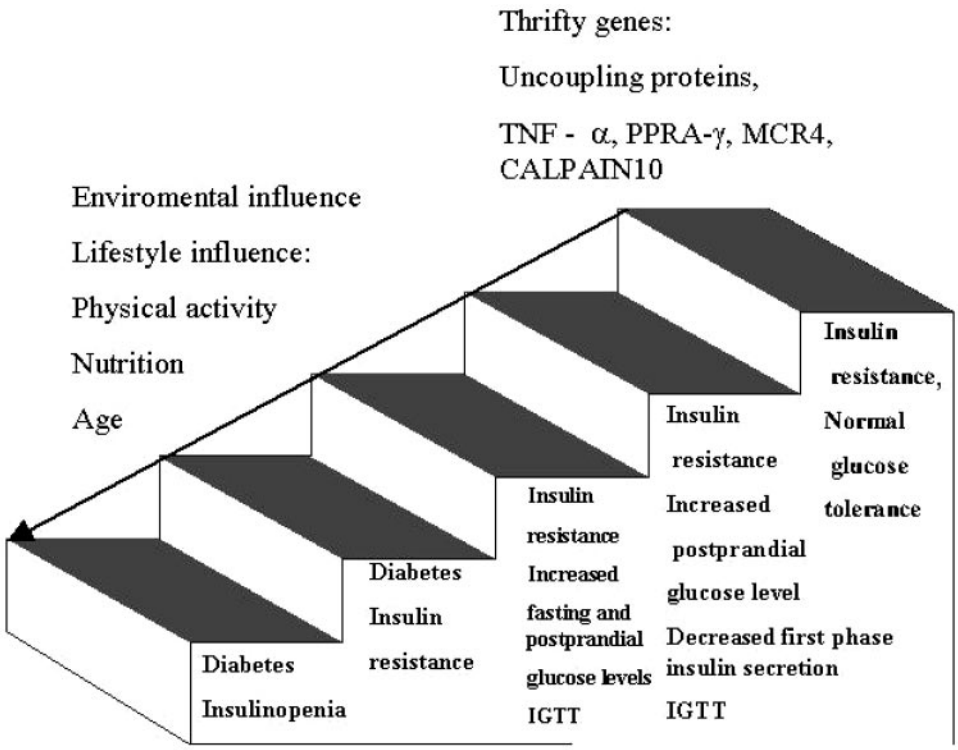

FIG. 3. Natural history of developing diabetes type 2.

excessive fall in glucose levels 3–4 h later, of sufficient severity to provoke symptoms of hypoglycemia (late reactive hypoglycemia). As the ability to secrete insulin declines, postprandial glucose intolerance appears, followed by fasting hyperglycemia and diabetes. On the basis of iv glucose testing, insulin release consists of two phases (50). In individuals with type 2 diabetes the second phase response is diminished, and the first phase response is almost absent. However, the first phase response decreases long before the development of type 2 diabetes. In the Insulin Resistance Atherosclerosis Study, subjects who were nondiabetic at baseline (n = 903) were reexamined after 5 yr when 148 had developed diabetes. Individuals who had a low AIR combined with high proinsulin levels experienced the highest diabetes risk (51). Such data were supported by the United Kingdom Prospective Diabetes Study (52) and studies in Pima Indians (53), in whom it was shown that a low AIR predicts the development of diabetes at a time when many subjects still have normal glucose tolerance. The DI is an excellent method to detect latent β-cell defects, albeit hyperinsulinism documented by a high AIR is a predictor of the rate of increased fat mass.

Hyperinsulinism and IR are not benign, even without diabetes

The majority of persons with IR will not develop type 2 diabetes. The genetic backgrounds on which hyperinsulinism and IR develop strongly influence the adequacy of pancreatic β-cell compensation (54). The heritability of β-cell function, assessed in relation to insulin sensitivity (Si × AIR glucose), demonstrated a heritability of 70% in 94 normal glucose-tolerant individuals (55). Pancreatic β-cell failure can represent independent genetic interactions that may be influenced by the human leukocyte antigen haplotype.

IRS individuals who can compensate by hyperinsulinemia may escape diabetes, but are still prone to other complications, such as early atherosclerosis, progression of obesity (especially central type), AN, increased skin tags, hypertension, dyslipidemia, hypercoagulation, PCOS, fatty liver infiltration, focal segmental glomerulosclerosis, and an increased cancer rate as well (4). Thus, IRS is not benign even when diabetes does not develop.

Hyperinsulinism- and IR-mediated pathologies (Tables 2 and 4)

Adipose tissue. It is widely believed that obesity itself, especially increased visceral fat accumulation, can lead to IR (56). Genetically induced IR can be the primary mechanism underling and evoking the progression of obesity. In contrast, nonobese, lean individuals can develop IR also. It has been shown that lean sisters and brothers of patients with obesity complicated by IR and PCOS can have IR, confirming that IR can be a primary mechanism. Generalized lipodystrophy can lead to IRS because of leptin deficiency and is dramatically reversible with leptin therapy.

Visceral fat. Visceral fat is a potent modulator of insulin action on hepatic glucose production (57). Central distribution of body fat (waist/hip ratio, >0.90 in females and >1.0 in males) is associated with an increased risk of stroke, CHD, diabetes, and early mortality and is a more sensitive indicator of impending morbidity than absolute fat mass. Waist circumference correlates with cardiovascular morbidity as well as BMI or percent body fat. Leptin levels are higher in sc fat

TABLE 4. Hyperinsulinism- and insulin resistance-mediated organ-specific symptoms and pathologies

Skin Hyperkeratotic AN, skin tags Striae Hirsutism Frontal alopecia	Gastrointestinal Hepatic steatosis, NASH, pancreatitis, cholecystitis, colon cancer
Adipose tissue Obesity, increased intraabdominal fat Fat infiltrations of muscle, liver, pancreas	Gonads Virilization or hirsutism, menstrual irregularity, persistent acne, scalp hair loss, hyperhidrosis, infertility or precocious pubarche in childhood
Cardiovascular Increased arterial wall thickness Endothelial dysfunction Early atherosclerosis CHD, stroke Hypertension	Adrenal Premature adrenarche, increased cortisol production and excretion, increased adrenal androgens and DHEA, normal catecholamines
Kidney Focal segmental glomerulosclerosis	GH axis Pseudoacromegaly, accelerated linear growth and bone age, decreased GH secretion, low IGFBP-1
Immune system Impaired cellular mediated immunity Asthma, eczema Increased cancer risk, *e.g.* breast	Inflammation Increased levels of CRP, raised erythrocyte sedimentation rates and increased TNFα levels, increased autoimmune thyroiditis
Psychological Depression, poor self-esteem ? cognitive defects	Neurological Stroke Pseudotumor cerebri
Respiratory Obesity hypoventilation syndrome Sleep apnea, ventilation/perfusion mismatches	Musculoskeletal Coxa vara slipped capital epiphysis, degenerative arthritis, Blount's disease, gout, muscle cramps

and show greater correlations with sc adiposity than with visceral adiposity (58). Visceral fat tissue, through its portal drainage, is an important source of FFA that increase hepatic lipogenesis and decrease glucose oxidation (57). *In vitro* (isolated adipocytes) and *in vivo* studies in humans (labeled FA flux) showed that visceral FA flux was increased in obese patients.

In comparison with sc fat, visceral fat has more glucocorticoid receptors and higher local concentrations of glucocorticoids. Omental adipose tissue contains significantly more 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) activity than sc adipose tissue (59), promoting increased cortisol production from conversion of inactive cortisone. GH (and/or IGF-I) was suggested recently to inhibit 11βHSD1, whereas in obesity, GH levels are decreased, leading to higher 11βHSD1 activity (60). 11βHSD1 activity correlates with IR (61). 11βHSD1 knockout mice have been shown to resist diet-induced IR and hyperglycemia (62). A local increase in glucocorticoid hormone action in visceral fat may contribute to the pathogenesis of key features of the metabolic syndrome. Clinically, we observed increased abdominal striae and biochemically increased urinary free cortisol levels in obesity.

Patients with Cushing's syndrome have high levels of serum cortisol, and the patient with IRS has low to normal levels, albeit both have increased levels of urinary free cortisol. The explanation lies in the decreased levels of corticosteroid-binding globulin (CBG) found in IRS, where circulating cortisol is disproportionately free and bioactive, with increased conversion of cortisone to the metabolically active cortisol. The clinical distinction between patients with Cushing's and IRS is that the former is invariably growth retarded, in contrast to the child with IRS in whom linear growth is excessive. In the future, specific inhibitors of 11βHSD1 to enhance insulin sensitivity and limit weight gain in obesity might have a place.

Fatty liver or hepatic steatosis. Hepatic steatosis is another complication of IR that may progress over years with inflammation and fibrosis (nonalcoholic steatohepatitis). At least 20% of such individuals eventually develop cirrhosis, liver failure, or hepatocellular carcinoma. Fatty liver affects 2.6% of children (63), and 22.5–52.8% of obese children and 10–25% of adolescents (64). In adult patients with diabetes and obesity, 100% have mild steatosis, 50% have steatohepatitis, and 19% have cirrhosis (65). The disease is usually silent over many years. Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase, and γ-glutamyltransferase are elevated and have been proposed as surrogate markers of hepatic fat accumulation (66). The ratio of aspartate aminotransferase to ALT is usually less than 1, but this ratio increases as fibrosis advances.

Although there is no accepted pharmacological treatment that can reverse fatty liver disease, all patients should be given a low fat diet and TG-lowering agents and encouraged to exercise. Leptin injections have been proven efficient in patients with generalized lipodystrophy (67); antioxidant therapy has been proposed (68), but has not produced sustained improvement; and insulin sensitizers, such as metformin, have been efficient in mice (69), but there are few

studies in humans (66). A decrease in liver volume and decreased ALT concentrations were shown in 20 adult patients treated with metformin (500 mg, three times daily) for 4 months by Marchesini *et al.* (66) and in 10 children treated with metformin (500 mg, twice daily) for 24 wk (70). Similar results were obtained with troglitazone (69).

Hypertension. Hyperinsulinemia can increase blood pressure by several mechanisms: via its effect to increase renal sodium absorption, via increased activity of the sympathetic nervous system, and via FFA-induced sensitivity to adrenergic stimuli and antagonized nitric oxide vasorelaxation (71). Also, transgenic mice that overexpress leptin develop hypertension.

IR as an initiator of atherosclerosis. Studies of adults have shown that there is an association between IR and atherosclerosis, Increased thickness of the arterial carotid wall and an atherogenic dyslipidemic profile that includes hypertriglyceridemia, low serum HDL cholesterol concentrations, and atherogenic low density lipoprotein (LDL) cholesterol particles compounded by low SHBG levels are factors for increased risk of atherosclerosis.

Importantly, hyperinsulinemia is an independent cardiovascular risk factor (72). The Muscatine Study linked childhood coronary risk factors to atherosclerosis in asymptomatic adults. The most predictive childhood risk factor was increased BMI. Coronary artery calcifications were also associated with increased blood pressure and decreased HDL cholesterol levels measured during childhood (73). Fatty streaks can be found in the aorta inchildren older than 3 yr of age and in coronary arteries by adolescence (74). The Bogalusa Heart Study confirmed that the same risk factors that are important for adults, such as elevated BMI, systolic blood pressure, serum TG, and LDL lipoproteins, convey greater atherosclerosis risk in the aorta and coronary arteries in children (74). The Pathobiological Determinants of Atherosclerosis in Youth study confirmed the origin of atherosclerosis in childhood, showed that progression toward clinically significant lesions may occur in young adulthood, and demonstrated that the progression of atherosclerosis is strongly influenced by CHD risk factors (75).

The thickness of the carotid wall, a validated surrogate marker for atherosclerosis in teenagers and young adults, is sensitive to the intake of cholesterol, serum levels of cholesterol and TGs, BMI, smoking, hypertension, and fasting glucose (76).

Endothelial dysfunction is an early event preceding the formation of plaques, representing an early disease process of atherosclerosis that begins in childhood and is associated with IR and hyperinsulinemia (77).

Low hormone-binding proteins and SERPINS. Decreased levels of multiple binding proteins]CBG, SHBG, IGF-binding protein-1 (IGFBP-1), thyroid binding globulin, and vitamin D-binding protein (VitD- BP)[have been reported in patients with obesity and metabolic syndrome X, suggesting a common underlying regulatory mechanism. The binding activities of these proteins are believed to modulate the biodisposal of hormones at the level of target cells. Deficiencies of hormonal binding proteins are implicated in clinical hirsutism, PCOS, Cushing-like features, pseudoacromegaly, thrombosis, inflammation, and even increased cancer risk in cases of IRS.

SHBG has been found to be negatively correlated with BMI and fasting insulin levels. Decreased SHBG increases testosterone bioavailability, leading to the development of hyperandrogenism, even when serum levels of testosterone are normal.

IGFBP-1 is often strikingly depressed in IRS, producing an excessive of free IGF-I, albeit the total level of IGF-I is usually normal. IGFBP-1 levels are regulated principally by insulin and to a lesser extent by glucose levels. Decreased IGFBP-1 in the face of IR leads to the increased tissue bioavailability of IGF-I, such that it can enhance the glucose-lowering effect of insulin. This can lead to the development of microvascular complications and pseudoacromegaly. We found that low levels of IGFBP-1 are associated with the degree of IR, whereas IGFBP-3 correlates directly with the degree of hyperinsulinism.

The low levels of CBG found in IRS lead to disproportionately free and active circulating cortisol. That can lead to clinical and metabolic overlap between Cushing's syndrome and IR. Increased conversion of inactive cortisone to active cortisol by 11βHSD1 in visceral fat compounds the effect. CBG secretion has been shown to be negatively regulated by both insulin and IL-6 (78).

Thyroid binding globulin levels in IRS are often depressed, leading to confusion as to the presence of hypothyroidism. Obese patients are thus often unnecessarily treated for hypothyroidism they do not have. They may, however, develop true hypothyroidism on the basis of associated Hashimoto's disease.

The low level of 25-hydroxyvitamin D_3 is associated with IR (79), and 1,25-dihydroxyvitamin D_3 is essential for normal insulin secretion. Although VitD-BP is known as a macrophage-activating factor, and polymorphism of VitD-BP is connected to diabetes risk in Pima Indians (80). Low levels of IGFBP-1 and 1,25-dihydroxyvitamin D were found in maternal and umbilical cord blood in preeclampsia (81).

CBG, thyroid binding globulin, and plasminogen activator inhibitor-1 (PAI-1) belong to a family of SERPINS, and insulin and cytokines levels in the case of IR can regulate their activity. These binding proteins (serine protease inhibitors) are substrates for elastase that is expressed at the surface of neutrophils. Therefore, the variability in circulating binding protein levels might be linked to their cleavage by activated neutrophils. Increased peripheral white blood cell count and neutrophils are usually found in both obesity and IR, which might facilitate serine protease availability and binding protein cleavage. This mechanism is likely to contribute to decreased serum binding globulins levels in obesity and IR.

Inflammation, asthma, eczema, and impaired immunity. IRS and type 2 diabetes have increased markers of inflammation, such as C-reactive protein (CRP), erythrocyte sedimentation rates, and TNFα levels. Data from the National Health and Nutrition Examination Survey III cohort of 5305 children showed that 24.2% of boys and 31.9% of girls with BMI greater than the 95th percentile had elevated CRP levels (82). Bogolusa and Pathobiological Determinants of Atherosclerosis in Youth studies confirmed the significance of elevated

CRP for future atherosclerosis development in children. BMI correlates with levels of CRP (83), and adiposity has been reported to be the major determinant of CRP levels in children. Among adults, those with baseline CRP in the top quartile were found to be twice as likely to develop diabetes over 3–4 yr of follow-up as those with lower levels (84). Our previous data revealed significantly elevated sTNF receptor type 2 in obese children compared with lean children, with significantly elevated levels in the group of obese children with IGT (Anhalt *et al*., personal communication).

Leptin has been shown to up-regulate the production of proinflammatory cytokines, including TNF-α and IL-6, to increase phagocytosis by macrophages, and to increase T helper cell type 1 (Th1) levels and suppression of Th2 cytokine production in mice (85).

A connection between leptin and autoimmunity was recently recognized in the light of understanding that leptin could favor proinflammatory cell responses and directly influence the development of autoimmune disease mediated by Th1 responses. Intraperitoneal injections of leptin accelerated autoimmune destruction of insulin-producing β-cells and significantly increased interferon-γ (IFNγ) production in peripheral T cells in nonobese diabetic mice. Similar observations were documented by leptin injections given to C57BL/6J-*ob/ob* mice that converted these mice from disease resistant to susceptible to autoimmune encephalomyelitis. This switch was accompanied by a Th2 to Th1 pattern of cytokine release and consequent reversal of Ig subclass production (86). Thus, leptin resistance evident in IRS could bias to Th2-type responses.

The role that leptin plays in the immunosuppression of malnutrition is increasingly recognized. Seven of 11 children in the family with a leptin mutation died of infections in childhood (87). At the same time it was shown that leptin treatment of human lymphocytes during a mixed lymphocyte reaction *in vitro* enhanced IFNγ production and blunted IL-4 production (85).

Significant association between asthma and obesity has been noted, especially during puberty. One of the possible mechanisms is that obesity represents a proinflammatory state, and leptin levels influence Th1 cytokine responses. Relationships between birth weight with adult BMI, and between obesity and asthma have been well recognized. BMI correlated with the prevalence of asthma in both boys and girls. It was noted that girls who became obese between ages 6–11 yr were 7 times more likely to develop new asthmatic symptoms at ages 11–13 yr (88). At the same time intervention trials documented the beneficial effect of weight loss on improvements in forced expiratory volume in 1 sec, FVC, dyspnea, use of rescue bronchodilators, and the median number of asthma exacerbations in the treatment group compared with the control group (89).

Hypoventilation and sleep apnea. Excess body fat leads to a decline in the expiratory reserve volume, vital capacity, total lung capacity, and functional residual volume, probably due to the excess body mass *per se*, albeit others implicate excessive leptin levels (90).

Significance of AN. AN is a skin lesion that is widely used as a clinical surrogate of laboratory-documented IR/hyperinsulinemia, denoting a subgroup with a high risk for type 2 diabetes. We suggest that AN should be documented in all children seen in practice, especially if they are obese or diabetic. Common sites of involvement include the axillae, posterior region of the neck, antecubital fossae, and groins. Less commonly, it involves the other flexural areas, umbilicus, submammary region, knuckles, elbows, and, in extreme cases, the entire skin. The severity of AN correlates well with the degree of insulin responses to IR. We find AN to precede IR documentable by OGTT or IVGTT. However, AN also persists into the decompensated phase of IR where insulin levels may be normal or low. Nearly 40% of Native American teenagers have AN, as do 13% of African American, 6% of Hispanic, less than 1% of white and non-Hispanic children, aged 10–19 yr. In Caucasian patients, the acanthosis often appears a light yellow/gray color, emphasizing that the lesion represents a thickening of the stratum corneum that becomes pigmented in a racially dependent manner. Both insulin and IGF-I receptors have been identified in cultured human keratinocytes. High levels of insulin can activate both receptors (91). Additionally, TNF-α and IFNγ cytokines that are often elevated in obesity, can induce up-regulation of PPARβ/δ and thereby keratinocyte proliferation (92, 93).

Hyperandrogenism and reproductive abnormalities

IR can present with overt virilization or hirsutism, menstrual irregularity, persistent acne, scalp hair loss, hyperhydrosis, infertility, or precocious adrenarche in childhood. Menstrual irregularity and evidence of hyperandrogenism, whether clinical (hirsutism, acne, or male pattern balding) and/or biochemical (high serum androgen concentrations) are associated with the PCOS. Hyperinsulinemia potentates ovarian hyperandrogenism by enhancing pituitary LH secretion, potentiating ovarian 17-hydroxylase and 17,20-lyase activities, and suppressing blood SHBG and CBG level capacities and inhibits both estradiol- and T_4-stimulated SHBG production (94). SHBG levels in the circulation are characteristically low, resulting in increased free and bioactive testosterone. Reducing IR by the administration of metformin, PPARγ agonists, D-chiro-inositol, or leptin lowers serum free testosterone concentrations, reduces cytochrome P450c17 (17-hydroxylase) activity, and normalizes SHBG levels, resulting in slowed bone maturation and adrenarche (94).

Pseudoacromegaly. Linear and acral growth is usually accelerated in IRS and may present as pseudoacromegaly. Hyperinsulinemia promotes linear growth by activating skeletal IGF-I receptors, whereas low levels of IGFBPs can promote IGF-I action by allowing it to be freely and metabolically available. Increased IGF-I/IGFBP-1 ratios are postulated to result in the development of AN and ovarian hyperplasia. Increased aromatization of androgens to estrogens secondary to obesity increases the propensity to adipo/gynecomastia in adolescent boys and enhances GH production (95). Estrogens affect longitudinal bone growth through their action on endochondral bone formation (96). Ghrelin is known to stimulate GH secretion, and in obesity ghrelin levels are decreased (97). However, Korbonits *et al.* (98) recently identified polymorphism in the ghrelin gene of 14 children who were tall and obese, suggesting a role of ghrelin in stature and

BMI. MC4R gene mutations are present in up to 5.8% of obese children who are tall (>2 SD above the mean for age) (99). Direct action of leptin on bone growth can predispose to pseudoacromegaly (100). Pseudoacromegaly is seen in the face of low plasma GH levels secretion typical for obesity. Leptin decreases GHRH receptor gene transcription, thereby reducing GH levels and reduces responsiveness to GHRH (101).

Other. Additional complications include focal (IgA type) segmental glomerulosclerosis, uric acid elevation, cholelilthiasis, pseudotumor cerebri, Blount's disease, slipped capital femoral epiphysis, and psychological problems.

Treatments

Decompensated and/or compensated patients. In children, IR is usually well compensated by hyperinsulinemia, whereas we find progressive failure of compensation through puberty with rising glucose and triglyceride levels. Weyer *et al.* (102) followed 48 Pima Indians, with normal glucose tolerance for 5 yr, and 17 progressed from normal glucose tolerance through IGT to diabetes. In these progressors, insulin secretion declined by 78%, whereas insulin sensitivity declined by 14%. In the 31 individuals who did not develop diabetes, a similar 11% decrease in insulin sensitivity was associated with a 30% increase in insulin secretion rather than a decrease. The latter 31 individuals had compensated IR. Compensated hyperinsulinism, however, can lead to numerous complications from fatty liver and atherosclerosis to increased cancer risk. It is thus increasingly obvious that this sequence of events will be most easily interrupted at the earliest phases of life, during childhood. The child with IRS should be aggressively treated by involvement in an exercise program, such as walking or swimming for 30–40 min most days of the week, because exercise provokes glucose entry into muscle without the involvement of insulin. We use pedometers as an adjunct to monitor this. Calorie and especially carbohydrate restriction is the key to reduce weight. However, where there is also an increased level of triglycerides, restriction of animal fats should be imposed. Fibrates may be required, especially when TG levels exceed 500 mg/dl, at which point acute pancreatitis and gall bladder disease become real risks. In this regard, behavioral therapy and metformin have been proven safe and effective in improving insulin sensitivity in pediatric patients (13–15). Laparoscopic surgery as well has been shown to be effective in decreasing weight, dyslipidemia, and IR in adults (103).

Behavior modification. Family-based behavioral interventions for obese children are considered safe and useful treatments for pediatric obesity. These interventions have been associated with reductions in total cholesterol, increases in HDL cholesterol, reductions in IR, and return of ovulatory cycles (104).

Metformin is approved for the treatment of type 2 diabetes in children, but is also the drug of choice for IRS. Some have suggested that it is the gastrointestinal side-effects of the drug that accounts for much of its action. However, the drug is effective in type 2 diabetes without weight loss, being found to reduce hepatic glucose output in particular. Metformin has various mechanisms of action in IR. It enhances insulin binding to insulin receptor in case of its down-regulation by insulin receptor autoantibodies (105, 106), and it otherwise increases binding of insulin to its receptor, with augmented phosphorylation and tyrosine kinase activity of the receptor (107). It is effective even in cases of insulin receptor mutations (108). It increases peripheral utilization of glucose though potentiating the phosphoinositol 3-kinase after engagement of the insulin receptor, increasing translocation of the glucose transporters GLUT1 and GLUT4 isoforms to cell membrane in different tissues (107, 109–112); increases the activity of adenosine monophosphate kinase in muscle and liver; and reduces cytochrome P450c17 activity (113). It is considered safe and effective in pregnant women to decrease extreme hyperandrogenemia (114, 115). It increases IGFBP-1 (116); decreases endothelin-1, a marker of vasculopathy; and decreases hepatic glucose output. Metformin down-regulates TNFα expression and uncoupling protein-2 mRNA concentrations in liver, thus decreasing hepatic lipid biosynthesis (69). Metformin is safe for the treatment of IRS in pediatric patients (13–15, 117). Our experience in treating obese children and adolescents with IRS or PCOS with metformin is likewise very positive. We treated 16 females, 15–28 yr of age, who had IR and hyperandrogenism with metformin (850 mg, three times daily) for a period of 8 months to 1 yr. Insulin sensitivity, area under the curve for insulin, SHBG, testosterone and androsterone levels, and levels of triglycerides improved significantly (118). When gradually increased doses were given to minimize gastrointestinal side-effects, this was a safe and affective agent.

The PPARγ agonists are a group of ligand-activated transcription factors that govern energy metabolism, cell proliferation, and inflammation (119). PPARγ agonists are effective at insulin sensitization, but are less useful in supporting weight loss. The PPARγ isotype is mainly expressed in adipose tissue, where it stimulates adipogenesis and lipogenesis. PPARγ agonists have been shown to decrease inflammatory proteins and adhesion molecules, decrease cytokine production, improve lipid oxidation, reduce FFA secretion from adipocytes, decrease 11βHSD1, reduce intramyocellular lipids, and reduce muscle IR (120); decrease PAI-1 expression in endothelial cells (121); decrease testosterone levels in IR females (122); and markedly induce adipocyte glycerol kinase gene expression. By inducing glycerol kinase, thiazolidinediones markedly stimulate glycerol incorporation into triglycerides and reduce FFA secretion from adipocytes (123).

Lipid-lowering agents. Fibrates lower triglyceride levels, as mediated through the PPARα transcription factor, mainly in liver, where it has an important role in FA oxidation, gluconeogenesis, and amino acid metabolism. Pretreatment of endothelial cells with a PPARα agonist (fenofibrate) reduced markers of inflammation such as vascular cell adhesion molecule-1 expression, CRP, fibrinogen, PAI-1, and IL-6. In cases of combined triglyceride-LDL cholesterol elevations, some combinations of fibrates and statins have been reported to induce serious rhadomyelysis. The use of different combinations or of a cholesterol uptake inhibitor such as zetia may be indicated.

Statins inhibit 3-hydroxy-3-methylglutaryl-CoA reductase, the rate-limiting enzyme in the mevalonate pathway through which cells synthesize cholesterol. To compensate for decreased synthesis and to maintain cholesterol homeostasis, cells, particularly hepatocytes, increase the expression of LDL receptors, which increases the uptake of plasma LDL, the main carrier of extracellular cholesterol, resulting in lower plasma LDL concentrations. Decreased plasma LDL levels reduce the progression of atherosclerosis and may even lead to the regression of preexisting atherosclerotic lesions. Statins have important immunomodulatory effects as well and are able to decrease the recruitment of monocytes and T cells into the arterial wall and inhibit T cell activation and proliferation *in vitro* (124).

Low doses of aspirin inactivate the enzyme cyclooxygenase, which catalyzes the conversion of arachidonic acid to prostaglandins G_2 and H_2. These prostaglandins are precursors of thromboxane, a potent platelet proaggregant and vasoconstrictor. Low doses of enteric coated aspirin (81 mg/d) are preferred. Aspirin should be used in diabetic individuals over the age of 30 yr who are at high risk for cardiovascular events and may have a place in dyslipidemic children with IRS prone to pancreatitis.

Surgery. Restrictive surgical procedures based on an adjustable silicone band placement around a stomach fundal pouch can create a functional partition of the stomach. This has been shown to be successful in adults. Whereas restrictive procedures are effective in reducing intake of solid foods, high consumption of more liquid high calorie foods may prevent weight loss (125). Intestinal bypass surgery in children should probably only be used only in cases of potentially life-threatening complications such as sleep apnea.

Summary

The U.S. obesity epidemic continues unabated, with ever increasing numbers of the nation's obese children becoming irreversibly obese adults, replete with the IRS in all of its burgeoning complications, notably progressive atherosclerotic disease, hypertension, and type 2 diabetes. The only rational long-term solution must lie in the realization that the epidemic has its genesis in childhood, and thus, the interventional focus should be placed in early life. IRS requires mass screening for physical and laboratory markers, whereas long-term therapeutic trials that can show the long-term benefits of aggressive prevention and intervention, initially targeting highly prone ethnicities, are urgently needed. New findings encourage the development of methods to block ghrelin or promote neuropeptide YY and may provide novel new therapies.

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References

1. **Reaven GM** 1988 Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37:1595–1607
2. **National Center for Health Statistics** 1999 Health E-stats 1999. Prevalence of overweight and obesity among adults: United States. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/obese/obse99.htm
3. **Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP** 2001 The continuing epidemics of obesity and diabetes in the United States. JAMA 286:1195–1200
4. **Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ** 2003 Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. N Engl J Med 348:1625–1638
5. **National Center for Health Statistics** 1999 Health E-stats 1999. Prevalence of overweight among children and adolescents: United States. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/overwght99.htm
6. **Willett WC, Stampfer M, Manson J, Van Itallie T** 1991 New weight guidelines for Americans: justified or injudicious? Am J Clin Nutr 53:1102–1103
7. **Andres R, Muller DC, Sorkin JD** 1993 Long-term effects of change in body weight on all-cause mortality. A review. Ann Intern Med 119:737–743
8. **Long SD, O'Brien K, MacDonald KG, Leggett-Frazier N, Swanson MS, Pories WJ, Caro JF** 1994 Weight loss in severely obese subjects prevents the progression of impaired glucose tolerance to type II diabetes. A longitudinal interventional study. Diabetes Care 17:372–375
9. **Benjamin SM, Valdez R, Geiss LS, Rolka DB, Narayan KM** 2003 Estimated number of adults with prediabetes in the U.S. in 2000: opportunities for prevention. Diabetes Care 26:645–649
10. **Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi 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
11. **DPP Research Group** 2002 Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393–403
12. **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 β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 51:2796–2803
13. **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
14. **Morrison JA, Cottingham EM, Barton BA** 2002 Metformin for weight loss in pediatric patients taking psychotropic drugs. Am J Psychiatry 159:655–657
15. **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
16. **Reaven GM, Chen YD, Hollenbeck CB, Sheu WH, Ostrega D, Polonsky KS** 1993 Plasma insulin, C-peptide, and proinsulin concentrations in obese and nonobese individuals with varying degrees of glucose tolerance. J Clin Endocrinol Metab 76:44–48
17. **Hanson RL, Pratley RE, Bogardus C, Narayan KM, Roumain JM, Imperatore G, Fagot-Campagna A, Pettitt DJ, Bennett PH, Knowler WC** 2000 Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. Am J Epidemiol 15:190–198
18. **Young-Hyman D, Schlundt DG, Herman L, De Luca F, Counts D** 2001 Evaluation of the insulin resistance syndrome in 5- to 10-year-old overweight/obese African-American children. Diabetes Care 24:1359–1364
19. **Gutt M, Davis CL, Spitzer SB, Llabre MM, Kumar M, Czarnecki EM, Schneiderman N, Skyler JS, Marks JB** 2000 Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. Diabetes Res Clin Pract 47:177–184
20. **Reaven GM, Brand RJ, Chen YD, Mathur AK, Goldfine I** 1993 Insulin resistance and insulin secretion are determinants of oral glucose tolerance in normal individuals. Diabetes 42:1324–1332
21. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC** 1985 Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
22. **Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ** 2000 Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 85:2402–2410
23. **Belfiore F, Iannello S, Volpicelli G** 1998 Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. Mol Genet Metab 63:134–141
24. **Cederholm J, Wibell L** 1990 Insulin release and peripheral sensitivity at the oral glucose tolerance test. Diabetes Res Clin Pract 10:167–175
25. **Matsuda M, De Fronzo RA** 1999 Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22:1462–1470
26. **Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Jarvinen H, Van**

Haeften T, Renn W, Gerich J 2000 Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care 23:295–301
27. **Soonthornpun S, Setasuban W, Thamprasit A, Chayanunnukul W, Rattarasarn C, Geater A** 2003 Novel insulin sensitivity index derived from oral glucose tolerance test. J Clin Endocrinol Metab 88:1019–1023
28. **McAuley KA WS, Mann JI, Walker RJ, Ledwis-Barned NJ, Temple LA, Duncan AS** 2001 Diagnosing insulin resistance in general population. Diabetes Care 24:460–464
29. **Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ** 2001 A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes Care 24:539–548
30. **Bergman RN, Prager R, Volund A, Olefsky JM** 1987 Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest 79:790–800
31. **Gower BA, Granger WM, Franklin F, Shewchuk RM, Goran MI** 2002 Contribution of insulin secretion and clearance to glucose-induced insulin concentration in African-American and caucasian children. J Clin Endocrinol Metab 87:2218–2224
32. **Sunehag AL, Treuth MS, Toffolo G, Butte NF, Cobelli C, Bier DM, Haymond MW** 2001 Glucose production, gluconeogenesis, and insulin sensitivity in children and adolescents: an evaluation of their reproducibility. Pediatr Res 50:115–123
33. **Cutfield WS, Bergman RN, Menon RK, Sperling MA** 1990 The modified minimal model: application to measurement of insulin sensitivity in children. J Clin Endocrinol Metab 70:1644–1650
34. **Rosner B, Prineas R, Loggie J, Daniels SR** 1998 Percentiles for body mass index in US children 5 to 17 years of age. J Pediatr 132:211–222
35. **Farooqi IS, Keogh JM, Kamath S, Jones S, Gibson WT, Trussell R, Jebb SA, Lip GY, O'Rahilly S** 2001 Partial leptin deficiency and human adiposity. Nature 414:34–35
36. **Croft JB, Morrell D, Chase CL, Swift M** 1995 Obesity in heterozygous carriers of the gene for the Bardet-Biedl syndrome. Am J Med Genet 55:12–15
37. **Dubern B, Clement K, Pelloux V, Froguel P, Girardet JP, Guy-Grand B, Tounian P** 2001 Mutational analysis of melanocortin-4 receptor, agouti-related protein, and α-melanocyte-stimulating hormone genes in severely obese children. J Pediatr 139:204–209
38. **Barker DJ** 2000 In utero programming of cardiovascular disease. Theriogenology 53:555–574
39. **Selak MA, Storey BT, Peterside I, Simmons RA** 2003 Impaired oxidative phosphorylation in skeletal muscle of intrauterine growth-retarded rats. Am J Physiol 285:E130–E137
40. **Wilkin TJ, Metcalf BS, Murphy MJ, Kirkby J, Jeffery AN, Voss LD** 2002 The relative contributions of birth weight, weight change, and current weight to insulin resistance in contemporary 5-year-olds: the EarlyBird Study. Diabetes 51:3468–3472
41. **Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH, Knowler WC** 1999 Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. Diabetes Care 22:944–950
42. **Murtaugh MA, Jacobs DR, Moran A, Steinberger J, Sinaiko AR** 2003 Relation of birth weight to fasting insulin, insulin resistance, and body size in adolescence. Diabetes Care 26:187–192
43. **Dabelea D, Knowler WC, Pettitt DJ** 2000 Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. J Matern Fetal Med 9:83–88
44. **Sobngwi E, Boudou P, Mauvais-Jarvis F, Leblanc H, Velho G, Vexiau P, Porcher R, Hadjadj S, Pratley R, Tataranni PA, Calvo F, Gautier JF** 2003 Effect of a diabetic environment in utero on predisposition to type 2 diabetes. Lancet 361:1861–1865
45. **Lustig RH** 2001 The neuroendocrinology of childhood obesity. Pediatr Clin North Am 48:909–930
46. **Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S** 2003 Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med 348:1085–1095
47. **McGarry JD, Dobbins RL** 1999 Fatty acids, lipotoxicity and insulin secretion. Diabetologia 42:128–138
48. **Nathan DM** 1998 Some answers, more controversy, from UKPDS. United Kingdom Prospective Diabetes Study. Lancet 352:832–833
49. **Koyama K, Chen G, Lee Y, Unger RH** 1997 Tissue triglycerides, insulin resistance, and insulin production: implications for hyperinsulinemia of obesity. Am J Physiol 273:E708–E713
50. **Daniel S, Noda M, Straub SG, Sharp GW** 1999 Identification of the docked granule pool responsible for the first phase of glucose-stimulated insulin secretion. Diabetes 48:1686–1690
51. **Hanley AJ, D'Agostino R, Wagenknecht LE, Saad MF, Savage PJ, Bergman R, Haffner SM** 2002 Increased proinsulin levels and decreased acute insulin response independently predict the incidence of type 2 diabetes in the insulin resistance atherosclerosis study. Diabetes 51:1263–1270
52. **Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC** 1998 UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. Diabet Med 15:297–303
53. **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
54. **Goldfine AB, Bouche C, Parker RA, Kim C, Kerivan A, Soeldner JS, Martin BC, Warram JH, Kahn CR** 2003 Insulin resistance is a poor predictor of type 2 diabetes in individuals with no family history of disease. Proc Natl Acad Sci USA 100:2724–2729
55. **Elbein SC, Hasstedt SJ, Wegner K, Kahn SE** 1999 Heritability of pancreatic β-cell function among nondiabetic members of Caucasian familial type 2 diabetic kindreds. J Clin Endocrinol Metab 84:1398–1403
56. **St-Pierre J, Lemieux I, Miller-Felix I, Prud'homme D, Bergeron J, Gaudet D, Nadeau A, Despres JP, Vohl MC** 2002 Visceral obesity and hyperinsulinemia modulate the impact of the microsomal triglyceride transfer protein-493G/T polymorphism on plasma lipoprotein levels in men. Atherosclerosis 160:317–324
57. **Barzilai N, She L, Liu BQ, Vuguin P, Cohen P, Wang J, Rossetti L** 1999 Surgical removal of visceral fat reverses hepatic insulin resistance. Diabetes 48:94–98
58. **Montague CT, O'Rahilly S** 2000 The perils of portliness: causes and consequences of visceral adiposity. Diabetes 49:883–888
59. **Bujalska IJ, Kumar S, Stewart PM** 1997 Does central obesity reflect "Cushing's disease of the omentum?" Lancet 349:1210–1213
60. **Stewart PM, Toogood AA, Tomlinson JW** 2001 Growth hormone, insulin-like growth factor-I and the cortisol-cortisone shuttle. Horm Res 56:1–6
61. **Walker BR, Best R** 1995 Clinical investigation of 11β-hydroxysteroid dehydrogenase. Endocr Res 21:379–387
62. **Kotelevtsev Y, Holmes MC, Burchell A, Houston PM, Schmoll D, Jamieson P, Best R, Brown R, Edwards CR, Seckl JR, Mullins JJ** 1997 11β-Hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress. Proc Natl Acad Sci USA 94:14924–14929
63. **Tominaga K, Kurata JH, Chen YK, Fujimoto E, Miyagawa S, Abe I, Kusano Y** 1995 Prevalence of fatty liver in Japanese children and relationship to obesity. An epidemiological ultrasonographic survey. Dig Dis Sci 40:2002–2009
64. **Oshibuchi M, Nishi F, Sato M, Ohtake H, Okuda K** 1991 Frequency of abnormalities detected by abdominal ultrasound among Japanese adults. J Gastroenterol Hepatol 6:165–168
65. **Silverman JF, Pories WJ, Caro JF** 1989 Liver pathology in diabetes mellitus and morbid obesity. Clinical, pathological, and biochemical considerations. Pathol Annu 24:275–302
66. **Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N** 2001 Metformin in non-alcoholic steatohepatitis. Lancet 358:893–894
67. **Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, Cline GW, De Paoli AM, Taylor SI, Gorden P, Shulman GI** 2002 Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest 109:1345–1350
68. **Lavine JE** 2000 Vitamin E treatment of nonalcoholic steatohepatitis in children: a pilot study. J Pediatr 136:734–738
69. **Lin HZ, Yang SQ, Chuckaree C, Kuhajda F, Ronnet G, Diehl AM** 2000 Metformin reverses fatty liver disease in obese, leptin-deficient mice. Nat Med 6:998–1003
70. **Schwimmer JB MM, Deutsch R, Lavine JE** 2003 Metformin as a treatment for non-diabetic NASH. J Pediatr Gastroenterol 37:342
71. **Despres JP, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ** 1996 Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 334:952–957
72. **Despres JP, Lamarche B, Mauriege P, Cantin B, Lupien PJ, Dagenais GR** 1996 Risk factors for ischaemic heart disease: is it time to measure insulin? Eur Heart J 17:1453–1454 (Editorial)
73. **Davis PH, Dawson JD, Riley WA, Lauer RM** 2001 Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. Circulation 104:2815–2819
74. **Berenson GS** 2002 Childhood risk factors predict adult risk associated with subclinical cardiovascular disease. The Bogalusa Heart Study. Am J Cardiol 90:3L–7L
75. **Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP, Herderick EE, Cornhill JF** 1999 Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. JAMA 281:727–735
76. **Sorof JM, Alexandrov AV, Cardwell G, Portman RJ** 2003 Carotid artery intimal-medial thickness and left ventricular hypertrophy in children with elevated blood pressure. Pediatrics 111:61–66
77. **Paradisi G, Steinberg HO, Shepard MK, Hook G, Baron AD** 2003 Troglitazone therapy improves endothelial function to near normal levels in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88:576–580
78. **Fernandez-Real JM, Pugeat M, Grasa M, Broch M, Vendrell J, Brun J, Ricart W** 2002 Serum corticosteroid-binding globulin concentration and insulin resistance syndrome: a population study. J Clin Endocrinol Metab 87:4686–4690
79. **Lind L, Hanni A, Lithell H, Hvarfner A, Sorensen OH, Ljunghall S** 1995 Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens 8:894–901
80. **Pratley RE, Thompson DB, Prochazka M, Baier L, Mott D, Ravussin E, Sakul H, Ehm MG, Burns DK, Foroud T, Garvey WT, Hanson RL, Knowler**

WC, Bennett PH, Bogardus C 1998 An autosomal genomic scan for loci linked to prediabetic phenotypes in Pima Indians. J Clin Invest 101:1757–1764
81. **Halhali A, Tovar AR, Torres N, Bourges H, Garabedian M, Larrea F** 2000 Preeclampsia is associated with low circulating levels of insulin-like growth factor I and 1,25-dihydroxyvitamin D in maternal and umbilical cord compartments. J Clin Endocrinol Metab 85:1828–1833
82. **Ford ES, Galuska DA, Gillespie C, Will JC, Giles WH, Dietz WH** 2001 C-Reactive protein and body mass index in children: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Pediatr 138:486–492
83. **Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB** 1999 Elevated C-reactive protein levels in overweight and obese adults. JAMA 282:2131–2135
84. **Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, Tracy RP** 2001 The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. Diabetes 50:2384–2389
85. **Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI** 1998 Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 394:897–901
86. **Matarese G, La Cava A, Sanna V, Lord GM, Lechler RI, Fontana S, Zappacosta S** 2002 Balancing susceptibility to infection and autoimmunity: a role for leptin? Trends Immunol 23:182–187
87. **Ozata M, Ozdemir IC, Licinio J** 1999 Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. J Clin Endocrinol Metab 84: 3686–3695
88. **Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD** 2001 Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. Am J Respir Crit Care Med 163: 1344–1349
89. **Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P** 2000 Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. Br Med J 320:827–832
90. **Phipps PR, Starritt E, Caterson I, Grunstein RR** 2002 Association of serum leptin with hypoventilation in human obesity. Thorax 57:75–76
91. **Mantzoros CS, Flier JS** 1995 Insulin resistance: the clinical spectrum. Adv Endocrinol Metab 6:193–232
92. **Tan NS, Michalik L, Noy N, Yasmin R, Pacot C, Heim M, Fluhmann B, Desvergne B, Wahli W** 2001 Critical roles of PPARβ/δ in keratinocyte response to inflammation. Genes Dev 15:3263–3277
93. **Michalik L, Desvergne B, Tan NS, Basu-Modak S, Escher P, Rieusset J, Peters JM, Kaya G, Gonzalez FJ, Zakany J, Metzger D, Chambon P, Duboule D, Wahli W** 2001 Impaired skin wound healing in peroxisome proliferator-activated receptor (PPAR)α and PPARβ mutant mice. J Cell Biol 154:799–814
94. **Dunaif A** 1999 Insulin action in the polycystic ovary syndrome. Endocrinol Metab Clin North Am 28:341–359
95. **Eakman GD, Dallas JS, Ponder SW, Keenan BS** 1996 The effects of testosterone and dihydrotestosterone on hypothalamic regulation of growth hormone secretion. J Clin Endocrinol Metab 81:1217–1223
96. **Nilsson LO, Boman A, Savendahl L, Grigelioniene G, Ohlsson C, Ritzen EM, Wroblewski J** 1999 Demonstration of estrogen receptor-β immunoreactivity in human growth plate cartilage. J Clin Endocrinol Metab 84:370–373
97. **Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, Grove KL, Strasburger CJ, Bidlingmaier M, Esterman M, Heiman ML, Garcia-Segura LM, Nillni EA, Mendez P, Low MJ, Sotonyi P, Friedman JM, Liu H, Pinto S, Colmers WF, Cone RD, Horvath TL** 2003 The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 37:649–661
98. **Korbonits M, Gueorguiev M, O'Grady E, Lecoeur C, Swan DC, Mein CA, Weill J, Grossman AB, Froguel P** 2002 A variation in the ghrelin gene increases weight and decreases insulin secretion in tall, obese children. J Clin Endocrinol Metab 87:4005–4008
99. **Farooque SP, Lee TH** 2003 Exercise-induced asthma: a review. Practitioner 247:279–288
100. **Steppan CM, Crawford DT, Chidsey-Frink KL, Ke H, Swick AG** 2000 Leptin is a potent stimulator of bone growth in *ob/ob* mice. Regul Pept 92:73–78
101. **Chen C, Roh SG, Nie GY, Loneragan K, Xu RW, Ruan M, Clarke LJ, Goding JW, Gertler A** 2001 The in vitro effect of leptin on growth hormone secretion from primary cultured ovine somatotrophs. Endocrine 14:73–78
102. **Weyer C, Bogardus C, Mott DM, Pratley RE** 1999 The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 104:787–794
103. **Pontiroli AE, Pizzocri P, Librenti MC, Vedani P, Marchi M, Cucchi E, Orena C, Paganelli M, Giacomelli M, Ferla G, Folli F** 2002 Laparoscopic adjustable gastric banding for the treatment of morbid (grade 3) obesity and its metabolic complications: a three-year study. J Clin Endocrinol Metab 87:3555–3561
104. **Pasquali R, Antenucci D, Casimirri F, Venturoli S, Paradisi R, Fabbri R, Balestra V, Melchionda N, Barbara L** 1989 Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. J Clin Endocrinol Metab 68:173–179
105. **Cigolini M, Zancanaro C, Benati D, Cavallo E, Bosello O, Smith U** 1987 Metformin enhances insulin binding to "in vitro" down regulated human fat cells. Diabetes Metab 13:20–22
106. **Di Paolo S** 1992 Metformin ameliorates extreme insulin resistance in a patient with anti-insulin receptor antibodies: description of insulin receptor and postreceptor effects in vivo and in vitro. Acta Endocrinol (Copenh) 126:117–123
107. **Matthaei S, Hamann A, Klein HH, Benecke H, Kreymann G, Flier JS, Greten H** 1991 Association of metformin's effect to increase insulin-stimulated glucose transport with potentiation of insulin-induced translocation of glucose transporters from intracellular pool to plasma membrane in rat adipocytes. Diabetes 40:850–857
108. **Rique S, Ibanez L, Marcos MV, Carrascosa A, Potau N** 2000 Effects of metformin on androgens and insulin concentrations in type A insulin resistance syndrome. Diabetologia 43:385–386
109. **Hundal HS, Ramlal T, Reyes R, Leiter LA, Klip A** 1992 Cellular mechanism of metformin action involves glucose transporter translocation from an intracellular pool to the plasma membrane in L6 muscle cells. Endocrinology 131:1165–1173
110. **Hamann A, Benecke H, Greten H, Matthaei S** 1993 Metformin increases glucose transporter protein and gene expression in human fibroblasts. Biochem Biophys Res Commun 196:382–387
111. **Matthaei S, Reibold JP, Hamann A, Benecke H, Haring HU, Greten H, Klein HH** 1993 In vivo metformin treatment ameliorates insulin resistance: evidence for potentiation of insulin-induced translocation and increased functional activity of glucose transporters in obese (*fa/fa*) Zucker rat adipocytes. Endocrinology 133:304–311
112. **Matthaei S, Hamann A, Klein HH, Benecke H, Kreymann G, Flier JS, Greten H** 1992 Evidence that metformin increases insulin-stimulated glucose transport by potentiating insulin-induced translocation of glucose transporters from an intracellular pool to the cell surface in rat adipocytes. Horm Metab Res 26(Suppl):34–41
113. **Nestler JE, Jakubowicz DJ** 1996 Decreases in ovarian cytochrome P450c17α activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. N Engl J Med 335:617–623
114. **Sarlis NJ, Weil SJ, Nelson LM** 1999 Administration of metformin to a diabetic woman with extreme hyperandrogenemia of nontumoral origin: management of infertility and prevention of inadvertent masculinization of a female fetus. J Clin Endocrinol Metab 84:1510–1512
115. **Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE** 2002 Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clin Endocrinol Metab 87:524–529
116. **De Leo V, La Marca A, Orvieto R, Morgante G** 2000 Effect of metformin on insulin-like growth factor (IGF) I and IGF-binding protein I in polycystic ovary syndrome. J Clin Endocrinol Metab 85:1598–1600
117. **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
118. **Ten S NI, Vogiatzi M, New M, Maclaren N,** Adrenal suppressibility by dexamethasone in women with polycystic ovarian syndrome (PCOS) determined by degree of insulin resistance. Program of the 85th Annual Meeting of The Endocrine Society, Philadelphia, PA, 2003, p 351 (Abstract P2-187)
119. **Kersten S** 2002 Peroxisome proliferator activated receptors and obesity. Eur J Pharmacol 440:223–234
120. **Aljada A, Ghanim H, Friedman J, Garg R, Mohanty P, Dandona P** 2001 Troglitazone reduces the expression of PPARγ while stimulating that of PPARα in mononuclear cells in obese subjects. J Clin Endocrinol Metab 86:3130–3133
121. **Marx N, Bourcier T, Sukhova GK, Libby P, Plutzky J** 1999 PPARγ activation in human endothelial cells increases plasminogen activator inhibitor type-1 expression: PPARγ as a potential mediator in vascular disease. Arterioscler Thromb Vasc Biol 19:546–551
122. **Dunaif A, Scott D, Finegood D, Quintana B, Whitcomb R** 1996 The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. J Clin Endocrinol Metab 81:3299–3306
123. **Guan HP, Li Y, Jensen MV, Newgard CB, Steppan CM, Lazar MA** 2002 A futile metabolic cycle activated in adipocytes by antidiabetic agents. Nat Med 8:1122–1128
124. **Palinski W, Tsimikas S** 2002 Immunomodulatory effects of statins: mechanisms and potential impact on arteriosclerosis. J Am Soc Nephrol 13:1673–1681
125. **Mason EE** 1992 Gastric surgery for morbid obesity. Surg Clin North Am 72:501–513

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