American Association of Clinical Endocrinologists (AACE) Consensus Conference on the Insulin Resistance Syndrome

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This is the first of two articles on the American Association of Clinical Endocrinologists (AACE) consensus conference on the insulin resistance syndrome (IRS), which was held in Washington, DC, on 25–26 August 2002. (See http://www.aace.com/pub/irscc/findings.php for summary.)

Woody Kessel (Washington, DC), the Deputy Surgeon General, introduced the conference, by discussing "leading health indicators," including physical activity, reduction of overeating, drug abuse, attention to sexual health, mental health, environmental health, injury prevention, and provision of access to care. The lifestyle factors underlying the metabolic syndrome are, he pointed out, highly prominent factors on this list.

Earl S. Ford (Atlanta, GA) discussed public health aspects of the IRS. He characterized "public health" as engaging not only in the assessment and in monitoring of the health of communities, but also in the formulation of public policies and the assurance of access to health care. Addressing the question of whether the IRS is a public health problem, he pointed to its high prevalence and its association with increased morbidity and mortality. Persons with the IRS show higher all-cause mortality, cardiovascular disease (CVD), diabetes, polycystic ovary syndrome (PCOS), and nonalcoholic steatohepatitis (NASH). The syndrome is likely to be very costly, with estimates that the related condition, obesity, leads to health costs in the U.S. of $100 billion yearly. Ford cited proposed AACE criteria defining persons as having the IRS if they do not have diabetes and if they meet two or more of the criteria of triglyceride ≥150 mg/dl, HDL <40 or 50 in men or women, respectively, blood pressure ≥130/85 mmHg or current use of antihypertensive medications, and 2-h glucose 140–199 mg/dl (with postload rather than fasting glucose chosen as being of greater sensitivity). He applied these criteria to data from the third National Health and Nutrition Evaluation Survey (NHANES III) carried out in 1988–1994, using a stratified representative sample of the U.S. population, including 20,050 persons age 17 years and over, with glucose tolerance testing performed in 3,302 persons age 40–74 years. The triglyceride criterion was positive in 34%, low HDL was present in 37%, 40% were hypertensive, and 24% met the glucose tolerance test (GTT) criterion. Among men and women, 25 and 34%, respectively, met none of the criteria and 29 and 30% had one abnormality, so that 42% were classified as having the IRS. Ford noted that with fasting glucose 110–125 mg/dl rather than the 2-h glucose criterion, only 32% of the population would be classified as having the IRS; with the more stringent Adult Treatment Panel (ATP) III criteria of three or more metabolic abnormalities, only 26% of the population was classified as such. There appeared to be no difference in frequency of the IRS when the GTT was performed in the morning or later in the day, as long as the individual had been fasting >8 h. The IRS was present in 33, 40, and 50% of persons at ages 40, 50, and 60 years; in 52% of Mexican Americans; in 36% of African Americans; and in 40% of Caucasians.

Ford suggested that there is need for ongoing refinement of the IRS definition, and that surveillance may prove challenging, with need to characterize the public health burden of the syndrome, particularly addressing the question of whether the IRS implies risks higher than those of the individual components. The use of administrative databases with the new ICD-9 code of 277.7 may be important in future studies. Whether screening, specific treatment, and prevention will be recommended is an important issue; physical activity, weight control, and pharmaceutical treatment are potential approaches. The Centers for Disease Control Behavioral Risk Factor Surveillance System data recorded annually from 1986 to 1998 suggests that approximately one-quarter of adults regularly participate in physical activity, but that 30% of persons are entirely inactive. These surveys also show that a "wave of obesity [has] washed across the U.S. over the past 15 years."

Discussion of the presentation in-

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Abbreviations: ADA, American Diabetes Association; AII, angiotensin II; AACE, American Association of Clinical Endocrinologists; ADMA, asymmetric dimethyl arginine; AP, activator protein; ATP, Adult Treatment Panel; CHD, congestive heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; Egr, early growth factor; eNOS, endothelial NO synthase; FFA, free fatty acid; G6P, glucose-6-phosphate; ICAM, intercellular adhesion molecule; IGT, impaired glucose tolerance; IκB, inhibitor of NF-κB; IRS, insulin resistance syndrome; IRS-1, insulin receptor substrate-1; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NASH, nonalcoholic steatohepatitis; NE, norepinephrine; NHANES III, third National Health and Nutrition Evaluation Survey; NMR, nuclear magnetic resonance; NO, nitric oxide; PC-1, plasma cell membrane glycoprotein-1; PCOS, polycystic ovary syndrome; PDGF, platelet-derived growth factor; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphatidylinositol 3 kinase; ROS, reactive oxygen species; SNS, sympathetic nervous system; SSPG, steady-state plasma glucose; TF, tissue factor; VCAM, vascular cell adhesion molecule.

cluded the exclusion of obesity and, in particular, central obesity from the proposed criteria for the IRS. The use of two of four rather than three of five criteria (including obesity or increased waist circumference as a fifth possible defining condition) was thought by some to increase the prevalence excessively. Other participants suggested that one should include persons with diabetes as having the IRS. The feasibility of glucose tolerance testing in the diagnosis of IRS, particularly in primary care, was another topic addressed.

Peter W.F. Wilson (Boston, MA) discussed aspects of the IRS from the perspective of the Framingham Offspring Study. Comparing persons with and without diabetes, he showed that the patterns of lipid abnormality are identical to those in persons with and without the metabolic syndrome. Triglyceride, insulin, and HDL cholesterol appear to have "J-curves," with slow increase over the normal glucose tolerance quintiles followed by an abrupt increase in persons with impaired glucose tolerance (IGT) and then with type 2 diabetes. Using cluster analysis suggests that hypertension "is not part of the central core" (1). Across glucose tolerance quintiles and in IGT and diabetes, obesity increases progressively, while HbA_{1c} shows no increase below the level of diabetes. Analyzing these variables together for the 1,249 men in the study, Meigs showed that the relative risks (RRs) of CVD, congestive heart disease (CHD), and diabetes at 8 years of follow-up for persons having three or more of the metabolic factors were 2.42, 2.4, and 11.22 and that the "population attributable risks" ([prevalence · (RR − 1)]/[1 + prevalence · (RR − 1)]) were 16, 16, and 58%, with obesity appearing to explain the particularly increased diabetes risk. Similar patterns were seen for the 1,452 women in the study. He noted that of the ten different ways to get combinations of three of the five metabolic syndrome variants, "each variable contributes in a major way," so he stated that he thought the approach of simply counting the number of risk factors optimized the definition of the metabolic syndrome.

Gerald M. Reaven (Stanford, CA) presented an overview of abnormalities related to insulin resistance and compensatory hyperinsulinemia, asking first, what is meant by insulin resistance? Second, why is insulin resistance important? And, finally, how does insulin resistance lead to CVD? Suppressing endogenous insulin with somatostatin and infusing insulin and glucose at a constant rate leads persons to establish a steady-state plasma glucose (SSPG) concentration. Reaven proposed that the SSPG directly measures insulin-mediated glucose disposal by muscle, and showed the sixfold variation in SSPG from the lowest to the highest decile in the population. He noted that the fasting insulin is a much poorer discriminator than the SSPG and that, although there is correlation with obesity, BMI explains less than one-quarter of the variance in SSPG. There is a strong relationship between insulin sensitivity and physical fitness, although Reaven pointed out that "no one ever measures it." Maximal oxygen consumption ($V_{O_{2\ max}}$), an indicator of fitness, is as important as obesity in predicting insulin sensitivity. There is great ethnic variability, with South Asian and most other non-European groups being twice as insulin resistant as Caucasians. Reaven estimated, then, that approximately one-quarter of insulin resistance is due to obesity and one-quarter is due to inactivity, with the remaining half caused by genetic factors.

Reaven stated that adipose tissue is essentially as insulin resistant as muscle, with basal free fatty acid (FFA) levels strongly correlated with SSPG. Different tissues in a given individual can be either insulin resistant or insulin sensitive. Insulin resistance not usually present at the level of the kidney, explaining the increased renal insulin effect in persons with insulin resistance, leads to sodium and uric acid retention insulin. Similarly, insulin resistance in muscle need not limit the CNS effects of insulin, leading to increased sympathetic tone. Persons with insulin resistance whose insulin response is inadequate develop diabetes, but those with adequate insulin response still have demonstrable abnormalities. These include dyslipidemia, a hypercoagulable state with increased plasminogen activator inhibitor (PAI)-1 and fibrinogen, PCOS, hypertension and/or increased sympathetic nervous system tone, endothelial dysfunction, and hyperuricemia, as well as NASH and increased risk of malignancies of breast, colon, and prostate.

Using fasting insulin as a proxy measure of insulin resistance, Reaven reviewed data from a large surveyed population in Italy. The 6-year incidence of IGT and type 2 diabetes was eight times greater in the fourth quartile than the lower three quartiles of basal insulin. Similarly, hypertension developed in 22 vs. 12% and CVD developed in 8 vs. 2%, respectively. The strongest epidemiologic link of insulin resistance to CVD, Reaven stated, is the triglyceride level, although this may be a marker for abnormalities of HDL, small dense LDL, or postprandial lipids. Persons with normal blood pressure but high triglyceride or low HDL had increased risk, while those with hypertension but normal lipids had no increase in risk, further suggesting the importance of this factor. Similarly, cigarette use was associated with little increase in CVD in persons with normal lipids, but with marked increase in CVD in persons with dyslipidemia. The IRS is associated with dyslipidemia because of adipose insulin resistance leading to increased FFAs, while muscle insulin resistance leads to a feedback increase in insulin secretion, which in turn increases triglyceride secretion (as well as leading to NASH). Remnant lipoprotein cholesterol and, particularly, triglyceride levels are increased in persons with insulin resistance, and these abnormalities are present not only in the fasting state but throughout the day. Study of persons in the first, second, and third tertiles of SSPG matched for BMI, $V_{O_{2\ max}}$, body fat, and age revealed that only those in the highest tertile of insulin resistance had hypertriglyceridemia and low HDL cholesterol. Atherogenesis is initiated by mononuclear cell binding to the endothelium. Reaven showed data that insulin resistance correlates with mononuclear cell binding to cultured endothelium, modulated by increased levels of E selectin and intercellular and vascular cell adhesion molecules (ICAM and VCAM). Asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthase, shows strong correlation with the SSPG and also appears to be a risk factor for CVD (2).

Michael Stern (San Antonio, TX) discussed the genetics of the IRS, pointing out the intrinsic importance of this topic as well as its importance as an antecedent state that allows ascertainment of genes related to diabetes. Persons with two diabetic parents are an important group to study, with higher fasting insulin and insulin sum on GTT than in those with no diabetic parents (3) and with decrease in

total body glucose disposal because of decrease in nonoxidative glucose metabolism. (4). Based on formal measurement of heritability in large populations, including Pima Indians, the Finland-United States Investigation of Non-insulin-dependent diabetes mellitus (FUSION), the Insulin Resistance Atherosclerosis Study (IRAS), and the Utah and San Antonio studies, adjusted for age, sex, and body fat, the heritability of insulin sensitivity on euglycemic clamp and of 2-h insulin is 40–50%, although the heritability of the fasting insulin level is lower. Stern pointed out the need for caution in attributing family resemblance to genetic causes, as these findings can also be caused by shared environment; by maternal effects, such as low birth weight, which particularly occurs with cigarette and/or alcohol use during pregnancy; or by bottle feeding versus breast feeding, all of which may have profound influence on childhood and perhaps adult obesity. A number of syndromes of severe insulin resistance are noteworthy as being caused by genes that influence insulin action, particularly those affecting the insulin receptor. Stern addressed the question of whether these or other mutations responsible for some portion of the insulin resistance are seen commonly in the general population. Calpain 10 (5) shows a single nucleotide polymorphism at position 43. Persons with the GG and perhaps the GA rather than the AA genotype have reduced calpain 10 mRNA and insulin resistance (6). The Q-allele of plasma cell membrane glycoprotein-1 (PC-1) is associated with insulin resistance (7,8). There is also a haplotype in the 3′ untranslated region affecting mRNA stability, which may be associated with insulin resistance (9). This gene is involved in the degradation of the insulin receptor tyrosine kinase. Finally, persons with the II genotype of the D/I polymorphism of the angiotensin-converting enzyme (ACE) gene have lower insulin sensitivity (10).

Whole genome scans for multipoint linkage analysis have suggested different potential genetic associations of insulin resistance (e.g., very low potential for association of Calpain 10 or of the insulin receptor). On chromosome 6 close to the site of PC-1, there appears to be a strong association, explaining 44% of the variance in fasting insulin, as well as showing linkage with serum leptin and BMI (11). Associations may also be present for sites on chromosome 3, although this includes several hundred genes so that it will be difficult to "ferret out" a specific gene abnormality (12).

Gerald Shulman (New Haven, CT) discussed the molecular basis of the IRS. Years prior to the development of diabetes, there are defects in glucose uptake in skeletal muscle, which can be studied with ^{13}C nuclear magnetic resonance (NMR) spectrum analysis in measuring glycogen synthesis in skeletal muscle in humans. Comparing persons with type 2 diabetes and control subjects, during hyperinsulinemic-hyperglycemic clamp, the rate of glycogen synthesis is approximately half in the former group. Using indirect calorimetry, nonoxidative glucose metabolism is almost completely accounted for by glycogen synthesis, with oxidative glucose metabolism less affected in diabetes. Potential rate-controlling steps are the GLUT4 glucose transporter, which controls glucose entry into the cell; hexose kinase, which controls glucose phosphorylation to glucose-6-phosphate (G6P); and glycogen synthase. With ^{31}P NMR spectrum analysis, intramyocellular G6P levels can be shown to increase in normal but not in diabetic persons during clamp study, implicating either hexose kinase or GLUT4. A similar failure of intracellular G6P to increase is seen in insulin-resistant offspring of two diabetic parents. To distinguish the GLUT4 and hexose kinase steps, intracellular free glucose was measured with ^{13}C NMR spectrometry, using mannitol to distinguish intra- versus extracellular compartment glucose levels. There was no evidence of increase in intracellular free glucose, suggesting transport to be the rate-limiting step.

The GLUT4 gene itself is normal in diabetes. Shulman noted the strong association between plasma FFA and insulin resistance. Proton NMR spectroscopy shows even stronger association of intramyocellular triglyceride with insulin resistance. Shulman recalled the Randle hypothesis that fatty acids increase the redox state, inhibiting pyruvate dehydrogenase, inhibiting phosphofructokinase, and feeding back to inhibit hexose kinase. In a study of the effect of elevating FFA levels on glucose metabolism in skeletal muscle, inhibition of glycogen synthesis can be demonstrated, but with marked decline in intramyocellular G6P levels and with decline in intramyocellular free glucose, similar to that seen in diabetic and prediabetic persons. Fatty acids may be causing this defect in insulin activation of GLUT4 by effect on vesicle trafficking, by inhibiting activity of GLUT4, or by interfering with the insulin signaling cascade, perhaps at the level of phosphatidylinositol 3 kinase (PI3K) activation. Skeletal muscle punch biopsies show that the normal insulin-induced increase in PI3K is blocked by fatty acids. In animal studies, insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation is blocked, but insulin receptor phosphorylation is not affected. This may reflect serine phosphorylation of IRS-1, which indeed is increased by fatty acids. Protein kinase Cτ is activated by fatty acid and appears to be one mediator of IRS-1 serine phosphorylation. Shulman also discussed studies of the transgenic "fatless mouse," which shows marked muscle and liver insulin resistance and high levels of muscle and liver fatty acyl CoA and triglyceride in these sites, has high serum triglyceride, fatty acid, and insulin levels, and typically develops diabetes. "Fat transplants" lower hepatic and muscle triglyceride stores and are effective in reversing the abnormalities.

Michael J. Quon (Bethesda, MD) discussed the relationship between insulin signaling and endothelial dysfunction, addressing interrelationships between insulin resistance and hypertension as they pertain to hemodynamic as well as metabolic insulin action in the endothelium. In clinical treatment, for example, insulin sensitizers tend to lower blood pressure, while ACE inhibitors improve glucose tolerance. The classic target tissues of glucose regulation are the β-cell, muscle, fat, and the liver. Insulin also has actions in nonclassic tissues, including the vascular endothelium, stimulating synthesis of the vasodilator nitric oxide (NO). Mice not expressing IRS-1 develop hypertension, and those not expressing endothelial NO synthase (eNOS) have insulin resistance as well as hypertension. Glucose metabolism increases blood flow; in addition, there is evidence that blood flow drives glucose metabolism, with capillary recruitment potentially producing a 30–40% increase in glucose uptake. The degree of vasodilation with insulin is strongly associated with the degree of insulin sensitivity of glucose metabolism. FFAs may link the metabolic and hemodynamic abnormalities, causing both

insulin resistance and endothelial dysfunction. eNOS is controlled by insulin. In classic insulin target tissues, insulin signaling increases phosphorylation of IRS-1–4, activating PI3K, leading to 3′-phosphoinositide-dependent kinase 1 (PDK1) phosphorylation, which leads to phosphorylation of Akt, causing GLUT4 translocation to the cell membrane. PI3K activation alone can be produced with platelet-derived growth factor (PDGF), without increasing translocation of GLUT4. In the endothelial cell, a similar pathway of insulin action increases Akt, leading to eNOS phosphorylation and activation, again with PDGF-induced Akt activation via PI3K not affecting eNOS. The common pathway suggests that insulin resistance might have both metabolic and hemodynamic consequences via NO. In a normal person, insulin has no net effect on blood pressure, but in the presence of insulin resistance, the compensatory hyperinsulinemia "can drive the non–insulin-resistant pathways," Quon suggested, with prohypertensive actions such as those involving endothelin-1 as well as several vasoconstrictive pathways of intracellular insulin action (13).

Paresh Dandona (Buffalo, NY) discussed the link between the IRS and inflammatory markers, pointing out that atherosclerosis is an inflammatory process, and that insulin is itself an anti-inflammatory signal. (14). With an increasing number of metabolic abnormalities (e.g., obesity, hypertension, increased triglyceride, low HDL, and hyperglycemia), C-reactive protein, fibrinogen, and white cell counts increase (15). The first event to occur in atherosclerosis is monocyte adhesion to the abnormal endothelium "insulted by hypertension or diabetes or estrogen deficiency or the state of obesity itself," with monocyte activation producing monocyte chemoattractant protein (MCP)-1, recruiting further inflammatory cells. Matrix metalloproteinases (MMPs) are produced, leading to weakening of the endothelial barrier, as the lipid-containing fatty streak is produced, with subsequent modification of lipids by reactive oxygen species (ROS) and change in monocyte phenotype to the flattened foam cell. When subsequently the plaque ruptures, the surface of the exposed foam cells activate tissue factor, leading to platelet aggregation and thrombus generation. With the influence of inflammatory cytokines and activation of protein kinase C, the transcription factor NF-κB (16) is released from the inhibitor of NF-κB (IκB) by phosphorylation of this protein. NF-κB is central to the expression of the adhesion molecules ICAM-1 and VCAM and to the production of enzymes leading to ROS generation. This leads to activator protein (AP)-1 and MMP production, with subsequent production of early growth (Egr)-1 and tissue factor (TF). Glucocorticoids act by binding to the promoter of IκB in the nucleus. Dandona pointed out that thiazolidinediones also have anti-inflammatory effects before the development of falls in glycemia (and noted evidence of their effects in arthritis, colitis, and psoriasis).

Insulin stimulates nitric oxide expression, and since nitric oxide has anti-inflammatory effects, Dandona asked whether insulin itself would have anti-inflammatory effects (17). With insulin infusion, maintaining normal glucose and potassium levels, in comparison to glucose plus potassium or saline alone, mononuclear cell ROS generation decreased by half, $p47^{phox}$ (a surrogate marker of NADPH oxidase) and NF-κB decreased, IκBα increased, soluble ICAM decreased, MCP-1 decreased, MMP-2 and -9 decreased, Egr-1 decreased, TF decreased, PAI-1 decreased, and AP-1 decreased (18). Dandona suggested this to be a potential mechanism of the beneficial effect of acute insulin administration in myocardial infarction and in administration to patients in the ICU setting.

Lewis Landsberg (Chicago, IL) discussed the relationship between the IRS and hypertension, suggesting that the four key manifestations of the IRS are obesity, particularly affecting the central, abdominal, or upper body region; hypertension; insulin resistance and hyperinsulinemia; and dyslipidemia, with insulin resistance also frequently associated with microalbuminuria, type 2 diabetes, hyperuricemia, small dense LDL, and procoagulant factors. The risk of the IRS increases with increasing BMI, as do those for type 2 diabetes, hypertension, and CVD, the latter produced in part by the interaction of obesity and hypertension. What is it about obesity, Landsberg asked, that causes hypertension? The sympathetic nervous system (SNS) plays a central role, with increased sympathetic activity in obesity, possibly caused by increased levels of insulin and of leptin. Angiotensin II (AII), perhaps via adipocyte angiotensinogen production, also may be involved in the genesis of hypertension. Central body fat distribution was initially noted by Jean Vague in the 1940s to be associated with CVD and metabolic abnormalities, with many epidemiologic studies showing effects on increase in mortality, CVD, hypertension, and type 2 diabetes. Landsberg mentioned the intriguing evidence of a relationship of 11-β-hydroxysteroid dehydrogenase type 1 in visceral fat to the abnormalities seen with central obesity, with the enzyme, which is stimulated by both insulin and cortisol, converting the inactive cortisone to cortisol. Visceral fat also produces angiotensinogen, with insulin resistance and hypertension associated with upper-body obesity.

The SNS shows an important mediating role. Circulating and 24-h urine norepinephrine (NE) levels increase with increasing BMI and waist-to-hip ratio. Muscle sympathetic nerve activity increases (19) while there is a decrease in the vasodilatory action of insulin in obese persons (20). "One thing [driving sympathetic activity in obese persons]," Landsberg stated, "is the insulin." As insulin levels increase through the physiologic range, plasma NE levels increase with increases in heart rate and blood pressure in young normotensive men. This may be relevant to the relationship between dietary intake and sympathetic activity, with fasting decreasing and overfeeding increasing sympathetic activity, with Landsberg suggesting that "the brain somehow must know what the nutritional status is. This is where insulin comes in." During fasting the small fall in glucose and the greater fall in insulin decrease metabolism of a portion of the ventromedial hypothalamus, leading to decrease in sympathetic activity, while with overfeeding this is reversed. This may explain the increase in thermogenesis following food intake. Basal metabolism accounts for 80%, exercise for 10%, and diet-induced thermogenesis for 10% of energy output in sedentary persons, so that variations in sympathetically medicated dietary thermogenesis may be important in the development of obesity. Viewed in this way, recruitment of the SNS in obesity, partially mediated by hyperinsulinemia, is an adaptive response to compensate for increase in caloric intake, but may be maladaptive in causing prohypertensive effects. Leptin is another important medi-

ator of the effect of obesity on SNS activity. Leptin infusion increases SNS activity and blood pressure, and it appears to complement the effect of insulin. Thus, Landsberg concluded, "The hypertension in the obese may be the byproduct of mechanisms developed to restore energy balance." These observations may be relevant to the evidence that β-blockers lead to weight gain, as well as the finding that weight loss, well before causing change in weight loss or body fat, is associated with decrease in insulin and then in sympathetic activity.

Tracy McLaughlin (Stanford, CA) discussed the relationship between insulin resistance and body mass, stressing that not all obese persons are insulin resistant, and addressed the questions of whether insulin resistance causes obesity and whether insulin resistance is associated with greater difficulty in achieving weight loss. She showed evidence of a linear relationship between SSPG and BMI. In a large population, 70% of persons in the highest tertile of insulin sensitivity had BMI <25 kg/m^2, 23% had BMI between 25 and 30 kg/m^2, and 7% had BMI >30 kg/m^2. In the middle tertile, these frequencies were 47, 34, and 19%, and in the highest tertile, 18, 45, and 37%, leading to the observation that not all obese persons are insulin resistant and not all insulin-resistant persons are obese.

McLaughlin reviewed prospective studies addressing the relationship between insulin lead and weight gain. Zavaroni followed 647 initially nonobese Italian persons, showing that quartiles of insulin 2 h after oral glucose were not associated with differences in weight gain over 14 years (21). Valdez divided 1,493 Mexican Americans and non-Hispanic whites into those whose weight increased or decreased during 8 years of follow-up. Fasting insulin was the only independent metabolic predictor of weight change, and only among the most obese tertile of the population, with those persons who had higher baseline levels of fasting insulin being less likely to gain weight (22). Similarly, Schwartz found that among 97 Pima Indians followed for 3 years, insulin secretion was negatively associated with weight gain (23), while Swinburn assessed insulin sensitivity among 192 obese Pima Indians, showing that those with insulin resistance had a 3.1-kg weight gain, while the insulin-sensitive group gained 7.6 kg over 3.5 years (24). Hoag measured insulin levels among 789 Hispanic and non-Hispanic white persons with normal glucose tolerance, showing those with the highest initial fasting insulin had lower risk of weight gain over a 4.3-year follow-up. In contrast to these findings, in a study of 328 prepubertal Pima Indians, Odeleye found that fasting insulin correlated with weight gain (25), and Sigal found that among 107 offspring of two diabetic parents, after 16.7 years the acute insulin response predicted weight gain in those persons who were insulin sensitive at baseline (26). McLaughlin concluded that prospective studies do not support the notion that hyperinsulinemia is associated with weight gain in adults.

In a study of 31 insulin-resistant versus insulin-sensitive persons with BMI between 28 and 35 kg/m^2 who were placed on a hypocaloric liquid diet, there was no correlation of either SSPG or insulin response to meals with weight loss (27). Interestingly, among persons placed on a 4-month hypocaloric diet and treated with sibutramine 15 mg daily, those who were insulin sensitive initially showed no change in insulin sensitivity with weight loss, while those who had insulin resistance at baseline showed improvement in the SSPG and in the pattern of glucose and insulin levels seen during a standard day (28). C-reactive protein (CRP) levels are higher in insulin-resistant obese persons and decrease with weight loss, while insulin-sensitive obese persons have lower CRP levels that do not change with weight loss. These observations suggest that insulin-resistant obese persons are at higher CVD risk than insulin-sensitive obese persons and have greater benefit from weight loss.

James R. Sowers (Brooklyn, NY) discussed the relationship between "overweight" and "obesity." In adults, a healthy weight is considered to be a BMI of 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2, and obesity >30 kg/m^2, with the prevalence of obesity in the U.S. increasing linearly over the past 12 years from ~12 to 22%. Among children and adolescents, in 1963–1970 obesity prevalence was 4 and 4.5%, increasing to 13 and 14% two decades later. Overweight and obesity are more common in minority populations, affecting 69 and 70% of Mexican-American men and women and 58 and 69% of non-Hispanic black men and women. Women of lower socioeconomic status (SES) are 50% more likely to be obese, but SES does not explain weight differences among men. Behavioral and metabolic interventions are the optimal approaches to overweight. The cost of food on a per-calorie basis has decreased markedly over the past two decades. Average french fry and soft drink portions had 210 and 85 kcal 20 years ago, but have 610 and 300 kcal today. Less than one-third of adults engage in recommended physical activity (30 min/day most days of the week) and 40% have no leisure activity. Many children do not engage in 60 min/day activity and half of children spend more than 2 h/day watching television.

Obesity increases mortality, accounting for ~300,000 deaths/year in the U.S. Furthermore, it is associated with diabetes, stroke, hypertension, and malignancies and results in psychosocial stigmatization. In the Nurses' Health Study, weight gain after age 18 was strongly related to diabetes risk, while loss of >5 kg strikingly decreased risk. Diabetes risk doubled and quadrupled with weight gains of 15 and 44 pounds, respectively (29).

Benefits of weight loss include decreases in diabetes, hypertension, and heart disease (30). Sowers stressed the role of counseling patients to increase physical activity. Lifestyle approaches were demonstrated to be effective in the Finnish Diabetes Prevention Study (31), the U.S. Diabetes Prevention Project (32), and the Da Qing Study (33). He noted that persons with mental illness, both depression and schizophrenia, have particular problems with increase in CVD risks of obesity, in part reflecting drug-related weight gain. Pharmacologic approaches to treatment include metformin, sibutramine, and orlistat, which Sowers suggested may be particularly helpful in centrally obese persons with CVD risk factors, perhaps as approaches to initiate weight loss. Sowers pointed out that in the Diabetes Prevention Project, metformin was most effective in persons aged 25–44 years who had a BMI of 36 kg/m^2. Bariatric surgery may be another useful approach.

Richard Hellman (Kansas City, KS) discussed the relationship between the IRS and type 2 diabetes. He noted that persons with the IRS are at high risk for type 2 diabetes, and that data from the Finnish Diabetes Prevention Study (34) and the U.S. Diabetes Prevention Project

(35) show that intensive lifestyle intervention decreases risk of progression to diabetes by 58%. One can focus such interventions on persons at particularly high risk, such as first-degree relatives of persons with diabetes, or those who had gestational diabetes. The American Diabetes Association's (ADA) Genetics of NIDDM study of 531 first-degree relatives of persons with type 2 diabetes showed that 36% had IGT and 19% had diabetes, although the use of fasting glucose alone would have failed to diagnose 52% of those with diabetes (36). A number of clinical characteristics are associated with greater risk of diabetes, including blood pressure >130/85, BMI >25, central obesity, acanthosis, HDL <40 in men and <50 in women, and triglyceride >150. A 2-h glucose between 140 and 199 mg/dl is more sensitive than fasting glucose, and the glucose tolerance test is widely used and relatively inexpensive. It is not, however, as reproducible as the fasting glucose; it is affected by exercise, starvation, stress, and medications; and, importantly, it is an indirect measure of the IRS unless insulin is measured directly. An ADA task force report found wide variation in insulin assays from different laboratories (37). Hellman suggested that the development of acceptable insulin measures would allow an important clinical approach to clinical assessment of the IRS. He noted the inverse curvilinear relationship between insulin secretion and insulin sensitivity, with evidence that glucose intolerance occurs at a late stage in the progression to diabetes (38).

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