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This is the second 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, 25–26 August 2002. (See http://www.aace.com/pub/irscc/findings.php for summary.)

Ele Ferrannini (Pisa, Italy) noted that the San Antonio Heart Study, which involved 3,000 individuals, shows a linear relationship between fasting plasma insulin and fat mass. Eight-year follow-up of 1,000 subjects showed that weight increase or decrease is associated with increase or decrease in fasting insulin, to a greater extent in men than in women. He presented data from the European Group for the study of Insulin Resistance (EGIR), a pooling project with insulin clamp data from 21 centers involving a "normal" population of 1,466 persons without diabetes, impaired glucose tolerance (IGT), or hypertension. The prevalence of hyperinsulinemia and of insulin resistance (based on top 10% for each for subjects with BMI <25 kg/m^2) were, respectively, 30 and 12% of those with BMI ≤ 28 kg/m^2, 48 and 35% of those with BMI ≤ 35 kg/m^2, and 80 and 60% of those with BMI >35 kg/m^2. Obesity, then, triples the risk of insulin resistance, although Ferrannini pointed out that in the EGIR analysis, many obese individuals were not insulin resistant. Visceral fat area shows an inverse relationship with insulin sensitivity, particularly in persons without diabetes (as those with diabetes may have additional causes of insulin resistance). Waist circumference is not, however, more strongly correlated than BMI, suggesting that the overall degree of obesity remains important. Either in the fasting state or during a hyperinsulinemic clamp, there is a negative relationship between circulating free fatty acid (FFA) levels and insulin sensitivity, suggesting that there is also "insulin resistance in lipolysis." The EGIR data show that both women and men have an association between hypertriglyceridemia and insulin resistance, suggesting that in the presence of insulin resistance, hepatic triglyceride synthesis increases. An inverse relationship was found in the EGIR between insulin sensitivity and both systolic and diastolic blood pressure, confirming the concept that essential hypertension is associated with insulin resistance.

The EGIR database suggests a "phenotype of the insulin-resistant subject" in 19% of individuals studied, with 35% having a family history of diabetes, mean BMI 30.4 kg/m^2, waist-to-hip ratio (WHR) 0.91, triglyceride level 244 mg/dl, HDL cholesterol 47 mg/dl, uric acid 7.2 mg/dl, and blood pressure 131/81 mmHg. These subjects have what Ferrannini characterized as "a dominance of fat oxidation over glucose oxidation." Limiting the analysis to lean persons, comprising approximately half of those studied, the phenotype is similar, with a family history of diabetes in 30%, WHR 0.89, triglyceride 212 mg/dl, HDL 51 mg/dl, and blood pressure 132/81 mmHg. Ferrannini considered the question of "how can we define a syndrome without mentioning insulin?" He suggested that there is a very shallow relationship between insulin sensitivity and plasma insulin levels, particularly in lean individuals, and that 60% of the variability in insulin levels is not due to changes in resistance, but rather is due to insulin clearance and BMI, with insulin sensitivity and plasma glucose acting as "minor contributors to the fasting insulin level." From the EGIR data he compared the 562 subjects with hyperinsulinemia and the 493 subjects with insulin resistance. There were only 288 persons in both groups, so that "in 40% of the cases you are going to be picking different individuals." Similarly, in the San Antonio Metabolism Study, analysis of 286 individuals, 15 and 50% with IGT and diabetes, respectively, showed that there is again an inverse relationship between insulin sensitivity and fasting plasma insulin; yet, 182 had insulin resistance and 143 had hyperinsulinemia, but only 122 had both abnormalities.

Subjects in the EGIR with insulin resistance but not with elevated fasting plasma insulin had increased triglyceride, FFAs, and hepatic glucose production, which indicates "insulin resistance in the liver and insulin resistance of lipolysis," while those with elevated fasting plasma insulin but not with insulin resistance had low WHR, low FFAs, low glucose production, and low insulin clearance, further suggesting that the insulin level itself is only partially useful in characterizing the IRS. Importantly, persons with elevated

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Abbreviations: AACE, American Association of Clinical Endocrinologists; ACEI, ACE inhibitor; CETP, cholesterol ester transfer protein; CHD, coronary heart disease; CVD, cardiovascular disease; EGIR, European Group for the study of Insulin Resistance; FFA, free fatty acid; GDM, gestational diabetes mellitus; IKK, IκB kinase; IRS, insulin resistance syndrome; LH, luteinizing hormone; LPL, lipoprotein lipase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PAI, plasminogen activator inhibitor; PCOS, polycystic ovary syndrome; TZD, thiazolidinedione; ULN, upper limit of normal; WHR, waist-to-hip ratio.

fasting plasma insulin but not with insulin resistance tended to have higher systolic blood pressure. Ferrannini suggested also that hyperinsulinemia without insulin resistance may be a risk factor for development of obesity. Thus, the presence of insulin resistance is commonly associated with hyperinsulinemia, reflecting β-cell compensation, but insulin resistance and hyperinsulinemia are separate phenomena, with both contributing to the phenotype of the IRS. Pima Indian data show that hyperinsulinemia, paradoxically, is associated with greater frequency of subsequent development of diabetes for a given degree of insulin resistance. Using the World Health Organization (WHO) criteria for the insulin resistance syndrome, which includes microalbuminuria, the syndrome is seen in ~10–20% of women and 15–25% of men, although it affects >40% of certain populations.

Ronald M. Krauss (Berkeley, CA) discussed the relationship between the IRS and dyslipidemia. Factor analysis from the Framingham Offspring Study suggests a central metabolic syndrome with high triglyceride, low HDL, high WHR, BMI, and fasting and 2-h insulin, with overlapping but separate clusters of hypertension (which is most closely associated with BMI) and hyperglycemia (which is most closely associated with fasting and 2-h insulin) (1). Dyslipidemia, then, is central to the insulin resistance syndrome. Krauss suggested that the cut-points for abnormal HDL and triglyceride have been based on statistical considerations, but that other phenotypic markers may allow a more conceptually sound definition of abnormal levels of these lipids. Using data from several hundred healthy individuals studied in his center, the triglyceride distribution is skewed to the right, and the triglyceride-to-HDL ratio suggests a bimodal distribution, the higher peak beginning at 3.2. Analysis of quartiles of triglyceride, triglyceride-to-HDL ratio, and log triglyceride-to-HDL ratio suggests that the latter measure has particular risk in the highest quartile (2). Interestingly, genetic linkage analyses suggest a locus on chromosome 7q with relationship to log triglyceride-to-HDL ratio, an area also associated with insulin resistance.

Another bimodal lipid distribution is that of LDL particle size (3). There is an inverse relationship between plasma triglyceride and peak LDL diameter, with those subjects having smaller LDL particles forming a cluster at triglyceride over 100 mg/dl. The log triglyceride-to-HDL ratio shows a negative linear relationship to LDL particle size. Using this approach, the point of bimodality of LDL size is at a triglyceride-to-HDL ratio of 3.5, similar to that derived from the prior analysis. Krauss asked, "What can we infer about the origins of this bimodality and its biological meaning?" Normal VLDL metabolism is rapid, with small VLDL particles degraded by lipoprotein lipase (LPL) yielding LDL, which in turn is rapidly cleared by the LDL receptor. At higher VLDL levels, produced under circumstances of hyperinsulinemia and high hepatic triglyceride synthesis with elevated apoC-III levels inhibiting LPL, VLDL remnants are formed, acting as an acceptor of HDL cholesterol via cholesterol ester transfer protein (CETP), leading to IDL, the latter an atherogenic pathway. This is one of the pathways accounting for the reciprocal relationship between triglyceride and HDL levels, with lower HDL cholesterol contributing to atherosclerosis. Remnant lipolysis by hepatic lipase produces small dense LDL particles, which are more slowly cleared by the LDL receptor. The longer duration of residence of these particles leads to increased oxidation, further increasing the likelihood of proatherosclerotic processes. Thus, high triglyceride, low HDL, and small dense LDL are interrelated atherogenic particles. The triglyceride-to-HDL ratio shows a linear relationship to plasma insulin, suggesting a relationship with insulin resistance. Factor analysis of the data shows three components, a lipid component including LDL size, triglyceride, log triglyceride-to-HDL ratio, and HDL, an adiposity measure, with waist circumference and BMI and, separately, blood pressure. All factors correlate with insulin, particularly the adiposity measure. There may then be four factors—lipids, blood pressure, adiposity, and insulin resistance—with "this mysterious syndrome" being at the center.

Krauss stressed that clinicians need clear and practical criteria for coronary heart disease (CHD) risk assessment and management, such as those proposed in the Adult Treatment Panel III (ATP III), and that clinical definition of the metabolic syndrome should not necessarily be considered to represent the underlying biological mechanisms at this point. He suggested the development of an operational definition that could be based on one or more clusters of risk factors that improve global CHD risk assessment beyond their individual contribution to risk, in particular the triglyceride-to-HDL ratio. Indeed, the triglyceride-to-HDL ratio may be a better marker than the fasting insulin level, particularly as it shows similar correlation with insulin sensitivity.

John E. Nestler (Richmond, VA) discussed the relationship between the IRS and polycystic ovary syndrome (PCOS). The PCOS is defined by chronic anovulation and hyperandrogenism, and it is seen in a variety of ethnic groups, affecting 6–10% of women of childbearing age (3.2–5.4 million women in the U.S.). The most common cause of female infertility (50–60%), insulin resistance, is a virtually universal feature, in both obese and nonobese women, and the frequency of the disease appears to be increasing. PCOS is associated with a 31–35% prevalence of IGT and a 7 .5–10% prevalence of type 2 diabetes. The Nurses' Health Study showed increased risk of diabetes in women with oligomenorrhea (4), and 82% of women with type 2 diabetes have polycystic ovaries on sonography (5). The woman with PCOS has high risk of being obese, having hypertension, vascular dysfunction, low HDL, high triglyceride, high plasminogen activator inhibitor (PAI)-1, and high endothelin-1, all of which increase cardiovascular disease (CVD) risk. Indeed, over age 45 years, women with PCOS have increased carotid intima-media thickness (IMT) and coronary calcification on ultrafast computed tomography. A 7.4-fold increase in risk of myocardial infarction is present among women who had ovarian wedge resection (6), and the history of irregular menses is associated with 1.5 and 1.9 increased risks of CHD and fatal myocardial infarction, respectively (7). This may then be a major general health risk for young women, and evaluation of women with PCOS, Nestler stated, should include glucose tolerance, blood pressure, and lipid testing as well as androgen measurement. In addition to reducing androgens and improving reproductive function, improvement in CVD risk should be a goal of treatment.

Insulin resistance plays a pathogenic role in the development of the disease. Hyperinsulinemia increases ovarian androgen production, alters luteinizing hor-

mone (LH) and follicle-stimulating hormone (FSH) release, and decreases sex hormone binding globulin, so treatment to improve insulin sensitivity should be useful in the disease, and, indeed, diet/lifestyle, metformin, thiazolidinediones, and D-*chiro*-inositol treatment are effective approaches to the illness. Treatment may be aimed at inducing fertility, with insulin sensitizers increasing spontaneous ovulation, increasing the success of induction of ovulation with clomiphene or gonadotropin, and improving fertility as well as possibly decreasing early pregnancy loss, perhaps also enhancing the quality of eggs retrieved for in vitro fertilization. Troglitazone shows dose-related action in improving ovulation and hirsutism in women with PCOS (8), and ovulation induction with clomiphene is seen in 90% of women receiving metformin but in only 8% of women without this treatment (9). Nestler discussed results of a 6-month treatment of 100 nonobese women with PCOS, which showed a somewhat greater effect of metformin than rosiglitazone and no benefit of administering both agents in combination. Long-term treatment with oral contraceptives decreases endometrial cancer, with a reduction in serum androgens and a decrease in hirsutism and acne, but may worsen insulin resistance (10) and lead to deterioration in glucose tolerance (11). Insulin sensitizers, on the other hand, should decrease endometrial hyperplasia by inducing regular menses, but may not be as beneficial in improving androgen-related symptoms (12). Note that the Nurses Health Study (NHS) (12a) showed increased risk of diabetes in oral contraceptive users. These considerations may be related to the finding that women who used oral contraceptives have increased risk of myocardial infarction (13). Thus, in view of the particular increase in CVD risk among women with PCOS, one might be less likely to recommend oral contraceptives, while insulin sensitizers may be of particular benefit, decreasing androgens, improving ovulation and fertility, and reducing the risk of diabetes and CVD.

Jorge H. Mestman (Los Angeles, CA) discussed the relationship between the IRS and gestational diabetes mellitus (GDM), which may be defined as glucose intolerance first recognized in pregnancy, occurring in 2–10% of pregnancies, with the postpartum conversion rate to diabetes variously reported as being from 3 to 50% depending on the duration of follow-up, criteria, and ethnic variations. The O'Sullivan criteria for GDM were based on maternal conversion to diabetes, which he noted to occur considerably more commonly with obesity, during 8 years of follow-up after the pregnancy (14). In a study of 1,340 women 6–12 weeks after pregnancy, those who had GDM had higher triglyceride and lower HDL cholesterol levels (15). Women who had GDM and developed diabetes subsequently had increased mortality, hypertension, stroke, myocardial infarction, and renal failure. Predictors of GDM are well known and include age, non-white ethnicity, obesity, and cigarette use (16). Based on these considerations, Mestman concluded that "we have the unique opportunity to detect and delay" the development of diabetes in women who have had GDM.

Michael E. Gottschalk (San Diego, CA) discussed adolescents, PCOS, and the IRS. PCOS is a disorder of gonadotropin secretion, of steroidogenesis, and of insulin resistance. Once this is seen in adults, the process may be advanced, suggesting that studying it in childhood and adolescence would be useful. The association between hyperandrogenism and hyperinsulinemia is well established, with the increase in insulin existing even with correction for BMI. Lewy et al. (17) showed a group of adolescents with PCOS to have increased insulin levels, both fasting and during the first and second phase after intravenous glucose, and decreased insulin sensitivity, with decreased peripheral glucose disposal but no change in hepatic glucose production. Ibanez et al. (18) studied a group of girls with premature pubarche, many of whom had low birth weight, and approximately half developing PCOS. Controlling for pubertal stage, serum insulin levels are increased in these girls, and at Tanner stage 3 and higher, androgen levels were elevated. Oppenheimer et al. (19) compared girls with premature pubarche with and without acanthosis nigricans, showing the former group to have insulin resistance. Abnormalities of glycemia are common among adolescents with PCOS, with 42 and 10%, respectively, having IGT and (undiagnosed) diabetes in one study (20). Gottschalk reported dyslipidemia to be common in his population of adolescents with PCOS; 57% had LDL >110, 50% had triglycerides >135, and 28% had HDL <37 mg/dl.

Addressing treatment, Ibanez et al. (21) administered metformin at a mean dose of 1,275 mg daily for 6 months, showing resumption of regular menses and decreases in androgens and in the LH and 17-OH progesterone response to gonadotropin-releasing hormone. LDL decreased, HDL increased, and mean insulin during a glucose tolerance test decreased. All abnormalities recurred with treatment withdrawal. In a subsequent study of metformin treatment, 2-h glucose levels decreased, with improvement in glucose disposal rates, improvement in insulin sensitivity, and improvement in androgen levels with a 45% decrease in free testosterone (22). Interestingly, there is improvement in lipid levels, but not in insulin or glucose levels, with the antiandrogen flutamide (23).

Francine R. Kaufman (Los Angeles, CA) discussed issues related to the IRS in childhood. Insulin resistance appears to be more common among African-American children, along with increasing prevalence of obesity, particularly in those with a family history of obesity. This is related to diet and to decreased activity, with the frequency of daily physical education classes among high school students decreasing from 41% in 1991 to 25% in 1996. By 9th grade, only 12% of children pass a "minimal standards" physical fitness test. Prediabetes is an important consideration in children, with a survey from an obesity clinic showing high prevalence of IGT as well as the beginning of the development of diabetes (24). Children presenting with diabetes are obese, mainly from ethnic minority groups, and with acanthosis nigricans, and many have hypertension, hyperlipidemia, sleep apnea, and depression. Childhood obesity is an important predictor of adult CVD mortality (25). There is evidence of increased carotid IMT in adolescents with versus without diabetes, further suggesting the importance of treatment. Kaufman commented that "there has been reluctance to have children lose weight" because of fear of preventing growth, so that most programs have been directed at weight maintenance, but that it is important to consider more aggressive efforts at such treatment. Similarly, consideration will need to be given for initiation of lipid treatment in children with diabetes and dyslipidemia. There are concerns about

aspirin in children, because of Reye's syndrome, and about use of drugs such as ACE inhibitors that may be contraindicated during pregnancy, but as obesity and consequent CVD risks increase, it may be necessary to reconsider these approaches.

Om P. Ganda (Boston, MA) discussed the insulin resistance syndrome in Asian populations, who have low obesity but high diabetes and CVD rates. The Center for Disease Control lists ~60 different Asian ethnic groups in the U.S.; the 2000 U.S. Census shows 23% to be Chinese, 18% Filipino, 15% Asian Indian, 11% Vietnamese, 11% Korean, and 8% Japanese. In 1995, India and China had 19.4 and 16 million persons with diabetes, respectively, and by 2025 these countries will have 57.2 and 37.6 million adults with diabetes. The prevalence of diabetes appears to be higher in migrant populations. The prevalence among Chinese is 3% in China, but 4% in Hong Kong, 8% in Singapore, 12% in Taiwan, and 18 and 11% among men and women in Mauritius. For Asian Indians, diabetes prevalence is ~2% among rural populations in India, but 8% in urban areas and ~12% in Mauritius, Fiji, and the U.K. The prevalence of type 2 diabetes was 5% among Japanese men in Tokyo, but was 20% in Seattle (4 and 16%, respectively, among Japanese women). Those in Seattle had higher insulin levels, and intra-abdominal fat was considerably higher, although BMI was similar. Intra-abdominal fat showed stronger correlation with hypertension and dyslipidemia measures than insulin sensitivity per se, and it was a marker for diabetes risk, with those in the lowest quartile having less than half the risk of those in the highest abdominal obesity quartile.

Ganda reviewed several studies of individuals of Asian ethnicity. Banerji assessed 20 healthy Asian Indian male volunteers, with a normal mean BMI of 24.5 kg/m^2 but increased body fat, averaging 33% of body weight, with increased visceral fat related to dyslipidemia and insulin resistance (26). Chandalia compared 21 healthy Asian Indian men and 23 Caucasian men of similar age and body fat content, showing the former to have decreases in insulin action (27). The Study of Health Assessment and Risk in Ethnic groups (SHARE) assessed 985 subjects, showing a higher prevalence of cardiovascular disease and an increased prevalence of glucose intolerance, higher total and LDL cholesterol, higher triglycerides, lower HDL cholesterol, and much greater abnormalities in novel risk factors, including higher concentrations of fibrinogen, homocysteine, lipoprotein(a), and PAI-1 among persons of South Asian ethnicity than among those of European or Chinese ethnicity (28). Ganda pointed out that there are limitations in all of the studies, which all have potential sampling, recruitment, and CVD event reporting bias, and noted important differences in access to health care: 29% of individuals of Asian ethnicity are below the poverty level in San Francisco, 43% of Asian American children are born into poverty in New York City, and there is a 37% poverty rate in Minnesota—three times that in the Caucasian population.

Jaime A. Davidson (Dallas, TX) discussed implications of the IRS for Latinos, pointing out that this is the fastest growing minority group in the U.S., with 75 million persons making the U.S. the third largest Latino population in the world. Of Latinos in the U.S., 33% are obese, 46% have abdominal obesity, 38% have hypertriglyceridemia, 40% have low HDL cholesterol, 37% have high blood pressure, and 20% have high fasting glucose levels. Thus, 36% of Latinos have the metabolic syndrome, making this the ethnic group with by far the highest IRS prevalence in the U.S. (29). Diabetes prevalence increased 39% among Latinos, as compared with 30% among African Americans and 27% among Caucasians from 1990 to 1998. Predictors of conversion to diabetes include higher LDL and triglyceride and lower HDL, higher blood pressure, and higher BMI (30). As such, Latinos have similar risk factors to those in other populations, but "the problem is magnified in this population." James R. Gavin (Atlanta, GA) noted that diabetes mortality increased in the late 1980s for African Americans, accompanied by high levels of atherosclerotic and renal complications, to levels approximately twice that for Caucasians. In persons with normal, impaired, and diabetic glucose tolerance, the presence of the metabolic syndrome conveys increased CVD risk (31). African Americans may have increased risk of CHD and may have worse outcome of episodes of CHD. In addition, they have had a lesser improvement in CVD rates than Caucasians over the past decade. Interestingly, African Americans have lesser degrees of dyslipidemia but greater prevalence of diabetes and hypertension. Compared with other ethnic populations, there has been a huge excess of development of type 2 diabetes among African-American adolescents. There has been increasing prevalence of obesity among African Americans, particularly among women, but additional risk factors may be present in this group.

Anna M. Diehl (Baltimore, MD) discussed the IRS and nonalcoholic fatty liver disease (NAFLD), pointing out that the liver is the major organ involved in lipid and glucose homeostasis. Similar to alcoholic liver disease, there is a spectrum of abnormalities, progressing to nonalcoholic steatohepatitis (NASH) with addition of inflammatory cells, potentially ultimately leading to fibrosis and cirrhosis. These histologic findings are sensitive but not specific, with alcoholic, viral, and certain congenital liver diseases potentially causing similar findings. Blood measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltranspeptidase (GGT) are usually less than four times the upper limit of normal (ULN), may be normal, and are also nonspecific and insensitive. Among individuals referred to gastroenterologists for liver function abnormality, 35 and 25% have steatosis and NASH, respectively, with populations having diabetes or obesity showing 50–90% prevalence of this finding. Further, hepatitis C progresses to cirrhosis particularly in subjects with visceral adiposity and hepatic steatosis, and similarly hemochromatosis particularly is associated with cirrhosis in persons with underlying hepatic steatosis. Abdominal ultrasound has positive and negative predictive values of 77 and 67%, respectively, for NAFLD, while proton NMR spectroscopy may be more specific but is a complex and expensive test.

NAFLD may be present to some extent in "just about everybody." The medical profession, then, is likely to diagnose NAFLD among obese middle-aged diabetic women, but is unlikely to diagnose NAFLD among individuals who consume alcohol in excess. According to the National Health and Nutrition Evaluation Survey (NHANES) III data on liver enzymes in ~12,000 subjects representative of the U.S. population, using cutoffs of AST, ALT, and GGT >30 in the absence of hepatitis B surface antigen, anti-hepatitis C antibody, elevated transferrin,

or excessive alcohol use, NAFLD was more frequently present in men than in women and in postmenopausal than in premenopausal women, and lower levels were seen in postmenopausal women taking hormone replacement therapy (HRT). NAFLD was more common in minority populations and was strongly associated with BMI. Triglyceride levles >200 increased risk by 1.3-fold, HDL >35 increased risk 2.8- and 3-fold, and diabetes increased the risk 1.4- and 3.5-fold in men and women, respectively. NAFLD was present in 32 and 43% of obese men and women. Diehl noted that lipodysptrophy is also associated with NAFLD and presented the concept that obesity may modify the risk for other liver toxicities, as, for example, persons ingesting large amounts of alcohol have 46 vs. 95% the risk of developing fatty liver with normal weight versus obesity. Alcohol use was not, however, associated with increased frequency of NAFLD in the NHANES III analysis. There is now evidence that malonyldialdehyde adducts are present in the absence of alcohol intake because of endogenous alcohol production by gut bacterial flora, suggesting increased sensitivity of obese individuals to this endogenous source. Dyslipidemia may be another potential cause of the association of obesity with NAFLD. Diehl suggested that NAFLD may be a consequence of the underlying insulin-resistant state, pointing out that IκB kinase (IKK)-β activation increases NF-κB, leading to release of inflammatory cytokines such as tumor necrosis factor-α, which in turn further increases IKK-β levels. Diehl suggested that insulin sensitizers may represent potential approaches to treatment.

In NHANES III, hepatitis B, hepatitis C, hemochromatosis, and alcohol together affected ~5% of the adult population and 24% had presumed NAFLD based on liver chemistries above the ULN. Even using 1.5× ULN as the criterion for liver disease, 12.5% had elevations; of these subjects, 11% had NAFLD. Diehl stated that one-third of liver transplants are performed for patients with cryptogenic cirrhosis, 70% of which may be due to NAFLD, and that mortality is actually greater in subjects with cirrhosis who have NAFLD than other forms, accounting for 50% of liver deaths. Persons with NAFLD have poorer perceived health status, and the liver disease may worsen CVD or other conditions.

Yehuda Handelsman (Tarzana, CA) discussed an approach to the pharmacologic treatment of the IRS based on "treat-[ing] the multiple risks with multiple treatments," suggesting that treatment at the stage of insulin resistance, hyperinsulinemia, obesity, β-cell dysfunction, elevated proinsulin, hypertension, dyslipidemia, and early atherosclerosis preceding diabetes may be of benefit. Approaches may include treatment to lower FFAs and to normalize lipids, blood pressure, PAI-1, fibrinogen, platelets, insulin resistance, and hyperinsulinemia and, perhaps, anti-inflammatory treatment. Treatment goals include BMI <25, with optimal levels of 22.6 and 21.1 for men and women, respectively, waist circumference <40 inches in men and 35 inches in women (these vary by ethnic group), and LDL cholesterol <100 mg/dl, triglycerides <150 mg/dl, and HDL >45 mg/dl in men and 55 mg/dl in women. To minimize CVD risk, any weight gain exceeding 5 pounds should be reversed, with both lifestyle modification and pharmacologic treatment including sibutramine, orlistat, and phentermine, as well as metformin and bupropion. The goal of blood pressure treatment is 130/85 mmHg (32). Handelsman discussed the independent association of cardiovascular mortality with microalbuminuria, as well as evidence in HOPE and MICRO-HOPE of decreased mortality, stroke, myocardial infarction, and cardiovascular death with the ACE inhibitor (ACEI) ramipril, although the Captopril Prevention Project showed only equivocal evidence that captopril had greater benefit than a β-blocker or diuretic (33). Regression of left ventricular hypertrophy (LVH) and decrease in microalbuminuria independent of blood pressure changes have been shown with the angiotensin receptor blockers (ARB) valsartan (34) and losartan (34a). The Heart Protection Study suggests that a statin should be given regardless of LDL cholesterol level (35). There is also evidence of association of triglyceride with CVD risk (36), with the suggestion that fibrate therapy is of benefit in individuals with low HDL cholesterol (37). He also pointed out that even with fasting glucose levels <110 mg/dl, subjects whose blood glucose 2 h after a glucose load was 140–199 and ≥200 mg/dl had, respectively, 50 and 100% increases in risk over those whose 2-h glucose was <140 mg/dl in the DECODE study (38). There may, then, be benefit for glycemic treatment in persons with the IRS. The first approach is lifestyle modification, but it is difficult to accomplish this, and one might consider adding metformin or, based on the TRoglitazone In the Prevention Of Diabetes study (39), a thiazolidinedione (TZD) to decrease risk.

Paul S. Jellinger (Miami, FL) expanded on these ideas, reviewing a number of questions pertaining to the IRS, suggesting that we may be able to "borrow from what we know about type 2 diabetes" and apply it to this syndrome. It may be worthwhile to treat modifiable CVD risk factors associated with the syndrome, including HbA_{1c} within the normal range (40), which may reflect subtle degrees of postprandial hyperglycemia as suggested by the DECODE study and the Honolulu Heart Program (41). Prevention of diabetes may include ACEIs (42) and statins (43). Ongoing studies of acarbose, metformin, TZDs, ACEIs, ARBs, and nateglinide will be completed over the coming 4 years. FFAs may respond to TZD and metformin treatment. HDL treatment may include peroxisome proliferator–activated receptor (PPAR) agonists, and new agents that are being studied appear to have particular benefit. Small dense LDL abnormalities are strongly associated with insulin resistance and respond to TZD, fibrate, and niacin treatment. Hypertension is associated with insulin resistance (44), and there may be a blood pressure–lowering effect of TZD treatment. Angiotensin II increases atherosclerosis, and ARB treatment decreases atherosclerosis in primate studies. PAI-1 is associated with abnormal glucose tolerance and with insulin resistance (45) and decreases with ACEI, ARB, metformin, and TZD treatment. Fibrinogen levels are particularly decreased by fenofibrate, whereas they surprisingly increase with gemfibrozil. Metformin inhibits platelet aggregation and decreases blood viscosity. Anti-inflammatory treatment, including aspirin, ACEI, ARBs, and statins, and agents that improve endothelial function, including ARBs, ACEIs, TZD, metformin, and statins, may have benefit via this mechanism.

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