Obesity, Hypertension, and Insulin Resistance

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[1]This article summarizes material presented at the meeting of the American Society of Hypertension (ASH) in New York, New York, May, 2002, as well as presentations at the American Diabetes Association (ADA) Annual Meeting in San Francisco, California, June, 2002.

At a symposium addressing the relationships between obesity, hypertension, and cardiovascular disease at the ASH, Roger Unger (Dallas, TX) discussed lipotoxicity and the metabolic syndrome. He pointed out that over that past 50 years there has been a great change in the food environment, so that the "mechanism for preloading calories, storing them for when a famine occurred," has led to "hypertrophy and hyperplasia of those adipocytes [. . .]. Famines were eliminated and replaced by a never-ending stream of high-quantity, high-fat, high-carbohydrate foods at the same time that physical exertion dropped to an all-time low." This has led to a progressive increase in obesity, particularly over the past two decades. "As long as the excess fat remains in the adipocyte," he stated, "health is not deleteriously affected," but an "increase in ectopic deposition of lipids" causes the insulin-resistant state, with insulin resistance per se characterized by Unger as "not the proximal cause of the syndrome." Unger examined monogenic disorders of lack of leptin action to understand "the mechanism of the disorder." These syndromes, which lead to components of the metabolic syndrome, suggest that leptin resistance or deficiency may be a more central cause than insulin resistance.

The normal actions of leptin can be seen in animal models of obesity, with overfeeding leading to hyperleptinemia, which may cause fat to deposit primarily in the adipocyte. Normal islets, as an example, "fill up with triglycerides" when incubated with fatty acids, but this can be prevented by administration of leptin. When leptin action is insufficient, as seen in the fatty/fatty (*fa/fa*) rat with loss-of-function mutation of the leptin receptor or the leptin-deficient *ob/ob* rat, there is a marked increase in tissue fat. *fa/fa* rats show both heart and muscle "loaded with triglyceride," suggesting that "leptin increases tolerance for fat just as insulin increases tolerance for glucose."

Obesity in the *fa/fa* animal leads to an increase in cardiac output to maintain the needs of excess body tissue. Cardiac function deteriorates, with initial cardiac hypertrophy leading to a pattern resembling that seen in dilated cardiomyopathy. Increased cardiomyocyte apoptosis, as shown by DNA laddering, can be seen in this setting. Levels of the sphingomyelin derivative ceramide increase with obesity and may mediate these effects, and blockers of serine palmityl transferase (which condenses palmityl CoA with serine to form ceramide) can prevent this process. Ceramide precursors lead to more rapid ceramide synthesis and increase insulin resistance in these animal obesity models. In the islets, after diabetes has occurred in these models, extensive mitochondrial damage is seen in β-cell remnants, a process prevented by troglitazone administration. High levels of fatty acids suppress anti-apoptotic processes, while a transgenic *fa/fa* model overexpressing leptin receptors in the islets is protected from this fat-induced apoptosis.

Aspects of these processes appear to occur in human obesity. Tissue triglyceride may be synthesized from glucose as well as from circulating free fatty acids (FFAs), or may derive from VLDL triglyceride, suggesting multiple potential sources of lipotoxicity. Myocyte fat levels, measured using magnetic resonance scanning, show correlation with the degree of adiposity and obesity may be associated with increased myocardial fat in humans. Unger suggested that the condition of "fatty heart," originally noted by William Harvey and subsequently studied by early cardiologists, should be more of a concern.

Gerard Ailhaud (Nice, France) discussed the differing metabolic characteristics of visceral and subcutaneous (SC) fat. Adipose tissue plays a role in energy regulation and can be considered a secretory organ supplying energy needs during exercise via FFAs. "The problem is the management of levels" of FFAs. In vitro studies suggest that the smaller visceral adipocytes undergo more lipolysis, with more β-adrenergic receptors leading to greater activity of hormone-sensitive lipase, while insulin has a stronger antilipolytic effect on the larger SC adipocytes, which have greater α-2 adrenergic receptor levels. Thus, the α-2 adrenergic response leads to accumulation of fat, but in a fashion of potential benefit in terms of sequestration of fatty acids in the adipocyte, with similarity to the effects of thiazolidinedione administration. Local production of cortisol may be greater in visceral fat, while tumor necrosis factor (TNF)-α and leptin are produced to a greater extent in SC fat. Exercise promotes mobilization of lipid from SC adipocyte tissue in nonobese individuals, but this process is decreased in obesity and can be restored by administration of the α-2 adrenoreceptor antagonist phentolamine.

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Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADA, American diabetes Association; ADMA, asymmetric dimethyl arginine; ARB, angiotensin receptor blocker; ASH, American Society of Hypertension; ATP, Adult Treatment Panel; BAT, brown adipose tissue; BP, blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; ESRD, end-stage renal disease; FA, free fatty acid; HOT, Hypertension Optimal Treatment; IDL, intermediate density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IRS, insulin resistance syndrome; LCAT, lecithin-cholesterol acyl transferase; LPL, lipoprotein lipase; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; PCOS, polycystic ovary syndrome; RGZ, rosiglitazone; SC, subcutaneous; SNS, sympathetic nervous system; SSPG, steady-state plasma glucose; TNF, tumor necrosis factor; UKPDS, U.K. Prospective Diabetes Study; WHO, World Health Organization.

Three research presentations at this symposium addressed further aspects of the interrelationship between obesity and hypertension. Weiguo Zhang et al. (Dallas, TX), noting that leptin might in principle either increase blood pressure (BP) by causing sympathetic activation or lower BP by renal vascular and metabolic effects, studied rodents with high-fat diet–induced obesity characterized by increased plasma leptin and increased BP and a second group with high-sodium diet–induced hypertension. They reported that with adenoviral leptin gene therapy to increase leptin levels, the BP decreased in both animal models, with reduced food intake and body weight in the high sodium diet animals. Raji et al. (Boston, MA) (also reported in 1453-P) studied the effect of rosiglitazone (RGZ) on BP, noting that potential mechanisms of the association between hypertension and insulin resistance include sympathetic activation, sodium retention, and impaired vasodilation (abstract numbers refer to the abstracts of the 62nd ADA Scientific Sessions, *Diabetes* 51 [Suppl. 2], 2002). Twenty-four normal-to-high renin hypertensive persons who were not receiving angiotensin-converting enzyme inhibitors (ACEIs) received RGZ 4 mg twice daily for 16 weeks. Mean 24-h BP decreased from 138/85 to 134/80 mmHg, the decrease correlating with the improvement in insulin sensitivity. "Nondippers" whose BP falls <10 mmHg in night versus day had similar BP fall to dipper, and showed restoration of circadian variation. Rahmouni et al. (Iowa City, Iowa) studied the molecular mechanisms of insulin-induced sympathetic excitation, showing that insulin increased sympathetic activity in lumbar sympathetic nerves and brown adipose tissue (BAT). This effect was not altered by the PKC-α inhibitor LY333531, although mitogen-activated protein kinase inhibitors blunted the BAT sympathetic response.

Hypertension and diabetes

At a symposium at the ASH meeting on the pathophysiology of hypertension in diabetes, Luis Ruilope (Madrid, Spain) further discussed the interrelationships among diabetes, obesity, insulin resistance, and hypertension. Ruilope suggested that obesity is the initiating factor and focused on the increasingly accepted importance of the metabolic syndrome. Obesity may affect BP via leptin, which increases sympathetic activity and may mediate increases in catecholamines, or via activation of the renin-angiotensin system. Angiotensin II levels are high in obesity, and the presence of increased glomerular pressures suggests activation of the renin-angiotensin system.

It is crucial, Ruilope stated, that general physicians diagnose the "quintet" of central obesity, hypertension, dyslipidemia (high triglyceride and low HDL), and glucose intolerance characterizing the metabolic syndrome. Based on data from the Third National Health and Nutrition Examination Survey (NHANES) and using the criteria for metabolic syndrome of the Adult Treatment Panel (ATP) III that one have at least three of BP measurements >130/85, fasting glucose ≥110 mg/dl, fasting triglycerides ≥150 mg/dl, HDL <40 mg/dl if male and <50 mg/dl if female, and waist circumference >102 cm if male and >88 cm if female (1), 47,000,000 subjects in the U.S. are affected (2). In Spain, despite "the so-called Mediterranean diet," Ruilope noted that the metabolic syndrome is seen in ~40% of the population over age 60 years. In a survey of 4,057 patients in hypertension and renal clinics in Spain, mean BMI was 29 kg/m^2, <20% had BP <130/80 mmHg, 20% of the patients had diabetes, and 15% had impaired fasting glucose (IFG). In addition, 30% of the subjects had microalbuminuria and an additional 10% had macroalbuminuria; decreased renal function was present in one-third, with the frequencies of diabetes and IFG doubled in this group. Cardiovascular disease (CVD) similarly appears to be associated with insulin resistance, with studies from Sweden showing that one-quarter of patients with myocardial infarction have previously undiagnosed diabetes, and an additional 41% have IGT (3).

Ruilope noted that most guidelines merely suggest that obese individuals with hypertension lose weight, without specifically addressing treatment issues in this group. Given the strong relationships among obesity, hypertension, and diabetes, to improve cardiovascular prognosis it may be important to more fully understand various approaches to BP for these patients. Diuretics may be less efficacious than ACEIs in lowering diastolic BP in obese individuals and may increase glucose levels (4). β-blockers appear to increase body weight, particularly in persons with diabetes, as shown in the U.K. Prospective Diabetes Study (5). α-Blockers may then be particularly suitable for subjects with insulin resistance, although this has not been demonstrated in trials addressing clinical events. (Indeed, there is some evidence of increase in CVD risk with use of this agent [ALLHAT Collaborative Research Group: *JAMA* 283:1967–1975, 2000].)

In a study presented at the ADA meeting, Aguilar-Salinas et al. (882-P) reported a nationwide survey of 1,962 individuals in Mexico tested after a 9- to 12-h fast, with 13.1% of the population having the metabolic syndrome as defined above, comprising 5.5, 10.6, 18.3, 24.8, and 31.4% of those with age in the 20s, 30s, 40s, 50s, and 60s, respectively. Kim et al. (937-P) assessed 1,230 persons in Korea, with the metabolic syndrome present in 18%. Ogihara et al. (951-P), addressing the interaction of genetics with environment, compared 211 diabetic and 203 nondiabetic native Japanese men with 68 diabetic and 150 nondiabetic second-generation Japanese-American men. Native Japanese had lower proportion of total caloric intake due to fat, particularly animal fat, and lower BMI, with lower subcutaneous fat levels than in Japanese-American men based on computerized tomography, but with similar visceral fat. Their fasting insulin levels were lower with similar glucose-stimulated insulin, suggesting less insulin resistance, and the prevalence of hypertension (35.3 vs. 67.9%), atherosclerosis of the lower extremities (5.5 vs. 24.4%), and ischemic heart disease (5.1% vs. 24.4%) were all much lower among native Japanese than among Japanese-Americans, respectively, confirming the impact of the metabolic syndrome. Further illustrating the complexity of these interrelationships, during a 5-year follow-up, Tsai et al. (122-OR) examined the influence of age-related changes in fasting plasma glucose on fat distribution in 216 Japanese-American men without diabetes at enrollment. Fasting glucose showed positive association with intra-abdominal fat, independent of age, while having a negative association with SC fat, particularly in older subjects.

Hirose et al. (926-P) noted newly diagnosed hypertension in 9.5, 15.7, and 20.6% of initially normotensive Japanese men in the lowest, intermediate, and highest tertiles, respectively, of insulin re-

sistance at 7 years of follow-up, with age and BMI being other significant factors in a multivariate analysis. Lorenzo et al. (944-P), however, reported that in a survey of individuals in San Antonio and Mexico City, the evidence for association of hypertension with IGT was equivocal, although there was a doubling of risk of hypertension among those with diabetes compared with those with normal glucose tolerance. Whyte et al. (979-P) presented further analysis of the NHANES data. Compared with subjects meeting none of the ATP III criteria, men with three, four, and five risk factors had 3.7-, 4.2-, and 5.2-fold increases, respectively, in 10-year coronary heart disease (CHD) risk. For women, CHD risks were increased 5.8-, 8.9-, and 11.3-fold, respectively. In a provocative analysis, Wilson et al. (980-P) analyzed 3,374 Framingham offspring with a mean age of 62 years, with 33, 31, 22, 10, 3, and 0.2% of men and 48, 31, 13, 7, 2, and 0.1% of women having zero, one, two, three, four, and five of the ATP III factors, respectively. Those with at least three risk factors (and hence classified as having the metabolic syndrome) had a 2.4-fold increase in risk over persons with no risk factors of coronary or overall CVD and an 11.2-fold increase in risk of diabetes, over subsequent follow-up. They noted, however, that there was a similar increase in risk for those with two or more risk factors, "suggesting the definition of the syndrome might be relaxed to include individuals with only two metabolic abnormalities."

Jon Levine (Nashville, TN) described risk factor evaluation approaches for CVD and diabetes at the ASH symposium, pointing out that there are currently no specific guidelines for therapy of the metabolic syndrome, which affects almost half of the population over the age of 60. The likelihood of developing a CVD event increases with age, with cigarette use, and with diabetes, which increases risk sixfold. Middle-aged persons with diabetes have a CVD rate similar to that in subjects without diabetes, but with have a greater history of myocardial infarction. Therefore, it is recommended that subjects with diabetes be treated as though they had already had a CVD event. Improvement in macrovascular disease prognosis with glycemic control in individuals with diabetes is suggested by the findings of the UKPDS. Levine noted that lipids and glucose appeared to be stronger risk markers for CVD than BP in subjects with diabetes in this study, and recommended intensive lipid treatment for diabetes to first reduce LDL cholesterol, to second increase HDL cholesterol, and to third decrease triglyceride levels. In most of the statin trials, he pointed out that there is greater benefit for persons with than for those without diabetes because, although the relative risk decrease is similar, the absolute risk decreases more because of underlying higher CVD rates. Furthermore, these agents may reduce new-onset diabetes and may therefore be beneficial for persons with the metabolic syndrome.

Systolic BP is a strong predictor of CVD risk, particularly in subjects with diabetes. In the UKPDS, BP treatment decreased both microvascular and macrovascular disease. The higher the BP, the greater the rate of loss of renal function, further suggesting benefit of treatment, with the most aggressive BP targets being applied to individuals with diabetes. In the Hypertension Optimal Treatment (HOT) Trial, as diastolic BP was reduced from 85 to 81 mmHg, events were reduced by 50% (6). Urine albumin is not only a predictor of renal disease but also of CVD, and in the HOPE trial the use of ramipril decreased CVD in parallel with the decrease in albuminuria (7). The target for treatment should be <130/80 mmHg, which will require use of three antihypertensive agents in the majority of persons with diabetes.

Thomas Giles (New Orleans, LA) reviewed clinical trial data focusing on the patient with CVD, diabetes, and hypertension. Potential strategies include aggressive control of glycemia, which he stated reduces complications "pretty much across the board." Blood pressure plays an important role in adverse outcomes. In the diabetes subgroup of the HOT study, in which enrollees were randomized to three groups, achieving diastolic BP of 85.2, 83.1, and 81.1 mmHg was associated with linear decreases in adverse outcomes. In the UKPDS there was a 10/5-mmHg difference in BP between the intensive and usual control group of the BP substudy, with a 50% decrease in congestive heart failure (CHF) (8). Tight BP control decreased stroke 45% while glycemic control decreased this end point only 5%. Similarly, BP treatment decreased retinopathy to a greater extent than that seen with glycemic treatment. In the HOPE study, high-risk subjects had a 22% decrease in the combined CVD and mortality risk with ramipril treatment. Individuals without diabetes showed a decrease in new diabetes onset with this treatment. The HOPE study showed decrease in end points with ramipril treatment to a similar extent in those with and without diabetes. Participants in the HOPE study with diabetes had a decrease in CHF by >20%. Also, the RENAAL study showed a decrease in hospitalization for CHF in persons with diabetes treated with losartan (9), and additional observations with this agent were reported in the LIFE trial, which further showed a 25% lower rate of appearance of new diabetes in nondiabetic subjects receiving losartan than among those treated with the comparator agent atenolol (10). Compared with the β-blocker, in patients with diabetes there was reduction in CVD mortality with losartan (11).

Giles emphasized that β-blockers are of benefit in individuals with diabetes, as shown in the MERIT trial of use of metoprolol in persons with CHF (12). Addressing use of calcium-channel blockers, he remarked that in the FACET trial there was worse outcome with amlodipine than with fosinopril alone, but that the combination of the two led to better outcomes than either alone; thus, that these are reasonable agents when used in combination with directly cardioprotective antihypertensive agents (13). Giles recommended as an overall strategy for the hypertensive subject with diabetes, then, the use of aggressive glycemic control as well as aggressive BP control, with ACEIs "the backbone of therapy" and angiotensin receptor blockers (ARBs) as additional important agents. β-blockers are, he suggested, underutilized and are as useful in individuals with as in those without diabetes. Calcium-channel blockers also play important roles for individuals who require multiple drugs to control BP.

Domenic A. Sica (Richmond, VA) pointed out that end-stage renal disease (ESRD) currently is caused by diabetes in half of cases, a frequency predicted to further increase over coming years. The renin-angiotensin axis can be modified with β-blockers, with ACEIs, or with ARBs. The combination of β-blockers with either of the latter two classes is effective, while it is not certain whether combined treatment with ACEIs and ARBs is effective. (There is however evidence that the latter combination does at least reduce al-

buminuria [Rossing et al.: *Diabetes Care* 25:95–100, 2002].) In persons with diabetic nephropathy, BP lowering substantially reduces the rate of decline in renal function. With urine albumin excretion rates of 30–300 mg/day, there is profound endothelial dysfunction at other sites in the body as well. Left ventricular hypertrophy showed strong concordance with microalbuminuria in the LIFE study, further evidence of this relationship. Microalbuminuria progresses to macroalbuminuria without treatment, suggesting the benefit of aggressive treatment. ACEIs are currently regarded as being the primary approach to treatment of subjects with type 1 diabetes and nephropathy, although the end points are less definite for this protective effect existing for individuals with type 2 diabetes and nephropathy. More definite "hard end point" studies have been done with the ARBs irbesartan in the IDNT study (14) and with losartan in the RENAAL study. One must realize that the majority of persons in these trials were treated with three antihypertensive agents in addition to the study drug, with diuretics being the first choice and calcium-channel blockers most often the second choice agents in attempts to lower BP levels. Sica noted that the degree of decrease in proteinuria is greater with the ACEI trandolapril than with calcium-channel blocker verapamil, but that the combination of the two in doses lowering BP to the same degree had even greater effect on proteinuria, suggesting benefit with this combination.

A number of studies at the ADA meeting addressed specific pharmacologic agents in the treatment of subjects with diabetes and hypertension. Wang et al. (1463-P) administered omapatrilat, an inhibitor of both enzymes degrading bradykinin, neutral endopeptidase, and angiotensin-converting enzyme, to insulin-resistant rats. Basal glucose production decreased 35% and glucose production showed a 2.7-fold greater suppression by insulin, while no consistent increase in insulin sensitivity was demonstrated with ramipril or losartan. The effects were blocked by administration of the bradykinin-2 receptor antagonist HOE-140, suggesting increased bradykinin action to mediate this effect. Black et al. (12-LB) compared the antihypertensive efficacy of omapatrilat with that of enalapril in daily dosages up to 80 and 40 mg, respectively, in 3,377 patients with diabetes. Of 775 previously untreated patients, systolic BP decreased 21 vs. 16 mmHg, with adjunctive treatment subsequently added in 15 vs. 25% to achieve levels <140/90 mmHg. For 1,823 previously treated patients, systolic BP decreased 10 vs. 5 mmHg, with adjunctive treatment subsequently added in 31 vs. 37%. An important caution for the new agent is that angioedema occurred in 1.3 vs. 0.4% of patients.

Jacob et al. (635-P) showed increase in fasting glucose from 183 to 198 mg/dl and in triglyceride from 221 to 265 mg/dl in 61 hypertensive individuals with diabetes treated with metoprolol. In contrast, the centrally acting anti-adrenergic moxonidine was associated with decrease in fasting glucose from 206 to 186 mg/dl and in triglyceride 222 to 182 mg/dl in 66 patients, with similar degrees of BP control. Viberti et al. (752-P) treated 223 hypertensive persons with diabetes and microalbuminuria with a combination of perindopril 2–8 mg and indapamide 0.625–2.5 mg daily. Albuminuria decreased 42%, significantly more than the 27% decrease in albuminuria in 224 such patients treated with enalapril 10–40 mg daily, suggesting synergistic benefit of the addition of a diuretic to ACEI treatment. Buckalew et al. (152-OR) treated 74 diabetic hypertensive patients with microalbuminuria with the selective aldosterone blocker eplerenone 200 mg daily, showing 62% decrease in albuminuria, in comparison to 45 and 74% decreases in albuminuria in 74 and 67 patients treated with enalapril 40 mg daily and with enalapril 10 mg plus eplerenone 200 mg daily, respectively. Withdrawal for hyperkalemia was necessary in 6, 2, and 14 subjects, respectively, in the three groups. Blood pressure levels were similar, and the decrease in albuminuria was independent of the degree of BP reduction, suggesting direct renoprotective effect of aldosterone blockade.

Management of the metabolic syndrome

Lewis Landsberg (Chicago, IL), introducing a symposium at the ASH on the mechanisms and management of the metabolic syndrome, stated that obesity and hypertension were first noticed to be associated more than 100 years ago, with prospective demonstration in the 1960s in the Framingham Study. Jean Vague in the 1940s observed the association between upper-body obesity and hypertension, with Scandinavian studies over the past two decades showing the quantitative relationship between the waist-to-hip ratio and these abnormalities. Hyperinsulinemia was shown to be a marker of the insulin-resistant state over the past two decades as well, with studies in the 1980s pioneered by studies of Reaven that showed the relationship between hypertension and insulin resistance. Studies beginning at that time showed the relationship among hypertension, insulin resistance, and sympathetic activation and subsequent recognition of a role of leptin in sympathetic activation and of insulin in the association of hypertension with obesity. Over the coming three decades, 40% of the U.S. population is projected to become obese, with the epidemic of obesity affecting the developing world as well. The age-adjusted prevalence of the metabolic syndrome is now ~24% in the adult population and reaches 50–60% over age 50 years.

James Poole of Baylor University (Houston, TX) discussed hypertension and lipid metabolism, pointing out the complexity of their inter-relationship, based on the contributions of the sympathetic nervous system (SNS) and renin-angiotensin system to the development of hypertension in the metabolic syndrome. There are three components to lipid metabolism, exogenous lipid entry, endogenous lipid synthesis, and remnant metabolism. The endogenous pathway produces VLDLs from endogenous precursors while the exogenous pathway uses breakdown products of dietary lipids to produce chylomicrons. Lipoprotein lipase (LPL) acts in the vascular lumen and is activated in the presence of specific particles, leading to production of intermediate-density lipoproteins (IDLs) from VLDLs, which are metabolized by hepatic lipase, leading to HDL production, with HDL levels enhanced by the action of cholesterol ester transport protein. On the exogenous side, chylomicrons are acted upon and reduced in size to more compact lipoproteins, upon which hepatic lipase then acts. The remnant pathway converts IDLs and chylomicron products into discoid particles, which are then acted upon by lecithin-cholesterol acyl transferase (LCAT) to produce HDL3, with LCAT acting on HDL3 to produce HDL2.

Nicotinic acid, fibrates, and statins

play roles in treatment, and, perhaps, alcohol and estrogens could be used to raise HDL cholesterol. Poole suggested a role for inhibition of the SNS at the postsynaptic level of the α-1 adrenoreceptor by prazosin, doxazosin, and related agents, which consistently influence metabolic pathways in a fashion separate from their effect on peripheral vascular resistance. The drugs decrease total and LDL cholesterol and, to a greater extent, triglyceride levels. Actions include upregulation of peripheral LDL receptors, decrease in gut cholesterol absorption, and upregulation of LPL expression, while synthesis and secretion of VLDL decrease. The degree of endothelium-dependent relaxation is also under SNS regulation and improved by α-1 receptor blockade. Such treatment, then, has the potential to decrease systolic, diastolic, and pulse pressure, to increase HDL cholesterol and apolipoprotein A1, to improve hyperinsulinemia, and to decrease LVH and the atherosclerotic process.

Ronald M. Krauss (Berkley, CA) further discussed the atherogenic lipoprotein changes associated with insulin resistance. The primary lipoprotein disturbances involve low HDL and high triglyceride levels, without a consistent effect on LDL cholesterol "the way we measure it in the clinic." The metabolic syndrome can be assessed with factor analysis, which illustrates the strength of the association of dyslipidemia with the metabolic syndrome and its strong association with adiposity and hyperinsulinemia. Glucose intolerance and hypertension in turn have relationships with dyslipidemia with this approach to statistical analysis. The dyslipidemia caused by abnormalities of the lipases described by Poole reflects impaired VLDL clearance, the effects of hepatic lipase on HDL catabolism, and the effects of hypertriglyceridemia on VLDL production. LDL itself is a heterogeneous set of particles, most arising from VLDL catabolism. The intermediate stage of clearance of abnormal VLDLs leads to production of a small LDL particles, with abnormal and increased transport of cholesterol from HDL into these particles contributing to the low HDL cholesterol level. Peak LDL size is inversely correlated with triglyceride levels, with two groups of individuals in the population, those with larger LDL and low triglyceride levels and those with smaller LDL and high triglyceride levels. The latter group of patients has higher postprandial glucose and insulin levels and lower insulin sensitivity, suggesting small LDL size not only to be associated with the dyslipidemia but also with the insulin resistance of the metabolic syndrome.

These are highly atherosclerotic particles, less rapidly cleared by the LDL receptor and more rapidly entering the subendothelial space and undergoing oxidation, with subsequent plaque formation and inflammatory response. Genetic susceptibility accounts for 40–50% of the variation in LDL size, with several candidate genes identified. Other important modifying effects include dietary fat and carbohydrate, obesity, and pharmacologic agents. Niacin appears to have the greatest effect, and fibrates are also useful in reducing levels of small LDL particles, while statins lower levels of all LDL fractions, and all agents that lower triglyceride levels also change the LDL size distribution to include more of the larger particles. In the Quebec Cardiovascular Study, the combination of low HDL and small LDL particle size was particularly associated with development of CVD (15). In the Familial Atherosclerosis Treatment Study (FATS), treatment of CHD with resins, statins, and niacin resulted in angiographic regression, the single most important predictor of which was the increase in LDL particle size, rather than the change in levels of LDL and of HDL (16). This appears to be particularly relevant to the treatment of individuals with the metabolic syndrome. Interestingly, the thiazolidinediones also appear to cause changes in LDL particle distribution with shift from small to large LDL, with effects documented for troglitazone and RGZ. The relationship between treatment of hypertension and lipoproteins in the metabolic syndrome suggests that α-blockers improve and β-blockers worsen this dyslipidemia, with particular effects on levels of remnant particles and the expected association with triglycerides. Krauss suggested that calculation of HDL-to-triglyceride ratios could be used to infer LDL particle size.

Gerold Reaven (Stanford, CA) discussed insulin resistance, hypertension, and CHD. The steady-state plasma glucose (SSPG) concentration during infusion of somatostatin, glucose, and insulin is a measure of insulin resistance, showing 10-fold variability in apparently normal populations. BMI correlates with higher SSPG, but only accounts for ~25% of the variability in insulin action from person to subject, with physical fitness, as measured by maximal aerobic capacity, also contributing approximately one-quarter of the degree of insulin sensitivity. The remaining half of the determination of insulin sensitivity is presumably genetic. Ethnic groups of European ancestry appear to have greater insulin sensitivity than other ethnic groups. Insulin resistance will lead either to type 2 diabetes and subsequent CHD, or, if insulin secretion is maintained, to the development of the metabolic syndrome without diabetes, and, again, to greatly increased risk of CHD. The metabolic syndrome is associated with increased SNS activity and hypertension, with procoagulant effects, with endothelial dysfunction, and with high uric acid, nonalcoholic steatohepatitis, and, perhaps, certain forms of cancer.

Daylong hyperinsulinemia and hypertriglyceridemia are characteristic of individuals with hypertension and of those with CHD. First-degree relatives of persons with hypertension show similar abnormalities. Hypertension is, however, heterogeneous. When comparing subjects with normal and high BP, hyperinsulinemia is seen in approximately half of the latter but in only one-tenth of the former group. There are important differences between individuals with hypertension and insulin resistance versus those who are insulin sensitive with hypertension, as the former group shows evidence of the characteristic dyslipidemia with low HDL and high triglyceride, evidence of glucose intolerance, and a greater prevalence of electrocardiographic abnormalities, which suggests underlying CHD. Those hypertensive persons with normal lipid patterns are less likely to have cardiac disease. Mononuclear cells from subjects with insulin resistance show enhanced endothelial binding, presumably contributing to CHD development. Asymmetric dimethyl arginine (ADMA) is an endogenous inhibitor of nitric oxide synthase that has been closely linked to CHD. Comparing individuals with and without insulin resistance, ADMA levels are higher in the insulin-resistant group, both with normal and with high BP. Reaven also discussed the triglyceride-to-HDL ratio, suggesting this to be as predictive of the degree of insulin sensitivity as is

the fasting insulin level, as well as suggestive of the individual's level of coronary disease risk. Insulin resistance is also associated with greater degree of sodium retention and greater increase in BP on a high-sodium diet.

In a presentation at the ADA meeting, Lawrence et al. (1670-P) presented data using isotope dilution and arterio-venous difference techniques to measure the rate of norepinephrine entry into the general circulation and into blood draining SC abdominal adipose tissue and forearm muscle as indices of systemic and local sympathoneuronal activity in 22 lean and obese volunteers. Systemic SNS activity was greater with obesity, increased further after feeding, and correlated with BP, while adipose tissue SNS activity was almost 50% lower with obesity and, unlike the finding in lean control subjects, did not increase after feeding. They suggested that obesity is associated with local SNS dysfunction despite increased systemic SNS activity, suggesting potential benefit of selective β_3 adrenoceptor agonists for treatment of obesity. Després et al. (1679-P) characterized 907 men and 937 women aged 18–74 years based on BMI tertile, with cutoffs at 23.2 and 26.6 kg/m^2, and based on the 50th percentile of waist circumference (with cutoff at 88 cm for men and 74 cm for women). BP was similar in men in the lowest BMI tertile with higher abdominal girth to that of men in the top BMI tertile; for women, the highest systolic BP was seen in those in the top BMI tertile with higher abdominal girth. There was no association between fasting insulin and BP when controlling for waist, suggesting that rather than assessing body mass per se it is more important to measure waist circumference in gauging the degree of obesity.

Insulin resistance

At a symposium at the ADA meeting on the insulin resistance syndrome (IRS), an alternative term for the "metabolic syndrome," James B. Meigs (Boston, MA) reviewed its definition and studies of its prevalence. The syndrome was first proposed and has continued to be studied by Gerald Reaven, who suggested that risk factors for heart disease and diabetes cooccur and termed the complex "syndrome X" (17). The San Antonio Heart Study showed that risk factors such as low HDL, hypertension, obesity, and hyperinsulinemia proceed the development of diabetes (18). In the Framingham Offspring Study, dyslipidemia, obesity, hyperinsulinemia, hypertension, and perhaps microalbuminuria occurred together with greater-than-chance frequency (19). Factor analysis has been used to suggest that insulin, triglyceride, HDL cholesterol, obesity, and increased waist circumference comprise the "central" components of the syndrome, with high glucose levels linked but existing as a separate factor and with hypertension again as a separate linked factor. Obesity and hyperinsulinemia may be the most crucial aspects of the IRS. The presence of IRS trait clusters predicts both the development of diabetes and CVD mortality. There are sex and ethnic differences in the causes of the IRS. Using the ATP-III factors and the NHANES data set, women more commonly have increased waist circumference, and men more commonly have increased triglyceride levels, with overall prevalence 24 and 23% in men and women, respectively, and levels increasing with age. Caucasians are more likely to have high triglyceride levels, while BP is more often elevated in African-Americans. The prevalence of the IRS is lowest among African-American males and highest among Mexican-American women. Combined analysis of data from the Framingham, NHANES, and San Antonio studies confirms these differences, with 24–28% of Caucasians and 32–38% of Mexican Americans having the IRS. The World Health Organization (WHO) suggests different criteria, proposing that the definition include increased 2-h postload glucose rather than fasting glucose as in ATP-III, increased BMI rather than waist circumference as in ATP-III, increased triglyceride or low HDL, hypertension (with different thresholds than ATP-III), and albuminuria (which is not included in ATP-III) (20). The Botnia study, which uses this definition, reports variation in prevalence from 34–46% in different European populations.

Meigs noted that the syndrome traits do not have equal predictive weights for specific outcomes, so that, for example, fasting blood glucose is more important than BMI, which in turn exceeds HDL cholesterol, with BP of least importance, in predicting diabetes. Meigs suggested a number of uncertainties, asking whether simply counting the number of traits is "good enough" or whether the traits should be weighed or grouped in clusters. If "trait clusters" are required rather than just counting the number of positive findings, the frequency decreases to ~15 and 25% in Caucasians and Mexican-Americans, respectively, an example of the impact of varying the definition on syndrome prevalence. Further questions are whether BMI or waist circumference is better for classifying individuals, whether insulin or urine microalbumin levels should be measured, and whether persons with diagnosed diabetes or diabetes based on glucose tolerance testing should be included. Meigs pointed out that one could "just identify the traits and treat them," rather than treating the syndrome, unless there is some way in which identifying the IRS confers added benefit. He concluded that there is not even agreement as to the name of the syndrome, and "we still don't actually agree" on many important aspects of the condition, but that it is clearly of great importance, as prevalence is likely to increase in the coming years as obesity increases.

Frederick Brancati (Baltimore, MD) discussed "emerging risk factors" for the IRS, noting that from the perspective of primary prevention it "sometimes feels like an inevitable sequence of events" that leads to diabetes and CVD. The Diabetes Prevention Project (DPP) and other studies suggest benefit of interventions, but even with optimal lifestyle modification there remained a 20% 5-year risk in the DPP and Finnish Prevention Study. Brancati recalled that Osler in 1892 discussed a number of risk factors for type 2 diabetes, including heredity, ethnicity, social class, adiposity, sedentary lifestyle, and overindulgence, as well as what one might now term novel risk factors such as "nervous strain" and worry, brain lesions, environment, infections, and liver disturbances. We now consider well-established risk factors to be age, obesity, inactivity, pregnancy, drugs, and endocrine and monogenic syndromes, and emerging risk factors to include genes, the fetal environment, inflammation, dietary macronutrients, and intracellular lipids, as well as newer risk factors including liver disease, mineral intake, stress and depression with hypothalamic-pituitary-adrenal (HPA) axis activation, abnormal lung function with sleep apnea, and endothelial dysfunction.

Based on NHANES data, subjects with hepatitis C show a 3.8-fold increase in diabetes risk (21), although Brancati

pointed out that either hepatitis C could cause diabetes, diabetes could increase risk of hepatitis C, or both could be caused by some underlying factor. The considerably more common illness, nonalcoholic steatohepatitis (NASH), is also associated with insulin resistance (22,23). In NHANES, 29.1% of adults in the U.S. had increased transaminase levels, with 2.3% related to alcohol use and 1.6% to hepatitis C, suggesting that almost one-quarter of adults have NASH, which is strongly associated with diabetes, particularly among women (24). Evidence that this is not due to alcohol intake has been assembled in a number of investigations. "If it's real," Brancati stated, "it could be associated with a very high population-attributable risk." Possible implications are for use of therapeutic agents targeted to the liver and for avoidance of hepatotoxic substances.

Serum magnesium <1.4 mg/dl is associated with doubling of diabetes risk, although it has some ambiguous features given that the mean level is lower in African-Americans than Caucasians, but magnesium is a stronger risk factor in the latter group (25). The mineral zinc may also be a factor, with Marreiro et al. (569-P) in a study presented at the ADA meeting randomizing 56 obese women with normal zinc levels and normal glucose tolerance to placebo or zinc 30 mg daily for 4 weeks, the latter showing a fall in insulin from 29 to 21 μU/ml, which is indicative of improvement in insulin sensitivity. Mineral supplementation may, then, play a role in preventive treatment of diabetes. As suggested by Osler, depression and stress may be factors in diabetes (26), although again the direction of causality is uncertain, with Brancati noting that subclinical hypercortisolemia from depression could cause insulin resistance (27). In the Atherosclerosis Risk in Communities Study, depressive symptoms were associated with increased fasting insulin, BMI, and triglyceride levels, with a 1.52-fold increase in risk of diabetes in the highest quartile of symptoms (28). A therapeutic implication is that depression/stress reduction might be relevant to diabetes prevention, or, perhaps, that anti-depressant treatment could ameliorate subtle abnormalities in the HPA axis.

Abnormal lung function and sleep apnea may be related to diabetes, as 2-h insulin levels show a progressive rise with increased frequency of sleep apnea. There is also an association of decreased forced vital capacity with diabetes, which might be related to cigarette use or to obesity. At the ADA meeting, Resnick et al. (955-P) reported overnight polysomnogram results in 4,882 persons ≥40 years old without history of CVD; of these subjects, 426 had diabetes. Subjects with diabetes had similar REM sleep times (18.9 vs. 20.1%), adjusted for age and BMI, but a twofold higher prevalence of periodic breathing, indicative of a central nervous system disorder and diagnosed if ≥10 consecutive minutes of a crescendo-decrescendo breathing pattern was observed. This suggested alterations in autonomic or metabolic control of ventilatory systems during sleep. It would be of interest to learn whether nondiabetic individuals with the metabolic syndrome in that study also had evidence of sleep abnormality.

Leif Groop (Malmo, Sweden) discussed genetic associations with what he termed the "dysmetabolic" syndrome. The Botnia study, named for the gulf of Botnia, which lies between Sweden and Finland, involves 9,315 persons from 1,389 families from the two countries. Groop noted that insulin sensitivity itself is only mildly hereditable, with monozygotic twins showing correlation with $r = 0.49$, but dizygotic twins only showing $r = 0.1$. Waist circumference, however, is much more strongly inherited. Genetic contributions to insulin resistance have been investigated by analyzing potential candidate genes and by random gene searches of the entire genome to find excess allele sharing in certain regions. A number of genes have been identified. The β-3 adrenergic receptor variant having substitution of tryptophan for arginine in position 64 is associated with the IRS (29,30), as well as with decreased metabolic rate, which might predispose to obesity. There is also a mutation at position 27 of the β-2 adrenergic receptor associated with high FFA levels. An intronic variant of the skeletal muscle glycogen synthase gene is associated with both insulin resistance and increased CVD mortality. (31,32). The mechanism of the association may be of affected subjects having a lesser effect of exercise on muscle metabolism. The proline 12 to alanine variant of the peroxisome proliferator–activated receptor (PPAR)-γ is a protective mutation that may account for 20% of the population risk of diabetes among Caucasians. (33). The variant is associated with a decrease in fat cell production and becomes manifest in individuals consuming a diet high in saturated fats. A mutation of calpain 10 is associated with insulin resistance and elevated FFA levels. Groop noted that calpain 10 mRNA expression is upregulated in individuals without family history of type 2 diabetes, but not in those at risk, and the level of expression in muscle is associated with insulin insensitivity. The winged helix/forkhead transcription factor gene (FOXC2) is another potential protective allele, which is expressed to a greater extent in visceral than in subcutaneous fat (34). Finally, a gene on chromosome 18P11 is linked to type 2 diabetes only in the highest BMI quintile of the population. The melanocortin receptor (which is also the ACTH receptor) is present in that region and may account for the linkage. Other linkages have been found without identification of potential causative genes, including one on chromosome 17 and one on chromosome 9. Thus, Groop concluded, a number of common variants, many of which influence FFA metabolism or impair scavenger factors, increase diabetes susceptibility.

In a study reported at the meeting, Hara et al. (157-OR) reported that allelic variations in the gene for PPAR-γ coactivator-1 were associated with differences in fasting insulin in 537 type 2 diabetic subjects and 417 nondiabetic subjects. Emphasizing the complexity of gene discovery, Yang et al. (1049-P) used DNA microarrays to analyze gene expression of SC adipose tissue and skeletal muscle biopsies specimens from eight insulin-sensitive and eight insulin-resistant persons. Of the thousands of sequences tested, 618 genes/expressed sequence tags were differentially expressed in adipocytes from the two groups, of which 199 upregulated genes could be assigned to known functional pathways, 101 involved in cell proliferation and 30 in cell growth.

Robert S. Schwartz (Denver, CO) discussed the IRS in the elderly, pointing out that aging is "the most important environmental factor" in causing insulin resistance. Body weight tends to increase through age 55 years in cross-sectional studies, but in longitudinal studies, weight actually tends to increase through age 65–70 years. Furthermore, there is a

decrease in lean body mass with age, so "for any given weight old people are fatter than young people." The deposition of fat shifts more to the visceral location in males after puberty and in women at menopause, and, while at all BMI levels individuals with a low waist-to-hip ratio (WHR) have diabetes risk approximately half that of those with normal or high WHR, even those individuals with normal BMI but high WHR have a threefold increase in diabetes rate. Thus, if obesity is more frequent with aging and , particularly, central obesity, one can expect the concomitants of hyperinsulinemia, diabetes, hypertension, dyslipidemia, coronary disease, elevated thrombotic factors, and homocysteine, as well as other features of obesity such as osteoarthritis, sleep apnea, and increased mortality rates. Analysis of NHANES data shows that the prevalence of diabetes increases with age in the U.S. population (35), and even individuals with normal glucose tolerance have higher postload glucose levels with increasing age.

In treatment, lifestyle intervention may be particularly appropriate for older subjects with the IRS, as shown in the DPP, where metformin had considerably less impact in those over age 60 years, while diet and exercise had similar benefit to that seen in younger age-groups. Schwartz also noted that although weight loss may not be as great with a program focused on exercise as with one focused on diet, the decrease in intra-abdominal fat will be similar with both approaches. Another area that may be important for future treatment is the potential for hormonal mediators of the features of the IRS that appear with aging. Schwartz noted that the IRS has many features in common with hypercortisolemic states, leading one to wonder whether this may be a factor. There is also intriguing evidence of relative decrease in growth hormone action with aging, shown by a decline in insulin-like growth factor 1 levels. Certainly, growth hormone deficiency is associated with increased fat mass, decreased muscle mass, and decreased insulin sensitivity. Finally, many features of hypogonadism appear with age, and there is some evidence that low testosterone is present with aging in men, perhaps similarly to the estrogen deficiency following menopause in women.

Michael Goran (Los Angeles, CA) discussed the IRS in children. He pointed out that type 2 diabetes is now an important problem among obese children and adolescents, having increased 10-fold in frequency over the past two decades in the U.S., particularly in minority populations. In a recent clinic-based study, 25 and 21% of obese children and adolescents, respectively, had IGT (36), and Goran described studies of Hispanic children with positive diabetes family history with IGT present in 38%. An important concept is that a healthy β-cell compensates for insulin resistance, but that in adolescents at risk of diabetes—because of underlying β-cell abnormality—the process is accelerated by the sudden decrease in insulin sensitivity occurring with puberty, which amounts to ~30% in normal adolescents (37) and is particularly prominent with obesity (38). Increased skeletal muscle intracellular lipid may play a role in this process (39). Approaches to treatment include metformin, which has been shown of benefit in adolescent girls with the polycystic ovary syndrome (PCOS) (40). There has been virtually no study of whether exercise is of benefit, and it will also be important to understand whether there is recovery of insulin sensitivity following puberty and what role this may play in the improvement of the IRS in affected adolescents.

In a study presented at the ADA meeting, Goran et al. (1439-P) reported African-American and Hispanic adolescents to have 35 and 29% decreases in insulin sensitivity, respectively, compared with Caucasians; these decreases were not explained by having higher visceral fat levels. Goran also found that the Hispanic adolescents had greater hepatic insulin uptake than the African-American group, which may explain the relatively low insulin levels in the former and higher insulin levels in the latter group. Klein et al. (938-P) reported on the prospective NHLBI Growth and Health Study of 2,379 girls aged 9–10 years at onset, showing that African American girls had higher BMI and fasting insulin levels initially, with a relative increase in obesity, compared with Caucasians during the 10 years of follow-up. Controlling for BMI and pubertal status, African-American ethnicity was associated with higher insulin levels, with differences between the groups increasing over time, potentially increasing risk of diabetes and CVD.

In view of the association of low birth weight with diabetes and CVD, Hermann et al. (1218-P) compared 14 men with birth weight below the 10th percentile and 16 matched control subjects with normal birth weight, all of whom were 21 years of age, and showed that glucose uptake during insulin infusion increased 1.5-fold vs. 2.5-fold, which is suggestive of insulin resistance, albeit forearm endothelial function and vascular reactivity to insulin were comparable. Jeffery et al. (1441-P), Kirkby et al. (1446-P), and Mallam et al. (1449-P) described results of the EarlyBird study of 307 5-year-old children and their parents. Only 1.4% of term infants had birth weight <2.5 kg, and there was no significant relationship between birth weight and insulin resistance, while current weight did show modest correlation with insulin sensitivity. Little correlation was noted between paternal and child insulin sensitivity. Resting energy expenditure measured by indirect calorimetry did not correlate with insulin sensitivity and showed positive correlation with body weight. Interestingly, girls had 27% more insulin resistance, in part due to higher SC fat and lower physical activity, and had higher triglyceride levels and lower HDL and sex hormone binding globulin levels.

Dunaif et al. (1054-P) reported studies of an allelic variation on chromosome 19p closely linked to the insulin receptor gene associated with PCOS. Women with PCOS positive for this allele had increased glucose without compensatory hyperinsulinemia, while brothers of women with PCOS who had the allele had high proinsulin levels, suggesting β-cell dysfunction. Hirschler et al. (1763-P) studied 74 obese Hispanic adolescents with mean age 12 years, 55% with acanthosis nigricans, with the physical finding showing strong correlation with the degree of obesity but not with glucose intolerance or insulin resistance per se. In a small study, Sellers et al. (1765-P) raised important caution about the use of metformin in children with type 2 diabetes. The authors randomized 18 children who had been treated without drugs for at least 3 months and who had HbA_{1c} >7% to either metformin, titrated slowly to a maximum of 2,250 mg daily, or placebo. HbA_{1c} and BMI were the same in both groups at 3, 6, and 12 months; five and four children in the metformin and placebo groups, respectively, required addition of insulin, and four in each group had <50% compliance. Side effects were ob-

served in four of the subjects who received metformin but in none of the subjects in the placebo group.

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