

Diabetes and Obesity

Part 1

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This is the fourth in a series of articles based on presentations at the American Diabetes Association's 67th Scientific Sessions, 22–26 June 2007 in Chicago, discussing aspects of the interrelationships between diabetes and obesity.

Obesity

Gerald Reaven (Stanford, CA) argued that obesity is not synonymous with insulin resistance. Measuring the steady-state plasma glucose (SSPG) during infusion of glucose and insulin to characterize insulin sensitivity, there is a continuous distribution of levels with a six- to eightfold variation from least to most insulin sensitive in the apparently normal population. SSPG correlates with both waist circumference and BMI in men and women but, Reaven noted, with “enormous variability” (1), only explaining ~25% of the variability in this measure. BMI and waist are similar in their power to identify individuals with abnormal SSPG, as well as in predicting abnormalities of glucose, triglyceride, HDL cholesterol, and other parameters associated with insulin resistance. A study of individuals of Malay, Chinese, and Indian ethnicity showed that metabolic syndrome frequently occurs without satisfying criteria for abdom-

inal obesity (2), with metabolic syndrome similarly only being moderately associated with directly measured visceral fat. Furthermore, not all obese individuals have insulin resistance, and those obese individuals showing metabolic benefits of weight loss belong to the insulin-resistant subset in the lowest tertile of insulin sensitivity. Comparing adipocyte cell size distributions of insulin-resistant versus insulin-sensitive obese individuals, the former have a greater proportion of small adipocytes, contradicting earlier concepts that large fat cells were metabolically less efficient. Preadipocytes from insulin-resistant obese individuals appear less capable of differentiating into mature adipocytes, perhaps explaining this finding.

In a study presented at the American Diabetes Association's 67th annual meeting, relevant to the concept of adipocyte subpopulations contributing to insulin resistance, Rittig et al. (abstract 18) measured perivascular brachial artery fat with magnetic resonance imaging, finding a significant correlation of this adipocyte depot with reduced insulin sensitivity, measured from euglycemic-hyperinsulinemic glucose clamp study (abstract numbers refer to the American Diabetes Association Scientific Sessions, *Diabetes* 56 [Suppl. 1], 2007).

Steven Schneider (New Brunswick, NJ) presented a series of observations complementary to Reaven's discussion, pertaining to cardiometabolic risk in the nonoverweight insulin-resistant patient, a type he termed metabolically obese normal weight (MONW) (3). Considering such individuals to be no more than 10% over ideal body weight and to exhibit hyperinsulinemia, he suggested other characteristics to include increased fat cell size (perhaps contradicting Reaven's observa-

tion that reduced adipocyte size may be related to insulin resistance), increased blood pressure, and increased triglyceride levels. Such individuals often are offspring of type 2 diabetic parents, themselves developing type 2 diabetes at relatively young ages, having history of myocardial infarction and of cholesterol cholelithiasis. Criteria for the MONW state are similar to those for metabolic syndrome (4), including hyperinsulinemic individuals with normal weight and multiple cardiovascular disease (CVD) risk factors (5). An alternative approach is to identify nonobese hypertensive individuals, recognizing this to be a group characterized by increased insulin and triglyceride levels and by decreased insulin sensitivity (6). In the U.S. National Health and Nutrition Surveys, MONW constitute a large number of at-risk individuals in the U.S. population (7). A Canadian study evaluating normal-weight individuals with features of insulin resistance showed a tripling in risk of CVD (8).

Schneider asked how knowledge of the existence of this group should influence our thinking, specifically addressing the usefulness of relying on simple measures of body weight, as the MONW concept implies that a large number of normal-weight individuals would benefit from interventions now thought appropriate for obese individuals. He discussed the usefulness of measures of adipose tissue other than that of total fat mass and the question of whether measures of insulin resistance and hyperinsulinemia would be useful in ascertainment of these abnormalities.

Clinically, we are not readily able to assess adiposity. The 75-kg man at age 53 years typically has 7 kg more fat and less lean mass than he had at the same weight at age 25 years, without apparent difference in physiognomy. Nondiabetic, nonobese offspring of type 2 diabetic parents will be found to have increased fat mass despite normal BMI (9). The concept of abnormal fat distribution dates to Vague's differentiation between benign and metabolic obesity, with relatively few metabolic abnormalities in the former group, the latter exhibiting the pattern of increased abdominal fat. There is clearly

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Abbreviations: CCK, cholecystokinin; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; ER, endoplasmic reticulum; IκB, inhibitor of κB kinase; IRS, insulin receptor substrate; JNK, c-Jun NH₂-terminal kinase; MONW, metabolically obese normal weight; SSPG, steady-state plasma glucose; TNF, tumor necrosis factor; UPR, unfolded protein response.

DOI: 10.2337/dc07-zb12

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an association between weight gain in adulthood and increased CVD and diabetes risks. Furthermore, regardless of the degree of obesity, the presence of greater abdominal fat is associated with greater reduction in insulin sensitivity (10). These observations have been confirmed in children (11), Asian Indians (12), and Japanese (13). Although fasting insulin predicts visceral obesity (14), Schneider commented that we cannot be certain that abdominal fat distribution is not a marker rather than a mediator of reduced insulin sensitivity. The concept of fat repartitioning is based on the notion that the presence of fat stores in liver and muscle is associated with metabolic abnormality. Lean offspring of patients with type 2 diabetes have increased intramuscular lipid concentration (15), and associations have been demonstrated between insulin resistance and increased intramyocellular lipid (16), as well as with increased hepatic insulin stores (17). A particular example exemplifying the MONW syndrome is HIV/protease inhibitor lipodystrophy, associated with increased intramyocellular and hepatic fat stores (18). Schneider pointed out that MONW always appears to be associated with decreased aerobic capacity (19), with offspring and other first-degree relatives of type 2 diabetic individuals having decreased aerobic capacity before development of diabetes (20,21). A possibility is that, rather than this being caused by a physically inactive lifestyle, poor aerobic exercise capacity might be associated with intrinsic abnormality of fat oxidation contributing to insulin resistance and, perhaps, to weight gain. There is intriguing evidence of mitochondrial dysfunction in thin offspring of type 2 diabetic parents (15).

Another relevant observation pertains to abnormal androgen metabolism. Mild testosterone deficiency has been demonstrated in type 2 diabetic patients, with an association with low testosterone and low sex hormone binding globulin (22). Population surveys have shown this hormonal pattern to be a predictor of metabolic syndrome (23), particularly increasing the likelihood of metabolic syndrome in nonobese individuals. Whether hypogonadism causes insulin resistance or certain effects of insulin resistance lead to abnormality of circulating androgens is not known. Certainly, Schneider concluded, it is important to develop approaches to the identification of MONW individuals, who exhibit high CVD risk, which often is not well treated. Energy

restriction and increased physical activity may be of therapeutic benefit in at least a subset of such individuals, with a number of studies suggesting that exercise improves insulin action in nonobese, as well as obese, individuals with and without diabetes (24).

Steven Blair (Columbia, SC) continued the line of observation, addressing the question of whether fitness protects against obesity. Sedentary lifestyle is strongly associated with type 2 diabetes, although many existing studies have been limited in relying on self-reported physical activity and diabetes. Blair reviewed a set of studies carried out over the past three decades, with maximal treadmill exercise testing for assessment of aerobic capacity. In a study of 7,442 men examined on two occasions, who had normal electrocardiogram and glucose tolerance and were without CVD, at 6 years' follow-up the risk factor-adjusted likelihood of impaired fasting glucose doubled with low fitness (25). Contrary to what one might expect, the number of obese individuals exhibiting acceptable physical fitness is not inconsequential, one study showing that 25% of women with BMI >36 kg/m² were physically fit (26).

The association between fitness and glycemic abnormality was similar in overweight and normal-weight groups. Blair reviewed further studies showing that metabolic syndrome incidence similarly is inversely proportional to maximal exercise capacity both in men and women. Among 1,200 individuals with impaired fasting glucose, fitness was associated with better outcome at follow-up, with similar studies in diabetic individuals showing fitness to protect against CVD mortality (27). Lack of physical activity and the proxy measure—the number of hours of television watching weekly—are associated with worse CVD outcomes, although one cannot be certain that the lack of activity itself is the mediator of adverse outcome. Mortality benefit is associated with greater physical fitness in diabetic individuals both with normal weight and with obesity (28). Taking into account both obesity and fitness, among fit individuals, there was no increased mortality with obesity; similarly, among unfit individuals, there was no increased mortality with obesity. “I’m not going to say ‘forget BMI,’” Blair concluded, “but we do need to pay more attention to fitness.”

Daniel Porte (San Diego, CA) presented further views of the relationship between obesity and diabetes, noting that

the effect of insulin in the brain is to decrease food intake, in a sense opposing its effect in the periphery, where it leads to fat storage. “The same molecule that acts in the periphery,” he said, “is playing a counterregulatory role for the regulation of food intake in the CNS [central nervous system].” Comparing animals during overfeeding, underfeeding, and ad lib feeding, body weight shows strong correlation with insulin levels (29). After the over- or underfeeding periods in this study, all animals had free access to food, and weight in all three groups rapidly equalized, which suggests that weight is closely regulated and that insulin might be a mediator of body weight stability. The hyperbolic relationship between insulin sensitivity and body weight in humans (30) is, of course, characteristic of a regulatory signal. Such observations led to the hypothesis of a feedback loop between insulin and central effectors of feeding, in which a central insulin sensor acts to decrease food intake (31). Direct intracerebroventricular administration of insulin in primates leads to rapid weight loss over a 20-day period (32), supporting this concept.

Central regulation of food intake is complex. Studies of cholecystokinin (CCK) administration reveal suppression of food ingestion with stable body weight (33). The compensation for CCK was an increase in meal frequency to stabilize caloric intake. Intracerebroventricular insulin administration potentiates the effect of CCK in decreasing food intake (34), suggesting that there are both short-term controls of food intake, influenced by various environmental, learned, and biological factors, and long-term controls, largely determined by biological factors promoting long-term stability of body fat mass, with the major candidates for the latter signals being insulin and leptin. Many short-term signals arise in the gut, either as hormonal factors or being relayed through vagal signals. Porte suggested, then, that there is a negative feedback system combining central and peripheral control of food intake, which may be considered programmable rather than exhibiting a hard wired set point (35). The afferent signals are, in general, circulating factors, including insulin, with insulin crossing the blood-brain barrier by a specific receptor-mediated transport system, as well as leptin, glucocorticoids, ghrelin, protein YY (3–36), glucagon-like peptide (GLP)-1, and amylin. These may be considered afferent sig-

nals of body adiposity, which are also regulated by nonadiposity factors. Single meal sizes are regulated by vagal neural inputs and by circulating hormones such as ghrelin and CCK, arising from the gastrointestinal tract, as well as what may be termed hedonic factors impacting the cerebral cortex. Central integration occurs in the hypothalamus; via amines such as norepinephrine, serotonin, dopamine, and neuropeptides Y; Agouti-related protein; melanocyte-stimulating hormone; cocaine-amphetamine-related transcript; orexin; and other factors. Central efferents lead to changes in food intake and energy expenditure. Obesity and cachexia, then, may be considered disorders of this regulatory system.

In animal models not expressing brain insulin receptors, obesity develops, as well as disruption of fertility (36). Similarly, reduction of hypothalamic insulin receptors increases food intake and fat mass in a dose-related fashion (37). Insulin activates the phosphatidylinositol 3-kinase pathway in the hypothalamus as it does in other insulin-responsive tissues (38). Animals not expressing insulin receptor substrate (IRS)-2 in the brain have a phenotype similar to that of those lacking the insulin receptor but, in addition, show an increase in circulating leptin levels (39). Porte suggested that leptin levels provide a measure of total fat mass, while insulin levels, increasing with the degree of insulin resistance, furnish a measure of visceral fat mass, with complex overall brain circuitry of insulin effect and that of other satiety signals (35,40). There also is evidence of acute central insulin effects, with intracerebroventricular administration of insulin antibodies increasing hepatic glucose production during euglycemic-hyperinsulinemic clamp, suggesting that part of the effect of insulin on the liver is centrally mediated (41). Porte summarized that an expanded view of insulin resistance includes the concept that reduced brain action of insulin, as well as of leptin, leads to positive energy balance causing obesity, while reduced insulin action in the periphery leads to hyperglycemia via deficiency in glucose uptake. There is fascinating evidence that intranasal insulin administration may lead to weight loss under certain circumstances (42), which may be interpreted to indicate enhanced brain uptake via this route. These considerations of the appetite-suppressing effect of insulin may explain the apparently lesser degree of weight gain when insulin detemir rather

than NPH is administered for glycemic control (43). Detemir may have a preferential effect on phosphorylation of hypothalamic IRS-2, perhaps caused by selective uptake of detemir into the brain when administered in a quantity producing similar peripheral effect to that of human insulin (44).

Inflammation: basis of obesity and diabetes

Gökhan Hotamisligil (Boston, MA), receiving the American Diabetes Association's Distinguished Achievement Award, reminded listeners that worldwide there were 200 million individuals with obesity in 1995 and 300 million in 2000, with projections for 500 million obese individuals in 2010, covering every area of the world, from the U.S. to sub-Saharan Africa. Obesity is associated with insulin resistance, type 2 diabetes, fatty liver, CVD, hypertension, and dyslipidemia, as well as with airway disorders, musculoskeletal conditions, neurodegenerative diseases, Alzheimer's—now being considered “diabetes of the brain”—and with malignancy. An important underlying mechanism appears to be the inflammatory relationship between metabolism and obesity may be relevant. Insulin action involves a complex signaling pathway. Increased tumor necrosis factor (TNF) α expression by white adipose tissue derived both from mature adipocytes and from stromal vascular cells occurs in a variety of states of obesity and of diabetes, with neutralization of TNF α improving insulin sensitivity (45). Mice not expressing TNF α are protected from obesity-induced insulin resistance, leading to improved glucose tolerance (46), with TNF α signaling acting on IRS-1 to increase serine phosphorylation, antagonizing the insulin receptor signaling effect of increased IRS-1 tyrosine phosphorylation. This appears to be a mechanism of action of many inflammatory cytokines, as well as explaining some aspects of lipid-induced inhibition of insulin action. There are multiple potential serine phosphorylation sites, so that the identification of specific effects of inflammatory cytokines on IRS-1 is extraordinarily complex. c-Jun NH₂-terminal kinases (JNKs) are intracellular mediators of inhibition of insulin action by TNF α (47). Another inhibitory kinase involved in this pathway, downstream of TNF α signaling, is the inhibitor of κ B kinase (I κ K), which plays a role in beneficial effects of aspirin (48).

Hotamisligil summarized, “The story

so far: IRS-1 serine phosphorylation occurs in insulin resistance and is critical. JNK regulation appears as mediator and therefore is expected to be a mechanism of insulin resistance in obesity and in type 2 diabetes.” JNK is markedly increased in obesity in muscle, liver, and adipose tissue (49). Obesity and type 2 diabetes lead to activation of the JNK1 isoform, a phenomenon not observed in an animal model deficient in this enzyme (50). Obesity is associated with a high degree of fatty infiltration of the liver, which is to a large extent blocked by absence of JNK1. JNK and I κ K act, then, in the development of insulin resistance, although it is not certain whether I κ K acts in the same fashion on IRS-1. This explanation of molecular mechanisms shows the central role of inflammation in insulin resistance and suggests potential approaches to treatment. Furthermore, there is evidence of a role of JNK in atherosclerosis, and there is now evidence that mutations in JNK binding proteins can cause diabetes (51), with the potential that small molecules inhibiting JNK may lead to new therapies for these processes (52).

JNK and I κ K may themselves activate the inflammatory cytokine response, potentially causing a “mini vicious loop.” An unanswered question is, “How do we get to [over] production of inflammatory cytokines in the first place?” Proinflammatory effects of excessive levels of nutrients, perhaps acting via reactive oxygen species or by causing mitochondrial dysfunction, appears to be an important initiating mechanism. Hotamisligil hypothesized that signals leading to alterations in JNK, transmittal of stress responses, or translation of metabolic stresses into inflammatory pathways may all take place at the organelle level and be communicated via intracytoplasmic signaling pathways. Dysfunction of the endoplasmic reticulum (ER) appears to be critical for metabolic disease. The ER is a vast membranous network covering much of the cell, acting as the synthetic organelle of cells, and plays a role in quality control by removing misfolded proteins. Excessive demand leads to the state termed “ER stress,” in which cellular responses referred to as the “unfolded protein response” (UPR) occur, a program activated by signals including excess protein load and a variety of other alterations in nutrients, energy, or calcium flux. UPR occurs with ER sensing of pathogen stress as well, suggesting that the ER may be thought of as an integrating system. UPR

involves nuclear transcription factor ATF-6, which controls gene expression of protein chaperones, used by the ER to compensate for stresses. Insulin response element-1 autophosphorylation activates X-box binding protein-1, another factor causing ER adaptation, and another kinase, PERK, leads to nuclear factor κ B activation, and suppresses protein synthesis, a negative feedback loop beneficially reducing the ER stress response. Given this background, a critical observation was the discovery that JNK is activated in the setting of ER stress, suggesting a role of the ER in activation of metabolic stress, with obesity potentially a condition of ER stress. XBP-1, in states of obesity, is associated with increased phosphorylation of JNK (53). ER stress, then, may lead to insulin response element-1-dependent JNK activation, resulting in insulin resistance, offering a potential route to the improvement of insulin sensitivity in type 2 diabetes, hepatic steatosis, and atherosclerosis. Mutations in UPR genes disrupt ER homeostasis and cause diabetes in animal models and in humans, while pharmacological modification of ER responses with chemical chaperones appears to represent an effective approach in animal models of diabetes. Obesity-induced JNK activation can be reduced to normal levels by administration of chemical chaperones, which decrease adipose tissue TNF α , interleukin-6, and other inflammatory mediator levels, reducing inflammation while not reducing fat mass.

If initiation of insulin resistance does take place within the cell at the organelle level, in addition to the ER, mitochondrial and/or nuclear abnormalities may be further causes. Hotamisligil discussed aspects of the linkage between nutrition and metabolism. Nutrient and pathogen-sensing pathways are integrated, as are metabolic and inflammatory pathways. "The way we respond to bugs," he said, "is not all that different from the way we respond to food." The fat body of the fruit fly, which corresponds to liver and hematopoietic tissues in mammals, also shows similarity to mammalian adipose tissue (54). The immune and metabolic systems, then, may be considered to have "once [been] part of the same organ structure . . . As such, these organs maintain their metabolic heritage." Metabolic and inflammatory cell types appear in close proximity both in adipose tissue and in liver. Under normal circumstances, an overt inflammatory response is not seen,

suggesting controlling mechanisms. Thus, an important question is not what causes obesity to be associated with inflammation, but rather, what prevents an inflammatory response from occurring following normal nutrient ingestion?

Molecular mediators are present in adipocytes and respond to nutritional cues. STAMP2 was found from a genome scan, appearing to act as an insulin-sensitizing agent, showing linkage to prostate cancer and highly expressed in white adipose tissue. In normal lean animals, STAMP2 is stimulated in visceral adipose tissue by feeding (55). In obese animals, this regulation by feeding is lost, with baseline levels increased in all tissues. The normal regulatory pathways may then not be active in obesity, perhaps explaining its association with inflammation, as animals not expressing STAMP2 show visceral adipose tissue macrophage infiltration and increased expression of interleukin-6, eventually developing the phenotype of metabolic syndrome with insulin resistance and glucose intolerance. In a variety of ways, then, nutrient and energy status is linked to health. Just as undernutrition is almost always associated with immune system suppression, overnutrition is associated with immune activation, suggesting the importance of optimal nutrition. If such a nutritional status is achievable, these mechanisms "could be exploited to assist" in reversing the abnormalities associated with excessive nutrient intake.

Genetic aspects of obesity

At a symposium on genetic aspects of obesity, Alan Shuldiner (Baltimore, MD) discussed findings from genetics studies of the Amish. He recalled Claude Bouchard's concepts of gene-nutrition and gene-physical activity interactions in the context of factors leading to development of type 2 diabetes, from the viewpoint that lifestyle/environmental factors lead to outcomes modulated by genetic heterogeneity, with unpredictable degrees of linearity or nonlinearity in responses to various genetic differences. As an example, he cited the findings of the Nurses' Health Study that polymorphisms of the alcohol dehydrogenase 3 gene modulate alcohol-induced increases in HDL cholesterol. Individuals having the γ 1/2 or γ 2/2 genotype have slower alcohol metabolism and show greater degrees of increase in HDL with alcohol ingestion. Similarly, there must be genetic determinants of weight gain. This was shown particularly

clearly in the overfeeding experiment carried out by Bouchard two decades ago. Twelve pairs of monozygotic twins were followed for 100 days while ingesting 840 calories daily in excess of their weight maintenance requirement, calculated during a 2-week basal period under sedentary circumstances (56). Weight gain, fat mass, and abdominal visceral fat of twin pairs showed high degrees of correlation, with the genetic effect explaining approximately half of the variance in increase in visceral adiposity. The degree of intrapair resemblance in fasting insulin level increased after overfeeding, and this association remained stable over 5 years. The resting metabolic weight increased by ~10% with weight gain, again showing strong correlation between twins.

Shuldiner noted that gene-nutrient interactions are seen in the GET READI Study of African American siblings, one with LDL cholesterol above the 50th percentile, on a high-carbohydrate, high-protein, low-fat, low-cholesterol diet, with increased fiber, potassium, magnesium, and calcium. Of the 170 individuals in the study, HDL decreased by 5 mg/dl and apolipoprotein A1 by 9 mg/dl, with marked variability, but great similarity between siblings, suggesting a gene-environment interaction. In a weight loss study, the Quebec Negative Energy Balance Study, seven pairs of monozygotic twins with increased body fat exercised for 15 min twice daily to achieve a 580 calorie daily energy deficit for 100 days, showing strong correlation between twins in change in weight, fat mass, and visceral fat levels. Similarly, a study of 14 pairs of obese monozygotic twins treated for 28 days with a 400 calorie per day diet showed strong correlations in the degree of weight loss and of fat loss. Three genes appear to account for 15% of the variance in weight gain, the genes for the ADRA2 α -adrenoceptor, the NR3C1 glucocorticoid receptor, and lipoprotein lipase. Activity of phosphofructokinase, oxoglutarate dehydrogenase, and cytochrome oxidase are markers of mitochondrial activity that may explain some of these phenomena.

In the HERITAGE family study, another gene-exercise interaction study, 99 families including 483 sedentary individuals without CVD, hypertension, or diabetes completed a thrice weekly exercise program, with a mean increase in energy expenditure of 380 calories per day (57). There was a within family association of calorie expenditure and of fasting insulin,

cardiac output, and a variety of other parameters. Gene markers of this phenomenon included the angiotensinogen and ACE genes (58). Thus, in a variety of settings, the benefits of physical activity and both benefits and adverse effects of changes in diet/nutrients are modulated by genetic heterogeneities.

Molly Bray (Houston, TX) further discussed the genetics of exercise-induced changes in body composition, noting the variability of response to diet interventions. Exercise-induced weight loss appears to be less, but more lasting, than that occurring with diet. A number of changes occur in gene expression with exercise. Muscle contraction decreases ATP, increases AMP, stimulating AMP kinase, endothelial nitric oxide synthase, p38, and acylCoA carboxylase, leading to increased muscle glucose uptake and consequently improving insulin sensitivity (59). Exercise increases the efficiency of fuel processing, increasing the metabolic rate. Genes may have different effects with and without exercise, as shown by variability among individuals in responses to exercise of HDL, VO_{2max} , heart rate, and numerous other physiologic parameters exhibiting familial components (60). The $\beta 2$ adrenoreceptor gene polymorphism GLN27GLU is associated with increased obesity and greater likelihood of hypertension in physically inactive individuals, but the deleterious allele fails to show an adverse phenotype in individuals engaging in regular physical activity (61). In the Atherosclerosis Risk In Communities cohort of 15,792 individuals, among African Americans, polymorphisms in the G-protein $\beta 3$ subunit showed opposite effect in likelihood of obesity among individuals with and without high levels of physical activity, with similar effects of the gene on hypertension. Particular adverse effect was associated with the combination of obesity and lack of physical activity, with TT homozygotes appearing to particularly benefit from lifestyle intervention. Altogether, Bray noted, some 200 genes have been found to be associated with effects of physical activity. In a further study of whether genes influence exercise adherence, college students were invited to participate in a thrice weekly exercise program, with variability in adherence to the program and in weight response. Age, sex, baseline activity, BMI, and self-motivation assessed by questionnaire did not correlate with these measures, while the degree of adherence and the change in waist were associated with

waist circumference and with the adiponectin, Agouti-related protein, dopamine D4 receptor, peroxisome proliferator-activated receptor γ coactivator 1, and proopiomelanocortin genes, suggesting genetic determinants enjoyment of regular exercise. Thus, as we need to better characterize genes affecting metabolism, it may also be useful to understand genes affecting what has been considered the psychological response to exercise training.

Jose Florez (Rockville, MD) reviewed new concepts of the transcription factor 7-like 2 (TCF7L2) gene, focusing on its relationship to metabolic measures and the response to interventions in the Diabetes Prevention Program (DPP). TCF7L2 was discovered as a diabetes-related gene in 2003 (62), with subsequent recognition that a polymorphism in TCF7L2 conferred risk of type 2 diabetes in populations in Iceland, Denmark, and the U.S. (63). TCF7L2 acts in a signal transduction pathway, leading to decreased phosphorylation of the cytoplasmic adhesion and nuclear signaling protein β -catenin. Mice not expressing TCF7L2 have a defect in gastrointestinal tract endocrine cells (64), which may reduce GLP-1 transcription (65). Human studies have confirmed an association of TCF7L2 with reduction in insulin secretion (66). In the DPP, 3,234 individuals with impaired glucose tolerance were enrolled, with metformin and lifestyle decreasing development of diabetes by 31 and 58%, respectively (67). Stratification of DPP participants by TCF7L2 genotype at rs79702 showed an explanation of diabetes risk, with carriers of the genotype having decreased insulin secretion (68). The increased diabetes risk was confirmed in a recent meta-analysis of multiple studies (69). The DPP lifestyle intervention included modest weight loss and an exercise program. Studying the lifestyle intervention-genotype interaction, the lifestyle intervention was particularly effective in those with the high-risk TT genotype, while the placebo group having the TT genotype had the highest diabetes risk. In contrast, metformin treatment response did not appear to be affected by this polymorphism.

Florez found that TT carriers had somewhat higher insulin sensitivity, although lower insulin secretion, noting that the apparent increase in insulin sensitivity may be an artifact of ascertainment and enrollment of individuals with impaired glucose tolerance not having diabetes in the DPP. Similarly, the finding

that the T-allele was more likely to be seen in lean controls and the C-allele in obese cases again may be related to the selection process. Population studies suggest that the T-allele is associated with decreased insulin secretion but not with reduced insulin sensitivity (70). Thus, the mechanism of the diabetogenic effect of TCF7L2 polymorphisms appears to be the association of the T gene with decreased insulin secretion and decreased incretin effect. Increased β -cell TCF7L2 expression appears to be associated with increased β -cell production but impaired processing of proinsulin, with preserved peripheral insulin sensitivity, but with decreased suppression of hepatic glucose production by insulin, indicating hepatic insulin resistance. Current studies do not show that GLP-1 levels vary by TCF7L2 genotype but rather that GLP-1-induced insulin secretion is decreased in T carriers. Full understanding of the effect of TCF7L2 on GLP-1 expression, on pancreatic β -cell gene expression, and in the liver and gastrointestinal tract is not yet available, and the molecular mechanism for impaired insulin processing and decreased incretin effect with TCF7L2 variants has not been established. Another important question is whether the assessment of TCF7L2 genotype would be useful in disease prediction and whether such information would allow more specific treatment.

In a study of another genetic variant related to diabetes presented at the American Diabetes Association's meeting, Powers et al. (abstract 271) reported that the rs1750330 polymorphism in the T-box15 gene, involved in embryonic development, was associated with obesity and increased waist circumference among women, but not in men, among 697 healthy, Caucasian, nondiabetic individuals. The T-box15 gene appears to inhibit adipocyte development, with the polymorphism suggesting a genetic variant with decreased activity, hence associated with increased adipocyte development and fat accumulation increasing the likelihood of obesity.

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