

Diabetes and Obesity

Part 2

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This is the fifth in a series of articles based on presentations at the American Diabetes Association's 67th Scientific Sessions, 22–26 June 2007, Chicago, Illinois. Clinical observations related to interrelationships between diabetes and obesity are presented.

Obesity prevention and treatment

Paul Whelton (New Orleans, LA) discussed approaches to lifestyle modification for weight loss, pointing out that the Nurses' Health Study showed that, compared with a BMI of 22 kg/m², BMI >25 and >30 kg/m² were associated with 5- to 10-fold and 30-fold increases in risk of developing type 2 diabetes, respectively, with each 5-kg increase in body weight associated with a 40% increase in diabetes (1). Of course, he pointed out, "it's not just diabetes"; obesity was also strongly associated with hypertension and hypercholesterolemia, as well as with mortality (2).

For a risk factor, Whelton pointed out, two features should be considered in calculating overall impact: the degree of risk of the condition and its prevalence in the population. In the U.S., >70% of men and >60% of women are overweight, and one-third of both sexes have obesity—"a

combination of high risk and huge prevalence." Overweight shortens life 3 years, and obesity 6 and 7 years for men and for women. Medical costs are 36% higher for obese than for nonobese persons, with a cost in the U.S. of approximately \$75 billion annually for obesity-related complications. "This is a crisis of national proportions," Whelton said, asking, "What strategies do we have to address this problem?"

We must ask whether lifestyle modification is effective in achieving weight loss, in changing risk factor profiles, and in reducing mortality. Further, we do not know whether persons achieving weight loss maintain lower weight over time. In a controlled trial of ~1,000 hypertensive persons on monotherapy enrolled in a trial of weight loss through behavioral intervention, reducing calories, and increasing physical activity, the control group had the same frequency of contact with the medical team (3). At 90 days, the control group experienced no weight loss, whereas the behavioral intervention group had a 4- to 5-kg weight loss, a finding typical of such studies, with the difference maintained over the 36-month period of intervention. At 90 days, the systolic blood pressure of the weight loss group decreased from 129 to 125 mmHg, and those with normal blood pressure were withdrawn from antihypertensive medication. Off treatment, blood pressure improvement was maintained in the intervention group, with 31% more not requiring pharmacologic treatment. Those also following a sodium-restricted diet had a 50% reduction in requirement to resume hypotensive medication. Whelton described a trial of hypertension prevention among 2,000 individuals with

high normal blood pressures. This trial involved a similar calorie and sodium reduction intervention and showed decreased development of hypertension by half over 18 months; the 7-year follow-up showed even more striking differences between the behavioral counseling and control groups. "Those individuals," Whelton said, "had retained the behavioral capacity to control their lifestyles." Weight loss has similarly been the most effective approach to the prevention of diabetes and to lipid reduction.

Whelton pointed out that we are not applying this knowledge, and that our current response to the obesity epidemic must be regarded as insufficient. Throughout the world, people eat more, with bigger portion sizes that are high in fat and sodium content, and this is "a huge problem." In China, there is "mass migration into the cities," with similar changes in body weight and worsening of risk factors (4) in the setting of marked reduction in physical activity (5). Understanding food labels, use of fruit and vegetable snacks, the availability of nutritional counseling for particular individuals, and the use of meal and calorie plans "can be done, [but] it's not occurring." We need to develop system approaches to address these problems and to provide appropriate interventions. "If obesity is one of our biggest national problems," Whelton asked, "why is it that we don't provide this care free to the patient?" He continued, "You have to be persistent [. . .]. With tobacco it took a long time to achieve the desired outcomes." As a further issue, Whelton noted that "many of the commercial [weight loss] programs [have paid] very little attention to quality control," perhaps in part explaining their lack of success in reducing weight.

Jack Leahy (Burlington, VT) discussed a particular problem for persons with diabetes: that of minimizing the weight gain often associated with insulin therapy. "The fear of weight gain related to starting insulin," he said, is an important consideration for patients and for physicians. In the UK Prospective Diabetes Study (UKPDS), all the interventions caused similar improvement in A1C, but there was considerably less weight gain

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Abbreviations: ADA, American Diabetes Association; CHO, carbohydrate; CPAP, continuous positive airways pressure; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; MUFA, monounsaturated fatty acid; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; UKPDS, UK Prospective Diabetes Study.

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with metformin, as compared with a 5-kg weight gain over 10 years with insulin. In a managed care database survey, larger weight gain was seen with insulin than with other therapies.

In type 1 diabetes, the subset of the Diabetes Control and Complications Trial (DCCT) intervention group in the highest quartile of weight gain had a mean 15 kg increased weight, which was associated with worsening of cardiovascular risk factors, suggesting potential harm, although both the UKPDS and DCCT interventions were, overall, successful in reducing cardiovascular risk. Not all persons starting insulin gain weight, but, he said, "there are likely to be subgroups," some of which benefit despite weight gain, such as those with highest initial A1C and greatest decline, those with greatest pretreatment weight loss, and those with greatest initial weight, while there may be lower risk of weight gain in those of Asian ethnicity and in older persons starting insulin. Potential mechanisms of weight gain with insulin include decreased glycosuria, decreased resting metabolic rate due to reduction in glycemia, decreased osmotic diuresis, and insulin's anabolic effect, particularly on adipose tissue. A concern is weight gain because of defensive eating to avoid hypoglycemia. In a recent study of diabetic persons gaining 6 kg on initiation of insulin treatment, nuclear magnetic resonance imaging showed most of the weight gain in fat, particularly subcutaneous rather than visceral, also with increased total body water. Energy intake has not been shown to be greater, and physical activity to be lower, with the most important factor being the reduction in glycosuria, explaining much of the excess calorie balance required to explain weight gain. A failure of resting metabolic rate increase, as usually seen with weight gain, suggests an additional mechanism of weight gain with insulin treatment.

Advising individuals who are beginning insulin treatment to carefully monitor their diets and to reduce snacking appears to have relatively little effect. Initiating insulin treatment well before the development of marked hyperglycemia, so that the phenomenon of abrupt reduction in glycosuria does not occur, may be more effective. A number of pharmacologic approaches may be considered to reduce weight gain with insulin treatment. Metformin may decrease energy intake. In a Finnish study of type 2 diabetic people treated with NPH at bedtime, the most effective strategy was its addition to met-

formin, which reduced weight gain and to some extent led to greater glycemic improvement (6). In a review of this topic, Leahy found seven prospective studies of insulin alone versus insulin plus metformin, and consistently showed the combination to be associated with lower A1C and lessening of weight gain. Leahy commented, though, that in "the real world," weight gain is not eliminated. Furthermore, administering metformin after individuals have begun insulin does not necessarily have the same outcome as adding insulin to metformin. Moreover, there is no evidence that the addition of metformin to insulin-treated individuals offers the same cardiovascular benefit as demonstrated in the UKPDS with metformin monotherapy. Another interesting question that has not been well explored is whether there is a role for metformin in overweight and/or suboptimally controlled individuals with type 1 diabetes.

Analog insulins may have relevance to weight gain. There is a consistent body of data suggesting less weight gain with insulin detemir than with NPH, perhaps because the fatty acid moiety allows differential tissue entry, and perhaps with detemir having a preferential effect on brain satiety mechanisms. In a 52-week trial comparing the two agents, A1C fell from 8.6 to ~7% with both, with a 3.9- vs. 3.0-kg weight gain with glargine versus detemir. Comparing the two treat-to-target 24-week trials of glargine and of detemir compared with NPH, there was greater weight gain with glargine than with detemir with an equivalent improvement in A1C.

Pramlintide is an analog of amylin, the peptide that makes up islet amyloid. Amylin is a 37-amino acid peptide secreted with insulin by β -cells; it reduces glucagon secretion after meals and slows gastric emptying, and has a centrally mediated satiety effect. In a 24-week trial of insulin-treated diabetic individuals receiving pramlintide versus placebo, A1C decreased from 8.1 to 7.6% in both groups, but with reduction in insulin dose and weight loss with the addition of pramlintide. Postprandial glucose decreased considerably with the agent, and because of its effect in delaying gastric emptying, some patients have better effect using regular insulin than rapid-acting analogs for preprandial boluses. Pramlintide may be particularly useful in insulin-treated type 2 diabetes and in insulin pump-treated individuals, and it should be considered in type 2 diabetic patients

receiving only a basal insulin in need of prandial treatment. The agent is being studied for weight loss in normoglycemic obese individuals. Exenatide may have similar effect, although the agent has not yet been studied in this fashion.

Jonathan Purnell (Portland, OR) discussed issues pertaining to weight gain in type 1 diabetic individuals, with focus on the DCCT. An important subset of post-pubertal participants in the study was the group of intensively treated individuals who had substantial weight gain. Compared with age, sex, and BMI-matched nondiabetic individuals, the conventionally treated group showed similar weight change with time. Excess weight gain in the intensively treated cohort was fully accounted for by those in the top quartile of weight gain (7). Their improvement in glycemia was identical to that of the lower three quartiles. Comparing the first with the fourth quartile, the former with no weight gain, those who gained weight had significantly higher LDL cholesterol, lower HDL cholesterol, and higher triglyceride levels. Lipoprotein fractionation showed increased VLDL, IDL, and dense LDL cholesterol levels; Purnell pointed out that all are atherogenic. Compared with the nondiabetic population, those in the lower quartile had improvement in lipids, while those in the top quartile "got the microvascular benefits but the macrovascular risks were worse." This subset of type 1 diabetic individuals with weight gain resembles those from the Pittsburgh Epidemiology of Diabetes Complications Study who appear to have worsening of 10-year cardiovascular outcome (8). Given the similarity of their dyslipidemia to that seen in the metabolic syndrome, the DCCT participants with weight gain were studied for evidence of insulin resistance. They indeed required higher insulin doses and had higher waist circumference and blood pressure levels, suggesting that "excessive weight gain with intensive diabetes management led to dyslipidemia. . . , central obesity, and insulin resistance." Those who gained the most weight had similar age, initial BMI, blood pressure, and C-peptide levels, but at baseline their A1C level was higher despite a similar insulin requirement, suggesting insulin resistance. In the overall intensive treatment group, using a modified set of metabolic syndrome criteria not including diabetes, the prevalence of this insulin-resistant state was 8%; including diabetes, the metabolic syndrome was seen in 14%, the same level seen in an

age-matched nondiabetic population. Those in the top quartile of weight gain, however, had increased prevalence of the syndrome. Furthermore, comparing the lowest and highest quartiles of weight gain, carotid intima-media thickness was increased. Purnell concluded that weight gain in this subset of type 1 diabetic individuals represents a barrier to attaining glycemic control, pointing to its association with reduced patient perception of health quality of life and to the potential for adverse cardiovascular outcome.

Richard Bergenstal (Minneapolis, MN) discussed pharmacologic strategies for weight loss in individuals with type 2 diabetes. Reaching glucose, lipid, and blood pressure targets; taking aspirin; and lifestyle modification all are important in these patients, he pointed out, commenting, "We like the incretins because of their either weight neutral or weight loss potential." When cost is a problem, these may not be appropriate. Other potential approaches include the two agents currently approved for long-term use in weight reduction, orlistat and sibutramine; rimonabant, which is available in Europe; and pramlintide, which is emerging as a potential therapeutic option. Bergenstal reviewed a number of analyses suggesting that increased risk does not begin until the BMI exceeds 30 kg/m², although recommendations have been made to consider pharmacologic weight-loss treatment in diabetic patients who have BMI levels exceeding 27 kg/m². "Lifestyle modification," he suggested, "should be the base," emphasizing the need for clear goals in managing these patients, ideally using "more than BMI," perhaps with measures of visceral fat, although he recognized the controversy pertaining to the use of waist circumference. Furthermore, it is crucial that individuals responding to weight loss medications continue these medicines long-term. For optimal benefit, weight loss medicines must be given along with behavioral interventions (9).

Phentermine is approved only for periods of <6 months, and similar agents have been shown to increase risk of valvular heart disease and hemorrhagic stroke, so caution is needed with this approach. Close to one-third of individuals receiving sibutramine lose at least 5% of initial weight, but Bergenstal noted that there is a modest increase in pulse and blood pressure, which is why the drug is not recommended for hypertensive patients. If only those individuals who show

a response to sibutramine continue the treatment, 2-year weight loss has been demonstrated. A long-term cardiovascular disease (CVD) outcome trial of ~9,000 individuals is in progress, with results to be available in 1–2 years. Orlistat blocks absorption of up to one third of ingested fat, and now is approved in a 60 mg dose as an over-the-counter product, which blocks ~20% of fat absorption. In Hollander's study of type 2 diabetic patients receiving this agent, weight decreased 6% over one year with a fall in A1C of 0.5%. Both sibutramine and orlistat show lipid benefit.

The cannabinoid receptor blocker rimonabant, Bergenstal said, represents "a fascinating system being explored." The agent is associated with weight loss and apparently with direct inhibition of lipogenesis. Diabetic patients show nearly a 6 kg weight loss, with 6 cm decrease in waist circumference, rise in HDL cholesterol, reduction in triglyceride, and improvement in A1C by 0.6–0.7%. There is, however, concern that rimonabant may be associated with increased likelihood of anxiety and depression. Ongoing studies in individuals with impaired glucose tolerance and in those with CVD will give further information.

Exenatide "addresses a lot of the defects," with open-label extension studies showing evidence of stable glycemia at 3 years and modest ongoing weight loss. The use of exenatide in a long-acting form may give greater A1C improvement and weight reduction. Comparing the immediate-release form of exenatide with insulin glargine, similar A1C improvement has been reported, but with weight loss rather than with weight gain, an experience also found in comparison of exenatide with mixed insulin preparations. The amylin analog pramlintide also has been reported effective in glucose-lowering with evidence of reduction in weight. Future studies may involve combination treatments with leptin, with evidence that the two have an additive effect. Peptide YY, topiramate, new lipase inhibitors, fatty acid binding protein inhibitors, "and lots of other endocannabinoids" are being developed. Bergenstal reminded the audience, however, to "consider these options but weigh the side effects," with lifestyle interventions more appropriate.

Additional aspects of obesity and its treatment were the subject of a number of presentations at the ADA meeting. Brehm et al. (abstract 64) compared two mod-

estly hypocaloric diets—one was comprised of 45% carbohydrate (CHO) and 40% fat, half of which was monounsaturated fat (MUFA); the other diet was made up of 60% CHO and 25% fat—for 1 year in 124 obese type 2 diabetic individuals with mean A1C 7.3%. (Abstract numbers refer to the American Diabetes Association Scientific Sessions, *Diabetes* 56 [Suppl. 1], 2007) Brehm et al. found similar 3.9- and 3.8-kg weight loss and improvements in blood pressure, A1C, and lipids. Paniagua et al. (abstract 1825) studied 11 offspring of obese type 2 diabetic parents during 28-day periods of diets enriched in saturated fat, in MUFA, and in CHO. The latter diet was associated with increased abdominal fat, reduced adiponectin in adipose tissue biopsy, and reduced insulin sensitivity. Stanhope et al. (abstract 62) compared 13 individuals with BMI 25–35 kg/m² ingesting fructose-sweetened beverages with 10 ingesting glucose-sweetened beverages comprising 25% of ingested calories, finding 24-h postprandial triglyceride levels to more than double with the former, while decreasing by 30% with the latter diet. Total and small dense LDL cholesterol increased 17 and 27%, apolipoproteins B 28%, and remnant lipoprotein triglyceride and cholesterol increased 77 and 53%, respectively, with the high fructose diet, with the abnormalities initially observed at 2 weeks and continuing through 10 weeks of observation. High-fructose corn syrup, a mixture of ~55% fructose and 45% glucose, is the sweetener used in most soft drinks in the U.S., with consumption of these products more than doubling over the past two decades, suggesting this to be an important factor contributing to dyslipidemia, and offering an important rationale for avoiding this dietary constituent.

Pharmacologic approaches to obesity were explored in a number of studies. Smith et al. (abstract 335) reported 12-month follow-up results of 143 nondiabetic individuals treated with pramlintide versus placebo, showing dose-related maintenance of 6-kg weight loss from baseline of 106 kg, with both 360 µg twice daily and 240 or 360 µg three times daily. Edelman et al. (abstract 1826) studied 44 type 2 diabetic individuals treated for 16 weeks with pramlintide 60–240 µg three times daily before meals (72% tolerated the full dose). Placebo-corrected weight decreased 3.7 kg and abdominal girth decreased 5 cm. A1C decreased from 6.5 to 6.4% with pramlintide, while

increasing to 7.1% with placebo. Manon Khazrai et al. (abstract 1,835) studied 20 obese individuals with a calorie-restricted diet and an exercise program, finding that those assigned to use a buccally absorbed glucose solution giving 0.5–2.0 g glucose daily for subjective hypoglycemia symptoms had 50 vs. 20% likelihood of >5% weight loss at 4 weeks.

Dixon et al. (abstract 1,834) randomized 60 individuals with BMI >30 and <40 kg/m² and diabetes of <2 years' duration to conventional treatment, including intensive lifestyle, or to laparoscopic adjustable gastric band placement, finding 21 vs. 2% weight loss at 2 years. Remission of diabetes, with fasting glucose <7 mmol/l and A1C <6.2%, without hypoglycemic treatment, was seen in 76 vs. 15%, and was strongly associated with weight loss, with a 13% weight loss cutoff providing an 85% sensitivity and 86% specificity for remission. The authors reported no serious complications in either treatment group. This may be a particularly good outcome, however, as a recently reported study of bariatric surgery in 39 type 2 diabetic patients with a mean BMI of 31 kg/m², though improving glycemia, led to one death, with four individuals requiring reoperation for serious complications and with major morbidity (10).

Comorbidities associated with obesity and insulin resistance

Eric Olson (Rochester, MN) discussed obstructive sleep apnea (OSA) as a metabolic risk factor associated with CVD and with disorders of glucose metabolism. Closure of the nasal and/or oropharynx during sleep leads to either partial or complete obstruction. An apnea/hypopnea (respiratory disturbance) index of five or more episodes per hour of sleep occurs commonly. In the Wisconsin Sleep Cohort, approximately half of men and one-quarter of women snore at night, with one-quarter of men and one-tenth of women having evidence of sleep apnea (11). Above a BMI of 40 kg/m², half of men have >15 breathing pauses per hour, and approximately one-quarter of diabetic men have >10 breathing pauses per hour. These are cyclic disturbances, with acute periods of altered respiration alternating with periods of normal sleep. Part of the difficulty in determining whether there is a relationship of OSA to CVD is in the shared risk factors. The strongest linkage is that between OSA and hypertension (12). Among 1,000 men

evaluated every 4 years initially with normal blood pressure, there was a two- to threefold increase in risk of hypertension with OSA. An observational study of a similarly sized Spanish cohort found that those with severe OSA had increased risk of stroke, and those treated with continuous positive airways pressure (CPAP) had a reduction in risk to a level similar that of individuals only exhibiting snoring. In the Sleep Heart Health Study of 6,000 individuals followed for development of heart disease, nocturnal cardiac arrhythmias were increased with apnea/hypopnea index >30/h. Individuals with OSA have increased risk of sudden death, and among individuals with OSA and congestive heart failure, CPAP was associated with a 10% improvement in ejection fraction at 1 and 3 months.

OSA is also associated with metabolic dysregulation. In animal models of intermittent hypoxemia, using the euglycemic clamp technique, insulin resistance can be shown after a several-day period, and there is evidence of sympathetic activation in this model, with sympathetic blockade preventing the development of insulin resistance. Other potential mechanisms include activation of cytokine release. There is also a U-shaped relationship between BMI and average hours of sleep per night, with BMI increasing as sleep deprivation worsens, suggesting another mechanism of association between OSA and dysglycemia. Although no longitudinal data as yet show that OSA predicts subsequent diabetes, among 2,656 participants in the Sleep Heart Health Study, those with apnea/hypopnea index >15/h had a 50% increase in likelihood of developing fasting glucose \geq 110 or 2-h glucose \geq 140 mg/dl (13), with the index strongly associated with the degree of insulin resistance after controlling for obesity.

Andrea Dunaif (Chicago, IL) discussed CVD risk in the polycystic ovarian syndrome (PCOS), proposing that androgen levels are a "new risk factor" for CVD. Anovulation and hyperandrogenism define PCOS, with high worldwide prevalence, associated with insulin resistance and obesity, with prevalence increased in premenopausal women with type 2 diabetes. 5% of nonobese and 20% of obese women have elevated androgen levels. Women with PCOS have a two- to threefold increase in prevalence of abnormal glucose tolerance, with ~10% of women with the syndrome having undiagnosed type 2 diabetes, and with ~70% of young

obese women with PCOS having the metabolic syndrome.

CVD risk has been well demonstrated to be associated with PCOS. Although CVD occurs infrequently in women of reproductive age having PCOS, so that it has been difficult to demonstrate increased events, there is evidence of coronary artery calcification, impaired fibrinolysis, and endothelial dysfunction with the syndrome, and PCOS is associated with increased diabetes risk even among women who are not obese. Women with PCOS and metabolic syndrome have higher androgen levels than do those without the syndrome, with androgens predicting increased risk of diabetes. Dunaif described a study of women with PCOS treated with the antiandrogen flutamide, reducing visceral adiposity and improving glucose tolerance. The risk of PCOS is increased among family members, with a 70% concordance between female siblings, and with "the common underlying phenotype elevated androgens," although only half of the sisters with increased androgens have chronic anovulation, suggesting hyperandrogenemia to be the primary mediator of the syndrome; among male family members, interestingly, androgen levels are low. Discussing OSA, Dunaif noted that she has shown an association of sleep apnea with PCOS, with correlation between the apnea/hypopnea index and testosterone level. She also pointed out that the most sensitive androgen measurement for the syndrome is the free testosterone, best calculated based on the bioavailable level using the total testosterone and sex hormone binding globulin level, with mass spectroscopy rather than radioimmunoassay the better assay for testosterone.

Anna Mae Diehl (Durham, NC) discussed nonalcoholic fatty liver disease (NAFLD), the spectrum of disease ranging from steatosis, the accumulation of fat, to nonalcoholic steatohepatitis (NASH), involving an inflammatory response, which may trigger fibrosis and go on to cirrhosis. NAFLD is strongly associated with obesity, with insulin resistance, and with type 2 diabetes. In a study presented at the ADA meeting, Oliveira et al. (abstract 1868) performed hepatic ultrasonography in 432 children and adolescents, finding the pattern of NAFLD to be associated with higher alanine transaminase, aspartate transaminase, γ -glutamyl transphosphatase, and triglyceride levels, with alanine transaminase >38 units/l offering the greatest degree of prediction,

though only with a positive predictive value of ~10%. Overeating is associated with increased liver fat deposition. Triglyceride is the end product of fatty acid metabolism, with hepatocytes having active fatty acid metabolism with potential to oxidize fat, to export fats as lipoproteins, or to store fat as triglyceride. One-third of adults in the U.S. are obese, and >80% of them have NAFLD. Visceral adipose tissue in particular promotes a cytokine pattern associated with decreased insulin sensitivity, leading to uncertainty as to whether increased fatty acid availability increases hepatic triglyceride synthesis; increased liver fat is caused by hepatic cytokine-related insulin resistance. In either event, there is crosstalk between liver and fat, either of which is potentially capable of initiating the cycle of fatty liver and insulin resistance. The question of why hepatic fat is harmful is not fully answered. Hepatocytes incubated in methionine-deficient media are subject to oxidative stress with reduced VLDL secretion, causing increased fat deposition and leading to increased apoptosis. In vivo, in a model of reduced triglyceride synthesis, oxidative damage is increased. It is possible, then, that fatty acids are the actual mediators of hepatic damage, with triglyceride a marker of increased fat exposure rather than directly causing hepatic damage. Not all models of NAFLD show response to insulin sensitizers, although there is evidence that pioglitazone is beneficial in approximately half of clinically treated individuals. Why, then, do diabetic individuals have worse NAFLD? Diabetes is associated with abnormalities of cellular repair, which affects the β -cell and is associated with microvascular disease. Diehl suggested that similar processes may lead benign NAFLD to progress to NASH. Myofibroblastic stellate cells produce growth factors for hepatocyte progenitor cells. Progression to fibrosis rather than initiation of reparative processes may involve abnormal signaling mechanisms, although it is uncertain whether this process is related to insulin resistance.

Another ectopic fat deposition disorder is lipotoxic heart disease. Lidia Szczepaniak (Dallas, TX) discussed this condition, noting that in animal models, both diabetes and obesity are associated with increased myocardial fat and with cardiac dysfunction. Ceramide production may mediate a portion of this condition, and myocardial apoptosis is increased. Szczepaniak showed evidence

that thiazolidinediones prevent cardiac steatosis in an animal model of acetyl CoA synthase overexpression with increased myocardial fat, with consequent improvement in cardiac function. There is some clinical evidence of a condition of “fatty heart,” with recent evidence that obesity is associated with increased cardiomyocyte fat levels. Localized proton magnetic resonance spectroscopy has been used to quantitate myocardial triglyceride in specific regions, correlating with decreased cardiac function, and is associated with greater BMI and with a lower degree of physical activity. Impaired glucose tolerance and diabetes are associated with high myocardial triglyceride and impaired diastolic function, but Szczepaniak reviewed a study with thiazolidinedione treatment showing reduced myocardial triglyceride without restoration of diastolic function in insulin-treated individuals, suggesting the need to initiate such treatment at an earlier time.

Diabetes studies

A number of studies presented at the ADA meeting addressed additional aspects of diabetes. Clausen et al. (abstract 80) studied 160 and 128 offspring, respectively, of women who had had type 1 diabetes during pregnancy and of nondiabetic women, the offsprings 18–27 years old, finding 9% vs. 3% with impaired fasting glucose or impaired glucose tolerance and 15% vs. 6% having metabolic syndrome, suggesting an effect of the abnormal intrauterine environment leading to subsequent abnormal β -cell function and/or to insulin resistance. In an observation potentially related to interactions between glucose and mineral metabolism, Flores et al. (abstract 68) found that 86% of individuals with fasting glucose >125 mg/dl, but 70% of those with lower glucose levels, had serum 25-hydroxy-vitamin D levels <70 nmol/l, with calcium intake \geq 1g daily associated with 54% reduction in the likelihood of diabetes. Vitamin D may also benefit the immune system, so that the association between glucose intolerance and vitamin D deficiency may be relevant to manifestations of autoimmunity. Libman et al. (abstract 1866) measured glutamic acid dehydroxylase-65 and IA-2 antibodies in 130 nondiabetic children mean age 13, with BMI above the 98th percentile. 16 had at least one β -cell antibody and six were positive for both, with the autoantibodies associated with lower adiponectin and higher C-reactive protein and leptin levels, but

with similar BMI, body fat, and glucose and insulin levels. Thus, the insulin-resistant state, which is associated with increased levels of inflammation, may also be associated with immunity at the level of the β -cell similar to that causing type 1 diabetes.

Pearson (abstract 953) reported data from the U.S. National Ambulatory Medical Care Survey that the number of adults who had been told of diabetes increased from 9 to 16 million from 1995 to 2004, while the number of office visits with diabetes as primary diagnosis increased from 13 to 27 million during this period. Mason et al. (abstract 40) studied the pattern of change in glucose among 274 Pima Indians progressing to diabetes over observation periods with biennial glucose tolerance testing ranging to >30 years. After a long period of slow increase in 2-h blood glucose by ~10 mg/dl, a considerably more rapid increase from ~140 to 200 mg/dl occurred over a period averaging 4.5 years, suggesting that there is a stage of more rapid deterioration in postprandial glycemia, presumably associated with abrupt loss of insulin secretory capacity, preceding the clinical appearance of diabetes. Looking further along the natural history of the disease, Bilo et al. (abstract 933) described use of diet alone, oral hypoglycemic agents, and insulin in a cross-sectional study of 6,850 type 2 diabetic individuals in the Netherlands with diabetes duration <2 to >20 years, with mean A1C increasing from 6.5 to 7.3%, and insulin use increasing from 2 to 64%, the latter finding suggesting that even with maintenance of relatively good glycemic control, insulin secretion then continues to decrease (though perhaps in a more gradual fashion) throughout the course of the disease.

Hanley et al. (abstract 41) studied determinants of diabetes among 1,070 initially nondiabetic individuals, of whom 85 developed diabetes over a 5-year period. Reduced insulin sensitivity and reduced acute insulin response were significant determinants, while visceral adipose tissue mass was not significantly associated with diabetes in the overall population, after adjusting for age, sex, ethnicity, impaired fasting glucose, and BMI, although the latter measures may have reduced the strength of an effect of visceral adiposity, and there was evidence of an association between visceral fat and diabetes among women. In a separate analysis of 868 individuals from this population, of whom 142 developed diabetes

over 5.2 years, Haffner et al. (abstract 44) showed similar 8–9% annual diabetes risk among individuals with metabolic syndrome who had fasting glucose either 100–125 or 110–125 mg/dl, suggesting the former range of glycemic abnormality to allow identification of a greater number of individuals at risk when additional features were also required. Gregg et al. (abstract 42) used data from 37,307 adult participants in three U.S. National Health and Nutrition Examination Surveys (NHANES) carried out from 1976 to 2004, a period during which diabetes prevalence increased from 5.1 to 8.8% of the adult population. Increases in overweight (BMI 25 to <30 kg/m²) contributed to approximately one-fifth of the increase in diabetes in the U.S. population, and increases in class I obesity (BMI 30 to <35 kg/m²) contributed approximately one-third, while increases in more severe obesity (BMI >35 kg/m²) contributed to approximately half of the increase in diabetes prevalence. Given the smaller size of the latter group and their relatively great effect on diabetes, this might be a particularly useful area of focus. Wilson et al. (abstract 43) followed 1,004 individuals with fasting glucose 100–125 mg/dl and/or 2-h glucose 140 to <200 mg/dl for 7 years, with 118 requiring diabetes treatment or developing fasting glucose >125 mg/dl. In multivariate analysis of the population, parental diabetes, obesity, and low HDL cholesterol each were independently associated with two- to -threefold increases in diabetes risk. Valensi et al. (abstract 950) studied 1,274 individuals with overweight or obesity, mean age 39 years, with only 1.4% having fasting glucose >125 mg/dl but 6.1% having diabetes based on glucose >200 mg/dl, 2-h after 75-g oral glucose; similarly 6.4% had fasting glucose >100 mg/dl but 19% had 2-h glucose >140 mg/dl. The authors concluded that the fasting glucose alone only recognizes one-quarter to one-third of obese/overweight individuals with dysglycemia. Bertoni et al. (abstract 922) studied 5,450 initially nondiabetic individuals at mean age 62 years, finding that over a 3.1-year follow-up, with 312 individuals developing diabetes, C-reactive protein and interleukin-6 were significant risk factors after adjustment for BMI, hypertension, and impaired fasting glucose, suggesting a role of inflammation in development of diabetes.

Devers et al. (abstract 946) measured waist circumference, blood pressure, fasting plasma glucose, triglyceride, and HDL

cholesterol in 1,429 individuals to address the criticism of the metabolic syndrome concept that it simply combines a number of cardiovascular risk factors, without in itself giving additional information as to disease status. The syndrome prevalence was greater than that obtained by appropriately combining the prevalences of the individual components, with a greater-than-expected number of individuals having four or all five abnormalities; the authors suggested this to confirm the validity of the syndrome. Furthermore, individuals with normal waist circumference had a lower-than-expected prevalence of metabolic syndrome, with the authors suggesting that the International Diabetes Federation definition, requiring increased waist circumference using ethnic-specific cutoffs, offers a reasonable approach.

Gregg et al. (abstract 126) and Tao et al. (abstract 127) reported outcome among diabetic individuals from the three 1971–1994 NHANES cohorts, showing a nearly 40% reduction both in total and in cardiovascular mortality rates. The reduction was, however, only seen among men, so that at the present time the mortality of diabetic women is similar to that of diabetic men. Furthermore, the reduction in mortality was less than that among nondiabetic adults, so that cardiovascular mortality rates for diabetic individuals were double those for nondiabetic individuals from the 1971–1975 cohort, but triple those in the 1988–1994 cohort. Hirai et al. (abstract 924) followed 567 insulin-treated individuals with diabetes onset at age >30 for 16 years, finding that each 1% increase in A1C was associated with a 17% increase in cardiovascular mortality, each 1 unit · kg⁻¹ · day⁻¹ increase in insulin dose was associated with a 75% increase, and each 1 nmol/l increase in C-peptide was associated with a 35% increase, after adjustment for age, sex, BMI, diabetes duration, time since last meal, history of CVD, hypertension, and smoking. Both poor glycemic control and insulin resistance may, then, be mediators of adverse outcomes.

Duan et al. (abstract 128) followed 14,699 individuals initially without coronary heart disease (CHD) for 9 years. Metabolic syndrome was present in 39%, with these individuals, but not those without the syndrome, showing an association between obesity as measured either by waist circumference or by BMI with CHD risk, mediated in part by the other syndrome components, elevated

triglycerides, lower HDL cholesterol, elevated blood pressure, and elevated fasting glucose. Gregoire et al. (abstract 915) found that 36,429 diabetic individuals age >65 years receiving initial diabetes treatment with metformin had reduced mortality by 37 and 24% during successive 21-month follow-up periods in comparison with 18,528 such individuals initially treated with a sulfonylurea, while 2,548 receiving the combination of both agents had 19 and 34% increased mortality, respectively. Although these findings may represent differences in patient selection criteria, the qualitative similarity to the findings of the UKPDS suggests that caution may be appropriate in the use of sulfonylureas in combination with metformin.

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