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This is the first of two articles covering the American Association of Clinical Endocrinologists Meeting in Chicago, 1–5 May 2002. Topics include the sequencing of the human genome, obesity and diabetes, PPAR agonists, and erectile dysfunction.

Sequencing the human genome

J. Craig Venter (Rockville, Maryland) gave the keynote address, discussing his work in the sequencing of the human genome using high-through-put technologies with biocomputational analysis. He reviewed his initial work in the field during the 1980s sequencing the epinephrine receptor, a task which took a decade. He subsequently developed an approach using a “shotgun sequencing strategy” utilizing mechanical shearing to cut a whole genome into different sized expressed sequence tags (ESTs), developing a computational algorithm to piece the EST into a full genome. With the development of more powerful algorithms and computers, his group progressed from sequencing the *Haemophilus influenzae* genome, 1.8 Mbp, in 1995, to analyzing the *Drosophila* genome, 120 Mbp, and to sequencing the 3,000-Mbp human genome, reported in June 2000. “The biggest surprise,” Venter stated, “was the small number of genes.” Approximately 26,000 different genes were present, with some sections of chromosomes highly dense in genes, but many sections with very few genes. Overall, only 1.1% of the genome actually encodes genes, and 42% of those discovered are of unknown function. Comparison of the genomes of *Drosophila* with man reveals that new genes appear in the immune and hemostatic systems as well as many aspects of cell signaling, particularly those transcription factors that regulate the expression of other genes.

Venter noted the phenomenon of repeat gene sequences in the human genome. Chromosome 19 has the highest density of genes, many of which are repeated in other chromosomes. Analysis of these repeats, he suggested, may allow assessment of our “genetic history.” The mouse genome is 90% the size of that of man, primarily because of fewer repeated DNA sequences, but in general both show “the same genes in the same order.” Current analysis shows there is 95% similarity between the two species in that regard. Comparing humans with chimpanzees, there is 98.3% similarity, and the X chromosomes are 99.1% similar, leading Venter to joke, “If we had put that on the Internet [as the human genome] I don’t think anyone would have known for decades.” Given this “essentially identical” genetic code, he asked, “How did we evolve?” Modification of gene expression with transcription factors appears to be the crucial explanation.

Discussing clinical implications, Venter stated that abnormal DNA mismatch repair enzymes appear to be present in some genetic colon cancer syndromes. Protective mutations such as the that in the CCR5 gene, which conveys protection against HIV (HIV-1 uses the CCR5 coreceptor to enter T-cells) appear to have evolved less than 1,000 years ago to protect against infection with Yersinia Pestis at the time that the plague decimated Europe. “I expect,” he concluded, “that within ten years every newborn that leaves the hospital will have his complete genome[. . .]. One of the biggest challenges for medicine is to learn how to intelligently interpret this.”

Peroxisome proliferator–activated receptor agonists

Charles F. Burant (Ann Arbor, MI) discussed the role of agonists to the transcription factor peroxisome proliferator—activated receptor (PPAR)-γ in β-cell preservation, aiming to “convince [the audience] that unloading the β-cell is the thing you want to do.” The early compensation for insulin resistance is in increasing insulin secretion, with attendant islet cell hyperplasia, which is followed by atrophy of islet cells, as shown by a decline in insulin secretion in response to maximal stimulation. Postprandial glucose increases early as insulin secretion fails, with subsequent increase in fasting glucose levels. One must, Burant pointed out, distinguish β-cell dysfunction from the decrease in β-cell mass, as both phenomena play a role in the development of hyperglycemia in diabetes.

As the fasting glucose increases, the ability to maximally secrete insulin decreases precipitously. At the time of diagnosis, there may have already been a 50% decrease in β-cell function, with gradual subsequent worsening, suggesting that the onset of β-cell dysfunction occurs more than a decade before the time of diagnosis. Thiazolidinediones appear to both reverse intrinsic β-cell dysfunction and preserve β-cell mass. The β-cell response to graded glucose infusion in persons with impaired glucose tolerance (IGT) is improved proportionately to the degree of improvement in insulin sensitivity following a 3-month period of treatment with troglitazone (TGZ), with improvement in insulin response to glucose oscillations, suggesting improvement in β-cell function (1). Studies in women with polycystic ovary syndrome (PCOS) similarly show that TGZ improves the acute insulin response to glucose (2).

In the Troglitazone in Prevention of...
Diabetes (TRIPOD) study, women who had had gestational diabetes and whose annual risk of developing diabetes was 14.3% were randomized to TGZ 400 mg daily vs. placebo for 60 months. Of those treated with placebo, 53% developed diabetes, but 19% of those receiving TGZ developed diabetes. The patients whose insulin secretory demand improved the most showed the lowest rate of progression to diabetes (3). After the conclusion of the trial, the placebo group continued to show development of diabetes, while those who had previously been treated maintained a low rate of progression to diabetes for the subsequent 8 months, suggesting that the drug did not merely treat early diabetes but appeared to have prolonged benefit.

-β-cell mass increases with insulin resistance or overfeeding, during pregnancy, following partial pancreatectomy, and with GLP-1 administration, among many other situations. -β-cell mass decreases following weaning of animals, post partum, with insulinomas, and after long periods of insulin resistance. These animal data appear to be confirmed in human diabetes (4). The effect of both TGZ and rosiglitazone (RGZ) on islets in Zucker Diabetic Fatty (ZDF) rats is to increase -β-cell mass (5). The filamentous protein nestin has recently been shown to be a marker of -β-cell precursor cells (6). Insulin resistance is associated with an increase in nestin-positive cells, but in animal models in which insulin resistance has caused diabetes, the number of nestin-positive cells decreases. In ZDF diabetic animals treated with RGZ, the nestin-positive cell mass increases. Burant concluded that the question of how early to intervene in man to prevent the inexorable decline in -β-cell number and function remains to be answered. He suggested that such protection should begin early, and that preservation of precursor cells may be crucial.

Bart Staels (Lille, France) discussed PPAR agonists in the cardiovascular system and their potential effects on vascular inflammation, suggesting that PPAR-α and -γ activation act both to correct metabolic abnormalities associated with insulin resistance and through direct antinfiammatory effects on the vascular wall (7). Atherosclerosis, he stated, is an inflammatory disease, with endothelial cell exposure to injury by factors such as hypercholesterolemia and cigarette smoking leading to formation of foam cells, which secrete inflammatory compounds such as cytokines, prostaglandins, and leukotrienes, producing a chronic cascade of inflammation. PPAR-α and -γ are expressed in atherosclerotic lesions of human coronary arteries.

The first step of atherosclerosis involves endothelial dysfunction, with activated endothelial cells producing cell adhesion molecules and chemokines. PPAR-γ agonists inhibit both chemokine-induced recruitment of T-cells and monocytes and their migration into the subendothelial space. PPAR activators inhibit the inflammatory signal cascade of nuclear factor (NF)-κB, signal transducer activation of transcription (STAT), and other signaling pathways, decreasing activation of inflammatory responses such as release of interleukin (IL)-2, -6, and -8, tumor necrosis factor (TNF)-α, and matrix metalloproteinases (MMPs). Dendritic cells express PPAR-γ, and activation of these receptors blocks the inflammatory responses. At the stage of rupture of the unstable atherosclerotic plaque, a thrombus forms, potentially acutely interrupting the circulation. MMP9 can destabilize the plaque, and PPAR-γ agonists such as TGZ decrease MMP9 production. PPAR-α agonists inhibit IL-1β-induced tissue factor gene expression in human monocytes, suggesting an antithrombotic mechanism of benefit. Aortas from mice that do not express PPAR-α display a heightened inflammatory response to lipopolysaccharide stimulation. In a study of administration of fenofibrate, plasma IL-6 levels decreased in individuals both with and without coronary disease, particularly in the former whose baseline IL-6 levels were higher.

The current model of the molecular effect of PPAR agonists is of activated PPAR binding as a heterodimer with the retinoid X-receptor (RXR) to a nuclear binding site, functioning as a trans-activator. However, the anti-inflammatory effects appear to involve trans-repression at gene sites, such as that for NF-κB message transcription. Staels pointed out that fenofibrate decreases plasma acute-phase protein production, decreasing fibrinogen and C-reactive protein levels, an effect also seen with thiazolidinediones (TZDs). PPAR-α activation inhibits a proinflammatory pathway activated by IL-6, perhaps explaining the decrease in hepatic fibrinogen secretion. PPAR-γ has a parallel action, decreasing production of adipocyte cytokines such as TNF-α and IL-6, which act on the liver to increase C-reactive protein and fibrinogen production. In mice lacking apoE and therefore prone to atherosclerosis, combination PPAR-α and -γ agonists decrease atherosclerotic lesion formation. In an animal model of stroke, administration of fenofibrate decreased infarct volume, suggesting a potential neuroprotective effect. This protection was lost in PPAR-α-deficient mice, further suggesting a direct mechanism.

Ronald E. Law (Los Angeles, CA) discussed the role of PPAR-γ in atherosclerosis and restenosis. The natural history of type 2 diabetes involves the development of macrovascular disease. An additional important vascular effect of type 2 diabetes is the increased risk of restenosis after intervention. Insulin resistance involves a signaling defect in the cascade of biochemical events that leads to translocation of GLUT4 from the cytoplasm to the plasma membrane, which is overcome by TZD administration. PPAR-γ is present in endothelial cells, monocyte/macrophages, and vascular smooth muscle cells. The function of PPAR-γ in vascular cells can be seen in mice not expressing the LDL receptor given a high-fat diet, which leads to early atherosclerotic lesion formation. TGZ inhibits lesion formation independently of effects on glycemia or on lipids, suggesting a direct vascular effect (8). When angiotensin II-induced hypertension is added to the model, more severe atherosclerosis develops. Pioglitazone (PGZ) markedly reduces this without improvement in blood pressure, suggesting a direct effect. Similar effects are seen with RGZ and with non-TZD PPAR-γ agonist administration. Inhibition of adherent monocyte migration can also be demonstrated. The zinc-finger transcription factor early growth response factor (Egr)-1 shows increased expression in human atheromas and in animal models, and PPAR-γ agonists inhibit the Egr-1 and the Egr-1 target genes MCP-1, TNF-α, and ICAM-1. Studies in animal models of restenosis show that TGZ and PGZ decrease neointima formation in coronary and carotid balloon injury models. PPAR-γ ligands also inhibit vascular smooth muscle cell migration and growth. The critical factor regulating the entry of resting cells into the growth phase involves phosphorylation of the ki-
nase Rb ("retinoblastoma," first identified as a growth protein in these tumors). PPAR-γ ligands block this via stimulation of the inhibitory factor P27, further contributing to protection against atherosclerosis.

**Obesity and diabetes**

James Gavin (Chevy Chase, MD) discussed the emerging perception of obesity as an important medical problem, reviewing data showing a marked increase in prevalence of obesity in the U.S. over the past decade, with > 20% of the population of half of the states in the U.S. having a BMI >30 kg/m² (9). Similar trends are seen in the National Health and Nutrition Examination Surveys (NHANES), with stable obesity prevalence through the 1980s, but a marked increase over the past decade. Obesity is particularly common among African-American women, with prevalence of obesity just over 40% in the 1960s, increasing progressively to almost 50% by the 1990s. The National Longitudinal Survey for Youth 1979 (NLSY79) was a longitudinal sample of 11,406 men and women born between 1957 and 1964, of whom 17% were Hispanic, 26% African-American, and 58% Caucasian. The risk of becoming obese was increased 1.6- and 2.3-fold among Black and Hispanic men, and 2.1-and 1.6-fold among women in these groups.

Factors accounting for earlier and increased obesity may include decreased levels of activity, greater desire for sweet taste among African Americans (10) or neurohumoral differences in balance between satiety and adiposity signals (11). The obesity epidemic portends an increase in diabetes, which indeed appears to be happening. The prevalence of diabetes increased by one-third in development of diabetes in high-risk groups must involve reduction of obesity, and, Gavin stated, "there is some urgency." Important questions include "what are we willing to do?" and "what do we want from basic research?"

The consequence of obesity, particularly with a known background of increased genetic risk for cardiovascular disease (CVD), is of increasing comorbidities that synergize for accelerated atherosclerotic outcomes. Obesity is associated with higher blood pressure and cholesterol. Obesity leads further to the development of insulin resistance, with adipose tissue, particularly the metabolically active adipose tissue in visceral distribution, having a major contribution to this metabolic disturbance, associated with increased lipolysis with free fatty acid release, as well as with release of humoral factors such as TNF-α, being associated with increased hepatic glucose production and decreased muscle glucose uptake. The higher the amount of visceral fat, the greater insulin resistance (13). Health implications of obesity include excess mortality, much driven by coronary artery disease, potentially explaining the lesser decline in coronary heart disease (CHD) mortality in African-Americans in comparison with Caucasians over the past decade.

Robert Ratner (Washington, DC) specifically addressed the issues of diabetes and obesity. The modifiable lifestyle risk factors are known, and observational and some experimental data suggest that type 2 diabetes is preventable, while treatment of symptomatic diabetes usually is not as successful. Early intervention can reduce the risk of severe complications and should lead to decreased major health care costs. The Da Qing IGT study (14) screened 110,660 persons with glucose tolerance testing, and randomized centers treating patients with IGT to diet, exercise, both, or neither, showing reduction by one-third in development of diabetes with either intervention. The Diabetes Prevention Study (DPS) in Finland counseled patients with IGT in diet and exercise with dietary counseling sessions and health club memberships. Decreased consumption of fat was seen in 87 and 70% of the intervention and control groups. Saturated fat decreased in 70 and 39%, the intervention group lost 3.5 kg, while the control group lost 0.8 kg in weight. Fasting, 2-h glucose, and fasting insulin decreased, and there was a 58% reduction in development of diabetes.

Ratner and, in a subsequent presentation, David Marrero (Indianapolis, IN) discussed the Diabetes Prevention Program (DPP) in which individuals with IGT were randomized to metformin, lifestyle, or control groups to assess the reduction in diabetes. (16). The linear relationship between obesity and diabetes risk (17) suggests that intervention to reduce obesity should curb the development of diabetes. To recruit for the DPP, 158,177 individuals were screened with fingerstick glucose measurement; of these subjects, 30,983 had glucose tolerance tests. A total of 4,719 persons with IGT were identified, of whom 3,819 were randomized to the study; ~600 were randomized to TGZ until that portion of the study was closed when the increased risk of hepatic dysfunction for this agent was determined. There were 1,079 subjects in the control group, 1,073 subjects were given metformin, and 1,082 were randomized to lifestyle intervention. Altogether, 55% were Caucasian, 20% African American, and 16% Hispanic. At study onset, the mean BMI was 34 and fasting glucose 107 mg/dl.

The lifestyle program aimed to achieve a loss of body weight at least equaling 7% of body weight, reducing fat to 25% of calories, reducing calories to 1200–1800 daily, and encouraging 150 minutes of exercise per week. A 16 session course conducted over 24 weeks used education and training in diet and exercise methods and behavior modification skills, emphasizing individuals' ability to monitor their own diet and solve problems with an individualized approach, addressing self-esteem, empowerment, and social support. Everyone in the program had "one on one contact" with a case manager at least once monthly but often more often. A maintenance phase continued after the weight goal had been achieved with monthly contact and visits at least every two months, with supervised exercise sessions, and periodic group classes and motivational campaigns, to prevent the pattern of losing and then regaining weight. Pedometers were found to be a useful device for encouraging ongoing exercise.

Of lifestyle participants, 50% lost 7% of their body weight at the conclusion of the core curriculum, although the effect was attenuated over time, with 38% showing this degree of weight loss by study end. Participants exercised 35 min daily in the lifestyle group, with this level of exercise maintained over the course of the study. This modest physical activity and weight loss reduced the development of diabetes by 58%. Exercise increased slightly in the metformin and placebo groups. Metformin was associated with a sustained 2% weight loss. The diabetes incidence decreased 31% with metformin. The effect of metformin was similar to that of the lifestyle intervention for
persons with baseline BMI >35 kg/m² and in individuals aged 25–44 years; treatment with metformin was somewhat less effective in subjects aged 45–59, while lifestyle maintained full efficacy, and metformin was ineffective in those aged 60 years and older, while lifestyle again decreased diabetes rates by 58% compared with placebo.

Marrero questioned whether we can “get our patients to change their lifestyles in real world practice.” He noted that a recent study of obese women with mean BMI 36 showed that their “dream weight” was 38% below the present level and that they would be disappointed with a 17% weight loss (18). The actual weight loss in this study was 16 kg, well below what the participants thought would be acceptable, but greater than that achieved in the DPP. The DPP, Marrero stated, has shown we need only encourage modest weight loss to prevent diabetes. Behavior modification, self-monitoring with food diaries and regular weight checks, stimulus control with persons learning only to eat when hungry and stop when full, cognitive restructuring with realistic goals, and healthiest approach. Exercise increases, focusing on reduction in fat from the “caloric restriction with realistic goals, and changing the response to slip-ups, stress management, and social support are “what works.” Modest reduction of calories, focusing on reduction in fat from the average level over 40%, is the most practical and healthiest approach. Exercise does not lead to weight loss without caloric restriction but has other benefits, and is important in preventing relapse after initial weight loss. Thus, Marrero pointed out, we should “consider obesity a chronic progressive disease, not a character flaw or failure of the medical model.” Helping patients keep food diaries, suggesting simple ways to eliminate 500 calories per day, “brainstorming” for approaches to exercise, and collaboration with nurses, nutritionists, and community groups are important. He also suggested that we ourselves “set a good example for our patients.”

Robert Kushner (Chicago, IL) discussed past, current, and potential future pharmacologic approaches to weight loss. Diet, physical activity, and behavior therapy are applicable to all persons with BMI >27, as well as to those with BMI >25 and a comorbid condition such as diabetes. Pharmacotherapy has been recommended for those persons with both comorbidity and BMI >27, and for all individuals with BMI >30. Surgery for obesity may be considered with BMI >35 in persons with comorbidity, and ≥40 for those without comorbidity. Kushner stressed the need for lifestyle intervention instruction given along with pharmacotherapy, showing a study in which administration of sibutramine, which inhibits reuptake of both serotonin and norepinephrine, led to little effect, with weight loss at 1 year of 4%. However, when given with both group lifestyle modification and a 1200–1500 kcal/day diet, there was 11% weight loss, and with addition of a portion-controlled 1,000 kcal/day diet there was 15% weight loss at 1 year (19). In another study, 500 individuals who had already lost ≥10% of weight with sibutramine were randomized to continued sibutramine vs. change to placebo, with evidence of continued benefit at 2 years, although hypertension and tachycardia were seen (20).

At least seven double-blind crossover trials have studied treatment with orlistat for up to 2 years, all showing prolonged clinical benefit with falls in blood glucose, LDL cholesterol, and insulin levels. Side effects included increased defecation, liquid stools, and fecal urgency, seen in at least 20–30% of patients to some degree (21). The antidepressant bupropion was associated with a modestly greater weight loss than placebo in a study lasting 24 weeks (22). Topiramate, an anticonvulsant, was noted to lead to weight loss of ~6% in patients with seizure disorder. Persons with BMI <30 and ≥30 had weight losses of 7 and 10% at 12 months, respectively, with weight loss maintained through 18 months. The proportionately greater weight loss in more obese individuals is unique to this agent. Body fat decreases and is responsible for much of the benefit of treatment. Kushner described a 14-week study in which topiramate appeared to dramatically improve binge-eating disorder, with a reduction from 6 binges per week at baseline to 3.4 binges per week with placebo, with 1 kg weight loss, while patients reported 0.3 binges per week and a 6 kg weight loss with active treatment. The mechanism of action of topiramate has not been defined. Future treatments for obesity and for diabetes may develop from our growing understanding of the adipocyte as an endocrine cell. Leptin may have potential as a weight loss agent, although clinical trials are disappointing (23). Manipulation of other adipocyte factors, including complement factors, adipin, IL-6, TNF-α, plasminogen activated inhibitor (PAI)-1, tumor growth factor (TGF)-β, and insulin-like growth factor (IGF)-1, may spawn future approaches to obesity treatment.

Priscilla Hollander (Dallas, TX) reflected on the strong linkage between obesity and the progression of diabetes, between obesity and the complexity of glycemic treatment, and on the potential aggravation of obesity by many treatments for diabetes. She pointed out that treatment of insulin resistance in muscle and fat must be distinguished, that β-cell failure plays an important role in the difficulty of treating diabetes, and that fat metabolism and absorption as well as carbohydrate absorption may imply a role of the gastrointestinal tract in the pathophysiology of type 2 diabetes. In the U.K. Prospective Diabetes Study (UKPDS), there was deterioration in HbA1c values over time. Overweight patients on conventional treatment showed increases of mean HbA1c levels from 7.5% at 0–5 years to 8.5% at 5–10 years and to 8.8% at 10–15 years, HbA1c levels of overweight patients treated with metformin were 6.7, 7.9, and 8.3% over these time periods (24). Combination treatment approaches are more effective in leading to glycemic control, but have increased cost and affect body weight (25). Diabetes itself may increase the difficulty of losing weight, with studies of spouses and patients given the same diet showing that those without diabetes lose more weight than those with diabetes (26). Discussing pharmacotherapy, Hollander pointed out that sibutramine may not effectively decrease HbA1c levels in persons with diabetes, although modest falls have been shown in triglyceride levels (27), while HbA1c fell ~0.5% in patients with diabetes treated with orlistat (28). Among patients treated with insulin, greater weight loss is seen with orlistat than with placebo, with decrease in insulin dose requirement and again a decrease in HbA1c by ~0.5% (29). Studies of combination of orlistat with metformin are also becoming available, with evidence of benefit. Hollander concluded that a dual-therapy algorithm should be explored with use of antiobesity drugs with lifestyle therapy, with single oral antidiabetic agents, with multiple oral antidiabetic agents, and with oral antidiabetic agents plus insulin, aiming for amelioration of fat-related worsening of the diabetic state.
Richard A. Dickey (Hickory, NC) pointed out the similarity between expert recommendations of the Adult Treatment Panel III (ATP-III) for cholesterol treatment (30), the sixth report of the Joint National Committee (JNC VI) on blood pressure treatment (31), and the American Diabetes Association recommendations for diabetes treatment (32) that “physicians should aggressively treat obesity as part of dietary management” of all three conditions, with modest weight loss, requiring a calorie deficit at least 1,000 kcal/day, improving all three risk factors and reducing mortality and adverse outcome. No more than 10% of persons with the three conditions have had pharmacologic treatment to improve weight loss, Dickey stated, an interesting dilemma suggesting that clinicians and patients have not accepted these as useful interventions, particularly given the years required for such therapeutic approaches.

Jaime Davidson (Dallas, TX) discussed additional aspects of the relationship between diabetes and obesity, pointing out the many diseases attributable to obesity, including pulmonary disease, gastrointestinal and hepatic disease, osteoarthritis, and malignancies, as well as diabetes and cardiovascular disease. He also discussed the relationship between BMI and mortality (33), the decrease in health-related quality of life in persons with worsening degrees of overweight (34), and the direct relationship between diabetes prevalence and body weight. Weight loss, in contrast, improves glycemia (35). Furthermore, the life expectancy of obese persons with type 2 diabetes is improved by weight loss in proportion to the degree of weight loss (36).

Adipose tissue, Davidson stated, is the “largest endocrine gland.” He discussed resistin, which causes insulin resistance and glucose intolerance in mice whose expression is downregulated by TZD. An interesting hypothesis is that insulin may modulate its own activity through resistin, and that increased resistin expression in abdominal fat may explain the hyperglycemic risk associated with central obesity (37). TNF-α shows positive correlation with the degree of obesity, the level of hyperlipidemia, and the degree of insulin resistance. TNF-α inhibits the signaling capacity of the insulin receptor, blocking its autophosphorylation as well as preventing downstream tyrosine phosphorylation. Leptin functions by affecting hypothalamic and pituitary signals in the brain, controlling hunger/feeding responses. Exogenous leptin leads to weight loss in a dose-dependent manner. Obesity may be caused by leptin resistance, which is associated with insulin resistance and with the development of type 2 diabetes, perhaps also playing a role in the reduced insulin response in this condition. Davidson wondered whether adipocyte cytokines increased the susceptibility to depression, which is present in 10–30% of persons with diabetes (38). The difficulties of weight loss in the obese person with diabetes, he stated, should lead to emphasis on prevention of weight gain in populations at risk for diabetes, and treatment of diabetes should reduce both blood glucose and body weight.

C. Christopher Donner (Santa Barbara, CA) discussed obesity as “the crux of the metabolic syndrome,” reminding his audience of the importance of measuring waist circumference as a “vital sign” along with weight, blood pressure, etc. The metabolic syndrome has now been given ICD-9 code 277.7. The ATP-III defined the metabolic syndrome by the presence of at least three of the following: increased abdominal girth (>35 inches in women or 40 in men), fasting glucose ≥110 mg/dl, triglyceride ≥150 mg/dl, HDL <40 mg/dl in men or 50 mg/dl in women, and blood pressure ≥130/85 mmHg. The syndrome is present in almost one-quarter of the U.S. population, affecting 6.7% of persons aged 20–29 years and >40% of those aged 60 and older (39). The two pillars of the syndrome are insulin resistance–mediated glucotoxicity and lipotoxicity, affecting liver, muscle, and the β-cell. Meta-analysis suggests linear relationship between fasting blood glucose and CVD in apparently normal populations. The causes are increased dietary intake, which Donner reminded the audience is a global problem (with the largest MacDonald’s in the world in Moscow), and decreased exercise.

In men one-quarter of adipose tissue is located in the abdominal subcutaneous and visceral depots, although somewhat less is present in the depots of women. Visceral fat, comprising 10% of fat in men and 5% in women, appears to be the major cause of metabolic syndrome. Donner discussed another aspect of adipose tissue as an endocrine organ, visceral fat cortisol production via the 11β hydroxysteroid dehydrogenase (HSD) enzymes, which metabolize cortisol to and from cortisone. HSD1 metabolizes cortisone to cortisol and HSD2 does the reverse. HSD2 is present in the adrenal, and HSD1 is present in the liver, central nervous system, and adipose tissue, and may play a major role in prereceptor regulation. HSD1 activity is low in subcutaneous fat, but quite high in visceral fat, both under basal and insulin- and cortisol-stimulated conditions. Cortisol in turn feeds back on visceral fat to stimulate HSD1 and to cause additional visceral fat production. Visceral fat, Donner stated, “has a direct conduit to the liver” via the portal system, and hepatic HSD1 may play a role in the development of hepatic insulin resistance and in the causation of nonalcoholic hepatosteatosis (NASH). The effect of cortisol in the liver may be to elevate triglyceride, lower HDL, and increase production of small dense LDL.

In muscle, increased intramyocellular HSD1 may increase accumulation of intramyocellular fat, which correlates strongly with insulin resistance (40). There is a negative correlation between insulin sensitivity and myoblast HSD1 activity, with transgenic mice overexpressing muscle HSD1 showing insulin resistance (41).

Donner discussed the importance of lifestyle change in both treatment and prevention of the metabolic syndrome (42). The benefit of modest degrees of weight loss may reflect a much greater relative decrease in visceral fat. He noted that sex steroids, growth hormone, and PPAR-γ agonists may all act as HSD1 antagonists, and that new agents such as fatty acid enzyme modulators and insulin and leptin analogs may offer further approaches to regulation of levels of this key enzyme.

Erectile dysfunction

Richard Spark (Boston, MA) discussed erectile dysfunction (ED), stating, “We’re in a transition phase where a problem which was managed by urologists now is managed by endocrinologists.” Spark’s early studies showed that, rather than being psychogenic, many individuals with ED have organic etiologies. Endocrine problems, including testosterone deficiency, hyperprolactinemia, and thyroid dysfunction, as well as diabetes, play a role in ED, with hypertension, coronary disease, depression, aging itself, and the
effects of antihypertensive agents, antidepresants, and finasteride being among the common additional causes. Spark stated that he believes screening for low testosterone is important, and cited studies suggesting that 35% of men with ED may have low testosterone, with replacement treatment improving symptoms (43). Spark reviewed studies showing a linear relationship between serum testosterone and nocturnal penile tumescence (44).

During sexual excitement, nitric oxide promotes vasodilation of the corpus cavernosum by increasing intracellular guanosine 3',5'-cyclic monophosphate (cGMP), increasing arterial inflow, compressing the cavernosal vein, and creating an erection. Subsequent detumescence involves cGMP metabolism by phosphodiesterase (PDE)-5, and the development of the PDE-5 inhibitor sildenafil has allowed effective and readily available clinical treatment for many subjects with ED. Physicians, Spark mentioned, often are reluctant to discuss ED, and he stressed that this should be considered a basic part of the medical evaluation, particularly for men with diabetes. Indeed, rather than being offended, most patients are appreciative of the efforts of the physician in initiating discussion of the problem.

Ajay Nehra (Rochester, MN) discussed current therapies for ED. The introduction of intracavernous prostaglandin (PG) E1 in 1995 and of intracavernosal PGE1 in 1996 led to effective treatment approaches, with sildenafil becoming available in 1998 and new PDE5 inhibitors now nearing clinical use. Alprostadil (PGE1) is rapidly metabolized and is administered by intracavernosal injection in a 1–60 µg dose requiring individual dosing titration with in-office training and assessment. It initiates erection across all etiologies of ED in 60–70% of patients, with superior performance to papaverine or papaverine-phenolamine. Adverse effects include the potential for prolonged erection, severe penile pain (in 4% of patients; mild pain in an additional 6–7%), and fibrosis. It should be considered an effective salvage treatment, with many patients failing to respond to sildenafil able to have satisfactory response to intracavernosal alprostadil treatment. The intracavernosal administration of a microsuppository pellet with 125–1,000 µg alprostadil is effective in ~35% of patients, with use of a constriction band increasing response somewhat. Systemic effects with hypotension may occur with higher dosages. There is also the potential for toxic effects for the female partner, and a condom must be used if the partner may be pregnant.

Sildenafil improves erectile function across all severities of ED in 43–89% of patients, with side effects including headache in 16%, flushing in 10%, dyspepsia in 7%, and nasal congestion in 4% of patients (45). Coitus induces a maximal workload of 3–4 metabolic equivalents (MET), lasting for less than 30 s, so patients able to exercise to more than 5–6 MET without ischemia can be considered at low risk of adverse effect. In patients with stable coronary insufficiency not receiving nitrates for at least 72 hours there is no change in exercise cardiac parameters with sildenafil administration.

Harin Padma-Nathan (Beverly Hills, CA) discussed the PDE5 inhibitors tadalafil and vardenafil, emerging oral therapies for ED likely to become available in the near future. These agents, as well as sildenafil, are structurally similar to cGMP. Tadalafil shows almost complete specificity for PDE5, while sildenafil and tadalafil also have some inhibitory effect on PDE6 and -7, leading to ocular effects, principally consisting of transient color vision symptoms. Tadalafil may have inhibitory action against PDE11 of uncertain significance. The pharmacokinetic properties of greatest interest are the time to maximal concentration (Tmax) and duration of activity. Tadalafil has a 2-h Tmax and a 17.5-h duration of activity in comparison to the <1-h Tmax and ~4-h duration of activity of sildenafil and vardenafil. Close to 60% of patients have response within 30 min to tadalafil, with 80% showing response up to 24 h. There is no decrease in absorption of the agent with ingestion of food or alcohol.

In studies of 1,112 patients treated with 2.5–20 mg tadalafil versus placebo, 21% had diabetes and 30% had hypertension; 35, 42, 50, 67, and 81%, respectively, showed improved erections with placebo and doses of 2.5, 5, 10, and 20 mg; 32, 36, 42, 61, and 75% of intercourse attempts were successful at these dosages. Adverse effects were headache in 14%, dyspepsia in 10%, and back pain, myalgia, and flushing in 6, 5, and 4%, respectively, of patients. Additional adverse effects include rhinitis and sinusitis. The adverse effects appeared to decrease in frequency over time. Studies in individuals with diabetes and ED have shown generally similar effects (46). Vardenafil shows similar efficacy and similar side effects and is given at doses of 5, 10, and 20 mg.

Vivian Fonseca (New Orleans, LA) discussed diabetes and ED. ED affects as many as 30 million men in the U.S. and compromises quality of life. A number of vascular abnormalities may contribute to ED, with clinical correlates including diabetes, CHD, and hypertension. Fonseca expressed a different opinion than Spark, stating that endocrine investigation for individuals with ED should be performed infrequently, when there is clinical suspicion of specific contributing disorder. The endothelium maintains vascular health and secretes vasodilatory as well as vasoconstrictive substances, with diabetes, hypertension, and atherosclerosis changing the normal balance. Decreasing nitric oxide release and responsiveness is found in diabetes, while the levels of the vasoconstrictor endothelin 1 are increased. Thus, Fonseca suggested, endothelial dysfunction and ED are interrelated, and autonomic neuropathy need not be the only explanation of ED in men with diabetes; individuals without evidence of neuropathy or poor glycemic control may have these symptoms.

Sildenafil is effective in patients with diabetes and ED, although to a somewhat lower extent than in nondiabetic patients. Flow-mediated brachial artery dilatation increases with administration of sildenafil in low dosage, suggesting benefit other than that limited to ED. Fonseca commented that theoretically it might be useful for patients to take sildenafil regularly to restore response. He mentioned that there is no evidence of adverse cardiovascular consequence among men treated with the agent (47).

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