

Approaches to Treatment of Pre-Diabetes and Obesity and Promising New Approaches to Type 2 Diabetes

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This article is based on presentations at the Tulane University Diabetes Update on 8 December 2007 in New Orleans, Louisiana; at the Mount Sinai Medical Center Diabetes Grand Rounds in New York, New York, on 6 December 2007; and at the American Diabetes Association's 55th Annual Advanced Postgraduate Course held 1–3 February 2008 in San Francisco, California. These lectures, addressing differing views of various speakers on various aspects of diabetes prevention, obesity, and new treatments for type 2 diabetes, are available online at <http://professional.diabetes.org>.

Preventing diabetes

Richard Bergenstal (Minneapolis, MN) reviewed approaches to treatment of pre-diabetes at the American Diabetes Association Postgraduate Course. The number of individuals with diabetes worldwide is projected to increase to 333 million by 2025, and the annual cost of diabetes in the U.S. today has reached \$174 billion (1). The burden of complications among diabetic individuals aged >65 years in the U.S. includes doubling of the rates of myocardial infarction and congestive heart failure (2). Bergenstal reviewed current guidelines for using ele-

mented fasting and 2-h glucose, as well as the growing use of A1C, in the assessment of the pre-diabetic state. The presence of both impaired fasting glucose (IFG) (≥ 100 mg/dl) and impaired glucose tolerance (IGT) (blood glucose 2 h after 75-g oral glucose ≥ 140 mg/dl) doubles the risk of progression to diabetes. Insulin secretory defects are seen in IFG and, to a greater extent, in IGT, and IGT appears to lead to greater cardiovascular disease (CVD) risk than does IFG. During the phase of abnormal glucose tolerance before development of diabetes, insulin resistance occurs in addition to insulin deficiency, leading to the condition variously referred to as metabolic syndrome, cardiometabolic syndrome, or insulin resistance syndrome, with controversy as to whether the syndrome is associated with risk beyond that of its component risk factors. Macrovascular disease often precedes the development of diabetes, while microvascular complications have been said to begin at the time of onset of diabetes (3), although there is now well-reported evidence of retinal abnormalities, microalbuminuria, and peripheral neuropathy preceding onset of diabetes. Interestingly, in addition to diabetes increasing CVD risk, the presence of CVD is associated with increased diabetes risk, an important consideration in screening for pre-diabetes.

It is possible to reduce the development of diabetes by intervening before its onset. In a meta-analysis, lifestyle interventions reduced diabetes by approximately one-half and pharmacologic interventions by approximately one-third (4). Major lifestyle studies included the Finnish Diabetes Prevention Study (DPS) (5) and the U.S. Diabetes Prevention Program (DPP) (6), both with reductions in

development of diabetes by 58%. In DPS, participants with greater numbers of influenced lifestyle variables showed greater reduction in development of diabetes. Follow-up of the DPS showed sustained reduction in diabetes, with rates remaining 39% lower 4 years after completion of the study, in association with increase in physical activity (7). In the DPP, treating 6.9 individuals with lifestyle intervention would prevent one case of diabetes over 3 years. A number of other studies have addressed approaches to lifestyle intervention. A study of treatment of individuals with existing diabetes rather than pre-diabetes, the Look AHEAD (Action for Health in Diabetes) study, illustrates the feasibility and effectiveness of lifestyle modification, with a 1-year outcome of 8.6% weight loss, 20.9% improvement in fitness, and 0.7% A1C lowering from a baseline of 7.3%, as well as improvements in blood pressure and lipids (8). The goal of the study is to maintain these behaviors for a decade to determine whether improvement in outcome can be demonstrated. Prevention of complications rather than just prevention of worsening glycemia should be the goal for diabetes prevention as well. An important question will be the cost-effectiveness of lifestyle modification in preventing diabetes. Estimates of the cost of the lifestyle intervention of the DPP, the Archimedes model (9,10), suggest that the approximate cost for prevention of diabetes is \$30,000–60,000 per individual. However, recent studies have explored less expensive approaches to lifestyle intervention (11); should this prove feasible, cost estimates for diabetes prevention will be greatly reduced.

Pharmacologic approaches are equally promising for diabetes prevention. Metformin was not as effective as the lifestyle intervention in the DPP, requiring treatment of 13.9 individuals for 3 years to prevent one case of diabetes, but it was particularly effective in younger individuals and in those who were overweight. These findings were confirmed in a recent meta-analysis (12). In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM)

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NEWS FROM THE FOOD AND DRUG ADMINISTRATION

From time to time, new announcements by the FDA pertaining to aspects of diabetes treatment will be highlighted in this section.

The FDA has made a very reasonable proposal to remove the confusing letter categories for risk associated with prescription medicines during pregnancy and lactation, replacing them with a three-part discussion: first, a “Fetal Risk Summary” of what is known about effects of the agent on the fetus and whether this is based on animal or on human studies; second, a discussion of clinical considerations including suggestions regarding the agents’ use prior to a woman knowing she is pregnant; and third, a detailed review of the available data for the effects of the medication during pregnancy and lactation.

The FDA plans to link Medicare Prescription Drug Benefit data with Medicare inpatient and outpatient claims data in order to create a database allowing monitoring of postmarketing adverse drug events. Eventually, this program, which will be called the Sentinel System, will be expanded to include additional large electronic claim and medical record data sources, with the aim of no longer depending on voluntary reporting of safety concerns—a system that has been demonstrably inadequate in providing information about adverse drug reactions.

Revisions have been made to the product label for oseltamivir, the antiviral agent used in treatment of influenza, emphasizing the occasional association of the drug with delirium and abnormal behavior. However, it is possible that some of these symptoms may be caused by influenza itself.

A new approach to coronary artery imaging during catheterization now has FDA approval: a device, the InfraReDx LipiScan, that uses infrared imaging to detect lipid core-containing plaques. The FDA has become aware that it is possible for patients to use LifeScan OneTouch Ultra test strips with Abbott Precision Xtra meters; the glucose readings so obtained will be erroneous, and it is important that patients be cautioned to use the correct strip with its correct meter.

study, ramipril did not prevent diabetes (although it was associated with a small but significant reduction in blood glucose) (13), while rosiglitazone-treated individuals experienced “remarkable benefit in prevention of diabetes,” although their risk of congestive heart failure increased (14). Acarbose has been shown to reduce both diabetes and CVD (15). Pharmacologic approaches to weight loss also should have benefit in preventing diabetes. Treatment with the cannabinoid receptor antagonist rimonabant is an effective approach to weight loss (16), although adverse psychiatric effects led to lack of approval by the FDA. Orlistat, which is now available as an over-the-counter product, promotes weight loss and has been shown to reduce progression to diabetes (17). Incretin-related treatment also appears attractive for early diabetes and, perhaps, for pre-diabetes, given the association of exenatide treatment with both weight loss and improvement in A1C, with studies of its use in monotherapy and for weight loss in progress. Lifestyle modification should

be the primary approach for individuals with either IFG or IGT, but for those with both abnormalities and for those aged <60 years with BMI ≥ 35 kg/m², positive family history, elevated triglyceride, low HDL cholesterol, hypertension, or A1C >6%, Bergenstal recommended adding metformin, suggesting that other pharmacologic approaches may be appropriate (18). Another appealing approach is to “just put the band in there,” he commented, reviewing a recent study in which 73% of diabetic individuals treated with adjustable gastric bands using laparoscopic surgery had remission of diabetes in association with 20.7% weight loss (19).

To identify those at high risk of diabetes, information regarding obesity, lack of exercise, childhood birth weight, and family history are useful, allowing the physician to “impress upon [these] individuals the seriousness of the risk.” A screening tool based on the Archimedes model is available (20), giving a classification tree for detecting pre-diabetes based on age, waist, family history, etc;

this calculating engine has been placed on the ADA Web site at www.diabetes.org/diabetesphd. The ADA Standards of Care Position Statement in January 2008 gave new nutrition recommendations, recognizing that both low-carbohydrate and low-fat diets are reasonable for different patients. There are a number of other new findings that may give insight into lifestyle changes reasonable for the prevention of diabetes. Whole-grain cereals were shown to be associated with reduced diabetes risk in some studies (21), but this finding was not confirmed in a meta-analysis (22). Although caffeine increases glucose in diabetic individuals during continuous glucose monitoring (23), in epidemiologic studies, coffee use has been associated with reduction in diabetes risk (24). Meat, fried foods, and diet soda are associated with increased risk of metabolic syndrome (25), with there being no difference between diet and regular soda in cardiometabolic risk (26). An effective strategy for increasing physical activity is the use of pedometers (27), with Bergenstal explaining, “you’ve got to set a goal,” while recognizing that many patients will not achieve it. Combinations of resistance and aerobic exercise may also be useful in lifestyle interventions (28). A final interesting aspect of lifestyle is that either too much or too little sleep may increase diabetes risk (29).

Is there an optimal diet for treatment of diabetes and obesity?

At the New Orleans meeting, Judith Wylie-Rossett (Bronx, NY) reviewed a number of diabetic diets, concluding that the optimal diet is “whatever diet you can stick to.” She suggested the importance of breaking the behavioral chain of overeating and the need to eliminate the “easiest calories first,” choosing a dietary plan that is safe and in keeping with the individual preferences of each patient, and she stressed the importance of being ready to switch approaches if a patient does not respond to a particular approach. None of the studied diets met the American Heart Association criterion of containing <7% of calories as saturated fats. The South Beach Diet is divided into three phases, with the first 2 weeks made up of lean meats, low glycemic index vegetables, low-fat cheese, nuts, and eggs, with subsequent gradual introduction of additional foods. In the Atkins diet, four phases are recommended: an induction phase with <20 g carbohydrates daily, subsequently adding 5 g carbohydrates

weekly, changing to a “premaintenance” phase when the patient is within 10 lbs of goal weight, allowing 30–60 g carbohydrates daily, and a maintenance phase when at goal allowing 40–100 g carbohydrates daily. Patients following such diets commonly have difficulty avoiding ice cream and fried foods, with other surveys suggesting problems with low-carbohydrate diets with regard to avoiding sugars and starches, drinking sufficient water, eating vegetables, exercising, increasing protein, avoiding soft drinks, eating fruit, and decreasing fat. Wylie-Rossett contrasted low carbohydrate diets with Mediterranean diets such as the Willett diet, which recommends fish, fish oils, walnuts, flax seeds, and flaxseed oil for n-3 fatty acids and legumes and olive oil for n-6 fatty acids. Low-glycemic index diets (30) are examples of diets recommending foods of low-energy density but that offer another approach. Vegetables are low in energy density, with the High Protein Weight Watchers diet and the Atkins diet containing few vegetables, while the Ornish diet, the South Beach diet, the “Glucose Revolution” diet, and the Zone diet contain more (31).

High-protein diets may decrease appetite, with a 12-month comparison of Atkins-type diets with diets higher in carbohydrates showing that although the latter contain less saturated fat, the former were associated with greater falls in triglyceride and blood pressure in the context of greater weight loss (32). Reviews comparing various diets suggest that low-carbohydrate diets do lead to greater initial weight loss (33), with greater improvement in large VLDL and in inflammation (34,35) but with greater increase in chylomicron levels (36). Wylie-Rossett’s studies of diabetic patients also suggest greater initial weight loss with low-carbohydrate diets, but she, too, found that this was not sustained. Other studies of diabetic patients suggest modest but significant reduction in A1C with low-glycemic index diet approaches (37). She noted that ketosis may be associated with fatigue in individuals following low-carbohydrate diets (38). The explanation for the catch-up in weight after 3 months in patients following a low-carbohydrate diet appears to be the greater difficulty in adherence to such approaches, leading to her recommendation that a diet be considered “a new way of eating. . . a little bit like religion.” The new ADA guidelines allow greater liberalization of dietary approaches, recognizing

that a variety of diets may be useful in successful dieting. Two new concepts being applied in nutrition are of “daily reference intakes,” related to the older concept of “recommended dietary allowances” and the concept of “net carbohydrates,” excluding fiber and sugar alcohols.

Pathogenesis of obesity

At Mount Sinai, Jeffery Flier (Boston, NY) discussed the pathogenesis of obesity, reviewing potential interactions between genes and the environment. There are rare, sporadic monogenic disorders associated with obesity, but the typical inheritance is polygenic. Environmental factors are dietary intake and physical activity. The decreasing cost of food and its increasing availability, as well as, perhaps, changes in the macronutrient composition of the diet with increasing amounts of rapidly absorbed carbohydrates, have led to an obesogenic diet. Interindividual variations in metabolic rate and in the thermic effect of food are important determinants of caloric expenditure, and an increasingly recognized factor, nonexercise activity thermogenesis (39), which includes activities like “fidgeting,” may have genetic determinants as well. Whether population weight gain is mainly caused by increased energy intake or decreased energy expenditure has not been resolved. Additional environmental factors, which may have genetic components as well, are the effects of prenatal and early childhood nutrition; effects of sleep deprivation, which may change diurnal patterns of leptin and other hormones; effects of viral infection; effects of gut flora, which may have impact on gut-brain signaling; and effects of stress and inflammation.

A basic concept involved in these studies is that evolution favors energy storage, with the current environment of plentiful food leading to increasing prevalence of obesity. Brain mechanisms include changes in behavior (in appetite, food intake, and physical activity); changes in autonomic function, leading to effects on thermogenesis and on metabolism; and changes in neuroendocrine function, with reproductive, growth, and thyroid systems all having impact on development of obesity. Hypothalamic satiety and feeding centers receive signals from peripheral sites—both 1) starvation signals, e.g., leptin, glucose, and perhaps fatty and amino acids, which in low levels stimulate food intake, and 2) satiety sig-

nals, including cholecystokinin, peptide-YY, ghrelin, glucagon-like peptide-1, and amylin, as well as vagally mediated neural signals. In addition, hedonic signaling via olfactory, taste, visual, and tactile senses are also important in promoting food intake. Flier noted the interesting parallels between circuits involved in appetite and hedonic pathways involved in addiction, with neurons involved in metabolic pathways as well as those related to hedonic centers expressing leptin receptors (40), suggesting that both are important in understanding obesity.

Adipocyte signals include free fatty acids, estrogen, and adiponectin. Flier reviewed his studies of adiponectin (41), a circulating protease mainly produced in fat, with levels reduced in obesity in rodents but not in humans. It is a complement protein, exemplifying the interaction of inflammation with obesity. Flier has also studied the roles in obesity of angiotensinogen (42) and of 11 β -hydroxysteroid dehydrogenase (HSD11), which activates intracellular adipocyte conversion of cortisone to cortisol. Leptin is a fat-derived cytokine originally thought to act as an endogenous anti-obesity factor (43). It has been increasingly recognized that there is leptin resistance in obesity (44,45), leading to the realization that falls in leptin level, acting as signals of decreased nutrient availability, appear to be more important than increases (46). Most obese individuals are, in fact, resistant to the action of leptin, possibly because of circulating antagonistic factors or a decrease in transport across the blood-brain barrier; typically, circulating leptin levels are increased in obesity. Approaches to pharmacologic use of leptin thus appear to require combination therapy. Sites of leptin action in the brain are the arcuate nucleus, where leptin stimulates pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript protein and inhibits agouti-related protein (AgRP)/neuropeptide Y neurons, the former producing α -melanocyte-stimulating hormones and the latter AgRP, which respectively stimulate and inhibit the effects on the melanocortin-4 receptor of the paraventricular and ventromedial portions of the hypothalamus. Loss-of-function mutations of this receptor are the main monogenic causes of human obesity. POMC and AgRP also have effects on melanin-concentrating hormone (MCH) and orexin and on other neurotransmitters in the lateral hypothalamus.

Flier showed that, after a high-fat

diet, mice do not respond to leptin with signal transducer and activator of transcription (STAT)3 activation (47). The suppressor of cytokine signaling (SOCS) family of cytokine-inducible proteins is important in obesity, with leptin increasing hypothalamic SOCS3 and overexpression of SOCS3 reducing the leptin effect, while heterozygous deficiency of SOCS3 increases leptin responsiveness (48). Flier suggested the concept that SOCS3 is rate limiting for leptin action and noted that an animal model specifically not expressing neuronal SOCS3 shows increased leptin response. Deletion of SOCS3 in POMC neurons results in increased leptin response and also improved glucose homeostasis, suggesting a divergence between effects of leptin on obesity and glucose homeostasis. Flier noted that SOCS3 is an antagonist of both leptin and insulin signals and that it is regulated by leptin, insulin, cytokines, resistin, and fatty acids. The effects of insulin parallel those of leptin, although insulin deficiency is associated with cachexia rather than weight gain. Other signals involved in weight regulation include ghrelin, peptide YY (PYY), serotonin, cannabinoids, glucose, free fatty acids, and AMP kinase. Another important obesity-related factor is MCH, overexpressed in the lateral hypothalamus of leptin-deficient *ob/ob* mice. When administered centrally, MCH causes obesity, while mice not expressing this peptide are lean (49). MCH type-1 receptor antagonists may offer a promising pharmacologic approach to obesity treatment.

An additional concept is whether brain circuitry itself can be modified. Ciliary neurotrophic factor (CNTF) stimulates cell survival and differentiation and has anorexic effects and benefits in models of obesity. It activates STAT3, leading to the concept that it may reduce the leptin resistance of obesity. Weight loss may persist even after administration of CNTF has been stopped, suggesting the possibility that it may stimulate neural stem cells, leading to formation of new neurons, including some expressing POMC and neuropeptide Y (50). Clinical trials failed with this agent because of the development of CNTF antibodies, but new approaches may be possible. Flier reviewed studies in which fetal stem cells developed into neurons, some expressing POMC and leptin-activated STAT3, which, when transplanted into *db/db* mice lacking the leptin receptor, led to weight loss and improved

glycemia, suggesting that it may be possible to “rewire the obese brain.”

Novel targets for diabetes treatment

At the New Orleans meeting, Vivian Fonseca (New Orleans, LA) pointed out that glycemic control should be considered a surrogate end point, akin to cholesterol and blood pressure levels, presumably acting to mediate clinical outcomes rather than simply being a marker associated with complications. Inflammation reduces insulin sensitivity, causes increased triglyceride and low HDL, and is associated with atherosclerosis, with the high-sensitivity C-reactive protein (CRP) and leukocyte counts demonstrated to be markers of vascular outcome. Fonseca suggested, however, that “the problem is that for people with diabetes it’s a totally useless test.” Elevated levels of CRP are associated with a number of insulin resistance syndrome features and, particularly, with obesity among women, a clinical finding that led to the realization of the importance of the adipocyte as a source of proinflammatory factors and of the increase in adipose tissue macrophages in obesity. Nuclear factor- κ B (NF- κ B) plays a key role in inflammation. NF- κ B is bound to the inhibitor of κ B (I κ B). The dissociation of NF- κ B from I κ B leads to NF- κ B entering the nucleus, increasing transcription of inflammatory mediators and cytokines such as interleukin-6, interleukin-1 β , tumor necrosis factor- α , resistin, γ -interferon, chemokines, and receptors. A variety of clinical measures reduce inflammation, including low-fat diet, weight loss, statins, insulin sensitizers, and aspirin. The effect of aspirin on insulin sensitivity suggests its potential for the treatment of diabetes, with studies performed more than four decades ago showing that in high doses it reduces glycemia (51). Aspirin reduces levels of NF- κ B (52,53), and it may be relevant that there is evidence of islet inflammation in diabetes. These findings led to study of salsalate treatment for diabetes, with evidence of reduction in fasting glucose, cholesterol, triglyceride, free fatty acids, and CRP and increase in adiponectin levels in nondiabetic individuals (54). A dose-response study, the Targeting INflammation using SALsate for type 2 Diabetes (TINSAL-T2D; www.tinsal-t2d.org) study, is in progress in individuals with type 2 diabetes.

Fonseca reviewed a number of other potential new diabetes treatments. Bile acid sequestrants appear to lower glucose

in diabetic patients, with data from more than a decade ago suggesting glycemic benefit from cholestyramine (55) and colesvelam now shown to lower glucose in combination with insulin, metformin, and sulfonylureas (56). Weight control is of great importance in the management of diabetes, and ghrelin receptor antagonist administration has been shown to reduce food intake in animal models, suggesting a promising area for study. The cannabinoid receptor antagonist rimonabant has definite weight loss benefit, which is of particular interest in view of the higher endocannabinoid levels in obese individuals, but has been found to be associated with anxiety and depression, leading to concern as to whether this will be a safe approach. Given the similarity between hypercortisolemia and type 2 diabetes/metabolic syndrome, with both conditions characterized by obesity, hypertension, insulin resistance, and dyslipidemia, the provocative question has been raised, “Does central obesity reflect Cushing’s disease of the omentum?” HSD1 increases conversion of cortisone to cortisol within the adipocyte and may act in other insulin-sensitive tissues, with a number of groups looking into the development of adipose tissue HSD1 inhibitors. Finally, the sodium/glucose cotransporter SGLT2 is responsible for 90% of renal tubular glucose reabsorption in proximal tubule, and its inhibition, by decreasing glucose absorption, results in glycosuria, with potential glucose-lowering benefit, although this approach may increase the likelihood of bladder and genital infection.

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