Type 2 Diabetes: The Epidemic of the New Millennium*

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ABSTRACT

The increasing prevalence of obesity, which has reached epidemic proportions, raises the likelihood that a similar increase in diabetes will follow. Linkage between the two conditions is clear. Overweight is not only an important risk factor for the development of diabetes, but also has a significant impact on progression and complications. Diagnostic criteria for the recognition of diabetes and for monitoring of the disease process will become increasingly important. The role of laboratory evaluation needs to be reassessed in light of new concepts regarding classification and diagnostic criteria. The relative utility of glucose and glycosylated protein measurements should be addressed, particularly the relationship between laboratory findings and clinical guidelines. Blood glucose monitoring depends on establishment of the threshold for diagnosis. Additional issues are bedside monitoring, the goal of noninvasive glucose sensors and targeting of therapy. The laboratory scientist is likely to play a key role in the application of advances in the detection and management of diabetes.

Introduction

The potential for a sharp rise in the incidence of type 2 diabetes is based on rapidly increasing obesity rates in the United States and elsewhere.1,2 A close relationship between obesity and diabetes is well established.3,4 Consequently, there is concern that currently 22.5 percent of the U.S. population is considered clinically obese, compared to only 14.5 percent less than 20 years ago.5 This obesity epidemic affects all demographic groups, including children.6

The link between excess weight and diabetes apparently depends on the type of fat distribution. There is growing evidence that abdominal fat increases the risk of diabetes7,8 and it is this form of obesity which is particularly on the rise. Abdominal fat cells rapidly break down stored lipids and release the resulting fatty acids into the blood stream. This can cause a significant elevation in blood glucose and triglyceride levels. Further problems arise from the effects of fatty acids on muscle cells, interfering with their ability to take up glucose. That raises blood glucose levels and thus the risk for type 2 diabetes.

According to the World Health Organization, 54 percent of U.S. adults are overweight,5 a dramatic increase over the past two decades. Although research advances have highlighted the importance of molecular genetic factors in determining individual susceptibility to obesity and diabetes9,10 such findings cannot explain the recent obesity epidemic. It is unlikely that genetic patterns have changed substantially in
a few short years. The evidence therefore points to behavioral factors, which, if they continue as they have in recent years, will lead to a major increase in a number of chronic diseases, particularly diabetes.

The National Health and Nutrition Examination Surveys, carried out by the National Center for Health Statistics, define obesity as having a body mass index (BMI) greater than 30. The BMI is calculated by dividing a person’s weight in kilograms by his/her height in meters squared. Although this definition does identify overweight persons, the distribution of the weight is not specified in the BMI. It appears that the distribution of fat throughout the body impacts on glucose and fat metabolism. Thus, even lower BMI levels may be risk factors for subsequent cardiovascular disease. A newer definition of obesity refers to the weight/hip ratio. When the waist measurement is a greater circumference than the hips (a ratio greater than 1.0), then the risk of subsequent cardiovascular disease is increased, despite a BMI less than 30.

Upper body obesity, primarily in the torso and viscera, predisposes to glucose intolerance, dyslipidemia and decreased sensitivity to insulin. Insulin resistance causes hyperglycemia on its own, thus potentiating the already elevated glucose levels. In addition, insulin promotes salt and water retention and thus a volume dependent hypertension may result. The complex of hypertension, dyslipidemia, hyperinsulinemia and hyperglycemia has been called Syndrome X. As clinicians have accepted this new “disease,” they have also realized that they must focus attention on the cause of the syndrome and not just treat all the components of this disease separately. With the increase in obesity in our population, Syndrome X will emerge as a significant problem in the new millennium.

**Diagnostic Criteria: Current Concepts**

**NEW DIAGNOSTIC CRITERIA AND IMPACT ON PREVALENCE**

An estimated 15.7 million people, or 5.9 percent of the American population, have diabetes. About 90 to 95 percent of people with diabetes have type 2 diabetes and only 5 to 10 percent have type 1 diabetes. Of the total, 5.4 million people remain undiagnosed. In June of 1998 the American Diabetes Association published a consensus statement in which it was suggested that the criteria for diagnosis be improved. The new guidelines are simpler and are likely to diagnose individuals before the complications of diabetes have taken their toll. The Consensus Committee reviewed the literature to date and found that when the fasting blood glucose level is greater than 126 mg/dl, or 7.0 mmol, the risk of retinopathy and nephropathy is exponentially increased. The previous diagnostic criterion for diabetes was a fasting plasma glucose greater than 140 mg/dl. Thus, 50 percent of people first diagnosed with diabetes already had evidence of end organ damage. Furthermore, a fasting plasma glucose cutoff of 7.0 mmol has a sensitivity for diagnosing diabetes similar to a two hour value of over 200 mg/dl (11.1 mmol/l).

Because lowering the diagnostic criteria will identify more individuals with diabetes, it is estimated that, rather than 5.4 million, the number of undiagnosed persons could be as high as 8 million. The laboratory database of the Mayo Clinic reveals that among the more than 7,500 individuals with follow-up fasting glucose, 10.3 percent progressed to diabetes by the new ADA criteria and 6.8 percent progressed to diabetes by the old criteria. If educational campaigns are successful in providing diagnostic tests to all persons at risk for the disease (>40 years, overweight, hypertensive, family history positive for diabetes, high-risk ethnic group, elevated lipid levels), then the total number of diagnosed diabetic people in the United States could be 18 million.

The new diagnostic criteria are outlined in table I. These criteria are revised from data of the National Diabetes Data Group and the World Health Organization. Three ways to diagnose diabetes are possible, and each must be confirmed on a subsequent day by one of the three methods given in table I. Those individuals who do not meet the criteria of a fasting plasma glucose greater than 126 mg/dl are
TABLE I

American Diabetes Association Criteria for the Diagnosis of Diabetes Mellitus

1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

2. Fasting plasma glucose ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least eight hours.

or

3. Two hour plasma glucose ≥200 mg/dl during an oral glucose tolerance test (OGTT). The test should be performed using a glucose load containing the equivalent of 75-grams anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use.

called “impaired glucose tolerance” if the fasting glucose is between 110 and 126 mg/dl or the two-hour value is greater than 140 but less than 200 mg/dl. The criteria for testing for diabetes in asymptomatic, undiagnosed individuals are outlined in table II.

The relationship of the fasting and the two-hour plasma glucose to the development of retinopathy was evaluated in Pima Indians over a wide range of plasma glucose cutoffs. Both variables were similarly associated with retinopathy, indicating that each could work equally well for diagnosing diabetes. Since the fasting plasma glucose measurement simplifies the testing of large populations, it has emerged as the diagnostic tool of choice for diabetes.

TABLE II

Criteria for Testing for Diabetes in Asymptomatic, Undiagnosed Individuals

1. Testing for diabetes should be considered in all individuals age 45 years and above and, if normal, it should be repeated at 3 year intervals.

2. Testing should be considered at a younger age or be carried out more frequently in individuals who:
   A. Are obese (≥120% desirable body weight or a BMI ≥27 kg/m²).
   B. Have a first-degree relative with diabetes.
   C. Are members of a high-risk ethnic population.
   D. Have delivered a baby weighing ≥9 pounds or have been diagnosed with gestational diabetes.
   E. Are hypertensive (≥140/90 mmHg).
   F. Have an HDL cholesterol level ≥35 mg/dl and/or a triglyceride level ≥250 mg/dl.
   G. On previous testing, had impaired glucose tolerance.

The OGTT or fasting plasma glucose test may be used to diagnose diabetes; however, in clinical settings the fasting plasma glucose is preferred because of ease of administration, convenience, acceptability to patients, and lower costs.
GLUCOSE VERSUS GLYCOSYLATED PROTEINS AS A DIAGNOSTIC METHOD

Although glycosylated hemoglobin reflects the mean blood glucose over the last six to 12 weeks, the literature still is divided as to the utility of glycosylated hemoglobin to identify and diagnose diabetes. Performance of fasting plasma glucose is the currently recommended method of diagnosing diabetes. Glycosylated hemoglobin, or HbA1c, may be affected by variables other than glucose, such as persistence of HbF, uremia, alcoholism and/or ingestion of large amounts of aspirin. In the majority of cases, it is only glucose elevation over time which raises the HbA1c above the normal range. The majority of people diagnosed with diabetes have a HbA1c value above 7.0 percent, i.e., four standard deviations above the mean of a normal population. The cutoff levels for HbA1c used in various studies were based on the fact that, above a certain level, the risk of developing chronic diabetic complications is increased markedly. The problem with establishing standards and norms for the HbA1c assay is that there are five different techniques for the measurement of HbA1c levels, and each needs to have the normal range established in the laboratory. Ideally, all laboratories should be standardized to the values of the Diabetes Control and Complication Trial where the normal range was 4.9 to 6.0 percent, using a high pressure liquid chromatographic method. Less expensive techniques, with high coefficients of variation and wider ranges of normal, unfortunately, are used more commonly. Until there is a "gold standard" for HbA1c levels comparable to that for the measurement of glucose, plasma glucose will continue to be the diagnostic variable utilized.

Leptin and Diabetes

Studies on the molecular physiology of leptin and its receptor suggest that leptin is a key factor in controlling body weight. The primary physiologic role of leptin appears to be as a regulator of energy homeostasis by providing a signal to the central nervous system regarding the amount of fat stores. The signal mediates changes in behavior and metabolism that tend to maintain body fat at a level determined by genetic, developmental and environmental factors.

A relationship of leptin to diabetes and obesity is evident in certain mouse strains. Intraperitoneal or intraventricular administration of recombinant leptin to ob/ob mice reverses virtually all the characteristics of the phenotype. Leptin decreases food intake, increases energy expenditure and causes rapid weight loss. Administration of leptin also decreases blood glucose and insulin concentrations in the ob/ob mouse, and stimulates glucose turnover and uptake by skeletal muscles and decreases liver glycogen content in lean mice.

In humans, plasma leptin concentrations are highly correlated with total fat mass. The concentration in plasma ranges from approximately 2 to 20 ng/ml in normal weight individuals, and 10 to 300 ng/ml in obese individuals. Plasma leptin concentrations per unit fat mass are two- to three-fold higher in females than in males. These differences may result in part from the higher percentage of body fat in subcutaneous depots in females, but differences in ambient gonadal steroids may also play a role. For example, premenopausal women have higher plasma leptin concentrations than postmenopausal women, suggesting that estrogen and/or progesterone may increase leptin gene expression. On the other hand, testosterone replacement normalizes elevated leptin concentrations in hypogonadal males, suggesting that androgens may suppress leptin expression.

Plasma leptin concentrations can be measured precisely by means of radioimmunoassay. Plasma leptin shows a diurnal rhythm, with the lowest concentrations occurring in the early afternoon and the highest levels from midnight to the early morning. Leptin circulates in both free and bound forms. Multiple leptin-binding proteins have been detected by gel filtration and sucrose gradient centrifugation. The ratio of free to bound leptin is lower...
in obese than in lean subjects, although the absolute concentration of free leptin is higher in the obese.

Short-term fasting by human subjects substantially reduces the plasma concentration of free leptin and decreases the ratio of free to bound leptin. Maintenance of a hypocaloric diet reduces the total plasma leptin concentration to approximately 50 percent of its concentration relative to weight-stable individuals with the same fat mass. However, overfeeding does not increase leptin expression beyond that expected for the increase of fat mass. These effects of short-term fasting and overfeeding, taken together with the biologic effects of leptin on food intake and energy expenditure, are consistent with a physiologic model in which leptin has evolved primarily to keep body fat mass at or above a set point.

From a clinical standpoint, this model suggests that monitoring of plasma leptin levels may be useful in helping the formerly obese to maintain a reduced body weight by providing a leptin signal comparable to that which preceded weight reduction. Because of the importance of weight regulation in diabetes, monitoring the diabetic patient may benefit from evaluation of leptin patterns at different stages of the evolution of the disease process. As a marker of disease progression and control, leptin may in the future take on an increasingly important role in the laboratory evaluation and management of diabetes.

Other Potential Markers for the Diagnosis of Diabetes

Serum Insulin Elevation

Although, classically, diabetes is diagnosed by the documentation of an elevated glucose level, if there are other markers for the diagnosis of diabetes and/or insulin resistant syndrome, or Syndrome X, before the glucose levels are high enough to indicate the disease, then it may be that the diagnostic markers in the future may include a routine test for serum insulin. The ability of insulin to stimulate glucose disposal varies widely in a healthy, non-diabetic population, and a substantial number of such individuals are as insulin-resistant as are patients with documented hyperglycemia. If hyperinsulinemia is a risk factor for subsequent cardiovascular disease, independent of the serum glucose, then documentation of normoglycemia is not sufficient as a screening tool. Hyperglycemia has been implicated as a predictor of cardiovascular disease (CVD) in a number of prospective epidemiological studies. However, controversy continues as to the status of hyperinsulinemia as a risk factor for CVD. One possible explanation for the lack of consensus may be that hyperinsulinemia is only a surrogate measure of insulin resistance and only one of the consequences of this defect. Results of several recent cross-sectional studies have suggested that insulin resistance is a more powerful predictor of CVD. In a study which examined the interaction between insulin resistance and associated atherosclerotic risk factors in the development of CVD over a four-year time period of observation, it was clearly shown that one of every five normoglycemic, non-obese, healthy subjects in the most insulin-resistant tertile had a serious clinical event. The authors concluded that we need not only to measure glucose levels. Insulin levels with a calculation of steady state plasma glucose concentrations as an estimate of insulin-mediated glucose disposal may also be necessary to document insulin resistance and thus be prognostic of individuals at risk for CVD.

Abnormal Lipid Profiles

Not all obese people have dyslipidemia or glucose intolerance, yet obesity is associated with several disturbances in lipid and glucose metabolism. Ideally, our efforts to prevent and treat obesity should be directed toward those individuals who have metabolic derangements associated with obesity. Those individuals who are obese and have normal lipid and glucose profiles may not be at high risk for cardiovascular events. Thus, the search for markers which identify the high risk individual who would manifest problems of cardiovascular dis-
ease should obesity develop would be cost effective when obesity is associated with dyslipidemia and the disturbance is manifested by high concentrations of serum triglyceride-rich lipoproteins and low concentrations of high-density lipoprotein (HDL) cholesterol. In contrast to lean individuals at high risk for cardiovascular disease, obese people usually do not have marked elevations of low-density lipoprotein (LDL) cholesterol. Most studies have found no effect of obesity on serum lipoprotein (a) [Lp(a)] levels. Altered levels of serum triglycerides and HDL cholesterol in obesity might be mediated by changes in the activities of key lipoprotein metabolizing enzymes (i.e., hepatic lipases), decreased or unchanged activity of postheparin plasma lipoprotein lipase, high, normal or low lecithin cholesterol acyltransferase activity, and/or high activity of cholesterol ester transfer protein.

Because not all obese subjects manifest dyslipidemia, two lines of research have emerged in an effort to explain this heterogeneity. One has to do with fat topography: subjects with upper body obesity, particularly visceral obesity, are more prone to low HDL cholesterol and high triglycerides than subjects with peripheral obesity. If visceral obesity is a precursor of dyslipidemia, then radiographic studies (i.e., magnetic resonance imaging to quantitate visceral fat deposits) to assess visceral obesity would be suggested for the future screening program for atherosclerotic heart disease. The second theory, and thus active research, pertains to genetic variations in apolipoproteins and other relevant genes as potential determinants of a subject’s susceptibility to dyslipidemia in the obese state. Here, genetic studies, if proven to predict high risk, would be the optimal screening test. A recent study analyzed the serum lipids, lipoproteins and lipid metabolizing enzymes in 23 pairs of identical twins (thus controlling for genetic variables) who were discordant for obesity. The mean intra-pair difference in body weight was 18 kilograms. The authors showed that when genetic factors are identical, obesity is associated with an atherogenic lipid profile, especially in subjects with high visceral fat. The lipid profile which emerged to identify the obese twin was high total cholesterol, triglycerides, lecithin cholesterol acyltransferase and hepatic lipase. Previous cross-sectional studies on the association between serum lipids and obesity have been hampered by the fact that it has not been possible to distinguish between the effects of obese subjects and those of all genetic factors affecting lipid metabolism. This problem can be avoided by examining the same obese subjects before and after weight reduction. Using response to a weight reduction program is onerous for a screening tool to identify individuals at risk. The identical twin study described above points the way to a laboratory screening protocol to identify those individuals at risk for obesity-induced cardiovascular disease.

Blood Glucose Monitoring

Bedside Monitoring

Over the past 20 years, technology for the bedside monitoring of glucose has advanced markedly. From the days of cumbersome reflectance meters and reagent strips more dependent on technique than concentration of glucose, we have arrived at an era of a systems tree of operator errors. The American Diabetes Association Consensus Statement describes a variety of uses for bedside monitoring in a hospital: as an educational tool to enhance understanding of diabetes by patients and their families; in emergency rooms for the rapid evaluation of patients; in the perioperative management of surgical patients; and in the management of patients given total parenteral nutrition. The system needs careful quality control, yet the accuracy in these settings needs only to be sufficient to identify glucose levels which are too low, normal, slightly high and too high (meaning immediate action). The systems are now more accurate than this qualitative bracketing of glucose levels. An understanding of the qualitative bracket, however, does open the door for less accurate, but perhaps more useful, continuous non-invasive sensors. Knowledge of the moment-
to-moment glucose bracket may be more important than infrequently measured blood glucose levels. Although a truly accurate continuous non-invasive sensor is probably not yet on the horizon, there are two “minimally” invasive sensors which can accurately bracket the blood glucose continuously into “too low,” “normal,” “slightly high” and “very high.” The two sensors in clinical trials are the Minimed Sensor (Minimed, Sylmar, CA) and the GlucoWatch (Cygnas, San Francisco, CA). Hopefully, the new millennium will produce the long-awaited accurate non-invasive glucose sensor. Development of such a sensor will facilitate the development of an artificial pancreas whereby the data obtained from the continuous sensor can be used to program a continuous insulin infusion device to regulate the blood glucose levels.

**Targeted Therapy**

Insulin-mediated glucose uptake and utilization occur primarily in skeletal muscle and are impaired in type 2 diabetes. Recently, troglitazone, a thiazolidinedione anti-diabetic agent, has been shown to reduce insulin resistance in liver and muscle. One mechanism by which troglitazone may mediate these effects is by binding to and activating the transcription factor, peroxisome proliferator-activated receptor-γ (PPARγ). PPARγ belongs to a family of PPARs which are nuclear receptors comprised of three subsets designated PPARα, PPARγ and PPARδ. PPARγ exists as two isoforms: PPARγ1, the major form present in a variety of tissues, and PPARγ2. The precise functions of the PPARγ receptors are unknown, but they are thought to regulate lipid homeostasis, adipocyte differentiation, and insulin action through coordinated effects on gene transcription.

Recent studies indicate that there is a close relationship between the capacity of various thiazolidinediones to stimulate PPARγ and their antidiabetic actions, suggesting that PPARγ is the receptor for this class of drugs. Chronic troglitazone treatment increases glucose transport and metabolism in type 2 diabetic subjects in association with enhanced expression of the glucose transporter-1 gene. In addition, this drug has been shown to augment insulin sensitivity by increasing expression of PPARγ as well as other genes involved in glucose and lipid metabolism. The thiazolidinediones have not only provided a probe to help understand the possible defects in type 2 diabetes, but have also enabled a major advance in treatment. Data from the “therapeutic” trial that these drugs have provided may be useful in considering the measurement of glucose transporter activity and/or PPARγ receptors. Monitoring of drug therapy may also be guided one day with serial measurements of glucose transporters and PPARγ.

Metformin is an oral antidiabetic agent which has been shown to have a profound effect on hepatic gluconeogenesis and glycogenolysis. Metformin increases mitochondrial fatty acid beta-oxidation, peroxisomal fatty acid beta-oxidation and anaerobic respiration. Additionally, metformin stimulates lipolysis. Because metformin affects catabolism, it is helpful in weight loss programs. The future wave of laboratory monitoring of the utility of metformin to impact on lipolysis and thus weight loss may involve using a mitochondrial-specific fluorescent dye. Laboratory assistance may be essential in the future to judge efficacy of treatment programs.

**Concluding Remarks**

From the foregoing discussion, it is evident that obesity has become, and will continue to be, a focal point in the diagnosis and management of diabetes. The problem of overweight is a global one, implicated in a variety of other diseases, such as coronary artery disease, hypertension and cancer. But the role of obesity in monitoring of diabetes may have particular relevance for the laboratory scientist. Markers for the early detection of diabetes will be needed. Prevention is a distinct possibility when risk factors can be defined and appropriate monitoring and lifestyle strategies instituted. At present, such markers remain to be developed and, in view of the impending epidemic, the search takes on special urgency.
One possible candidate is leptin. Currently under active investigation for its role in obesity and diabetes, this protein and its receptor represent excellent targets for development of clinically applicable tests. The day may not be far off when measurements of leptin and related compounds will be used to evaluate the propensity for and management of diabetes.

Another significant factor may be growth hormone. Already implicated in other metabolic disorders, growth hormone could also be involved in type 2 diabetes and its complications in a clinically useful way. That is, its measurement and regulation might provide a means for assessing the development and progression of the diabetic process.

Genetic markers also represent a potential laboratory approach. As mapping of the human genome progresses, the hope is that specific markers for diabetes may be defined, just as now exist for certain forms of cancer and other diseases. Should this occur, laboratory scientists would have to play a key role in the clinical application.

Is there a particular role for the anatomic pathologist in the detection and monitoring of diabetes? While this may not appear evident at the present time, the rapidly expanding field of immunohistochemistry and related techniques could offer some possible approaches. Problems associated with insulin resistance and related metabolic disorders might be manifest in alterations of basement membrane proteins, collagen components or other intercellular matrix elements. Such changes would be amenable to skin biopsy or needle aspiration of specific organs. Certainly the possibilities are wide open and will depend on major advances in understanding of the changes associated with diabetes.

The challenge is significant, for the indications are that diabetes could well become the epidemic of the new millennium. What is encouraging is that scientific progress in the area is approaching the threshold of clinical application. The laboratory scientist should be prepared to play a major role in the support and application of developments in diabetes research.

References


