Diabetes Mellitus: an Overview

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AREA REVIEW: DIABETES MELLITUS

DIABETES MELLITUS: AN OVERVIEW[1,2]

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Diabetes Mellitus is an ancient medical term which early physicians used to designate a mysterious disease characterized by profuse, sweet-tasting urine. As medicine progressed the meaning of the term changed considerably. Unfortunately, the concept that diabetes mellitus is a disease—a distinct pathological entity—has persisted and has caused much confusion both among the general public and within the health care professions. In fact, diabetes is a highly complex phenomenon which defies any simple explanation. It is clear, however, that diabetes is a major health problem which affects up to 5% of the American population and which causes both premature death and major morbidity including blindness, kidney failure, premature cardiovascular disease, and gangrene of the lower extremities. The purpose of this overview is to present a framework for assembling all of the countless facts about diabetes for investigators and practitioners in behavioral medicine. Because of the breadth and complexity of the subject we have had to limit depth of coverage. More detail can be found in the references and in two recently published textbooks (1,2).

DEFINITION AND DIAGNOSIS OF DIABETES

There is a tendency in the medical literature to define diabetes in terms of underlying pathophysiologic processes such as insulin deficiency. We prefer to define diabetes simply as chronic hyperglycemia (high blood glucose concentration). The word chronic is important because hyperglycemia can occur acutely with little or no implication for health. However, to have hyperglycemia for a long period of time usually has a major impact on health. The word hyperglycemia permits a very general point of view regarding what causes diabetes and avoids a number of paradoxes, such as the fact that some people with diabetes actually have elevated levels of insulin in their blood. Furthermore, making the diagnosis of diabetes is virtually always based upon measurement of blood glucose concentration.

Making the diagnosis of diabetes, a seemingly simple task, often presents problems. The reason is that the parameters used for diagnosis, such as fasting blood glucose level or glucose tolerance test results, are continuously distributed in most populations; that is, there is no cut off level of blood glucose above which one clearly has diabetes or below which one clearly does not have diabetes. In clinical practice it is generally wise to err on the side of under diagnosing diabetes, and most physicians now use a conservative criterion of plasma glucose exceeding 140 mg/dl after an overnight fast on at least two occasions (3). The glucose tolerance test is rarely useful in clinical situations. On the other hand, for research projects which require a definite, if arbitrary, distinction between diabetes and nondiabetes, the glucose tolerance test is the procedure of choice. Standardized methods of procedure and interpretation are available (3).

Classification of Diabetes

Classification of different types of diabetes on the basis of etiology or pathogenesis would be extremely useful for both clinical and research purposes. Unfortunately, such a classification is impossible because of inadequate knowledge regarding the causes of diabetes. For most of this century, the terms juvenile onset and adult onset were used to differentiate the two most common diabetic syndromes. However, classification by age of onset was never satisfactory because juvenile type diabetes can begin late in life and adult type diabetes can begin early in life. In 1979, the National Commission on Diabetes proposed a classification system based on insulin dependence (3), i.e. whether an individual requires insulin in order to survive. Insulin-dependent diabetes (IDDM or Type I) characteristically has its onset before age 30 and affected individuals are usually at or below normal body weight. By definition a person who has IDDM will develop ketoacidosis and die within days to weeks, if not treated with insulin. Non-insulin-dependent diabetes (NIDDM or Type II) characteristically begins after age 40 and 60–90 percent of affected individuals in the U.S. are above normal body weight. Ketoacidosis in NIDDM is rare and generally occurs only following severe physical stress. Non-insulin-dependent diabetes is approximately 20 times more common than insulin-dependent diabetes.

Classification based on insulin dependence is also not entirely satisfactory because many non-insulin dependent diabetics take insulin for its blood glucose lowering effect in hope of delaying or preventing the complications of diabetes. Thus, the majority of people in the United States who take insulin actually have non-insulin-dependent diabetes. Fortunately, the new classification system permits the use of Type I and Type II for IDDM and NIDDM respectively. The new classification system also employs the following terms: gestational diabetes (GDM), for hypergly-

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[1] For simplicity and brevity, we use the term "diabetes" throughout this paper. It is important to realize, however, that there are other kinds of diabetes (e.g. diabetes insipidus) and that the proper term is "diabetes mellitus."

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cemia only during pregnancy; impaired glucose tolerance, for individuals who have abnormal glucose tolerance tests but do not have diagnostic fasting blood glucose levels; history of impaired glucose tolerance, for persons who had at one time but do not presently have hyperglycemia; and abnormality of glucose tolerance, for persons at risk of developing diabetes because of a strong family history or other factors. These terms are extremely useful.

THE ETIOLOGIES OF DIABETES MELLITUS

Diabetes mellitus, in general, occurs because of some interplay of genetic and environmental factors (4). A few forms of diabetes are purely genetic, for example the syndrome called "maturity onset diabetes of youth," or purely environmental, following ingestion of a rodenticide called vacor. However, the great majority of diabetics probably inherit a susceptibility but only develop the condition after experiencing some set of environmental conditions during life.

Insulin dependent diabetes is associated with certain histocompatability (HLA) antigens, indicating that a gene conferring susceptibility to this form of diabetes may reside on chromosome 6 near the HLA locus (4). One environmental factor that may trigger the onset of IDDM is a viral infection (5). Any of several types of viral infections involving the pancreas may lead to damage to the insulin producing (beta) cells. As a consequence, the body's immune system may begin producing antibodies directed against the beta cells in the pancreas, leading to destruction of these cells (5) and an inability to sustain normal insulin levels in the blood. Since insulin is a hormone which acts to remove glucose from the blood, hyperglycemia is a major feature of the insulin-deficient state.

Non-insulin-dependent diabetes is a more strongly inherited condition than IDDM (6). However, at present, there are only a few clues as to the location of the abnormal genes. The environmental factor that appears to be the most common trigger for this type of diabetes is overabundance of food. Chronic overeating stimulates insulin production by the pancreas leading to elevated blood levels of insulin, which may cause two things to occur. First, cells or tissues which normally respond to insulin may become resistant to the action of this hormone as a result of long standing exposure to excessive amounts. Second, in the face of long standing overstimulation, the insulin producing cells in the pancreas may become damaged or exhausted leading to insufficient insulin production. Insulin resistance, insulin deficiency, or both may contribute to the development of hyperglycemia in NIDDM (7).

It is important to realize that the explanations just given for the causes of IDDM and NIDDM, while attractive, are still incomplete and speculative. While we await a better understanding of its causes, it is useful to think of diabetes in the context of a more general process—fuel metabolism (8). The most important function of glucose, by far, is to serve as a source of energy or fuel for the brain and certain other organs in the body. Thus, diabetes can be considered to be an abnormal accumulation of fuel in the blood, and any event or set of events that interferes with normal fuel processing leading to an accumulation of fuel in blood "causes" diabetes. In a most general sense, insulin acts to remove glucose from blood into cells where it is either burned to provide energy or converted to a storage form for later use. Thus, it is no surprise that either insulin deficiency or resistance to the action of insulin may lead to hyperglycemia. The virtue of the fuel metabolism model is that it permits explanations for hyperglycemia that are unrelated or only indirectly related to insulin physiology. For example, overeating can be considered to "cause" diabetes by presenting the body with more fuel than it can handle. Another example is the fact that a variety of drugs including steroids, diuretics, and antiseizure agents may interfere with normal fuel processing and cause the blood glucose level to rise. A final advantage of the fuel model is that it minimizes the importance of the "burning" of glucose, a concept which is more confusing than helpful.

ACUTE COMPLICATIONS OF DIABETES

Hyperglycemia *per se* can cause a variety of signs and symptoms that constitute the acute complications of diabetes. These signs and symptoms may occur at any time during the course of the disorder and range in severity from none to lifethreatening. It is important to realize that Type II diabetes and conventionally treated Type I diabetes may be clinically silent, i.e. the affected person has no symptoms of sufficient severity to require seeking medical attention. This is so in at least half of the cases of diabetes in the United States. Persons with clinically silent diabetes are at risk of developing both acute and chronic complications of diabetes.

The classic symptoms of diabetes are polyuria (excessive urine) and polydipsia (excessive thirst). Nocturia (urinating more than once or twice during the night) is a particularly useful symptom because it describes a generally abnormal behavior and is semi-quantitative. Other typical but less common symptoms include weight loss, polyphagia (excessive appetite) and blurred vision. A very large number of other symptoms may occur as a result of diabetes, but, in general, these are due to the chronic complications of diabetes.

The lifethreatening acute complications of diabetes include ketoacidosis and hyperosmolar coma (9). Diabetic ketoacidosis is a syndrome of extremely high blood sugar with resulting dehydration. In addition, co-existing abnormalities of fat metabolism lead to accumulation of acids in the blood. If not treated, diabetic ketoacidosis leads to death within days to weeks. Hyperosmolar coma is a virtually identical disorder except that the acid condition of the blood is not present. Ketoacidosis is a common complication of Type I diabetes and a rare complication of Type II diabetes. Hyperosmolar coma is a complication of Type II diabetes.

Pathogenesis of Acute Complications

Hyperglycemia, if sufficiently severe, may lead to glucosuria (glucose in the urine). Normally, the urine is free of glucose unless blood glucose concentrations exceed about 180 mg/dl. Above this threshold, glucose may accumulate in the urine in substantial amounts. If this occurs, urine volume may increase dramatically causing polyuria. Polydipsia occurs as a compensatory mechanism to make up for water lost in the urine. Severe insulin deficiency may lead to breakdown of constituents of body tissue such as fat and muscle which the liver uses to make additional glucose. This condition leads to weight loss and a conpensatory polyphagia. Blurred vision occurs in diabetes as a result of marked changes in blood glucose concentration. As the blood glucose rises

or falls, the osmotic pressure of blood increases or decreases causing the lens to shrink or swell with resulting changes in the refractive index.

In severe diabetes, the loss of water in the urine may exceed the ability of the patient to compensate by drinking more resulting in extreme dehydration. At the same time body fat is broken down. Certain by-products of fat metabolism are organic acids which cause the blood to become acidic. This combination of circumstances is the cause of diabetic ketoacidosis. Hypersmolar coma is very similar except that the acid breakdown of body fat with resulting acid production does not occur.

CHRONIC COMPLICATIONS OF DIABETES

Over the course of many years or decades virtually all organs of the body may be damaged as a result of diabetes. The so-called chronic complications of diabetes are usually classified as being due to microangiopathy (disease of small blood vessels), macroangiopathy (disease of large blood vessels), or neuropathy (damaged nerves). Microangiopathy occurs in all tissues but is clinically significant mainly in the back of the eye (retina) and the kidneys. Diabetic retinopathy is primarily a sign that can be detected by physical examination and represents the visible changes in the retina which occur as a result of damage to the small blood vessels supplying the eye. If sufficiently severe, diabetic retinopathy can cause impairment of vision and/or blindness. While diabetes is the most common cause of new blindness in the United States, fortunately, it occurs only in a small percentage of diabetics, although impairment of vision is very common. Diabetic nephropathy (kidney disease) represents a slow but relentless destruction of the kidneys, leading to kidney failure and the necessity for dialysis or kidney transplant.

The macroangiopathy of diabetes simply means that persons with high blood sugar, over a long period of time, have a substantially increased risk of developing such conditions as heart attacks, stroke, and gangrene of the feet, which also occur frequently in non-diabetic individuals. Diabetic neuropathy is of two types, peripheral and autonomic. Peripheral neuropathy typically causes pain and other abnormal sensations in the feet and progressively leads to loss of sensation in affected areas. Autonomic neuropathy occurs throughout the body and presents as dysfunction of organ systems regulated by the autonomic nervous system. Typical symptoms of autonomic neuropathy include dizziness upon standing up, diarrhea, nausea, urinary incontinence, sexual impotence in males, and abnormal sweating.

Pathophysiology of Chronic Complications

At the present time, the weight of scientific evidence and opinion favors the concept that chronic complications of diabetes occur because of long standing hyperglycemia (10,11). There is no question that these complications are directly related to the duration and severity of diabetes. However, it is important to realize that evidence also exists that the chronic complications of diabetes may develop independently from hyperglycemia (10). The implication of this latter theory is that treatments directed primarily at long term reduction of blood glucose level would have no impact on the development of the chronic complications.

Hyperglycemia may damage cells and tissues in at least two ways (10). One theory holds that in tissues such as the eye, the small blood vessels, and the nerves, metabolic breakdown of glucose leads to accumulation of by-products, e.g. sorbitol, which damage these cells. The second theory holds that in hyperglycemia glucose becomes tightly (covalently) bound to structural and functional proteins throughout the body. This attachment of glucose to proteins leads to damage and dysfunction over a long period of time.

TREATMENT OF DIABETES

The treatments for diabetes are of two general types, primary and secondary. Primary treatment of diabetes is directed at normalization of blood glucose concentration. Finding some combination of lifestyle change and pharmacologic therapy that reverses or compensates for the genetic and environmental events leading to hyperglycemia in an individual patient is a very pragmatic art. Secondary treatment of diabetes is treatment of the acute and chronic complications of the disorder and is beyond the scope of this overview.

Patient Education and Self-monitoring

In order to be successful in the treatment of diabetes, one must appreciate that essentially all treatment methods require understanding and participation on the part of the patient. Thus, any approach to diabetes treatment must begin with and continually include the education of the patient as to the nature of the diabetes and the specific therapies employed.

As previously noted, untreated diabetes is often clinically silent. Furthermore, inadequately treated diabetes may also be clinically silent. Thus, it is desirable for diabetic patients to be able to monitor the status of the disorder on a day-in and day-out basis and a variety of methods are available for this purpose. The traditional monitoring method, measurement of urine sugar, is now known to be of limited value and many diabetes treatment centers have abandoned the use of this procedure (12). Self-measurement of blood glucose concentration, however, is now technically and economically feasible and represents a major advance in diabetes treatment (13). Self-measurement of blood glucose enables diabetics to learn what works and what doesn't work to keep blood glucose at or near normal levels and enables them to take corrective action when the blood sugar level is abnormal. The clinical application of self-measurement of blood glucose varies considerably. Typical approaches include measurement before each meal and before bed for Type I diabetics and daily measurement of fasting blood glucose for Type II diabetics.

Nutrition and Exercise

Proper diet is the traditional cornerstone of virtually all diabetes treatment programs. Unfortunately, expectations of diet therapy have been too high and many misconceptions have arisen (14). At the present time, the position of the American Diabetes Association is that a diabetic diet should be nutritious, adjusted in caloric content to achieve or maintain normal body weight, and timed appropriately in light of pharmacological agents employed such as insulin. A variety of nutritional measures such as high carbohydrate, high fiber, and very low calorie diets are available. The use of any of these diets is justifiable provided that the diet is effective and conforms to the standards of the American Diabetes Association.

A program of daily exercise is generally considered to be a desirable component of any treatment program. Unfortunately,

this is also an area that suffers from considerable overexpectation and misconception. Exercise in the treatment of diabetes is a subject in need of further research. Until more information is available, it is reasonable to encourage diabetics to engage in a program of moderate, daily aerobic exercise.

Insulin

Insulin for treatment of diabetes is available in a variety of preparations (15). The duration of action of an insulin preparation may be short, intermediate, or long term. The source of the insulin may be from pork or beef. In addition, recombinant DNA technology has recently made insulin available which is identical in structure to human insulin.

Type I diabetics by definition must take insulin injections in order to remain alive. This can usually be accomplished by taking a single injection of intermediate acting insulin on a daily basis. However, a single daily injection of insulin, while capable of sustaining life and preventing acute complications of diabetes cannot, in general, produce normalization of blood glucose concentration. Thus, Type I diabetics taking a single daily dose of insulin are in very poor control. During the past 10 years this realization has led to the development of much more intensive insulin treatment schedules for Type I diabetes (13). These include multiple daily injections of combinations of intermediate or very long acting insulin with short acting insulin. Furthermore, insulin infusion pumps which can deliver both a steady basal rate of insulin as well as increased infusion rates before meals are now available. Adjustment of insulin dose either by injection or by pump infusion is done daily based on the results of self-measured blood glucose levels. It is important to realize, however, that these new intensive approaches to insulin treatment, while important, are still inadequate due to the multiplicity of other factors which impact on blood glucose.

Insulin is also used in the treatment of Type II diabetes for the purpose of reducing blood glucose toward normal levels. Most often this form of treatment is limited to one or two injections of intermediate acting insulin daily rather than using the more intensive approach currently being evaluated for Type I diabetes. This limited use of insulin for Type II is based on the generally milder nature of this condition as well as limited effectiveness due to insulin resistance.

There are several complications of insulin therapy. By far the most important of these is "insulin reaction" (hypoglycemia or low blood sugar) due to exercise or inappropriately timed insulin injection. Insulin injections can also cause allergic reactions and either build up or break down fatty tissue under the skin at the injection site.

Oral Agents

In the 1950's oral hypoglycemic agents (15) became available for the treatment of Type II diabetes. These drugs probably act by promoting insulin production in the pancreas. They may also reduce insulin resistance in peripheral tissues. In 1970 the results of a prospective, randomized trial suggested that the oral agents may accelerate atherosclerosis. This study, by the University Group Diabetes Program (15), was subsequently criticized extensively, so it is currently impossible to make a statement regarding the safety of these drugs. It is also not clear whether they are effective in preventing long term morbidity and mortality associated with diabetes. The use of the oral agents is now generally limited to select Type II diabetics who respond to the drugs in terms of lowering blood glucose and who have failed to respond to more conservative measures.

Other Factors

While diet, exercise, and medication are traditional corrections of diabetes treatment, it is important to realize that other factors such as physical and emotional stress and certain drugs may contribute to the development or degree of hyperglycemia. Sensitivity to these other factors and measures may be of substantial benefit to diabetic patients.

ASSESSMENT OF SEVERITY AND RESPONSE TO TREATMENT

For many years measurement of glucose concentration in urine was the only practical method for assessing diabetes control. Urinary glucose is, at best, an indirect and semiquantitative way of estimating blood glucose level. Furthermore, because of the "threshold" phenomenon, blood glucose must usually be elevated to greater than twice normal level before glucose "spills" into the urine. Many centers have abandoned the use of urine glucose testing. Direct measurement of blood glucose is now technically trivial. However, isolated values are of limited usefulness because blood glucose level fluctuates and the value obtained is highly dependent on when the blood sample was obtained. Many clinicians now view blood glucose measurement as a tool to aid diabetics in making decisions during everyday life.

During the past 10 years a new test, hemoglobin Al (Hgb Al, Hgb Alc, glycohemoglobin), has emerged as a powerful tool for assessing severity and response to treatment of diabetes. Hgb Al is normal hemoglobin with a glucose molecule tightly (covalently) attached. For reasons beyond the scope of this discussion, Hgb Al level provides a reasonable estimate of what the average blood glucose *has been* during the prior two months (16). Thus, this test can be used on a first encounter to assess severity and then followed at 2 to 6 month intervals to assess response to treatment.

SUMMARY

Diabetes mellitus (chronic hyperglycemia) can be viewed as an outcome of the interplay among the underlying disease process, the environment, and the behavior of the affected individual. Most of the efforts of the health care team are directed at behaviors such as diet, exercise, and medication, because little can be done at present about the underlying problems and the environment. Thus, at the clinical level, diabetes is a nearly pure example of behavioral medicine. Ultimately, we must cure or prevent diabetes, but for now management of diabetes mellitus is a behavioral art and science.

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