Review: Current Trends and New Approaches in the Management of Diabetes Mellitus

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Abstract. Current trends in the management of type 2 diabetes mellitus, based on the 20-year United Kingdom Prospective Diabetic Study, include intensive treatment to control the blood glucose level and blood pressure in order to prevent or delay microvascular and cardiovascular complications. In the new millennium, type 2 diabetes will become epidemic in developing countries. If diabetes were to develop in 10% of the 1.2 billion population of China, the expense of intensive treatment would be immense. Laboratory tests are useful for detecting risk factors before the onset of the disease and convincing the general public to take preventive measures. Glucose tolerance testing is one of these tests. When glucose tolerance is impaired, 25% of β-cell function is lost. Determining the plasma proinsulin level is another useful evaluation; impaired glucose tolerance accompanied by increased plasma proinsulin level is indicative of an enhanced risk that type 2 diabetes will develop within 5 years. Educating the public about eating a healthy diet and exercising may prevent the development of diabetes and thereby reduce the global prevalence of type 2 diabetes. (received 11 April 2000; accepted 8 June 2000)

Keywords: diabetes mellitus, hyperglycemia, hypertension, insulin, proinsulin, glucose tolerance, diet, exercise

Introduction

Diabetes mellitus was the major focus of the 1999 meetings of the Endocrine Society and the American Diabetes Association. Of all patients with diabetes, 90% to 95% have type 2, or adult-onset, diabetes; the remainder have type 1, or juvenile, diabetes. The major causes of type 2 diabetes are β-cell dysfunction in the pancreatic islets and insulin resistance in target tissues. A recent trend in the management of type 2 diabetes involves combined therapy using various pharmaceutical agents, including oral drugs that stimulate endogenous insulin secretion, oral drugs that reduce insulin resistance, and the injection of exogenous insulin. Combined therapy fits well with the intensive treatment suggested by the United Kingdom Prospective Diabetes Study (UKPDS), a long-term study that had 4,209 patients at the start and continued for more than 20 years, from 1977 to 1998 [1-9]. The reports of the UKPDS encourage the treatment of type 2 diabetes, and the prevention of its complications, not only with drugs that lower blood glucose but also with drugs that control blood pressure. In addition, new drugs have been discovered that reduce insulin resistance, such as several thiazolidinediones, which have been approved or are being considered for approval by the U.S. Food and Drug Administration (FDA). Thiazolidinediones are the only drugs that reduce insulin resistance by mechanisms that have been elucidated at the molecular level. The development of these drugs, and the adoption of intensive combination drug therapy, as suggested by the UKPDS, herald a new era in the management of type 2 diabetes.

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"Diabetes in the New Millennium" was an educational program transmitted as a live, interactive satellite videoconference for U.S. physicians and medical professionals on 15 June 1999.* It focused on "the latest breakthroughs in the treatment and management of type 2 diabetes." The program faculty warned that diabetes may soon become epidemic in developing nations, and particularly in countries around the West Pacific Rim, including China and India. The faculty reviewed the current management of type 2 diabetes through intensive pharmacological control of blood glucose and blood pressure, and they emphasized that adopting a healthy lifestyle may reduce the prevalence of type 2 diabetes and delay the onset of its complications.

The prevalence of type 2 diabetes in developing countries is still low. In China, during the years when food was rationed and the bicycle was the preferred mode of transportation, the prevalence of type 2 diabetes was less than 1%. Public health education programs can help the populace to understand the diagnostic use of laboratory tests, why the fasting plasma glucose test is used to screen for diabetes, how glucose tolerance tests can detect "hidden diabetes," and why the hemoglobin A1c test is used to monitor blood glucose control. These laboratory tests can be used in conjunction with public health education to promote diet and exercise programs.

### Intensive Drug Treatment

The 1998 UKPDS reports [1-5] strongly suggest that intensive treatment with pharmaceutical products is the best method for management of type 2 diabetes. Patients with diabetes treated intensively with hypoglycemic drugs had a better chance of maintaining their fasting plasma glucose level <140 mg/dl and HbA1c value <7% than patients treated by dietary control. The plasma glucose limit of <140 mg/dl was employed in the UKPDS for statistical analysis, and does not represent the upper limit of the reference range, which is <6 mmol/L or 108 mg/dl. The drugs used in the UKPDS included the first and second generations of sulfonylureas, metformin, and insulin.

After 9 years of treatment, fasting plasma glucose levels that stayed <140 mg/dl were observed in 8%, 24%, and 42% of patients that were managed, respectively, with dietary control, sulfonylureas, and insulin therapy. For the goal of a HbA1c level <7%, the percentages were 9%, 24%, and 28% for patients on dietary control, sulfonylureas, and insulin therapy, respectively [4]. After 15 years of treatment, the average HbA1c level reached 8.9% in patients on conventional diet control and 8% in patients who received single-drug therapy, including sulfonylureas, metformin, or insulin injection [1]. Better control was achieved by combining an insulin-secretory drug (sulfonylurea) with an insulin-sensitizer (metformin), or insulin injection with an insulin sensitizer [4]. In addition to controlling hyperglycemia, control of blood pressure was also necessary to reduce the risk of complications such as myocardial infarction and microvascular diseases [6-7]. The major drugs used were angiotensin-converting enzyme (ACE) inhibitors, which inhibit the conversion of angiotensin I to the active hormone angiotensin II, and β-adrenergic blockers to maintain the blood pressure at <130/82 mm Hg [8].

The UKPDS demonstrated that intensive treatment with polypharmacy for prevention of complications was more economical than the treatment of complications [9,10]. It should be emphasized that the combined therapy of diabetes with insulin-secretory and insulin-sensitizer drugs has been practiced for many years in many countries; the UKPDS was a long-term systematic and statistical study that endorsed it. The UKPDS can serve as a model for developing countries on how to treat diabetes in order to prevent its complications.

There are several insulin sensitizer drugs; the most common is metformin (Glucophage®). Metformin increases peripheral uptake of glucose and decreases hepatic output of glucose [3]. Metformin was used in the UKPDS as a monotherapy agent for obese patients with type 2 diabetes and as an insulin sensitizer for combined therapy with sulfonylureas or insulin [2-4]. The molecular mechanisms of metformin action are largely unknown. It is believed that metformin can inhibit gluconeogenesis and glycogenolysis, presumably

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* This program, sponsored by SmithKline Beecham Pharmaceuticals, was endorsed by the Endocrine Society and the American Association of Diabetes Educators. It was broadcast during the Endocrine Society's annual meeting. The faculty included Jay S. Skyler, Peter C. Butler, Harold E. Lebovitz, Alan J. Garger, and Ian Smith.
by increasing the translocation of the glucose transporter GLUT-4. Metformin has been used in Europe, Asia, and the United States for many years with good results. It is relatively safe, even though its sister compound, phenformin, has been reported to cause lactic acidosis [11,12].

The newly discovered insulin sensitizers are the thiazolidinediones [13-14]. The first one on the market was troglitazone (Rezulin®). The maximum dose of this drug is 600 mg/day. Troglitazone contains a side chain of vitamin E structure on its thiazolidinedione ring; both troglitazone and vitamin E inhibit platelet aggregation [16]. Reports indicate that troglitazone can cause liver damage in patients. During clinical trials, troglitazone was reported to have no toxicity and was approved by the FDA [15], but after 80 deaths were attributed to its use, the FDA ordered the manufacturer to remove it from the market. Does the vitamin E structure of its side-chain increase the toxicity of troglitazone, already high because of the high doses needed? The answer is unclear at present.

The newest thiazolidinedione is rosiglitazone (Avandia®). Because its maximum dose is only 8 mg/day, it may be less toxic than its sister compound, troglitazone. The pharmaceutical industry has proclaimed rosiglitazone a “breakthrough” in the treatment of type 2 diabetes because its mechanism is the intervention of insulin resistance instead of increased insulin secretion, and because it has relatively low toxicity. Soon there will be another new thiazolidinedione, pioglitazone, which, unlike troglitazone, does not inhibit platelet aggregation.

Extensive studies of thiazolidinediones at the molecular level indicate that they act on peroxisome proliferator-activated receptor gamma (PPAR-γ). PPAR-γ is a nuclear receptor that mediates adipocyte differentiation and modulates insulin sensitivity. Thiazolidinediones activate PPAR-γ receptor, increase glucose transporter synthesis, and differentiate stem cells into adipose tissue. PPAR-γ is abundantly expressed in the adipose tissue and is also present in skeletal muscle, which is the major organ for glucose utilization. A potential problem with thiazolidinedione is the increase of adipose tissue mass [17-21].

Other antihyperglycemic agents were also included in the UKPDS. The most unique one is acarbose. Acarbose is an antidiabetes agent, but it does not stimulate endogenous insulin secretion, as do sulfonylureas, nor is it an insulin sensitizer. It is an α-glucosidase inhibitor. Without this enzyme action, the intestines will not absorb polysaccharides and disaccharides such as starch and dextrin [22,23]. With improvement in postprandial hyperglycemia and hyperinsulinemia, acarbose may be useful to reduce insulin resistance and to prevent progression to type 2 diabetes in patients with impaired glucose tolerance [24]. Miglitol, a new pseudomonosaccharide α-glucosidase inhibitor not included in the UKPD study, is under clinical trial and may soon be on the market.

Several newly discovered pharmaceuticals, not included in the UKPDS, may be used in the future. Glimepiride (Amaryl®) is a new sulfonylurea that stimulates insulin secretion from a functioning pancreas. Clinical studies demonstrate that glimepiride, in addition to stimulating insulin secretion, also increases the sensitivity of peripheral tissue to insulin. Other sulfonylureas already in use, such as glyburide, may have the same ability. Repaglinide (Prandin®) stimulates the pancreas to secrete insulin; the action is similar to that of sulfonylureas. Structurally, repaglinide is different from sulfonylureas. Repaglinide belongs to a new family of the meglitinides [25,26].

Lispro insulin (Humalog®) is an analog of human regular insulin produced by inverting the sequence of the 28 and 29 amino acid residues of the β-chain in regular insulin to lysine and proline. These changes reduce the analog's capacity for self-association in solution and avidity to form hexamers with zinc. Lispro exhibits monomeric behavior in solution and has an increased absorption rate after subcutaneous injection. Lispro has the same glucose-lowering potency as regular insulin on a molar basis, but its more rapid action and shorter duration offer advantages over regular insulin for controlling the postprandial blood glucose level [27]. Lispro can be used in type 2 diabetes that requires insulin, as well as in type 1 diabetes. Whether lispro insulin will have higher immunogenicity than regular insulin, and stimulate the production of autoantibodies in patients, remains to be determined.

Patients may soon be able to use inhaled insulin, which is currently under clinical trial. Dermal patches for insulin administration are envisioned. In the future, the discomfort of insulin injection may be avoidable.
Public Health Education

Polypharmacy management of type 2 diabetes is hardly a solution. At best, it can delay the complications of diabetes. The willingness of the populace to maintain a healthful lifestyle may be a key factor in controlling the disease. Public health education can disseminate guidelines for such a healthy lifestyle. The World Health Organization anticipates that diabetes will become a global burden. An epidemic is predicted in developing countries, where the incidence of diabetes is projected to rise from 84 million in 1995 to 228 million in 2025, a 2.7-fold increase. In developed countries, the incidence is projected to rise from 51 million in 1995 to 72 million in 2025, a 41% increase [28]. Other studies have corroborated these projections [29]. It may be possible to mitigate this problem through public health education, since evidence from epidemiologic studies indicates the possibility of preventing type 2 diabetes or at least delaying its onset.

The cause of type 2 diabetes is complicated; genetic and environmental factors play a part. The major environmental risk factors are a sedentary lifestyle and consumption of too much food. During the videoconference “Diabetes in the New Millennium,” a viewer called in this question: “Why do African-Americans have a much higher prevalence of type 2 diabetes than Africans?” The answer, according to A. J. Garber, a member of the faculty, was simple: “In America, food is too easy to get, but exercise is too hard to get.” Eskimos who previously lived on the Soviet Union side of the Bering Strait had a prevalence of type 2 diabetes of about 0.2%; however, Eskimos who live on the United States side of the Bering Strait have a prevalence of about 9% [30]. Type 2 diabetes is four times more common among Japanese-Americans who live in Seattle than among Japanese who live in Tokyo. Japanese-Americans with type 2 diabetes are not necessarily overweight or obese; they do have increased visceral fat, an internal obesity that can be measured by computed tomography [34-38].

China is another example. In 1980, at the beginning of economic reform and the end of food rationing, the prevalence of type 2 diabetes was 0.67% (31); by 1996 the prevalence had increased to 3.21%, with the group having impaired glucose tolerance comprising approximately 4.7% [32]. These data were obtained from 300,000 people in 14 provinces. Presumably, the prevalence will reach 11%, the same as the ethnic group of Chinese who live in Taiwan [33]. Good public health education may stop or at least slow the increase. In China’s large population, 1.2 billion, a reduction in prevalence by 1% or even a delay in the onset age by 1 year would be highly advantageous.

Public health education to encourage people to have a healthful, active lifestyle and to restrict their dietary intake can reduce the prevalence of type 2 diabetes and may prevent its development. Public health education in combination with pharmacological treatment can delay or avoid the complications of type 2 diabetes.

Early Laboratory Diagnosis

Fasting plasma glucose is a simple test for diagnosing type 2 diabetes. The upper reference range of fasting plasma glucose generally is agreed to be <6 mmol/L or <108 mg/dl. Levels between 110 and 125 mg/dl are considered to indicate impaired fasting plasma glucose. Increased levels of >126 mg/dl on several occasions are diagnostic of diabetes. At a borderline stage, the diagnosis of diabetes is difficult. However, early diagnosis of diabetes in asymptomatic patients can be beneficial because they can start a diet, exercise, and weight-reduction program. At the Mayo Clinic, the upper limit of the reference range for fasting plasma glucose is 100 mg/dl (5.6 mmol/L). Three morning samplings of increased fasting plasma glucose indicate diabetes. Due to a difference in fat metabolism between Asians and Caucasians, slight modifications of World Health Organization criteria for this test have been suggested in screening for diabetes in Asians [39].

In clinical laboratories, fasting blood glucose values are measured in plasma or serum samples by methods based on the hexokinase, glucose oxidase, or glucose dehydrogenase reactions, with a coefficient of variation of <5%. It is preferable to use plasma collected in the presence of a fluoride-oxalate mixture to prevent glycolysis and coagulation, but for home monitoring and point-of-care testing in hospitals, glucose values are measured by using 1 drop of whole blood; the accuracy is reasonable with a portable reflectance meter. Glucose concentrations derived from whole blood assays are 10% to 15% lower than from plasma or
serum. Home monitoring increases the frequency of blood glucose measurement and is helpful in the control of diabetes.

The oral glucose tolerance test is time-consuming, but is useful for detecting impaired glucose tolerance, a risk factor for type 2 diabetes and macrovascular disease [40]. One major cause of type 2 diabetes is impaired islet β-cell function. When glucose tolerance becomes impaired, about 25% of β-cell function has been lost. By the time diabetes develops, 49% of β-cell function still remains. After 6 years of diabetes, only 28% of β-cell function remains [5].

Another major cause of type 2 diabetes is insulin resistance. It has long been known that insulin response to the oral glucose tolerance test is slower and the amount of insulin secretion is greater in patients with type 2 diabetes than in healthy subjects. The peak insulin secretion during this test is around 60 min in healthy subjects, 90 min in patients with impaired glucose tolerance, and 120 min in type 2 diabetics. The total amount of insulin secretion in type 2 diabetics is much greater than in healthy subjects; therefore, the amount of insulin secretion and the peak time of insulin secretion during the oral glucose tolerance test are both markers of type 2 diabetes [30,33]. The oral glucose tolerance test has its limitations: Poor absorption of orally administered glucose may cause a low response, and some people cannot tolerate large amounts of oral glucose. In such cases, an intravenous glucose tolerance test may be used; blood is collected at 10-min intervals for 1 hr.

Proinsulin, the precursor of insulin, is converted to insulin and C-peptide within β cells by membrane-bound enzymes. Small amounts of proinsulin are secreted into the circulation. An increased plasma level of proinsulin (more than 20 pmol/L) indicates impairment of β-cell function, which is concomitant with hyperglycemia in type 2 diabetes. Another disease that exhibits increased proinsulin and hypoglycemia is insulinoma [41]. Increased proinsulin levels can be detected at an early stage of type 2 diabetes with a sensitive immunochemiluminoassay [42,43]. Recently, Kahn et al [44-46] used proinsulin levels to predict the development of type 2 diabetes and coronary artery disease in a Japanese-American population. At baseline, Japanese-American men with impaired glucose tolerance and higher proinsulin levels had a greater risk for development of type 2 diabetes within 5 years than did patients with impaired glucose tolerance and lower proinsulin levels.

The insulin resistance index can serve as a guide in the treatment of diabetes. The insulin resistance index is computed using a homeostasis model assessment (HOMA) based on fasting plasma insulin and fasting plasma glucose concentrations (fasting insulin x fasting glucose/22.5) [47-49]. Treatment of diabetic patients with increased insulin resistance should focus on insulin-sensitizing intervention instead of interventions that further increase insulin secretion [47]. In an early stage of type 2 diabetes, such patients already have hyperinsulinemia.

Conclusions

In the new millennium, insulin secretagogues, insulin sensitizers, and insulin (and its analog) are available to control the hyperglycemia of type 2 diabetes, and antihypertensive drugs to manage hypertension. Intensive treatment with multiple drugs can reduce the risk of complications in diabetic patients.

To prevent or retard the development of diabetes in the apparently healthy population, we have to rely on public health education to promote exercise and restrict food consumption.

Laboratory tests have an important role in early detection of risk factors for type 2 diabetes; the results of laboratory tests can prompt individuals to adopt a healthy lifestyle years before the onset of the disease.

References


