

The Challenge of Type 1 Diabetes Mellitus

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Abstract

Diabetes mellitus is a heterogeneous group of diseases characterized by high blood glucose levels due to defects in insulin secretion, insulin action, or both. With the number of cases expected to increase rapidly in the years to come, diabetes is a growing health challenge worldwide. Of the approximately 16 million diabetics in the United States, about 1.5 million suffer from type 1 diabetes. In this catabolic disorder afflicting predominantly young individuals, blood insulin is almost completely absent, leading to hyperglycemia and alterations in lipid metabolism. Type 1 diabetes is thought to be induced by a toxic or infectious insult that occurs in genetically predisposed individuals. With recent advances in the understanding of the involved immunology and cellular and molecular mechanisms, researchers strive to battle the disease with new preventive and corrective strategies.

Key Words: complications; diagnosis; pathology; therapy; type 1 diabetes

Introduction

A chronic disorder of carbohydrate, fat, and protein metabolism, type 1 and type 2 diabetes mellitus affected 135 million people worldwide in 1995. According to World Health Organization (WHO¹) experts, this number will increase to 300 million individuals in 2025 (King et al. 1998; WHO 1997). In the United States, 3 to 8% of the Caucasian population suffers from the disease, but the

prevalence is much higher among ethnic minorities living in industrialized countries such as the Indian Asians in Great Britain or the Pima Indians in the United States (Williams and Pickup 1999). A serious cause of morbidity and mortality with an annual financial cost exceeding \$100 billion, the disease not only represents a burden to the affected individuals but also poses staggering economic costs (Bjork 2001, Ettaro et al. 2004). An obvious need exists for new therapeutic options for this common and devastating condition, and the current issue of *ILAR Journal* features promising research toward this end.

Diabetes mellitus is a syndrome that encompasses a collection of disorders with hyperglycemia as a common element. The classification of the two most common variants of the disease, which arise from primary defects of the pancreatic beta cell-insulin signaling system, has changed several times over the last decades of the 20th century. In 1980, the WHO endorsed the recommendation to distinguish the two major forms of diabetes mellitus by a clinical description of the patient—having either insulin-dependent diabetes mellitus (IDDM¹ or type 1 diabetes) or non-insulin-dependent diabetes mellitus (NIDDM¹ or type 2 diabetes). Use of the older terms “juvenile-onset” and “adult-onset” diabetes mellitus was abolished (National Diabetes Data Group 1979). In 1997, experts from the American Diabetes Association introduced a new classification system also used today, which abandoned the terms IDDM and NIDDM and retained the terms type 1 and type 2 diabetes (ADA 1997). Type 1 diabetes is the main focus of this journal issue.

Clinical Features and Pathogenesis

Type 1 diabetes accounts for approximately 10% of all cases of diabetes mellitus and generally afflicts a younger population, with a peak age of around 14 yr. It is a T cell-mediated autoimmune disease characterized by the destruction of insulin-secreting beta cells in the pancreatic islets of Langerhans. *What triggers the immune system, which usually protects us from foreign invaders, to turn on the organ itself?*

One possible explanation is molecular mimicry, in which immune responses may be generated against a common determinant present both in a viral protein and in host cells. This process could induce a tissue-specific immune reaction by production of cross-reactive effector lympho-

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¹Abbreviations used in this article: AGE, advanced glycation endproduct; HLA, human leukocyte antigen; ICA, islet cell antibody; IDDM, insulin-dependent diabetes mellitus; LDL, low-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus; NOD, nonobese diabetic; PKC, protein kinase C; RAGE, receptor for advanced glycation endproducts; Th1, T helper 1; WHO, World Health Organization.

cytes or antibodies that recognize self-proteins on pancreatic beta cells (Kukreja and Maclaren 1999). The coxsackie B4 virus, for example, contains a sequence of 18 amino acids with considerable sequence similarity to glutamic acid decarboxylase, a beta-cell enzyme (Kaufman et al. 1992). In another scenario, viruses could also directly cause mild beta-cell injury, followed by an autoimmune reaction against previously sequestered antigens in virally altered beta cells. Yet other studies have identified an endogenous retroviral genome in diabetic islets, but whether the virus is an initiator for the disease, a precipitator, or simply a marker remains to be determined (Benoist and Mathis 1997). Regardless of the trigger's identity, when beta cell-specific autoreactive T cells become activated, they expand clonally and infiltrate the pancreatic islets. Current evidence indicates that islet beta cell-specific autoreactive T cells belong to a T helper 1 (Th1¹) subset. These Th1 cells produce characteristic cytokines such as interferon-gamma and interleukin-2, which are believed to induce islet inflammation (insulinitis) and beta-cell destruction (Kukreja and Maclaren, 1999; Suarez-Pinzon and Rabinovitch 2001).

As a result of the loss in beta-cell mass, severe insulin depletion leads to overt hyperglycemia in the patient. This sequence is a consequence of hepatic overproduction of glucose via glycogenolysis and gluconeogenesis pathways and decreased cellular uptake of glucose by peripheral tissues such as muscle and adipose tissue. In addition, excessive fat breakdown and fatty acid oxidation may lead to hyperlipidemia and ketosis. Symptoms seen in the diabetic patient include polyuria secondary to osmotic diuresis in the presence of hyperglycemia, thirst as a result of the hyperosmolar state, weight loss due to the depletion of triglyceride stores, neurotoxicity in the presence of high blood glucose levels, and ketoacidosis. If left untreated, symptoms may worsen and lead to circulatory collapse, coma, and death. More common but ultimately equally devastating are the complications that arise from both the micro- and macrovascular changes associated with chronically elevated blood glucose concentrations. As a result of these vascular sequelae, people with diabetes have an increased risk of developing ischemic heart disease, cerebral vascular disease, peripheral vascular disease with gangrene of lower limbs, chronic renal disease, visual impairment, and even blindness, as well as autonomic and peripheral neuropathy. These problems reduce the overall life expectancy of the patient by about 25% (Williams and Pickup 1999), with complications of heart and kidney disease being the most common causes of death.

Animal models have played a major role in uncovering the disease-associated pathophysiology that is difficult to define in humans, and animal research has led the way for human studies such as the Diabetes Control and Complications Trial. This study revealed a strong correlation between hyperglycemia and diabetic micro- and possibly macrovascular complications (DCCTR 1993). The basis of these complications is the subject of a great deal of research. To date, the following four major explanations for the involve-

ment of hyperglycemia in the genesis of described complications have been hypothesized:

1. Nonenzymatic glycosylation (Vlassara 1997);
2. Intracellular hyperglycemia with associated disturbances in the polyol pathway (Gabbay 1975);
3. Activation of protein kinase C (PKC¹) (Koya and King 1998); and
4. Increased hexosamine pathway flux (Kolm-Litty et al. 1998).

Nonenzymatic glycosylation describes the irreversible formation of advanced glycation endproducts (AGEs¹) via the Maillard reaction, and it is probably the best-studied aspect for the cause of diabetic complications. Pathological effects of AGEs are induced by alteration in function of the glycosylated product and by activation of AGE receptors on endothelial cells, monocytes, macrophages, lymphocytes, and mesangial cells. The increased risk of heart disease in the diabetic patient is thought to be attributable, at least in part, to AGE formation. Glycosylation of type IV collagen in basement membranes of blood vessels, for instance, results in cross-link formation, thus trapping interstitial proteins and lipoproteins such as low-density lipoproteins (LDLs¹) (Vlassara 1996). In addition, LDL itself may become glycosylated and subsequently oxidized, a process also referred to as glycoxidation (Bucala et al. 1993). The modified LDL may then be uptaken by non-downregulating macrophage scavenger receptors (CD36). The resultant foam cell formation and development of the so-called fatty streak in the subendothelial space represent initiating events in atherosclerosis (Horiuchi et al. 1996; Jinnouchi et al. 1998; Nathan 1996; Ohgami et al. 2001).

Because AGE apoprotein B and AGE phospholipid levels have been found to be several-fold higher in diabetic patients, and diabetics also show a three- to four-fold increased risk for developing cardiovascular disease and vascular insufficiency (Bucala et al. 1994), many believe that the nonenzymatic glycation process is responsible for induction of events leading to the vascular occlusion (Brownlee 1995; Bucala et al. 1994; Peppas et al. 2004). Other studies point out the contribution of AGE formation to hypertension, kidney problems, and male impotence seen in the diabetic patient. These alterations are now understood to be due to AGEs present on the vascular matrix, where they are thought to inhibit the vasodilatory action of endothelium-derived nitric oxide (Bucala et al. 1991) and to increase the expression of endothelin-1, a potent vasoconstrictor (Quehenberger et al. 2000). Many of the effects of AGEs are also receptor mediated. The best-characterized receptor for AGEs is the receptor for advanced glycation endproducts (RAGE¹), a member of the immunoglobulin superfamily of cell surface molecules (Stern et al. 2002). Studies in rodent models have shown that blockade of RAGE can suppress vascular hyperpermeability and reduce atherosclerotic lesion development (Bucciarelli et al. 2002; Wendt et al. 2002). These results suggest that the AGE-

RAGE system could be a promising target for prophylaxis and therapy.

Changes in polyol pathway flux, induced by hyperglycemia, have been implicated in Schwann cell and pericyte injury where sorbitol accumulation is thought to disrupt ion pumps such as the Na^+/K^+ ATPase (Raccach et al. 1998) and in overhydration of the lens due to osmotic changes (Giusti 2003). Several alterations in vascular cells induced by activation of the diacylglycerol-PKC pathway also appear to be important in explaining micro- and macrovascular complications in diabetes. These alterations include the following: changes in renal and retinal blood flow (Ishii et al. 1996), increased vascular permeability and contractility, and thickening of capillary basement membranes as well as increased cell proliferation (Lang and Kampmeier 2002). Finally, the hexosamine biosynthetic pathway has been hypothesized to be involved in the development of diabetic vascular complications, particularly diabetic nephropathy (Schleicher and Weigert 2000), by inducing various changes in gene expression and protein activity in addition to the stimulation of matrix production via glucose-induced transforming growth factor- β release by mesangial cells (Kolm-Litty et al. 1998). These findings underscore the importance of glycemic control and emphasize the need for additional studies to increase our understanding of the development of the disease in an effort to identify new preventive or corrective strategies.

Several exciting recent discoveries have the potential of paving the way for the prevention of hyperglycemia-induced micro- and macrovascular alterations. Current studies have established a common link between the four discussed pathways: Overproduction of superoxide by the mitochondrial electron transport chain is found in each pathway (Brownlee 2001; Hammes 2003). Cell culture experiments now demonstrate promising results on the ability to interfere with at least three of the pathways by administration of a drug that activates the pentose phosphate enzyme transketolase (Hammes et al. 2003). Studies in animals and, if proven safe, clinical trials are still necessary to establish the applicability of this important finding. Inhibition of the PKC pathway, however, has already proven successful in improving various aspects of renal function. After administration of a PKC-inhibitor, researchers have observed the normalization of glomerular hyperfiltration, a decrease in permeability of the glomerular network as evidenced by a reduced albumin excretion, decreased production of glomerular transforming growth factor- β -1, and diminished extracellular matrix production in various animal models of diabetes (Tuttle and Anderson 2003). Clinical trials will determine whether these improvements hold promise as a novel strategy to ameliorate micro- and macrovascular outcome.

Diagnosis

An international committee of diabetes experts has recently revised the diagnostic criteria for identifying human patients

with type 1 diabetes. Diagnosis is now based on any of the three criteria that follow:

- Classic symptoms of diabetes (polyuria, increased thirst, unexplained weight loss, blurred vision) AND a random plasma glucose concentration of ≥ 200 mg/dL (11.1 mmol/L).
- Fasting plasma glucose of ≥ 126 mg/dL (7.0 mmol/L) after an overnight (at least 8 h) fast.
- Two-hour postload plasma glucose of ≥ 200 mg/dL (11.1 mmol/L) during a standard 75-g oral glucose tolerance test.

Experts caution that in the absence of unequivocal hyperglycemia with acute metabolic decompensation, the diagnosis should be confirmed on a subsequent day by any of the three methods (ADA 1997).

Although it has been shown that glucose tolerance remains normal until the clinical onset of diabetes, beta-cell function and insulin release decrease even during the pre-clinical period (McCulloch et al. 1987). It is thought that approximately 90% of beta-cell mass must be destroyed before overt hyperglycemia will occur. Diagnostic tools other than blood glucose measurements include the screening for glycosylated hemoglobin, which has been proven successful in the initial evaluation of the patient and in the assessment of effectiveness of therapeutic measures (Peters et al. 1996). The major form of glycohemoglobin is hemoglobin A_{1c} , which directly reflects the level of blood glucose concentration over the preceding 8 to 12 wk, making it an effective tool to assess chronic diabetic control. In certain circumstances, measurements of insulin or C peptide levels as well as levels of counter-regulatory hormones (growth hormone, glucagon, cortisol, and epinephrine) may prove useful as well.

Additional attention is now being focused on the “honeymoon period” in the diabetic patient. This critical period between the time of clinical diagnosis and ample destruction of beta-cell mass may be exploited to find avenues that could prevent insulinitis and obviate the need for insulin restoration. This early intervention is desirable because even as intensive exogenous insulin therapy used after extensive beta-cell loss can closely mimic the physiological control of glucose and delay the onset of chronic complications, multiple daily injections or continuous subcutaneous infusion of insulin can be quite burdensome to the patient. To launch successful attempts at intervening with the autoimmune process and preventing the destruction of a beta-cell mass sufficient to support the patient’s insulin needs, it is first necessary to identify persons at risk of developing the disease.

It is now clear that inherited susceptibility to type 1 diabetes depends on several genes at different loci. The strongest linkage was found with the human leukocyte antigen (HLA¹)-D genes that are located within the major histocompatibility complex region on chromosome 6p21 (now called the “type 1 diabetes 1” locus) (Cudworth and

Woodrow 1974; Kukreja and Maclaren 1999; Nerup et al. 1974). In addition to the established involvement of HLA-linked genes, at least 20 other chromosomal regions are thought to play a role in predisposing a person to the development of type 1 diabetes. It is believed that an environmental trigger is necessary to promote the autoimmunity, because studies of homozygous twins have demonstrated that genetic predisposition alone is insufficient to cause type 1 diabetes (Redondo et al. 2001). Environmental factors include viruses, toxic chemicals, and various dietary components such as cow's milk. The fact that genetic predisposition alone will not cause the disease has caused debates on prevention based on genetic screening. Opponents to screening also question the potential ethical and psychological implications of genetic screening, particularly because none of the therapies attempted thus far has produced long-term remissions in new-onset type 1 diabetes patients and no therapies have been shown to prevent the disease completely (Gustafsson Stolt et al. 2003). Furthermore, if genetic screening techniques are used to identify persons at risk, one must be aware of the presence of several alleles that play a role in protecting against the disease. This shielding effect is thought to occur via binding of a common protective peptide (Undlien et al. 1997).

However, if genetically predisposed individuals at risk can be identified, they can be targeted for frequent measurement of signs of beta-cell autoimmunity. Long before a person develops clinical signs of diabetes, autoantibodies to islet beta cells and their antigens called islet cell antibodies (ICAs¹) can be detected. ICAs are found in 70 to 80% of newly diagnosed patients with type 1 diabetes and also in prediabetic subjects (Atkinson and Maclaren 1994), making them a very effective and major screening tool during the preclinical period. Diabetes risk and time to the onset of disease have been found to correlate closely with the amount of autoantibodies present (Kukreja and Maclaren 1999). Several autoantigens have been recognized that may play a role in initiation or progression of autoimmune islet cell destruction. Associated antibodies include ICAs, insulin autoantibodies, and glutamic acid decarboxylase. Antibodies against islet ganglioside and carboxypeptidase H have also been observed. The role of these antibodies is still not well defined.

Therapy

To date, insulin therapy remains the only treatment proven safe and effective after clinically significant beta-cell destruction takes place. Many different formulas of exogenous insulin are currently available in the United States, including the following principal types with regard to onset and duration of action: ultra-short-acting insulin, short-acting insulin, intermediate-acting insulin, and long-acting insulin. By using various combinations of these insulins, it is now possible to achieve acceptable control of blood glucose lev-

els. Furthermore, portable insulin infusion pumps, which allow for establishment of a basal insulin profile, are becoming increasingly popular. The pumps allow patients more flexibility and freedom in eating with less regard to timing of infusions because the basal insulin level maintains blood glucose levels between meals. Highly purified recombinant human insulin preparations have also markedly reduced the immunogenicity associated with animal insulins.

The search for new preventive strategies compared with the corrective strategies described above has relied heavily on the use of animal models for autoimmune diabetes. The nonobese diabetic (NOD¹) mouse and the Bio-Breeding rat animal models have greatly enhanced our knowledge about the early etiology and pathogenesis of the disease. Treatment with anti-CD3 antibodies has been shown to re-establish normoglycemia successfully after restoration of beta-cell tolerance in the NOD mouse (Chatenoud et al. 1994), and short-term administration of CD3-specific antibodies is now also showing promising results in clinical trials (Chatenoud 2003). Other immune intervention studies have provided mixed results: Administration of the free radical scavenger nicotinamide was associated with protective effects in a population-based study in New Zealand (Elliott et al. 1996), but the procedure has not proven useful in the Deutsche Nicotinamide Intervention Study (Lampeter et al. 1998). Although often performed successfully, pancreas transplantation remains essentially reserved for patients with complicated long-standing diabetes who are in need of a concurrent kidney transplant. However, recent successes in islet cell transplantation and advances in the generation of beta-cell stem or progenitor cells hold promise as feasible modalities for curing diabetes in the future. Advances in the development of nonhuman primate models of diabetes, which would ensure a similar genetic background to the human model, will allow testing of antigen-specific and gene-directed immunotherapies, thereby further advancing progress in islet transplantation. Researchers strive to exploit the increased ability for environmental manipulation and discovery of innovative genetic and genomic tools in animal research to unravel the complex causes of autoimmunity further, to explore new strategies, and hopefully to prevent the disease one day.

Conclusion

We have witnessed tremendous advances in our understanding of the pathogenesis and the treatment of diabetes mellitus since the discovery of insulin by Banting and Best in 1921 (Rosenfeld 2002). Laboratory animal research continues to play a pivotal role, not only by increasing our knowledge of the causes and pathogenesis of this costly disease but also by helping identify potential therapeutic and interceptive modalities. Researchers have heretofore devised at least 125 distinct methods for prevention or delay of type 1 diabetes in the NOD mouse model (Atkinson and Leiter 1999), and although findings in rodents cannot always be

directly extrapolated to the human model, investigations of NOD mice have at minimum enhanced our understanding of the complexity of the disease. Together with advances in molecular biology, continued gains from laboratory animal research hold the promise not only to prevent but also to identify a cure for this devastating disorder.

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