Pathogenesis of Type 2 Diabetes Mellitus

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Summary

The pathophysiology of type 2 diabetes is complex, with many different elements acting to cause the disease. This review proposes a sequence of events that is based on a careful analysis of the human and animal model literature. It seems certain that a genetic predisposition is needed although, until recently, little was known about specific genetic mutations. Whether the diabetes phenotype then occurs depends on a large number of environmental factors that share an ability to stress the glucose homeostasis system by promoting insulin resistance or worsening β-cell function. We propose that a lowered β-cell mass through genetic and/or β-cell cytotoxic factors is an important predisposing factor for glucose intolerance. As the blood glucose level rises to a minor degree above normal, acquired defects in the glucose homeostasis system occur—a key early one is an impaired first phase insulin response to a meal—that cause the blood glucose level to rise further into the prediabetes range. This increase in glycemia, perhaps in concert with hyperlipidemia, causes additional deterioration in β-cell function and, to a smaller extent, resistance, resulting in a blood glucose level that continues to rise to full blown diabetes. This sequence provides insight into prevention and treatment of type 2 diabetes. One can modify predisposing environmental factors, although that is not easily done. Alternatively, one expects that, as the molecular basis for the organ dysfunctions are discovered (β-cell dysfunction and death, and muscle and hepatic insulin resistance), novel therapies will be developed that target those defects.

Key Words: β-Cell dysfunction; insulin resistance; glucose toxicity; lipotoxicity; β-cell apoptosis.

INTRODUCTION

Type 2 diabetes is a worldwide health crisis. In the U.S., 20.8 million are affected at a cost of $132 billion in 2002 (1), and the numbers will likely continue to increase. The Centers for Disease Control and Prevention estimates there are more than 40 million people in the U.S. with prediabetes. Given that the Diabetes Prevention Program showed an 11% yearly conversion rate of impaired glucose tolerance (IGT) to diabetes (2), there could be as many as 4 million new cases each year. Furthermore, the incidence of type 2 diabetes is rising around the world (3), with a recent prediction that the worldwide prevalence will increase from 2.8% in 2000 to 4.4% in 2030, resulting in 366 million affected people (4).

Much of the current crisis stems from our modern lifestyle. Furthermore, the global shift from an agrarian existence to city living, resulting in less physically demanding office and factory jobs, is taking its toll. In the U.S.,
Fig. 1. Proposed sequence of the key pathological features of type 2 diabetes as discussed in this review.

these changes have been most evident in children—numerous studies have reported the epidemic of childhood obesity (5) and its root causes of reduced physical activity and high caloric intake (6,7).

Although returning to healthy lifestyles likely would reverse the rising incidence of type 2 diabetes, this may be an impractical solution. Instead the current focus is to investigate the pathogenesis, hoping to develop pharmaceuticals that target the key pathogenic elements. We entered the 1990s knowing that type 2 diabetes was characterized by the triad of ß-cell dysfunction, excess glucose production from the liver, and insulin resistance, defined as impaired insulin-mediated glucose clearance into skeletal muscle (8). However, the link among these organs was unknown. Considerable insight has been gained over the last decade, although much remains to be learned. This review provides an overview of the current understanding of the pathogenesis of type 2 diabetes (Fig. 1). A major focus of the proposed sequence relates to defects in the mass and function of islet ß-cells, as they are known to be important elements in the early stages of the disease.

GENETIC PREDISPOSITION

The fact that type 2 diabetes is a genetic disease was confirmed more than 2 decades ago by a famous study of identical twins in the U.K. that found essentially a 100% concordance rate (9). However, this kind of study provides no insight into the underlying genetic defect(s) either directly impairing the glucose homeostasis system or causing insulin resistance or another defect that exceeds the capacity of a normal glucose homeostasis system. With the advent of molecular biology, the basis is now known for many monogenic forms of diabetes, such as mitochondrial genome defects and their association with diabetes and deafness (10), Wolfram’s syndrome (11), several syndromes of extreme insulin resistance (12), and most of the MODY syndromes (13). Still, these account for only a small proportion of diabetes cases.

In contrast, genetic insight into type 2 diabetes has been frustratingly slow. One identified gene is calpain 10, a member of a ubiquitously expressed family of cysteine proteases. In the mid 1990s, linkage analysis identified a locus on chromosome 2 that was calculated to account for about 30% of type 2 diabetes in Mexican-Americans (14). The specific gene was later shown to be calpain 10 (15). However, the role of calpain 10 in glucose homeostasis remains unclear, with a current focus on a regulatory role in insulin exocytosis (16).

A recent study of isolated islets from humans with type 2 diabetes reported a 90% reduced mRNA expression of aryl hydrocarbon receptor nuclear translocator (ARNT), a transcription factor previously unknown to the diabetes field (17). Mice were created with a ß-cell specific knockout of the ARNT gene. These animals developed glucose intolerance and impaired glucose-induced insulin secretion, along with a ß-cell mRNA expression profile that closely matches the human type 2 diabetes islets. Considerable interest was generated by these findings, and a role for ARNT in type 2 diabetes is under investigation.

Other chromosomal “hot spots” have been identified in various populations, and looking for the specific genes is now much faster because of the human genome project. Also, many research groups have focused on various gene polymorphisms. To date, all have lacked a strong association with type 2 diabetes after rigorous study. An