Atypical Forms of Type 2 Diabetes

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Contents

Introduction
Diabetes Associated With Adipose Tissue Disorders: Lipodystrophy Syndromes
Diabetes Owing to Genetic Disorders of β-Cell Function
Diabetes Owing to Diseases of the Exocrine Pancreas
Diabetes Owing to Genetic Disorders of Insulin Action: Insulin Receptor Mutations
Diabetes Owing to Acquired Insulin Receptor Antibodies
Diabetes Owing to Other Endocrinopathies
Diabetes Owing to Drug Therapy
Conclusions
References

Summary

Patients with “typical” type 2 diabetes are generally obese and display varying degrees of insulin resistance and insulin secretory defects. The onset of type 2 diabetes occurs mostly after the third decade of life, and these patients do not spontaneously develop ketosis or need insulin for survival. Many other patients present with “atypical” forms of type 2 diabetes; insulin resistance or insulin secretory defects occur owing to certain other specific etiologies. These include various genetic and acquired causes leading to adipose tissue disorders, β-cell dysfunction or impaired insulin action. Other endocrinopathies and drug therapy may also result in atypical diabetes. Lipodystrophies are characterized by selective loss of adipose tissue leading to excess fat accumulation in aberrant tissues such as the liver and muscle, which causes insulin resistance. Although the degree of fat loss and the resultant metabolic abnormalities varies among patients with the different types of lipodystrophies, diabetes in most lipodystrophic patients is characterized by marked insulin resistance and high insulin requirements. Maturity-onset Diabetes of the Young (MODY) is a group of heterogeneous forms of monogenic diabetes characterized by autosomal dominant inheritance, young age at onset and pancreatic β-cell dysfunction. Similarly, mutations or deletions in mitochondrial DNA also cause diabetes owing to β-cell dysfunction, which is maternally inherited, whereas insulin receptor mutations cause autosomal dominant or recessive syndromes of extreme insulin resistance such as type-A insulin resistance syndrome, Rabson-Mendenhall syndrome, and Leprechaunism. The clinical features and management of patients with these rare syndromes are distinct from those for patients with typical type 2 diabetes. Recognition of these patients is important, as it helps to tailor therapy based on the underlying pathophysiologic process. These syndromes have also greatly contributed to our understanding of glucose homeostasis and the pathogenesis of diabetes in general.

Key Words: Type 2 diabetes; lipodystrophy; MODY; mitochondrial diabetes; insulin resistance syndromes.

Introduction

Patients with type 2 diabetes, who account for 90–95% of all patients with diabetes, commonly have metabolic defects resulting in insulin resistance as well as relative insulin deficiency. These patients do not need insulin treatment for survival, though many may require insulin in the later stages for optimal glucose control. Ketoacidosis seldom occurs spontaneously, and decline in β-cell function is not owing to autoimmune processes. The vast...
Table 1
Etiologic classification of Atypical type 2 diabetes

A. Diabetes associated with adipose tissue disorders
   Genetic
   - Congenital Generalized Lipodystrophy, types 1 and 2 (AGPAT2 and BSCL2 mutations)
   - Familial Partial Lipodystrophy (LMNA, PPARG and AKT2 mutations)
   - Mandibuloacral Dysplasia associated Lipodystrophy (LMNA and ZMPSTE24 mutations)
   Acquired
   - Highly Active Anti Retroviral Therapy-induced Lipodystrophy in HIV infected patients
   - Acquired Generalized Lipodystrophy
   - Acquired Partial Lipodystrophy

B. Diabetes owing to impaired β-cell function
   Genetic
   - MODY1 (HNF4A mutations)
   - MODY2 (GCK mutations)
   - MODY3 (TCF1/HNF-α mutations)
   - MODY4 (IPF-1 mutations)
   - MODY5 (TCF2/HNF-1β mutations)
   - MODY6 (NEUROD1 mutations)
   - Mitochondrial DNA mutations
   Acquired
   - Disorders of exocrine pancreas owing to pancreatitis, trauma, surgery, cystic fibrosis, or hemochromatosis

C. Diabetes owing to impaired insulin action
   Genetic
   - Type A Insulin Resistance (INSR mutation)
   - Rabson-Mendenhall syndrome (INSR mutations)
   - Leprechaunism (INSR mutations)
   Acquired
   - Type B Insulin Resistance owing to anti-insulin receptor antibodies

D. Diabetes owing to other endocrinopathies
   - Acromegaly, Cushing’s syndrome, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma

E. Diabetes owing to drug therapy
   - Glucocorticoids, Pentamidine, Nicotinic Acid, Diazoxide, Thiazides, β-adrenergic agonists, α-Interferon

majority of patients with “typical” type 2 diabetes are obese, and their clinical features and management has been discussed in earlier chapters. In contrast, “atypical” forms of type 2 diabetes are not necessarily associated with the obesity phenotype, and are characterized by a variety of distinct clinical features. The etiology of these uncommon varieties of diabetes involves several genetic and acquired defects, based on which this diverse group of disorders can be classified, as shown in Table 1. Studying these rare forms of diabetes not only enhances our understanding of the pathophysiology of glucoregulation, but also helps us identify patients who may require unconventional therapeutic interventions. The clinical features, etio-pathogenesis and management of a few atypical forms of type 2 diabetes, which are distinct from the hitherto discussed typical variety, are reviewed in this chapter.

DIABETES ASSOCIATED WITH ADIPOSE TISSUE DISORDERS: LIPODYSTROPHY SYNDROMES

Lipodystrophies are a heterogeneous group of inherited or acquired disorders, characterized by selective loss of adipose tissue. The pattern and extent of adipose tissue loss varies among the different types of lipodystrophies. Further, there is considerable genetic heterogeneity, with mutations in six genes, AGPAT2, BSCL2, LMNA, PPARG, ZMPSTE24, and AKT2, having been described in patients with various forms of lipodystrophy (1–7). Based on the extent of fat loss (localized, partial or generalized), etiology (genetic or acquired), and other