Introduction

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Diabetes mellitus is a major cause of illness and death across the globe, is responsible for a growing proportion of national health care expenditures.

Diabetes is known to increase the risk for multiple infections with serious infections a common reason for hospital admission. Type 1 diabetes, a disease characterized by beta-cell failure and insulin deficiency. Type 2 diabetes, by contrast, is characterized by defects in both insulin secretion and insulin action, with insulin deficiency usually emerging later in the course of the disease ***(Holman et al., 2008).***

The mechanism of harm from hyperglycemia on various organ systems has not been well defined but it is known that hyperglycemia alters the activity of phagocytes, interfering with neutrophil and monocyte functions. Hyperglycemia also increases inflammatory cytokines, oxidative stress and promotes apoptosis. Cell and tissue injury caused by hyperglycemia through oxidative stress adversely affects the immune, cardiovascular and nervous system as well as hemostasis, inflammation, and endothelial cell function ***(Duckworth et al., 2009).***

In the last 30 years, marked advances in feeding techniques in ICU, venous access. Enteral and parenteral nutrition

formulations have made it possible to provide nutrition support to almost all patients. Despite the abundant medical literatures and wide spread use of nutritional therapy, many areas of nutrition support remains controversial ***(Mc Clave et al., 2009).***

Enteral nutrition is an effective and generally safe means of offering many of nutritional support. Access options need careful consideration in each patient as well as levels of feeding, rates of administration, and the type of feed to be used ***(Heidegger et al., 2009).***

Chapter 1
Diabetes Mellitus

Diabetes Mellitus

Definition

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels ***(American Diabetes Association;2006)***.

Etiologic classification of diabetes mellitus

1- Type 1 diabetes mellitus

Beta cell destruction, usually leading to absolute insulin deficiency.

- Immune mediated
- Idiopathic

2- Type 2 diabetes mellitus

May range from predominant insulin resistance with relative insulin deficiency to predominant secretory defect with insulin resistance.

3- Gestational diabetes mellitus

Onset or recognition of glucose intolerance in pregnancy

4- Other specific types

a- Genetic defects of beta cell function

* Chromosome20, HNF-4alpha (formerly MODY1)
* Chromosome 7, glucokinase (formerly MODY2)
* Chromosome 12, HNF-1alpha (formerly MODY3)
* Mitochondrial DNA
* Others

b- Genetic defects in insulin action

* Alstrom syndrome
* Leprechaunism
* Lipoatrophic diabetes
* Rabson-Mendenhall syndrome
* Type A insulin resistance

3- Infections

* Congenital rubella
* Cytomegalovirus
* Others

4-Uncommon forms of immune-mediated diabetes:

* Anti-insulin receptor antibodies
* 'Stiff-man' syndrome
* Others

5-Drug or chemical induced:

* Atypical antipsychotics
* Beta-adrenergic agonists
* Diazoxide

* Glucocorticoids
* Interferon alfa
* Nicotinic acid
* Pentamidine
* Phenytoin
* Protease inhibitors

6- Others Diseases of the pancreas

* Cystic fibrosis
* Fibrocalculouspancreatopathy
* Hemochromatosis
* Neoplasia
* Pancreatitis
* Trauma/pancreatectomy
* Others

7- Endocrinopathies

* Acromegaly
* Aldosteronoma
* Cushing syndrome
* Glucagonoma
* Hyperthyroidism
* Pheochromocytoma
* Somatostatinoma
* Others
* Thiazide diuretics

-Others:

Other genetic syndromes sometimes associated with diabetes:

* Down syndrome
* Friedreich's ataxia
* Huntington's chorea
* Klinefelter syndrome
* Laurence-Moon-Bardet-Biedl syndrome
* Myotonic dystrophy
* Porphyria
* Prader-Willi syndrome
* Turner syndrome
* Wolfram syndrome
* Others

HNF = hepatocyte nuclear factor MODY = maturity-onset diabetes of the young ***(Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus,2003).***

Pathogenesis of D M

A. Type 1 diabetes

(ß-cell destruction, usually leading to absolute insulin deficiency)

1- Immune-mediated diabetes

This form of diabetes, previously encompassed by the terms insulin-dependent diabetes, type 1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the ß-cells of the pancreas ***(Atkinson &Maclaren, 1994)***.

Markers of the immune destruction of the ß-cell include islet cell autoantibodies (ICAs), autoantibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2ß***(Baekkeskov et al., 1982).***

One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected. Also, the disease has strong HLA associations, with linkage to the DQA and B genes, and it is influenced by the DRB genes***(Huang et al., 1996).***

At the latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life ***(The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003)***

Autoimmune destruction of ß-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are rarely obese when they present with this type of diabetes, the presence of obesity is not incompatible with the diagnosis. These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, and pernicious anemia***(The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).***

2- Idiopathic diabetes

Some forms of type 1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. This form of diabetes is strongly inherited, lacks immunological evidence for ß-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go***(American Diabetes Association, 2006).***

B. Type 2 diabetes:

This form of diabetes, previously referred to as non-insulin-dependent diabetes, type 2 diabetes, or adult-onset diabetes, is a term used for individuals who have insulin resistance and usually

have relative (rather than absolute insulin deficiency***(Olefsky et al., 1982).***

There are probably many different causes of this form of diabetes, and it is likely that the proportion of patients in this category will decrease in the future as identification of specific pathogenic processes and genetic defects permits better differentiation among them and a more definitive subclassification. Although the specific etiologies of this form of diabetes are not known, autoimmune destruction of ß-cells does not occur, and patients do not have any of the other causes of diabetes listed above or below***(The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).***

Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region***(Bogardus et al., 1985).***

Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher

blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their ß-cell function been normal***(Polonsky et al., 1996).***

The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior gestational DM(GDM) and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups ***(Zimmet, 1992)***.

It is often associated with a strong genetic predisposition, more than is the autoimmune form of type 1 diabetes. However, the genetics of this form of diabetes are complex and not clearly defined ***(Newman et al., 1987)***.

Pathogenesis of Type 2 Diabetes

1- Insulin Resistance

With few exceptions, type 2 diabetes is characterized by marked impairment in insulin action. The insulin dose-response curve for augmenting glucose uptake in peripheral tissues is shifted to the right (decreased sensitivity), and the maximal response is reduced, particularly with more severe hyperglycemia. Other insulin-stimulated processes such as inhibition of hepatic glucose production and lipolysis also show

reduced sensitivity to insulin. The mechanisms responsible for insulin resistance remain poorly understood ***(Robert & Silvio, 2007)***.

Early studies focused on defects in insulin binding to its receptor. Mutations in insulin receptors result in the syndrome called "leprechaunism", characterized by severe growth retardation and insulin resistance. Two other rare syndromes of extreme insulin resistance have been identified and are characterized by either a profound deficiency of insulin receptors (most often affecting young females with acanthosisnigricans, polycystic ovaries, and hirsutism) or the presence of anti-insulin receptor antibodies *(associated with acanthosisnigricans and other autoimmune phenomena)* ***(Robert & Silvio, 2007).***

Although insulin receptors may be reduced in some type 2 diabetic patients, defects in more distal or "post-receptor" events play the predominant role in insulin resistance. An important component of this defect is reduced capacity for translocation of GLUT 4 to the cell surface in muscle cells. A separate defect in glycogen synthesis is also likely to be present. Whether the defects uncovered are primary or secondary to the disturbance in glucose metabolism is uncertain. Possibly, a variety of genetic abnormalities in cellular transduction of the

insulin signal may individually or in concert produce an identical clinical phenotype ***(Robert & Silvio, 2007).***

No evidence has shown that the mechanisms of insulin resistance in non-obese patients differ from those of their obese diabetic counterparts, but the coexistence of obesity accentuates the severity of the resistant state. In particular, upper body or abdominal as compared with lower body or peripheral obesity is associated with insulin resistance and diabetes. It is now believed that intra-abdominal visceral fat (detected by computed tomography or magnetic resonance imaging) may be a key culprit.

Abdominal fat cells have a higher lipolytic rate and are more resistant to insulin than is fat derived from peripheral deposits. Cortisol hypersecretion and/or hereditary factors influence the distribution of body fat, the latter contributing an additional genetic influence on expression of the disease. The adverse effects of increased free fatty acid levels include accelerated hepatic gluconeogenesis and impaired muscle glucose metabolism and beta cell function ("lipotoxicity"). The release of tumor necrosis factor alpha by adipocytes may also interfere with insulin-stimulated glucose uptake by altering the

pattern of phosphorylation of insulin-signaling molecules ***(Robert & Silvio, 2007).***

2- Pancreatic β-cell failure

In the early stages of type 2 diabetes, there is only moderate reduction in the total mass of pancreatic islet tissue. Some pathological changes are typical of type 2 diabetes, the most consistent of which is deposition of amyloid. An attractive, but as yet unproven, hypothesis to explain β-cell destruction in type 2 diabetes is that the polypeptide amylin is secreted together with insulin, so that in the presence of insulin resistance the excessive demand for insulin secretion also results in the formation of excess amylin which forms insoluble fibrils of amyloid and ultimately destroys β cells. While β-cell numbers are typically reduced by 20-30% in type 2 diabetes, α-cell mass is unchanged and glucagon secretion is increased, which may contribute to the hyperglycemia. ***(Frier& Fisher, 2007).***

Clinical significance of insulin resistance

The clinical importance of insulin resistance cannot be overstated, given the mortality and morbidity associated with the many disorders that are likely a consequence of this condition. Indeed, there is considerable epidemiologic evidence