DIABETES MELLITUS

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underused, producing hyperglycemia ***(Alberti et al., 1998).***

It is said to be assotiated with increased prevalence of microvascular complications ***(Baynes and Throp, 1999).***

World Health Organization (1995) announced that diabetes mellitus is a common disease affecting approximately 5% of the world population.In 2003 the American Diabetes Association, reported that, in the United States, there are 12 million diagnosed diabetics and another million undiagnosed patients.the continuing increase in number of diabetic patients exceeding 30 millions is expected by 2030 ***(Kim et al., 2005).***

Aproject conducted between 1991 and 1994 by the Diabetes Institute and Central Health Laboratories, Cairo, Egypt in collaboration with the center for disease control and prevention, Atlanta, USA revealed a prevalence of 9·3% in the Egyptian population ≥20 years of age.Hence diabetes is considered as a major and emerging clinical and public health problem in Egypt ***(Herman et al., 1995).***

In fact diabetes was described as"one of the main threats to human health in the twenty-first century" ***(Zimmet et al., 2001).***

Classification:

In 1995, the classification and diagnosis of diabetes mellitus were re-examined by a workgroup established by the American Diabetes Association.The revised classification which was puplished in 1997 eliminated the terms insulin-dependent and non-insulin dependent diabetes mellitus, which are now termed type1 and type 2 diabetes, respectively.

In ***1997 Kuzuya and Mastud*** as well as the expert committee of the Diagnosis and Classificaton of diabetes mellitus suggested a classification which encompasses both the pathological and etiological types of diabetes mellitus:

Pathological Classification:

This classification reflects the hyperglycemia, regardless of its etiologic progress through several clinical stages during its natural history.

Diabetes mellitus is subdivided according to insulin requirement into:

- Insulin required for survival (Type 1).
- Insulin required for control rather than survival or non-required insulin (Type 2).

- Impaired glucose tolerance:it is not itself type of diabetes;it refers to a metabolic state intermediate between normal glucose homeostasis and diabetes.

Etiological Classification:

Improved understanding of the cause of diabetes resulted into this classification.

- Type 1 that results from β-cell destruction usually leading to absolute insulin deficiency.
- Type 2 that results from a progressive insulin secretory defect on the background of insulin resistance.
- Other special types of diabetes due to other causes;genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine function of pancreas, and drug induced.
- Gestational diabetes that is diagnosed during pregnancy.

Impaired fasting glucose and impaired glucose tolerance were officially termed "pre-diabetes", which are considered as risk factors for future diabetes and cardiovascular diseases ***(Diabetes Control and Complication Trial Research Group, 1993).*** However, these categories of previous abnormality of

glucose tolerance had been eliminated ***(American Diabetes Association, 2004).***

American Diabetes Association (2010) provided the latest modification of the classification of diabetes mellitus and other categories of glucose regulation:

-Type 1 diabetes

- Immune mediated diabetes.
- Idiopathic diabetes.

-Type 2 diabetes

- β-cell dysfunction.
- Insulin resistance.

-Other specific types of diabetes

- Genetic defects of the β-cell.
- Genetic defects in insulin actions.
- Diseases of exocrine pancreas.
- Endocrinopathies.
- Drug or chemical-induced diabetes.
- Infections.

- Gestational diabetes.

Pathogenesis of type 1 diabetes mellitus:

Type 1 diabetes mellitus results from a cellular mediated autoimmune destruction of the insulin-secreting cells of pancreatic β-cells ***(Atkinson and Eisenbarth, 2001).***

The most practical markers of β-cell autoimmunity are circulating antibodies;this can be detected in the serum years before the onset of hyperglycemia ***(Harrison, 2001).***

The best characterized antibodies are:

1- Islet cell cytoplasm antibodies (ICA):

They react with a sialoglyco-conjucate antigen in the cytoplasm of all endocrine cells of the pancreatic islets.These antibodies are detected in the serum of 0.5% of normal subjects and 75% to 85% of patients with newly diagnosed type 1 diabetes ***(Atkinson and Maclaren, 1994).***

2-Antibodies to the 65-KD isoforms of glutamic acid decaroxylase (GAD65):

Baekkesko et al. (1994) found these antibodies up to 10 years before the onset of clinical type 1 diabetes and were present in approximately60% of patients with newly diagnosed diabetes.GAD65 antibodies may be used to identify patients with apparent type 2 diabetes who will progress to type1 diabetes.

3-Insulin antibodies (IAA):

These are present in more than 9% of children who develop type1 diabetes before the age of 5 years, but in fewer than 40% of individuals developing diabetes after the age of 12 years, their frequency in healthy people is similar to that of ICA ***(Sacks et al., 2002).***

4-Insulinoma-associated antigen antibodies (IA-2A, IA-2BA):

These are directed against 2 tyrosine phosphatases and have been detected in more than 50% of newly diagnosed type 1 diabetes patients ***(Atkinson and Eisenbarth, 2001).***

It is assured that susceptibility to type 1 is inherited, but the mode of inheritance is complex ***(Todd, 1995).***

Besides inheritance, reports described that environmental factors are involved in initiating diabetes. Viruses, such as rubella, mumps, and coxackie virus B, have been implicated ***(Hyoty and Taylor, 2002).***

Pathogenesis of type 2 diabetes mellitus:

It is believed that type 2 diabetes is caused by a complicated interplay of genes, environment and insulin abnormalities (reduced insulin secretion and/or insulin resistance) ***(Porte and Halter, 1981).***

Various studies have proven that there are at least two major identifiable pathological defects in patients with type 2 diabetes; insulin resistance and β-cell dysfunction ***(Sacks and McDonald, 1996).***

Also, enviromental factors, such as diet and exercise, are important determinants in the pathogenesis of type 2 diabetes.A rising prevalence of diabetes is believed to be a consequence of the increase in obesity(defined as body mass index greater than or equal to 30 kg/m^2) ***(Mokdad et al., 2003).***

Clinicians have long observed that fatter people are more likely to develop type 2 diabetes, and overwhelming scientific evidence has proven this clinical impression to be accurate.the association of obesity with type 2 diabetes has been observed in comparison of different populations and within populations. Prospective studies of pre-diabetic subjects have conclusively shown that obesity and its duration are major risk factors for type 2 diabetes.Despite the remarkable consistency of the association between the two diseases, obesity is neither sufficient nor necessary for the development of type 2 diabetes ***(Pietro and Emilio, 2005).***

It is also widely acknowledged that genetic factors contribute to the development of type 2 diabetes.they include:

1-Body weight gene, which is expressed only in adipose tissue (ob).

It has been cloned and its protein product, Leptin, has been proposed to be a vital signaling factor regulating body weight homeostasis and energy balance ***(Friedman and Halaas, 1998).***

2-Insulin resistance genes, which have been identified as having numerous mutations of the insulin receptor.Many patients with these defects have extreme insulin resistance ***(Almind et al., 2001).***

3-Insulin secretion genes, which include genes that are expressed in β-cells, such as amylin, glucagon-like peptide-1 receptor, glucokinase regulatory protein, and islet-1 protein ***(Sacks et al., 2002).***

Criteria for the diagnosis of diabetes mellitus: (Table 1)

Table (1): Diagnosis and classification of diabetes mellitus ***(American DiabetesAssociation, 2006).***

Any of the following is diagnostic:*

Category	Specification according to ADA
D M	1. Classic symptoms of diabetes and casual[1] plasma Glucose concentration›200 mg/dl. 2. Fasting[2] plasma glucose›126 mg/dl. 3. 2 hour post load glucose concentration >200 mg/dl during OGTT.
IFG+	FPG+: 110-125 mg/dl
IGT+	Two criteria must be met: 1. Fasting plasma glucose‹ 126 mg/dl. 2. 2 hour OGTT+ plasma glucose 140-199 mg/dl
* If positive confirm by repeating the test on a subsequent day. 1. Regardless of the time of the preceeding meal. 2. No caloric intake for at least 8 hours. + FPG: Fasting plasma glucose;IFG:Impaired fasting glucose;IGT:Impaired glucose tolerance; OGTT: Oral glucose tolerance test.	

Glycated hemoglobin A1c (HbA1c) has been proposed lately as a useful method of both screening for and diagnosing diabetes ***(Saudek and Brick, 2009).***

Its assay provides a reliable measure of chronic glycemia and correlates well with the risk of long-term complications, so that it is currently considered the test of choice for both monitoring and chronic management of diabetes. Recently, HbA1c testing has been included in the diagnostic criteria recommended for diabetes by the American Diabetes Association ***(Lippi andTargher, 2010).***

The International Expert Committee recommends that the diagnosis of diabetes be made if HbA1c level is greater than, or similar to 6.5% and confirmed with a repeated HbA1c test.Fasting plasma glucose, 2-hour post glucose-load plasma glucose tests are recommended for the diagnosis of diabetes only if HbA1c is not possible due to unavailability of the assay, patient factors that preclude its interpretation, and, during pregnancy. HbA1c testing has advantages of greater clinical convenience, pre-analytical stability, and assay standardization, but when used as the sole diagnostic criterion for diabetes, it has the potential for systematic errors.factors that may not be clinically evident impact HbA1c test results and may systematically raise or lower the value relative to the true level of glycemia.For this reason, HbA1c should be used in combination with plasma glucose determinations for the diagnosis of diabetes ***(Herman and Fajan, 2010).***

Table (2): Diagnostic criteria for diabetes mellitus and related stages of hyperglycemia ***(American Diabetes Association, 2010).***

Category	Specification according to ADA
Normoglycemia	1. FPG* <110mg/dl or 2. 2 hour post load glucose‹140mg/dl.
IFG+	FPG*: 110-125 mg/dl.
IGT+	2 hour post load glucose:140-199 mg/dl.
DM	1.HbA1c ≥ 6.5%.The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) Certified and standardization to theDiabetes Control and Complication Trial(DCCT) assay or 2. FPG* ≥ 126 mg/dl or 3. 2 hour post load glucose≥200mg/dl or 4. Classic symptoms of hyperglycemia or hyperglycemic crisis plus casual PG ≥200mg/dl.
*FPG: Fasting plasma glucose. IFG: Impaired fasting glucose. IGT: Impaired glucose tolerance.	

Insulin Resistance:

Insulin resistance(IR)was described as a pathological situation characterized by a lack of physiological response of peripheral tissues to insulin action ***(Ford et al., 2002).***

The ability of insulin to stimulate glucose disposal varies at least six folds in apparently healthy individuals, and approximately

one-third of the population that is most resistant to this action of insulin is at greatly increased risk to develop a number of adverse clinical outcomes. Type 2 diabetes occurs when insulin resistant individuals are unable to secrete enough insulin to compensate for the defect in insulin action, and this was the first clinical syndrome identified as being related to insulin resistance.Although the majority of insulin resistant individuals are able to maintain the level of compensatory hyperinsulinemia needed to prevent the development of a significant degree of hyperglycemia, the combination of insulin resistance and hyperinsulinemia greatly increases the likelihood of developing a cluster of closely related abnormalities.It was also proved that overweight and sedentary life style decreases insulin sensitivity ***(Reaven, 2005).***

The interest of insulin resistance and metabolic syndrome lies in their high prevalence in the population and the associated high death rate, fundamentally through coronary heart disease, even in non-diabetic subjects ***(Isomaa et al., 2001).***

It is possible to have insulin resistance without hyper-insulinemia and, conversely, it is possible to have hyper-insulinemia without insulin resistance ***(Keskin et al., 2004).***

Diagnosing insulin resistance by simple quantitative methods:

For epidemiological and clinical studies, simple, indirect methods have been advocated for quantification of insulin resistance, based on measuring plasma insulin levels during fasting or after glucose stimulus and on the insulin-glucose ratio calculated with different mathematical formulas ***(Bergman et al., 1985).***

• The homeostasis model assessment(HOMA)Uses the formula:

Fasting insulin (μIU/ml) × FPG(mg/dl)/405 ***(Matthews et al., 1985).***

- It includes also the mathematical calculations known as **QUICKI** (quantitative insulin sensitivity check index) based on the logarithmic transformation:

1/(log fasting insulin (μIU/ml) + log fasting glucose in mg/dl) ***(Katz et al., 2000).***

- The last method is the McAuley indexes, based on the increase of plasma triglycerides and insulin, using the equation=exp (2.63-0.28(insulin in mU/L)-0.31 (TGs in mmol/L) ***(McAuley et al., 2001).***

As HOMA index has been validated with the hyper-insulinemic-euglycemic clamp technique the "gold standard" for

diagnosis by ***Bonora et al. (2000),*** it is considered a valid method to assess peripheral insulin sensitivity in epidemiological studies. ***Hrebicek et al. (2002)*** stated that with respect to the QUICKI index, its sensitivity and specificity are the same as HOMA index.

the hyperinsulinemic-euglycemic clamp study, is a complicated time consuming and expensive study in which insulin and glucose are infused intravenously at several different doses to see what levels of insulin, control different levels of glucose ***(Keskin et al., 2004).***

COMPLICATIONS OF DM

Diabetes is a complex condition which can result in long term complications. There is no such thing as 'mild' diabetes. Whether diabetes is managed by healthy eating and physical activity alone, or in conjunction with tablets and/or injections, poorly controlled diabetes will cause damage to your body. High blood glucose levels over a period of time can damage the small and large blood vessels and nerves. The most common Diabetic complications can be as microvascular or macrovascular disease. Microvascular complications include neuropathy (classified broadly nerve damage), nephropathy (kidney disease) and vision disorders (eg retinopathy, glaucoma, cataract and corneal disease). Macrovascular complications include heart disease, stroke and peripheral vascular disease (which can lead to ulcers, gangrene and amputation). Other complications of diabetes include infections, metabolic difficulties, impotence, autonomic neuropathy and pregnancy problems ***(Cameron et al., 2011).***

In patients with type 2 diabetes the risk of diabetic complications was strongly associated with previous hyperglycaemia. Any reduction in HbA_{1c} is likely to reduce the risk of complications ***(Stratton et al., 2000).***

With respect to prevention of complications, our results indicate that older people have a graded relationship between A1C and complications. On the other hand, we observed a distinct U-shaped relationship between A1C and mortality. Our