INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a group of disorders characterized by hyperglycemia and associated with microvascular and macrovascular complications ***(Wolfs et al., 2009).***

Nephropathy associated with type 2 diabetes is the most frequent cause of end stage renal disease. The first sign of renal involvement in patients with type 2 diabetes is most often microalbuminuria (urinary albumin excretion, 20 to 200µg per minute in an overnight urine sample), which is classified as incipient nephropathy ***(Ruggenenti and Remuzzi, 1997).*** Progression to macroalbuminuria (urinary albumin excretion, >200µg per minute) or overt nephropathy, occurs in 20 to 40 percent of patients over a period of 15 to 20 years after onset of diabetes. Hypertension and proteinuria may accelerate the decline in glomerular filtration rate and the progression to end-stage renal disease ***(Ritz and Orth, 1999).***

Chemerin is an adipokine that has been reported to modulate immune system function through its binding to the chemerin receptor ***(Ernst et al., 2012).*** Chemerin serum concentration are elevated in insulin resistance, and inflammatory states in vivo and suggested to be an obvious cause of insulin resistance ***(Hart and Greaves, 2010).***

The recent discovery of chemerin as a chemotactant adipokine linking increased adipose tissue mass to adipose

tissue infiltration of immunocompetent cells and inflammation ***(Sell and Eckel, 2009)*** suggests a plausible novel pathway linking increased uraemic fat mass with inflammation, insulin resistance and dyslipedaemia. A study has reported circulating chemerin in a CKD, finding increased levels in haemodialysis (HD) patients as well as an inverse correlation with residual renal function ***(Pfau et al., 2009).***

Early detection of nephropathy in patients with diabetes is feasible and has important practical implications for improving the outcome.

AIM OF THE WORK

To determine the relation between plasma chemerin levels in type 2 diabetic patients with renal dysfunction.

Chapter I

DIABETES MELLITUS

A. Definition:

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both ***(WHO,1999).***

The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs ***(Rother, 2007).***

Type 2 diabetes mellitus (T2DM) constitutes about 85% to 95% of all diabetes cases in developed countries and accounts for an even higher percentage in developing countries mostly due to increased urbanization, westernization, and economic development, which predispose to obesity due to high consumption of industrialized foods and physical inactivity ***(Wild et al., 2004).***

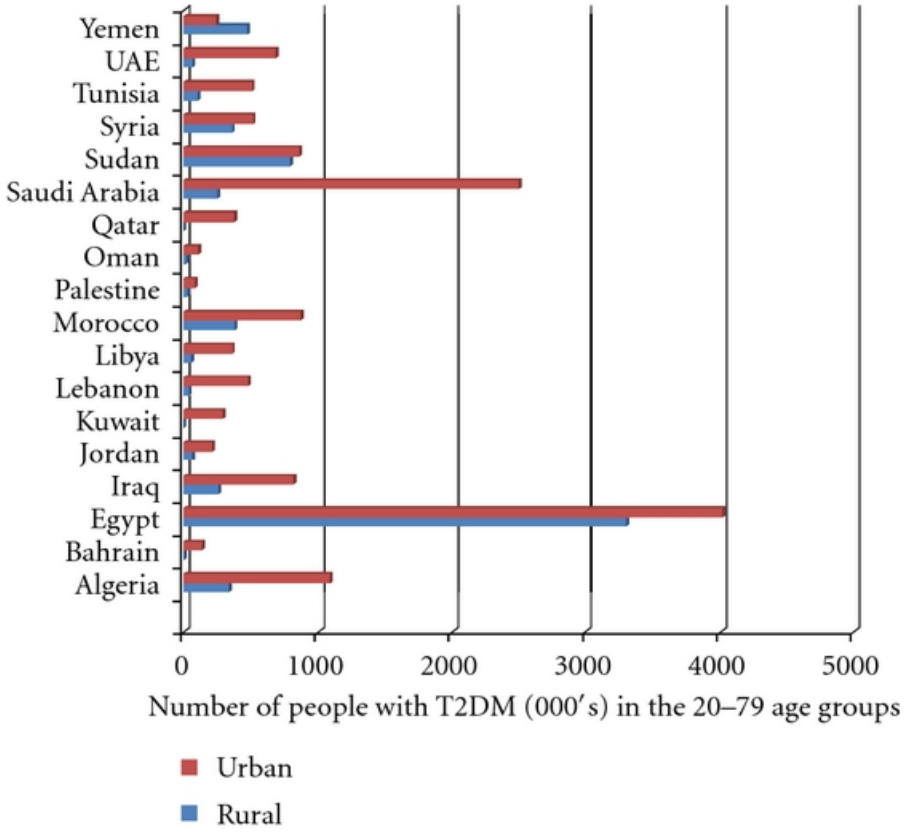
T2DM is a group of disorders characterized by hyperglycemia and associated with microvascular and macrovascular complications. Hyperglycemia results from lack of endogenous insulin or resistance to the action of insulin in muscle, fat, and liver in addition to an inadequate response by the pancreatic beta cells ***(Wolfs et al., 2009).***

B. Epidemiology:

Prevalence:

An estimated 19.2 million people in the Eastern Mediterranean and Middle East Region (EMME), or 7% of adult population, have diabetes. This is anticipated to more than double by 2025 and reach 39 million people. Moreover, the Middle East and Northern Africa (MENA) are considered to have the highest prevalence of diabetes as a world region, with six MENA countries making the top ten ranking (tab. 1) ***(international Diabetes Federation (IDF), 2010).***

Table (1): Prevalence of T2DM in Middle East and North Africa region, IDF, 2010.



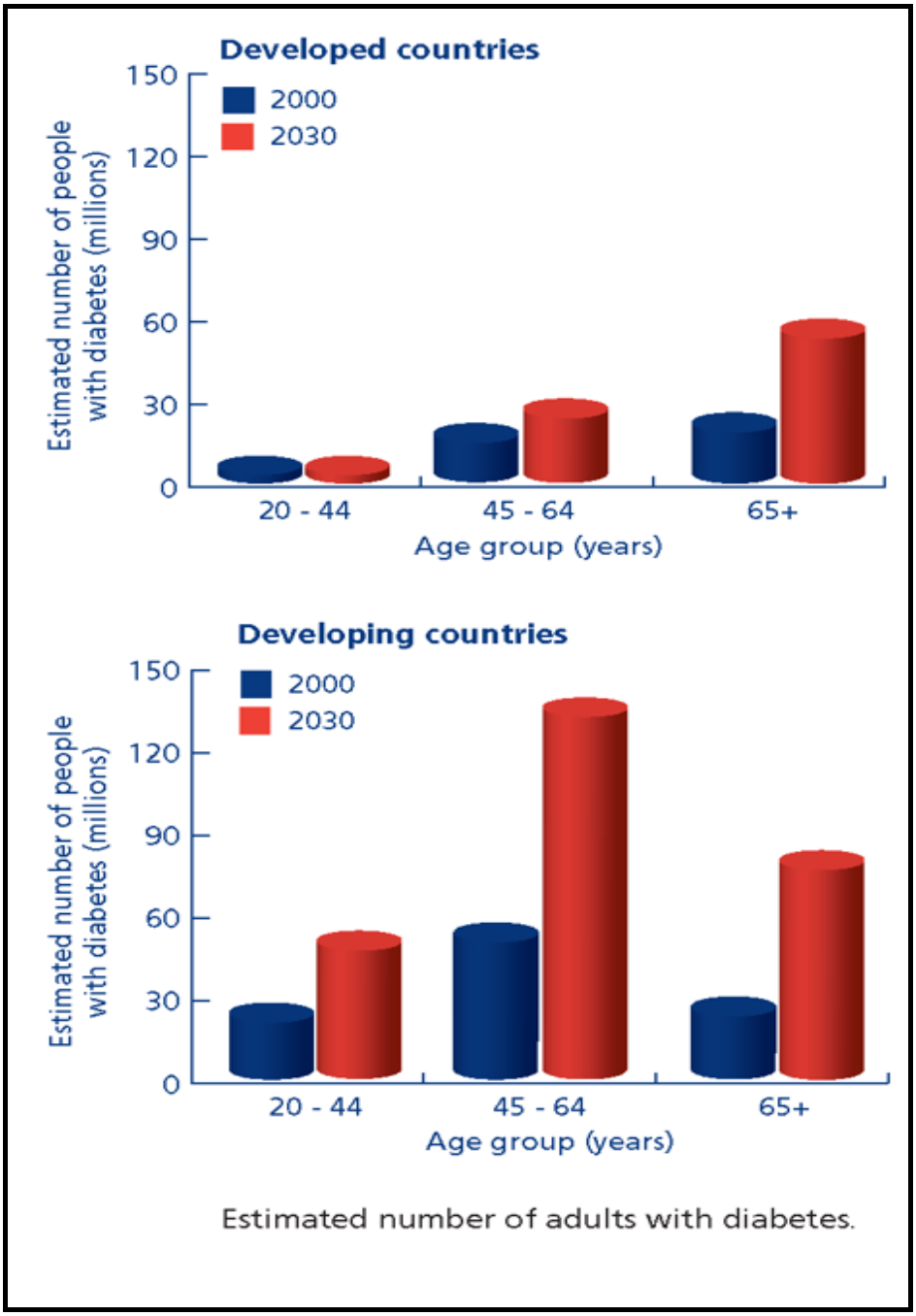


Figure (1): World wide prevalence of diabetes ***(WHO, 1999)***

The total number of people world wide with (T2DM) was expected to increase from 171 million in 2000 to 366 in 2030 ***(Wild et al., 2004).*** Unfortunately, the prevalence world wide already reached 366 by 2011 according to the International Diabetes federation ***(IDF, 2011)***, and the projection are that prevalence of diabetes on a global scale could well reach 530 million people in 2030 ***(Wild et al., 2004), fig. (1).***

Because clinical experience suggested that diabetes was an emerging problem in Egypt, Egyptian Ministry of Health and Population and the United States Agency for International Development conducted a study to gather information about the prevalence of diabetic risk factors, diagnosed diabetes mellitus and previously undiagnosed diabetes in population 20 years of age and older by age, sex, residence and socioeconomic status, projections for Egypt developed by the United Nations ***(Herman et al., 1997).***

When these age, sex, and residence, specific diabetic prevalence rates are applied to the projected demographics of the Egyptian population for the years 2000 and 2025, it was estimated that the total number of persons with diagnosed and undiagnosed diabetes in Egypt will increase from 3.24 million to 3.80 million in 2000 and to 80 million by the year 2025, and these data inform about large number global prevalence of diabetes mellitus in the year 2010 among adults has been estimated to be 6.4%. It is estimated that by the year 2030, Egypt will have at least 8.6 million adults with diabetes. The

prevalence of diabetes in Egypt is 13.5%. Diabetes is also considered the eleventh most important cause of premature mortality in Egypt, and is responsible for 2.4% of all years of life lost (YLL). Similarly, diabetes is the sixth most important cause of disability burden in Egypt ***(Herman et al., 2012).***

Mortality& Morbidity:

Diabetes is associated with reduced life expectancy; the significant morbidity associated with diabetes arises from microvascular complications, increased risk of macrovascular complications (ischemic heart disease, stroke, and peripheral vascular disease), and diminished quality of life ***(WHO, 1999).***

(T2DM) – realted mortalities account for 4.6 million deaths in 2011 for people aged 20- 79 years, accounting for 8.2% of global all – cause mortality for people in this age group with an estimated rate of one death every seven seconds ***(IDF, 2011)***. The number of deaths has increased by 13.3% from estimates for the year 2010 ***(Roglic and Unwin, 2010).*** The magnitude of the estimated number of deaths due to diabetes is similar to the combined deaths from several infectious diseases like HIV / AIDS, malaria, and tuberculosis that are ranked as top public health priorities ***(IDF, 2011).***

C. Classification of Diabetes Mellitus:

In 1979 a work group of the National Diabetes Data Group proposed a classification scheme which recognized two major forms of diabetes: type I; insulin dependent diabetes

mellitus (IDDM) and type II; non insulin dependent diabetes mellitus (NIDDM) ***(National Diabetes Data Group, 1979).*** The term (type 1 diabetes) has universally replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term (type 2 diabetes) has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and non-insulin dependent diabetes mellitus (NIDDM). This classification system went on to include evidence that DM was an etiologically and clinically heterogonous group of disorders that share hyperglycemia in common. Such evidence was used by an International Expert Committee working under the sponsorship of the American Diabetes Association (ADA) to establish a classification based on the disease etiology rather than the type of pharmacological treatment. This classification includes type 1 DM, type 2 DM, specific types of diabetes, gestational DM (GDM), impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (table 1) ***(American Diabetes Association, 2007).***

Table (2): Etiological Classification of Diabetes Mellitus and other categories of glucose intolerance.

1- Type 1 diabetes
a. Immune mediated
b. Idiopathic
2- Type 2 diabetes
3- Other specific types of diabetes
a-Genetic defects of islet ß-cell function
b-Genetic defects of insulin action
c-Diseases of the exocrine pancreas
d-Endocrinopathies
e-Drug- or chemical- induced diabetes
f-Infections
g-Uncommon forms of diabetes
h-Other genetic syndromes
4- Gestational diabetes mellitus (GDM)
5- Impaired glucose tolerance (IGT)
6- Impaired fasting glucose (IFG)

Tab (2) ***(modified from the American Diabetes Association, 2007).***

1. Type 1 Diabetes Mellitus:

Type 1 Diabetes Mellitus (previously called insulin-dependent or Juvenile-Onset Diabetes) account for 5% to 10% of all cases of DM. Although the peak incidence is in childhood and adolescence; age at presentation is not a criterion for classification. Patients usually have abrupt onset of symptoms as,

diabetic ketoacidosis may quickly develop. In type 1 DM, insulin production is absent because of autoimmune destruction of pancreatic β cells possibly triggered by an environmental exposure in genetically susceptible people. Destruction progress is subclinically over months or years until β cell mass decreases to the point that insulin concentration is no longer adequate to control plasma glucose levels ***(Godsland et al., 2004).***

The exact cause of type 1 DM is unknown, it may be idiopathic or it may be related to autoimmune β cell destruction involving interaction between autoantibodies, genetic susceptibility and environmental factors that cause the body to mistakenly attack the cells in the pancreas that make insulin ***(Sacks, 2006).***

a. Auto-antibodies:

The most practical markers of β-cell autoimmunity are circulating antibodies, which can be detected in the serum years before the onset of hyperglycemia. The best characterized antibodies are: islet cell cytoplasmic antibodies (ICAs), insulin autoantibodies (IAAs) and antibodies to the 65-kD isoform of glutamic acid decarboxylase (GAD65) ***(Rother, 2007).***

b. Genetic susceptibility:

Susceptibility to type 1 diabetes is inherited, but the mode of inheritance is complex and has not been defined. It is a multigenic trait, and the major locus is the major histocompatibility complex on chromosome 6. At least 11 other

loci on 9 chromosomes, also contribute, with the regulatory region of the insulin gene on chromosome 11pl5 being an important locus. The concordance rate between identical twins is approximately 30%, and approximately 95% of whites with type 1 diabetes express either HLA-DR3 or HLA- DR4 histocompatibility antigens. The multiplicity of independent chromosomal regions associated with a predisposition to type 1 diabetes suggests that other susceptibility genes will be identified ***(Walley et al., 2008).***

c. Environmental factors:

Reports describe that environmental factors are involved in initiating diabetes. Viruses, such as rubella, mumps, and coxsackie virus B, have been implicated. Other environmental factors that have been suggested include chemicals and cow's milk. It seems likely that autoimmunity to β-cells is initiated by a viral protein (that shares amino acid sequence with a β-cell protein) ***(Hyoty and Taylor, 2002).***

2. Type 2 Diabetes Mellitus:

Pathophysiology of type 2 DM:

Type 2 DM is a multifactorial disease. Hyperglycemia is related to a decrese in glucose peripheral uptake, and to an increase in hepatic glucose production, due to reduced insulin secretion and insulin sensitivity. Multiple insulin secretary defects are present, including loss of basal pulsatility, lack of early phase of insulin secretion after intravenous glucose

administration,decreased basal and stimulated plasma insulin concentration, excess in prohormone

Type 2DM has greater genetic association than type 1DM. Enviromental effect may be a possible reason for the higher concordance rate for type 2 DM than type 1DM ***(Kaprio et al., 1992)***. Type 2 DM affects 1- 2% of Caucasians ***(Cook., et al 1993)***, but it is much higher in some ethnic groups such as Pima Indians ***(Knowler et al., 1990)*** and Arabs ***(Richens et al., 1988)***, an approaches 50% in South India. This indicates that genetic factors are more important than environmental factors. Except for maturity onset diabetes of the young (MODY), the mode of inheritance for type 2DM is unclear ***(Froguel et al., 1993).***

MODY, inherited as an autosomal dominant trait, may result from mutations in glucokinase gene on chromosome 7p. Glucokinase is a key enzyme of glucose metabolism in beta cell and the liver ***(Hattersley, 1992).*** MODY is defined as hyperglycemia diagnosed before the age of twenty-five years and treatable for over five years without insulin in cases where islet cell antibodies (ICA) are negative and HLA-DR3 and DR4 are heterozygous. MODY is rare in Caucasians, less than 1% and more in blacks and Indians, more than 10% of diabetes. Chronic complications in MODY were thought to be uncommon but later were found to be common, indicating its heterogencity. Considering MODY as a seperate entity may maskuerade its associations with specific genetic diseases; and without a definite genetic marker, it should be treated as type

1DM ***(Tattershall et al., 1991)***. Identification of a nonsense mutation in glucokinase gene and its linkage with MODY was reported for the first time in a French family, implicating a mutation in a gene involved in glucose metabolism in the pathogenesis of type 2DM ***(Vionnet et al., 1992).*** Later, sixteen mutations were identified in 18 MODY families. Hyperglycemia in these families was usually mild and begin in childhood, where the hyperglycemia of MODY families without glucokinase mutations usually appeared after puberty ***(Froguel et al., 1993).***

Immunogenetic factors:

Molecular genetic studies in type 2 DM, the exception of MODY, have not been as successful as in type 1 DM. Mutations in the insulin gene lead to the synthesis and secretion of abnormal gene products, leading to what are called insulinopathies ***(Gabbay, 1980).*** Most of the patients with insulinopathies have hyperinsulinemia, inherited in autosomal fashion,heterozygous for normal and mutant alleles, and normally respond to exogenous insulin administration ***(Chan, 1987).*** The association of the polymorphic 5 flanking region of the human insulin gene and type 2 DM is lacking in some population groups, indicating that it may be one of many factors in a multifactorial disease. Even MODY patients have shown no association with region. It was mentioned earlier that there a strong association between HLA –DR3/4 and type 1 DM. It was also reported that such an association is present

with type 2 DM, rendering HLA-DR3/4 markers for beta cell destruction in these patients ***(Tattershall, 1991).***

The genetic information in the family history has been used in clinical assessment of T2DM. There is an ample evidence that T2DM has a strong genetic component, which includes monogenic disease such as MODY1-6 under 25 years of age and polgenic disease such as common T2DM. The lifetime risk of T2DM is about 7% in a general population, about 40% in offspring of one parent with T2DM, and 70% if both parents have diabetes ***(Vionnet et al., 1992).***

The first degree family with a history of T2DM is associated with two fold increased risk of future T2DM ***(Eriksson et al., 1992).***

Genetic studies including linkage analysis,candidate gene approaches, and most recent genome – wide association studies have identified 20 common genetic varients associated with T2DM ***(Herder and Roden, 2012).*** Many loci appear to regulate the capcity of β-cells to increase insulin secretion in response to an increase in insulin resistance or obesity, which includes eight genes such as TCF7L2, KCNJ11, HHEX, SLC30A8, CDKAL1, CDKN2A/2B, IGF2BP2, and KCNQ. PPARG gene is related to insulin sensitivity; CAPN10 gene is related to glucose transport; MC4R and FTO genesare related to obesity; eight other loci have unknown roles in T2DM ***(Herder and Roden, 2012).***