Utility of Serum Inflammatory Chemokines as Markers of Metabolic Syndrome and Type II Diabetes Mellitus

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استخدام الكيموكينات كدلائل لمتلازمة التمثيل الأيضي ومرض السكري من النوع الثاني

رسالة مقدمة من

دعـــاء نبيـل صالـح

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INTRODUCTION

Type II diabetes mellitus is a group of disorders characterized by hyperglycemia and associated with micro-vascular (i.e. retinal, renal and neuropathic) and macrovascular (i.e. coronary and peripheral vascular) complications.Hyper-glycemia results from lack of endogenous insulin or resistance to the actions of insulin in muscle, fat and liver. In addition to an inadequate response by the pancreatic beta cells***(Wolfset al., 2009).***

Type II diabetes mellitus accounts for 90 to 95% of the incidence of diabetes. It is predicted that by the year 2030, 438 million people will be diabetic. The explosive increase in number of people diagnosed with diabetes makes this disease a real health threat in the 21st century. Understanding the etiology and finding a way to prevent type II diabetes mellitus is an urgent challenge for the health care of our society ***(Frank, 2011).***

On the other hand, the metabolic syndrome is a cluster of coronary heart disease (CHD) risk factors including high blood pressure, dyslipidemia, hyperglycemia and central obesity that are associated with decreased ability of insulin to stimulate glucose disposal on peripheral target tissues, referred to as insulin resistance ***(Reaven, 2004).***

Insulin resistance is determined by impaired sensitivity of insulin to its main target organs, i.e. adipose tissue, liver, and muscle. Obesity, particularly central obesity, is the prominent risk factor for insulin resistance and results in type II diabetes

mellitusand metabolic syndrome. More evidence has emerged that obesity is associated with inflammation that is causally involved in the development of insulin resistance ***(Zeyda and Stuling, 2009).***

Adipose tissue represents an active endocrine organ that releases a large number of bioactive mediators (adipokines) that signal to organs of metabolic importance including brain, liver, skeletal muscle, and the immune system thereby modulating hemostasis, blood pressure, lipid and glucose metabolism, inflammation and atherosclerosis. These adipokines include adiponectin, leptin, omentin, resistin, retinol binding protein 4, tumor necrosis factor-α, interleukin-6, vaspin, visfatin and chemerin ***(Rabe et al., 2008).***

Chemerin, also known as tazarotene induced gene 2 (TIG2) and retinoic acid receptor responder 2(RARRES2), is an adipokine thathas been reported to modulate immune system functionthrough its binding to the chemerin receptor***(Roh et al., 2007).***

Chemerin is secreted as an 18kDa inactive pro-protein and undergoes extracellular serine protease cleavage of the C-terminal portion of the protein to generate the 16kDa active chemerin which is present in plasma and serum ***(Dongand Zhang, 2011).*** It is secreted by the mature adipocytes and expressed abundantly in adipose tissue. Furthermore, chemerin and its receptor/ChemR23 are expressed in mature adipocytes, suggesting its function in autocrine/paracrine fashion ***(Takahashi et al., 2008).***

It has been reported that chemerin serves as a chemo-attractant for cells of the immune system such as macrophages and immature dendritic cells that express the cognate receptor chemokine-like receptor-1 (CMKLR1). Also chemerin acts as a positive regulator of adipocyte differentiation ***(Goralski and Sinal, 2009).***

Recent studies have shown that obesity induces inflamm-ationin adipose tissue and since chemerin is a proinflammatory cytokine thatrecruits and activates immune cells, it may link obesity and inflammation. Therefore, a possible relation of chemerin to inflammatory proteins in obesity and type II diabetes mellitus is demonstrated ***(Weigert et al., 2009).*** It has been demonstrated that chemerin is strongly associated with markers of inflammation and components of metabolic syndrome ***(Lehrke et al.,2009).***

Furthermore, chemerin is also related to insulin level, body fat deposition and lipid metabolism suggesting that it may play a role in the pathophysiology of obesity and metabolic syndrome ***(Wang et al., 2009).***

Christian and Christoph, (2007) stated that the effect of adipokines on metabolic syndrome and type II diabetes mellitus seems to stem from the influence of a combination of adipokines rather than from the effect of a single adipokine.

Tumor necrosis factor-alpha (TNF-α) also known as (cachexin or cachectin) is a cytokine involved in systemic inflammation and is a member of a group of cytokines that

stimulate the acute phase reactions. It is primarily produced as a 212 amino acid long type II transmembrane protein arranged in stable homotrimers and is produced mainly by macrophages, but they are produced also by a broad variety of other cell types including (lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts and neuronal tissue ***(Tang et al., 1996).***

TNF-α is known to affect insulin sensitivity, glucose and lipid metabolism and is synthesized and secreted by adipocyte. TNF-α acts as an inducible cytokine with a wide range of important proinflammatory and immunoregulatory actions ***(Beutler et al., 1989).***

Interleukin -6 is a protein that in humans is encoded by the IL-6 gene. It acts as both a proinflammatory and anti-inflammatory cytokine. Its anti-inflammatory role is mediated through its inhibitory effects on TNF-α. It affects glucose homeostasis and metabolism directly and indirectly by action on skeletal muscle cells, adipocytes, pancreatic beta cells and neuroendocrine cells ***(Christian et al., 2007).***

AIM OF THE WORK

The aim of the present study is to evaluate the level of some inflammatory cytokines such as chemerin, tumor necrosis factor alpha and interleukin-6 and their implication in diagnosis, prognosis and severity of metabolic syndrome and type II diabetes mellitus as well as their role in obesity.

1- REVIEW OF LITERATURE

1.1. DIABETES MELLITUS

Diabetes mellitus (DM) was an invariably fatal illness in the pre-insulin era. In 1889, Oskar Minkowski first demonstrated that removal of the pancreas led to diabetes in dogs, documenting that diabetes is caused by the absence of a factor produced by the pancreas. In 1921, Frederick Banting and Charles Best, with the help of James Collip, purified the factor from the pancreas and named it “insulin”. Thus, their discovery revolutionized the treatment of diabetes***(Chan et al., 2006).***

Diabetes mellitus is a metabolic disorder characterized by a state of chronic hyperglycemia. It occurs due to disturbances of carbohydrate metabolism resulting from defects in insulin secretion, insulin action or both. The effects of diabetes mellitus include long-term damage,dysfunction and failure of various organs ***(Rother, 2007).***

1.1.1. Epidemiology and prevalence of DM:

Diabetes is now described as one of the main threats to human health in the twenty-first century.Its prevalence is not exactly known. In 2010, according to the World Health Organization, at least 285 million people, or 6.4% of population, worldwide suffer from DM. Its incidence is increasing rapidly and it is estimated that by the year of 2030 this number will be doubled ***(Shaw et al., 2010).***

The prevalence of diabetes mellitus increases with age, and approximately half of the diabetic patients are older than 55 years ***(Zimmet et al., 2001 and Mokdad et al., 2003).***

The highest rates of diabetes worldwide are in Indians of Arizona ***(Quinn, 2001).***Furthermore, the highest percentages of increases in disease prevalence are likely to be in non-Western and developing nations, with major increases in the Middle-East, Sub-Saharan Africa, India, Asia and Latin America. These increases reflect rapidly changing lifestyles in developing countries ***(Wild et al., 2004).*** In addition, certain populations in developing countries, such as South Asian Indians, have an increased tendency to develop diabetes compared with Western populations exposed to a similar diet and lifestyle ***(Misra et al., 2007).***

1.1.2. Classification of DM:

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).*** These terms now have been eliminated because this classification is based on the therapeutic requirements, and any patient with diabetes mellitus may require insulin therapy at certain stage of the disease, irrespective of the classification ***(Philip et al., 2001).***

Therefore, the American Diabetes Association (ADA) established a work group to re-examine the old classification of diabetes mellitus and published the revised classification based on the origin and pathogenesis of diabetes in 2010. It established a new

classification of diabetes mellitus and other catergories of glucose regulation(Table 1)***(American Diabetes Association, 2010).***

Table (1): Etiological classification of diabetes mellitus

(a) Type I Diabetes Mellitus (Type I DM):

i-Immune mediated.

ii-Idiopathic.

(b) Type II Diabetes Mellitus (Type II DM).

(c) Other Specific Types of Diabetes:

i-Genetic defects of islet ß-cell function.

ii-Genetic defects of insulin action.

iii-Diseases of the exocrine pancreas.

iv-Endocrinopathies.

v-Drug- or chemical- induced diabetes.

vi-Infections.

vii-Uncommon forms of diabetes.

viii-Other genetic syndromes.

(d) Gestational Diabetes Mellitus (GDM).

(American Diabetes Association, 2010)

1.1.2.1. Type I diabetes mellitus (Type I DM):

Type I Diabetes Mellitus (previously called insulin-dependent or Juvenile-Onset Diabetes) accounts 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 includinghyperglycemia, excessive urine production, compen-

satory thirst, increased fluid intake, blurred vision, unexplained weight loss, lethargy and changes in energy metabolism***(Lin and Sun, 2010).***In type I DM, insulin production is absent because of autoimmune destruction of pancreatic β-cells, which is possibly triggered by an environmental exposure in genetically susceptible people. The progress of destruction remains subclinical 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 pathogenesis of type I DM may be idiopathic or related to autoimmune β cell destruction involving incompletely understood interaction between auto-antibodies, geneticsusceptibility and environmental factors.The presence of auto-antibodies results in autoimmune destruction of β-cell of the pancreas that leads to absolute insulin deficiency ***(Janett, 2012).***

The most practical markers of β-cell autoimmunity are circulating antibodies, which can be detected in the serum. The best characterized antibodies are: Islet Cell Cytoplasmic Auto-Antibodies (ICAs), Insulin Auto-Antibodies (IAAs), antibodies to the 65-kDa isoform of Glutamic Acid Decarboxylase (GAD65) expressed in the pancreas andInsulinoma-Associated Antigens (IA-2A, and IA-2βA) ***(Rother, 2007).***

Some studies revealed that autoimmunity to β-cells may be initiated by a viral proteinthat shares amino acid sequencewith a β cell protein such as rubella, mumps and coxsackie virus Bthat shares amino acid sequence with a β-cell protein or may be initiated by some other environmental insults. Other

environmental factors that have been suggested include chemicals and cow's milk. This milk contains β-casein A1 molecule which differs from that present in breast milk. Casein is a disulfide bonded and hard to digest, so elects the help of lactobacillus species to break lactose by bacterial lactases to get lactic acid.***(Hyoty and Taylor, 2002).***

Susceptibility to type I DM 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(Figure 1). The concordance rate between identical twins is approximately 30%***(Walley et al., 2006).***

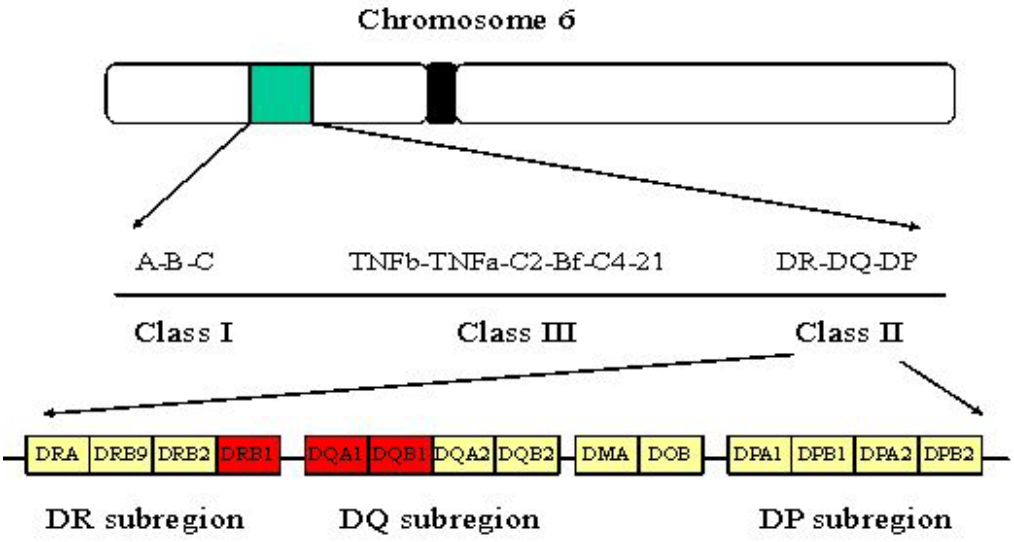

Figure (1): The human leukocyte antigen (HLA) on chromosome 6. The type I diabetes associated haplotypes are DRB1*03-DQB1*02 and DRB1*04-DQB1*0302.

(Kathleen, 2011)

1.1.2.2.Type II diabetes mellitus (Type II DM):

TypeII DM is currently thought to occur in genetically predisposed individuals who are exposed to a series ofenviron-mental influences that precipitate the onset ofclinical disease. Patients with type II DM usually have minimal symptoms and they are not prone to ketosis and not dependant on insulin. Insulin concentrations may be normal, decreased, or increased and most of these patients have insulin resistance. It is commonly associated with obesity ***(Zimmet et al., 2001).***

1.1.2.2.1.Incidence and prevalence of type II DM:

Type II DM (formerly called non insulin-dependent or adult-onset diabetes) comprises approximately 90% of all cases of diabetes. Type II DM in children and adolescents is an emerging and significant problem ***(Lang et al., 2008).*** The disease is more common in women and its incidence increases in certain racial and ethnic groups. Age is also a critical factor***(Buse et al., 2008).***

1.1.2.2.2.Risk factors and pathogenesisof type II DM:

- Overweight (Body mass index $\geq$ 25 kg/m^2): About 80% of cases of type II diabetes are associated with obesity and sedentary life styles ***(Venables and Jeukendrup, 2009).*** In obesity, the disparity between uptake of fatty acid into skeletal muscle and oxidation results in excessive accumulation of triacylglycerol and fatty acid metabolites.
- Age $\geq$ 45years: Indeed, increases in abdominal adiposity may precede changes in insulin action and dyslipidemia ***(Lovejoy et al., 2008).***

- Positive family history of type II DM: The first-degree family with a history of type II diabetes is associated with two fold increased risk of future type II DM in the offspring ***(Majithia and Florez, 2009).***
- History of GDM or delivery of an overweight baby (wt > 4kg):Women who have had gestational diabetes have a 20% to 50% increased risk for developing type II DM later in life***(England et al.,2009).***
- Polycystic ovary syndrome:Women with PCOS suffer from consequences of insulinresistance, suchas a significant risk for the development of type II DM and cardiovascularrisk factors ***(Ehrmann et al., 1999).***
- Hypertension: (Blood pressure ≥140/90 mmHg in adults).
- High density lipoprotein-cholesterol (HDL-C): ≤ 35mg/dl or triglycerides ≥ 250 mg/dl***(David and Robertson, 2013).***

There are at least two major identifiable pathological defects in patients with type II DM. One is a decreased ability of insulin to act on the peripheral tissues; this is called insulin resistance. The other is β-cell dysfunction, which is an inability of the pancreas to produce sufficient insulin to compensate for the insulin resistance ***(De Fronzo et al., 1992).*** Other minor pathological defects in patients with type II diabetes include environmental and genetic factors. The fundamental molecular defects in insulin resistance and insulin secretion result from a combination of environmental and genetic factors ***(Sacks and McDonald, 1996).***

1.1.2.2.3. Insulin resistance:

Insulin resistance is defined as a decreased biological response to normal concentrations of circulating insulin. It is found in both obese nondiabetic individuals and patients with type II DM. A number of factors are included in the incidence of type II DM such as age, weight, sex, ethnicity, body fat(especially abdominal) and pregnancy influence insulin resistance. There is also a strong influence of genetic factors on predisposition to insulin resistance and therefore to type II DM***(Flier, 1992).***

There is a broad clinical spectrum of insulin resistance, ranging from euglycemia (with marked increase in endogenous insulin) to hyperglycemia despite large doses of exogenous insulin.Insulin resistance is thought to be the primary underlying abnormalityleading to impaired glucose tolerance, type II DM as well as metabolic syndrome ***(Deedwania, 2004).***

Insulin receptoris a transmembrane glycoprotein composed of two α subunits and two β subunits covalently linked through disulfide bonds to form α2 β2 heterotetramer.Theα subunit is entirely extracellular and contains the sites for insulin binding, whereas the β subunits has a small extracellular portion, a transmembrane domain and an intracellular insulin-regulated tyrosine kinase activity. Binding of insulin to α subunits induces a conformational change in the receptor, resulting in activation of tyrosine kinase that catalyzes the phosphorylation of tyrosine residues on a number of specific intracellular proteins which mediate insulin signaling (Figure 2)***(Ueki and Khan, 2000).***