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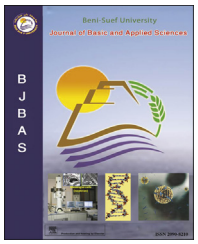

Full Length Article

Chemerin is associated with markers of inflammation and predictors of atherosclerosis in Saudi subjects with metabolic syndrome and type 2 diabetes mellitus

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ABSTRACT

Chemerin is a novel adipokine, suggested to be involved in insulin resistance in obesity and type 2 diabetes and may be an attractive candidate for assessing risk of atherosclerotic cardiovascular disease. The aim is to examine the relationship of chemerin and markers of inflammation, and predictors of atherosclerosis in the metabolic syndrome, and type 2 diabetes mellitus in Saudi Arabians. Twenty healthy control subjects (group I), 20 patients with type 2 diabetes mellitus (group II), in addition to 20 subjects with metabolic syndrome (group III) are examined by anthropometric and blood pressure measurement, laboratory investigations including fasting and post-prandial blood sugar, fasting serum insulin, lipid profile and serum chemerin and leptin levels. Moreover, tumor necrosis factor – α (TNF – α), high sensitivity C-reactive protein (hsCRP) levels, and interleukin 6 (IL6) are measured. Vascular health was assessed by the brachial – ankle pulse wave velocity (baPWV) and carotid intima-media thickness (IMT). Homeostasis Model Assessment-Insulin Resistance Index (HOMA-IR) and the cardio-vascular risk value were calculated. Our present study revealed a significant a positive correlation between serum chemerin level and fasting and post-prandial blood sugar, IL6 and TNF-α ($p < 0.05$, respectively) in group II and III. Moreover, IMT and baPWV are positively associated with chemerin in both groups ($p < 0.01$, respectively) but not with leptin. In group III, it was revealed that, chemerin, systolic blood pressure and waist circumference are risk factors determining baPWV values and the three variables together account

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for 76.9% of the variance in baPWV values ($F = 17.713$, $p = <.001$). Chemerin is associated with markers of inflammation and predictors of atherosclerosis in the metabolic syndrome, and type 2 diabetes and it is an independent factor determining arterial stiffness in Saudi Arabians.

1. Introduction

Adipose tissue is now considered as an active endocrine organ that secrets a large number of bioactive mediators (adipokines) that signal to brain, liver, skeletal muscle, and the immune system, the important metabolic organs in the body (Yan et al., 2012). These adipokines include adiponectin, leptin, omentin, resistin, retinol binding protein-4(RBP-4), tumor necrosis factor-α (TNF-α), interleukin-6 (IL6), vaspin, visfatin and chemerin (Yan et al., 2012). Dysregulation of pro inflammatory and anti inflammatory adipokines secretion in obesity may serve as a pathogenic link between obesity, insulin resistance and cardiovascular diseases (Roh et al., 2007; Goralski, 2007). Chemerin, also known as tazarotene induced gene 2 (TIG2) and retinoic acid receptor responder 2 (RARRES2), is a recently discovered adipokine that has been reported to act by its binding to the chemerin receptor (Chemerin R, chemokine like receptor 1, G protein-coupled receptor) (Roh et al., 2007). It is secreted as an 18 kDa inactive pro-protein and undergoes extracellular serine protease cleavage of the C-terminal portion of the protein to generate the 16 kDa active chemerin which is present in plasma and serum (Goralski et al., 2007). The functions of chemerin vary dependent on the ways how it is cleaved. For example, chemerin 21–157 has a strong chemotactic effect and is responsible for an early inflammatory reaction of the immune cells, whereas chemerin 21–154 is anti-inflammatory *via* inhibiting macrophage activation (Du et al., 2009). Chemerin and its receptor/ChemR23 are expressed abundantly in adipose tissue, suggesting its function in autocrine/ paracrine fashion (Ernst et al., 2012). Type 2 diabetes mellitus 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).

It was originally reported to be present in circulation in plasma and serum, respectively, at 3.0 and 4.4 nM concentrations in humans, and 0.6 and 0.5 nM concentrations in mice (Goralski et al., 2007). Serum chemerin concentrations are elevated in obese, insulin-resistant, and inflammatory states in vivo and suggested to be an obvious cause of insulin resistance (Hart and Greaves, 2010).

It may link obesity and inflammation since chemerin is a pro-inflammatory cytokine that recruits and activates immune cells and contributes to inflammation by promoting macrophage adhesion to vascular cell adhesion molecule-1 (VCAM-1) and fibronectin, (Ouchi et al., 2011). Pulse wave velocity (PWV) is a marker of arterial stiffness (Asmar et al., 1995; Lehmann, 1999 and Yufu et al., 2004) and a reliable indicator of vascular damage. It is not only a marker of vascular damage (Cohn, 1999; van Popele et al., 2001) but also a prognostic predictor (Cruickshank et al., 2002; Laurent et al., 2003; Pannier et al., 2005).

Obesity and atherosclerosis are increasingly viewed as inflammatory states. Biomarkers that integrate metabolic and inflammatory signals may be attractive candidates for assessing risk of atherosclerotic cardiovascular disease (Rajala et al., 2003).

The accumulation of chemerin in an atherosclerotic lesion could attract immune cells which add to the remodeling of the vessel wall, the alteration of insulin sensitivity and glucose uptake in adipocytes and skeletal muscle and the direct inflammatory effect on vascular endothelial cells all could contribute to development of atherosclerosis (Yamawaki, 2011).

A cluster of coronary heart disease (CHD) risk factors including high blood pressure, dyslipidemia, hyperglycemia and central obesity is known as the metabolic syndrome that is associated with decreased ability of insulin to stimulate glucose disposal on peripheral target tissues (Olufadi and Byrne, 2008).

Obesity, particularly central obesity, is the prominent risk factor for insulin resistance and results in type 2 diabetes and metabolic syndrome (Zeyda and Stulnig, 2009). In addition to its immunomodulatory effects, chemerin was reported to be associated with components of the metabolic syndrome and the parameters of type II diabetes (Bozaoglu et al., 2007) including body mass index (BMI), plasma triglyceride (TG) levels, and blood pressure. Chemerin was shown to modulate the expression of adipocyte genes involved in glucose and lipid homeostasis such as glucose transporter-4, fatty acid synthase, adiponectin, and leptin (Goralski, 2007) and to enhance insulin signaling in 3T3-L1 adipocytes (Takahashi et al., 2008). Recently, it was reported that CMKLR1 is expressed in vascular endothelial cells and its expression is up-regulated by tumor necrosis factor (TNF)-α, interleukin (IL)-1β, or IL-6 (Kaur et al., 2010). However, mechanisms of actions of chemerin on vascular endothelial cells remain to be fully clarified. The known junction of adipocyte and macrophage function of chemerin may provide an interesting link between obesity, inflammation, and atherosclerosis and diabetes mellitus type 2 in humans (Lehrke et al., 2009).

As chemerin has a regulatory role in adipogenesis and adipocyte metabolism, and influencing chemerin and chemerin R signaling might to lead to novel therapeutic approaches in the treatment of obesity, diabetes mellitus type 2, and cardiovascular diseases (Goralski et al., 2007).

The aim of the present study is to examine the relationship of chemerin, markers of inflammation and predictors of atherosclerosis in the metabolic syndrome and type 2 diabetes, and to investigate its correlation with clinical and laboratory parameters of these conditions in Saudi Arabians.