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Levels of Chemerin and Asymmetric Dimethylarginine (ADMA) in Obese Type 2 Diabetic Patients

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Abstract

Diabetes Mellitus has reached epidemic proportion and has become one of the most challenging health problems of the 21st century. Moreover, it is the 4th leading cause of death by disease globally, where every 10 seconds a person dies from diabetes-related causes. Obesity, insulin resistance, dyslipidemia and hypertension are associated with type 2 diabetes mellitus (T2DM), termed together as metabolic syndrome. Mobilization of free fatty acids and secretion of certain inflammatory adipokines from adipose tissue promote insulin resistance in obese diabetics by interference with insulin sensitivity, and metabolism of glucose and lipid. Chemerin, a specific adipokine, has an essential role in glucose and lipid metabolism. It plays a role in pathogenesis of obesity and T2DM. It has also important roles in energy metabolism, adipogenesis, and inflammation. Asymmetric dimethylarginine (ADMA) is considered a natural analogue of the essential amino acid arginine and a metabolic by-product obtained from processes of protein turnover of all human cells cytoplasm.

Keywords: ADMA; chemerin; obesity; type 2 diabetes mellitus

1. Introduction

Diabetes mellitus is a chronic disorder characterized by hyperglycemia and the late development of vascular and neuropathic complications. Regardless of its cause, the disease is associated with a common hormonal defect— namely, insulin deficiency—that may be absolute or relative in the context of coexisting insulin resistance. This effect plays a primary role in the metabolic derangements linked to diabetes. Hyperglycemia, in turn, plays an important role in the disease-related complications (Belfiore and Malaguarnera, 2011).

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues (Shaaban et al., 2016).

Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of the hormone action (Ruan et al., 2016).

Rec. Pharm. Biomed. Sci. 3(1), 4- 10,

2019

Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia (Jangid et al., 2017). Life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome (Maletkovic and Drexler, 2013).

2. Major types of diabetes mellitus:

2.1. Type 1 diabetes

The cause of type 1 diabetes is an absolute deficiency of insulin secretion (American Diabetes Association, 2015). Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers (Atkinson et al., 2014).

2.2. Type 2 diabetes

The cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (Kahn et al., 2014). In this category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma
glucose in the fasting state or after a challenge with an oral glucose load. The degree of hyperglycemia may change over time, depending on the extent of the underlying disease process. A disease process may be present but may not have progressed far enough to cause hyperglycemia (Anjaneyulu et al., 2017).

In some individuals with diabetes, adequate glycemic control can be achieved with weight reduction, exercise, and/or oral glucose lowering agents. These individuals therefore do not require insulin. Other individuals who have some

residual insulin secretion but require exogenous insulin for adequate glycemic control can survive without insulin (Handelsman et al., 2015). Individuals with extensive β-cell destruction and therefore no residual insulin secretion require insulin for survival. The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its treatment more than the nature of the process itself (Liston et al., 2017).

3. Diagnosis of Diabetes Mellitus:

Usually, diagnosis of diabetes is made on the basis of levels of plasma glucose in the blood, measured either with the fasting plasma glucose test or the 2-hour plasma glucose level after a 75-g oral glucose tolerance test (OGTT). The onset of T2DM in most cases occurs as a latent phase of glucose intolerance or impaired glucose regulation. This condition of impaired glucose regulation is known as pre-diabetes, and is characterized by impaired fasting glycaemia and/or impaired glucose tolerance (American Diabetes Association, 2015).

3.1. Glycated hemoglobin (HbA1c):

HbA1c is the gold standard biomarker for measuring blood glucose levels and thus for identifying diabetes status. HbA1c is a laboratory test that measures average blood sugar over a three month period. The last three months contribute to the overall HbA1c value, thus, any alteration in HbA1c within the last six weeks is considered to be a result of dietary modification or treatment in this period (Adepoyibi et al., 2013)

3.2 Fructosamine:

Fructosamine is a term that has come into acceptance and refers to both glycoalbumin and glycated total protein (Armbruster, 1987). As the average life span of these proteins is about 2-3 weeks, the level of fructosamine provides a reflection of the average glucose concentration over that time (Davis and Lunn, 2011).

Interestingly, because of the shorter life span of the glycated albumin and total proteins, fructosamine measurements are more sensitive to changes in diabetic control (Ma et al., 2010, Li et al., 2015).

4. Obesity and diabetes:

There are controllable risk factors associated with diabetes, including obesity and an inactive lifestyle. However, other uncontrollable risk factors, such as ethnicity and genetics, also play a dramatic role. The health risk of obesity is largely associated with T2DM within the frame of the metabolic syndrome, including diabetes, hypertension, hyperlipidemia, and cardiac disease. Moreover, the rising risk of T2DM may be a result of the growing obesity and the increase in mean fat mass in the individual (Wong et al., 2016). Body mass index (BMI) has a strong relationship to diabetes and insulin resistance (Basraon et al., 2016).

Obesity and T2DM can substantially decrease life expectancy, diminish quality of life and increase healthcare costs. The incidence of obesity and diabetes continues to rise by epidemic proportions (Shamseddeen et al., 2011).

The term "diabesity" has been coined to describe obesity dependent diabetes (Wong et al., 2016). It has been shown that obesity plays a major role in the pathophysiology of T2DM and its macrovascular complications. It has also been suggested that an adverse metabolic profile in patients with normal weight increases the risk of subsequent development of T2DM and other cardiovascular diseases (CVD) (Fuster et al., 2016).

4.1. Adipokines and diabetes:

Adipose tissue releases a large number of mediators, which influence body weight homeostasis as well as insulin sensitivity and lead to alterations in lipids, blood pressure, coagulation, fibrinolysis and inflammation (Feijóo-Bandín et al., 2016).

Adipose tissue is an active endocrine organ that secretes several inflammatory cytokines, namely, adipokines, which interfere with insulin sensitivity, glucose and lipid metabolism, and the inflammatory process (Ballak et al., 2014). There is a pathophysiologic link between obesity and T2DM, and adipokines seem to play an important role in this concern (Blüher, 2014).

4.1.1. Chemerin:

Chemerin is an adipokine that has attracted considerable interest due to the increasing body of evidence supporting roles for this adipokine in adipogenesis, energy metabolism, and inflammation. In particular, In particular, chemerin has been hypothesized as a possible link between obesity and the development of T2DM (Yoo and Choi, 2014). Expression of chemerin was found to increase in states of obesity (Bozaoglu et al., 2007).

A growing body of human experimental data indicates that serum chemerin levels are elevated in patients with obesity and that they exhibit a positive correlation with various aspects of the metabolic syndrome. Thus, the role of chemerin in metabolism might provide a link between obesity and obesity related disorders such as T2DM (Ernst and Sinal, 2010).

Significant positive association was found between circulating chemerin and BMI, glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and serum triglycerides (Tan et al., 2009). These studies suggest that chemerin may play a potential role in obesity induced insulin resistance and the development of T2DM.

5- Endothelial dysfunction:

One of the major mediators that are released by healthy endothelial cells is nitric oxide (NO) (Lundberg et al., 2015).

5.1. Nitric oxide:

Nitric oxide (NO) is a free radical that has been recognized as a neural messenger molecule. Nitric oxide is formed by the enzyme NO synthase (NOS) from the amino acid precursor L-arginine. Nitric oxide is involved in a vast number of regulatory processes within the cardio vascular system (Lundberg et al., 2015).

Besides its potent vasodilatory effects, NO also acts as an endogenous inhibitor of platelet aggregation. Furthermore, NO inhibits the adhesion of monocytes and leukocytes at the healthy vascular endothelium - an effect that, once disturbed, precedes the immigration of inflammatory cells into the vascular wall at sites that later become plaques. NO alos inhibits the proliferation of vascular smooth muscle cells - this might be of great importance during the development of restenosis after angioplasty. Moreover, NO reduces vascular release pf superoxide radicals that are involved in the inflammatory and cytotoxic processes as well as inhibiting lipid peroxidation (Vanhoutte et al., 2016).

Rec. Pharm. Biomed. Sci. 3(1), 4- 10,

2019

5.2. Nitric oxide inhibitors:

In 1992, Patrick Vallance and co-workers were the first to describe substances that show structural homology to L-arginine, but differ from it in that they contain one or two methyl groups, acting as inhibitors of NO synthesis. These substances which have accordingly been named dimethylarginines (containing two methyl groups) are present endogenously in human plasma and urine (Vallance et al., 1992a).

5.2.1. Assymetric Dimethyl Arginine (ADMA):

Vallance and colleagues reported that asymmetric dimethylarginine (ADMA) was the member of this group of substances that is present in sufficiently high concentrations to inhibit NO synthesis (Vallance et al., 1992b). In contrast to ADMA, its structural isomer symmetric dimethyl arginine (SDMA) had no effect on NO production (Böger, 2003). Hyperglycemia may result in a decrease of NO production and/or inactivation of NOS by reactive oxygen and nitrogen species. It was reported that elevated blood glucose levels drive production of reactive oxygen species (ROS) via multiple pathways, resulting in uncoupling endothelial NOS activity and reducing NO availability (Sarwar et al., 2010)

Experimental studies in various laboratories have shown that ADMA inhibits NO production in vitro within a concentration range that can be measured in plasma of patients with CVD (Luiking et al., 2010). In cultured human macrophages (which express the inducible isoform of NOS), ADMA inhibits NO production in a concentration-dependent manner (Leiper and Nandi, 2011).

6. Diabetes therapy:

First approaches to the treatment of T2DM include diet modification and oral hypoglycemic medications, while insulin is the drug of choice in T1DM (Chaudhury et al., 2017). At present there are six classes of oral hypoglycemic drugs:
a. Biguanides (e.g Metformin).
b. Sulfonylureas (e.g Glimepiride).
c. Meglitinides (e.g Rapaglinide).
d. Thiazolidinediones (e.g Pioglitazone).
e. Dipeptidyl peptidas IV inhibitors (e.g Vildagliptin).
f. α glucosidase inhibitors (e.g Acarbos).

6.1. Biguanides:

They work through reducing glucose production by the liver, reducing absorption of glucose, and enhancing uptake of glucose into skeletal muscles. (McCreight et al., 2016).

6.2. Sulfonylureas:

They work by binding to sulfonylurea receptors on β-cells of the pancreas and enhancing insulin secretion from the pancreas (Proks et al., 2018).

6.3. Meglitinides:

They are prandial insulin releasers that stimulate fast insulin emission. They improve early-stage prandial insulin reaction by expanding the affectability of β-cells to raised glucose levels, delivering a more noteworthy insulin discharge under hyperglycemic conditions (Bösenberg and van Zyl, 2008).

6.4. Thiazolidinedione:

They act by binding to the peroxisome proliferative insulin activated receptors (PRAR) enhancing insulin sensitizing effect at liver and muscle (Bays et al., 2004). Pioglitazone, a full agonist of peroxisome proliferator-activated receptor-gamma (PPARγ) is a widely used drug for the treatment of T2DM. It decreases plasma glucose as well as HbA1c values in patients with T2DM by improving insulin sensitivity (Daniels et al., 2016). Pioglitazone depends on the presence of insulin for its mechanism of action. It decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output (Bajpeyi et al., 2017). The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance (Tozzo et al., 2015). It also elevates levels of high-density lipoprotein cholesterol (HDL-C) and reduces triglyceride levels (Nissen et al., 2008).

6.5. Dipeptidyl peptidas IV inhibitors:

The Dipeptidyl peptidas 4 (DDP-4) inhibitors are another class of oral medications for treatment of T2DM. They repress the activity of DDP-4, the enzyme in charge of the peripheral degradation of glucagon like peptide-1 (GLP-1)

(Patal and Ghate, 2014). One example is vildagliptin that binds covalently to the catalytic site of DPP-4 and has been reported to be a potent, selective, reversible inhibitor (Berger et al., 2018). Inhibition of DPP-4 by vildagliptin prevents the degradation of endogenous GLP-1, thereby increasing plasma levels of their intact (active) form (Andersen et al., 2017).

DPP-4 inhibitors increase circulating levels of GLP-1 and glucose dependent insulinotropic polypeptide regulating glucose-dependent insulin secretion. In addition, GLP-1 suppresses glucagon secretion, delays gastric emptying and increases satiety (Mulvihill 2018).

6.6. Alpha Glucosidase inhibitors:

They competitively inhibit alpha glucosidase enzyme in the small intestine which delays the breakdown of complex carbohydrates and glucose, thus decreasing postprandial glucose levels (Ghani, 2015).

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Rec. Pharm. Biomed. Sci. 3(1), 4- 10,

2019

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