Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.47.007431

IL-6 and Type 2 Diabetes Mellitus Associations

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ARTICLE INFO

Received: October 26, 2022

Published: November 02, 2022

Citation: Lourdes Serrano García. IL-6 and Type 2 Diabetes Mellitus Associations. Biomed J Sci & Tech Res 47(1)-2022. BJSTR. MS.ID.007431.

ABSTRACT

It is necessary the understanding of the associations between IL-6 and Type 2 Diabetes Mellitus to mitigate risks in patients. This study aims to effectuate a brief literature recollection to demonstrate the latest insights regarding to the molecular role of IL-6 at the establishment of this pathology that flagellate humanity nowadays.

Keywords: Type 2 Diabetes Mellitus; IL-6; Insulin Resistance; Inflammation; Obesity; Biomarkers

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Brief Initial Preamble about Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is a group of metabolic syndromes characterized by hyperglycemia associated with the defect of insulin action. Globally, the number of people with diabetes mellitus (DM) has been increased by four folds in the past three decades because of urbanization and associated lifestyle change [1]. According to International Diabetes Federation (IDF), there are 463 million people with diabetes in 2019 in the world, and this number is expected to increase up to 700 million by 2045. About 1 in 11 adults worldwide now has diabetes mellitus, around 90% of them have T2DM, and 75% of DM patients are living in developing countries [1]. It has been expected that the fastest increase of patients living with T2DM will found to be in Sub Saharan Africa countries in the next two decades. In the United States, an estimated 29.1 million Americans or 9.3% of the population have diabetes and it is estimated that another 27.8% are undiagnosed [2]. A systematic review in Europe shows that odds are 6-fold higher among some ethnic groups compared with the European host populations [2].

The major threat of T2DM patients is associated with micro and macro vascular complications, which is considered as the major cause of morbidity and mortality. Recently, low level of chronic inflammation has been found to have great implication on the onset and progression of T2DM. It has been shown that high level of inflammatory and anti-inflammatory cytokines such as IL-6 and IL-10 are detected in plasma of patients with T2DM and thus, associated with its complication [1].

IL-6, Inflammation, Obesity and T2DM

Interlikun-6 (IL-6) is a pleiotropic cytokine mainly produced by T cells and macrophages, mapped to human chromosome 7p15p21. It regulates a wide range of immune activities, production of cell adhesion molecules, acute phase protein, and facilitates the release of other cytokines in response to inflammatory stimuli. In addition, it affects glucose homeostasis and metabolism directly or indirectly by acting on muscle cells, hepatocytes and pancreatic β cells. In fact, different ethnic populations have different levels of variability in single nucleotide polymorphisms (SNPs) [1]. Exercise acutely stimulates circulating IL-6 to levels that are 50-100 times higher than those observed during resting conditions. When increased to these levels, it is associated with heightened insulin sensitivity and nutrient availability [3]. IL-6 is a multifunctional cytokine and is secreted by many types of cells, mainly T cells, macrophages, endothelial cells, smooth muscle cells, adipocytes, and hepatocytes [4].

A series of new investigations demonstrated the four following molecular mechanisms of IL-6 involved in the inhibition of glucose-stimulated insulin: reduction of expression of glucose-transporter-4(GLUT-4); diminution of insulin receptor substrate 1(IRS-1); blockage of phosphoinositide 3-kinase (PI3K) and finally, the epigenetic alteration of glycogen synthesis [5]. It has been identified a novel adipo-entero-endocrine axis driven by IL-6 in the regulation of glucose-stimulated insulin release and glucose tolerance in obesity. Such an axis may sensitize pancreatic b-cells to glucose and thus, counteract adipose tissue-induced insulin resistance. Moreover, it may offset carbohydrate and/or leptin resistance of entero-endocrine cells, resulting in augmented glucagon-like peptide 1 (GLP-1) levels in obesity [6].

Evidence from animal models and observational epidemiology points to a role for chronic inflammation, in which IL-6 is a key player, in the pathophysiology of T2DM. In this sense, N. Bowker et al, investigated the possible etiologic role of IL-6 and IL-6 receptor (IL-6R) related pathways in T2DM risk. According to what was reported by them in a meta-analysis of a large-scale human prospective and genetic data it was evidenced that IL-6 mediated inflammation is implicated in the etiology of T2DM but suggested that the impact of this pathway on disease risk in the general population is likely to be small [7].

Insulin resistance has significantly been associated with obesity. This is possibly due to the release of bioactive metabolites such as free fatty acids, monocyte chemo-attractant protein-1 (MCP-1) and pro-inflammatory cytokines by the adipocytes. In fact, increased evidence has displayed that obesity constitutes a low-grade inflammatory state. Furthermore, metabolically unhealthy obesity leads to the overexpression of IL-6, resulting in bigger possibilities to be ill with T2DM and the development of obesity-related comorbidities. About one third of the total circulating IL-6 is released from the adipose tissue [8]. In the same line, another study evaluated the importance of IL- 6, TNF-α, and IL-10 levels and their associations with gene polymorphisms in T2DM disease and the obesity. Among the cytokine's levels measured, only IL-6 levels were higher in the T2DM group [9]. Also, higher levels of IL-6 have been associated with left ventricular systolic dysfunction and hypertrophy and can be used as early non-invasive markers for detection of them in patients with T2DM. This elevated concentrations of IL-6 in T2DM support their possible role or inflammatory process in diabetogenesis [10].

Increases in IL-6 during pregnancy have been linked to gestational insulin resistance, particularly due to placental production. Numerous investigations have determined a positive correlation between the concentration of IL-6, insulin sensitivity and plasma glucose levels and gestational/postpartum body fat percentages. The association of this cytokine with gestational diabetes mellitus (GDM) is described as follows:

a) the inflammation of macrophages in the pancreas and adipocytes that cause a raise in the production of IL-6;

b) other immunocytes also contribute to infiltration and

c) the destruction of pancreatic β-cells results in low insulin synthesis and apoptosis, which leads to high levels of blood glucose.

Women with GDM are more likely to develop T 2DM and cardiovascular disorders after gestation. In addition, children of women with GDM are also more likely to suffer from T2DM and obesity during their early days of

life [11].

IL-6 and Oxidative Stress

A substantial knowledge on the pathogenesis of DM by oxidative stress and inflammation is available. As is known these metabolic disorders harmfully affects the insulin activity through several interacting pathways and generating the reactive oxygen species (ROS) such as hydrogen peroxide and superoxide anions, which could deteriorate the islets β-cells. Berberine is a biologically active botanical that can combat oxidative stress and inflammation and thus ameliorate DM, especially T2DM. In diabetic animal studies, the modified levels of IL-6 and oxidative stress markers were observed after administering berberine. In renal, fat, hepatic, pancreatic and several other tissues, berberine-mediated suppression of oxidative stress and inflammation has been noted. In this way, berberine acts against oxidative stress and inflammation through a very complex mechanism consisting of several kinases and signaling pathways involving various factors, including NF-κB (nuclear factor-κB) and AMPK (AMP-activated protein kinases). Moreover, MAPKs (mitogen-activated protein kinases) and Nrf2 (nuclear factor erythroid-2 related factor 2) also have mechanistic involvement in oxidative stress and inflammation. Despite above advancements, the mechanistic aspects of the inhibitory role of berberine still necessitate additional molecular studies. These studies will be useful to examine the new prospects of natural moieties against DM [12].

Newest findings shed light on how heredity of T2DM confers increased susceptibility to oxidative stress and inflammation. This could provide early insights into the underlying mechanisms and future risk of first-degree relative with T2DM and its associated complications [13]. IL-6-driven reactive oxygen species (ROS) reduction is associated with an increase in the master antioxidant factor NRF2, which rapidly translocate to the mitochondria to decrease mitochondrial activity and stimulate mitophagy. IL-6 also initiates a robust transient decrease in cellular cAMP levels, likely contributing to the stimulation of mitophagy to mitigate ROS. These

findings suggest that coupling autophagy to antioxidant response in b-cells leads to stress adaptation that can reduce cellular apoptosis. Previous outcomes have implications for b-cell survival under diabetogenic conditions and present novel targets for therapeutic intervention [14].

IL-6 Gene Polymorphisms and T2DM

A fundamental understanding of IL-6 gene polymorphisms with its expression is critical in understanding of cellular mechanism of insulin resistance as well as T2DM intervention. That is the reason for B. Ayelign et al, carried out a study aimed to assess IL-6 (−174G/C) and IL-10 (−1082 A/G) gene polymorphism, and its association with T2DM in Northwest, Ethiopia [1]. They conducted a comparative cross-sectional study with participants T2DM and apparently healthy controls. Participants carrying the GG genotype of IL-6 (−174) were a high likelihood of having T2DM compared to those carrying the CC and AA genotypes. AA and AG genotypes of IL-10 (−1082) were at lower odd of developing T2DM compared to those carrying the GG genotype. In addition, individuals carrying the G allele of IL-6 (−174) have 2.82-fold odds of developing T2DM compared to individuals carrying the C allele. The study revealed that genetic polymorphisms of IL-6 (−174) GG genotype is the potential host genetic risk factors to T2DM, while IL-10 (−1082) AA genotype is negatively associated with T2DM. Therefore, they concluded that IL-6 (−174) and IL-10 (−1082) genetic variation may be considered as a biomarker for early screening and diagnosis of T2DM [1].

The IL-6 gene works via a receptor composed of two components, the IL-6 receptor (IL-6R) and gp130. Single nucleotide polymorphisms in the regulatory areas of IL-6R genes influence their expression levels and are linked to a higher risk of T2DM. Considering this evidence, current research carried out in Kirkuk city, studied the relation between IL-6 receptor gene (rs2229238, rs4845625) variants and the risk of suffer the disease in the population. In this case, results indicated the significant correlation between rs4845625 IL6R polymorphism with the ill. Researchers suggested the diagnostic utility of this polymorphism [15].

Final Considerations

A better understanding of IL-6 and T2DM molecular associations can produce approximated information about the presence of risk factors in the host. These studies would supply more details about the physiopathology mechanisms that predisposes to developed T2DM, favoring the finding of new medical strategies for the treatment or prevention of illness.

Acknowledgment

The author wishes to express her sincere gratitude to the Financial and Editorial offices of the Biomedical Journal of Scientific & Technical Research (BJSTR) for the complete financing of this manuscript.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.47.007431

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