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Impaired Glucose Tolerance, Obesity and Inflammatory Mediators

Ayfer Colak and Gulden Diniz

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1. Introduction

1.1. Plasma glucose levels and prediction of future type 2 diabetes

Prediabetes (PD) is a dysmetabolic state of glucose level between diabetes mellitus and normal glucose tolerance (NGT) which includes basically impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). All these conditions are becoming a considerable public health problem worldwide [1]. Measurement of glucose in plasma of fasting subjects is widely accepted as a diagnostic criterion for diabetes. Oral glucose tolerance test (OGTT) evaluates the efficiency of the body to metabolize glucose. For many years, fasting plasma glucose (FPG) test and OGTT have been used as “gold standards” for diagnosis of glucose metabolism disorders [2]. In addition hemoglobin A1C (HbA1C) measurement has also become the focus of considerable attention for diagnosis of diabetes. HbA1C is formed by the nonenzymatic attachment of glucose to the N-terminal valin of the beta chain of hemoglobin and its normal range is between 4% and 6% [2-4]. Because of the long life span of erythrocytes, HbA1C reflects long-term glycemic exposure, representing the average glucose concentration over the preceding 8-12 weeks [2].

The hyperglycemic diagnostic criteria defined by American Diabetes Association (ADA) is widely used for the evaluation of glucose metabolism disorders [1]. Fasting plasma glucose (FPG) is less than 100 mg/dl and 2-hour postprandial plasma glucose (2hPG) [75g glucose OGTT) level is less than 140 mg/dl in normal glucose tolerance (NGT). If the FPG level is between 100 and 125 mg/ dl, but the 2hPG level is less than 140 mg/dl, this situation is defined as IFG. In IGT, the FPG level is between 100 and 125 mg/ dl, the 2hPG level is between 140 and 200 mg/dl. If 2hPG level is more than 200 mg/dl, it is termed as diabetes according to the ADA's criteria [1,2]. Similarly, the glycated hemoglobin (HbA1c) level is found more than 6.5% in type 2 diabetes [1,2].

There are some fundamental problems in using IGT and IFG to characterize abnormal glucose metabolism. These problems can be classified as; the best means of identifying at-risk populations, whether they characterize the same degree of risk, and whether IFG and IGT represent manifestations of the same process or fundamentally different mechanisms [5].

The results of recent studies demonstrate that, although both IFG and IGT are characterized by β -cell dysfunction, the defects in insulin secretion in IFG and IGT are very distinct [6]. Subjects with IGT have impaired late-phase insulin secretion and increased insulin resistance (IR) in skeletal muscle. In contrast, subjects with IFG have impaired early-phase insulin secretion and increased IR in liver [6-8]. Similarly there are some discrepancies between the clinical features of IFG and IGT. Subjects with isolated IFG are more insulin resistant, and subjects with isolated IGT exhibit a more severe deficit in insulin secretion [8]. IFG and IGT have been associated with other features of insulin resistance, including dyslipidaemia, hypertension, abdominal obesity, microalbuminuria, endothelial dysfunction, and markers of inflammation and hypercoagulability [5]. Combinations of these components have also been associated with progression to type 2 diabetes mellitus (T2DM), cardiovascular disease and increased mortality [10].

Impaired β -cell function and increased IR in several peripheral tissues are both present in type 2 diabetes mellitus (T2DM) [9]. Currently it is understood that T2DM is also associated with obesity, hypertension and combined hyperlipidemia [10-12]. Populations at high risk for development of T2DM and atherosclerosis can be identified using markers of abnormal glucose metabolism, and recent studies have demonstrated that lifestyle modification and some pharmacological therapies have a favorable effect on reducing the risk for development of T2DM and increased mortality [5,10].

2. Relationship between obesity and glucose metabolism

Obesity is associated with an array of health problems including IR and T2DM, fatty liver disease, atherosclerosis, airway diseases, degenerative disorders, and various types of cancer [11,12]. IR is determined by impaired insulin sensitivity of its main target organs, such as adipose tissue, liver, and muscle. Insulin regulates glucose uptake and circulating free fatty acid (FFA) concentrations. Insulin decreases lipolysis in adipose tissue and inhibits gluconeogenesis in liver. Insulin resistance leads to increased circulating FFA concentrations and ectopic fat accumulation that impede insulin mediated glucose uptake in skeletal muscle and elevated glucose production in liver [13]. Finally, IR together with abnormalities in insulin secretion leads to T2DM [13].

Obesity is defined as abnormal or excessive fat accumulation and it is measured with body mass index (BMI) [10]. The conceptual transformation of adipose tissue from a passive organ to an active participant of homeostasis, has emerged relatively recently [12,14]. In 1994, adipose tissue was identified as the source of the hormone leptin, opening the door for a new area of research focused on adipocyte endocrinology [14]. Our understanding of the

pathogenesis of obesity and its metabolic disturbances have advanced significantly over the past decades [11-14]. The growing evidence on obesity and associated pathologies has led to understand the role of adipose tissue as an active potential participant in controlling the physiological and pathological processes [11-15]. For many years, adipose tissue was regarded merely as a heat insulator and a store of excess FFAs that could be released when needed [14]. To date, the adipose tissue is considered as an endocrine organ able to mediate biological effects on metabolism and inflammation, contributing to the maintenance of energy homeostasis and, probably, pathogenesis of obesity-related metabolic and inflammatory complications [10-16]. Nowadays, worldwide increased obesity prevalence has been accompanied by a parallel rise in the glucose metabolism disorders [11,17]. There is evidence that IR and T2DM is also related to a chronic low-grade inflammatory state [17]. Therefore weight loss is associated both with an improvement of the inflammatory profile and a decreased risk of glucose metabolism disorders [9-11,13-15].

3. Effects of inflammatory mediators on glucose metabolism

Many complex signaling pathways regulate chronic low-grade inflammation associated with both the metabolism and immune systems [18]. Pro-inflammatory cytokines are mediators of these pathways and they enter the circulation as a result of lipolysis [10]. Recent data indicates that macrophages in adipose tissue are a major source of them [10-18]. Especially in obesity, adipose tissue is characterized by an increased production and secretion of a wide range of pro-inflammatory molecules which have been recognized as an active participant in numerous immunologic processes [13-16]. Cytokines play the crucial roles in many physiological and pathological processes such as hematopoiesis, angiogenesis, inflammation, atherosclerosis, allergy and autoimmunity [18]. The increased concentrations of circulatory cytokines are commonly determined in cardiovascular disease (CVD), the metabolic syndrome and T2DM. These cytokines are produced by different cell types and are secreted into circulation where they regulate different tissues through their local, central or peripheral action [19].

It is demonstrated that increases of these cytokines effect through intracellular signaling pathways which involve the nuclear factor kappa B (NF- κ B) and c- Jun N-terminal kinase (JNK) systems [10]. Leptin also impairs glucose-stimulated insulin production of human β cells through activation of JNK. Moreover, hyperglycemia induces IL-1 β production by pancreatic β -cells, which putatively contributes to glucotoxicity in human pancreatic islets [13].

The name of adipokine is nowadays generally given to any protein or cytokine that can be synthesized and secreted by adipocytes [11]. Several studies have shown that adipokine production is altered in obesity [11]. The first link between obesity and elevation of Tumor Necrosis Factor- Alpha (TNF- α) came from a study almost 20 years ago and this finding led to the concept of inflammation in obesity and demonstrated that adipocytes express TNF- α [17-23]. TNF-alpha is a pro-inflammatory cytokine, overproduced in adipose tissue of several rodent models of obesity and has an important role in the pathogenesis of IR in these

species [21]. Interleukin-1 (IL-1) is one of the first identified cytokines and exert strong pro-inflammatory functions [10,20]. IL-1 α has been demonstrated to be involved in the pathogenesis of glucose metabolism disorders in mice [18]. IL-1 β is able to reduce IRS-1 expression at a transcriptional level through a mechanism that is ERK dependent and at a posttranscriptional level independent of ERK activation [18]. By targeting IRS-1, IL-1 β is capable of impairing insulin signaling and action and could thus participate, in the development of IR, in concert with other cytokines [18-21]. IL-6 is also among the first identified cytokines and acts on the liver to stimulate the production of a number of acute-phase proteins [10]. It is implicated as a pathogenetic marker of IR and CVD. IL-1 β together with IL-6 concentration is suggested as a predictor for T2DM in humans better than either cytokine alone [9,19,23-28].

Similarly interleukin 8 (IL-8) is a pro-inflammatory cytokine, overproduced in adipose tissue of several rodent models of obesity and has an important role in the pathogenesis of IR in these species [12,21,29,30]. However, IL-8 is basically evaluated as a cytokine with atherogenic properties and its actual involvement in glucose metabolism disorders remains controversial in humans [29-31]. Through its multiple actions, IL-8 might promote intimal thickening and atherosclerosis. This cytokine is also able to increase the instability of atherosclerotic plaque [29-31]. Elevated circulating IL-8 levels were also reported in type 1 and type 2 diabetic patients. It was hypothesized that this cytokine could be involved in the pathogenesis of diabetic macroangiopathy. Especially T2DM is associated with accelerated atherogenesis and it is recognized as an independent risk factor for CVD. Precise mechanisms linking those conditions are not fully understood [18,19]. In recent years, theories about the role of chronic low-grade inflammation in the pathogenesis of both glucose metabolism disorders and atherosclerosis have been developed. Some investigations reported that elevated plasma IL-8 concentrations are related to obesity and hyperlipidemia [12].

C-reactive protein (CRP) is an acute-phase reactant, the elevation of which is indicative of acute or chronic inflammation [32,33]. CRP is produced solely by the liver [19]. An etiologic role for chronic inflammation in the development of IR has been hypothesized [32,33]. It has been recognized that elevation of CRP concentrations is an independent predictive parameter of T2DM, which is also associated with various components of the metabolic syndrome such as obesity, IR, and dyslipidemia [20-24]. A number of previous study have reported that high sensitivity (hs) CRP is also related to circulating IL-6 levels [24,32,33] and IL-6 is a powerful inducer of CRP production in the liver [18]. In addition, abdominal obesity is associated with elevated plasma hs-CRP concentration and it has shown that elevation of hs-CRP concentration is an independent predictive parameter of T2DM [32,33] Actually CRP is a most sensitive marker of inflammation and it is associated with features of IR [15,16].

More recently, hormone leptin has also been linked to inflammation in human. Leptin, is the product of the *ob* gene. It is involved in the regulation of energy homeostasis and is almost exclusively expressed and produced by white adipose tissue (WAT) and more particularly

by differentiated mature adipocytes [11]. Circulating levels and adipose tissue mRNA expression of leptin are strongly associated with BMI and fat mass in obesity. Therefore, leptin appears as a real marker of adipose tissue mass in humans [11]. Leptin acts mainly at the level of the central nervous system to regulate food intake and energy expenditure. In addition, there is a relationship between leptin and the low-grade inflammatory state in obesity. It was suggested that leptin could exert peripheral biological effects as a function of its cytokine-like structure. It is similar to the IL-2 and receptors of leptin belong to the cytokine class I receptor family [14]. Some works have reported that there is an increased inflammatory response associated with the presence of hyperleptinemia without obesity. Leptin-deficient mice or humans display an altered immune status. The reduction in leptin levels could be responsible for fat-associated immunosuppression [11]. Leptin is able to control TNF- α production and activation by macrophages, however, the underlying mechanisms have not been clearly identified [11,14].

Adiponectin is an adipokine mainly produced by the adipose tissue and it is induced by activity of the nuclear peroxisome-proliferator-activated receptor (PPAR) γ . It exists both as a full-length protein as well as a proteolytic cleavage fragment, also known as globular adiponectin. Adiponectin circulates at high concentrations in human serum [5 to 10 $\mu\text{g/mL}$] and has a wide spectrum of biological activities. Adiponectin is unique that, unlike other adipokines, circulating concentrations are reduced with obesity. Serum levels of adiponectin are reduced in individuals with visceral obesity and states of IR. TNF- α suppresses the transcription of adiponectin in adipocytes, which might explain the lower adiponectin levels in serum in individuals who are obese. Weight loss induces adiponectin synthesis, as activation of PPAR γ by its ligands thiazolidinediones (TZDs), which are used in the treatment of T2DM [19,21]

Data from epidemiological studies indicate that circulating adiponectin is reduced in patients with CVD and T2DM. Importantly, low adiponectin concentrations are strongly correlated with IR. In addition, adiponectin reduces glucose production in the liver by directly inhibiting the gluconeogenic enzymes phosphoenolpyruvate carboxykinase and glucose 6 phosphate, improving glycemic control and insulin sensitivity. The reduction in adiponectin with obesity and diabetes most likely arises from increased adipose tissue macrophage infiltration resulting in inflammation. In contrast, high concentrations of adiponectin are related to higher insulin sensitivity and decreased risk for CVD. The proinflammatory cytokines TNF α and IL-6 reduce adiponectin expression. Conversely, adiponectin has an antiinflammatory effect, inhibiting activation of NF κ B by TNF α [19].

Resistin, also called FIZZ3 (found in inflammatory zones) or adipocyte secreted factor (ADSF) has been discovered in 2001 while looking for new molecular targets of TZDs in adipocytes [11,33]. It was shown that resistin levels were increased in obese rodents and resistin knock-out mice have lower fasting glycaemia, increased glucose tolerance and insulin sensitivity associated with a reduced liver glucose production [11]. Resistin is also expressed in the WAT, especially in the WAT of abdominal region and female gonadal adipose tissue [33]. Resistin has been linked with many facets of the metabolic syndrome,

principally, obesity, insulin resistance and hyperlipidemia. The effect of resistin upon insulin resistance is mediated through increased expression of suppressor of cytokine signaling-3 (SOCS-3), which is a known inhibitor of insulin signaling [33]. Mice injected with resistin showed insulin resistance. Resistin was thus found to attend endocrine functions that led to insulin resistance. Increased expression of resistin was found to be associated with dyslipidemia and non-alcoholic fatty liver disease (NAFLD) in a few medical ranks. In patients with NAFLD, serum resistin levels were higher than those in control cases. The presence of metabolic syndrome with elevated levels of plasma resistin is associated with increased cardiovascular risk [33-35].

Osteopontin (OPN) actually is a secreted matrix glycoprotein and pro-inflammatory cytokine playing an important role in cell-mediated immunity. Its ability to interact with integrin surface molecules through an Arg-Gly-Asp sequence and with the CD44 receptor has established this mediator as an important signaling molecule [34]. Indeed, tissue infiltration of macrophages as observed in obesity is dependent on the expression of OPN, which promotes monocyte chemotaxis and motility. Obese mice lacking OPN showed improved insulin sensitivity and decreased macrophage infiltration into adipose tissue. These experiments add OPN to a long list of pro-inflammatory pathways involved in the development of IR [21]

However, actual involvement of all these mediators in glucose metabolism disorders in humans remains controversial. It is suggested that these mediators may alter insulin sensitivity by triggering different key steps in the insulin signaling pathway and overproduction of them is associated with the glucose metabolism disorders [36-40]. Many mediators contribute to the pathogenesis of impaired glucose homeostasis and most of them are overproduced during obesity. It now appears that obesity is associated with a low-grade inflammation of adipose tissue, resulting from activation of innate immune system. Especially in obesity, adipose tissue is characterized by an increased production and secretion of a wide range of pro-inflammatory molecules including IL-1 β , IL-6, IL-8, TNF- α , CRP, leptin, resistin and so on [23-35]. Recent data indicate that macrophages in obese adipose tissue are major source of most mediators. Therefore weight loss is associated with a reduction in the macrophage infiltration of adipose tissue and an improvement of the inflammatory profile [39-45].

4. Conclusion

During the last decades, understanding of the biology of adipose tissue and especially its secretory functions, have dramatically improved. This development has completely modified the understanding of the pathogenesis of obesity, glucose metabolism disorders and inflammation. Several cytokines attracted considerable attention as potential effectors in the pathology and physiology of insulin resistance associated with type 2 diabetes mellitus (T2DM) and obesity. Recent studies have implicated a number of inflammatory mediators including cytokines and adipokines in the inflammatory responses that accompany the glucose metabolism disorders. Therefore measurement of serum levels of inflammatory

mediator is important in determining glucose regulation disorders and provides an improvement in therapeutic approaches to modulate the inflammatory responses and thereby alter disease progression. Elucidation of the mechanisms that link obesity with inflammation and glucose metabolism will contribute to the understanding of the physiopathology of obesity. As well as it will be probably provide the new strategies in the development of new therapeutic approaches.

Author details

Ayfer Colak

Izmir Tepecik Research Hospital, Biochemistry Department, Turkey

Gulden Diniz

Izmir Dr.Behcet Uz Children's Hospital, Pathology Department, Turkey

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