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IL-6 as a Surrogate Biomarker: The IL-6 Clinical Value for the Diagnosis of Insulin Resistance and Type 2 Diabetes

Rafik R[1*], Andrew RR[1], Mark RR[1] and Alaa I[2]

[1]Canada Metabolic Inflammation Diagnostics Inc. (CMID INC.) - Toronto, Canada

[2]Lake Mary, Pulmonary and critical care Medicine -Florida, USA

1. Abstract

Insulin Resistance is the leading cause of Type 2 diabetes mellitus (T2D). It occurs as a result of lipid disorders and increased levels of circulating free fatty acids (FFAs). FFAs accumulate within the insulin sensitive tissues such as muscle, liver and adipose tissues exacerbating different molecular mechanisms. Increased levels fatty acid has been documented to be strongly associated with insulin resistant states and obesity causing inflammation that eventually causes type 2-diabetes. Among the biomarkers that are accompanying low grade inflammation include IL-1β, IL-6 and TNF-α. The current review point out the importance of measuring the inflammatory biomarkers especially focusing on the conductance and measurement for IL-6 as a screening laboratory test and its diagnostic value in clinical practice.

2. Keywords: Clinical biochemistry; Molecular; Diagnostic; Endocrinology; Insulin resistance; Free Fatty Acids (FFAs) and type 2 Diabetes; Interlukin-6 (IL-6)

3. Introduction

In 2017, more than 693 million people were affected by diabetes worldwide and projections point to a sustained rise in its prevalence in the next decades [1]. It has been estimated that about 90% of all patients show insulin resistance before it progresses to T2D. Diabetes is one of the defining medical challenges worldwide in the 21st century. High caloric food overconsumption has led to unprecedented increases in obesity. Epidemiological studies showed that in United States, the combined prevalence of diabetes and prediabetes is over 50% [2]. Diabetes is a chronic disease affecting ~ 5% of the population in the industrialized nations as it is becoming a huge concern. In Canada about ~1.3 million (~ 4.9 5.8% of the total Canadian population) aged greater than or equal to 12 years have diabetes [3-5]. The predicted 10-year risk of developing diabetes for the Canadian population in 2011/2012 was 9.98%, corresponding to 2.16 million new cases [6]. In another part of the world, it is estimated that Diabetes Mellitus is a major emerging clinical and public problem that creates a global epidemic concern [7].

T2D is the most prevalent form of diabetes, it represents more than 90% of the cases [8]. The pathogenesis of type 2 diabetes is complex, involving progressive development of insulin resistance and a leading cause of the onset of hyperglycemia. This relative deficiency in insulin secretion that is the

***Corresponding author:** Dr. Rafik Ragheb, PhD, Clinical Scientist/Director at Canada Metabolic Inflammation Diagnostics Inc. (CMID Inc.), Toronto, Canada and Program Chair, Medical laboratory Department - Anderson College, Toronto, Canada, Tel: 1-6474013185, E-mail: rafik.ragheb@utoronto.ca

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review outlines and focuses on the specificity in determining the high risk individuals and patients through the measurements of novel diagnostic inflammatory biomarkers as IL-6 and TNF- α.

T2D patients [4-6] are characterized by increased hepatic glucose production (HGP), the inability of insulin to increase the uptake of glucose (peripheral insulin resistance) and suppress HGP (hepatic insulin resistance) and impairment of insulin secretion [9-11]. The release of FFAs in obese patients, is associated with insulin resistance as one of the key features of T2D, mainly [13-18] and secondary the release of inflammatory cytokines [18] from the expanded adipose tissue mass [13-19]. Studies conducted from our own laboratory and others (i.e., Drs. Defronzo and Reaven) laboratories have clearly shown that individuals with obesity [20-24], T2D [25] and obesity linked T2D [21-25] have elevated plasma FFA levels.

Not only are the plasma FFAs levels elevated in obesity; there is also an increased FFAs flux. The increased FFAs flux is mainly due to increased lipolysis from the expanded adipose tissue stores, to resist the insulin's antilipolytic action due to increased sensitivity to lipolytic hormones [26]. Many studies have shown that FFAs are an important causative link between obesity, insulin resistance linked low grade inflammation and type 2 diabetes mellitus [9,13,17-19]. The increase of plasma FFAs has been shown to impair insulin action for the development of type 2-diabetes as a final outcome [27].

3.1. What is IL-6?

Interleukin 6 (IL-6) is known as a B cell differentiation factor [28]. It is an expressed protein found in different cell types including immune cells, endothelial cells, skeletal and smooth muscle cells, thyroid cells, fibroblasts, mesangial cells, keratinocytes, microglial cells, astrocytes, certain tumor cells and islet β-cells [29]. It has been reported that IL-6 is involved in inflammatory processes as hematopoiesis, liver and neuronal regeneration [30-31]. The synthesis of IL-6 and its secretion are induced upon stimulation of Toll-like receptor (TLR) by lipopolysaccharide or upon stimulation of cells by interleukin 1 (IL-1) or tumor necrosis factor (TNF). Further, IL-6 is unique as it influences various cell types and has both pro- and anti-inflammatory effects [32]. Strong body of literatures have shown that dysregulation of IL-6 signaling has been implicated in the pathogenesis of several autoimmune and inflammatory diseases including T2D [29]. The focus of the current article is to illustrate IL-6 linked insulin resistance involvement in the development of T2D. Other reports have shown different actions orchestrated by IL-6 and insulin resistance development [33]. Here, we provide an overview of IL-6 as a surrogate biomarker to assist in the diagnosis as a tool for monitoring T2D treatment efficacy.

3.2. The link between IL-6 and Diabetes

Research studies in human populations have shown that pro-inflammatory cytokines, acute phase proteins and several indirect markers of inflammation to consider as predictors of T2D and glucose disorders in relation to FFA elevation [34]. Interestingly, interleukin-6 (IL-6) levels have been reported to be elevated in subjects with T2D [35] and correlates directly and indirectly with insulin resistance [36]. Cytokine receptor activation activates signaling pathways that directly or indirectly impair insulin action. Efforts are made to decipher the close mechanistic relation between cytokine receptor activation and impaired insulin signaling. It has been shown a pleiotropic effector of both cytokine signaling and ER stress. For example, JNK. JNK induces a complex pro-inflammatory transcriptional program that directly phosphorylates IRS1. In addition, JNK activity is increased in obese insulin-resistant liver and skeletal muscle [36]. A strong body of literature documented the inflammatory markers IL-6 and TNFα. They are playing a major role in the pathophysiology of metabolic syndrome and T2D development [37-41]. This highlights the importance

of measuring the inflammatory proteins in the clinical setting. Normal cellular fatty acid balance reflects on the equilibrium between processes that generate or deliver FFAs and processes that utilize it. FFAs are generated through the de-novo synthetic pathway and liberated when triglycerides and phospholipids are hydrolyzed by lipases [42]. High plasma FFAs and triglyceride levels cause an increased flux of FFAs into non-adipose tissues, contributing to intracellular lipid accumulation. Non-adipose tissues such as liver and skeletal muscle [43] have a limited capacity for lipid storage leading to cellular disturbances, the phenomenon that is known as lipotoxicity. Studies have documented that primary hyperlipidemia, serum triglycerides [44-45] and FFAs [45-46] are elevated in type 1 diabetes and T2D in obese individuals [47]. Insulin resistance is believed to be the primary cause of T2D. Studies have shown that elevated plasma levels of FFAs might increase insulin resistance in muscle and liver. So, lowering the levels of FFAs is considered a potential therapeutic target for T2D. Our previous research work was focused on elucidating the molecular mechanisms by which FFAs induce insulin resistance in two insulin sensitive tissues, muscle and liver. Specifically, we investigated in details the mechanisms and the effects of two FFAs the oleate, the monounsaturated FFA (18:1) and palmitate, the saturated FFA (16:00) as they are the most predominant two fatty acids in the circulation [48]. We studied their effect on glucose metabolism and insulin action in two insulin sensitive tissues the muscle and the liver and investigated on how they can induce the insulin resistance at the molecular level in vitro in two different experimental designs for insulin resistance.[49-51].

There is a strong correlation between insulin resistance and the increased lipid availability in the muscle tissue as manifested from the literature and our own data. Several mechanisms that affect insulin signal transduction have been identified [52]. In our laboratory we found that oleate does not affect the total protein level of PKB/Akt total but partially reduces the phosphorylation of PKB in oleate and dramatically in palmitate treated cells. On the other hand, our data suggest that the monounsaturated fatty acid; oleate muscle insulin resistance mainly via PKC. In the contrary, the saturated fatty acid, palmitate induces insulin resistance mechanistically through the PKB inhibition that is well documented through the ceramide formation and PP2A activation. In addition, the two FFAs are also to activate the NFκB and the stress kinases that contribute to the induction of serine 307 phosphorylation of IRS-1 and the development of insulin resistance in the C2C12 muscle model [49-51]. The serine 307 phosphorylation of IRS-1 is considered as a potential therapeutic target for the early intervention with the onset of the disease. Wang C, et al. have reported that palmitate specifically induced insulin resistance by PKC theta-dependent activation of mTOR/S6K pathway in C2C12 myotubes [53] However, more studies are still required to further elucidate the exact consequences of PKC activation following FFA(s) treatment with other species.

Furthermore, our second set of data is to represent the experimental work that was conducted in the fructose fed hamster as a liver model for diet induced insulin resistance. The data pointed the FFA - induced PKC activation and its impact on dyslipidemia seen in the liver model. The fructose fed hamster model as a model of diet induced model for studying insulin resistance in the liver, has revealed the importance of PKC activation for both insulin resistance and de novo lipogenesis. As reported Ragheb R, et al. have demonstrated that the antioxidant, Taurine was capable of reversing the oleate-induced insulin resistance in myocytes as manifested from the glucose uptake data [49]. Han P, et al. have also reported that Taurine prevented FFAs-induced hepatic insulin resistance in association with inhibiting JNK1 activation and improving insulin signalling in vivo [54]. Taurine is considered as a potential therapeutic

target in protecting from insulin resistance caused by elevated FFAs caused by different mechanisms of oxidative stress and inflammatory pathways. Further, we highlights the clinical importance for measuring the inflammatory biomarkers for diagnostic and monitoring the therapy efficacy [55]. Specifically, the inflammatory markersIL-1β, IL-6 and TNFα are among the key players that are manifesting a major role in the pathophysiology of insulin resistance syndrome and type 2 diabetes development.

3.3. The pathogenesis of T2D linked IL-6

Lipid excess and specifically visceral adiposity, leads to the development of chronic low-grade inflammation [56]. As discussed above low-grade inflammation among other factors, as elevated circulating levels of inflammatory cytokines such as IL-6 as contributing to the pathogenesis of the disease [56]. Systemic levels of IL-6 are elevated in T2D patients (Data not shown from our laboratory) and others [57]. This puts a lot of attention for considering high concentrations of circulating IL-6 is an independent predictor of T2D [58]. Other reports have shown that certain polymorphisms in IL-6 gene have a significant association with T2D [59]. The role of IL-6 is explained either through its effect on insulin action [60-61] or through its role to maintain the state of balance of the circulated glucose level [62-63].

3.4. The importance of using the cytokine biomarkers for the prevention and early diagnosis

Many reports have revealed that macrophages are central mediators of inflammation in T2D. These cells are classified into two distinct sub-types: the classically activated macrophages known as M1. The M1 cells are to secrete pro-inflammatory cytokines including IL-6. However, the activated macrophages termed M2 are to secrete anti-inflammatory cytokines [64]. The M1 macrophage infiltration into insulin sensitive tissues and pancreatic islets increases the development of a low grade inflammation [65]. Together adipose cells and mast cells exacerbate insulin resistance and promote glucose intolerance by producing IL-6 and interferon-γ [66]. In addition, it has been reported that neutrophils play an important part in the regulation of IL-6 signal-ling during inflammatory process. Neutrophils are among the first cells to accumulate at the sites of inflammation [32] . The above data, clearly highlights the importance of having the measurements of the inflammatory markers as a diagnostic tool to screen and predict those patients that their basal level is showing a higher levels of the inflammatory cytokines in the circulation.

3.5. The importance of Il-6 associated diabetic complications

As we discussed earlier, IL-6 plays a multi-functional role. IL-6 is involved in the improvement of insulin sensitivity, insulin secretion and glucose balance in our body through the suppression of inflammatory processes in obesity and/or T2D in addition to its deleterious effect. This pleiotropic behavior is closely related to whether IL-6 acts via two pathways, the classic or trans-signaling mechanism. The effect of IL-6 on pancreatic islets, which in turn leads to increased insulin secretion by β-cells and improvement in glycemia is mediated through classic signaling [67]. Moreover, given the presence of mbIL-6R in hepatocytes, the beneficial effect of IL-6 on insulin sensitivity, glucose tolerance and inflammatory processes in the liver is most likely mediated by classic rather than trans-signaling of IL-6. On the other hand, IL-6 trans-signaling is involved in the infiltration of macrophages into expanding adipose tissue, resulting in the establishment of a chronic inflammatory state and insulin resistance in obese individuals [68]. In addition, the lack of mbIL-6R on endothelial cells and vascular smooth muscle cells points to trans-signaling as the main mechanism involved in the deleterious effect of IL-6 on vasculature, which in turn could lead to atherosclerosis and various macrovascular complications in diabetics. IL-6 impairs the vasodilator effects of insulin in endothelial cells [69].

Additionally, IL-6, via trans-signaling, promotes the secretion of various chemokines and adhesion molecules in both endothelial and vascular smooth muscle cells, leading to the attraction of circulating leukocytes and consequent resolution of inflammatory reactions [70]. From these data it can be concluded that IL-6 trans-signaling through sIL-6R is mainly associated with pro-inflammatory and harmful actions of the cytokine in the pathogenesis of T2D. Conversely, classic signaling via mbIL-6R is mostly linked with anti-inflammatory and regenerative activities of IL-6 and probably has a beneficial effect on glucose metabolism.

Diabetic retinopathy (DR) is one of micro-complications emerged of diabetes that causes of blindness worldwide [71-73] It presents as a non-neovascular form or non-proliferative diabetic retinopathy (NPDR). With the aggravation of the disease, DR enters into the proliferative diabetic retinopathy (PDR) stage [74-75]. The mechanisms accounting for this progression include abnormal metabolic pathways, oxidative stress and subclinical inflammation [76-78]. The exact mechanism is still not fully understood. Meanwhile, some therapeutic approaches targeting inflammation, such as intravi-treal injections of corticosteroids or anti-vascular endothelial growth factor (anti-VEGF) agents, have been shown to be effective for slowing down the development of DR.11,12 The inflammation process likely plays an important role in the development of DR. Published reports has shown that the level of IL-6 is higher in DR patients than that in the control group, Future studies should focus on the mechanisms of IL-6 caused DR and whether the IL-6 inhibitor can serve for treatment of DR patients.

3.6. Clinical significance of IL-6

Many published studies and reports have suggested that IL-6 contributes to the onset and progression of chronic inflammation diseases such as T2D [79]. The pathological role of IL-6 is further supported by research work whereby IL-6 blockade (using anti-IL-6 or anti-IL-6R antibodies, or IL-6−/− mice) demonstrated preventive and suppressive effects on the development of various immune-related disorders. Important to note, the humanized anti-IL-6R antibody tocilizumab has been approved for the treatment of Rheumatoid Arthritis (RA) in more than 100 countries. Tocilizumab mode of action is through the inhibition of binding IL-6 to both mbIL-6R and sIL-6R that results in complete blockade of IL-6 signaling [80,81]. Tocilizumab and other anti-IL-6R antibodies have shown promising results in the treatment of other immune-related disorders [82]. Tocilizumab has been reported to improve insulin sensitivity and decrease glycated hemoglobin (HbA1c) levels in humans [83,84]. The current data support the notion that IL-6 signaling is a potential therapeutic target for the treatment of inflammatory-mediated disorders including T2D.

Tocilizumab and many other IL-6R anti-bodies block both classic and trans-signaling of IL-6. This global inhibition of IL-6 signaling pathways, disrupts both pro- and anti-inflammatory activities of the cytokine and may result in various physiological dysfunctions. Moreover, global IL-6 blockade has been associated with increased risk of bacterial infections, liver malfunction and elevation of cholesterol and weight gain [80,81]. These findings have led to the suggestion that specific inhibition of trans-signaling, as compared to the global inhibition of IL-6, may result in better therapeutic outcomes with fewer undesired side effects. The sgp130Fc protein is a recombinant version of sgp130, which consists of the extracellular portion of gp130 fused to the Fc region of a human immunoglobulin G1 (IgG1) anti-body. Sgp130Fc specifically blocks IL-6 trans-signaling, without affecting classical IL-6 signaling. Therefore, sgp130 inhibits the pro-inflammatory actions of IL-6, while leaving its anti-inflammatory and protective activities intact. Sgp130Fc has demonstrated robust efficacy in the treatment of many autoimmune and inflammatory diseases, with better side effect profile

than global blockers of IL-6 signaling [82-84]. Sgp130Fc selectively blocks the chemotactic signaling mediated by sIL-6R, therefore prevents high fed diets induced-macrophage infiltration into obese adipose tissue [85]. In addition, treatment with sgp130Fc significantly reduces atherosclerosis, decreases expression of endothelial adhesion molecules and intimal smooth muscle cell infiltration and thus reduces monocyte recruitment and the subsequent progression of atherosclerotic plaques [86]. Moreover, none of the adverse effects of complete IL-6 blockade was demonstrated with sgp130Fc [85-86].The above-mentioned data clearly highlight the therapeutic potential of selective inhibition of IL-6 trans-signaling for treatment of T2D and its vascular complications. Furthermore, given the specificity of sgp130Fc to inhibit trans-signaling, this protein can be used as a molecular tool to identify whether a certain effect of IL-6 (e.g. effect of IL-6 on glucose metabolism) is mediated via classic or trans-signaling [82]. This approach could be particularly useful to study the signaling pathways of IL-6 in mb-IL-6R expressing cells (e.g. hepatocytes and pancreatic islet cells), which can be stimulated by both the classic and trans-signaling pathways. Therefore, in addition to its therapeutic properties, the sgp130Fc protein allows us to discriminate between different IL-6 signaling pathways and thus advance our knowledge on the pathophysiological role of IL-6 signaling in the development of T2D in different tissues and contexts. This pleiotropic nature is at least in part dependent on the signaling pathway which is activated by IL-6. Increasing evidence from clinical and animal studies suggest that, in many inflammatory conditions, selective blockade of trans-signaling is therapeutically more effective and safer than global inhibition of IL-6, supporting the concept that pro-inflammatory and harmful activities of the cytokine are mainly mediated via trans-signaling. Of particular note, the sgp130Fc protein, which is a specific inhibitor of IL-6 trans-signaling, has been shown to completely prevent macrophage infiltration into obese adipose tissue and significantly reduce the extent of atherosclerosis. These results indicate that specific blockade of IL-6 trans-signaling with sgp130Fc could be considered as a potential therapeutic strategy for treatment of T2D and its macrovascular complications. Blockade of IL-6 trans-signaling, in combination with other anti-inflammatory treatments, such as anti-IL-1β agents have been reported. Anakinra, is a biologic drug acts as an antagonist for IL-1 activity that is used for the treatment of Rheumatoid Arthritis (RA) and other auto-immune disorders. Anakinra, effectively decreased glycated (HbA1C) in the circulation with the increase of C-peptide level after 13 weeks of treatment [87]. Furthermore, anakinra showed an improvement of the glucose disposition index during oral glucose tolerance test in obese patients without T2D [88]. Similar results were shown in patients with impaired glucose tolerance represented a significant improvements of insulin secretion after 4 weeks of anakinra treatment [89]. Other reports showed Gevokizumab that reduced HbA1C level as well in T2D patients with 0.03-0.1 mg/kg dosage (90-91). In addition, Canakinumab is a biologic treatment that inhibits IL-1β that improved the fasting glucose and insulin section after 4 weeks of treatment [92]. These evidences manifest the importance of the inflammatory cytokine measurements as a diagnostic tool to closely monitor and guide for the development of more efficacious strategies for early intervention and treatment of T2D.

4. Conclusion

This review has outlined the importance of IL-6 as a surrogate marker and its clinical value for diagnosing of insulin resistance, pre-diabetic and T2D patients. Our research work data showed a direct evidence for the desensitization of muscle cells following FFAs exposure but no observable changes in hepatic insulin signaling at the insulin receptor level. Furthermore, the data have demonstrated the importance of PKC

activation in two different models for FFAs induced insulin resistance, the muscle and liver that impact the inflammation process. In 1997, the WHO has recognized the importance of insulin resistance and its link to T2D, the growing problem that of great deal for the public health globally. Further insight to the field will be invaluable and of great impact on the treatment and the early intervention of the disease onset that is tightly linked to a number of other diseases such as lipid disorders, cardiovascular and autoimmune diseases that are accompanied with low grade inflammation. In addition, the early measurement of the inflammatory biomarkers, IL-6, IL-1β, TNFα and FFAs levels in plasma have a great clinical significance. As discussed IL-6 utilization as a diagnostic tool would benefit patients with insulin resistance syndrome through the implementation of an early intervention protocols for preventing and early diagnosing of pre-diabetic patients. Furthermore, the measurement of cytokines is considered a potential diagnostic tool to control the growing epidemic of diabetes and monitor closely the efficacy of different treatment regimens being followed.

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