



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

Rafik R., Mark R., Andrew R., Alaa I.

Canada Metabolic Inflammation Diagnostics Inc. – Toronto, Canada



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 of fatty acid have 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-1 β , IL-6 and TNF- α . The current poster points 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.

Introduction

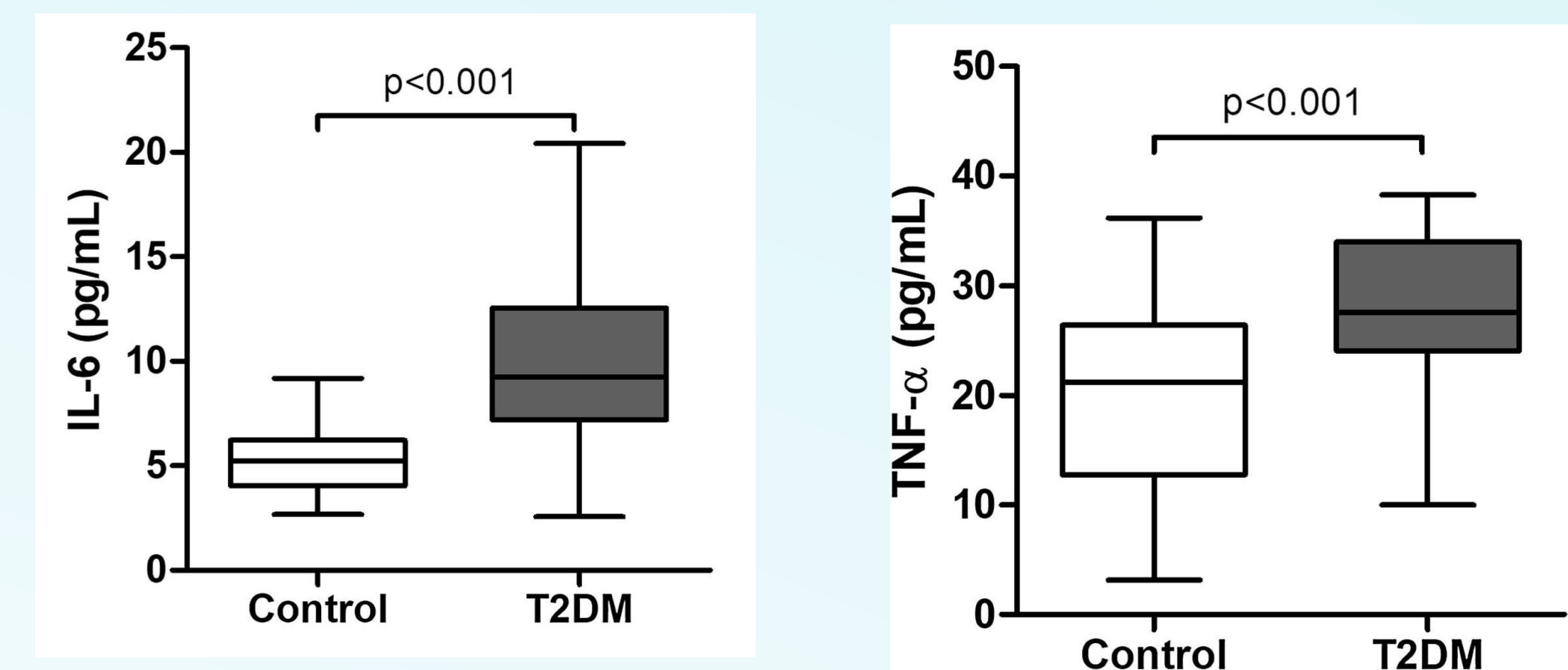
- 420 million people globally are affected by diabetes, with type 2 diabetes being the most prevalent representing more than 90% of cases (1).
- Pathogenesis of type 2 diabetes is complex, involving progressive development of insulin resistance and a relative deficiency in insulin secretion that is the leading cause of the onset of hyperglycemia.
- This poster 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 .

What is IL-6

- Interleukin 6 (IL-6), known as a B cell differentiation factor, 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. (2).
- IL-6 is unique as it influences various cell types and has both pro- and anti-inflammatory effects.
- Recent Studies have shown that dysregulation of IL-6 signaling has been implicated in the pathogenesis of several autoimmune and inflammatory diseases including T2D.

The Link Between IL-6 and Diabetes

Figure 1: Serum levels of IL-6 and TNF α in control and T2D study groups (3).



- interleukin-6 (IL-6) levels have been reported to be elevated in subjects with T2D and correlates directly and indirectly with insulin resistance (3).
- Cytokine receptor activation activates signaling pathways that directly or indirectly impair insulin action.
- 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 (4).
- Further, we highlights the clinical importance for measuring the inflammatory biomarkers for diagnostic and monitoring the therapy efficacy. Specifically, the inflammatory markers IL-1 β , IL-6 and TNF α are among the key players that are manifesting a major role in the pathophysiology of insulin resistance syndrome and type 2 diabetes development.

The Pathogenesis of T2D Linked IL-6

- Lipid excess and specifically visceral adiposity, leads to the development of chronic low-grade inflammation which results in elevated circulating levels of inflammatory cytokines such as IL-6 as contributing to the pathogenesis of the disease (5).
- This puts a lot of attention for considering high concentrations of circulating IL-6 is an independent predictor of T2D.

Importance of Using Cytokines in Early Diagnosis

- Adipose cells and mast cells exacerbate insulin resistance and promote glucose intolerance by producing IL-6 and interferon- γ (6).
- Neutrophils play an important part in the regulation of IL-6 signaling during inflammatory process as they are the first cells to accumulate at the site of inflammation.
- This 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.

Importance of IL-6 Linked Diabetic Complications

- 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.
- 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 (7).
- IL-6 trans- signaling is also 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 (8).
- 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 (9).
- 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.

Clinical Significance of IL-6

- 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 mIL-6R and sIL-6R that results in complete blockade of IL-6 signaling. Tocilizumab and other anti-IL-6R antibodies have shown promising results in the treatment of other immune-related disorders by improving insulin sensitivity and decrease glycated hemoglobin (HbA1c) levels in humans (10).

- Studies 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.
- Studies highlight the importance of 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.

Conclusion

- This poster 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.
- 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 several other diseases such as lipid disorders, cardiovascular and autoimmune diseases that are accompanied with low grade inflammation.
- The early measurement of the inflammatory biomarkers, IL-6, IL-1 β , TNF α and FFAs levels in plasma have a great clinical significance.
- 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.
- IL-6 is a valuable surrogate biomarker for T2D.

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