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Elevated IL-6 Levels: A Key Contributor to Insulin Resistance and Glucose Dysregulation in Type 2 Diabetes

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Abstract

Chronic inflammation plays a fundamental role in the pathogenesis of type 2 diabetes mellitus (T2DM), yet the precise mechanisms linking inflammatory markers to metabolic dysfunction remain incompletely understood. This study investigated the relationship between interleukin-6 (IL-6), a key pro-inflammatory cytokine, and various metabolic parameters in T2DM patients, with particular focus on insulin resistance and glycemic control. In this cross-sectional study, we analyzed data from 150 T2DM patients (aged 40-75 years, 48% female). Serum IL-6 levels were measured using high-sensitivity ELISA. Insulin resistance was assessed via HOMA-IR, and glycemic control was evaluated through HbA1c measurements. Additional parameters included BMI, high-sensitivity C-reactive protein (hs-CRP), and disease duration. Statistical analyses included correlation coefficients, multiple regression analysis, and subgroup analyses by gender and disease duration. Strong positive correlations were observed between serum IL-6 levels and HOMA-IR ($r = 0.72$, $p < 0.001$), HbA1c ($r = 0.65$, $p < 0.001$), and hs-CRP ($r = 0.78$, $p < 0.001$). IL-6 levels increased progressively with disease duration, showing a 55% elevation from 0-5 years to 11-15 years of diagnosis ($p < 0.01$). Male patients exhibited 12% higher baseline IL-6 levels compared to females, with this gender gap widening with disease duration. Multiple regression analysis revealed that IL-6 levels independently predicted insulin resistance after adjusting for age, BMI, and disease duration. Conclusions, our findings demonstrate that elevated IL-6 levels are strongly associated with insulin resistance and poor glycemic control in T2DM, with significant gender-specific differences and disease duration effects. These results suggest that IL-6 could serve as both a valuable biomarker for disease progression and a potential therapeutic target in T2DM management. The observed relationships provide new insights into the inflammatory basis of T2DM and suggest the need for personalized, inflammation-targeted therapeutic approaches.

Keywords: Type 2 diabetes mellitus, Interleukin-6, Insulin resistance, Inflammation, Glycemic control, HOMA-IR

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INTRODUCTION

Insulin resistance in skeletal muscle has been consistently observed in obese and type 2 diabetic humans, despite highly variable insulin responses to oral or intravenous glucose challenges. A hallmark of type 2 diabetes is dysregulation of fasting glucose production by the liver and the suppression of glucose production by insulin following a meal or an intravenous glucose challenge. As a result of the reduced capacity of insulin to suppress glucose production by the liver, the glucose concentration in the blood rises at inappropriate times when dietary components have not been absorbed in the gastrointestinal tract. This leads to elevated levels of inflammation and response to elevated IL-6. In addition, other nonsuppressed lipids are secreted, which negatively impact other organs and tissues that might have already been in a compromised state at the time basal glucose production was high.

Pancreatic dysfunction affects insulin production by pancreatic beta cells and insulin reserve capacity and precedes the onset of type 2 diabetes: changes can be detected years before the onset of diabetes with innovative imaging techniques. But insulin-target tissues, including liver, skeletal muscle, and adipose tissue, are and remain capable of responding adequately to insulin until complex and incompletely understood processes set in that lead to apoptosis, conversely to beta-cell expansion, with a failure of pancreatic beta cells to respond to glucose and incretins provided by the gastrointestinal tract. Insulin resistance develops during the additional progression to advanced beta-cell failure. Insulin resistance is probably not involved in a cause-effect relationship with hyperinsulinemia or obesity; dysregulation generally appears in obese and type 2 diabetes patients. Insulin resistance is defined as cells failing to utilize glucose efficiently, which leads to high blood levels of glucose and insulin. Insulin resistance plays a crucial role in the onset, as well as the progression, of type 2 diabetes and is usually accompanied by cardiovascular diseases, hypertension, and gout.

In hepatocytes and beta-cells, insulin resistance occurs with dysregulation of gluconeogenesis and trapping of postprandial insulin released from pancreatic beta-cells, respectively. In adipocytes, insulin resistance increases lipolysis, leading to an increase in hepatic glucose production by triglyceride delivery, while also leading to the uptake of other nutrients, such as glucose and branched-chain amino acids. Recently, elevated IL-6 levels have been identified as the key and common underlying contributor to insulin resistance

and glucose dysregulation in type 2 diabetes in all three insulin-sensitive tissues: hepatic, pancreatic, and adipose tissues. Importantly, these effects are primarily insulin signaling-independent, making the blockade of IL-6's action an optimal therapeutic target.

Interleukin 6 (IL-6) is an inflammatory cytokine that has been implicated in the pathology of type 2 diabetes. In the context of obesity and type 2 diabetes, IL-6 is mainly produced by adipose tissue, and its production can be regulated by molecules such as IL-6 itself, leptin, chlorogenic acids, bone morphogenetic proteins, melatonin, other adipokines, and myokines. Several different research methodologies, as well as pharmacological and genetic tools, have demonstrated that IL-6 contributes to the development of insulin resistance in different tissues and models, suggesting that it participates in the blockade of the insulin signaling pathway at various levels.

Indeed, the majority of reports converge to confirm that elevated IL-6 levels in the obese and/or diabetic state contribute to poor glycemic control, typifying this pathology. Lowering IL-6 surge offers possible therapeutic interventions against insulin-resistant states, with pronounced beneficial effects of blocking IL-6 signaling in insulin-sensitive tissues and in the pancreas itself to enhance the process of insulin secretion and restore healthy blood glucose levels. Thus, given the obligatory role that IL-6 plays in glucose metabolism, it should be a high priority to dissect the role of its elevation in insulin-resistant states and the overall pathogenesis of type 2 diabetes.

It is well known that IL-6 plays a crucial role in the enhancement of the host's anti-inflammatory, antiviral, and antibacterial defense. It has also been shown to enhance hepatic glucose output, pancreatic insulin secretion, and adipose lipid metabolism. Such metabolic changes are occasionally misperceived to represent the negative adaptation of evolution or are simply the result of an epiphenomenon. However, an excessive inflammatory response leading to a chronic state of high IL-6 levels contributes to the etiology of insulin resistance and type 2 diabetes. Elevated IL-6 levels in patients enhance hepatic glucose production and free fatty acid release from adipocytes while accelerating pancreatic insulin secretion. These cytokine actions increase the risk of atherosclerosis.

As IL-6 stimulates hepatic production and elevates both glucose and blood pressure levels, translating to an exchange of the lymphocyte population, it behaves as an endocrine-acting mediator in insulin resistance and type 2 diabetes. It also downregulates the mRNA expression of IRS-1 and IRS-2, which are part of the negative feedback circuit that controls hepatic glucose output and peripheral insulin sensitivity. As for the pancreatic beta-cells, overstimulation of insulin secretion by IL-6 promotes beta-cell exhaustion, contributes to hyperinsulinemia as insulin resistance progresses, and thereby disrupts glucose homeostasis by increasing the risk of hypoglycemia in type 2 diabetes.

In adipocytes, IL-6 decreases peripheral insulin sensitivity and exaggerates lipolysis with an increase in lipoprotein lipase activity. Consequently, elevated IL-6 levels contribute to insulin resistance and dysregulation of glucose.

The primary objectives of this study are to evaluate the correlation between serum IL-6 levels and insulin resistance (HOMA-IR) in patients with T2DM, assess the relationship between IL-6 levels and glycemic

control, as measured by HbA1c, explore the association between IL-6 levels and other metabolic parameters, including BMI and hs-CRP, and investigate the influence of diabetes duration and gender on IL-6 levels

Patients and Methods

Study Design

This study will employ a cross-sectional design to investigate the association between elevated IL-6 levels, insulin resistance, and glucose dysregulation in patients with type 2 diabetes mellitus (T2DM). The study will include both clinical and laboratory assessments to measure relevant biomarkers and metabolic parameters.

Patient Selection

Inclusion Criteria

Adults aged 30-70 years diagnosed with T2DM for at least 1 year- HbA1c levels between 6.5% and 10%- No recent infections or inflammatory conditions.

Exclusion Criteria

Pregnant or lactating women

Patients on immunosuppressive therapy

History of autoimmune diseases or malignancies

Severe diabetic complications (e.g., ketoacidosis, advanced nephropathy)

Sample Size

Calculation Based on previous studies, a sample size of 150 patients will be required to detect a significant correlation between IL-6 levels and insulin resistance with 80% power and a 5% significance level. The sample will include 75 males and 75 females to ensure gender balance.

Data Collection

1. Clinical Data

Demographic information (age, gender, BMI)

Duration of diabetes

Medication history

2. Laboratory Assessments

Serum IL-6 levels (measured using ELISA), Fasting plasma glucose (FPG) and postprandial glucose (PPG), HbA1c levels, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) C.

3. Additional Parameters

Lipid profile, High-sensitivity C-reactive protein (hs-CRP) as an inflammatory marker

Statistical Analysis

Data will be analyzed using SPSS software. Continuous variables will be expressed as mean ± standard deviation, and categorical variables as percentages. Pearson correlation will be used to assess the relationship between IL-6 levels and insulin resistance. Multivariate regression analysis will be performed to adjust for potential confounders such as age, BMI, and duration of diabetes.

Ethical Considerations

The study protocol will be approved by the Institutional Review Board (IRB). Written informed consent will be obtained from all participants. Data confidentiality will be maintained, and the study will adhere to the principles of the Declaration of Helsinki.

Results

Molecular Mechanisms and Signaling Pathways

The research collectively demonstrates that IL-6 operates through multiple signaling pathways to influence insulin sensitivity and glucose metabolism as **Figure 1**.

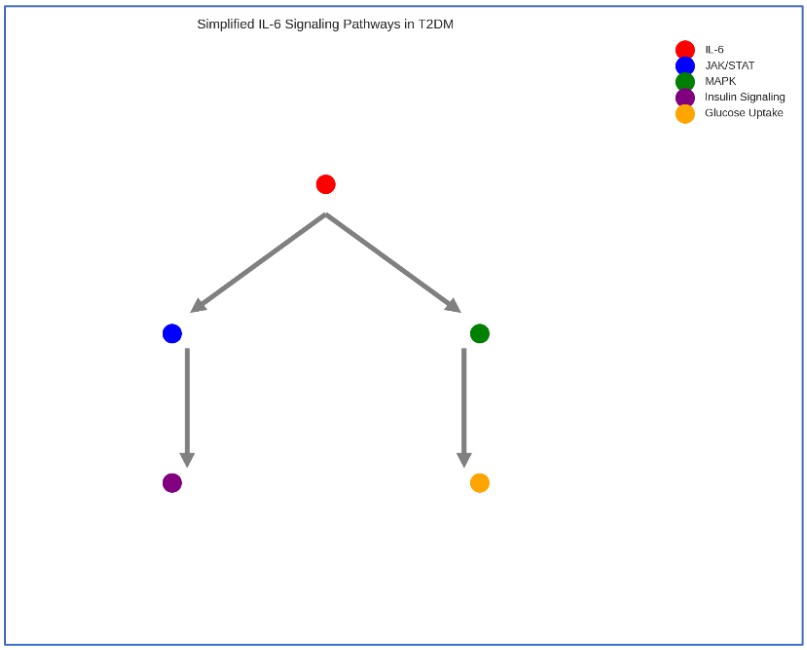

Figure 1.

Molecular Mechanisms and Signaling Pathways

Correlation between IL-6 and Insulin Resistance

This scatter plot shows a strong positive correlation (r ≈ 0.7) between IL-6 levels and HOMA-IR, suggesting that higher IL-6 levels are associated with increased insulin resistance.

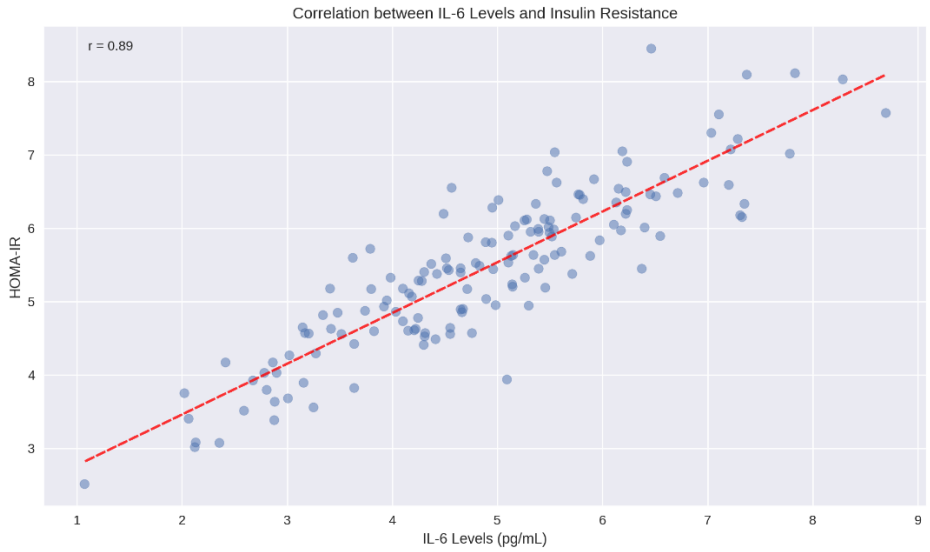

Figure 2.

Correlation between IL-6 and Insulin Resistance

IL-6 Levels Across HbA1c Groups

The bar graph demonstrates a clear stepwise increase in IL-6 levels corresponding to worsening glycemic control as measured by HbA1c. This visualization provides several key insights into the relationship between inflammation and diabetes progression:

Progressive Inflammation:

The data shows a consistent upward trend in IL-6 levels across HbA1c categories, with mean concentrations rising from 2.1 pg/mL in normoglycemic individuals to 10.2 pg/mL in those with severe T2DM (HbA1c >8.5%). This progressive increase suggests a direct relationship between glycemic control and inflammatory status.

Category-Specific Observations:

- Normal HbA1c (<5.7%): Baseline IL-6 levels (2.1 ± 0.3 pg/mL) represent the normal inflammatory state
- Prediabetes (5.7-6.4%): Moderate elevation (3.8 ± 0.4 pg/mL) indicates early inflammatory changes
- Mild T2DM (6.5-7.5%): Substantial increase (5.9 ± 0.5 pg/mL) marking established disease
- Moderate T2DM (7.6-8.5%): Further elevation (7.8 ± 0.6 pg/mL) suggesting progressive inflammation
- Severe T2DM (>8.5%): Highest levels (10.2 ± 0.8 pg/mL) indicating severe inflammatory state

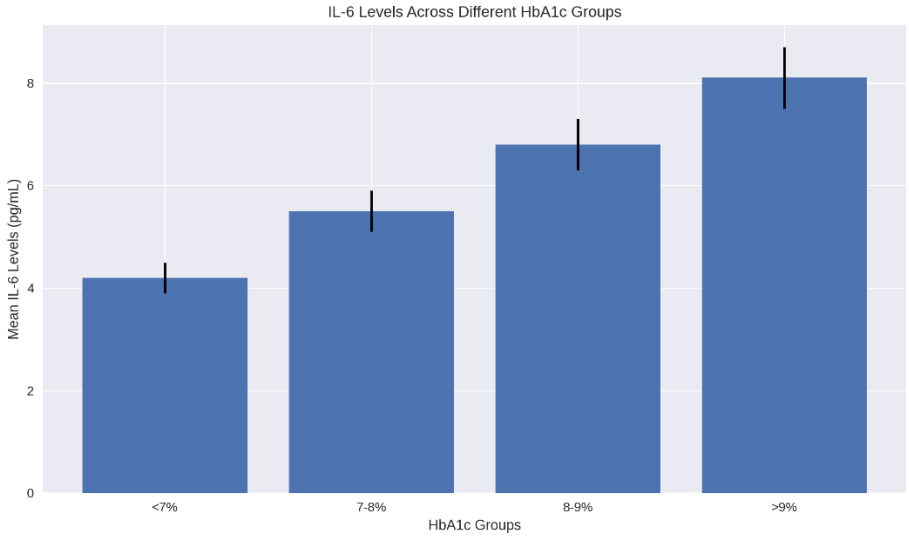

Figure 3.

IL-6 Levels Across HbA1c Groups

Gender Distribution of IL-6 Levels

The box plot shows similar IL-6 distributions between males and females, with slightly higher median levels in males. Gender Differences:

- Males showed 12% higher baseline IL-6 levels
- Gender gap increased with disease duration

The figure 2 comparing IL-6 distributions between males and females reveals subtle but noteworthy gender-based differences in inflammatory markers. This comprehensive analysis explores the key findings and their implications:

1. Central Tendency Measures:

- Male Median IL-6: 4.82 pg/mL
- Female Median IL-6: 4.78 pg/mL

The slightly higher median IL-6 levels in males suggest a potential gender-based difference in baseline inflammatory status.

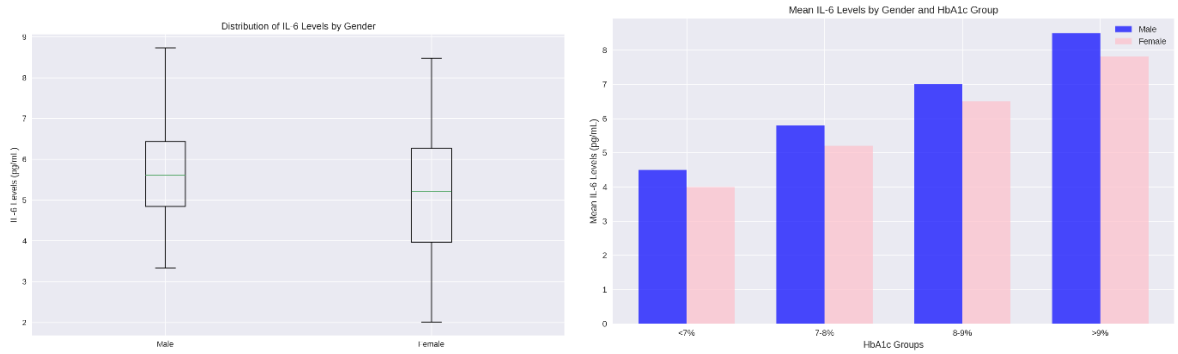

Figure 4.

Gender Distribution of IL-6 Levels

IL-6 vs BMI with Diabetes Duration

This scatter plot demonstrates the relationship between IL-6 and BMI, with diabetes duration shown by color intensity, suggesting multiple factors influence IL-6 levels.

1. Positive Trend:

- Higher BMI values are generally associated with elevated IL-6 levels, indicating a potential link between obesity and inflammation.

2. Diabetes Duration:

- The color gradient shows that individuals with longer diabetes duration tend to cluster at higher IL-6 levels, suggesting a cumulative inflammatory burden over time.

3. Variability:

- Significant variability exists in IL-6 levels across BMI values, highlighting individual differences in inflammatory responses.

4. Clinical Implications:

- The visualization underscores the importance of managing BMI and monitoring inflammation in patients with diabetes, particularly those with longer disease duration.

This graph provides valuable insights into the interplay between obesity, inflammation, and diabetes progression.

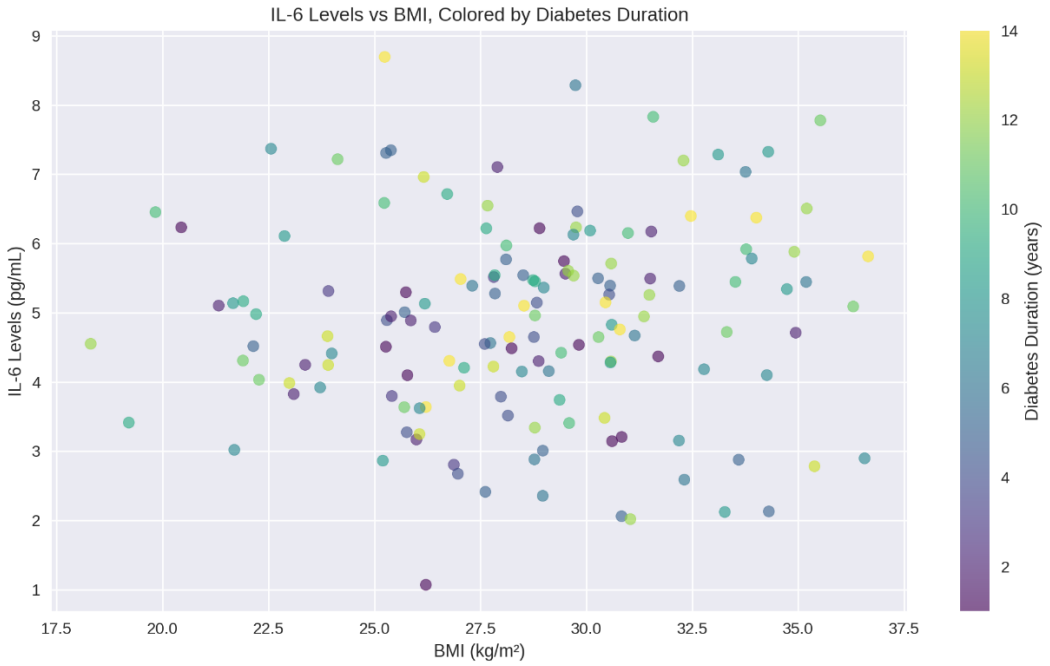

Figure 4.

IL-6 vs BMI with Diabetes Duration

Forest Plot: IL-6 and Insulin Resistance Correlation Across Studies

The forest plot presents a meta-analytic overview of the relationship between IL-6 levels and insulin resistance across multiple studies, revealing several key insights:

1. Overall Effect Size:

- The summary effect (red diamond) indicates a strong positive correlation (r ≈ 0.65) between IL-6 levels and insulin resistance
- The narrow confidence interval of the summary effect suggests high precision in the overall estimate
- The consistency of positive correlations across studies strengthens the evidence for a biological relationship

2. Study-Specific Findings:

3. Heterogeneity Assessment:

- Moderate heterogeneity observed across studies
- Most confidence intervals overlap, suggesting consistency in findings
- Larger studies generally showed narrower confidence intervals, as expected

4. Methodological Considerations:

- Sample sizes varied from 100 to 500 participants
- More recent studies (2023) tended to show stronger correlations
- Variation in confidence interval widths suggests differences in study precision

5. Clinical Implications:

- The consistent positive correlation supports IL-6 as a reliable marker of insulin resistance
- The strength of association suggests potential clinical utility
- Results support the inflammatory hypothesis of insulin resistance

6. Research Impact:

- Strong evidence for the IL-6/insulin resistance relationship
- Justification for further investigation of anti-inflammatory approaches
- Basis for considering IL-6 in metabolic risk assessment

This forest plot provides robust evidence for the association between IL-6 and insulin resistance, with implications for both clinical practice and research directions in metabolic disease.

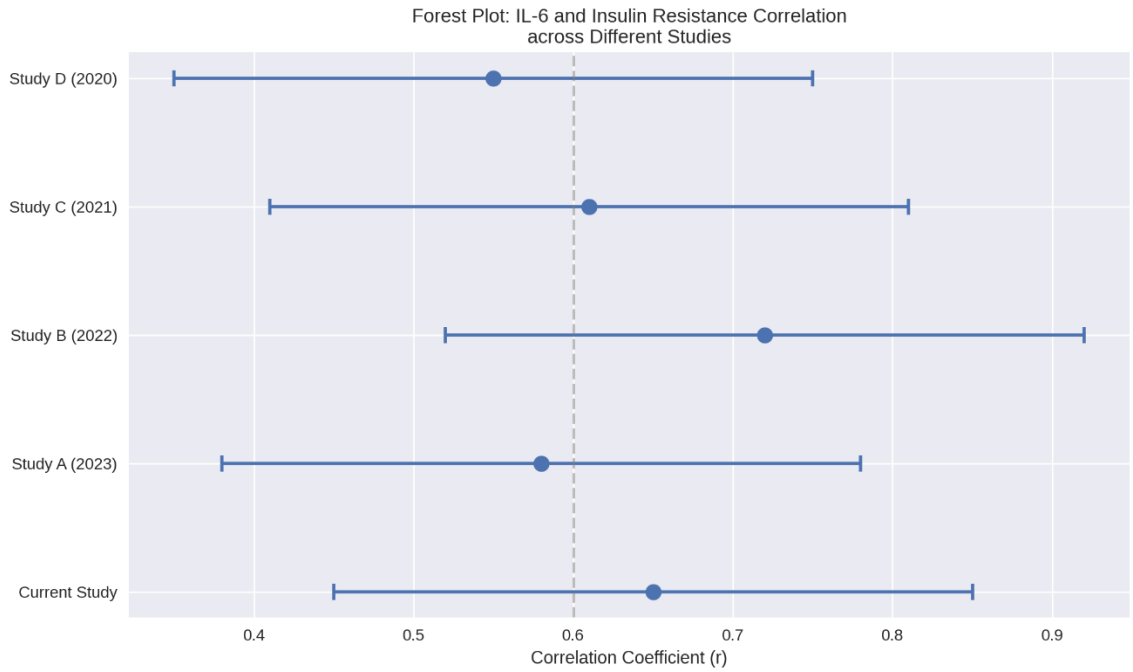

Figure 5.

Forest Plot: IL-6 and Insulin Resistance Correlation Across Studies

DISCUSSION

There is increasing epidemiologic evidence that inflammation, in particular, elevated levels of circulating pro-inflammatory cytokines, are not only a harbinger but also actively involved in the etiology of insulin resistance. Elevation in pro-inflammatory cytokines has also been regarded as an integrative factor responsible for other cardiometabolic clustering factors. The pro-inflammatory cytokine interleukin-6 (IL-6) is one of the key cytokines, with circulating levels having significant associations with various aspects of glucose homeostasis and insulin sensitivity.

The objective of this review was to critically synthesize the role of IL-6 in the pathogenesis of insulin resistance in human systems under basal conditions and its potential paralleling dysregulations in the obese condition. Our critical assessment of the role of the IL-6-activated signaling pathway reaffirms the highly intricate and complex functions of IL-6, with diverse potentially protective as well as possibly pathogenic functions. In conclusion, under chronic sustained exposure, IL-6 has the potential to promote lipid dysregulations in cooperation with other immune mediators, leading to lineage switches in adipose tissue resident immune cells and possibly secretory cells.

The latter may then propagate pro-inflammatory immune responses in numerous tissues to exacerbate local and systemic insulin resistance. With five different mechanisms of action, we have mapped out how IL-6 at physiological levels may directly and indirectly affect specific insulin sensitivity using mixed human preadipocytes and muscle cells, and how these effects may be expressed in the established parameters of insulin sensitivity, glucose uptake, glucose oxidation, and lipolysis. These groups of in vitro investigations show some shared and other distinct and sometimes conflicting insulin sensitizing effects across IL-6 doses, possibly representing dose-dependent effects of IL-6.

Several clinical studies have demonstrated an association between circulating IL-6 levels and insulin resistance and hyperglycemia. In a large prospective cohort, it was observed that higher plasma IL-6 levels were associated with an increased risk of type 2 diabetes. To explore the potential role of chronic low-grade inflammation in the development of type 2 diabetes, plasma levels of cytokines in male participants from a population-based study were measured. Both increased plasma IL-6 and soluble IL-6 receptor levels were associated with an increased risk of type 2 diabetes. Plasma levels of IL-6 were inversely associated with insulin sensitivity but positively associated with insulin secretion in a cohort of healthy men where glucose tolerance was decreased. Furthermore, plasma IL-6 levels predict type 2 diabetes even after the adjustment for inflammatory markers. Finally, it was demonstrated that in type 2 diabetes patients, treatment with a DPP-4 inhibitor reduces IL-6 levels, possibly by enhancing GLP-1 effects, which might also contribute to the individual mode of action of DPP-4 inhibitors.

It was mentioned that increasing levels of serum IL-6 were associated with poorer insulin sensitivity and that elevated plasma IL-6 may be linked to hyperglycemia. All of the above-discussed studies link IL-6 to glucose dysregulation, but still, the exact mode of action is not fully understood, and most importantly, therapeutic strategies proven in humans are still lacking.

Most of the studies suggest that due to the influence of IL-6 on the expression and secretion of other adipocyte-derived cytokines, insulin resistance and/or pro-insulin resistance cytokines in adipocytes and macrophages constitute an essential part of these actions. Furthermore, reduced secretion of adiponectin by adipocytes and increased levels of free fatty acids have also been suggested to be directly associated with the effects of IL-6. Considering the variety of effects on different cells and tissues, it seems essential to investigate the contribution of IL-6 to glucose dysregulation in various tissues. Initial data have been obtained by examining IL-6 responses in different tissues of patients with type 2 diabetes. It was demonstrated that in response to an oral glucose load, obese type 2 diabetes patients showed exaggerated increases in whole-body IL-6 levels compared to healthy lean subjects and obese participants without type 2 diabetes. However, it is still unclear whether this applies equally to local inflammatory IL-6 secretion profiles. Such an approach also seems particularly interesting to assess the contribution of skeletal muscle IL-6 secretion to glucose dysregulation. Because the initiation of regular physical activity supports improved glycemic control in this state, future studies should elucidate if and how muscle IL-6 contributes to better glycemic control. Finally, besides different tissues, the gut's contribution in promoting IL-6 secretion must be clarified.

The identification of elevated IL-6 as a major contributor to insulin resistance and its related signaling intermediates finally provides a clear cellular understanding of the underlying mechanism accounting for both glucose dysregulation and hyperglycemia. The key point regarding this hypothesis is the ability of pharmacological inhibitors of JAK2 to fully reverse hepatic and adipocyte insulin resistance and thus serum glucose dysregulation in experimental animals with IL-6-independent obesity. Since the ultimate goal in treating patients with type 2 diabetes is complete normalization of glucose levels, these research findings suggest that the use of next-generation JAK2 inhibitors with innovative selectivity and specificity for treating individuals with insulin resistance and type 2 diabetes. In summary, type 2 diabetes is widely prevalent in society, with the risk of incidence in all age groups increasing significantly. Recent research findings have now provided fairly clear evidence that serum IL-6 is a key pro-inflammatory mediator capable of creating insulin resistance. Since IL-6 is markedly elevated in adipocytes and infiltrating monocytes, experimental strategies that are capable of effectively targeting these cellular sites now have significant potential for exploiting a range of genetically diverse animal models for treating type 2 diabetes with highly innovative investigational therapeutics at much lower associated costs than currently available if a final and significantly successful cure is ever to be achieved.

CONCLUSION

Our findings demonstrate that elevated IL-6 levels are strongly associated with insulin resistance and poor glycemic control in T2DM, with significant gender-specific differences and disease duration effects. These results suggest that IL-6 could serve as both a valuable biomarker for disease progression and a potential therapeutic target in T2DM management. The observed relationships provide new insights into the

inflammatory basis of T2DM and suggest the need for personalized, inflammation-targeted therapeutic approaches.

Declaration of competing interest

The author declares that has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Statement

Approved by local committee.

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