

The Role of IL-6 level with IR in type II diabetes mellitus: A brief study

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Abstract:

OBJECTIVE: IL-6 (Interleukin-6) is a key pro-inflammatory cytokine recognized for its role in the development and progression of insulin resistance (IR) in Type 2 Diabetes Mellitus (T2DM) in the body. Elevated IL-6. IL-6 interferes with insulin signaling by promoting hepatic gluconeogenesis, altering adipocyte function, and activating inflammatory pathways such as JAK/STAT and NF- κ B. This study is mainly focusing on the possible role of proinflammatory markers interleukin-6 along with insulin resistance in type -2 diabetic subjects.

MATERIAL AND METHODS: The study was conducted in 200 human subjects out of whom 100 were normal healthy individuals (group I) and 100 were type 2 diabetic subjects with complications (group II).

RESULTS; Showing the comparative changes of immunological and insulin resistance (HOMA-IR) parameters in group I healthy male and female subjects and group II diabetic male and female subjects. IL-6,(HOMA-IR) were highly significant at ($P < 0.001$).

CONCLUSION: Outcome of this study showed that IL-6 plays an important role in insulin resistance. The adipokines produced by adipocytes or by adipose tissue infiltrating macrophages, are able to induce a low grade inflammation state that could play a central role in obesity and type-2 diabetes related insulin resistance.

Keywords; IL-6, Diabetes mellitus, insulin resistance, Proinflammatory cytokines

Introduction:

Diabetes mellitus, a common metabolic disorder resulting from defect in insulin secretion, increases in insulin resistance (IR) in conjugation with the inability of pancreatic beta cells to secrete sufficient insulin to compensate(1) that is persistent hyperglycemia. The inhibition of signaling PI3K–Akt and IRS-1/IRS-2 downstream signaling of the insulin receptor. It is a primary mechanism through which inflammatory signaling leads to insulin resistance. Insulin resistance and insulin deficiency give rise to a hyperglycemic state that is a major risk factor for the development of diabetic and its complications (2). A close connection between insulin resistance and classic inflammatory signalling pathways has also recently been

identified (3). Recently it has become clear that inflammatory signalling pathways can also become activated by metabolic stresses originating from inside the cell as well as by extracellular signalling molecules. It has been demonstrated that obesity overloads the functional capacity of the ER and that this ER stress leads to the activation of inflammatory signalling pathways and thus contributes to insulin resistance (4,5,6). Insulin resistance is the driving force of hyperglycemia, impaired glucose tolerance obesity that leads to type- 2 diabetes (7,26). Several studies have demonstrated elevated levels IL-6 among individuals with insulin resistance (8,9). Proinflammatory cytokines, IL-6 is one of several proinflammatory cytokines that have been associated with insulin resistance and type-2 diabetes (10). Stimulation of IL-6 and resistance of insulin by impairing the phosphorylation of insulin receptor and insulin receptor substrate-1 by inducing the expression of SOCS-3, a potential inhibitor of insulin signaling. IL-6 is produced by adipose tissue, immune cells, skeletal muscle, and endothelial cells. Impairments of insulin signaling pathway, it does not allow the entry of glucose into the muscles and adipose tissues by GLUT-4 transporter. This causes elevated IL-6 levels which are commonly observed in T2DM and may serve as an important biomarker for metabolic inflammation (25). Understanding the relationship between IL-6 levels and IR is crucial for identifying at-risk populations, improving early diagnostic approaches, and developing targeted anti-inflammatory treatment strategies. . This study aims to explore the biological significance of IL-6 and evaluate its association with insulin resistance in T2DM.

Material and methods:

The study was conducted in Department of Biochemistry L.L.R.M Medical College Meerut UP, India. with 200 human subjects out of whom 100 were normal healthy individuals (group I) and 100 were type 2 diabetic subjects with complications (group II) like retinopathy, neuropathy, muscular trophy, obesity etc. in both equal male as well as female. Age matched healthy control subjects were selected from known families. The written consent of patients was also taken before starting the study. A record of clinical history and previous investigations of patients disorders were compiled in a Performa (Performa enclosed). A Performa containing the relevant findings of **clinical data** like- Age, gender, BMI, waist circumference, duration and type of diabetes **biochemical parameters** like fasting plasma glucose, fasting insulin, HbA1c, Lipid profile, serum IL-6 levels (measured using ELISA) and **physiological investigations** were recorded on preset questionnaires as base line records. All ethical measures were taken prior and during the study.

5 ml of blood sample was withdrawn from the antecubital vein following overnight fasting. The blood sample was collected in plain, fluoride and EDTA vacutainers. The blood sample was analyzed for biochemical and immunological.

Investigations.

Immunological markers interleukin-6 and tumour necrosis factor-were estimated by a highly sensitive sandwich-enzyme linked immunosorbent assay (ELISA) method in a commercially available kit (Immunotech, Beckman Coulter, France). The assay was performed exactly as recommended by the manufacturer. Data analysis was performed by using SPSS software version 16.0 by one way ANOVA utilizing the Dunnett T3 test.

Result and observation:

The comparative analysis of immunological IL-6 and insulin resistance parameters revealed a highly significant difference between healthy and diabetic subjects of both genders. In male subjects, Group I

(healthy, n = 52) showed a mean HOMA-IR value of 1.10 ± 0.42 , while Group II (diabetic, n = 70) exhibited a markedly elevated mean HOMA-IR of 4.80 ± 1.35 , indicating severe insulin resistance. Similarly, serum IL-6 levels were significantly higher in diabetic males (28.50 ± 8.00 pg/ml) compared to healthy males (8.70 ± 1.45 pg/ml). This difference was found to be highly significant at $P < 0.001$, as illustrated in Graph 1 and Graph 2.

In female subjects, a similar trend was observed. Healthy females (Group I, n = 48) exhibited a mean HOMA-IR of 2.12 ± 0.74 , while diabetic females (Group II, n = 30) showed a significantly increased mean HOMA-IR of 4.79 ± 1.39 . Correspondingly, IL-6 levels were significantly elevated in diabetic females (24.81 ± 6.65 pg/ml) compared to healthy females (8.96 ± 1.59 pg/ml). The differences in both HOMA-IR and IL-6 levels between Group I and Group II females were also highly significant ($P < 0.001$). These findings demonstrate a strong association between elevated IL-6 levels and increased insulin resistance in both male and female type 2 diabetic subjects.

Table 1 and Graph 1 Showing the comparative changes of immunological and insulin resistance (HOMA-IR) parameters in group I healthy male subjects (N=52) and group II (N=70) diabetic male subjects. IL-6, (HOMA-IR) were highly significant at ($P < 0.001$) in group II subjects.

Table1: Showing comparative changes of biochemical and immunological parameters in group I and group II male subjects

Group	Parameters	Min	Max	Mean \pm SD
Group I Male subject , n= 52	Home -IR	0.08	2.76	1.10 ± 0.42
	IL-6 (pg/ml)	5.20	12.80	8.70 ± 1.45
Group II male subject , n= 70	Home -IR	2.20	8.60	4.80 ± 1.35
	IL-6 (pg/ml)	11.80	49.20	28.50 ± 8.00

Highly significant difference between Group I and Group II at $P < 0.001$ for both HOMA-IR and IL-6 levels.

Graph 1: showing the comparative change in HOMA-IR in Group I and Group II male subjects.

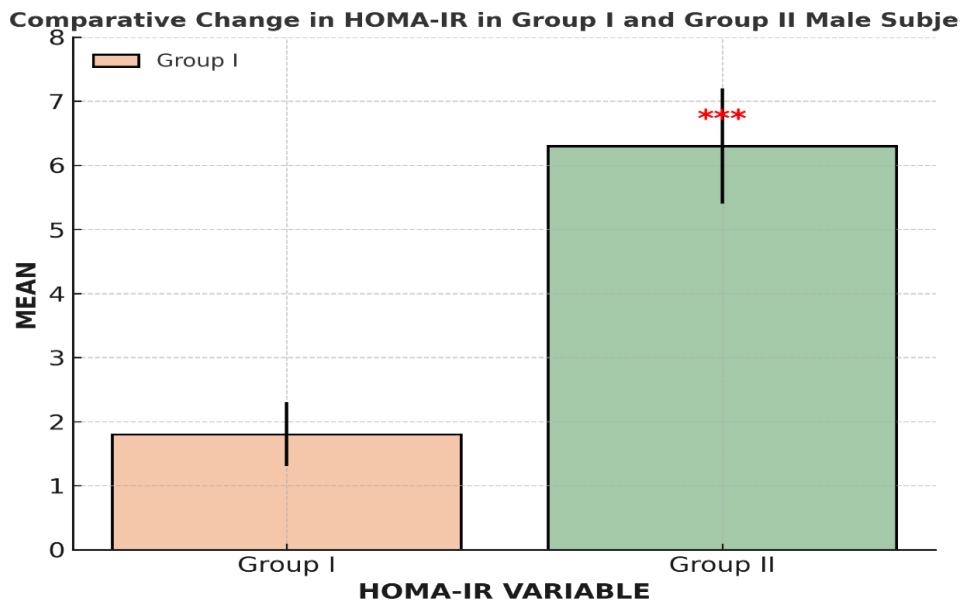


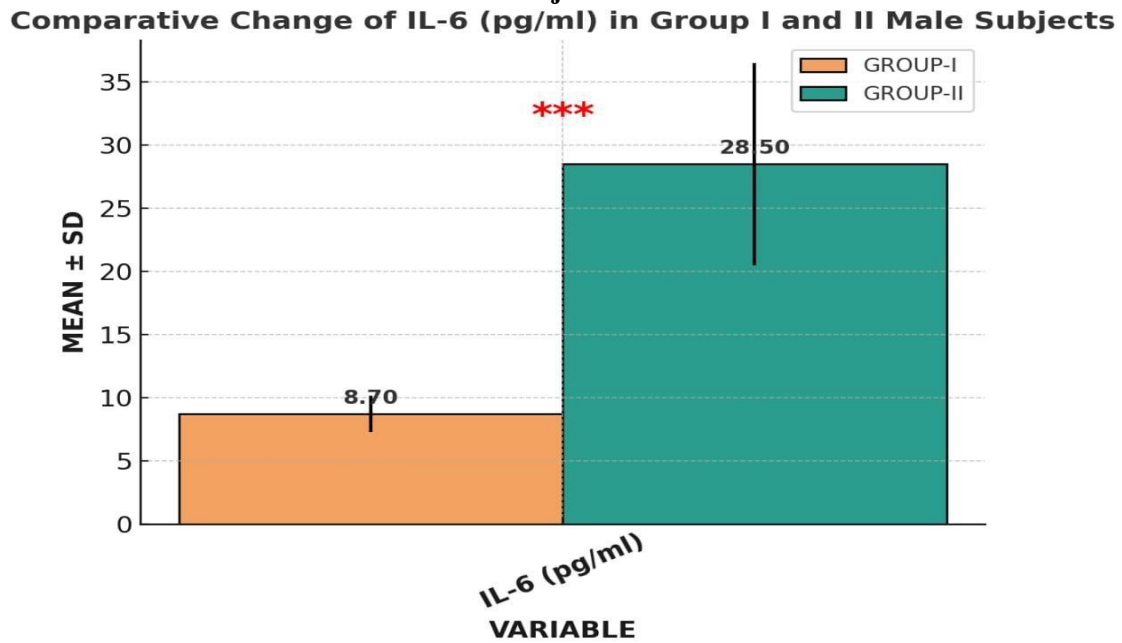
Table 2 and graph 2 Showing the comparative changes of immunological and insulin resistance (HOMA-IR) parameters in group I healthy female subjects (N=48) and group II diabetic female subjects (N=30). IL-6, and HOMA-IR were highly significant at (P<0.001) in Group II subjects.

Table 2: Showing comparative changes of biochemical and immunological parameters in group I and group II female subjects.

Group	Parameters	Min	Max	Mean ± SD
Group I female subject N = 48	Home -IR	0.15	3.43	2.12 ± 0.74
	IL-6	5.60	13.40	8.96 ± 1.59
Group II female subject N= 30	Home -IR	1.82	8.86	4.79 ± 1.39
	IL-6	14.00	39.50	24.81 ± 6.65

Highly significant difference between group I and group II (p < 0.001) for both Home -IR and IL-6.

Graph 2: showing the comparative changes of immunological parameters group I and II male subjects.



Discussion:

Many investigations have suggested that diabetes mellitus has an inflammatory component, as chronic elevations in blood glucose can activate elements of the innate immune system. Skeletal muscle expresses several innate immune-related receptors, including cytokine receptors and toll-like receptors (TLRs). Prolonged stimulation of these pathways, together with genetic predisposition and environmental influences, is thought to shift the inflammatory response from a reparative process to one that contributes to the onset of type-2 diabetes. In both newly diagnosed and established cases of type-2 diabetes, increased concentrations of acute-phase markers and proinflammatory cytokines have been reported, and these elevations often show a positive association with insulin resistance.

In the present study, we observed marked increases in serum interleukin-6 (IL-6) concentrations and in HOMA-IR values among male and female subjects with type-2 diabetes, emphasizing the close link between ongoing inflammation and disrupted insulin signaling. Other biochemical variables, including urea and creatinine, displayed similar significant changes in both diabetic groups (group II males and females) when compared with the control group (group I) ($P < 0.01$). IL-6 levels, in particular, showed a highly significant rise ($P < 0.001$). These observations align with previous research that has highlighted the contribution of IL-6 and other inflammatory mediators to insulin resistance in individuals with type-2 diabetes.

Although IL-6 was traditionally believed to originate mainly from immune cells such as macrophages and mononuclear cells, more recent data indicate that adipose tissue is a substantial source of circulating IL-6, and the amount released increases in proportion to adiposity. IL-6 has been implicated in several metabolic disturbances, including changes in hepatic glycogen metabolism, promotion of lipolysis, enhanced triglyceride synthesis, and increased gluconeogenesis, all of which may intensify hyperglycemia. The significantly higher IL-6 levels recorded in our diabetic participants therefore provide a plausible mechanistic basis for the elevated HOMA-IR values found in group II subjects. These findings support the concept that IL-6 may act as a regulator of glucose metabolism.

Our results show a highly significant difference between group II and group I ($P < 0.001$), as displayed in Tables 1–2 and Graphs 1–2. IL-6 is believed to influence insulin resistance partly by promoting serine phosphorylation of insulin receptor substrate-1 (IRS-1), which interferes with its capacity to engage the β -subunit of the insulin receptor and thereby disrupts downstream signaling. Insulin resistance forms a central abnormality that precedes the broader insulin-resistance syndrome, pancreatic β -cell dysfunction, and ultimately the clinical presentation of type-2 diabetes.

These insights strengthen the rationale for developing therapeutic strategies that target inflammatory pathways. With continued research, anti-inflammatory interventions may eventually play a meaningful role in improving metabolic outcomes and reducing the complications associated with diabetes.

Conclusion:

The present study clearly demonstrates that serum interleukin-6 (IL-6) levels and insulin resistance, as assessed by HOMA-IR, are significantly elevated in type 2 diabetic subjects of both genders when compared to healthy controls. The highly significant increase in IL-6 concentrations observed in diabetic males and females strongly correlates with the marked rise in HOMA-IR values, indicating a close association between chronic inflammation and impaired insulin sensitivity. The findings support the mechanistic role of IL-6 in disrupting insulin signaling through inflammatory pathways involving SOCS-3 and the PI3K–Akt cascade, ultimately leading to reduced glucose uptake and persistent hyperglycemia. Therefore, IL-6 may serve as a valuable inflammatory biomarker for early detection of insulin resistance and progression of type 2 diabetes mellitus. Targeting IL-6-mediated inflammatory pathways may offer a promising therapeutic approach for preventing or delaying the development of insulin resistance and its associated metabolic complications. Modulation of inflammatory processes in the setting of diabetes is nowadays a matter of great interest

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