e-ISSN: 0975-1556, p-ISSN:2820-2643
Available online on www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2025; 17(01); 314-318

Original Research Article

Comparative Analysis of Serum Insulin, Insulin Resistance and Inflammatory Markers in Type 2 Diabetes Mellitus Patients and Healthy Controls

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Received: 26-10-2024 / Revised: 27-11-2024 / Accepted: 28-12-2024
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Conflict of interest: Nil

Abstract:

Background: Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin resistance and chronic inflammation. The most prevalent kind of diabetes is Type 2 Diabetes, or non-insulin dependent diabetes mellitus (NIDDM). Non-insulin dependent diabetes mellitus (NIDDM) accounts for more than 90% of diabetes and typically features insulin resistance or insulin secretory defects.

Objectives: In this study, we aimed to assess serum insulin, insulin resistance and inflammatory markers in T2DM patients and healthy controls. And also investigate the relationship between insulin resistance and inflammatory markers in T2DM patients.

Materials and Methods: A total number of 100 patients were included in the hospital based analytical cross–sectional study. This includes 50 subjects of NIDDM and 50 healthy control of age group of 20 to 65 years. After an overnight fast of 10-12 hours, venous blood sample was drawn from anticubital vein of each subject by using standard aseptic techniques. Serum was separated by centrifugation and used for the following biochemical analysis. Serum Insulin and inflammatory markers (CRP, IL-6, serum ferritin) was estimated using Fully Automatic Analyzer and Insulin Resistance was calculated using HOMA-IR. Statistical analysis was analyzed using Student's t-test.

Results: There is highly significant increase in the levels of serum insulin, serum insulin resistance index, serum ferritin, CRP and IL-6 in subjects of NIDDM as compared to healthy controls ($p < 0.0001$).

Conclusion: Our study revealed hyperglycemia, hyperinsulinemia, and dyslipidemia in non-insulin dependent diabetes mellitus (NIDDM) subjects and inflammatory markers are also high due to low grade inflammation. These findings have implications for understanding the pathophysiology of T2DM and developing therapeutic strategies to target insulin resistance and inflammation.

Keywords: NIDDM, Serum insulin, Inflammatory markers, Hyperglycemia, Hyperinsulinemia, CRP.

Introduction

One of the most prevalent endocrine disorders, diabetes mellitus affects several organ systems and causes substantial morbidity and mortality because of its concomitant consequences. It is described as a class of metabolic disorders marked by hyperglycemia brought on by deficiencies in either the action or secretion of insulin, or both. Patients with type-2 diabetes mellitus have increased risk of cardiovascular disease associated with atherogenic dyslipidemia[1].

In recent decades, the prevalence of Type 2 Diabetes Mellitus (T2DM) has seen a marked increase, positioning it as a pressing public health concern worldwide. Characterized by insulin resistance and relative insulin deficiency, T2DM not only disrupts glucose metabolism but also correlates with heightened levels of inflammatory markers that may exacerbate disease progression[2].

The most prevalent kind of diabetes is Type 2 Diabetes, or non-insulin dependent diabetes mellitus (NIDDM). It happens when glucose accumulates in the bloodstream because the body cannot utilize insulin properly[3,4]. The World Health Organization has described diabetes under the clinical classes of Diabetes Mellitus (DM) and impaired glucose tolerance (IGT). The major classes of DM include:

- Insulin Dependent Diabetes Mellitus (IDDM), known as type l DM.
- Non-Insulin Dependent Diabetes Mellitus (NIDDM), known as type 2 DM[5].

Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes are responsible for metabolic abnormalities in carbohydrates, lipids and proteins[6]. Insulin is a dimer, containing A and B chains respectively, linked by disulphide bridges, and containing 51 amino acids with isoelectric pH 5.5[7]. Non-insulin dependent diabetes mellitus (NIDDM) accounts for more than 90% of diabetes and typically features insulin resistance or insulin secretory defects[8].

CRP stands for C-reactive protein, which is a type of protein produced by the liver in response to inflammation in the body. CRP is an important marker of inflammation and can be used to indicate the presence and severity of inflammation in various conditions, including infections, autoimmune disorders, and cardiovascular disease. Elevated CRP levels in individuals with type 2 diabetes mellitus may increase the risk of cardiovascular disease, which is a common complication of this condition [9].

Ferritin is a universal intracellular protein that is primarily responsible for storing and releasing of iron in the body. In the context of type 2 diabetes mellitus, ferritin levels have been found to be elevated in some individuals. This may be due to the chronic low-grade inflammation that is associated with this condition. Elevated ferritin levels in individuals with type 2 diabetes mellitus may also be linked to insulin resistance and an increased risk of cardiovascular disease. Some studies have suggested that elevated ferritin levels may be a marker of inflammation and oxidative stress, which is both, associated with type 2 diabetes mellitus. Other studies have suggested that low ferritin levels may be associated with an increased risk of developing type 2 diabetes mellitus[10].

Elevated IL-6 levels in individuals with type 2 diabetes mellitus may be linked to insulin resistance, endothelial dysfunction and an increased risk of cardiovascular disease. Lowering IL-6 levels through lifestyle modifications or medication may also help reduce the risk of complications in individuals with type 2 diabetes mellitus. Elevated glucose levels in diabetes mellitus could trigger microvascular inflammation and lead to increased production of inflammatory markers[11].

This comparative analysis aims to elucidate the variances in serum insulin levels, degrees of insulin resistance, and inflammatory markers among T2DM patients versus healthy individuals. By exploring these critical factors, the study seeks not only to enhance comprehension of T2DM at a physiological level but also to contribute to the development of targeted therapeutic strategies that may mitigate the long-term complications associated with the disease.

The objectives of our study includes –

a) To assess serum insulin, insulin resistance and inflammatory markers in T2DM patients and healthy controls.

b) To investigate the relationship between insulin resistance and inflammatory markers in T2DM patients.

Material and Methods

Source of Data and Study Design: It is a hospital based analytical cross–sectional study, conducted at the Dr. S.N. Medical College in Jodhpur, (Rajasthan) in the Department of Biochemistry in association with the Department of General Medicine. Samples were analyzed for biochemical investigations in the Department of Biochemistry, Dr. S.N. Medical College in Jodhpur.

Inclusion Criteria: NIDDM subjects without any other illness.

Exclusion Criteria: Subjects with Obesity, Alcoholics, Smokers, Chronic Liver Disease, Hypertension, Coronary Artery Disease, Bone Disease and Hormone Replacement Therapy (HRT) were excluded from the study.

Sample Collection: 5 ml venous blood was drawn from subjects after overnight fasting of 10-12 hours under aseptic precautions. Serum was separated by centrifugation and used for the following biochemical analysis. Serum Fasting Glucose, Serum Insulin and inflammatory markers (CRP, IL-6, serum ferritin) was estimated using Fully Automatic Analyzer and Insulin Resistance was calculated using HOMA-IR.

Statistical Analysis: All the data was presented in number % percentage. Mean and Standard Deviation were used to determine the data. The data was analyzed in SPSS software. The difference in mean among the groups was analysed using student's t test and significance of result was calculated by p- value. Statistical significance among different parameters was evaluated. A p-value less than 0.05 were considered statistically significant.

Results

A total number of 100 patients were included in the study. This includes 50 subjects of NIDDM and 50 healthy control of age group of 20 to 65 years. There are 25 (50%) and 25 (50%) were males and females subjects in healthy control group whereas 30 (60%) and 20 (40%) were males and females subjects in NIDDM group.

It is evident from the given table that there were increased levels of fasting serum glucose, serum

insulin, insulin resistance (HOMA-IR) and inflammatory markers (CRP, ferritin, IL-6) in NIDDM subjects as compared to healthy control subjects, which was statistically highly significant (p- value < 0.0001). There is also significant increased in age and body mass index (BMI) in NIDDM subjects as compared to healthy control subjects.

Table 1: Shows Distribution of Variables in Healthy Control and NIDDM Subjects

Variables	Healthy Control	NIDDM Subjects	t- test	P- Value
Age (years)	30.32 ± 4.76	51.63 ± 3.91	23.46	0.0001
BMI (kg/m^2)	23.89 ± 1.81	26.22 ± 1.57	6.472	0.0001
Fasting Serum Glucose (mg/dL)	90.21 ± 6.81	154.8 ± 12.32	32.44	0.0001
Fasting Serum Insulin (µIU/ml)	18.82 ± 3.96	30.96 ± 4.0	15.30	0.0001
Insulin Resistance (HOMA-IR)	4.83 ± 0.75	11.87 ± 1.84	29.68	0.0001
CRP (mg/L)	3.57 ± 0.67	13.13 ± 3.02	21.85	0.0001
Ferritin (ng/mL)	109.5 ± 49.8	465.05 ± 66.35	30.30	0.0001
IL-6 (pg/mL)	4.15 ± 1.04	19.51 ± 3.93	26.71	0.0001

Not significant ($p > 0.05$) and **Highly significant** ($p < 0.001$)

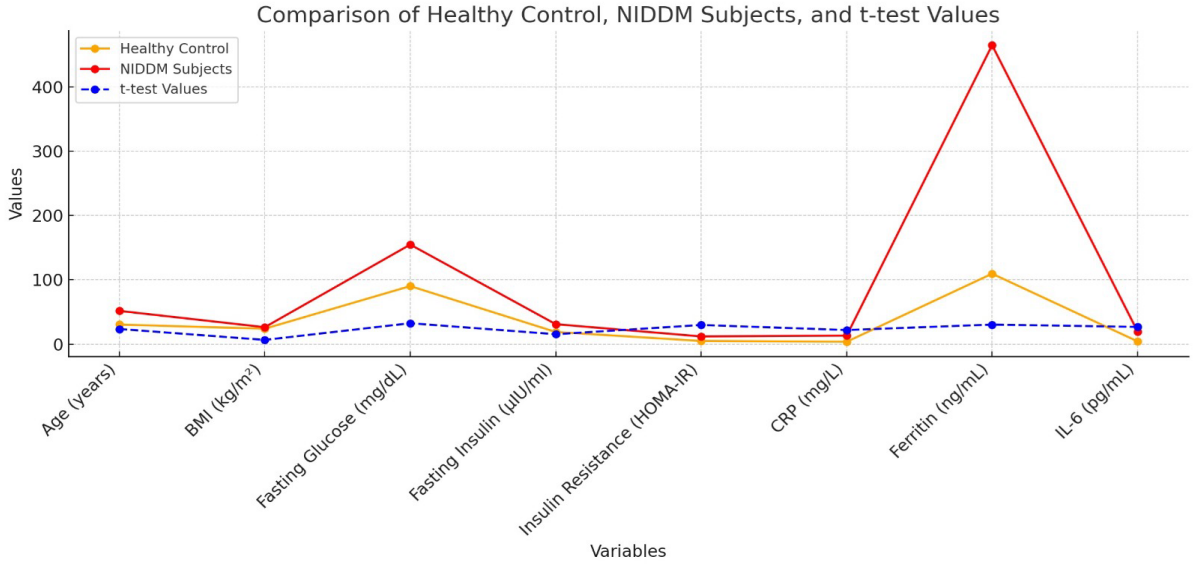

Figure 1: Shows Distribution of Variables in Healthy Control and NIDDM Subjects

Discussion

In the present study, we included a total of 100 patients based on inclusion and exclusion criteria. These patients were divided into 50 healthy control subjects and 50 NIDDM subjects. The mean age (years) in healthy control and NIDDM subjects was 30.32 ± 4.76 years and 51.63 ± 3.91 years respectively. The ratio of males was high as compared to females in NIDDM subjects as compared to healthy controls. NIDDM subjects (26.22 ± 1.57 kg/m^2) have high BMI as compared to healthy control subjects (23.89 ± 1.81 kg/m^2). Hillier TA et al (2001) show inverse linear relationship between BMI and age at diagnosis of type 2 diabetes (p<0.001). On univariate analysis, adults with early type 2 diabetes were more obese (BMI 39 vs. 33 kg/m^2, $p < 0.001$), were more likely to be female ($p = 0.04$), had slightly worse glycemic control (HbA1C 7.7 vs. 7.5%, $p = 0.03$), had a higher prevalence of diastolic hypertension (37 vs. 26%, $p < 0.001$), despite a lower prevalence of systolic hypertension (34 vs. 55%, $p < 0.001$), and had an equally high rate of abnormal lipids (82 vs. 78%, $p = 0.13$) than adults with usual type 2 diabetes[12].

We evaluated serum levels of fasting glucose, fasting insulin and insulin resistance (HOMA-IR) in both the groups. The normal reference ranges used for these parameters were fasting serum glucose is 70 – 110 mg/dL, fasting serum insulin is 2.0 – 29.0 µIU/ml and insulin resistance is calculated with HOMA-IR respectively. We found statistically significant increased levels of serum fasting glucose, fasting insulin and insulin resistance in NIDDM subjects as compared to healthy control subjects (p < 0.0001).

In concordance with our findings, Joshi KR et al (2014) find higher levels of fasting serum glucose in subjects of type 2 diabetes mellitus as compared to healthy control[13]. Kahn S E et al. (1997) reported

that Insulin, together with its principal counter-regulatory hormone glucagon, regulates blood glucose concentrations. Pancreatic β cells secrete 0.25–1.5 units of insulin per hour during the fasting (or basal) state, sufficient to enable glucose insulin-dependent entry into cells.

This observation aligns with the pathophysiological principle that insulin resistance, a hallmark of Type 2 diabetes mellitus, drives a compensatory hyperinsulinemia in an attempt to maintain glucose homeostasis. However, in patients with advanced Type 2 diabetes mellitus, the relationship was weaker, likely due to progressive beta-cell dysfunction and insulin secretion failure[14].

DeFronzo et al. (1988) and subsequent investigations have described the compensatory hypersecretion of insulin in the face of insulin resistance, which eventually fails as beta-cell function deteriorates.

In patients with elevated insulin levels, interventions focusing on improving insulin sensitivity, such as lifestyle modifications or insulin-sensitizing medications like metformin, could be beneficial. Conversely, patients with low insulin levels and high FBG might benefit more from therapies aimed at enhancing insulin secretion (e.g., sulfonylureas or GLP-1 receptor agonists) or direct insulin supplementation[15].

We also evaluated inflammatory markers (CRP, Ferritin, IL-6). The normal reference ranges used for these parameters were CRP is 0.5 – 200 mg/L, Ferritin is 20 – 300 ng/mL and Interleukin-6 (IL-6) is 0 – 7 pg/mL respectively. We found statistically significant increased levels of CRP, Ferritin and IL-6 in NIDDM subjects as compared to healthy control subjects ($p < 0.0001$).

Soinio et al. (2009) found that serum CRP levels were significantly higher in patients with T2DM compared to controls, and that CRP levels were positively correlated with fasting plasma glucose levels and HbA1c[16].

Another study by Hanley et al. (2003) found that higher serum CRP levels were associated with an increased risk of developing T2DM[17]. Moreover, a meta-analysis of 21 studies conducted by Xu et al. (2013) found that serum CRP levels were significantly higher in patients with T2DM compared to controls, and that CRP levels were positively correlated with markers of insulin resistance, such as fasting insulin levels and HOMA-IR[18].

Pradhan AD et al. (2001) studied C-reactive protein (CRP), IL-6, and the risk of developing non-insulin-dependent diabetes mellitus and observed higher CRP and IL6 levels in diabetics. They concluded that inflammation has a role in diabetogenesis[19].

Gao S et al. (2017) found that higher serum ferritin levels were significantly associated with an increased risk of T2DM. The authors suggested that elevated serum 78 ferritin levels may contribute to the development of T2DM through its role in promoting inflammation, oxidative stress, and insulin resistance[20].

Pickup et al. (1997) found that serum IL-6 levels were significantly elevated in patients with T2DM compared to healthy controls. The study included over 70 participants and found that serum IL-6 levels were positively correlated with fasting glucose levels and HbA1c, a marker of long-term blood glucose control[21].

A meta-analysis of 32 cases conducted by Herder et al. (2007) found that higher serum IL-6 levels was associated with an increased risk of developing T2DM. The authors suggested that IL-6 may contribute to the development of T2DM through its role in promoting inflammation and insulin resistance. Interleukin 6 (IL-6) is a multifunctional cytokine that has been implicated in the pathogenesis of type 2 diabetes. The elevated circulating levels of IL-6 are an independent predictor of NIDDM and are considered to be involved in the development of inflammation, insulin resistance, and beta cell dysfunction[22].

The study highlights the potential of using serum insulin levels as a biomarker to stratify patients based on their insulin resistance or beta-cell functionality. Such stratification could inform personalized treatment plans and improve glycemic outcomes. The findings suggest that elevated insulin resistance and associated inflammatory markers play a significant role in the pathophysiology of T2DM. The findings indicate that T2DM patients exhibit markedly higher levels of serum insulin and elevated inflammatory markers, suggesting a robust link between inflammation and insulin resistance in this population. These results underscore the necessity for clinicians to integrate assessments of inflammatory markers in routine diabetes management, potentially guiding more personalized therapeutic strategies.

The limitations of the present study are that it has a limited number of participants that reduces the generalizability of the findings. There is also lack of control for confounding variables such as diet; physical activity and medication use along with longitudinal follow-up in type 2 diabetes mellitus patients.

Conclusion

This cross-sectional study demonstrates a significant increase in serum insulin, insulin resistance, and inflammatory markers in type 2 diabetes mellitus patients as compared to healthy control subjects. These findings suggest that insulin resistance and

chronic inflammation play a crucial role in the pathophysiology of type 2 diabetes mellitus. The elevated levels of serum insulin, insulin resistance, and inflammatory markers in type 2 diabetes mellitus patients may contribute to the development of insulin resistance, pancreatic beta-cell dysfunction, and vascular complications associated with the disease. This study highlights the importance of early detection and management of insulin resistance and inflammation in type 2 diabetes mellitus patients to prevent or delay the onset of complications. Further studies are needed to explore the underlying mechanisms and to identify potential therapeutic targets for the treatment of type 2 diabetes mellitus.

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