Original Research Article

Insulin resistance in Type II Diabetes Mellitus patients and their first degree relatives

Abstract: Type II diabetes (T2DM) is caused by a combination of environmental, genetic, environmental, metabolic, and unknown variables. In diabetics, insulin resistance is the most common cause of prolonged hyperglycemia. T2DM is induced by insulin resistance and cell dysfunction. The interaction of genetics and environment further complicates T2DM development. Insulin resistance and cell dysfunction are two of the most common Type 2 Diabetes Mellitus symptoms. A vicious triangle of cell failure (80% cell function) and insulin resistance in the muscles and liver causes major physiological issues. A group of diabetes patients (Group I), non-diabetic first-degree relatives of diabetic patients (Group II), and a non-diabetic healthy control group (Group III) were studied.The diabetes patients had the greatest systolic and diastolic blood pressures, followed by first degree relatives and healthy controls. We found that diabetics had higher fasting and postprandial sugar, glycated haemoglobin than diabetic offsprings and control group. Moreover, fasting insulin levels are higher in first degree relatives than in diabetes patients in the control group. The HOMA-IR levels of diabetics and their progeny do not differ much. Insulin resistance in diabetics and their first degree relatives is clearly evident from the results.

Key words: First degree relatives, Insulin resistance, HOMA-IR, pancreatic beta cells, metabolic syndrome.

Introduction:

Diabetes mellitus is a assembly of metabolic illnesses demarcated by hyperglycemia triggered by insulin production or insulin action, or both(Journal, 2014). In Diabetes' insistent hyperglycemia leads to damage, malfunction, and failure of multiple organs, including the kidneys, eyes, nerves, heart, and blood vessels. Shaw et al. (Shaw et al., 2010) reported that dDiabetes would affect 285 million people worldwide in 2010, with a global incidence of 6.4% per cent expected to rise to 7.7% per cent and 439 million persons by 2030 (Leon, 2015). Between 2010 and 2030, the number of adults with dDiabetes would increase by 69% per cent(Glovaci et al., 2019) in developing nations and by 20% per cent(Glovaci et al., 2019) in developed countries. India, the world's 2nd -most populous country with 1.3 billion people, has the highest number of diabetes patients, with a 7.8% per cent prevalence(Hernandez et al., 2020).

Studies in India have shown a growing incidence of dDiabetes across urban and rural populations due to the urbanisation and various of lifestyle factorschoices (Doria et al., 2008). Macrovascular (cardiovascular disease) and microvascular problems (diabetic kidney disease, retinopathy, and neuropathy) upsurge mortality, blindness, kidney failure, and general quality of life in people with Diabetes (Mohan et al., 2013). Clinical risk factors and glycemic management cannot envisage the advance of vascular problems on their own(García-Ocaña et al., 2020); multiple genetic investigations(Tremblay & Hamet, 2019) have revealed a definite hereditary component to both Diabetes and its consequences(Cole & Florez, 2020).

T2DMType 2 diabetes is evidently associated with insulin resistance. Compensatory high levels of insulin in blood aids in the maintenance of normal glucose in blood—often for years—before the onset of frank Diabetes (Liu, 2019). Conclusively, pancreatic beta cells are not able to overpower insulin resistance by over secretion and is manifested by increased glucose levels, leading to diabetes. Glucose levels increase, and Diabetes could be diagnosed(L. Yang et al.,

2021). Patients with ~~type 2 diabetes~~T2DM are hyperinsulinemic until the illness has progressed to an advanced state. Only in extreme situations, when fasting sugar levels exceed 180 to 198 mg/dL ie,.10 to 11 mmol/L, ~~are~~ low plasma insulin levels are found. Insulin resistance (IR) and related metabolic abnormalities have been linked to metabolic syndrome, ~~type II diabetes mellitus~~T2DM, and heart disease in adults and the elderly(Kumar et al., 2005). Insulin resistance is commonly characterised as a reduced sensitivity or responsiveness to ~~I~~insulin's metabolic activities, such as insulin-mediated glucose clearance and suppression of hepatic glucose synthesis. ~~Because~~ As insulin resistance normally develops years before the manifestation of diabetes, ~~diseases manifest~~, diagnosing and ~~curing~~ addressing insulin resistance in individuals~~-resistant people has the potential to be~~is extremely beneficial in terms of disease prevention(Stančáková & Laakso, 2016). Insulin resistance could be suspected in people with a first-degree relative with Diabetes (J. Yang et al., 2012).

The euglycemic-hyperinsulinemic clamp method(ter Horst & Serlie, 2020), the minimum model methodology, and the steady-state plasma glucose method are all ways of measuring insulin resistance. However, due to cost and labour problems, these approaches are not always appropriate for clinical usage. The insulin resistance index (HOMA-IR) is a simple approach published by Matthews et al(ter Horst & Serlie, 2020). that is based on the concept that basal glucose and insulin interactions are mostly regulated by a simple feedback loop(Ikeda et al., 2001). The current study sought to assess insulin resistance (IR) and glycemic markers in first-degree relatives/ offsprings of Type II diabetes mellitus patients.

Comment [M1]: Should be rewritten

Materials and methods:

The research was carried out at a Tertiary care Hospital in Dehradun, Uttarakhand, India. In the ~~department~~ Department of ~~medicine~~Medicine, an observational, cross-sectional, and prospective

investigation was done. Data was obtained through personal interviews using a standardised questionnaire, as well as from the patients' medical files. The study was carried out for a period of six months. Prior consent was taken from the patients before enrolment into the study. The investigation started after due approval by the Institutional Ethics Committee of the hospital. Three groups of subjects (including both genders) were studied:

Group, I consisted of 48 Type II diabetic patients. After obtaining their consent, the patients visiting the medicine department for treatment were enrolled. Their non-diabetic first-degree relatives (48) were included in Group II. The control group III comprised 51 patients who visited the hospital for executive health checkups. The American Diabetic Association (ADA) criteria for the diagnosis of Diabetes was adopted. According to ADA, either of the following criteria was considered for diabetic patients:

1. FPG ≥7.0 mmol/L or
2. 2-h PG ≥ 1.1 mmol/L during OGTT or
3. A1C ≥48 mmol/mol or
4. a random plasma glucose≥ 11.1 mmol/L.

   Patients suffering from co-morbidities like cardiovascular disease and hormonal disorders were not enrolled in the study. Patients suffering from Type I Diabetes was excluded.

After a twelve-hour overnight fast, blood was taken from the ante-cubital vein and collected for testing fasting and post prandial blood sugar, glycated haemoglobin, and fasting insulin levels. A "high-performance liquid chromatography" approach was used to test glycosylated haemoglobin(Chauhan, 2017). The VITROS GLU Slide was used to quantitatively test glucose levels in blood plasma(Fernandez et al., 2013). An Immunometric Immunoassay approach was

used to determine insulin levels(Chauhan, 2017). Patient profile forms were used to capture demographic information and pertinent medical history.

The datasets were evaluated and analysed using IBM SPSS Statistics 20 software. Data were depicted as mean ± standard deviation. The analysis of variance was used to compare variable means and differences across groups. When the value of p was less than 0.05, the findings were statistically significant.

Results: This analysis includes 132 participants (40 diabetes patients in group I, 40 non-diabetic offsprings of diabetic patients in group II, and 52 non-diabetic healthy controls in group III). There were 45% males and 55% females among the total T2DM patients and 52.5% males and 47.5% females in the first-degree relatives' group. Similarly, 46% and 54% of the 52 healthy controls were males and females, respectively. The average age for T2DM patients, first degree relatives and controls was 66.32, 39.21 and 38.78 years, respectively. The findings revealed that the mean systolic blood pressure and diastolic blood pressure levels in T2DM patients were substantially higher ($P<0.05$) than in first degree relatives and controls (Table 1).

Table 1: Baseline demographic and clinical characteristics of three groups:

Variables	Group I (Diabetic Patients)	Group II (non-diabetic offsprings of diabetic patients)	Group III (non-diabetic healthy controls)
Number of patients	40	40	52
Males/Females	18/22	21/19	24/28
Age in years (mean±SD)	66.32±5.16	39.21±3.09	38.78±3.77
Systolic Blood Pressure (mean±SD)	138.24±5.68	122.25± 2.12	120.23±1.49
Diastolic Blood Pressure (mean±SD)	90.15±3.35	83.40±1.01	80.68±1.29

Table 2 represents mean values and multivariate comparisons for variables.

Table 2: Groupwise multivariate comparisons for biochemical parameters

Variables	Group I (Mean values)	Group II (Mean values)	Group III (Mean values)	P values among the groups	
				Group	**P value**
Fasting blood sugar (mg/dl)	163.93±45.16	96.53±5.01	87.95±8.06	I Vs II	00.0*
				II Vs III	00.0*
				I Vs III	00.0*
Post prandial blood sugar (mg/dl)	269.65±51.3	118.28±8.67	110.73±6.27	I Vs II	00.0*
				II Vs III	**0.35**
				I Vs III	00.0*
HbA1c (%)	7.05±2.21	5.63±.34	5.10±.24	I Vs II	00.0*
				II Vs III	00.0*
				I Vs III	00.0*
Fasting Insulin (mIU/l)	9.57±4.61	11.75±4.29	3.90±1.45	I Vs II	**0.11**
				II Vs III	00.0*
				I Vs III	00.0*
HOMAIR	3.95±1.75	2.85±1.15	1.67±.35	I Vs II	**0.46**
				II Vs III	00.0*
				I Vs III	00.0*

** p <0.05 is statistically significant.*

The values are expressed as mean ± standard deviation.

Apropos the biochemical indices, statistically significant augmentation in fasting blood sugar, postprandial blood sugar and glycated haemoglobin were observed in the T2DM patients (Group

I) as compared to their offsprings(Group II) and the control group(Group III) (Table 3). Among Group I and II, there is no significant difference between the values of Fasting insulin (p=0.111) and HOMA-IR(p=0.457). Still, Group II has significantly higher values for the same parameters than Group III. P-value < 0.05 is considered statistically significant. The offspring of type 2 diabetic parents had reportedly higher fasting insulin ($p<0.05$) and were more insulin resistant ($p<0.005$).

Discussion:

Type II diabetes mellitus is a conglomeration of environment, genetic factors, external toxins, metabolic milieu and other unidentified factors. Resistance to insulin action is the most prevalent cause of persistent hyperglycemia in diabetics . (Franzago et al., 2020). T2DM is caused by the activation of ~~activating~~ several pathways and factors related to insulin resistance(Ozder, 2014) and cell dysfunction. Furthermore, the interplay of genetics and environmental factors(Zimmet, 1982) complicates the development of T2DM. Insulin resistance and cell dysfunction are ~~two of~~ the most commonly observed abnormalities in T2DM ~~prevalent Type 2 Diabetes Mellitus~~ (T2DM)(Seino et al., 2010) ~~symptoms, both~~ caused by a disturbance in homeostasis(Mambiya et al., 2019). The primary physiological problems are generated by a vicious triangle of cell failure (80% cell function) and insulin resistance in the muscles and liver(Romao & Roth, 2008).

Comment [M2]: This appears to be redundant

In this study, we examined blood sugar levels, glycated haemoglobin levels and fasting Insulin in three groups of diabetic patients(Group I), non-diabetic first-degree relatives of diabetic patients(Group II) and: non-diabetic healthy control group with no obvious genetic link. (Group III). The HOMA-IR values were calculated as HOMA-IR = (insulin * glucose) / 405, for

glucose in mg/dL and insulin in mIU/L. The systolic and diastolic blood pressure values were reported highest in the diabetic patients' group, followed by the first degree relatives and healthy controls. We discovered that fasting and post prandial sugar, glycated hemoglobin are considerably greater in ~~all the~~the entire diabetic group compared to the off springs and control group. This was also evident in the study by Manjrekar et al(Manjrekar et al., 2012). Furthermore, our data revealed that fasting insulin ~~levels are~~levels are substantially greater in first degree relatives than in diabetes patients followed by the control group. However, there is no significant difference in HOMA-IR values between diabetes individuals and their offsprings. It contends the prevalence and development of insulin resistance in diabetes individuals and their first degree relatives.

According to O'Rahilly S et al.(O'Rahilly et al., 1988), ~~In~~ in fasting non-diabetics, insulin is produced in regular pulses every 12 to 15 minutes, but individuals with non-insulin-dependent diabetes lack normal oscillatory insulin production. They studied ten slightly glucose-intolerant first-degree relatives of patients with non-insulin-dependent Diabetes and ten controls who were age and weight matched to examine if abnormal insulin oscillations are an early feature of Diabetes. Fasting blood glucose levels were greater in relatives than in controls, as in our research. When compared to controls, relatives' first-phase (0 to 10 minute) insulin secretory responses to intravenous glucose treatment were not substantially affected. They hypothesised that abnormal oscillatory insulin secretion may be an early sign of non-insulin-dependent diabetes. Insulin sensitivity and secretion were assessed (Eriksson et al., 1989) in 26 first-degree relatives of NIDDM (non-insulin-dependent diabetes mellitus) patients. These people were compared to 14 healthy control persons with no family history of NIDDM and 19 NIDDM sufferers. Insulin secretion was shown to be normal in relatives with normal glucose tolerance.

Insulin resistance and low insulin production are essential for these individuals to develop impaired glucose tolerance. According to Strączkowski et al.(Strączkowski et al., 2003), Insulin resistance can be detected in young, thin individuals who are predisposed to type 2 diabetes. Our data suggest that insulin resistance is a fundamental flaw in the aetiology of this disease. Schmitz O.(Schmitz et al., 1997) explained that enhanced insulin secretion of glucose-tolerant relatives of NIDDM patients is disorderly.

Conclusion:

~~Type II Diabetes Mellitus~~T2DM has historically been regarded as an insulin deficit and resistance syndrome. Still, emerging insights into its pathophysiology suggest other essential factors in insulin insufficiency and functional incapacity. Some of these factors may be reflected in the offspring, although it may be relatively difficult to segregate these factors in the subgroups of offspring. However, the combined effect of these identifiable and unidentifiable risk factors may manifest as either insulin resistance or development of metabolic syndrome without frank Diabetes. This subgroup needs to be identified and intervened as these measures are likely to prevent Diabetes in the future course. Further, there is also a need to segregate these risk factors in the offspring. Identifying and segregating the risk factors in this sub-group is relatively easier than a group where Diabetes is manifested and full-blown and accompanied by various complications.

Statement on Data Sharing: The corresponding author will share data gathered throughout the course of this study if requested.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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