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Insulin resistance in Type II Diabetes Mellitus patients and their first-degree relatives- An observational study.

Abstract: Type II diabetes (T2DM) is caused by environmental, genetic, metabolic, and unknown variables. In diabetics, insulin resistance is the most 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 beta 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 people with diabetes had higher fasting (FBS) and postprandial sugar, glycated haemoglobin (HbA1c) 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 (Homeostatic Model Assessment of Insulin Resistance) levels of diabetics and their progeny do not differ much. The HOMA-IR measures insulin resistance severity. Common reference levels for HOMA-IR insulin resistance range from 0.7 - 2. Insulin resistance in diabetics and their first-degree relatives is evident from the results.

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

Introduction:

Diabetes mellitus is an assembly of metabolic illnesses demarcated by hyperglycemia triggered by insulin production, 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 diabetes would affect 285 million people worldwide in 2010, with a global incidence of 6.4% expected to rise to 7.7% and 439 million persons by 2030 (Leon, 2015). Between 2010 and 2030, the number of adults with diabetes would increase by 69% (Glovaci et al., 2019) in developing nations and by 20% (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% prevalence(Hernandez et al., 2020).

Studies in India have shown a growing incidence of diabetes across urban and rural populations due to urbanization and various lifestyle choices (Doria et al., 2008). Macrovascular (cardiovascular disease) and microvascular problems (diabetic kidney disease, retinopathy, and neuropathy) upsurge mortality, blindness, kidney failure, and affect the 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).

T2DM is associated with insulin resistance. Compensatory high levels of Insulin in the blood aids in the maintenance of normal glucose in the blood—often for years—before the onset of diabetes (Liu, 2019). Conclusively, pancreatic beta cells cannot overpower insulin resistance by over secretion and manifest by increased glucose levels, leading to diabetes(Yang et al., 2021). Patients with T2DM are hyperinsulinemic until the illness has progressed to an advanced state. In extreme situations, low plasma insulin levels are found when fasting sugar levels exceed 180 to 198 mg/dL, ie,.10 to 11 mmol/L. Insulin resistance (IR) and related metabolic abnormalities have been linked to metabolic syndrome, T2DM, and heart disease in adults and the elderly(Kumar et al., 2005a). Insulin resistance is commonly characterized as a reduced sensitivity or responsiveness to Insulin's metabolic activities, such as insulin-mediated glucose clearance and suppression of hepatic glucose synthesis. As insulin resistance normally develops years before the manifestation of diabetes, diagnosing and addressing insulin resistance in individuals is extremely beneficial for disease prevention(Stančáková & Laakso, 2016). Insulin resistance could be suspected in people with a first-degree relative with Diabetes (Yang et al., 2012).

The euglycemic-hyperinsulinemic clamp method(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. (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 T2DM patients.

Materials and methods:

The research was carried out at a Tertiary care Hospital in Dehradun, Uttarakhand, India. In the Department of Medicine, an observational, cross-sectional, and prospective investigation was done. Data was obtained through personal interviews using a standardized 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 40 Type II diabetic patients. After obtaining their consent, the patients visiting the medicine department for treatment were enrolled. Their non-diabetic first-degree relatives (40) were included in Group II. The control group III comprised 52 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(“Medical Care in Diabetes-2020),” :

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 who have Type I Diabetes was excluded.

The patients had Blood Pressure measured at the outpatient unit by nurses using a stethoscope and mercury sphygmomanometer(Masding et al., 2001). After a twelve-hour overnight fast, blood was taken from the ante-cubital vein and collected for testing fasting and postprandial 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 analyzed 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.

Ethical approval: Approval from the Institutional Ethics Committee of Shri Guru Ram Rai Institute of Medical and Health Sciences, Shri Guru Ram Rai University, Patel Nagar Dehradun Uttarakhand was duly obtained for all test procedures.

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±5.16, 39.21±3.09 and 38.78±3.77 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	66.32±5.16	39.21±3.09	38.78±3.77
Systolic Blood Pressure (mm of Hg)	138.24±5.68	122.25± 2.12	120.23±1.49
Diastolic Blood Pressure (mm of Hg)	90.15±3.35	83.40±1.01	80.68±1.29

The values are expressed as mean ± standard deviation.

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 2). 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 higher fasting insulin ($p<0.05$) reportedly 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. (Franzago et al., 2020)T2DM is caused by 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 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 beta cell failure and insulin resistance in the muscles and liver(Romao & Roth, 2008). Insulin resistance is clinically and epidemiologically significant among first degree relatives of type-2 diabetic patients because they are at high risk of getting diabetes in the future and insulin resistance has been linked to several clinical and metabolic problems.

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 postprandial sugar and glycated haemoglobin are considerably greater in the entire diabetic group than in the offsprings 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 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 offspring. It contends the prevalence and development of insulin resistance in diabetes individuals and their first-degree relatives.(Kumar et al., 2005b) Arvind et al found that normoglycemic first-degree relatives had higher mean fasting insulin levels (31.24.5 U/ml) than controls (14.44.08 U/ml). Also, when glucose tolerance worsened in first-degree relatives, the mean fasting insulin level and prevalence of insulin resistance increased, from normoglycemic to type-2 diabetes mellitus, indicating that the rise in mean fasting insulin level followed the disease's natural path.

According to O'Rahilly S et al.(O'Rahilly et al., 1988), in fasting non-diabetics, insulin is produced in regular pulses every 12 to 15 minutes. Still, 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 age and weight-matched controls 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. Compared to controls, relatives' first-phase (0 to 10 minute) insulin secretory responses to intravenous glucose treatment were not substantially affected. They hypothesized that abnormal oscillatory insulin secretion might 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 developing impaired glucose tolerance. According to Strączkowski et al.(Strączkowski et al., 2003), insulin resistance can be detected in young, thin individuals 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:

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 the 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. The current study recommends fasting plasma insulin as a simple and accurate test for detecting insulin resistance in diabetics and their first-degree relatives. Thus, it is likely that preventing type-2 diabetes will be more effective if started when blood glucose levels are still normal. A simple test for insulin resistance is needed for both population-based research and clinical practise.

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

Competing interest's disclaimer:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly used in our research area and country. There is 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 litigation but the advancement of knowledge. Also, the research was not funded by the producing company. Rather it was financed by the personal efforts of the authors.

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