Original Article

ASSOCIATION OF FAMILY HISTORY OF TYPE 2 DIABETES MELLITUS WITH INSULIN RESISTANCE

Thejaswini K.O[1], Dayananda G[2], Chandrakala S.P[3]

ABSTRACT

Background: Diabetes Mellitus (DM) is an "iceberg" disease seen in all age groups. India shall have the largest number of diabetics by 2030. Type 2 DM is a metabolic disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin (Insulin resistance - IR) or both. IR is genetically programmed and is influenced by a combination of environmental and physical factors like diet and obesity. IR could increase risk for the early onset of DM in children of diabetics.

Methods: The body mass index (BMI), waist circumference (WC), blood pressure (BP), fasting plasma glucose (FPG), fasting plasma insulin (FPI), HOMA-IR (Homeostatic model assessment – IR) parameters were measured and statistically compared in 30 nondiabetics with family history of type 2 DM and 30 age matched nondiabetics without family history of type 2 DM.

Results: The FPI (8.79 ± 3.06) and HOMA-IR (1.94 ± 0.86) were statistically significant ($p<0.05$) in the FH^+ group when compared to the FH^- group. WC and BP showed a trend towards increase in the FH^+ group.

Conclusion: There is hyperinsulinemia and IR in the FH^+ group. The complex genetic predisposition to IR and its association with the increasing WC in the FH^+ group predisposes such individuals to the development of type 2 DM.

Keywords: Body mass index, family history, fasting plasma glucose, fasting plasma insulin, type 2 diabetes mellitus, waist circumference.

INTRODUCTION

There is a significant increase in the incidence and prevalence of Diabetes Mellitus (DM) worldwide. This increase is seen across all age groups. It is being recently acknowledged by the WHO that India has the largest number of diabetics than any country and by the year 2030 would be having higher numbers of diabetics than the rest of the world. The adaptations of a westernized life style and industrialization observed in the country probably have a contributing role to this developing trend [1]. The development of Type 2 DM has a genetic component which plays an important and a very essential role. There is an increased risk among the children of diabetics for the early onset of Type 2 DM since they share the genetic resemblances [2]. Type 2 DM is a metabolic disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. There are also associated disturbances concerned with protein, carbohydrate and lipid metabolism [3]. The reduced biological effectiveness of insulin / Insulin resistance (IR) is a clinical condition that is characterized by reduced cellular glucose uptake in response to a given concentration of insulin and which has been identified as a public health problem [4, 5]. IR is genetically programmed and is influenced by a combination of environmental and physical factors like diet and obesity [6]. The recent understanding of insulin resistance is based on a lipocentric perspective, by which an accumulation of intramuscular lipids would inhibit translocation of GLUT-4 to the plasmatic membrane [7]. This renders the cell unable to uptake glucose for its activities. Further, the fat accumulation may cause metabolic syndrome (IR syndrome) which is a cluster of abnormalities that enhance cardiovascular risk, including impaired glucose tolerance, dyslipidemia, hypertension, low grade inflammation, etc [8]. This necessitates employing alternate methods of identifying insulin resistance based on indicators associated with body fat content. Family history of type 2 DM seems to increase the risk of hypertension, dyslipidemia and atherogenesis leading to coronary heart disease (CHD) in nondiabetic subjects [9] and even in nondiabetic

offspring of type 2 diabetic patients [10]. Differences in anthropometric parameters, blood pressure levels, insulin resistance, lipid profile, endothelial function, hemostatic factors, and acute-phase reactants may explain the relationship between a genetic predisposition to type 2 diabetes and atherogenesis[8, 11].

In the present study, the researchers have studied and compared the anthropometric indices (BMI, WC), FPG and HOMA-IR index in individuals with and without family history of T2DM. The hypothesis of the study is that, there is a positive association of family history of T2DM with IR which leads to the development of T2DM.

METHODS

The present study design was a case control type having a study group of 60 subjects – 30 non diabetics with family history with at least one first degree relative being Type 2 DM (FH^+ group / cases) and 30 non diabetics without family history of Type-2 DM (FH^- group / controls). Subjects included were both males and females in the age group 30-40 years. The study was conducted at Sree Siddhartha Medical College and Research Hospital, Tumkur, Karnataka, India. Subjects underwent a complete general physical health examination. Details pertaining to family history and clinical were taken through a standard proforma and questionnaire. Informed, written, witnessed consent was taken from all the subjects prior to the investigation. None of the study subjects had any obvious disease (i.e., Diabetes Mellitus, hypertension and endocrinopathies). Also those who were on medications like antidiabetic / antihypertensive / glucocorticoids / other drugs which might have an effect on the study were excluded from the study. The study was approved by the Institutional Ethical Committee.

PROCEDURES

Anthropometry: The anthropometric measurements were recorded with the subjects in light clothing without shoes. Height and weight were both measured in standing position. Height was measured with a horizontal wall mounted height meter to the last complete 0.1 cm and weight with a digital weighing scale to the last complete 0.1 kg. BMI (in kg/m2) was calculated for each subject. WC (in cm) was measured with an insertion tape at the midpoint between the iliac crest and the lower ribs measured at the sides.

Blood Pressure measurement: After a brief rest for 10-15 mins, the blood pressure (BP) was measured on the right arm in the sitting position, using a standard mercury manometer. Two readings at 5 min intervals were recorded from each subject. The lower of the two was recorded as subject's BP. BP was measured by the same doctor / examiner for all subjects.

Biochemical parameters: About 3 ml blood sample was drawn from the anterior cubital vein by a trained technician at the laboratory between 08:00 and 09:00 AM from all subjects after an overnight fast of about 08-10 hours. Samples were centrifuged, plasma separated within 30 minutes of collection and stored at – 20 °C. Fasting plasma glucose (FPG) and lipid analyses were done on the day of blood collection using auto analyser. FPG was estimated by using ERBA diagnostics liquixx glucose kit [6]. Fasting plasma insulin (FPI) was determined by radioimmuno assay (RIA) using human specific antibody RIA kit. HOMA (Homeostatic Model Assessment), to assess IR (HOMA-IR) was calculated [12].

STATISTICAL ANALYSIS: [13, 14]

All data collected were analysed using SPSS 16.0 statistical analysis software. Two tailed independent student t test has been used to assess the significance of anthropometry parameters, BP, FPG, FPI and HOMA-IR parameters between the FH^+ group (cases) and FH^- group (controls). MS offices' excel and word was used to generate the tables.

RESULTS

This case-control, comparative study comprised total 60 subjects. FH^- group - 30 without family history and FH^+ group - 30 with family history (with at least one first degree relative being Type 2 DM) of Type 2 DM. Anthropometric measurements, BP, FPG, FPI, HOMA-IR parameters of the two groups were recorded and compared for statistical significance.

Anthropometry parameters did not show significant

difference between the two groups ($p > 0.05$). (Table-1)

The baseline BP (systolic, diastolic) did not show significant difference between the two groups ($p > 0.05$). (Table-2)

The FPG did not show significant difference between the groups ($p > 0.05$). (Table-2)

The FPI, HOMA-IR was significantly higher in the FH^+ group ($p < 0.05$). (Table-2)

	FH^- group	FH^+ group	p value
Age	34.42 ± 3.17	35.35 ± 3.41	0.208
Body mass index (BMI)	22.29 ± 1.43	22.88 ± 1.35	0.165
Waist circumference (WC)	94.30 ± 7.93	100.30 ± 7.27	0.059

Table - 1 : COMPARISON OF AGE, BMI AND WC BETWEEN THE FH – GROUP AND THE FH + GROUP

Parameters	FH^- group	FH^+ group	P value
Systolic BP (mmHg))	114.16 ± 3.84	116.65 ± 4.44	0.060
Diastolic BP (mmHg)	74.64 ± 3.01	77.65 ± 3.62	0.061
Fasting Plasma Glucose (FPG) (mg/dl)	88.85 ± 8.41	90.85 ± 6.16	0.281
Fasting Plasma Insulin (FPI) (μU/ml)	5.66 ± 1.24	8.79 ± 3.06	0.005 **
HOMA-IR	1.19 ± 0.31	1.94 ± 0.86	0.006 **

Table - 2 : COMPARISON OF BP, FPG, FPI, HOMA-IR AND LIPID PARAMETERS BETWEEN THE FH – GROUP AND THE FH + GROUP

DISCUSSION

In the present study, the FH^+ group were associated with higher fasting plasma insulin and HOMA-IR values. These findings strongly suggest a genetic predisposition to the causation of insulin resistance leading to the development of Type 2 DM later. There is also interplay between environmental and genetic factors in the pathogenesis of type 2 diabetes. This pathogenesis of diabetes is evident by studies in twins [15] , those who have one first degree relative suffering from diabetes (have a 40% risk) and in those if diabetes is seen in both parents (the risk is doubled)[16].

The FH^+ group were found to have fasting hyperinsulinemia and IR despite a normal FPG. These findings are probably due to target tissue insensitivity to insulin or a reduced number of insulin receptors on the target cell surface. Fasting hyperinsulinemia reflects the compensatory beta cell response to the underlying IR. This facilitates to maintain a normal FPG. Further decrease in insulin response to a glucose load suggests decreased beta cell responsiveness, is a predictive factor of type 2 DM [17]. The IR can be attributed to obesity and it seems to have a genetic predisposition. Also, the contribution of physical inactivity to the development of IR is unknown [18].

These findings of the study support previous reports of hyperinsulinemia, IR and altered lipids in well controlled type 2 DM patients. This probably develops concomitantly with the failure of insulin activity. Other studies also hypothesise that IR leads to the release of fatty acids from adipose tissue, increased delivery of free fatty acids to the liver and increased hepatic synthesis and output of very low-density lipoproteins and glucose [19]. Thus there is an altered carbohydrate and lipid metabolisms [20]. Earlier reports also suggest that hypertensive patients demonstrate an altered lipid profile than does the general population [15]. This study involved normotensive subjects and further, the inclusion of hypertensive subjects would probably have shown more underlying lipid abnormalities leading to the causation of diabetes.

Obesity is associated with many metabolic risks. Fewer studies of obesity-related disorders have been performed in the Asian countries [5]. BMI is the widely used measurement to reflect general obesity. However, BMI does not take into account the proportion of weight related to increased muscle or the distribution of excess fat within the body, both of which affect the health risks associated with obesity [16]. Individuals with a similar BMI can vary considerably in their abdominal fat mass [17]. Also its limitations are its dependency on race, with Asians having large percentages of abdominal fat at low BMI values [18]. This difference may be explained by the different ethnicity and nutritional status. For these reasons, WC is a desirable measure of the increased risk of obesity related illnesses [19].

The FH^+ group had an increasing WC ($p = 0.059$), though not significant,. The increased WC may involve excess exposure of the liver to fatty acids [20]. The molecular mechanisms by which obesity

contributes to glucose intolerance and dyslipidemia remain elusive. It probably involves a combination of genetic factors and mechanisms by which skeletal myocytes and central adipocytes play a determining role [21]. Thus this study supports the use of WC as a simple and non-invasive method for detection of obesity causing IR and dyslipidemia as important cardiovascular risk factors.

The high prevalence of DM and the considerable percentage of nondiagnosed diabetics make it necessary to generalise the screening methods of DM. Especially for those who have cardiovascular risk factors such as positive family history, are overweight or obese and older than 30 years of age. Additional promotional knowledge of the risk factors, symptoms and side effects of DM can play an effective role in the prevention, timely diagnosis and control of the disease.

The favourable impact of regular physical activity on diabetes risk extends beyond issues of weight management. Physical activity is directly associated with improved carbohydrate metabolism, as demonstrated by decreased insulin levels, increased insulin sensitivity, and a lower incidence of diabetes[18].

CONCLUSIONS

There is hyperinsulinemia, IR and an altered lipid metabolism in the FH $^{+}$ group. The complex genetic predisposition to IR and its association with the increasing WC in the FH $^{+}$ group predisposes such individuals to the development of type 2 DM. This strong familial aggregation cannot be modified after birth. There is also interplay between environmental, metabolic and genetic factors in the pathogenesis of type 2 diabetes [22].

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1. **Thejaswini K.O**
Dept of Physiology,
Sree Siddhartha Medical College and
Research Hospital, Tumkur,

2. **Dayananda G**
Dept of Physiology,
M S Ramaiah Medical College, Bangalore.

3. **Chandrakala S.P**
Dept of Anatomy,
Sree Siddhartha Medical College and
Research Hospital, Tumkur, Karnataka, India.