ORIGINAL ARTICLE

Glucose Intolerance, Insulin Resistance and Obesity Risk in Children with Family History of Type II Diabetes

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Abstract:

Background: Genetic milieu increases the risk of diabetes; it results in disturbance of a number of metabolic pathways involved in blood glucose levels regulation and body weight. Family history of type II diabetes is one of the potential risk factors for developing diabetes.

Objective: The objective of the research was to determine early disturbance in the carbohydrate metabolism and the risk of overweight and obesity among children with family history of type II diabetes.

Materials and Methods: A total of 184 subjects (males & females) with and without family history of diabetes (FHD) were included in the study. Body weight, height and waist circumference was measured, BMI was calculated. Fasting blood glucose (FBG), 2hr oral glucose tolerance test (2hr OGTT), HbA1C and serum insulin levels were determined in duplicate, and HOMA-IR was calculated for insulin resistance index. Results: It was observed that children of type II diabetic parents had significantly higher body weight, BMI, waist circumference, FBG, HbA1C, 2hr OGTT and HOMA-IR. There was high degree of prevalence of overweight, obesity, impaired fasting glucose (IFG) and impaired 2hr oral glucose tolerance test in subjects with FHD compared to those with no FHD. There was significant association of HbA1-C, IFG, impaired 2hr-OGTT and BMI with FHD. There was no association of FBG with BMI.

Conclusion: Children of type 2 diabetic parents have metabolic disturbances at an early age resulting in glucose intolerance and insulin resistance which predisposes them at a risk of type II diabetes and obesity.

*There is no conflict of interest between authors

Introduction

Type 2 diabetes (T2D) accounts for 90% of the cases globally and is the predominant form of diabetes affecting a large number of individuals[(1)]. T2D is a multifactorial and heterogeneous disease due to complicated interaction between genetics and environment to which person is exposed[(2)]. The epidemic of diabetes is strongly associated to the rapidly changing life style and socioeconomic change[(3)]. T2DM usually has its onset after 40 years of life. In recent years there is marked decrease in age of onset of diabetes. It is a bitter reality that there is an increase in incidence of diabetes in children, adolescent and young adults in high rates. There is a high prevalence of T2D among close relations along with a high incidence among twins. It is seen that diabetes is more common in certain ethnic groups which shows a definite relation between genetic relation of occurrence of disease [(4,5)].

Family history (FH) of T2D is a potential risk factor for developing diabetes. First degree non diabetic relatives are shown to have disturbance of carbohydrate and lipid metabolism[(6)]. There is

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definitely some relationship of genes with dysfunction of beta cell and insulin resistance in these individuals[7] Recent genome-wide study has further strengthened the role of complicated interaction of genetics, epigenetics, and the environmental factors in the development of T2D[8]. History of diabetes in pregnancy or before that is associated with poor control of blood glucose in children suggesting that exposure of fetus to disturbed intra uterine metabolic environment that may have long term effects on offspring [9,10].

Ethnic and racial differences have also been implicated in the occurrence of T2DM. After different research it is apparent that peoples in particular area, population and ethnicity are more prone to disease. Genetic factors, intra uterine and early childhood environment are important in determining these ethnic differences. It is also reported that South Asian adults are more predisposed to T2D[11]. Consumption of large amount of saturated fats have important role in decreasing insulin sensitivity, dysfunction of β-cell, increase in body weight and disturbance of glucose regulation in genetically predisposed subjects [12].

Furthermore, both obesity and FH increase the risk of T2DM.[13] In a certain groups, high BMI is strongly related with impaired insulin secretion, insulin resistance and disturbed glucose metabolism[14]. A study regarding the frequency of T2D in family members of diabetic subjects of black South African ethnicity, reported that 27.3% diabetic subjects had a FH[15]. The present study was carried out to determine the early disturbances of the carbohydrate metabolism and the risk of overweight and obesity among children and adolescents with family history of type II diabetes.

Materials and Methods

A selected number of 184 healthy subjects (male=84, females=100) between the 10-20 years of age were included in the study with permission from Institutional Review Board of Shalamar Institute of Health Sciences Lahore Pakistan and a written informed consent from every subject or his parents .A study designed proforma was distributed among all participants to get all information with special focus on their family history of diabetes and any other major related disease. As far exclusion criteria is concerned subjects with history of T1DM in either of the parents, taking medications known to alter body metabolic process, with endocrine diseases like Cushing's syndrome, acromegaly, or any major disease, . Subjects with both or either of the parents not alive were also not included in the study. Parents having FBG ≥126mg/dl were labeled as diabetic[16]. All subjects included in the study had fasting blood glucose levels (FBG) <126mg/dl and no signs of any disease.

It was a cross sectional comparative study. On the basis of detailed medical and family history of diabetes, the participants were divided into the following groups:

Healthy subjects with H/O one or both parents with type 2 diabetes (FHD) (n=124; mean age: 17.52 yrs)

Healthy subjects with no H/O type 2 diabetes in either parent (control group) (n=60; mean age: 16.68 yrs)

All the subjects underwent a detailed general physical examination, body weight, height and waist circumference were recorded in each case (17). Body height was measured by digital scale. The height was measured by wall-mounted stadiometer. Body mass index (BMI) was determined as:

$$BMI = \text{Body weight (kg)} / \text{Body height (m)}^2$$

WHO criteria for obesity and overweight was used[17]. About 4 ml of venous blood was taken after overnight fasting of 12 h. Two ml of sample was added to a fluoride EDTA tube for glucose estimation by glucose oxidase method, whereas 2 ml of sample was added to an EDTA tube for HbA1-C measurements. In order to see glucose tolerance a Glucose tolerance test (2 hr-OGTT) was done, according to the standard international procedure[18]. All subjects were advised to take food having at least 150 gm of carbohydrates for 3 days before this OGTT. The subjects were given 75 gm anhydrous

glucose dissolved in plain water and the two ml of blood samples were collected 2 h thereafter. The blood samples were used to determine glucose levels on the same day.

All tests were done by standard methods. The diabetes was reconfirmed by determining fasting blood glucose (FBG levels). Parents having FBG ≥126mg/dl were labeled as diabetic. Subjects with fasting blood glucose ≥100mg/dl & <126mg/dl were considered to have Impaired fasting glucose (IFG) and those with >140mg/dl blood glucose 2h after OGTT were labeled as Impaired 2 hr-OGTT [16]

Blood glucose levels were estimated by the glucose oxidase method using RANDOX Laboratories, England reagent kit. HbA1-c was done by affinity liquid chromatography method. Fasting Serum Insulin levels were determined by ELISA using commercial kits. In order to determine insulin resistance a method called HOMA-IR (Homeostasis model assessment of insulin resistance) and following equation was used.

HOMA-IR = Insulin(Fasting) (μU/ml) x glucose (Fasting) (mmol/l) / 22.5 [19].

SPSS version 17 was used for analysis of data. All Quantitative d data were expressed as mean ± standard error of mean (SEM). Student't' test was used to determine significance of differences among the groups. Then it is Chi- Square test and to see the association of FHD with BMI, HbA1-C, IFG, 2hr-OGTT and HOMA-IR. p value < 0.05 was considered statistically significant.

Results

There were 124 subjects with family history of one or both parents with type 2 diabetes (FHD) with a mean age of 17.52 yrs and 60 subjects mean age 16.68 with no history of type 2 diabetes in either parent.

As far as Body weight, BMI and waist circumference of the subjects is concerned it was significantly higher in those who have family history of diabetes as compared to controls (p<0.05). There was no statistically significant difference in the body height of subjects with and without family history of diabetes (Table 1).

There was higher prevalence of overweight and obese subjects (36%) with FHD compared to those with no FHD (10%) (Table 3). When the group with FHD was further analyzed 16% of the subjects were overweight (BMI>25&<30) and 19% were obese (BMI>30).

Glycosylated Hemoglobin (HBA1C), Blood Glucose Fasting (FBG) and 2hr OGTT:

Subjects with FHD had significantly higher HbA1-C, FBG and 2hr-OGTT (P<0.05) compared to control group (Table 2). Large number of subjects (41%) with one or both parents with type 2 diabetes had HbA1-C > 5.5% as compare to controls (16%). There was also significant association of HbA1-C with FHD (p< 0.0009) (Table 3).

There was significantly higher number of subjects with IFG (29%) and impaired 2hr-OGTT (22%) in the group with FHD compared to those with no FHD. There was significant association of FHD with IFG (p<0.0001) and 2hr-OGTT (p<0.0002) (Table 3). We did not find any association of FBG with BMI (p>0.05).

Fasting insulin levels although were high in subjects with FHD compared to control group but this difference was statistically not significant (p>0.05) (Table 2)

Subjects with FHD had significantly higher HOMA-IR (P<0.05) compared to control group (Table 2). Significant number of subjects (37%) with FHD had insulin resistance as shown in Table3.

Table1: *Anthropometric Characteristics of subjects with Family History of Diabetes (FHD) and non diabetic parents (control)*

Group	n	Body weight (Kg)	Height (m)	BMI Kg/m ^{2}	Waist circumference
FHD	124	64.82±1.9 [a]	1.66±0.01	25.90±0.68 [a]	86.02±0.90 [a]
Control	60	61.48±1.5	1.68±0.01	21.49±0.42	73.11±0.86

Mean ± SEM of study variables, a significantly different from the appropriate group (P<0.05; student t-test): a FHD vs Control

Table 2: *Metabolic Characteristics of subjects with FHD and non diabetic parents (control)*

Group	Hb A1-c%	Glucose (mg/dl)	2hr –OGTT (mg/dl)	Fasting Insulin (µIU/L)	HOMA-IR	p value
FHD	5.63±0.05 [a]	97.76±1.16 [a]	119±2.94 [a]	12.51±1.08	3.44±0.31 [a]	0.002
Control	5.11±0.08	84.34±1.19	97.22±2.53	9.97±0.79	1.74±0.13	0.1

Mean ± SEM of study variables, a Significantly different from the appropriate group (P<0.05; student t-test): a FHD vs Control

Table 3: *BMI, HbA1-C, Impaired Fasting Glucose (IFG), Impaired 2hr oral Glucose (2hr-OGTT) and HOMA-IR of the subjects with and without FHD*

	FHD	Control	X^2/P/OR
BMI>25	(36 %)	(10%)	13.9/0.0001/5.12
HbA1-C >5.5%	(41%)	(16%)	10.92/0.0009/3.4
Impaired Fasting Glucose (IFG) ≥100mg/dl & <126mg/dl	(29%)	(5%)	13.98/0.0001/7.7
Impaired 2hr oral Glucose Tolerance Test (2hr-OGTT) >140mg/dl	(22%)	(1.6%)	13.2/0.0002/17.2
HOMA-IR	(37%)	(10%)	12.5/0.0001/5.02

Percentages in parenthesis, P<0.05 statistically significant, X2 = Chi-square and OR= Odds ratio

Discussion

In the present study children with history of diabetic parents had significantly high body weight, BMI and waist circumference, 36% of the subjects were found to be overweight and obese. 19% of the subjects with FHD were obese which is consistent with reports from India but lower when compared with studies from Eastern Europe and Middle East[20,21].

FBG, HbA1C and 2hr OGTT of the children of diabetic parents was also significantly higher as compared to control group, there was high prevalence of IFG and impaired 2hr OGTT in subjects with FHD compared to those with no FHD in the current study. It was further confirmed by a contemporary study which indicated that glucose tolerance was interconnected with a family history of diabetes[22]. Other studies have reported the fact that FHD is positively linked to disturbance of carbohydrate metabolism associated complications and obesity in children[5,23,24]. Our data clearly demonstrates that there are dysregulated carbohydrate and lipid metabolism in these children. FHD confer a risk for metabolic disturbances such as IFG, Impaired 2hr-OGTT, insulin resistance and obesity. Parental History of T2D has been associated with vigorous expression of T2D associated risk factors in adolescents and young male adults[25]. Similarly in Italian overweight and obese children high prevalence of glucose intolerance has been reported as compared to Europeans [26].

Disturbance of glucose metabolism in genetically predisposed individuals due to reduced insulin sensitivity and beta-cell function have indicated the involvement of multiple factors in patho-

physiology of Impaired Glucose Tolerance and T2D[2]. We did not find any association of FBG with BMI suggesting that disturbance of glucose metabolism is linked to genetic background and is independent of body fat mass. Whereas a recent study has reported the association of high BMI with decreased insulin sensitivity in Chinese with type 2 diabetes mellitus[27]. In the current study the subjects with FHD had high HOMA-IR indicating the occurrence of insulin resistance in children. The high frequency of insulin resistance seen in adults is apparent in children at a very younger age[14]. Small sample size and failure to perform hyperinsulinemic clamp test for insulin resistance due to limited resources and facilities are the weakness of the study. However this study has provided us with markers of early disturbance of glucose regulation in healthy children of diabetic parents. Further studies on a large sample size and in children between 5 to 10 years of age should be carried out to investigate how early we must take measures to adopt healthy life style in children to prevent onset of glucose intolerance and insulin resistance.

Conclusion

The children with parental history of T2D must be monitored for glucose intolerance, insulin resistance and BMI annually. Parental history of T2D increases the risk of not only glucose intolerance and T2D but also other cardio-metabolic risk factors like overweight and obesity. It has been seen that those individuals found to have IFG and IGT, with an A1C of 5.7–6.4% suffer from insulin resistance and are more prone to diabetes as well as heart and vascular disease and they should be advised to adopt effective strategies in the form of change in life style to lower their risks.

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