Original Article

Family History of Diabetes and Parental Consanguinity: Important risk for Impaired Fasting Glucose

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Abstract

Objective: Offspring of type 2 diabetics have increased risk of metabolic disturbances. The aim of the study was to access the potential effect of family history of type 2 diabetes (FHD) and parental consanguinity on fasting plasma glucose (FPG) levels.

Design: Non diabetic offspring of one or both parents with type 2 diabetes and healthy controls of comparable age, without a FHD were the subjects of this study. FHD was defined by the presence of type 2 diabetes in one or both parents of the subject. Consanguinity was defined as history of marriage with first cousin. FPG levels were determined in cases and controls.

Results: IFG was identified in 42% subjects with a FHD and in 14% without FHD. We found a strong independent association of FHD with impaired fasting glucose in both males and females by logistic regression analysis after adjusting the data for age sex and BMI. Parental consanguinity modifies the effect of FHD on IFG.

Conclusion: We concluded that family history of diabetes and parental history of consanguinity determine the risk for impaired fasting glucose in our population.

Keywords: Impaired fasting glucose; Parental consanguinity; Family history of diabetes.

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Introduction

Type 2 diabetes mellitus (T_2DM) is the predominant form of diabetes accounting for 90% of all cases paralleling an increase in the incidence of obesity.[1,2] It is one of the major public health challenges of 21st century and its global prevalence has attained an epidemic proportion.[3] Recent increase in the prevalence of diabetes reflects the environmental, behavioral and life style changes with consumption of high caloric diet and reduced physical activity. Previously T_2DM was a disease of middle aged and older people, usually presents at age > 40 years. In the recent decades the age of onset of T_2DM has decreased and increasingly it is being observed at a younger age.[4] Much attention has been paid in the last few years on the identification of individuals at risk for developing T_2DM.

T_2DM is a multifactorial and heterogeneous condition due to complex interaction of genetic and environmental factors. The high incidence of T2DM among first degree relatives, a high concordance in identical twins and the increased prevalence in certain ethnic groups, provide strong evidence that genetic factors underlie the susceptibility to diabetes[5,6]. Genetic background of diabetes increases the risk of metabolic abnormalities.[7,8] Evidence is available suggesting disturbances of carbohydrate and lipid metabolism in individuals with a history of T_2DM in first degree relatives.[9-12] Previous studies reported higher fasting plasma glucose (FPG) in non-diabetic males with a FHD as compared to those with no FHD.[13,14] A study reported that Asian Indian adolescents with both diabetic parents had high FPG was as compared to one diabetic parent.[15] While another study failed to report any difference of FPG in subjects with FHD as compared to the subjects without FHD.[16] Some of the studies also reported the association between FHD and hyperglycemia.[17,18] IFG is associated with cardiovascular risk factors, such as hypertension and dyslipidaemia[19]. Impaired fasting glucose (IFG) has been reported in 19.1% of Mexican children and adolescents demonstrating a high prevalence of Prediabetes in these subjects.[20] Moreover the presence of FHD in Mexican children and adolescents associated with IFG.[21] Obesity is also considered a contributing factor for T_2DM. In overweight Latino children with FHD increased risk of impaired glucose tolerance test has also been observed.[22]

The association of FPG with BMI have been reported in children in some studies while others do not support this association.[23,24,13] Furthermore studies in different populations and geographical areas demonstrate an increase susceptibility of certain ethnic groups to develop T_2DM. The consanguineous marriages are quite common in Pakistan (South East Asia), with first cousin marriages being the most common. Consanguinity along with cultural and environmental factors may be responsible for early onset of the disease in our population. Keeping in view the genetic, ethnic and cultural variations, we investigated the interaction between FHD and parental consanguinity on IFG in Pakistani subjects.

Materials and Methods

Study Design

It was a cross – sectional study.

Setting

Study was carried out in the Center for Research in

Endocrinology and Reproductive Sciences (CRERS) University of Health Sciences Lahore Pakistan.

Selection and Description of Participants

A total of 226 subjects of both sexes between 10 – 25 years of age were included in the study. Subjects were divided in the following 2 groups:

Group I: Subjects with a history of T_2DM in one or both parents (n = 124).

Group II: Subjects with no history of T_2DM in any parent (n = 102).

A total of 500 known diabetic parents from diabetic centers and clinics in Lahore were enrolled for the study. Male and female offspring (n = 124, age 10 – 25 years) of (one or both) diabetic parents volunteered and were selected to participate in the study. Non diabetic friends, neighbors and distant relatives of diabetic parents were also enrolled for the control group. Age matched 102 offspring of non diabetic parents volunteered and included in the study. Subjects of 15 – 25 years were included to examine the effect of FHD and parental consanguinity at a younger age group and more over the age for the onset of T_2DM has also decreased in the recent decade. FHD was defined by the presence of T_2DM in one or both parents of the subject.

Written informed consent from the subjects / and or parents was obtained before administering the questionnaire. Questionnaire was completed regarding the detailed FHD, medical history, past history and history of parental consanguinity. Presence of T_2DM in either parent was ascertained by detailed history, medical examination, laboratory investigations (FPG, HbA1-C) and/or verification of present and past clinical records of both parents. FPG and HbA1-C levels of non diabetic parents were determined to reconfirm absence of diabetes. All non diabetic parents had normal FPG (< 126 mg/dl) and HbA1-C (3.5 – 5.5%).

Three generation pedigrees were drawn to ascertain the family history and consanguinity in the parents. Consanguinity was defined as history of marriage with first cousin.

Individuals of estranged or bereaved parents, type 1 diabetic parents, were excluded from the study. Individuals with a history of Cushing' syndrome, thyrotoxicosis, or a major illness and those on medication known to affect body composition, were excluded from the study. All subjects underwent detailed medical examination. IFG was defined by fasting plasma glucose between 100—125 mg/dl (5.6—6.9 mmol/L).[25]

Physical Measurements and Blood Collection

Body height was measured with a stadiometer to the nearest centimeter and weight to the nearest kg. Body mass index (BMI) was calculated according to the formula:

$BMI = BW (kg) / height (m)^2$

In all cases blood was withdrawn between 0800 – 0900 h. Two ml of venous blood was drawn from the cubital vein after overnight fasting of 12 h. Sample was added to a fluoride EDTA tube for glucose estimation.

Analytical Methods

FPG of both subjects and parents were determined. Blood glucose levels were determined by the glucose oxidase method using a commercial reagent kit (RANDOX Laboratories, Crumlin, UK) with a Huma-Star 180 chemistry analyzer (Human, Wiesbaden, Germany) in duplicate. HbA1-c of the parents was estimated by affinity liquid chromatography with a D-SI Glycomat (Provalis Diagnostics, Deeside, UK).

Statistical Analysis

Numerical values were reported as mean ± standard error of means (S.E.M) and categorical variables as proportions. Chi-square test and independent sample t-test were used to compare the two groups for categorycal data and numerical respectively. Age, sex and BMI adjusted logistic regression analysis was performed to determine the association between FHD (independent variable) and IFG (dependent variable), parental consanguinity (independent variable) and IFG (dependent variable). p value < 0.05 was considered statistically significant. All calculations were carried out with the SPSS version 16 (SPSS, Inc. Chicago, IL, USA).

Results

A total of 226 healthy non diabetic subjects of both sexes with average age (19.9 ± 0.25) years were selected. It included 151 male and 75 female subjects. There was no significant difference in the age groups of male and female subjects with and without FHD (Table 1). Parental consanguinity was found in (69%) of subjects with FHD and (29%) of the subjects without FHD (Table 2). BMI of the subjects with FHD was significantly higher ($p < 0.001$) as compared to the subjects without FHD (Table 2). BMI of the subjects with FHD and parental history of consanguinity both was higher as compared to those with no FHD and no parental history of consanguinity (Table 3). Males with a FHD had significantly higher BMI as compared to the males without FHD whereas no statistically significant difference in the BMI of the female subjects with and without FHD was found (Table 1). Similarly there was no significant difference in the BMI of the male and female subjects with FHD. The prevalence of obesity, overweight and normal weight in the group with FHD was 19%, 17% and 64% respectively while it was 2%, 7% and 9% respectively in group without FHD (Table 2). We did not find any association of BMI with FPG levels in any of the groups.

The mean FPG (5.42 ± 0.06 mmol/L) of subjects with a FHD was significantly greater ($p < 0.001$) than those without FHD (4.82 ± 0.06 mmol/L) (Table 2). Subjects with FHD and parental history of consanguinity both, had FPG levels significantly higher ($p < 0.001$) than those with no FHD and no parental history of consanguinity (Table 3). IFG was identified in 42% subjects with a FHD and in 14% without FHD (Table 2) which was higher in females (51%) as compared to males (36%) in the group with FHD (Table 1). But

Table 1: Mean ± SEM of age, body mass index (BMI), fasting plasma glucose (FPG) and prevalence of impaired fasting glucose (IFG) and obesity in male and female subjects according to the family history of diabetes (FHD).

*P<0.05 statistically significant difference between the groups with and without FHD

	FHD +ve		FHD -ve	
	Male	**Female**	**Male**	**Female**
N	79	45	72	30
Age	20.13 ± 0.29	18.07 ± 0.49	21.23 ± 0.43	18.83 ± 0.82
BMI	25.69 ± 0.82*	24.05 ± 1.15	21.35 ± 0.40	21.26 ± 0.34
FPG (mmol/L)	5.34 ± 0.07*	5.56 ± 0.10	4.79 ± 0.07	4.90 ± 0.12
IFG %	28 (36%)	23 (51%)	9 (12%)	6 (20%)
Obese	8 (18%)	8 (17%)	1 (2%)	0%

Table 2: Mean ± SEM of body mass index (BMI), fasting plasma glucose (FPG) and prevalence of impaired fasting glucose (IFG), obese, overweight, non obese and parental history of consanguinity according to the family history of diabetes (FHD).

	FHD +ve n = 124	FHD-ve n = 102
Age	19.38 ± 0.31	20.56 ± 0.40
BMI	25.09 ± 0.67*	21.33 ± 0.30
Fasting Plasma Glucose (FPG) mmol/L	5.42 ± 0.06*	4.82 ± 0.06
Impaired Fasting Glucose (IFG)%	52 (42%)	15 (14.7%)
Obese	24 (19%)	2 (2%)
Over weight	21 (17%)	7 (7%)
Non obese	79 (64%)	93 (91%)
History of Consanguinity	86 (69%)	30 (29%)

*P<0.05 statistically significant difference between the groups with and without FHD

Table 3*:* Mean ± SEM of body mass index (BMI), fasting plasma glucose (FPG), prevalence of impaired fasting glucose (IFG) and obesity of subjects according to the family history of diabetes (FHD) & parental history of consanguinity.

	FHD +ve Parental history of Consanguinity +ve n = 86	FHD –ve Parental history of Consanguinity –ve n = 73
Age	20.05 ± 0.38	20.70 ± 0.50
BMI	25.76 ± 0.89*	21.17 ± 0.31
Fasting Plasma Glucose (FPG) mmol/L	5.61 ± 0.07*	4.87 ± 0.07
Impaired Fasting Glucose (IFG)%	43 (51%)	14 (19%)
Obese %	21 (24%)	5 (6.8%)

*P < 0.05 statistically significant

there was no difference in the prevalence of IFG between obese male and female subjects in this group. Prevalence of IFG increased to 51% in the group with FHD along with parental consanguinity as compared to 19% in those no FHD and no history of parental consanguinity (Table 3).

We found independent association of FHD with IFG in both males and females [Chi square = 13.89, (p-value = 0 < 0.001); odds ratio (OR) 13.89] by logistic regression analysis after adjusting the data for age sex and BMI. We also found significant association [Chi square = 16.31 (p-value = 0 < 0.001); odds ratio (OR) 4.21] of (FHD × parental history of consanguinity) with IFG, suggesting that there is strong interaction of FHD and parental consanguinity on IFG.

Discussion

The results of this study indicated that parental consanguinity modifies the effect of FHD on IFG. FHD and parental history of consanguinity determine the risk for impaired fasting glucose.

T_2DM is a heterogeneous and multifactorial condition due to complex interaction of genetic environmental and cultural factors. Studies identifying risk factors for T_2DM has gained momentum in the last few years due to increasing prevalence and onset of the disease at a much younger age. Genetic background of diabetes predisposes to abnormal carbohydrate and lipid metabolism.[7,8] Studies carried out in different populations and ethnic groups reported high prevalence of obesity and metabolic abnormalities in offspring of diabetic parents, predisposing them at the risk of developing diabetes.[11,22,21] In our study 19% of the subjects (age 15 – 25 years) with FHD are obese which is in consistent with the study reported recently from India but lower when compared with[26,27] studies from Eastern Europe and Middle East. When parental consanguinity was also considered along with FHD the prevalence of obesity increased to 24% which showed the effect of parental consanguinity on metabolic disturbances in the offspring.

FPG levels of both male and female subjects with FHD were within normal range but significantly hig-

her as compared to those without FHD. These observations are in agreement with our earlier observations in male offspring with both diabetic parents.[13]

When subjects with FHD × parental consanguinity were compared with the subjects with no FHD × parental consanguinity, FPG levels were significantly ($p < 0.05$) higher. This suggests disturbances of glucose metabolism are more robustly expressed in subjects with both FHD and parental consanguinity. We did not find any association between BMI and FPG levels suggesting that disturbances of glucose metabolism are independent of body fat mass. We also analyzed the data after adjusting for BMI and the results were significant indicating interaction of FHD × parental consanguinity on fasting glucose levels.

IFG was identified in 42% of the subjects with a FHD and the prevalence of IFG was even higher (51%) when parental consanguinity and FHD were considered together.

The prevalence observed in our study is higher than that reported in Mexicans.[20] This suggests that cultural factors such as parental consanguinity a contributing factor for high prevalence of Prediabetes and diabetes in South East Asians. We observed a strong association of FHD × parental consanguinity with IFG independent of obesity suggesting that individuals with FHD and parental consanguinity should be screened for Prediabetes at an early age. Similar association between FHD and IFG has been reported in Mexicans children (7 – 15 years) with FHD in first degree relative.[21] High prevalence and association of IFG with FHD and parental consanguinity suggest that defects of glucose metabolism are genetically determined.

Conclusion

In conclusion our study suggests parental consanguinity modifies the effect of FHD on IFG. FHD and parental history of consanguinity determine the risk for impaired fasting glucose in our Pakistani population. This finding could help in the screening of at risk population for T_2DM. It is therefore recommended that children with a FHD and parental consanguinity should be screened at an early age for the detection of Prediabetes. Those found with IFG should be monitored and managed with life style modifications to prevent or delay the development of T_2DM.

Future studies on a large sample size, prepubertal children and different ethnic groups need to be carried out to further elaborate the role of FHD and parental consanguinity.

Acknowledgements

This study was supported by a research grant from the Higher Education Commission, Pakistan.

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