

# Family History of Diabetes and Parental Consanguinity: Important Risk for Impaired Fasting Glucose in South East Asians

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## ABSTRACT

**Objective:** Offsprings of Type 2 diabetics have increased risk of metabolic disturbances. The aim of the study is to assess the potential effect of family history of Type 2 diabetes (FHD) and parental consanguinity on fasting plasma glucose (FPG) levels.

**Subjects and Methods:** Non-diabetic offsprings of one or both parents with Type 2 diabetes and healthy controls of comparable age, without a FHD were the subjects of this study. Family history of Type 2 diabetes 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 a first cousin. Fasting plasma glucose levels were determined in cases and controls.

**Results:** Impaired fasting glucose (IFG) was identified in 42% of subjects with 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, gender and body mass index (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 this study population.

**Keywords:** Family history of diabetes, impaired fasting glucose, parental consanguinity

# Historia Familiar de Diabetes y Consanguinidad de los Padres: Riesgo Importante para la Glucosa en Ayunas Alterada en Asiáticos Sudorientales

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## RESUMEN

**Objetivo:** Los hijos con diabetes de Tipo 2 tienen un riesgo mayor de trastornos metabólicos. El objetivo de este estudio es evaluar el efecto potencial de la historia familiar en la diabetes Tipo 2 (HFD) y la consanguinidad de los padres en los niveles de glucosa plasmática en ayunas (GPA).

**Sujetos y Métodos:** Los hijos no diabéticos de uno o ambos padres con diabetes de Tipo 2 y controles sanos de edad comparable, sin HFD, constituyeron los sujetos de este estudio. La historia familiar de diabetes de Tipo 2 se definió por la presencia de la diabetes de Tipo 2 en uno o ambos padres del sujeto. La consanguinidad se definió como la historia del matrimonio con un primer primo o prima. Los niveles de glucosa plasmática fueron determinados en los casos y los controles.

**Resultados:** La glucosa en ayunas alterada (GAA) fue identificada en el 42% de los sujetos con HFD y en 14% sin HFD. Se halló una fuerte asociación independiente fuerte de HFD con la glucosa en ayunas alterada tanto en varones como en hembras, mediante el análisis de regresión logística después de ajustar los datos de edad, género e índice de masa corporal (IMC). La consanguinidad de los padres modifica el efecto de HFD sobre la GAA.

**Conclusión:** Se llegó a la conclusión de que la historia familiar de diabetes y la historia de consanguinidad de padre y madre determina el riesgo de glucosa en ayunas alterada en la población bajo estudio.

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**Palabras claves:** historia familiar de diabetes, glucosa en ayunas alterada, consanguinidad de padre y madre

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## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes, accounting for 90% of all cases and paralleling an increase in the incidence of obesity (1, 2). It is one of the major public health challenges of the 21<sup>st</sup> century and its global prevalence has attained epidemic proportion (3). Recent increase in the prevalence of diabetes reflects the environmental, behavioural and lifestyle changes with consumption of a high caloric diet and reduced physical activity. Previously, T2DM was a disease of middle aged and older people and usually presented above age 40 years. In recent decades, the age of onset of T2DM has decreased and increasingly it is being observed at a younger age (4). Much attention has been paid in the last few years to the identification of individuals at risk for developing T2DM.

Type 2 diabetes mellitus 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 T2DM in first degree relatives (9–12). Previous studies reported higher fasting plasma glucose (FPG) in non-diabetic males with a family history of Type 2 diabetes mellitus (FHD) as compared to those with no FHD (13, 14). A study reported that Asian Indian adolescents with both diabetic parents had high FPG as compared to those with one diabetic parent (15). Another study reported no significant 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 hyperglycaemia (17, 18). Impaired fasting glucose (IFG) is associated with cardiovascular risk factors such as hypertension and dyslipidaemia (19). Impaired fasting glucose has been reported in 19.1% of Mexican children and adolescents, demonstrating a high prevalence of pre-diabetes in these subjects (20). Moreover, the presence of FHD in Mexican children and adolescents has been found to be associated with IFG (21). Obesity is also considered a contributory factor to T2DM. In overweight Latino children with FHD, an increased risk of impaired glucose tolerance test has also been observed (22).

The association of FPG with body mass index (BMI) has been reported in children in some studies while others do not support this association (13, 23, 24). Furthermore, studies in different populations and geographical areas demonstrate an increased susceptibility of certain ethnic

groups to develop T2DM. 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.

## SUBJECTS AND METHODS

This is a cross-sectional study carried out in the Center for Research in Endocrinology and Reproductive Sciences (CRERS), University of Health Sciences, Lahore, Pakistan.

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

Group I: subjects with a history of T2DM in one or both parents (n = 124); Group II: Subjects with no history of T2DM in any parent (n = 102). Non-probability sampling technique was utilized. A total of 500 known diabetic parents from diabetic centres and clinics in Lahore were enrolled in the study. Male and female offsprings (n = 124, age 10–25 years) of (one or both) diabetic parents volunteered and were selected to participate in the study. Non-diabetic friends, neighbours and distant relatives of diabetic parents were also enrolled for the control group. One hundred and two age-matched offsprings of non-diabetic parents volunteered and were included in the study. Family history of T2DM was defined by the presence of T2DM in one or both parents of the subject.

Written informed consent from the subjects and parents was obtained before administering the questionnaire. A questionnaire was completed regarding the detailed FHD, medical history, past history and history of parental consanguinity. Presence of T2DM in either parent was ascertained by detailed history, medical examination, laboratory investigations (FPG, HbA<sub>1c</sub>) and/or verification of present and past clinical records of both parents. Fasting plasma glucose and HbA<sub>1c</sub> levels of non-diabetic parents were determined to reconfirm absence of diabetes. All had normal FPG (< 126 mg/dL) and HbA<sub>1c</sub> (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 a first cousin. Individuals of estranged or bereaved parents, and Type 1 diabetic parents were excluded from the study. Individuals with a history of Cushing's syndrome, thyrotoxicosis, or a major illness and those on medication known to affect body composition were also excluded from the study. All subjects underwent detailed medical examination. Impaired fasting

glucose was defined as fasting plasma glucose between 100–125 mg/dL [5.6–6.9 mmol/L] (25).

The study was approved by the Ethical Committee and Research Board, University of Health Sciences, Lahore, Pakistan. Body height was measured with a stadiometer to the nearest centimetre and weight to the nearest kilogram. Body mass index was calculated according to the formula: BMI = BW (kg)/height (m)<sup>2</sup>.

In all cases, blood was withdrawn between 08:00 and 09:00 hours. Two millilitres of venous blood was drawn from the cubital vein after overnight fasting of 12 hours. The sample was put into fluoride EDTA tube for glucose estimation.

Blood glucose levels were determined by the glucose oxidase method using a commercial reagent kit (RANDOX Laboratories, Crumlin, UK) with a HumaStar 180 chemistry analyser (Human, Wiesbaden, Germany) in duplicate. HbA<sub>1c</sub> was estimated by affinity liquid chromatography with a D-SI Glycomat (Provalis Diagnostics, Deeside, UK).

Numerical values were reported as mean ± standard error of means and categorical variables as proportions. Chi-square test and independent sample *t*-test were used to compare the two groups for categorical and numerical data, respectively. Age, gender 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 genders with average age 19.9 ± 0.25 years were selected. The study 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). Body mass index of the subjects with FHD was significantly higher (*p* < 0.0001) as compared to the subjects without FHD (Table 2). Body mass

index of the subjects with FHD and parental history of consanguinity was higher 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

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 Type 2 diabetes (FHD)

n	FHD +ve		FHD -ve	
	Male 79	Female 45	Male 72	Female 30
Age (years)	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 mol/L	5.34 ± 0.07*	5.56 ± 0.10	4.79 ± 0.07	4.90 ± 0.12
IFG %	36%	51%	12%	20%
Obese	18%	17%	2%	0%

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

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 (years)	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%)
Overweight	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) and parental history of consanguinity.

	FHD +ve Parental history of consanguinity +ve n = 86	FHD -ve Parental history of consanguinity -ve n = 73
Age (years)	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)%	51%	19%
Obese %	24%	6.8%

the group with FHD was 19%, 17% and 64%, respectively while it was 2%, 7% and 91%, respectively in the group without FHD (Table 2). We did not find any association of BMI with FPG levels in any of the groups.

The mean FPG ( $5.42 \pm 0.06$  mmol/L) of subjects with FHD was significantly greater ( $p < 0.05$ ) than those without FHD [ $4.82 \pm 0.06$  mmol/L] (Table 2). Subjects with both FHD and parental history of consanguinity had FPG levels significantly higher ( $p < 0.05$ ) than those with no FHD and no parental history of consanguinity (Table 3). Impaired fasting glucose was identified in 42% of subjects with FHD and in 14% without FHD (Table 2); this was higher in females (51%) compared to males (36%) in the group with FHD (Table 1). But 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 with no FHD and no history of parental consanguinity (Table 3).

We found an independent association of FHD with IFG in both males and females [Chi-square = 13.89, ( $p$ -value =  $< 0.001$ ); odds ratio (OR) 13.89] by logistic regression analysis after adjusting the data for age, gender and BMI. We also found significant association [Chi-square = 16.31 ( $p$ -value =  $< 0.001$ ); odds ratio (OR) 4.21] of FHD x 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. Family history of Type 2 diabetes and parental history of consanguinity determined the risk for impaired fasting glucose.

Type 2 diabetes mellitus is a heterogeneous and multifactorial condition due to complex interaction of genetic, environmental and cultural factors. Studies identifying risk factors for T2DM have 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 offsprings of diabetic parents, predisposing them to the risk of developing diabetes (11, 21, 22). In the present study, 19% of the subjects (age 15–25 years) with FHD are obese which is consistent with the study reported recently from India but lower when compared with studies from Eastern Europe and the Middle East (26, 27). 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.

Fasting blood glucose levels of both male and female subjects with FHD were within normal range but significantly higher when compared to those without FHD.

These observations are in agreement with earlier observations in male offsprings with both diabetic parents (13).

When subjects with FHD and parental consanguinity were compared with the subjects with no FHD and no 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 analysed the data after adjusting for BMI and the results were significant, indicating interaction of FHD and parental consanguinity on fasting glucose levels.

Impaired fasting glucose was identified in 42% of the subjects with FHD and the prevalence of IFG was even higher (51%) when parental consanguinity and FHD were considered together. The prevalence observed in this study is higher than that reported in Mexicans (20). This suggests that cultural factors such as parental consanguinity are a contributing factor for the high prevalence of prediabetes and diabetes in this population of South East Asians. We observed a strong association of FHD and 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 Mexican children (7–15 years) with FHD in first degree relatives (21). High prevalences and associations of IFG with FHD and parental consanguinity suggest that defects of glucose metabolism are genetically determined.

In conclusion, the present study suggests that parental consanguinity modifies the effect of FHD on IFG. Family history of Type 2 diabetes and parental history of consanguinity determined the risk for impaired fasting glucose in this Pakistani population. This finding could help in the screening of at risk populations for T2DM. 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 lifestyle modifications to prevent or delay the development of T2DM. 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.

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