Full Length Research Paper

Early metabolic defects including oral glucose tolerance, serum insulin and blood glycated hemoglobin in different age groups of first degree relatives and increased risk for diabetes mellitus

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Abstract

Back ground: A cross sectional comparative study of one year was designed to find out blood parameters for screening the first degree relatives of diabetes who may be at risk of developing diabetes. Material and Methods: Patients with positive family history (n = 50) were selected by consecutive patients sampling from 14-50 years old people. 30 age matched subjects with no history of any disease were taken as controls. On the basis of age, patients were divided into 3 groups i.e. group A with age range 14-25 year, group B with age range 26-35 and group C with age range 36-50 year. All participants were interviewed for general demographic characteristics and current use of medications. Blood sample was collected from all participants to measure fasting plasma glucose and HbA1c. In order to confirm the diagnosis of diabetes an oral glucose tolerance test was performed. Results showed that the increased BMI, fasting blood sugar and blood sugar after 30 min and increased insulin may be an early predictor of diabetes in group A with age range 14-25 years. In group B with age range 26-35 year it was observed that significant increased fasting blood sugar, HbA1c and insulin with impaired glucose tolerance or IGT was a good prediction of developing diabetes in FDR. In group C age range 36-50 years showed that significantly increased BMI, HbA1c, serum insulin IFG and IGT are the good predictor of T2DM in FDR of diabetes. An inter group comparison between group A, B and C showed that aberrant release of insulin in young age may be responsible for normal HbA1c and OGTT. In later ages, release of insulin was decreased which may increased the level of HbA1c and impaired the OGTT. Conclusion: It is therefore concluded that screening of diabetes in first degree relatives should be carried out in all age groups i.e. adolescent, middle age and older age. Oral glucose tolerance test alone is not a single predictor of diabetes in first degree relatives but there is need to examine the level of insulin, HbA1c along with OGTT to reach on better conclusion.

Keywords: First degree relatives, oral glucose tolerance, insulin and HbA1c.

INTRODUCTION

Family history of diabetes is a major risk factor for developing diabetes in the first degree relatives (FDR) of diabetics. It includes a variety of tools designed to detect either people at risk of diabetes or people with undiagnosed diabetes. Screening of diabetes is important as it has a prolonged asymptomatic phase, which includes impaired fasting glucose, impaired glucose tolerance, and the early stages of diabetes (Valdez, 2009).

There has been a marked increase in the global prevalence of diabetes mellitus during the last two decades. The prevalence of type 2 diabetes is expected to increase faster than the other types. Incidence of type 2 diabetes was highest among American Indian individuals aged 15-19 years. Second and third highest incidence belonged to Asian-Pacific Islander and black individuals aged 15-19 years respectively (Dabelea et al., 2007).

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Approximately 35-50% of FDR of type 2 diabetic patients are asymptomatic and unaware of their condition (Powers, 2005). The incidence of type 2 diabetes in children and adolescents has markedly increased to the point that it accounts for as many as one third of all the new cases of diabetes diagnosed in adolescents (Lieberman, 2003). The American Diabetes Association recommends that younger people and individuals aged above 45 years with positive family history of diabetes recommends for diabetes screening (American Diabetes Association, 2006).

Longitudinal studies have demonstrated that, during the transition between normal glucose tolerance to diabetes, 31% of the person's insulin-mediated glucose disposal capacity is lost, whereas 78% of the acute insulin response is also lost during the same period (American Diabetes Association, 2000).

Type 2 diabetes spans a continuum from impaired glucose tolerance and impaired fasting glucose to frank diabetes that results from progressive deterioration of both insulin secretion and action (Weyer et al., 1999). In parallel, as a result of decreased insulin sensitivity in the liver, endogenous glucose output increase adds to the already hyperglycemic milieu, worsening both peripheral insulin resistance and beta-cell function. Failure of the beta cell to keep up with the peripheral insulin resistance is the basis for the progression from impaired glucose tolerance to overt clinical type 2 diabetes (Matthews et al., 1998; Grinstein et al., 2003).

The prevalence of type 2 diabetes (T2DM) was 9.2% by OGTT-defined diabetes and 7.9% by HbA_{1c} ≥6.5 (Janghorbani M and Amin, 2010). HbA1c is a more sensitive screening test than OGTT, but lacks specificity. OGTT is more specific (Raman and Mitra, 2000). However a meta-analysis by Peters et al., 2000 suggested that a single measurement of glycated hemoglobin could be used in place of the OGTT.

It is therefore a need of screening of different age groups of FDR of diabetics which may be prone to T2DM. This may be helpful in preventing diabetes, a major health problems in a sizable portion of the population. This study examined the level of parameters include fasting glucose, glucose tolerance test, serum insulin and HbA1c for screening and emphasizes the use of a family history of diabetes as a screening tool.

METHODS

Subjects

The present study was performed at the Fatima Jinnah Medical College, Lahore, Pakistan from 2008 to 2009. Subjects with positive family history (n = 50) were enrolled. They were selected by consecutive first degree relative sampling from 14-50 years old people. 30 age matched subjects with no history of any disease were taken as controls. On the basis of age, first degree relatives (FDR) were divided into 3 groups i.e. group A with age range 14-25 year included 16 FDR, group B with age range 26-35 included 16 FDR and group C with age range 36-50 year included 23 FDR. All participants were interviewed for general demographic characteristics and current use of medications. The patients with T2DM, normal oral glucose tolerance, pregnant women and those who were taking corticosteroids were excluded from the study,

A questionnaire on demographics, history, clinical examination and laboratory tests was filled out for each patient. Blood sample was collected from all participants to measure fasting plasma glucose (FPG) and HbA1c. In order to confirm the diagnosis of diabetes an oral glucose tolerance test (OGTT) was performed. The study was approved by the Medical Ethics Committee Fatima Jinnah Medical College, Lahore, Pakistan and all participants gave written consent.

Anthropometric and Laboratory Measurements

All Participants underwent a 75 g oral glucose tolerance test after 10-12 hours of overnight fasting. Venous sampling was done after 0, 30, 60 and 120 minutes of glucose taking. The American Diabetes Association (ADA) criteria were used for definition of prediabetes[13]. Isolated IFG was considered as fasting plasma glucose (FPG) between 100-125 mg/dl and 2 hour plasma glucose after glucose load = < 140 mg/dl. Isolated IGT was defined as FPG < 100 mg/dl. Body mass index (BMI) was calculated by weight in kilograms divided by the square of height in meters[14]. Plasma glucose was measured by GOD-PAP and HbA1C by ion-exchange chromatography methods. Serum insulin level was estimated by ELIZA technique.

Statistical analysis of the data was performed using SPSS 17 for windows. Data was expressed as mean and standard deviation (SD). Independent t student test was used for the comparison of quantitative variables (age, BMI, blood glucose, HbA1C, insulin), between FDR subjects and their controls. P values less than 0.05 were considered statistically significant.

Table 1: Blood glycosylated hemoglobin and serum insulin in relation to oral glucose tolerance test in the first degree relatives age range 14-25 year of type 2 diabetics and comparison with their controls.

RESULTS

Glucose tolerance test in first degree relatives' age ranged 14-25 years of diabetics (group A) as compared to their controls was tabulated (Table 1). It was observed that the BMI of first degree relatives of male was significantly greater (P<0.001) as compared to controls.

Table 1. Values are expressed as mean±SD

Parameters	Subjects(n=16)	Controls(n=10)
Age (years)	19.00±2.24	21.4±4.77
BMI (Kg/m^2)	30.48±5.34**	23.20±1.30
Blood HbA1c (%)	4.91±1.5	4.0±0.7
Serum insulin (μIU/ml)	25.45±23.59**	6.5±2.1
Fasting blood glucose (mg/dL)	112.40±18.12**	70.0±10.0
I/2 hr blood glucose (mg/dL)	143.80±7.36**	100.0±28.28
1hr blood glucose (mg/dL)	123.0±15.95±	107.0±14.83
1and1/2 hr blood glucose (mg/dL)	109.0±16.73	104.0±29.56
2 hr blood glucose (mg/dL)	100.80±14.60	89.0±15.97

Legend:**$P<0.001$= Highly significant difference

Table 2. Blood glycosylated hemoglobin and serum insulin in relation to oral glucose tolerance test in the first degree relatives age range 26-35 year of type 2 diabetics and comparison with their controls.

Parameters	Subjects(n=16)	Controls(n=10)
Age (years)	30.20±2.86	34.40±7.79
BMI (Kg/m^2)	30.44±5.36	26.10±2.60
Blood Hb A1c (%)	6.28±1.26**	4.0±0.7
Serum insulin (μIU/ml)	14.16±13.79*	6.5±2.1
Fasting blood glucose(mg/dL)	112.20±28.78**	73.20±8.51
I/2 hr blood glucose (mg/dL)	144.20±22.71*	116.90±16.15
1hr blood glucose (mg/dL)	139.20±19.27	127.70±14.55
1and1/2 hr blood glucose(mg/dL)	122.80±18.78	116.90±16.15
2 hr blood glucose (mg/dL)	108.20±29.14	101.50±8.83

Legend:**$P<0.001$= Highly significant difference, Values are expressed as mean±SD

Level of fasting sugar and sugar after ½ hour is significantly greater (P<0.001) as compared to their controls. On the other hand level of blood glucose after 1, 1;30min and 2hr was although raised in first degree relatives but this showed no significant difference. Level of both blood HbA1c and serum insulin were increased but significant different (P<0.001) was only observed in case of serum insulin when compared with controls.

Glucose tolerance in first degree relatives age ranged 26-35 years of diabetics (group B) as compared to their controls was tabulated (table 2). It was observed that the BMI of first degree relatives of male was significantly greater (P<0.001)as compared to control. Level of the fasting blood sugar was more as compared to control and it showed a highly significant difference (P<0.001). Level of blood sugar after ½hr, 1hr, 1;30min, 2 hr was although raised in first degree relatives but this showed no significant difference. Level of both blood HbA1c and serum insulin were significantly increased (P<0.001, P<0.05) respectively when compared these levels with

Table 3. Blood glycosylated hemoglobin and serum insulin in relation to oral glucose tolerance test in the first degree relatives age range 36-50 year of type 2 diabetics and comparison with their controls.

Parameters	Subjects(n=22)	Controls(n=10)
Age (years)	41.80±5.67	34.40±7.79
BMI (Kg/m^2)	34.40±3.65**	26.10±2.60
Blood HbA1c (%)	7.19±1.76**	4.0±0.7
Serum insulin (µIU/ml)	10.17±9.12*	6.5±2.1
Fasting blood glucose(mg/dL)	123.0±3.32**	73.20±8.51
l/2 hr blood glucose(mg/dL)	171.0±14.09**	116.90±16.15
1 hr blood glucose (mg/dL)	151.80±7.89**	127.70±14.55
1and1/2 hr blood glucose(mg/dL)	124.0±8.22	116.90±16.15
2 hr blood glucose (mg/dL)	134.0±7.06**	101.50±8.83

Legend:* P<0.05 = Significant difference, **P<0.001= Highly significant difference
 Values are expressed as mean±SD

Table 4. Comparison of diabetic related parameters in different groups of FDR based on their ages

Parameters	Group A (40) (age 14-25 yrs)	Group B (50) (age 26-35 yrs)	Group C (60) (age 36-50 yrs)
Age (years)	19.00±2.24	30.20±2.86	41.80±5.67
BMI (Kg/m^2)	30.48±5.34	30.44±5.36	34.40±3.65
Blood HbA1c (%)	4.91±1.5	6.28±1.26	7.19±1.76*
Serum insulin (µIU/ml)	25.45±23.59**	14.16±13.79*	10.17±9.12
Fasting blood glucose (mg/dL)	112.40±18.12	112.20±28.78	123.0±3.32
l/2 hr blood glucose (mg/dL)	143.80±7.36	144.20±22.71	171.0±14.09**
1 hr blood glucose (mg/dL)	123.0±15.95±	139.20±19.27*	151.80±7.89**
1and1/2 hr blood glucose (mg/dL)	109.0±16.73	122.80±18.78	124.0±8.22
2 hr blood glucose (mg/dL)	100.80±14.60	108.20±29.14	134.0±7.06**

Legend:* P<0.05 = Significant difference, **P<0.001= Highly significant difference

their controls.

Glucose tolerance in first degree relatives age ranged 36-50 years of diabetics (group C) as compared to their controls was tabulated (table 3). It was observed that the BMI of first degree relatives of male was more as compared to control and it showed a highly significant difference (P<0.001) .Level of the fasting blood sugar and sugar after ½, and 1 hour was more as compared to control and it showed a highly significant difference (P<0.001). Level of blood sugar after1and 2 hour was significantly greater (P<0.001)as compared to control. On the other hand level of blood sugar after 1 and1/2 was although increased but it showed no significant

difference. Level of both blood HbA1c and serum insulin were significantly increased (P<0.001, P<0.05) respectively when compared these levels with their controls.

Table 4 showed the comparison of diabetic related parameters in different groups of FDR based on their ages. An increased BMI was observed in all groups of FDR. A level of HbA1c was significantly higher in group B and C. On the other hand the levels of insulin was significantly higher in group A as compared to other groups. Values of OGTT showed a normal profile or curve. While an impaired OGTT was more prevalent in group C than group B.

DISCUSSION

First-degree relatives (FDRs) of patients with type2 diabetes develop diabetes at a greater rate than the normal population, Warram et al., 1990 and have been used to uncover early abnormalities that may be important in the development of type 2diabetes. This may include disturb circadian cycles of insulin secretion rate i.e. rising in the early morning, peaking in the afternoon, and declining during the night, and plasma insulin levels (Boden et al., 2000).

Present study was observed that the increased BMI, fasting blood sugar and blood sugar after 30 min (an impaired glucose tolerance test) and increased insulin may be an early predictor of diabetes in group A with age range 14-25 years. A study also reported that higher BMI and elevated fasting plasma glucose are of the main predictors of progression to T2DM (Fonseca et al., 2009). However study in contrast to studies who observed that in glucose-tolerant FDRs, defects in insulin action precede defects in insulin secretion (Eriksson et al., 1990; Lillioja et al., 1988). Others, however, have shown the opposite: namely, defects in insulin secretion preceding defects in insulin action (Pimenta et al., 1995).

Aberrant insulin signaling and glucose metabolism in skeletal muscle from type 2 diabetic patients may arise from genetic defects and an altered metabolic milieu (Karlsson et al., 2006) and a constellation of features, including hyperglycemia, hyperlipidemia, hyperinsulinemia, and excessive cytokine production, develop. These secondary factors are known to influence insulin sensitivity and may obscure efforts to identify the primary cause of type 2 diabetes (Rossetti et al., 1999). First-degree relatives of type 2 diabetic patients with impaired glucose tolerance may exhibit metabolic abnormalities characteristic of overt type 2 diabetes, such as insulin resistance and excessive hyperglycemia (Henriksen et al., 1994).

We observed that in group B with age range 26-35 year there is no relationship of diabetes prediction with BMI. However it was observed that significant increased fasting blood sugar, HbA1c and insulin with impaired glucose tolerance or IGT was a good prediction of developing diabetes in FDR. A non significant increase in HbA1c and BMI showed that these may be weak predictor of T2DM. Some studies are in line of our study. According to a study, first degree relatives of T2DM with isolated impaired fasting glucose are definite. Study suggested that IFG should be included in the primary preventive program for diabetes (Iraj et al., 2010). A study stated that diabetes screening is an effective means of detecting unknown cases of diabetes, improving glycemic control and mitigating CVD risk factors (Amini et al., 2008). Another study observed that disturbance in insulin release is a primary event in the development of type 2 diabetes in FDR (Van Haeften et al., 1998).

These findings highlight the fact that more marked alterations in both insulin sensitivity and β cell function must exist for impaired glucose tolerance or diabetes to exist, and emphasize the importance of insulin-independent glucose disposal to glucose tolerance (Kahn et al., 1994; Best et al., 1996). A study found that FDRs with normal glucose tolerance had defects in insulin action and secretion. The newly recognized insulin secretory defect consisted of disruption of the normal circadian ISR cycle, which resulted in reduced insulin secretion (and glucose uptake) during the ascending part of the 24 hour insulin secretion rate (Boden et al., 1999).

First degree relatives with group C age range 36-50 years showed that significantly increased BMI, HbA1c, serum insulin IFG and IGT is the good predictor of T2DM in FDR of diabetes. Our study is in accord with a number of studies who observed that impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) were initially recognized as conditions with increased risk of T2DM development (Rao et al., 2004). However, they are now considered to be the independent cardiovascular risk factors (Shaw et al., 2002; Unwin et al., 2002). A study proposed that IFG and IGT have different pathophysiological mechanism. The main defects in subjects with IFG are the increased hepatic glucose output production and early insulin secretion dysfunction. Subjects with IGT have moderate to severe insulin resistance in level of muscles (Unwin et al., 2002).

An inter group comparison between group A, B and C showed that in group A, there was an aberrant release of insulin which may normalize the OGTT and HbA1c. On the other hand in group B the insulin release was less aberrant so this may impair the OGTT and level of HbA1c. While in group C, there is a mild increase release of insulin which may impair OGTT and level of HbA1c more than group B.

Our study is in contrast with a study who reported that first-degree relatives of young-onset type 2 patients (diagnosed at <45 years of age) have a higher rate of diabetes when compared with relatives of diabetic patients diagnosed after 45 years of age[33]. Some studies confirmed our results and suggested a need of primary prevention programs for T2DM in subjects with IFG IGT (Unwin et al., 2002; Nathan et al., 2007)

It is thought that overt type 2 diabetes mellitus (T2DM) is preceded by two major asymptomatic indicators of imbalance in the metabolism of glucose: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). These two indicators, collectively labeled as pre diabetes, are correlated but they may also appear separately. This indicates that early stages of T2DM are asymptomatic and people with the disease may go undiagnosed for prolonged periods. In the continuum of plasma glucose distributions (fasting or 2 hour), the escalation from pre diabetes to T2DM is marked by a sharp increase the risk of complications, which, in the long run, can seriously affect a variety of organs and

tissues, such as eyes, kidneys, nerves, and blood vessels (American Diabetes Association, 2009; Valdez, 2009).

CONCLUSIONS

It is therefore concluded that screening of diabetes in first degree relatives should be carried out in all age groups i.e. in adolescent, middle age and old age. Oral glucose tolerance test alone is not a good predictor of diabetes in FDR but there is need to examine the level of insulin, HbA1c along with OGTT to reach on better conclusion. However, this research has some limitations. One of the limitations is its cross sectional nature which cannot find a cause and effective relationship. Another limitation is that it was not a multicenter study number of subjects are also small.

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