Original Article

Insulin sensitivity and β-cell function in normoglycemic offspring of individuals with type 2 diabetes mellitus: Impact of line of inheritance

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ABSTRACT

Aims: The aim was to study the effect of family history of type 2 diabetes mellitus (T2DM) on insulin sensitivity and β-cell function in normoglycemic offspring. **Material and Methods:** Offspring of T2DM patients (cases) and individuals without family history of T2DM (controls) were the subjects for this cross-sectional study. All participants underwent 75 g OGTT and samples were collected for plasma insulin, C-peptide, and proinsulin at 0, 30, 60, and 120 minutes. **Results:** A total of 271 cases (age 22 ± 10 years; 53% males) and 259 controls (28 ± 10 years, 66% males) were enrolled for the study. BMI, plasma insulin, C-peptide, proinsulin, HOMA-IR, and insulinogenic index (0-120) were significantly higher and whole-body insulin sensitivity (WBISI) and disposition index (0-120) [DI 120] were lower in cases compared to controls. After adjusting for BMI, proinsulin at 120 minutes, area under the curve (AUC) of proinsulin (during OGTT) and AUC proinsulin/AUC C-peptide were significantly higher in cases. Cases were subdivided into four groups according to inheritance pattern; paternal DM (PDM), maternal DM (MDM), grandparental DM (GPDM), and both parents DM (BPDM). The magnitude of differences varied with relationship (greater when both parents and grandparents were affected). Mean HOMA-IR was higher by 127% and 50% and DI 120 was lower by 33% and 18% (adjusted for age and gender) in the BPDM and GPDM groups respectively compared to controls. **Conclusions:** We observed higher BMI, plasma insulin, C-peptide, and proinsulin and lower insulin sensitivity and β-cell compensation in normoglycemic offspring of T2DM subjects compared to controls. Differences were greater when both parents and grandparents had T2DM.

Key words: β-cell function, grandparental history of DM, insulin sensitivity, normoglycemic, offspring of individuals with type 2 diabetes

INTRODUCTION

Overweight, especially obesity at younger age, significantly increased lifetime risk of type 2 diabetes mellitus (T2DM).[1] Family history of T2DM is associated with higher body mass index (BMI), dyslipidemia, and impaired glucose tolerance (IGT) in offspring.[2-5] There seems to be a vicious cycle, where obesity increases risk for T2DM and a family history of T2DM increasing the risk for obesity.[1,6] Parental history of T2DM is one of the dominant risk factors for development of T2DM.[7] The phenotype varies depending on which parent is affected and if the child was exposed to hyperglycemia in utero.[7,8] β-cell dysfunction has been observed even in nondiabetic offspring of T2DM, more accentuated among those with maternal T2DM compared to paternal inheritance.[4] Here we report the effect of family history of diabetes on insulin sensitivity and β-cell function in normoglycemic subjects.

MATERIAL AND METHODS

Offspring of patients with T2DM and individuals without a family history of T2DM were the participants for this study.

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Only participants with normal glucose tolerance (NGT) as per American Diabetes Association 2003 criteria[9] were included in this study. This was a continuation of the "offspring of individuals with T2DM" study.[10]

Recruitment of cases

Patients who were undergoing treatment for T2DM in the endocrine clinic of our hospital were informed of this study and asked to invite their children and grandchildren to participate. Only children and grandchildren with age ranging from 5 to 55 years were included. Those with diabetes mellitus, pregnancy, lactation, or presence of any chronic illness were excluded.

Recruitment of controls

In addition to requiring age to be between 5 and 55 years, controls had to have a negative history for T2DM in parents, siblings, and grandparents. Students and members of residents' associations of different areas were informed about the study with the help of a medical social worker. The study details were explained during group discussions. The exclusion criteria were the same as those for the cases.

A detailed family history was recorded for all participants, with emphasis on the history of T2DM in parents, siblings, and grandparents. For the oral glucose tolerance test (OGTT), subjects were advised to maintain their normal diet and abstain from alcohol for 3 days prior to the test. After a 10- to 12-hour overnight fast, the OGTT was performed using a 75 g (1.75 g/kg body weight in the case of children, up to a maximum dose 75 g) oral glucose dose. Blood samples were collected at 0, 30, 60, and 120 minutes after oral glucose dosing, from which to determine plasma glucose, insulin, C-peptide, and proinsulin measurements.

Analytical measurements

Plasma glucose was measured by the glucose oxidase method on a Labmate-20 analyzer (Trivitron Diagnostics, Chennai, India). Plasma insulin was measured by electro-chemiluminescence assay by ELECSYS 2010 (Roche Diagnostics, IN, USA). This assay uses monoclonal antibodies against insulin and has 0.05% cross-reactivity with human proinsulin and its split forms. Intra-assay coefficient of variation (CV) was 5.1% and Inter-assay CV was 5.7%. C-peptide was also measured by electro-chemiluminescence assay. For C-peptide Intra-assay CV was 3.8% and Inter-assay CV was 3.9%. Plasma proinsulin was measured by a radioimmunoassay kit (Catalog no. HPI-15K, Millipore Corporation, Billerica, MA, USA). This assay cross-reacts neither with human insulin (<0.1%) nor with C-peptide (0.1%). It has 100% specificity for intact human proinsulin and 95% with des 31,32 human

proinsulin. Intra- and Inter-assay CVs of proinsulin were 5.9% and 6.9% respectively.

The area under the curve (AUC) was calculated according to Tai's method.[11] Whole-body insulin sensitivity was measured as whole-body insulin sensitivity index (WBISI) as described by Matsuda *et al*.[12] HOMA-IR (homeostasis model assessment-insulin resistance) was measured as proposed by Matthews *et al*.[13] AUC of C-peptide (0-120) was divided by AUC of glucose (0-120) to determine insulinogenic index (0-120) [IGI 120], a measure of β-cell secretion, as described by Stadler *et al*.[14] Disposition index (0--120) [DI 120] was calculated as the product of IGI 120 and WBISI, making a variation from the formula described from Retnakaran *et al*.;[15] where plasma insulin was used in the place of C-peptide for the measurement of IGI 120. IGI 30 is measured as insulin pmol/l (30 minutes--0 minute)/glucose mmol/l (30 minutes--0 minute). A second disposition index, DI 30, was calculated by multiplying IGI 30 with WBISI.

Statistical analysis

Statistical analysis was done using SPSS version 15 software (Lead Technologies, Chicago, USA). The data were expressed as mean $\pm$ SD (SE) for various continuous parameters studied. Skewed data were normalized by applying log transformation for insulin, C-peptide, proinsulin, HOMA-IR, WBISI, DI 120, DI 30, IGI 120, IGI 30 and for AUCs of plasma insulin, C-peptide, and proinsulin. The general linear model was used for adjusting for confounding variables such as age and gender. *Post hoc* comparison was done by the Bonferroni method. Binary logistic regression analysis was done for finding the odds ratio with 95% confidence interval. Tests were considered significant if *P* values were less than 0.05.

RESULTS

A total of 358 subjects with family history of T2DM (cases) and 287 subjects without family history of T2DM (controls) underwent OGTT. Fifty-seven cases and 28 controls were excluded because of glucose intolerance. There were 301 (age 22 $\pm$ 10 years, 52% males) normal glucose tolerant cases and 259 (age 28 $\pm$ 9 years, 66% males) controls (subjects with no parent with T2DM [NPDM]).

There were 30 subjects who had mother and paternal grandparent with T2DM or father and maternal grandparent with T2DM. To avoid the confounding effect of grandparental T2DM on paternal DM or maternal DM groups, these subjects were excluded from the analysis. Among the cases, 93 (34%) subjects had father but not

mother with T2DM (PDM); 82 (30%) had mother but not father with T2DM (MDM). A total of 26 (9.6%) subjects had both parents with T2DM (BPDM) and there were 70 (26%) subjects who had grandparents with T2DM (GPDM), while parents were nondiabetic.

The GPDM group had the lowest mean age at the time of study (18 ± 9 years), compared to PDM (22 ± 10), MDM (25 ± 11), and BPDM (25 ± 11 years). The mean age at the time of diagnosis of T2DM for parents in the PDM group was 42.6 ± 8.5 years, in the MDM group it was 42.6 ± 8.2, and in the BPDM group it was 43.7 ± 10.1 years. In the GPDM group, mean age of father was 46 ± 9 years and of mother was 42 ± 9 years. BMI was highest in the BPDM group, 27.1 ± 8.0 kg/m², compared to PDM (21.9 ± 6.1), MDM (23.4 ± 4.8), and GPDM groups (21.8 ± 6.1 kg/m²).

Plasma glucose levels were not significantly different between cases and controls. There was a significant difference in age ($P < 0.001$) between cases and controls. The details of hormonal parameters and derived insulin sensitivity and β-cell function indices, after adjusting for age and gender, are given in Table 1. BMI was higher in cases compared to controls with an odds ratio of 1.17

(95% confidence interval [CI] of 1.11 to 1.23). Significantly higher plasma insulin, C-peptide, proinsulin levels (at different time points during OGTT), HOMA-IR, IGI 120, and AUC of proinsulin (0-120) /AUC of C-peptide (0-120) were observed in cases compared to controls. WBISI and DI 120 were significantly lower in cases. The odds ratio in cases compared to controls for fasting insulin was 1.06 (95% CI; 1.03 to 1.1), for HOMA-IR was 1.3 (95% CI; 1.1 to 1.5), and for fasting proinsulin was 1.06 (95% CI; 1.03 to 1.09). The odds ratio for DI 120 was 0.78 (95% CI; 0.65 to 0.94) and for WBISI was 0.97 (95% CI; 0.94 to 1.0). However after adjusting for BMI along with age and gender, proinsulin at 60 minutes ($P = 0.03$), proinsulin at 120 minutes, AUC of proinsulin ($P = 0.02$), and AUC of proinsulin/AUC of C-peptide ($P < 0.001$) were significantly higher in cases.

A subanalysis of the cases was done, based on the line of inheritance of T2DM in the family [Table 2]; data were adjusted for age and gender. Fasting insulin, fasting C-peptide, HOMA-IR, and AUC of insulin showed an increasing trend in the order of NPDM, PDM, MDM, GPDM, and BPDM while WBISI and DI 120 decreased in the same order [Figure 1]. After adjusting for age,

Table 1: Plasma insulin, C-peptide, proinsulin, insulin sensitivity indices, and β-cell function indices in cases and controls; data are expressed as mean ± SE

	Cases (NGT)	NPDM (NGT)	*P* value	
			Adjusted for age and gender	Adjusted for BMI, age, and gender
n	271	259		
% of males	53%	66%		
Age (years)	22.1±0.6	28±0.5		
BMI (kg/m²)	23.6±0.26	21.0±0.3	<0.001	–
Waist to hip ratio	0.885±0.005	0.874±0.005	0.103	0.950
Insulin 0 minute (μU/ml)	11.5 ±0.5	8.7 ± 0.6	0.001	0.832
Insulin 30 minutes (μU/ml)	92.5 ±4.1	76.0±4.0	0.007	0.883
Insulin 60 minutes (μU/ml)	79.0 ±3.7	63.0±3.9	0.006	0.990
Insulin 120 minutes (μU/ml)	52.8 ±2.7	37.6±2.6	0.002	0.315
C-peptide 0 minute (pmol/l)	778 ±20	657±21	<0.001	0.940
C-peptide 30 minutes (pmol/l)	2660±69	2423±67	0.015	0.803
C-peptide 60 minutes (pmol/l)	2836±76	2615±77	0.141	0.207
C-peptide 120 minutes (pmol/l)	2327 ±61	2074±63	0.036	0.831
Proinsulin 0 minute (pmol/l)	15.1±0.5	12.1±0.5	0.004	0.850
Proinsulin 30 minutes (pmol/l)	37.8± 1.2	31.3±1.3	<0.001	0.060
Proinsulin 60 minutes (pmol/l)	46.8± 1.4	37.9±1.5	<0.001	0.020
Proinsulin 120 minutes (pmol/l)	49.8±1.5	40.2±1.6	<0.001	0.025
Homeostasis model assessment-insulin resistance [HOMA-IR] (μU/ml, mmol/l)	2.49 ±0.12	1.86±0.12	0.001	0.650
Whole body insulin sensitivity index [WBISI] (μU/ml, mg/dl)	6.5±0.34	7.5±0.35	0.001	0.714
Area under the curve [AUC] of glucose (0-120) (mmol/l/min)	728± 6.8	721±7.0	0.550	0.630
AUC of insulin (0-120) (nmol/l/min)	54.8± 2.2	43.3±2.3	0.003	0.821
AUC of proinsulin (0-120) (nmol/l/min)	4.9± 0.13	4.0±0.15	<0.001	0.024
AUC of proinsulin (0-120) /AUC of C-peptide (0−120)	0.019±0.001	0.016±0.001	0.001	<0.001
Insulinogenic index (0-30) [IGI 30](pmol/mmol)	280±18	258±18	0.192	0.515
Disposition index (0-30) [DI 30]	1424±158	1608±156	0.172	0.647
Insulinogenic index (0-120) [IGI 120] (nmol/mmol)	0.386±0.007	0.358±0.008	0.048	0.243
Disposition index (0-120) (DI – 120)	2.08 ±0.07	2.35±0.07	0.003	0.960

Table 2: Plasma insulin, C-peptide, insulin sensitivity indices, and β-cell function indices in cases according to line of inheritance; data are expressed as mean ± SE

	GPDM	PDM	MDM	BPDM	*P* value	
					Adjusted for age, gender	Adjusted for age, gender, and BMI
n	70	93	82	26	-	-
% of males	41%	56%	58%	54%	-	-
Age (years)	17.5±1.0	22.1±1.0	25.3±1.2	25±2.2		
BMI (kg/m^2)	23.3±0.6	21.9±0.5	22.4±0.5	26.1±0.9	0.002*	-
Waist to hip ratio	0.887±0.009	0.860±0.007	0.886± 0.007	0.874± 0.014	0.06	0.06
Insulin 0 minute (µU/ml)	12.9 ± 1.2	8.70±1.1	10.9±1.2	20 ± 2.1	0.001†	0.003†
Insulin 120 minutes (µU/ml)	54.6 ±6.3	40.6±5.2	54.2 ±5.7	81± 9.6	0.040‡	0.274
C-peptide 0 minute (pmol/l)	836±48	651±40.1	748±43	993±76	<0.001§	0.030
C-peptide 120 minutes (pmol/l)	2359±131	2099±108	2277±118	2701±205	0.137	0.631
HOMA-IR (µU/ml,mmol/l)	2.80±0.3	1.80±0.2	2.30±0.3	4.2±0.4	<0.001†	0.004†
WBISI (µU/ml, mg/dl)	6.23±0.7	7.76±0.5	6.85±0.6	4.74±1.1	0.001‖	0.081
AUC of glucose (0-120) (mmol/l/min)	724±13	724±11	695±12	750±21	0.100	0.175
AUC of insulin (0-120) (nmol/l/min)	54.0±4.8	45.6±4.0	52.2±4.4	80.7±7.5	0.010#	0.426
IGI 30 (pmol/mmol)	275±38	208±29	379±32	319±53	0.015**	0.010**
IGI 120 (nmol/mmol)	0.385±0.016	0.355± 0.014	0.387±0.015	0.436± 0.026	0.147	0.721
DI 120	1.9 ±0.12	2.33 ±0.10	2.12 ±0.11	1.64 ±0.2	<0.001††	0.020††

P value represents the overall *P* value obtained in ANCOVA analysis. Pairwise post hoc comparisons after Bonferroni adjustment were noted as follows:
*BMI was significantly higher in BPDM compared to PDM and MDM (*P* < 0.03).
†Insulin 0 minute and HOMA-IR were significantly higher in the BPDM group compared to PDM and MDM (*P*<0.03), and in GPDM compared to PDM (*P* = 0.002). After adjusting for BMI, age, and gender, insulin 0 minute and HOMA-IR were significantly higher in BPDM and GPDM compared to PDM (*P* < 0.05).
‡Insulin at 120 minutes was significantly higher in BPDM compared to PDM (*P* = 0.04).
§C-peptide at 0 minute was significantly higher in BPDM compared to PDM (*P* = 0.001) and MDM (*P* = 0.05), and in GPDM compared to PDM (*P* = 0.016).
‖WBISI was significantly lower in BPDM compared to PDM and MDM (*P* < 0.02).
#AUC of insulin was significantly higher in BPDM compared to PDM (*P* = 0.006) and MDM (*P* = 0.05).
**IGI 30 was significantly higher in MDM compared to PDM (*P* = 0.02) and (persisted even after adjusting for BMI.
††DI 120 was significantly lower in BPDM compared to PDM and MDM (*P* < 0.006), and in GPDM compared to PDM (*P* = 0.03). After adjusting for BMI, DI 120 was lower in BPDM compared to PDM (*P* = 0.05).
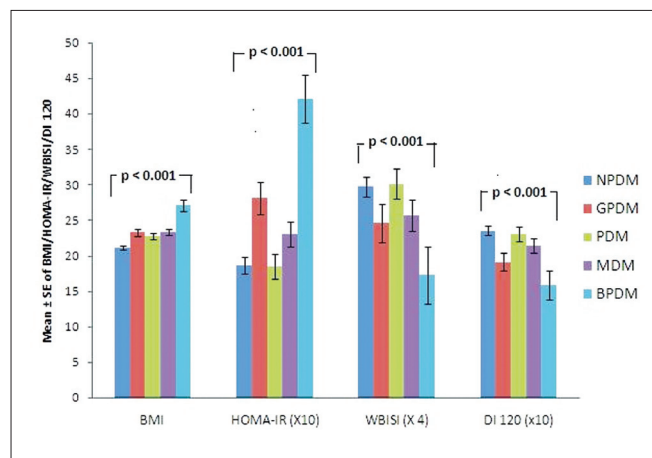
Figure 1: BMI, HOMA-IR, WBISI and DI 120 in controls and subgroups of cases. For representing in the same figure, results of HOMA-IR and DI 120 were multiplied by 10 and WBISI by 4. *P* values represent the overall *P* value obtained in ANCOVA analysis

gender, and BMI, fasting insulin and HOMA-IR were significantly higher in GPDM and BPDM compared to PDM and NPDM. DI 120 was significantly lower in the BPDM group compared to PDM (*P* = 0.05). All other comparisons became insignificant when adjusted for BMI along with age and gender.

When compared to the NPDM group, mean HOMA-IR was higher by 127% and 50% in the BPDM and GPDM groups respectively. WBISI was lower by 42% and 17% and DI 120 was lower by 33% and 18% in the BPDM and GPDM groups respectively. In the GPDM group, with reference to the PDM group, mean HOMA-IR was higher by 50% and mean WBISI and DI 120 were lower by 18%.

A second subanalysis was done by dividing cases into three groups based on the number of affected family members [Table 3]. For this, we have counted history of T2DM in parents and grandparents in the family. The FHD1 group included subjects who had one family member with T2DM, the FHD2 group had two affected family members and the FHD3 group had three or more affected family members. The FHD3 group had significantly higher BMI, fasting insulin, fasting C-peptide, HOMA-IR, IGI 120 (*P* < 0.005), and lower WBISI (*P* = 0.02) and DI 120 (*P*=0.001) compared to controls (NPDM), the FHD1 and FHD2 groups. After adjusted for BMI, insulin at 0 minute and

Table 3: Hormonal parameters, insulin sensitivity indices, and β-cell function indices according to increasing genetic load of T2DM; data are expressed as mean ± SE

	Controls	Cases (n=271)				
		1 member with T2DM (FHD1)	2 members T2DM (FHD2)	≥3 members T2DM (FHD3)	*P* value	
					Adjusted for age, gender	Adjusted for age, gender, and BMI
n	259	170	62	39		
BMI (kg/m^2)	21.0±0.3	23.1±0.3	22.9±0.5	26.7±0.7	<0.001*	–
HOMA-IR (μU/ml,mmol/l)	1.86±0.12	2.3±0.1	2.0±0.2	4.0±0.3	<0.001†	0.03†
WBISI (μU/ml, mg/dl)	7.5±0.35	6.7±0.4	7.5±0.6	4.1±0.7	<0.001‡	0.06
Plasma insulin 0 minute (μU/ml)	8.60±0.5	10.6±0.6	9.6 ± 0.9	19.2±1.3	<0.001†	0.03†
Plasma insulin 120 minutes (μU/ml)	37.6±2.6	50.0 ±3.2	43.1 ± 5	81 ±6.8	<0.001§	0.35
Plasma proinsulin 120 minutes (pmol/l)	40.1±1.6	47.3±1.8	50.0±2.9	60±3.7	<0.001‖	0.07
IGI 30 (pmol/nmol)	258±18	271±23	263±39	351±49	0.030¶	0.40
DI 30	1608±156	1421±196	1475±332	1356±411	0.447	0.89
IGI 120 (nmol/mmol)	0.358±0.008	0.377±0.009	0.355±0.01	0.481±0.01	<0.001**	0.04**
DI 120	2.35±0.07	2.12±0.08	2.25±0.13	1.63±0.13	0.001††	0.49

P value represents the overall *P* value obtained in ANCOVA analysis. Pairwise post hoc comparisons after Bonferroni adjustment were noted as:
*BMI was significantly higher in FHD3 compared to FHD1, FHD2 and controls (*P* < 0.001). BMI was also higher in FHD2 and FHD1 compared to controls (*P* < 0.006).
†Insulin at 0 minute and HOMA-IR were significantly higher in FHD3 compared to FHD1, FHD2, and controls (*P* < 0.001). After adjusting for BMI, insulin 0 minute, and HOMA-IR were significantly higher in FHD3 compared to controls and FHD2 (*P* < 0.05).
‡WBISI was significantly lower in the FHD3 group compared to FHD1 and FHD2 and controls (*P* < 0.001).
§Insulin at 120 minutes was significantly higher in the FHD3 compared to controls (*P* < 0.001) and FHD2 (*P* = 0.03).
‖Proinsulin at 120 minutes was significantly higher in FHD3, FHD2, and FHD1 compared to controls (*P* < 0.02).
¶IGI 30 was significantly higher in the FHD3 compared to controls (*P* = 0.02).
**IGI 120 was significantly higher in FHD3 compared to FHD1, FHD2, and controls (*P*<0.001). After adjusting for BMI, IGI 120 was significantly higher in FHD3 compared to FHD1 (*P* = 0.05).
††DI 120 was significantly lower in FHD3 compared to controls (*P* < 0.05).

HOMA-IR were significantly higher in the FHD3 group compared to NPDM and FHD2. All other differences became nonsignificant when adjusted for BMI.

DISCUSSION

The effect of family history of T2DM on offspring and first-degree relatives has been studied extensively. Defects in both insulin sensitivity and β-cell secretion have been reported among offspring and first-degree relatives of patients with T2DM.[4,14,16] However the precise nature of defects is still being debated. The difficulties in accurately assessing insulin sensitivity and β-cell function are the major reasons for this.

WBISI, originally described by Matsuda *et al*.,[12] has good correlation with the euglycemic hyperinsulinemic clamp technique in adults. In a large-scale study in the Finnish population,[17] the M value measured by clamp showed significant correlation with WBISI derived by Matsuda's formula. There is a hyperbolic relationship (physiological feedback loop) between OGTT-based AUC insulin/AUC glucose and WBISI. The product of these two indices, the disposition index, is recommended for use in large-scale studies.[15] Subsequent studies[14,18] have shown better precision of measurement with AUC of C-peptide to AUC of glucose (a variance from the conventional insulinogenic

index developed by Retnakaran *et al*). The product of AUC C-peptide (0-120)/AUC glucose (0-120) and WBISI was used as DI 120 in the present study.

The present study assessed β-cell function among normoglycemic offspring of T2DM subjects and controls without family members with T2DM. We observed higher BMI, plasma insulin, C-peptide, and proinsulin levels in the fasting state and after oral glucose, in the normoglycemic offspring of individuals with T2DM compared to controls. Insulin sensitivity (WBISI) and β-cell compensation (as measured by DI 120) were also significantly lower in the offspring of subjects with diabetes. However after adjusting for BMI, only differences in plasma proinsulin at 60--120 minutes of OGTT and AUC proinsulin (0-120)/AUC C-peptide (0-120) remained significant.

We were able to find 20 published reports since 1988 (five after 2003), which studied insulin sensitivity and or β-cell function in offspring or first-degree relatives of T2DM subjects. Mean age of subjects was 30 years or more for 16 studies. Eight of these studies where cases and controls were not matched for BMI reported higher BMI for offspring of subjects with T2DM.[19-21] Studies that matched for age, gender, and BMI have shown reduced insulin sensitivity and beta cell function in offspring of subjects with diabetes.[14,22,23] Pimenta *et al*., observed similar insulin

sensitivity and loss of first-phase insulin secretion in subjects with family history of DM compared to BMI-matched controls.[24] van Haeften *et al.*, observed similar insulin sensitivity but reduced insulin secretion at 90 and 120 minute during OGTT in offspring of individuals with T2DM.[25] There were three reports where mean age of subjects was less than 16 years. Two of these reports where cases and controls were matched for BMI have reported lower insulin sensitivity in offspring/ first-degree relative using clamp studies.[22,26] The third which did not match cases and controls for BMI observed higher BMI, fasting insulin levels, and HOMA-IR for cases and the differences were not significant after adjusting for BMI.[27] A longitudinal study in Pima Indians reported a twofold greater increase in weight in subjects who progressed to diabetes compared to the nonprogressors.[28] Our observation of higher BMI in offspring of subjects with T2DM compared to controls is in accordance with these above-mentioned studies. The San Antonio heart (SAH) study has shown that both mean fasting insulin levels and mean insulin sums increased in a stepwise fashion as the family history of diabetes became stronger. The significance of fasting insulin became marginal when adjusted for BMI and waist to hip ratio.[20] Mean age of offspring (22 years) in the present study was lower compared to the SAH study which is 42 years. There was significantly higher plasma insulin, C-peptide, HOMA-IR, and BMI when three or more family members were affected (FHD3 group). DI 120 and WBISI were significantly lower in the FHD3 group compared to controls. After adjusting for BMI, significantly higher fasting insulin, C-peptide, and HOMA-IR were observed in the FHD3 group; however, the differences in WBISI and DI 120 became nonsignificant.

The present study also analyzed the data of cases (offspring of T2DM subjects) subdivided on the basis of line of inheritance. The fasting plasma insulin, fasting C-peptide, HOMA-IR, and AUC of insulin increased in the order of NPDM, PDM, MDM, GPDM, and BPDM. A similar but decreasing trend was observed for WBISI and DI 120. Although there was a trend toward higher fasting insulin and HOMA-IR and lower WBISI and DI 120 in MDM compared to PDM, it was not statistically significant. Among the subgroups of cases, fasting insulin levels and HOMA-IR were highest in the BPDM group followed by the GPDM group. There were more pronounced changes in the mean HOMA-IR (50% increase) than the changes in WBISI (18% decrease), in the GPDM group compared to the PDM group. Since HOMA-IR predominantly indicates hepatic insulin resistance,[29] our results indicate a major impact on hepatic insulin resistance by familial T2DM, compared to muscle insulin resistance. Most previous studies that assessed impact of line of inheritance had

not taken note of history T2DM among grandparents. Jouret *et al.*,[5] observed that children with one or more grandparents with T2DM were at greater risk for obesity during childhood.

Fasting insulin levels were significantly higher in the BPDM and GPDM groups compared to PDM and controls even after adjusting for BMI. Our observation of higher plasma insulin among offspring of subjects with T2DM is in agreement with studies by Haffner *et al.*,[30] Perseghin *et al.*,[31] Gulli *et al.*,[32] and Natali *et al.*.[4] High-fasting insulin has been shown to predict the development of TDM, independent of insulin resistance.[33] Hyperinsulinemia itself may be a primary metabolic defect and obesity may be a consequence of hyperinsulinemia.[6,34]

Controls (NPDM) for this study were subjects without family history of T2DM. However family members of these subjects were not tested for T2DM. Some may have undiagnosed T2DM, as routine periodic health checkup is not common in this region. Since the groups MDM, PDM, and BPDM also included some subjects with grandparents with T2DM, a direct comparison of the GPDM group with the other groups is difficult.

To conclude, we observed higher BMI, plasma insulin, C-peptide, proinsulin, and lower insulin sensitivity and β-cell compensation in normoglycemic offspring of T2DM subjects compared to controls. Differences were greater when grandparents, both parents and more than two family members affected with T2DM.

Acknowledgments

References

1. Narayan KM, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on lifetime risk for diabetes in the US. Diabetes Care 2007;30:1562-6.
2. Tan JT, Tan LS, Chia KS, Chew SK, Tai ES. A family history of type 2 diabetes is associated with glucose intolerance and obesity-related traits with evidence of excess maternal transmission for obesity-related traits in a South East Asian population. Diabetes Res Clin Pract 2008;82:268-75.
3. Shaw JT, Purdie DM, Neil HA, Levy JC, Turner RC. The relative risks of hyperglycaemia, obesity and dyslipidaemia in the relatives of patients with Type II diabetes mellitus. Diabetologia 1999;42:24-7.
4. Natali A, Muscelli E, Mari A, Balkau B, Walker M, Tura A, *et al.* Relationship between insulin sensitivity and cardiovascular disease

investigators: Insulin sensitivity and beta-cell function in the offspring of type 2 diabetic patients: Impact of line of inheritance. J Clin Endocrinol Metab 2010;95:4703-11.

5. Jouret B, Ahluwalia N, Cristini C, Dupuy M, Nègre-Pages L, Grandjean H, *et al*. Factors associated with overweight in preschool-age children in south western France. Am J Clin Nutr 2007;85:1643-9.

6. Chathurvedi D, Khadgawat R, Kulshrestha B, Gupta N, Joseph AA, Diwedi S, *et al*. Type 2 diabetes increases risk for obesity among subsequent generations. Diabetes Technol Ther 2009;11:393-8.

7. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: The Framingham Offspring Study. Diabetes 2000;49:2201-7.

8. Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. J Matern Fetal Med 2000;9:83-8.

9. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27(suppl 1):S5-10.

10. Praveen EP, Kulshreshtha B, Khurana ML, Sahoo JP, Gupta N, Kumar G, *et al*. Obesity and metabolic abnormalities in offspring of subjects with diabetes mellitus. Diabetes Technol Ther 2010;12:723-30.

11. Tai MM. A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. Diabetes Care 1994;17:152-4.

12. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: Comparison with the euglycemic insulin clamp. Diabetes Care. 1999;22:1462-70.

13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

14. Stadler M, Pacini G, Petrie J, Luger A, Anderwald C; RISC Investigators. Beta cell (dys)function in non-diabetic offspring of diabetic patients. Diabetologia 2009;52:2435-44.

15. Retnakaran R, Shen S, Hanley AJ, Vuksan V, Hamilton JK, Zinman B. Hyperbolic relationship between insulin secretion and sensitivity on oral glucose tolerance test. Obesity (Silver Spring) 2008;16:1901-7.

16. Jensen CC, Cnop M, Hull RL, Fujimoto WY, Kahn SE; American Diabetes Association GENNID Study Group. Beta-cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the US. Diabetes 2002;51:2170-8.

17. Stancakova A, Javorsky M, Kuulasmaa T, Haffner SM, Kuusisto J, Laakso M. Changes in insulin sensitivity and insulin release in relation to glycemia and glucose tolerance in 6,414, Finnish men. Diabetes 2009;58:1212-21.

18. Herzberg-Schafer SA, Staiger H, Heni M, Ketterer C, Guthoff M, Kantartzis K, *et al*. Evaluation of fasting state-/oral glucose tolerance test-derived measures of insulin release for the detection of genetically impaired β-cell function. PLoS One 2010;5:e14194.

19. Stewart MW, Humphriss DB, Berrish TS, Barriocanal LA, Trajano LR, Alberti KG, *et al*. Features of syndrome X in first-degree relatives of NIDDM patients. Diabetes Care 1995;18:1020-2.

20. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Increased insulin concentrations in nondiabetic offspring of diabetic parents. N Engl J Med 1988;319:1297-301.

21. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Ann Intern Med 1990;113:909-15.

22. Arslanian SA, Bacha F, Saad R, Gungor N. Family history of type 2 diabetes is associated with decreased insulin sensitivity and an impaired balance between insulin sensitivity and insulin secretion in white youth. Diabetes Care 2005;28:115-9.

23. Fernández-Castañer M, Biarnés J, Camps I, Ripollés J, Gómez N, Soler J. Beta-cell dysfunction in first-degree relatives of patients with non-insulin-dependent diabetes mellitus. Diabet Med 1996;13:953-9.

24. Pimenta W, Korytkowski M, Mitrakou A, Jenssen T, Yki-Jarvinen H, Evron W, *et al*. Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM: Evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. JAMA 1995;273:1855-61.

25. van Haeften TW, Dubbeldam S, Zonderland ML, Erkelens DW. Insulin secretion in normal glucose-tolerant relatives of type 2 diabetic subjects: Assessments using hyperglycemic glucose clamps and oral glucose tolerance tests. Diabetes Care 1998;21:278-82.

26. Danadian K, Balasekaran G, Lewy V, Meza MP, Robertson R, Arslanian SA. Insulin sensitivity in African-American children with and without family history of type 2 diabetes. Diabetes Care 1999;22:1325-9.

27. Srinivasan SR, Elkasabani A, Dalferes ER Jr, Bao W, Berenson GS. Characteristics of young offspring of type 2 diabetic parents in a biracial (black-white) community-based sample: the Bogalusa Heart Study. Metabolism 1998;47:998-1004.

28. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999;104:787-94.

29. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 2006;29:1130-9.

30. Haffner SM, Miettinen H, Stern MP. Insulin secretion and resistance in nondiabetic Mexican Americans and non-Hispanic whites with a parental history of diabetes. J Clin Endocrinol Metab 1996;81:1846-51.

31. Perseghin G, Ghosh S, Gerow K, Shulman GI. Metabolic defects in lean nondiabetic offspring of NIDDM parents: A cross-sectional study. Diabetes 1997;46:1001-9.

32. Gulli G, Ferrannini E, Stern M, Haffner S, DeFronzo RA. The metabolic profile of NIDDM is fully established in glucose-tolerant offspring of two Mexican-American NIDDM parents. Diabetes 1992;41:1575-86.

33. Weyer C, Hanson RL, Tataranni PA, Bogardus C, Pratley RE. A high fasting plasma insulin concentration predicts type 2 diabetes independent of insulin resistance: Evidence for a pathogenic role of relative hyperinsulinemia. Diabetes 2000;49:2094-101.

34. Arslanian SA, Saad R, Lewy V, Danadian K, Janosky J. Hyperinsulinemia in african-american children: Decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity. Diabetes 2002;51:3014-9.