Insulin sensitivity and $\beta$-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 $\beta$-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) 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 $\beta$-cell compensation in normoglycemic offspring of T2DM subjects compared to controls. Differences were greater when both parents and grandparents had T2DM.

Key words: $\beta$-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). Family history of T2DM is associated with higher body mass index (BMI), dyslipidemia, and impaired glucose tolerance (IGT) in offspring. There seems to be a vicious cycle, where obesity increases risk for T2DM and a family history of T2DM increasing the risk for obesity. Parental history of T2DM is one of the dominant risk factors for development of T2DM. The phenotype varies depending on which parent is affected and if the child was exposed to hyperglycemia in utero. $\beta$-cell dysfunction has been observed even in nondiabetic offspring of T2DM, more accentuated among those with paternal T2DM compared to maternal inheritance. Here we report the effect of family history of diabetes on insulin sensitivity and $\beta$-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.
Only participants with normal glucose tolerance (NGT) as per American Diabetes Association 2003 criteria were included in this study. This was a continuation of the “offspring of individuals with T2DM” study.

**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. Whole-body insulin sensitivity was measured as whole-body insulin sensitivity index (WBISI) as described by Matsuda et al. Homeostasis model assessment-insulin resistance was measured as proposed by Matthews et al. 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. 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. 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 ± 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 ± 10 years, 52% males) normal glucose tolerant cases and 259 (age 28 ± 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) | 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   | 0.88±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, mg/dl) | 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±8.8 | 721±7.0    | 0.550                       | 0.630                            |
| AUC of insulin (0-120) (mmol/l/min) | 54.8±2.2 | 43.3±2.3   | 0.003                       | 0.821                            |
| AUC of proinsulin (0-120) (mmol/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) | 0.38±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                            |

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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 | 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/m²)    | 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±0.007 | 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† | 0.30 |
| C-peptide 120 minutes (pmol/l) | 2359±131 | 2099±108 | 2277±118 | 2701±205 | 0.137 | 0.631 |
| HOMA-IR (µU/ml, mg/dl) | 2.8±0.3 | 1.8±0.2 | 2.3±0.3 | 4.2±0.4 | <0.001† | 0.004† |
| WBISI (µU/ml, mg/dl) | 6.2±0.7 | 7.7±0.5 | 6.85±0.66 | 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 | 0.75 |
| AUC of insulin (0-120) (nmol/l/min) | 54.0±4.8 | 45±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).
|| 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 = 0.001) 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).

Comparing among the groups, 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

Comparisons became insignificant even after adjusting 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)                    | P value |
|----------------|----------------------------------|---------------------------------|---------|
|                | 1 member with T2DM (FHD1)        | 2 members T2DM (FHD2)           | ≥3 members T2DM (FHD3) | Adjusted for age, gender | Adjusted for age, gender, and BMI |
| n              | 259                              | 170                             | 62       | 39                     |                                  |
| BMI (kg/m²)    | 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±8.1               | <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). After adjusting for BMI, only differences in plasma proinsulin at 60--120 minutes of OGTT and AUC proinsulin (0-120)/AUC glucose (0-120) and WBISI was used as DI 120 in the present study.
- 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. 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., has good correlation with the euglycemic hyperinsulinenic clamp technique in adults. In a large-scale study in the Finnish population, 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. Subsequent studies 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 glucose (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 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. 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.\cite{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.\cite{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.\cite{22,24} 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.\cite{27} A longitudinal study in Pima Indians reported a twofold greater increase in weight in subjects who progressed to diabetes compared to the nonprogressors.\cite{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.\cite{29} 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,\cite{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.,\cite{3} 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.,\cite{30} Perseghin et al.,\cite{31} Gulli et al.,\cite{32} and Natali et al.\cite{34} High-fasting insulin has been shown to predict the development of TDM, independent of insulin resistance.\cite{33} Hyperinsulinemia itself may be a primary metabolic defect and obesity may be a consequence of hyperinsulinemia.\cite{33,34}

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.

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