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Impaired compensatory hyperinsulinemia among nonobese type 2 diabetes patients: a cross-sectional study

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Abstract

Aims: Obesity associated prolonged hyperinsulinemia followed by β-cell failure is well established as the pathology behind type 2 diabetes mellitus (T2DM). However, studies on nonobese T2DM have reported it to be a distinct clinical entity with predominant insulin secretory defect. We, therefore, hypothesized that compensatory hyperinsulinemia in response to weight gain is impaired in nonobese subjects.

Methods: This was a cross-sectional study from a community-based metabolic health screening program. Adiposity parameters including body mass index (BMI), waist circumference (WC), body fat percentage, plasma leptin concentration and metabolic parameters namely fasting insulin, glucose, total cholesterol, and triglycerides were measured in 650 individuals (73% healthy, 62% nonobese with a BMI <25).

Results: In contrast to obese T2DM, nonobese T2DM patients did not exhibit significant hyperinsulinemia compared with the nonobese healthy group. Age, sex, and fasting glucose adjusted insulin levels, homeostatic model assessment of insulin resistance (HOMA-IR) and HOMA-beta cell function (HOMA-B) were increased in obese T2DM compared with nonobese T2DM. Although adiposity parameters showed strong correlation with fasting insulin in obese healthy ($r = 0.38$, 0.38, and 0.42, respectively; all p values < 0.001) and T2DM ($r = 0.54$, 0.54, and 0.66, respectively; all $p < 0.001$), only BMI and leptin showed a weak correlation with insulin in the nonobese healthy group (0.13 and 0.13, respectively; all $p < 0.05$) which were completely lost in the nonobese T2DM.

Conclusions: Compensatory hyperinsulinemia in response to weight gain is impaired in the nonobese population making insulin secretory defect rather than IR the major pathology behind nonobese T2DM.

Keywords: β-cell failure, body mass index, hyperinsulinemia, leptin, nonobese, type 2 diabetes

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Introduction

Weight gain is the most important risk factor for type 2 diabetes mellitus (T2DM).[1–5] Typically weight gain is considered to be the first step in the pathogenesis of T2DM[2,6] causing insulin resistance (IR), therefore, inducing hyperinsulinemia where β-cells produce higher levels of insulin to maintain normal blood glucose levels.[6–11] It is the progressive and gradual failure of β-cells to sustain this increased insulin production in the presence of IR that leads to T2DM.[6,12] However, studies have also reported that insulin levels increase with obesity even in the absence of IR.[13] Therefore, obesity itself is considered to be a state of primary insulin hypersecretion.[13]

While the association of T2DM with obesity and IR are clinically and pathophysiologically well

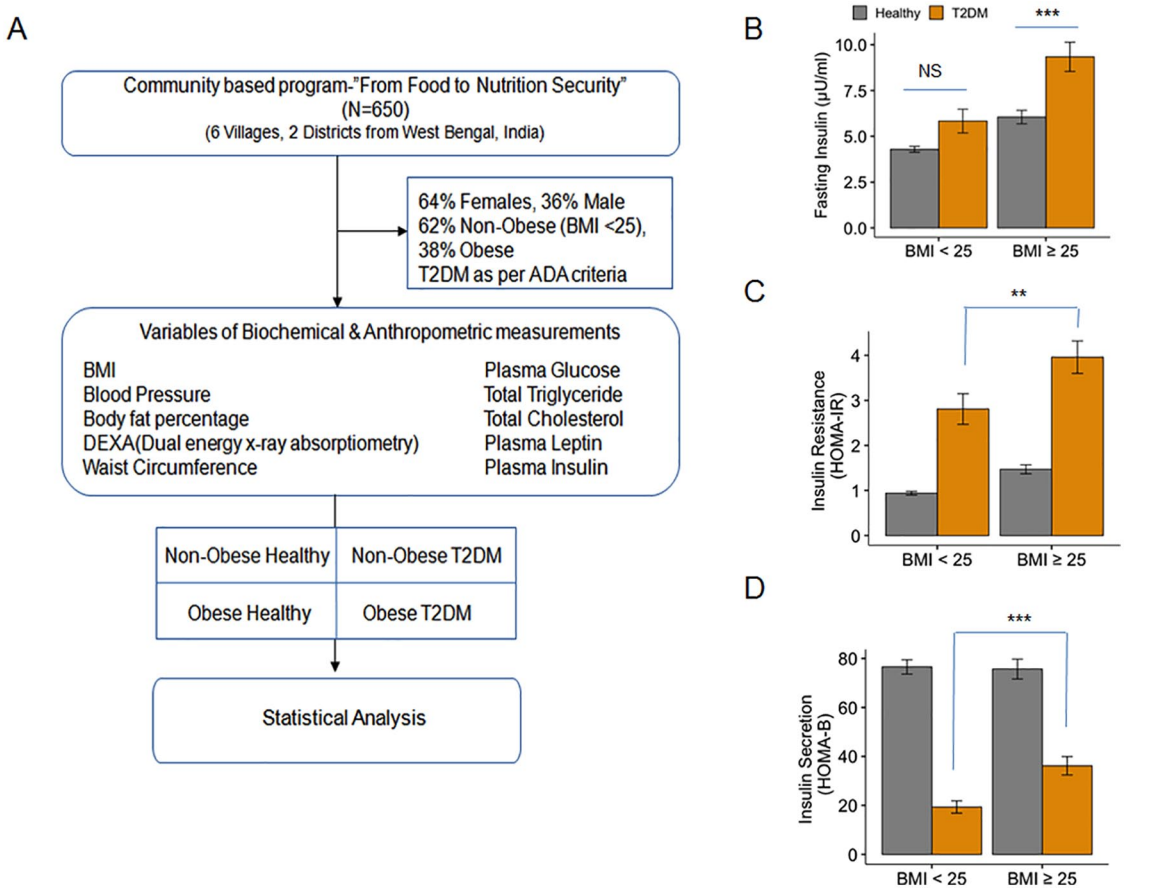

Figure 1. Study design and insulin, HOMA-IR and HOMA-B in nonobese and obese T2DM: (a) flow diagram of the research study; (b) fasting insulin levels; (c) IR expressed as HOMA-IR; and (d) insulin secretion expressed by HOMA-B for healthy and T2DM groups in nonobese and obese BMI categories. Data represent the values as mean ± SE. $^{**}p < 0.01$, $^{***}p < 0.001$.

established, the distinct and less frequently studied nonobese T2DM phenotype with predominant β-cell dysfunction, evident in middle- and low-income countries, has recently attracted much attention.[14–16] In this context, whether the hypersecretion of insulin with a corresponding increase in body weight occurs in the nonobese population group remains unknown. The obvious prevalence of nonobese individuals among the T2DM group ranges from 51.5% in India to 80% in Vietnam,[16] and requires an in-depth examination of compensatory hyperinsulinemia within the nonobese population.

Conducting experiments on a cohort of the population, we investigated whether the compensation in insulin levels in response to an increase in body weight is different between nonobese and obese groups.

Materials and methods

Patient recruitment

A total of 650 volunteers (64% females, 62% nonobese with a BMI <25) were recruited from a community-based metabolic health screening program 'From Food to Nutrition Security' run by a not-for-profit organization, SWANIRVAR. Volunteers were recruited from the program from January 2017 to September 2018. Only newly diagnosed T2DM patients were recruited, before starting any antidiabetic agents, for sample collection in addition to healthy controls. Volunteers were recruited from six villages in two districts in the state of West Bengal, India. Volunteers were classified as T2DM according to the criteria of American Diabetes Association.[17] All of the volunteers were divided into nonobese and obese groups based on a BMI <25 (Figure 1a). The

study was approved by human ethics committee of CSIR-IICB and all the volunteers gave written informed consent.

Sample collection and anthropometric measurements

All blood samples were collected in sodium fluoride/Na_2 EDTA vials (BD Vacutainer, NJ, USA). Blood samples were collected after overnight fasting for 8–10 hours. Plasma was immediately separated at the field offices of SWANIRVAR for community-based collection and was then transported to the laboratory where they were stored at −80°C for long-term storage. Height, weight, and waist circumference (WC) were measured as anthropometric parameters. BMI was calculated from height and weight. WC was measured midway between the lowest point of ribcage and the highest point of the iliac crest as a marker of central obesity. Body fat percentage was calculated from the following formula: (0.13 × age in years) + (1.5 × BMI in kg/m^2) − 23.5 (for men) or − 11.5 (for women).[18] The formula was validated by us in a subsample of the cohort ($n = 33$) where we found a strong correlation ($r = 0.87$, $p < 0.001$, data not shown) between body fat percentage calculated using this formula with body fat percentage measured by a dual energy X-ray absorptiometry (DEXA) scan. Blood pressure was measured for the volunteers recruited from the community-based program using digital sphygmomanometer (model HEM-8712, OMRON Healthcare Ltd, Kyoto, Japan) in sitting position. All of the measurements were performed by a single trained person.

Biochemical measurements

Plasma was used for biochemical measurements with reagents from Randox Laboratories Ltd (County Antrim, UK). Plasma glucose was measured using a glucose oxidase method, total cholesterol was measured using a cholesterol oxidase method, and total triglycerides was measured using a lipase/GPO-PAP method. Plasma insulin (Merck Millipore, MA, USA), plasma C-peptide (Merck Millipore), and plasma leptin (R&D Systems, MN, USA) levels were measured by enzyme-linked immunosorbent assay (ELISA). Correlation between insulin and C-peptide was validated by testing both the values in a subsample of 16 patients ($r = 0.89$, $p < 0.001$, data not shown). Because insulin levels are routinely used in clinical practice we used insulin as a marker of β-cell function in our study. Homeostatic model assessment (HOMA) was performed to calculate HOMA-IR for IR and HOMA-B for β-cell function according to the formula: HOMA-IR = (fasting insulin × fasting glucose)/22.5; HOMA-B = (20 × fasting insulin)/(fasting glucose − 3.5).

Statistical analysis

A descriptive summary of the data is represented by mean and standard error of the mean. The Shapiro–Wilk (W) test was performed to assess normality of the variables. Numerical variables were compared between groups by independent-sample two-sided Student's t test or Mann–Whitney U test as appropriate. Categorical variables were tested using chi-squared test. Age and sex adjusted mean and standard error are presented for all the subjects. Age, sex, and fasting plasma glucose adjusted mean and standard error are presented for the obese and nonobese T2DM subjects. Adjustments were carried out for each variable using linear modeling using the *lsmeans* package in R. Partial correlation was calculated between adiposity parameters and markers of insulin response and IR after adjusting for age, sex, and fasting plasma glucose. We considered $p < 0.05$ to be statistically significant. Statistical analysis was performed in RStudio (Version 1.1.447).

Results

Nonobese T2DM patients showed no compensatory hyperinsulinemia even after an increase in BMI compared with nonobese healthy controls

In the community-based cohort, fasting plasma glucose, total cholesterol, triglyceride, insulin, and leptin levels were measured in T2DM subjects ($n = 175$) diagnosed for the first time who had not received any antidiabetic medications and in healthy controls ($n = 475$). The mean values of different clinical and biochemical parameters in T2DM and healthy subjects are shown in Table 1. Volunteers were grouped into nonobese (BMI <25, T2DM = 98, healthy = 307) and obese (BMI ⩾25, T2DM = 77, healthy = 168) and subgroup analyses between T2DM and healthy were performed within each group. Comparisons were made between nonobese and

Table 1. The subject characteristics of healthy and T2DM groups and their biochemical parameters.

	Nonobese (BMI <25)			Obese (BMI ⩾25)			Nonobese T2DM *versus* obese T2DM	Nonobese non-T2DM *versus* Obese non-T2DM
Variable	**Non-DM**	**DM**	***p* value**	**Non-DM**	**DM**	***p* value**	***p* value**	***p* value**
N (Male/Female)	307 (102/205)	98 (53/45)	<0.001	168 (57/111)	77 (21/56)	0.373	<0.001	0.957
Age (years)	42.98 ± 0.89	50.11 ± 1.24	<0.001	42.65 ± 0.9	46 ± 1.04	0.011	0.015	0.856
Adiposity parameters								
BMI (kg/m^2)	21.07 ± 0.15	21.8 ± 0.24	0.023	28.96 ± 0.38	30.7 ± 0.71	0.03	<0.001	<0.001
WC (cm)	78.96 ± 0.59	84.18 ± 0.85	<0.001	94.71 ± 0.91	100.83 ± 1.71	0.001	<0.001	<0.001
Body Fat (%)	22.68 ± 0.38	23.79 ± 0.71	0.055	35.24 ± 0.7	39.13 ± 1.14	0.004	<0.001	<0.001
Leptin (ng/ml)	21.18 ± 1.24	15.26 ± 3.2	0.001	42.85 ± 3.95	58.05 ± 10.14	0.323	<0.001	<0.001
Metabolic parameters								
FBS (mg/dl)	86.89 ± 0.68	195.23 ± 6.45	<0.001	94.88 ± 1.09	176.86 ± 5.83	<0.001	0.028	<0.001
TG (mg/dl)	111.09 ± 5.34	167.48 ± 11.9	<0.001	118.65 ± 4.65	154.64 ± 8.45	<0.001	0.751	0.001
TC (mg/dl)	160.95 ± 2.41	178.86 ± 5.86	0.007	161.25 ± 3.78	185.83 ± 7.76	0.002	0.466	0.69
SBP (mmHg)	125.8 ± 1.56	130.15 ± 2.92	0.083	129.85 ± 1.57	128.95 ± 3.12	0.465	0.801	0.003
DBP (mmHg)	77.97 ± 0.84	81.19 ± 1.54	0.082	83.62 ± 1.05	81.29 ± 1.69	0.135	0.988	<0.001
Fasting insulin (μU/ml)	4.29 ± 0.16	5.83 ± 0.65	0.5	6.05 ± 0.37	9.34 ± 0.8	<0.001	<0.001	<0.001
HOMA-IR	0.94 ± 0.04	2.81 ± 0.34	<0.001	1.47 ± 0.1	3.96 ± 0.36	<0.001	0.001	<0.001
HOMA-B	76.55 ± 2.91	19.33 ± 2.5	<0.001	75.67 ± 4.07	36.19 ± 3.76	<0.001	<0.001	0.672

BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment insulin resistance; HOMA-B, homeostatic model assessment β-cell function; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WC, waist circumference. Data represented by means ± SE. Nonobese are individuals with BMI <25. A p value < 0.05 was considered statistically significant.

Table 2. Age and sex adjusted subject characteristics of healthy and T2DM patients and biochemical parameters.

	Nonobese (BMI <25)			Obese (BMI ⩾25)		
Variable	**Non-T2DM**	**T2DM**	***p* value**	**Non- T2DM**	**T2DM**	***p* value**
Adiposity parameters						
BMI (kg/m^2)	21.2 ± 0.16	22.1 ± 0.29	0.01	28.9 ± 0.44	30.9 ± 0.72	0.019
WC (cm)	80.7 ± 0.58	84.1 ± 1.06	<0.005	96.1 ± 1.05	101.3 ± 1.74	0.011
Body Fat (%)	21.6 ± 0.33	24.1 ± 0.6	<0.001	34.3 ± 0.72	38.1 ± 1.19	0.006
Leptin (ng/ml)	17.9 ± 1.33	18.8 ± 3.19	0.78	35.4 ± 4.58	45.5 ± 13.19	0.471
Metabolic parameters						
FBS (mg/dl)	87.6 ± 1.99	197.5 ± 3.64	<0.001	95.7 ± 2.47	175.5 ± 4.07	<0.001
TG (mg/dl)	113 ± 6.09	177 ± 11.16	<0.001	122 ± 5.42	165 ± 8.82	<0.001
TC (mg/dl)	160 ± 2.77	184 ± 5.13	<0.001	158 ± 4.68	191 ± 7.61	<0.001
SBP (mmHg)	128 ± 1.42	127 ± 3.24	0.632	130 ± 1.68	124 ± 3.17	0.133
DBP (mmHg)	79.4 ± 0.85	81.9 ± 1.9	0.23	83.4 ± 1.21	78.9 ± 1.99	0.056
Fasting insulin (μU/ml)	4.28 ± 0.24	5.39 ± 0.44	0.029	6.03 ± 0.45	9.47 ± 0.75	<0.001
HOMA-IR	0.95 ± 0.1	2.51 ± 0.19	<0.001	1.46 ± 0.17	3.94 ± 0.27	<0.001
HOMA-B	74.7 ± 2.73	18.6 ± 4.99	<0.001	74 ± 3.76	37.6 ± 6.21	<0.001

BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment insulin resistance; HOMA-B, homeostatic model assessment β-cell function; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WC, waist circumference. Data represented by means ± SE. Nonobese are individuals with BMI <25. A p value < 0.05 was considered statistically significant.

obese subgroups within the T2DM and healthy groups.

Age was found to be significantly increased in T2DM compared with the healthy volunteers in both obese and nonobese groups, and there was a difference in sex between the T2DM and healthy volunteers only in the nonobese group. Although BMI, WC, and body fat (%) were all were increased in the T2DM compared with healthy volunteers, in both groups body fat percentage showed a modest trend of increase only in the nonobese BMI group, with a statistical significance of $p = 0.055$. Of interest, we observed a decrease in leptin levels among the nonobese T2DM compared with the nonobese healthy volunteers (15.26 ± 3.2 *versus* 21.18 ± 1.24, $p = 0.001$) which was lost after adjustment for age and sex (Table 2) and was probably an effect of increased leptin levels in females rather than in males.

As expected, there was compensatory hyperinsulinemia in obese T2DM compared with the obese healthy group (9.34 ± 0.8 μU/ml *versus* 6.05 ± 0.37 μU/ml, $p < 0.001$). Of interest, we found no compensatory hyperinsulinemia in nonobese T2DM compared with the nonobese healthy group (5.83 ± 0.65 μU/ml *versus* 4.29 ± 0.16 μU/ml, $p = 0.5$) which suggests that insulin secretory defects occur to a greater extent among the nonobese T2DM during T2DM diagnosis (Figure 1b). Although fasting insulin levels in nonobese T2DM increased after adjustment of age and sex, the increase was 26% in the nonobese group compared with 57% in the obese group (Table 2).

On comparing within the T2DM groups, we found nonobese T2DM displayed lower IR (measured by HOMA-IR, 2.81 ± 0.34 *versus* 3.96 ± 0.36, $p = 0.001$) and lower insulin

Table 3. Age, sex, and FBS adjusted subject characteristics of nonobese and obese T2DM subjects and their biochemical parameters.

Variable	Nonobese (BMI <25) T2DM	Obese (BMI ⩾25) T2DM	*p* value
Adiposity parameters			
BMI (kg/m^2)	22 ± 0.46	30.3 ± 0.6	<0.001
WC (cm)	84.4 ± 1.16	100.4 ± 1.61	<0.001
Body Fat (%)	24.3 ± 0.81	37.4 ± 1.05	<0.001
Leptin (ng/ml)	16.4 ± 4.84	34.1 ± 10.69	0.136
Metabolic parameters			
TG (mg/dl)	170 ± 10.2	155 ± 14.6	0.409
TC (mg/dl)	179 ± 5.9	191 ± 8.33	0.248
SBP (mmHg)	129 ± 2.88	124 ± 4.18	0.312
DBP (mmHg)	81.8 ± 1.54	79.2 ± 2.26	0.339
Fasting insulin (μIU/ml)	5.64 ± 0.69	9.09 ± 0.9	0.003
HOMA-IR	2.56 ± 0.32	4.05 ± 0.42	0.005
HOMA-B	20 ± 2.75	33.1 ± 3.58	0.004

BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment insulin resistance; HOMA-B, homeostatic model assessment β-cell function ; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WC, waist circumference. Data represented by means ± SE. Nonobese are individuals with BMI <25. A p value < 0.05 was considered statistically significant.

secretion (measured by HOMA-b, 19.33 ± 2.5 *versus* 36.19 ± 3.76, $p < 0.001$) than the obese T2DM group [(Figure 1(c) and (d)]. Results were found to be the same between the two groups even after adjusting for age, sex, and fasting plasma glucose (Table 3). HOMA-B decreased by fourfold with T2DM in the nonobese group in contrast to a twofold decrease within the obese group. Of interest, we found no difference in insulin secretion (measured by HOMA-B) in obese healthy compared with nonobese healthy despite the former gaining significantly more weight and showing increased IR compared with the later.

These results highlight the fact that obesity associated IR is compensated by increased insulin secretion (hyperinsulinemia) that results in the normoglycemic state among the healthy obese group. However, the degree of compensatory hyperinsulinemia is reduced in the nonobese T2DM group which suggests an impaired ability to secrete higher levels of insulin among them in contrast to the obese T2DM patients who have preserved the ability to secrete higher levels of insulin. We then tested whether such compensatory hyperinsulinemia occurs in a linear fashion with increasing BMI in the nonobese and obese groups.

Correlations between adiposity parameters with insulin levels are exceedingly lost in nonobese T2DM

Obesity has been independently suggested to cause an increase in insulin secretion irrespective of IR.[13] Therefore, we examined whether insulin level, HOMA-IR and HOMA-B increase in a linear manner, with an increase in all of the adiposity parameters across the four groups in our study population. Partial correlations were calculated between adiposity parameters (BMI, WC, and leptin) and fasting insulin, HOMA-IR, and HOMA-B after adjusting for age, sex, and fasting

Table 4. Age, sex, and FBS adjusted correlations of fasting insulin, HOMA-B, and HOMA-IR with adiposity markers.

Obese (BMI ⩾25)						
	Obese healthy			**Obese T2DM**		
Variable	**Fasting insulin**	**HOMA-IR**	**HOMA-B**	**Fasting insulin**	**HOMA-IR**	**HOMA-B**
BMI (kg/m^2)	0.38 (<0.001)	0.38 (<0.001)	0.32 (<0.001)	0.54 (<0.001)	0.54 (<0.001)	0.48 (<0.001)
WC (cm)	0.38 (<0.001)	0.39 (<0.001)	0.31 (<0.001)	0.54 (<0.001)	0.48 (<0.001)	0.57 (<0.001)
Leptin (ng/ml)	0.42 (<0.001)	0.44 (<0.001)	0.27 (0.006)	0.66 (<0.001)	0.66 (<0.001)	0.59 (<0.001)
Nonobese (BMI <25)						
	Nonobese healthy			**Nonobese T2DM**		
Variable	**Fasting insulin**	**HOMA-IR**	**HOMA-b**	**Fasting insulin**	**HOMA-IR**	**HOMA-b**
BMI (kg/m^2)	0.13 (0.024)	0.12 (0.034)	0.12 (0.034)	0.08 (0.444)	–0.002 (0.986)	0.14 (0.185)
WC (cm)	0.09 (0.15)	0.08 (0.211)	0.1 (0.091)	0.09 (0.393)	0.02 (0.828)	0.14 (0.2)
Leptin (ng/ml)	0.13 (0.044)	0.12 (0.064)	0.1 (0.108)	–0.01 (0.956)	0.01 (0.948)	–0.02 (0.91)

BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment insulin resistance; HOMA-B, homeostatic model assessment β-cell function; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WC, waist circumference.
Nonobese are individuals with a BMI < 25. A p value < 0.05 was considered statistically significant.

plasma glucose. In the healthy obese group, fasting insulin, HOMA-IR and HOMA-B increased with a corresponding increase in adiposity parameters. All of the parameters showed even stronger positive correlation with fasting insulin, HOMA-IR and HOMA-B in the obese T2DM group, the lowest correlation was between BMI and HOMA-B ($r = 0.48$, $p < 0.001$) and the highest correlation was between leptin and fasting insulin ($r = 0.66$, $p < 0.001$) (Table 4). These results highlight the strong presence of compensatory hyperinsulinemia with increased body weight in the obese group both in the presence and absence of T2DM. In contrast, none among BMI, WC, and leptin correlated with fasting insulin, HOMA-IR or HOMA-B in the nonobese T2DM group. Of interest, only BMI and leptin showed a weak correlation with fasting insulin, HOMA-IR, and HOMA-B in the healthy nonobese group (Table 4).

In combination, within the normoglycemic status in the obese group, fasting insulin levels and insulin secretion increase with increasing BMI, which is also maintained (or even better maintained) in the obese T2DM group, due to the phenomenon of compensatory hyperinsulinemia. This correlation, being weak within the nonobese healthy group highlights the fact that there is a reduced compensation in basal insulin secretion with increasing BMI within the nonobese healthy group. In addition, this weak correlation is lost in the nonobese group with the clinical manifestation of T2DM.

Discussion

In this study, we demonstrated that the basal level of plasma insulin is not increased in the nonobese T2DM population compared with the nonobese healthy population. However, the obese T2DM group demonstrates compensatory hyperinsulinemia with a significant rise in fasting insulin levels compared with its obese healthy counterpart. In addition, insulin levels increase linearly with an increase in all the adiposity markers (BMI, WC, and leptin) in the healthy and the T2DM subgroups only in the obese group. Even if similar correlations were weakly present within the nonobese healthy group, they were completely absent in the nonobese T2DM group.

Compensatory hyperglycemia is the hallmark of IR, an effect that was weakly present in the nonobese healthy group and was totally lost in the nonobese T2DM group. Because impaired basal

insulin secretion has been linked with isolated impaired fasting glucose (IFG), our results explain the higher proportion of prediabetic patients with IFG rather than with impaired glucose tolerance in the South Asian population that has been reported in several epidemiological studies.[14,19] This decrease in the basal insulin secretion may be attributed to the reduced β-cell mass in the nonobese T2DM. This has been reported in autopsy studies where it was found that β-cell apoptosis increased 10-fold in obese T2DM but only 3-fold in nonobese T2DM compared with their healthy counterparts.[20,21] This reduced insulin secretion may be the result of a genetic predisposition of Asians that has previously been reported.[22,23] In addition, our findings of reduced insulin secretion due to the inability to expand β-cell secretion in response to T2DM among the nonobese group explains the reduced insulin secretion capacity in oral glucose tolerance tests in the Asian population.[24]

Obesity has been reported to be a state of primary insulin hypersecretion[13] and, therefore, BMI has been shown to exert a positive effect irrespective of IR status. Quantitative measures reveal that increased BMI is associated with an increase in β-cell mass leading to a 10–30% increase for every 10 kg of body weight.[13] The adiposity parameters in our study show a strong correlation with fasting insulin and insulin secretion (HOMA-B) in the obese group, this reflects the previously mentioned phenomenon and confirms the absence of β-cell impairment among the obese T2DM group at the time of diagnosis. In contrast, absence of such a correlation between adiposity parameters and basal insulin secretion in the nonobese group reveals the predominance of impaired β-cell function in the nonobese T2DM group at the time of diagnosis. Reduced ability to sustain insulin secretion in the nonobese group may be attributed to protein–energy undernutrition during fetal development or early childhood and has been reported in several studies.[25–27] In addition, early β-cell defect in the development of disease among the nonobese T2DM population results in a state of chronic glucose toxicity, therefore, putting more load on the β-cells and causing more severe β-cell defect.[28] However, there is no reduction or death of β-cell mass in nonobese T2DM as previously mentioned.[20,21] The classical pathway of T2DM development is obesity followed by IR and impaired insulin secretion.[6,16] However, it could be that the previously mentioned pathway is characteristic of the obese T2DM group. Therefore, an inability to secrete and sustain increased insulin secretion in the nonobese group may, potentially, proceed to T2DM *via* a different pathway where insulin secretory defect is the predominant pathology. This inability to secrete and sustain increased insulin secretion among the nonobese group may be attributed to *in utero* undernutrition or low birth weight as has been suggested in several reports.[16,29]

Our study has several strengths and limitations. T2DM patients were recruited over a long period of time from the community which is a strength of the study because it ensured that the patients were diagnosed for the first time with T2DM and none had received any antidiabetic treatment before sample collection. The formula used by us to calculate the body fat percentage was validated by us in a subsample of our cohort using a DEXA scan. One limitation of this study was using HOMA modeling to calculate insulin secretion and resistance. In addition, we could not differentiate the fat compartments and body fat distribution in the volunteers, because body fat distribution is known to specifically regulate IR.

Conclusion

Fasting insulin and insulin secretion (HOMA-B) are compromised more in nonobese T2DM. Compensatory hyperinsulinemia in response to weight gain is impaired and absent in the healthy and T2DM subgroups respectively within the nonobese group, that makes the insulin secretory defect rather than IR as the major pathology behind nonobese T2DM. Reduced insulin secretion among the nonobese T2DM group at first diagnosis gives an indication to revisit the therapeutic guidelines as well as the screening criteria for T2DM for the nonobese population. Among the present global epidemic of obesity, epidemiological evidence is accumulating from the low- and middle-income countries leading to an increasing appreciation of this distinct metabolically unhealthy nonobese population exhibiting a higher risk of mortality from cardiovascular events, a phenomenon termed the 'obesity paradox'.[30–32] These patients largely represent the unhealthy nonobese phenotype of South Asian countries and have been characterized by impaired insulin secretion driven T2DM. Further prospective studies are required to quantify the degree, timing, and duration of β-cell dysfunction in the

development of T2DM among the nonobese phenotype. Because several epidemiological studies from Asia have revealed an overwhelming proportion of nonobese phenotype within the T2DM group we need to reconsider and discover specific therapeutics for nonobese T2DM in the context of β-cell revival. Detection of the proper timing of β-cell dysfunction in the development of nonobese T2DM will help prevent the pathogenesis at an earlier stage and provide better preventive and curative options to the patients.

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Conflict of interest statement

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References

1. Colditz GA, Willett WC, Stampfer MJ, *et al.* Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 1990; 132: 501–513.
2. Bray GA. Medical consequences of obesity. *J Clin Endocrinol Metab* 2004; 89: 2583–2589.
3. Hossain P, Kawar B and El Nahas M. Obesity and diabetes in the developing world—a growing challenge. *N Engl J Med* 2007; 356: 213–215.
4. Eckel RH, Kahn SE, Ferrannini E, *et al.* Obesity and type 2 diabetes: what can be unified and what needs to be individualized? *Diabetes Care* 2011; 34: 1424–1430.
5. Estampador AC and Franks PW. Precision medicine in obesity and type 2 diabetes: the relevance of early-life exposures. *Clin Chem* 2018; 64: 130–141.
6. Kahn SE, Hull RL and Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; 444: 840–846.
7. Kahn BB and Flier JS. Obesity and insulin resistance. *J Clin Invest* 2000; 106: 473–481.
8. Kahn SE. The importance of the beta-cell in the pathogenesis of type 2 diabetes mellitus. *Am J Med* 2000; 108(Suppl. 6a): 2S–8S.
9. Kahn SE. The importance of β-cell failure in the development and progression of type 2 diabetes. *J Clin Endocrinol Metab* 2001; 86: 4047–4058.
10. Festa A, Williams K, D'Agostino R, *et al.* The natural course of beta-cell function in nondiabetic and diabetic individuals: the insulin resistance atherosclerosis study. *Diabetes* 2006; 55: 1114–1120.
11. Tabák AG, Jokela M, Akbaraly TN, *et al.* Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet* 2009; 373: 2215–2221.
12. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia* 2003; 46: 3–19.
13. Ferrannini E, Camastra S, Gastaldelli A, *et al.* Beta-cell function in obesity: effects of weight loss. *Diabetes* 2004; 53(Suppl. 3): S26–S33.
14. Staimez LR, Weber MB, Ranjani H, *et al.* Evidence of reduced β-cell function in Asian Indians with mild dysglycemia. *Diabetes Care* 2013; 36: 2772–2778.
15. Unnikrishnan R, Anjana RM and Mohan V. Diabetes in South Asians: is the phenotype different? *Diabetes* 2014; 63: 53–55.
16. Gujral UP, Weber MB, Staimez LR, *et al.* Diabetes among non-overweight individuals: an emerging public health challenge. *Curr Diab Rep* 2018; 18: 60.
17. Of S and Carediabetes M. Standards of medical care in diabetes—2018. *Diabetes Care* 2018; 41: S7–S12.

18. Gallagher D, Visser M, Sepúlveda D, *et al*. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol* 1996; 143: 228–239.

19. Anjana RM, Deepa M, Pradeepa R, *et al*. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR–INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol* 2017; 5: 585–596.

20 Butler AE, Janson J, Bonner-Weir S, *et al*. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 2003; 52: 102–110.

21. Saisho Y, Butler AE, Manesso E, *et al*. β-cell mass and turnover in humans: effects of obesity and aging. *Diabetes Care* 2013; 36: e112.

22. Snehalatha C, Ramachandran A, Satyavani K, *et al*. Study of genetic prediabetic south Indian subjects. Importance of hyperinsulinemia and beta-cell dysfunction. *Diabetes Care* 1998; 21: 76–79.

23. Kodama K, Tojjar D, Yamada S, *et al*. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. *Diabetes Care* 2013; 36: 1789–1796.

24. Iwahashi H, Okauchi Y, Ryo M, *et al*. Insulin-secretion capacity in normal glucose tolerance, impaired glucose tolerance, and diabetes in obese and non-obese Japanese patients. *J Diabetes Investig* 2012; 3: 271–275.

25. Becker DJ, Pimstone BL, Hansen JD, *et al*. Patterns of insulin response to glucose in protein-calorie malnutrition. *Am J Clin Nutr* 1972; 25: 499–505.

26. Smith SR, Edgar PJ, Pozefsky T, *et al*. Insulin secretion and glucose tolerance in adults with protein-calorie malnutrition. *Metabolism* 1975; 24: 1073–1084.

27. Rao RH. The role of undernutrition in the pathogenesis of diabetes mellitus. *Diabetes Care* 1984; 7: 595–601.

28. Yki-Järvinen H. Glucose toxicity. *Endocr Rev* 1992; 13: 415–431.

29. Narayan KM. Type 2 diabetes: why we are winning the battle but losing the war? 2015 Kelly West Award Lecture. *Diabetes Care* 2016; 39: 653–663.

30. Han SJ and Boyko EJ. The evidence for an obesity paradox in type 2 diabetes mellitus. *Diabetes Metab J* 2018; 42: 179–187.

31. Gajalakshmi V, Lacey B, Kanimozhi V, *et al*. Body-mass index, blood pressure, and cause-specific mortality in India: a prospective cohort study of 500 810 adults. *Lancet Glob Health* 2018; 6: e787–e794.

32. Chen Z, Iona A, Parish S, *et al*. Adiposity and risk of ischaemic and haemorrhagic stroke in 0·5 million Chinese men and women: a prospective cohort study. *Lancet Glob Health* 2018; 6: e630–e640.