

# Clinical Assessment of Obesity and Insulin Resistance in Type 1 Diabetes Subjects seen at a Center in Kolkata

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## Abstract

**Objectives :** Type 1 diabetes mellitus (T1DM) is characterized by a selective destruction of pancreatic beta cells. Recent data suggest a role of insulin resistance (IR) along with the deficient insulin reserve.

**Methods :** Fifty-eight consecutive patients of T1DM, with low C-peptide levels were included. Patients with an obvious secondary cause like steroid therapy, fibrocalculous pancreatic disease, chronic infections or comorbid illness were excluded.

A clinical assessment for the presence of obesity was made based on anthropometric data. Clinical markers of IR and the insulin dose required to achieve a stable glycemic control calculated in terms of body weight were also studied.

**Results :** There were 30 males and 28 females with a mean age of  $16.5 \pm 2.3$  (5-39) years. The mean body mass index (BMI) was  $19.21 \pm 3.7$  and the waist circumference was  $67 \pm 5.2$  cms. Nineteen (32.75 %) and six (10.34 %) patients were overweight (BMI>23) and obese (BMI>27) respectively while 16 (27.58 %) had abdominal obesity. The body fat percentage was high (>25 %) in 34 (58.62 %), mean  $28.33 \pm 11.4\%$ . Acanthosis nigricans was found in 14 (24.13 %) cases, hypertension in two (3.4 %) but none of the girls had clinical polycystic ovarian syndrome (PCOS). The insulin dose required was  $1.11 \pm 0.41$  u/kg (0.3-2.9) at a glycated haemoglobin A1C (A1C) of  $7.56 \pm 1.04$  % (4.9-9.3), it was more than 0.6 u/kg/day in 38 (65.51 %) patients.

**Conclusions :** The study concludes that IR is present in a large number of Indian T1DM patients along with a high body fat percentage.

## Introduction

Type 1 diabetes mellitus (T1DM) constitutes about 10% of the total diabetic population. Along with an epidemic rise in the incidence of type 2 diabetes, especially in children, an increase in type 1 cases has also been recorded across the globe. Type 1 DM is characterized by a selective destruction of pancreatic  $\beta$  cells and consequent loss of insulin secretory reserve.<sup>1</sup> Recent data suggest a role of insulin resistance in its pathogenesis along with insulinopenia.<sup>2</sup> This is particularly important in children with type 1 DM who are in the pubertal age group or who are obese, with markers of insulin resistance (IR). Insulin resistance may however, be present in nonobese patients of T1DM also. Although euglycemic clamp is regarded as the "gold standard" in measuring IR and HOMA (Homeostatic Model Assessment) -IR is well validated for its evaluation,<sup>3</sup> a high dose of Insulin requirement to achieve a stable glycemic control is often used as its surrogate marker.<sup>4</sup> The concept of IR in T1DM patients has important implications in its management as it allows a use of insulin sensitizers along with exogenous insulin.

## Aims & Objectives

A study was planned to evaluate the presence of IR in T1DM patients from clinical markers like hypertension, acanthosis

nigricans, dyslipidemia and polycystic ovarian syndrome (PCOS) in girls and the dose of insulin required to achieve a stable glycemic control. Anthropometric data were studied including BMI (body mass index), waist circumference, WHR (waist: hip ratio) and body fat percentage for a clinical assessment of obesity in these subjects

## Material & Methods

The study was conducted at the Department of Endocrinology, SSKM Hospital and IPGME & R. Consecutive patients of Type 1 DM over a period of two years (Jan 2004 to Jan 2006) were included. The major criteria for eligibility was an onset of diabetes below 39 years of age, an acute presentation with or without ketosis with insulin dependence, as evidenced by a deficient C-peptide secretion (when feasible) i.e., a C-peptide value less than 0.5 (0.6-3.2) ng/ml and a duration of diabetes of at least one year. Patients of at least one year duration were selected to exclude acute or "honeymoon" phases. Those with an obvious secondary cause like steroid therapy or fibrocalculous pancreatic disease, chronic infection or comorbid illness were excluded. None of the patients were receiving any drugs apart from insulin.

All patients were evaluated for anthropometric data that included body weight by a digital scale to the nearest 0.1 kg and height (cms) in triplicate from a wall mounted stadiometer. The BMI was calculated by dividing the weight in kilograms by the height in meters squared. Body fat percentage was also measured by bioelectrical impedance method by two different machines, one by the hands and another by the feet method, by a single

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Table 1 : Demographic data (n=58)

Sex	
Males	30 (51.7%)
Females	28 (48.2%)
Age	
Mean	16.5 ± 2.3 years (5 - 39)
less than 13 years	17 (29.33%)
13 – 18 years	24 (41.3%)
more than 18 years	17 (29.33%)

Table 2 : Anthropometric data including prevalence of general and abdominal obesity (n=58)

BMI (kg/m <sup>2</sup> )	
Mean	19.21 ± 3.7
< 18.5 (Lean)	18 (31.03 %)
18.5 – 22.9 (Normal)	15 (25.26 %)
23 – 26.9 (Overweight)	19 (32.75%)
> 27 (Obese)	6 (10.34 %)
Waist circumference (cms)	
Mean	67 ± 5.2
> 90 (males), > 80 (females)	16 (27.58 %) 10 males & 6 females
Abdominal obesity	
WHR	0.82 (0.6 – 0.8)
Body fat percentage (%)	
Mean	28.33 ± 11.4 % (41. 37 %)
> 25	34 (58.62 %)

BMI : Body mass index; WHR : Waist hip ratio

observer by taking an average of three values. A value exceeding 25% was taken as indicative of high body fat mass in adults while in children (age < 15 years) it was calculated by a validated formula<sup>5</sup> discussed below. The waist and hip circumferences were measured in centimeters by a standard tape, and an average of three readings were taken to calculate the WHR. The WHO Asia Pacific guidelines<sup>6,7</sup> were used to determine prevalence of obesity, overweight and abdominal obesity by BMI, WHR and waist circumference values.

All patients below 18 years were assigned to a prepubertal (Tanner stage 1) or pubertal (Tanner stage 2 or more) group. Apart from a detailed clinical examination and routine laboratory investigations, dilated fundoscopy, urine microalbuminuria and lipid profile by standard methods.

The insulin dose required over 24 hours to achieve a stable and optimal glycemic control with an HBA1C (HPLC method) of 6-8 % and reasonable blood glucose values over a one week period was calculated in terms of units/kg body weight.

The study was approved by the institutional ethics committee and an informed consent was obtained from the patients or their guardians (in case of minors).

#### Statistical Analysis

All values were expressed as mean ± SD. Data input and basic evaluation was done by standard SPSS software.

## Results

Fifty-eight patients were enrolled in the study comprising of 30 (51.7%) males and 28 (48.2%) females (Table 1). The mean age was 16.5 ± 2.3 years (5 to 39 years) 24(41.3%) patients were adolescents, between 13-18 years of age while the number in the preadolescent i.e. less than 13 years and those above 18 years of age were 17 (29.3%) in each group. All patients were of Indian

Table 3 : Clinical Profile and Complications (n=58)

Duration of DM	2.6 ± 1.8 yrs
Positive Family history (Type 2 DM)	4(6.8%)
Smokers	None
Acanthosis nigricans	14 (24.13%)
Hypertension	2 (3.4%)
PCOS	None
Goitre	38 (35.5 %)
Primary hypothyroidism	9 (15.51 %)
Ketosis	14 (24.13 %)
Chronic renal failure	2 (3.4%)
Macroalbuminuria	2 (3.4 %)
Microalbuminuria	4(6.8 %)
Non-proliferative retinopathy	4(6.8%)
Proliferative retinopathy	1(1.7%)
Autonomic neuropathy	1(1.7%)
Clinical sensorimotor neuropathy	1(1.7%)
Dyslipidemia	2(3.4%)

(Asian) origin. The duration of diabetes was 2.6 ± 1.8 years. 4 (6.8%) patients had a positive family history of type 2 (none had type 1) diabetes. None were past or current smokers.

The mean BMI was 19.21 ± 3.7 kg/m<sup>2</sup> (13.5 – 24.9). Fifteen (25.26 %) patients were of normal weight (BMI = 18.5 - 22.9) while 18 (31.03%) were lean (BMI <18.5). 19 ( 32.75 %) and 6 (10.34 %) patients were overweight (BMI = 23 - 26.9 ) and obese (BMI >27) respectively (Table 2).

The mean waist circumference was 67 ± 5.2 cms. 16 (27.58 %) had abdominal obesity (waist circumference >80 cms in females and >90 cms in males). The WHR was 0.82 (0.6 – 0.8).The body fat percentage was high in 34 (58.62 %), mean 28.33 ± 11.4 %. It was 22.82% (11.5-40.4) by the hand while it was 29.32% (15.6-42.9) by the foot method

Acanthosis nigricans was noted in 14 (24.13%) patients, all of whom were females but none had a history of oligomenorrhea or hirsutism suggestive of PCOS. Hypertension was present in 2 (3.44%) patients. Two (3.4%) patients had chronic renal failure and the same number had urine protein positive by dipstick method while it was in the microalbuminuric range in 4 (6.8%) patients. Mild to moderate non-proliferative retinopathy was present in four patients while one had proliferative retinopathy. One had unequivocally documented autonomic with peripheral sensory neuropathy while the rest did not have any neuropathic symptoms, loss of sensation by a 6 point 10 gm monofilament test or an absent ankle jerk. Dyslipidemia with a raised total and LDL cholesterol was present in 2 (3.4%) cases (Table 3).

Autoantibodies to both GAD and IA2 could be tested in 12 out of 30 cases tested, cases, six had only GAD while three had only IA2 positivity. Thus 21 out of 30 (70%) tested positive for autoantibodies.

The mean HbA1C was 7.56 ± 1.04 % (4.9-9.3) while the mean Insulin dose requirement overall was 1.11 ± 0.41 u/kg body weight. Adolescents required 1.1 ± 0.12 u/kg while the dose of insulin in the pre and post-pubertal age groups were 1.3 ± 0.29 u/kg and 1.2 ± 0.06 u/kg respectively (Table 4). These doses were much higher than the standard requirement of 0.6 – 0.7 u/kg body weight in case of an insulinopenic type 1 diabetic, it was more than 0.6 u/kg/day in 38 (65.51 %) patients.

Table 4 : Glycemic Control and Insulin Requirements (n=58)

Glycated hemoglobin (A1C %)	7.56 ± 1.04 (4.9-9.3)
Insulin dose (units/kg of body weight/day)	
Mean	1.11 ± 0.41 (0.3 – 2.9)
Less than 13 years	1.3 ± 0.29 (0.6-2.9)
13 – 18 years	1.1 ± 0.12 (0.3-2.7)
More than 18 years	1.2 ± 0.06 (0.8-2.4)
Number of patients. requiring > 0.6 u/kg/day	38 (65.51 %)

## Discussion

Type 1 diabetes is due primarily to  $\beta$  cell destruction leading to insulinopenia – classically this is a type of diabetes in which insulin is required for survival. It is subclassified into two main categories – type 1A and 1B.<sup>1</sup> In type 1A, individuals have one or more of anti-islet cell (including GAD and IA2) or anti-insulin antibodies. However, especially in nonwhites, type 1 diabetes can occur in the absence of these autoantibodies and without evidence of any autoimmune disorder. Nevertheless, it is characterized by low insulin and C peptide levels similar to type 1A, they are prone to ketoacidosis but the pathogenetic basis for their insulinopenia remains obscure. This is called type 1B diabetes.

Recent developments suggest a role of insulin resistance or glucose disposal defect<sup>8,9</sup> apart from the insulinopenia in type 1 diabetes. These reports are primarily from nonwhite countries. Type 1 patients who are obese are particularly likely to have insulin resistance. This is in parallel to the increasing prevalence of obesity and type 2 diabetes in children and adolescents. These patients are said to be at an increased risk of developing cardiovascular disorders.<sup>10</sup>

Puberty plays a key role in the development of a resistance to insulin action. Growth hormone levels are higher in adolescents along with sex steroids.<sup>11</sup> Also there is a selective resistance to the metabolic rather than the anabolic effects of insulin at this stage. These may partly explain the reduced insulin stimulated glucose disposal in diabetic as well as non-diabetic adolescents. This is particularly true for girls who have 30% lower insulin stimulated glucose disposal at Tanner stage II-IV as compared to Tanner stage 1 or in adults. This may account for the higher dose of insulin required in our population in which about 40% of the patients were in the adolescent age group.

Obesity on the other hand causes insulin resistance by various mechanisms.<sup>12</sup> Visceral fat liberates large amounts of non-esterified fatty acids, which stimulate neoglucogenesis in the liver and diminish glucose uptake in the muscles. Local intramyocellular triglyceride accumulation may also play a role. In addition, obesity is associated with increased activity of the sympathetic nervous system, which along with direct release of TNF $\alpha$ , resistin and other hormones liberated from adipocytes contribute to insulin resistance. Thus, obesity and the physiological changes at puberty can partly explain the insulin resistance found to occur in T1DM patients.<sup>11-14</sup> However some of the patients in our study were either lean or of normal weight and BMI. Their waist circumference and the WHR were also well within normal range. Also, almost a third of the subjects were prepubertal but with a high requirement of insulin for good glycemic control suggesting IR along with insulinopenia (low C peptide levels).

Body fat percentage is calculated in children aged 15 years or below, by many validated formulae based on the BMI, age and sex, e.g., Body Fat % = 1.51 x BMI - 0.70 x age - 3.6 x sex (males

= 1, females = 0) + 1.4.<sup>5</sup> The percentage of body fat was high in about half of the subjects. Although normative data for waist circumference, WHR and body fat percentage for children who constituted about one-third of our cases and for people of Indian or Asian origin are scant in literature, it could be argued that our study population had a low-normal BMI against a high body fat composition. A paradox is often reported in literature that subjects of Asian or African descent often have low or normal BMI but increased visceral or total body fat mass.<sup>15,16</sup> This is what is called the “thin-fat” phenotype. They also have marked insulin resistance and an increased predisposition to develop type 2 diabetes and cardiovascular disease. It is thus believed that ethnic-specific cutoffs with BMI and waist circumference will help in more accurate characterization of obesity and metabolic syndrome in our populations.<sup>17</sup>

Clinical markers of insulin resistance like acanthosis nigricans was common but others like hypertension, dyslipidemia or PCOS were not commonly found in our subjects. However, the dose of insulin required for control of hyperglycemia was high in most of the patients of all age groups – this is well established as a surrogate marker of insulin resistance. Similar studies<sup>2</sup> have been reported in literature.

A drawback of our study is that a more objective assessment of glucose disposal defect by euglycemic clamp<sup>18</sup> is lacking. HOMA-IR has been validated against a variety of physiological methods.<sup>19,20</sup> It has been used to assess IR and  $\beta$ -cell function as a one-off measure in more than 150 epidemiological studies examining subjects of various ethnic origins with varying degrees of glucose tolerance. It is possible to use to assess insulin sensitivity in subjects treated with insulin, but it is imperative to ensure that samples are taken when glucose and insulin concentrations are in a steady state. This is an area of ongoing research. Also, quantitative total body fat or visceral fat estimation by dexta scan, or by magnetic resonance imaging have not been done. A correlation between BMI, body fat percentage and insulin stimulated glucose disposal rate would be ideal in these subjects.

A realization of the occurrence of insulin resistance<sup>21</sup> in patients of type 1 diabetes has important implication in their management. Use of insulin sensitizers like metformin<sup>22</sup> and rosiglitazone<sup>23</sup> along with insulin leading to a better glycemic control has been well established in a large number of studies in type 1 diabetes patients. Most of patients in these studies are obese. Studies in their use in patients of lean type 1 diabetics with evidence of insulin resistance are lacking. Further research in this area is needed to open up the field of therapy of type 1 diabetes to oral agents, which act as sensitizers of insulin action.

## Conclusions

In conclusion, insulin resistance is present in type 1 diabetes patients based on the presence of acanthosis nigricans, increased body fat percentage and requirement of high dose of insulin for stable glycemic control. The incidence of autoantibody positivity, prevalence of microvascular complications and thyroid dysfunction were similar to those quoted in literature. A more objective assessment of this proposed insulin resistance in a larger number of patients, its correlation with body fat parameters and a possible therapeutic role of oral sensitizers is required in future.

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