

Islets B Cell Response and Glucose Homeostasis in Low Body Weight Type 2 Diabetes

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Abstract

Introduction: Low body weight Type 2 Diabetes Mellitus (LB T2 DM) is not a distinct clinical entity that is related clinically or pathophysiologically to latent autoimmune diabetes in adults (LADA) nor to Type 1DM, have absence of markers for autoimmune destruction of β -cells and good insulin and C-peptide reserve for a prolonged period of life. They constitute an independent variant of Type 2 DM with inherent peculiarities of insulin kinetics in the liver along with altered profile and behavior of key enzymes related to carbohydrate metabolism which are marked by excess extraction of insulin in the hepatic bed, hyperactive cytochrome system and non-suppressible glucokinase activity. These peculiarities are reflected in the peripheral circulation as low circulating insulin levels and severe persistent hyperglycemia despite fairly preserved β cell reserve for insulin. Peripheral persistent hyperglycemia could be the likely cause for higher prevalence of peripheral neuropathy, infections and endothelial cell dysfunction. In view of higher prevalence of infective complications and coexistent severe hyperglycemia, many of these diabetics may not respond to Oral Anti diabetic Drugs (OAD) adequately at the initiation of therapy. However, due to existence of insulin resistance and good β -cell reserve for insulin, despite of lean habitus, glucose homeostasis and normo glycemia is often maintained with OAD for long periods of life, as may be comparable with any other phenotype of Type 2 DM. The insulin resistance observed in LB T2 DM is not related to anthropometric parameters like central obesity and Waist Hip Ratio (WHR).

Conclusion: LB T2DM are variant of classical (obese) Type 2 DM where the lean habitus is neither consequent to under nutrition, having low circulating insulin levels, nor due to autoimmune β -cell destruction but have inherent metabolic aberrations in hepatic bed extracting more insulin causing low circulating insulin levels. They do have peripheral insulin resistance. The management although akin to classical Type 2 DM, biguanides are avoided, the complications profile are visibly different from the Type 2 DM seen in the West.

Keywords: Low bodyweight Type 2 DM; HOMA-IR; HOMA-B; Glucokinase; Hepatic-microsomal enzyme hyperactivity; Insulin C-peptide disparity; β cell reserve; Glucose homeostasis; Anti-GADAb; Anti-ICA ab

Introduction

In India and other developing countries, majority of Type 2 Diabetics are non-obese and around one fourth of them are underweight with a BMI below 18.5 [1]. Epidemiological data over the past decades have shown that the clinical pattern and phenotypic profile of subjects with Type 2 diabetes (T2DM) are very different in India as well as in certain developing countries of Asia and Africa as compared to the West. The consensus statement adopted at the "International Workshop on Types of Diabetes Peculiar to the Tropics" held at Cuttack in 1995 and proceedings published in the Diabetes Care, duly acknowledges the same [2].

Type 2 DM, previously called Non-insulin Dependent Diabetes Mellitus (NIDDM), is the most prevalent form of DM seen in India and constitutes more than 95% of the diabetic population [3]. Interestingly, almost 80% of Indian patients with Type 2 DM are non-obese in contrast to the picture in the West [3,4]. The body habitus, far from being overweight, is often 'lean' or low bodyweight, i.e. more than 20% below the ideal bodyweight for height and gender. Clinical picture of typical subjects with Low body weight Type2DM (LB T2 DM) is presented in Figure 1. In a prospective study, sponsored by the Indian Council of Medical Research (ICMR), it was observed that about one fourth of our Type 2 DM patients had a Body Mass Index (BMI) below 19, or in other words were low bodyweight/lean. Analysis of data from the 9 centres across India indicated that the prevalence of LB T2 DM varied from 11 to 25%. This characteristic persisted even at the end of



Figure 1: Photograph of typical patients with Type 2 DM-Lean.

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the study period of five years (1985-90). Therefore, leanness was the inherent characteristic and not related to the diabetic state [4]. Lower socio-economic status was not a sine qua none of Low bodyweight Type 2 DM as more than 80% of these types of diabetics were from the middle socio-economic class. Analysis of dietary intake revealed that they were not protein deprived. The purpose of this review is to highlight the issues of β cell response and glucose homeostasis in subjects with LB T2 DM as well as the peculiarities regarding its pathophysiology.

Glycemic Status, B Cell Function and Glucose Homeostasis

LB T2 DM subjects have moderately severe to severe basal hyperglycemia [1,4]. Levels of glycosylated Hb are significantly higher than in the classical patients with Type 2 DM at diagnosis [4]. Unlike in subjects with classical Type2 DM, the LB T2 DM patients are advised to increase calorie intake (males: 1548 to 1998 kcal/day; and females: 1473 to 1818 kcal/day). Metformin is avoided in LB T2 DM subjects while other Oral Anti Diabetic drugs (OAD) are prescribed to maintain glycemic control. With these measures, in the majority of patients fair glycemic control is possible with observed significant decrease in levels of glycosylated Hb (from 10.1 ± 2.4 to $6.36 \pm 0.9\%$ in males and 10.9 ± 2.4 to $6.3 \pm 1.5\%$ in females respectively) over one year of treatment.

It is a well-known fact that, in subjects with Type 2 DM, the islet β cells and their secretory apparatus become refractory to the changing blood glucose levels owing to glucotoxicity, while retaining their responsiveness to other stimuli like non-CHO diet, amino acids, glucagon and catecholamines [5]. Using a non-CHO diet or a mixed meal to evaluate the beta-cell reserve for insulin in different types of diabetics i.e. LB T2 DM, patients suffering from Malnutrition Related DM (MRDM) along with healthy controls, it was found that the increment in insulin-glucose index following different dietary challenges (isocaloric) was highest with diet containing agrinine, in controls as well as subjects with LB T2 DM but least in those with MRDM (Table 1) [6]. Changes in the insulin/glucose index following oral glucose challenge in control subjects and these two groups of subjects with DM is presented in Figure 2. It obviated the presence of significant insulin reserve in subjects with LB T2 DM.

The issue of good β cell reserve of insulin for non-glucose dietary secretagogues was an indirect evidence for preserved β cell function in LB T2 DM but did not explain the reason for low levels of circulating insulin and consequently persistent severe hyperglycemia. Subsequent study assessing the response of β cells to glucose and glucagon challenge observed that, the subjects with LB T2 DM had much higher FBG levels than obese Type 2 DM subjects at the basal state [5]. The response of β cell to glucagon was much higher than that for oral glucose in both

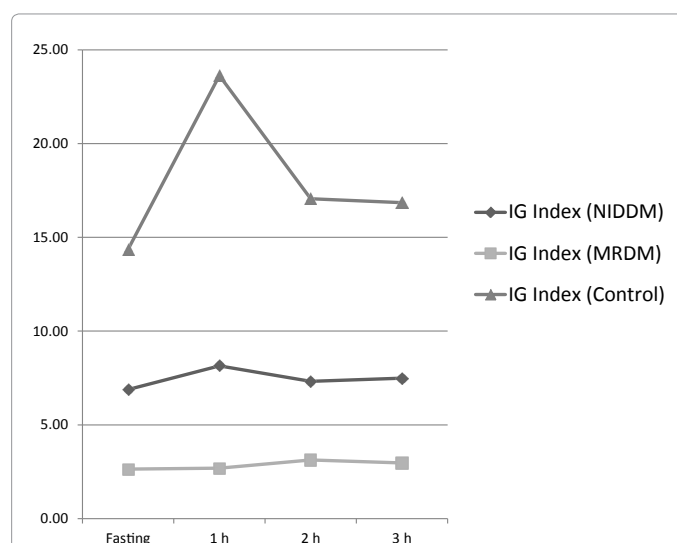


Figure 2: Changes in the insulin glucose index in subjects with lean NIDDM / LB T2 DM, MRDM and healthy controls following oral glucose changes.

	Plasma insulin (μ u/ml) Basal	Post-Glucose	Post-Glucagon
Cuttack [6]			
Healthy controls	11.9 (3.5)	30.9 (5.5)	
Type 2 DM-lean	18.5 (4.1)	29.4 (6.9)	
MRDM [5]	8.1 (4.5)	15.9 (6.3)	
LB Type 2 DM	15.3 (9.6)	27.8 (17.0)	39.7 (24.0)
Obese Type 2 DM	28.9 (14.7)	69.4 (59.6)	123.8 (70.5)
Hyderabad [1]			
Type 2 DM-lean	23.2 (14.4)	33.7 (16.2)	
Obese Type 2 DM	24.4 (21.5)	64.0 (51.6)	

Table 2: Plasma levels of insulin in Lean, obese Type 2 DM and MRDM at basal and post-stimulated state: mean (\pm SD).

groups, yet the serum insulin levels were persistently lower in the subjects with LB T2 DM at all stages (Table 2 and Figure 3). On the contrary, the C-peptide levels were surprisingly similar (Table 3 and Figure 4) [5]. This suggested that, although in the subjects with LB T2 DM the β cell function was fairly preserved to non-glycemic challenges, there was excess extraction of insulin in the porto-hepatic circulation causing lower circulating levels of insulin as compared to typical subjects with Type 2 DM. Disparity between circulating levels of insulin and C-peptide, more so in the post-stimulated state, can be reasonably considered as a marker for LB T2 DM and the reason behind lower levels of circulating insulin and severe hyperglycemia.

Insulin Resistance in Low Body weight Type 2 DM

Insulin action involves a series of cascades initiated by insulin binding to its receptor eliciting receptor auto-phosphorylation and activation of receptor tyrosine kinase resulting in tyrosine phosphorylation of insulin substrate receptor (IRS). Phosphorylation of IRS leads to activation of Phosphatidylinositol-3-Kinase (PI3K) which subsequently causes activation of Akt and its downstream mediator AS-160. This leads to stimulation and migration of glucose transporters to the cell surface and glucose entry into the target cells. Impaired insulin activation of IRS-I /PI3K/Akt signaling pathway which are critical steps in the regulation of glucose transport in response to insulin are

	Fasting		1 h		2 h		3 h	
	Glucose	IRI	Glucose	IRI	Glucose	IRI	Glucose	IRI
NIDDM	268.3	18.5	382.5	31.2	401.7	29.4	354.7	26.6
(SD)	54.0	4.1	60.9	4.0	82.5	6.9	88.8	6.5
IG Index	6.89		8.15		7.32		7.49	
MRDM	306.5	8.1	490.6	13.2	508.0	15.9	420.0	12.5
(SD)	42.6	4.5	64.8	5.3	50.5	6.3	44.4	4.6
IG Index	2.64		2.69		3.13		2.97	
Control	82.8	11.9	130.8	30.9	100.2	17.1	90.2	15.2
(SD)	12.7	3.5	17.8	5.5	12.8	6.3	9.4	4.2
IG Index	14.37		23.62		17.06		16.85	

Table 1: Blood glucose (in mg/dl) and serum insulin in IU/ml in response to OGTT (standard deviation-SD) and insulin-glucose index [6].

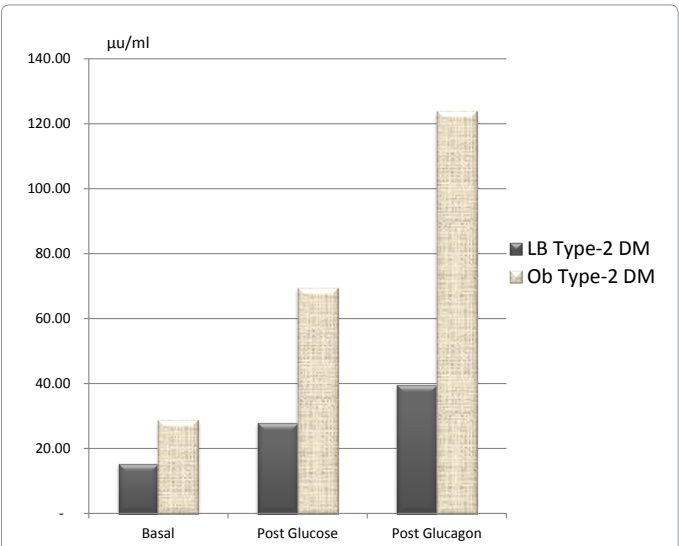


Figure 3: Plasma insulin level in low body weight and obese Type-2 DM at basal and following 2 hour Post Glucose and Post Glucagon challenge.

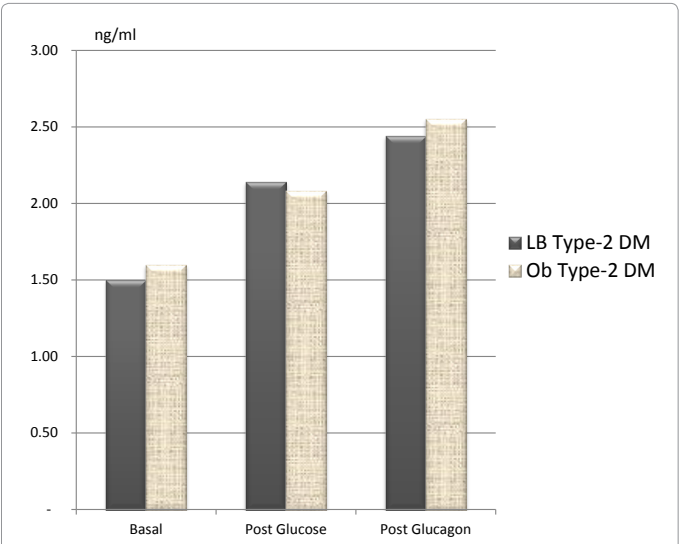


Figure 4: Plasma C-peptide level in low body weight and obese Type-2 DM at basal and following 2 hour Post Glucose and Post Glucagon challenge.

mechanisms responsible for IR in T2 DM. Diminished phosphorylation of As-160, defective rho-kinase (Rock) activity in skeletal muscle may also contribute to IR in classical subjects with T2 DM [7].

Studies on insulin resistance using homeostatic model of assessment (HOMA-IR) had revealed that the subjects with LB T2 DM have high values of HOMA-IR inspite of lower body mass index (BMI) and Waist Hip Ratio (WHR) [7,8]. Increased activation of c-Jun-NH2-Kinase (JNK) pathway with a corresponding increase in Insulin Substrate Receptor-I (IRS-I) serine phosphorylation in skeletal muscle tissue, the site responsible for majority of insulin mediated glucose disposal has been reported in lean subjects. Such serine phosphorylation instead of tyrosine phosphorylation is accompanied by reduced post receptor activation of the insulin signaling pathway in the target cells, at the levels of IRS-I and Akt [8]. This is probably the mechanism behind IR in the LB T2 DM. Therefore, the cause of insulin resistance is these

subjects with LB T2 DM are likely to be different from that of classical Type 2 diabetics (Tables 4 and 5).

Glucose Metabolism and Homeostasis in the Liver

Subjects with Type 2 DM have an increased Hepatic Glucose Output (HGO) [9]. In health, increase in blood glucose levels induces repression of key hepatic glycolytic enzymes and the suppression of gluconeogenic enzymes [10]. This is one of the key physiologic mechanisms responsible for maintaining glucose homeostasis. The entry of glucose into hepatocytes is not dependent on insulin but the subsequent metabolism of glucose is very much influenced by insulin deficiency or resistance in the hepatic bed. Insulin probably acts on certain genetic loci that coordinate the expression of specific enzymes

Plasma C-peptide levels	Basal	Post-glucose	Post Glucagon
Madurai (in ng/ml)			
Healthy controls		4.40 (1.68)	
Type 1 DM		0.73 (0.44)	
Type 2 DM-Lean		2.66 (0.55)	
Obese Type 2 DM		3.73 (1.34)	
Cuttack Cuttack (in ng/ml)			
Type 2 DM-Lean	1.5 (0.50)	2.14 (0.60)	2.44 (0.79)
Obese Type 2 DM	1.6 (0.60)	2.08 (0.60)	2.55 (0.77)
Madras (Chennai) (in pmol/ml)			
Type 2 DM-Lean	0.74 (0.52)	1.51 (0.89)	
Obese Type 2 DM	0.88 (0.51)	1.88 (0.72)	
Type 1 DM	0.9 (0.10)	0.14 (0.08)	
Calcutta (Kolkata) (in ng/ml)			
Type 2 DM-Lean	2.16 ± 0.48	2.96 ± 0.92	37%
Non-obese Type 2 DM	3.12 ± 0.55	3.68 ± 0.86	10%
Obese Type 2 DM	3.76 ± 1.28	3.98 ± 0.48	6%

Table 3: Plasma levels of C-Peptide in Lean and obese Type 2 DM at basal and post-stimulated state: mean (± SD) [1,5].

	Unnikrishnan et al. [8]	Das et al. [7]	P value
Mean Age (yrs)	44.9 ± 10.6	42.48 ± 6.32	0.4
BMI (kg/m²)	15.8 ± 2.0	16.04 ± 2.05	0.7
FBG (mg %)	271.8 ± 109.8	229.83 ± 58.3	0.1
HOMA – IR	21.83 ± 13.92	13.50 ± 42.83	0.2
HOMA – B (%)	92.62 ± 114.64	57.41 ± 153.18	0.3

Table 4: Comparison of autoimmunity, HOMA - B, HOMA- IR in GAD Antibodies negative low body weight cases of Unnikrishnan et al. [15] and current study [7,8].

		BMI	WHR	HOMA- IR	HOMA - B
LOW BODY WEIGHT	BMI	1.0	0.39	- 0.05	0.01
	WHR	0.39	1.0	0.23	0.23
	HOMA - IR	-0.05	0.23	1.0	0.98*
	HOMA - B	0.01	0.23	0.98*	1.0
NORMAL BODY WEIGHT	BMI	1.0	0.50*	0.52*	0.55*
	WHR	0.50*	1.0	0.39	0.43
	HOMA - IR	0.52*	0.39	1.0	0.99*
	HOMA - B	0.55*	0.43	0.99*	1.0

* Significant at 5% level of probability

Table 5: Correlation between BMI, WHR, HOMA - IR and HOMA – B in patients of LB and NW Type 2 DM [7].

participating in carbohydrate (CHO) cycles within the hepatocytes [11,12]. Glucokinase, the key enzyme having high Km for glucose, catalyses the first step of CHO cycles which are almost an irreversible reaction. This step involves the conversion of glucose to glucose-6-phosphate and operates optimally at a blood glucose concentration of more than 100 mg/dl [12]. Therefore in health, this reaction and the levels of glucokinase activity in plasma are low in the fasted state. Studies done on the levels of circulating glucokinase in subjects with different types of Type 2DM (Table 6) had revealed that they were higher in subjects with LB T2 DM ($p<0.01$) as compared to other T 2 DM [12,13]. In healthy controls, there was a negative correlation between values of Fasting Blood Glucose (FBG) and glucokinase ($r = -0.66$, $p<0.05$) as is expected physiologically, while no such relationship was established in subjects with LB T2 DM [12,13]. This data suggested that hepatic enzymes concerned with CHO cycles operate differently and at higher levels in subjects with LB T2 DM. Such increase in levels of glucokinase could be the inherent characteristic of this subset of Type 2 diabetics and greatly contributes to the lack of glucose homeostasis despite good β cell reserve for insulin.

Hepatic Microsomal Enzyme Activity

Current knowledge reveals that in subjects with T2 DM, hepatic glucose uptake is normal while Hepatic Glucose Output (HGO) is high owing to hepatic insulin resistance with hyperglucagonemia and increased flux of gluconeogenic precursors from the peripheral bed [7,8]. Hepatic insulin resistance plays an important role in the hyperglycemia of T2 DM, and the impaired suppression of the HGO appears to be quantitatively similar to, or even larger than, the defect in stimulation of peripheral glucose disposal. There is direct relationship between increased HGO and fasting hyperglycemia. Insulin mediated suppression of HGO is impaired at both low and high plasma insulin levels in T2 DM. In the fasted state, plasma glucose levels are maintained by a balance between HGO and glucose uptake by peripheral tissues. Hepatic enzyme systems involved in the carbohydrate (CHO) cycles are insulin modulated. Insulin increases the availability of glycolytic and decreases the gluconeogenic enzymes. Thus hepatic insulin resistance leads to decreased glycolysis and increased gluconeogenesis [9,12]. Hepatic enzyme functions and the CHO-cycles operate at a lower rate in patients with T2 DM. They have fewer futile CHO cycles as a result of insulin resistance in the hepatic bed, which leads to lesser utilisation of insulin by the liver and consequential occurrence of peripheral hyperinsulinemia [13]. Western literatures reveal that hepatic enzyme functions and the CHO cycles operate at a slower pace in T2 DM; they have less of futile CHO cycles, insulin resistance in hepatic bed leading to less trapping of insulin in the liver with consequent higher circulating levels of insulin. Low circulating levels of insulin are a universal observation in patients with LB T2 DM [4,13]. Hepatocytes are also the main site for the metabolism of drugs. It takes place through the process of functionalization and conjugation. Both these phases depend on the co-factor NADPH. A major part of both CHO and drug metabolism takes place through Mixed Function Oxidase (MFO) in the smooth endoplasmic reticulum of hepatocytes. MFO are membrane-bound electron transport systems with cytochrome P450 as the terminal oxidase. These systems require NADPH and oxygen. Thus, NADPH forms the link between drug and CHO metabolism. Drugs metabolized by hitherto identified microsomal enzymes serve as probes to ascertain their functional status [4,9,13]. Antipyrine is the gold standard, non-toxic, rapidly and completely absorbed orally, metabolized through different isoenzymes of cytochrome P450 follows first-order kinetics and its plasma elimination half-life ($t_{1/2}$) is an excellent indicator of hepatic microsomal enzyme activity.

	BMI	FBG (mg/dl)	Glucokinase (IU/L)
Healthy Controls	23.8 ± 3.4	82.8 ± 10.3	36.5 ± 5.6
Type 2 DM-Lean	17.4 ± 1.2	181.1 ± 105.7	40.5 ± 9.6
Type 2 DM (Others)	23.2 ± 3.2	112.9 ± 35.2	34.2 ± 8.0
Type 2 DM vs. Healthy Controls	$p<0.01$	$p<0.001$	-
Type 2 DM-Lean vs. other Type 2 DM	$p<0.01$	$p<0.01$	$p<0.01$

Table 6: Fasting serum levels of glucokinase in healthy controls, Lean and other Type 2 DM subjects (mean ± SD) [13].

	Indian		Finnish (Europe)	
	Lean	Obese	Obese	Healthy Controls
BMI	15.6 ± 1.5	28.4 ± 2.8	29.0 ± 4.1	26.7 ± 2.6
FBG (mMol/ L)	17.9 ± 4.2*	8.6 ± 1.4	7.9 ± 1.7	-
A) Serum ALT (IU/L)	33.6 ± 16.9	32.4 ± 21.3	-	-
x) MEGX (IU/L)	43.5 ± 18.1	45.4 ± 30.4	57.9 ± 35.9	35.9 ± 11.0
y) Antipyrine; $t_{1/2}$	8.2 ± 3.5**	14.2 ± 0.9	17.5 ± 4.3	11.1 ± 6.1

Test of significance: * = $P<0.05$, ** = $P<0.01$

Table 7: Results of Antipyrine clearance and Lidocaine metabolic (MEGX) conversion study in Indian and Finnish Type 2 DM patients [14].

Antipyrine was used as in vivo probes in healthy controls and subjects with Type 2 DM, both Obese and LB T2 DM, from India and in Finland as part of the Indo-Finnish collaborative study on liver metabolism in Type 2 DM [4,9]. Antipyrine $t_{1/2}$ (half-life) was markedly low ($p<0.01$) in the subjects with LB T2 DM as compared to other diabetics, both Indian and Finnish (Table 7). In addition, there was a positive correlation between serum Alanine Transaminase (ALT) and Antipyrine $t_{1/2}$ in obese Type 2 DM, suggesting that drug metabolism was dependent on the functional status of the hepatocytes, whereas no such equation could be established in LB T2 DM [4,9,13].

Thus, subjects with LB T2 DM have hyperactive futile cycles of CHO metabolism in their liver (Table 7), an excess of glucokinase activity (Table 6) which could be responsible for excess insulin utilization in the liver leading to release of lesser quantity of insulin to systemic circulation resulting in poor glucose homeostasis and higher blood glucose levels.

This result indicated that such a hyperactive metabolic state observed in the liver of these diabetics with low body weight is probably an inherent characteristic which is responsible for excess utilization of insulin during its first pass [4,9,13].

These observations point to an important conclusion that insulin kinetics during the first pass and hepatic handling of CHO metabolism are probably the two most important denominators that can explain these peculiar characteristics observed in subjects with LB T2 DM.

B-Cell and Autoimmunity in Low Bodyweight Type 2 DM

Recognition of Late Autoimmune Diabetes In Adults (LADA) necessitated evaluation of the functional status of β cells, i.e. insulin and C-peptide reserve, and an estimation of the titers of immunological markers testifying autoimmune beta-cell destruction [1,2,4]. Prospective studies have revealed that Islet Cell Antibodies (ICA) were absent in the serum of subjects with LB T2 DM, while even obese Type 2 DM revealed 7.5% ICA positivity (Tables 8 and 9). Similarly, the levels of antibodies to Glutamic Acid Decarboxylase (GAD) were comparable and without statistical difference in all these three groups of subjects with T2 DM [7,14]. Subsequent studies by Unnikrishnan et

		Mohan et al. [15]		Das et al. [7]	
		(n)	(%)	(n= 23)	(%)
LB (lean)	GADA Ab+	3/31	9.6	0/23	0
	ICA/IA ₂ Ab+	0/10	0	1/23	4
Ideal/ NW	GADA Ab+	2/39	5.1	0/10	0
	ICA/ IA ₂ Ab+	4/30	13.3	1/10	10%
Obese	GADA Ab+	2/48	4.2	-	-
	ICA Ab+	3/40	7.5	-	-

Table 8: Incidence of anti-GAD Ab and anti ICA/ IA₂ Ab in Asian Indians with low body weight (lean) Type 2 DM [7,15].

Global Perspective (Type 2 DM)	ICA	IA-2	GADA
UKPDS (Caucasians)	10	-	6
Tuomi et al (Finnish)	-	-	9.3
a) those GADA pos.	-	17	-
b) those GADA neg.	-	0.5	-
Thai et al (Chinese)	5		16
INDIAN PERSPECTIVE			
Mohan et al in Type 2			
a) Low Body Weight (Lean)	0	-	10
b) Normal Body Weight	13	-	5
c) Obese	7	-	4
Mohan et al. [16]			
a) Type 1	54	-	48
b) Type 2	5	-	6
Ramachandran et al.			
In Type 2 DM	-	-	12.5
a) on OHA	-	-	9.1
b) on insulin	-	-	15.2
in Non-Diabetic Controls	-	-	4.8
Bhatia et al			
a) Young Type 2	-	4	25
b) Type 1	-	22	40
c) PDDM	-	-	25

Table 9: Prevalence of autoantibody positivity in different type of diabetics and various population groups (in percent) [1].

al. [15], samples collected from four different locations of India, tried to segregate Lean Type 2 diabetics into two groups i.e. GAD 65 positive and negative [15]. This study was based on the concept that all GAD 65 positive diabetics were evolving Type 1 diabetics. They had grouped the Lean subjects with DM as GAD ab positive and GAD ab negative groups. Comparison of their subset of GAD ab negative LB T2 DM and our subject with LB T2 DM was published in 2007. The comparison between BMI, FBG, HOMA-IR and HOMA-B are presented in Table 4. Both the groups revealed fair β cell reserve for insulin as also significant insulin resistance.

Mere presence of antibodies against islet-cell or any of its component per se does not mean that the subjects are cases with Type 1 DM [10,16]. Approximately 10 percent of NIDDM patients were positive for cytoplasmic Islet-Cell Antibodies (ICA), as reported

in earlier studies, whereas the ICA frequency of nearly 70 percent is observed in newly diagnosed subjects with Type 1 DM [1,4]. Studies in western populations have found that anti GAD antibody are present in a frequency of 10-20% among patients with Type 2 DM (Table 9). In contrast to anti GAD Ab, the frequency of IA-2 antibodies, directed against antigen tyrosin phosphatase is infrequent in Type 2 diabetics [7].

B Cell Function in Low Bodyweight Type 2 DM

Observations from different centers, as given in Table 3, had revealed good β cell function in subjects with LB T2 DM14. Evaluation of β cell function and insulin resistance using homeostatic assessment models i.e. HOMA-B and HOMA-IR respectively showed a strong positive correlation between HOMA-IR and HOMA-B in both LB T2 DM and Normal Weight Type 2DM, suggesting that they were typical cases of Type 2 DM (Table 5) and not to be confused with either LADA or Type1 DM. The lean habitus does not reflect either poor β cell function or loss of body weight due to long standing uncontrolled diabetic state. The cause of insulin resistance in these lean subjects is unlikely to be similar to that observed in subjects with classical Type 2DM since anthropometric parameters like BMI and WHR did not reveal any correlation with insulin resistance (Table 5). Therefore, neither BMI nor WHR is appropriate anthropometric indicator of insulin resistance in this phenotype of diabetic population who have low body weight. This is likely to be an inherent characteristic of these diabetic subjects with low body weight.

Conclusion

Low Body weight Type 2 DM is a distinct clinical entity, having absence of markers for autoimmune destruction of β cells and good insulin and C-peptide reserve for a prolonged period of life. They constitute an independent variant of Type 2 DM with inherent peculiarities of insulin kinetics in the liver along with altered profile and behavior of key enzymes related to carbohydrate metabolism. Even if lean by habitus, subjects with LB T2 DM do have insulin resistance. These peculiarities are reflected in the peripheral circulation as states of hypoinsulinemia, poor glucose homeostasis with persistent hyperglycemia. However, due presence of insulin resistance and fair β cell reserve for insulin, despite low body weight, most of them respond well to OAD for long periods of life for maintenance of good glycemic control, as may be comparable with any other phenotype of subjects with Type 2 DM.

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