CHAPTER

12

Lean Type 2 Diabetes Mellitus : Profile, Peculiarities and Paradox

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Introduction

Epidemiological data over the past decades have shown that the pattern and profile of DM are very different in India as well as in certain developing countries of Asia and Africa as compared to the West. These observations have been endorsed by the international community following the consensus statement adopted at the international workshop on Types of Diabetes Peculiar to the Tropics, held at Cuttack.[1]

Type 2 DM , previously nomenclatured as Non-insulin Dependent Diabetes Mellitus (NIDDM),[2] is the most prevalent form of DM seen in India and constitutes more than 95% of the diabetic population.[3] Interestingly, almost 80% of our Type 2 diabetic patients are non-obese whereas 60 to 80% of such diabetics in the West are obese.[4,5] The build and habitus, far from being overweight, is often 'lean' or low bodyweight, i.e. more than 20% below the ideal bodyweight for height and gender. In a prospective study, sponsored by the Indian Council of Medical Research (ICMR), we 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 centers spread over India, which included three metropolises viz. Delhi, Calcutta (Kolkata), Madras (Chennai), indicated that the prevalence of Type 2 DM-Lean varied from 11 to 25%. This characteristic persisted even at the end of the study period of five years (1985-90). Therefore leanness was the inherent characteristic and not related to the diabetic state.[3]

Table 1 : Prevalence of Type 2 DM- Lean and other Type 2 DM at different centers (in per cent)

	Obese	Standard body weight	Lean
Hospital based data			
Cuttack (3)	7.8	65.8	26.4
Hyderabad (5)	25.4	56.7	17.9
Private Paying clinic based data			
Jaipur (7)	90.8	9.2	
Madras (9)	32.9	63.5	3.5

Incidence of Lean and other bodyweight Type 2 diabetics, as observed at different parts of India are presented in Table 1. Lower socio-economic status was not a sine qua non of Type 2 DM-Lean as more than 80% of these type of diabetics were from the middle socio-economic class.[4] Analysis of dietary intake revealed that they were not protein deprived as the mean daily intake was over 50 g. Recent data on Type 2 DM-Lean from both Cuttack and Jaipur (Western India) also revealed that over 80% were not poor.[6,7] As a matter of medical history, an earlier presentation made by Tripathy and Kar in 1965 on clinical types of DM showed that 27% of elderly diabetics were lean.[8] Nearly half a century later, there have been changes in the profile and presentation of diabetes on the whole, yet Type 2

Table 2 : Prevalence of complications in Type 2 DM-Lean at different places versus pooled data on Type 2 DM of all types (in per cent)

	Lean Type 2 DM				ICMR
	Cuttack[a]	Jaipur[b]	Madras[c]		data[d] on
			Males	Females	NIDDM
Hypertension	8.8	14.5	-	-	26.4
CAD	8.8	9.1	18.9	21.0	24.7
PVD	5.5	7.5	5.2	7.0	-
Peripheral neuropathy	49.5	23.3	44.6	38.6	-
Nephropathy	6.6	9.1	4.7	4.4	17.0
Retinopathy	19.8	16.9	37.3	33.3	36.0
Tuberculosis	7.7	9.6	-	-	-
Other infections	28.6	-	-	-	-

DM-Lean has not been eliminated. Its prevalence varies depending on type of population, ethnic origin and geo-political situation under study. Table 1 depicts the relative incidence of Type 2 DM-Lean both at State run charitable hospitals and paying private clinics. This striking peculiarity in the Type 2 DM population is bound to influence the natural history of DM.

Peculiarities in Clinical Profile and Mortality (Table 2)

Anthropometry is not the only criterion that distinguishes these subjects with Type 2 DM as a distinct entity. Studies on newly diagnosed patients with Type 2 DM revealed that peripheral neuropathy (PN) was the commonest presenting feature in the lean, while hypertension (HTN) and coronary artery disease (CAD) were more common in the obese and microangiopathy in the non-obese-standard weight (BMI > 19 and < 25) Type 2 DM.[10] These observations were corroborative with many previous publications on such lean subjects (erroneously entitled undernourished NIDDM or UND in the past) where infection and PN were the visibly prevalent clinical presentations in Type 2 DM-Lean.[4, 10]

The clinical presentation and profile of associated complications are visibly different in Type 2 DM-Lean and differs from those described for classical Type 2 diabetics in standard books (Table 2). The complications in Type 2 DM as a whole were pooled from the data obtained from nine centers (Delhi, Udaypur, Lucknow, Calcutta, Cuttack, Jabalpur, Pune, Madras and Trivandrum) as part of a multicentric study on morbidity events in Type 2 DM sponsored by the ICMR.[11] The Type 2 DM-Lean patients had a marked lower incidence of hypertension, CAD, nephropathy vis-a-vis a marginally higher prevalence of retinopathy and a markedly higher incidence of peripheral neuropathy and infections.[6, 7, 9, 11]

Furthermore, a higher incidence of PN and infections with a lower prevalence of CAD, HTN and other macrovascular diseases and a relatively higher presence of microvascular complications like retinopathy form the typical natural history of these lean diabetics (Table 2).

Many independent studies on such Type 2-Lean diabetics undertaken in various areas of India, i.e. Madurai to Jaipur, Hyderabad to Cuttack, revealed a similar clinical profile.[4-7, 9, 11, 12] Such a clinical profile, observed over decades and at various places of the subcontinent, so different from what is depicted in classical books on DM, cannot be by chance but must serve as a clinical markers for Type 2 DM-Lean. Most interestingly, on post-counseling follow-up of these diabetics, it was found that 80.5% of Type 2 DM-Lean patients were well controlled on oral hypoglycemic agents (OHA) while only 16% were secondary failures and 4.5% required combination therapy (insulin and OHA). It is well established that Type 2 DM-Lean patients have good beta-cell reserve for insulin and are sulfonylurea responsive.[4, 13] The observations from Madras, Jaipur, Madurai and Hyderabad also revealed a similar experience with regard to management where 69 to 76% of Type: 2 DM were well controlled with OHA.[5, 7, 9, 12] The therapeutic response to oral hypoglycemic drugs, sulfonylureas in particular, was therefore similar to subjects with classical Type2 diabetes and so these sub-set of diabetics should not be confused

Table 3 : Fasting serum levels of glucokinase in healthy controls, Lean and other Type 2 DM subjects (mean ± SD)

	BMI	FBG (mg/dl)	Glucokinase (I/U)
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	$p < 0.01$	$p < 0.01$	$p < 0.01$

with Malnutrition related Diabetes Mellitus (MRDM).[3,8,13]

As with the clinical profile, the causes of death in patients with Type 2 DM, where non-obese and lean dominate the population with Type 2 DM, are also appreciably different from those of the West. Long-term follow-up studies from the UK have shown that there is a 'U' shaped distribution in the mortality profile with regard to bodyweight. All causes of mortality were higher with BMI less than 20 and over 30.[14] In a prospective study we reported that infection, nephropathy, CVA and coma are more important causes of death than CAD.[15] This observation was obviously different from that reported from the mortality profile of diabetic subjects from the West.

Glycemic Status and Hepatic Carbohydrate Metabolism

Type 2 DM-Lean patients have moderately severe to severe basal hyperglycemia.[4,13] Levels of glycosylated Hb are significantly higher than in the classic Type 2 DM at diagnosis.[3] Unlike in most classical diabetics, treatment requires the advice to increase calorie intake (males: 1548 to 1998 kcal/day; and females: 1473 to 1818 kcal/day) as the daily intake is often lower than desirable for physical activity and lifestyle of the patient with Type 2 DM-Lean. Proper exercise and addition of sulfonylurea in the majority of these diabetics induces fair glycemic control with a significant decrease in levels of glycosylated Hb (from 10.1 ± 2.4 to 6.36 ± 0.9% in males and 10.9 ± 2.4 to 6.3 ± 1.5% in females respectively). Although there was a slight gain in bodyweight with the change in BMI, the mean value remained within the definition of low bodyweight in both males and females.[6,7,9] Having high basal hyperglycemia and failure to gain weight consequent to attaining good glycemic control, it emphasized that defect in the type 2 DM-lean could be in the metabolic mechanisms of glucose handling in the hepatic bed.

Basal hyperglycemia reflects hepatic glucose output. It is an established fact that patients with Type 2 DM have an increased hepatic glucose output (HGO).[16] In classical Type 2 DM such hyperglycemia follows the repression of key hepatic glycolytic enzymes and the depression of gluconeogenic enzymes.[17] 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. This is because insulin probably acts on certain genetic loci that coordinate the expression of specific enzymes participating in carbohydrate (CHO) cycles within the hepatocytes.[17,18] Insulin stimulates glycolysis by causing an increase in the synthesis of glucokinase, phosphofructokinase and pyruvatekinase, and at the same time suppresses the enzymes participating in gluconeogenesis. Interestingly, glucokinase, the key enzyme which has a high km for glucose, catalyses the first step of CHO cycles which is almost an irreversible reaction. This step is the conversion of glucose to glucose-6-phosphate and operates optimally at a blood glucose concentration of more than 100 mg/dl.[18] Therefore, in health, this reaction and the levels of glucokinase are supposed to be low in the fasted state. We studied the levels of circulating glucokinase in different types of Type 2 diabetics (Table 3) and observed that they were higher in Type 2 DM-Lean ($p < 0.01$) as compared to other Type 2 DM.[19] In healthy controls, there was a negative correlation between values of fasting

Table 4 : Results of antipyrine clearance and lidocaine metabolic (MEGX) conversion study in Indian and Finnish Type 2 DM patients

	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 : * = $P < 0.05$, ** = $P < 0.01$

blood glucose (FBG) and glucokinase ($r = -0.66$, $p < 0.05$) as is expected physiologically, while no such relationship was established in Type 2 DM-Lean. It suggests that hepatic enzymes concerned with CHO cycles operate differently and at higher levels in Type 2 DM-Lean such increase in levels of glucokinase could be their inherent characteristic.

Hepatic Microsomal Enzyme Activity in Different Subsets of Type 2 DM

Current knowledge reveals that hepatic glucose uptake is normal in Type 2 DM, while HGO is high owing to hepatic insulin resistance vis-a-vis hyperglucagonemia and increased flux of gluconeogenic precursors from the peripheral bed.[16] Studies from the west has shown that the hepatic enzyme functions and the CHO-cycles operate at a lower rate in patients with Type 2 DM. They have fewer futile CHO cycles as a result of insulin resistance in the hepatic bed, which leads to lesser trapping of insulin by the liver and consequential occurrence of peripheral hyperinsulinemia.[20] Low circulating levels of insulin are a universal observation in Type 2 DM-Lean.[4-6, 12, 13] Bearing all these observations in mind, it was necessary to evaluate the level of activity of hepatic microsomal enzyme systems as they are usually depressed in classical Type 2 DM with hyperinsulinemia.[20] 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. Currently, there is no in vivo method to assess directly the activities of hepatic microsomal enzyme systems in human beings, yet drugs metabolized by hitherto identified microsomal enzymes can serve as probes to ascertain their functional status, which in turn can testify to the fate of insulin in the liver.[20] As there is polymorphism of drug oxidation, more than one drug is required to study the MFO system. 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. Lidocaine, another safe drug given intravenously, is metabolized rapidly by cytochrome P3A4 isoenzyme and converted to MEGX, the level of which is estimated in plasma. These drugs were used as in vivo probes in healthy controls and patients with Type 2 DM, both Obese and Lean, from our center and in Finland (Europe) as part of the Indo-Finnish collaborative study on liver metabolism in Type 2 DM.[6, 22] The results are presented in Table 4. Antipyrine $t^1/_2$ (half-life) was markedly low ($p < 0.01$) in the Type 2 DM-Lean as compared to other diabetics, both Indian and Finnish. 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 Type 2 DM-Lean. Lidocaine study also revealed that metabolite production was dependent on gross functional status of hepatocytes in the obese while it was independent in Type 2 DM-Lean. Interestingly, the interrelationship between the metabolism of the two drugs revealed

Table 5 : Plasma levels of insulin in Lean, obese Type 2 DM and MRDM at basal and post-stimulated state: mean (± SD)

Plasma insulin (mðu/ml)	Basal	Post Glucose	Post Glucagon
Cuttack			
Reference 13			
Healthy controls	11.9 (3.5)	30.9 (5.5)	-
Type 2 DM-lean	18.5 (4.1)	29.4 (6.9)	-
MRDM	8.1 (4.5)	15.9 (6.3)	-
Reference 22			
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			
Reference 5			
Type 2 DM-lean	23.2 (14.4)	33.7 (16.2)	-
Obese Type 2 DM	24.4 (21.5)	64.0 (51.6)	

an interdependence in the obese Type 2 DM but not in Type 2 DM-Lean. These results indicate that such a hyperactive metabolic state observed in the liver of these diabetics with lean habitus is probably an inherent characteristic which is responsible for excess utilization of insulin during its first pass.[6, 21]

Hormonal Profile and Response

Circulating levels of insulin (IRI) have been found to be lower in Type 2 DM-Lean, whether fasting or post prandial, and in all studies as compared to classic Type 2 DM. Persistence of lower insulin levels had provoked many investigators to designate these diabetics as late onset IDDM/ Type 1 DM or the adult form of MRDM. But after years, these lean subjects do have substantial levels of insulin in circulation which are similar to levels seen in healthy controls in a fasted state.[4, 5, 7, 9, 12, 13] Plasma insulin levels of Type 2 DM-Lean subjects from different centers are presented in Table 5.

It is a well-known fact that in Type 2 DM the beta-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.[23] Even by eating a non-CHO diet or a mixed meal, which act as insulin secretagogues , one can evaluate the beta-cell reserve for insulin in different types of diabetics.[24,25] This was studied in Type 2 DM-Lean along with patients suffering from MRDM and healthy controls for comparison. They were fed with oral glucose and a diet containing low (R&C) and high arginine (S) levels. The increment in insulin-glucose index following these dietary challenges (isocaloric) was highest with S in controls as well as Type 2 DM-Lean but least in MRDM.[13] This not only testified to the presence of significant insulin reserve in Lean but also differentiated Type 2 DM-Lean from both MRDM and Type I DM.

Earlier studies had established that high basal levels of growth hormone (hGH) and its paradoxical rise following glucose challenge are a reasonable marker for MRDM.[27, 28] The same was tested in both Lean and obese Type DM and the levels of hGH were found to be at low normal values in the fasted state with hardly any change after oral glucose.[22] This not only differentiated Type 2-Lean DM from MRDM but also distinguished it as not to be influenced by chronic malnutrition as proposed to be the modulator for Malnutrition Modulated Type 1 Diabetes Mellitus (MMDM).[1,22]

Further, in order to probe the beta-cell function and reserve in subjects with Type 2 DM, both Lean and Obese, cases were so selected that their mean age was in the mid-forties and the mean duration of diabetes more than four years. Hypoglycemic drugs were stopped for one week before the tests. The lean Type 2 diabetics had much higher FBG levels than obese patients on withdrawal of drugs. They were subjected to insulin-secretagogues such as oral glucose and intravenous glucagon on different occasions. The response to glucagon was much higher than that for oral glucose in both groups, yet the IRI levels were persistently lower in the Type 2 DM-Lean at all stages (Table 5). On the contrary the C-peptide levels were surprisingly similar (Table 6), suggesting a good beta-cell reserve in the Lean with probably excess extraction of insulin in the porto-hepatic circulation leading to lower levels of circulating insulin.

Table 6 : Plasma levels of C-Peptide in Lean and obese Type 2 DM at basal and post-stimulated state: mean (± SD)

Plasma C-peptide levels	Basal	Post glucose	Post Glucagon
Madurai **Ref.12** (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 **Ref. 22** (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) **Ref. 9** (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) **Ref.28**			
(in ng/ml)	Basal	Post Prandial	% rise
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	06%

Studies on insulin and C-peptide levels in Type 2 Lean diabetics both at fasted and post-stimulation states, also yielded similar results at other centers when compared with classic Type 2 DM.[9, 12, 29] Studies done on C-peptide levels at different places in India (Table 6), have revealed good beta-cell reserve in Type 2 DM-Lean on par with other Type 2 DM which happens to be complementary to earlier reports.[9, 22] This finding corroborated well with our concomitant observation that Type 2 DM-Lean patients have hyperactive futile cycles of CHO metabolism in the liver (Table 4), an excess of glucokinase activity (Table 3) which could be responsible for excess insulin utilization in the liver.

Disparity between circulating levels of insulin and C-peptide, more so in the post-stimulated state, can be reasonably considered as a marker for Type 2 DM-Lean. 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 Type 2 DM-Lean and its pathogenesis.

Biochemical Milieu vis-a-vis Complications

Both clinical presentation and mortality profile indicate that neither CAD nor other macrovascular complications are common in Type 2 DM-Lean (Table 2).[4, 10, 15, 30, 31] Analyses of the biochemical milieu followed up in two consecutive years, in a prospective study, revealed that those patients with Type 2 DM did not have hyperlipidemia which would have been conducive to the development of atherosclerosis and CAD. The high density lipoprotein cholesterol (HDLc) levels were never low even in a glycemically uncontrolled state with mean glycosylated Hb values above 10%. In our first publication in 1984 we showed that Indian Type 2 DM, particularly underweight diabetics (Type 2 DM-Lean), do not have low HDLc.[31] This could be owing to the fact that hepatic lipase activity, which like all other enzymes is primed by insulin during its first pass, is in excess in lean patients with Type 2 DM, and is directly related to HDLc metabolism.[19,32] The plasma cholesterol level was just high-normal to slightly raised at the beginning but soon remained within 200 mg/dl. The triglycerides (Tg) value in blood was higher, which could be owing to both poor metabolic state and high CHO diet to start with, but on achieving good glycemic control also went down to normal levels.[31,33,34] Higher levels of Tg in these diabetics were a fact established by us which was duly acknowledged by the international community.[35] Type-IV hyperlipoproteinemia is by far the commonest form of dyslipidemia seen in these diabetics, and that too in a glycemic uncontrolled state.[36] In one of our recent studies assessing the clinical, biochemical profile as well as autoimmune status and state of insulin resistance has also revealed that Lean Type diabetics had lower cholesterol vis a vis raised Tg and normal HDLc levels as depicted in Table 7.[37] On the whole, these diabetics have a favorable lipid profile that could be a consequence

Table 7 : Clinical, biochemical parameters, Beta Cell functions, Insulin resistances and autoimmunity status in patients of lean and normal body weight Type 2 DM

Parameters	LB (mean+SD)	NW (mean+SD)	P value
BMI (Kg/m^2)	16.04 ± 2.05	22.80 ± 1.53	< .001
WHR	0.89 ± 0.04	0.92 ±0.02	0.1
FBG (mg%)	229.83 ± 58.13	184.4 ±33.29	< 0.05
2hr PGBG (mg%)	308.35 ± 60.11	252.3 ±85.90	< 0.05
Hb A_1C (%)	8.52 ± 1.13	7.84 ±0.27	0.1
TC (mg%)	176.57 ± 43.87	199.7 ±20.43	< 0.05
TG (mg%)	171.82±65.39	130.9±17.61	0.1
HDL (mg%)	40.57 ±8.64	39.9 ± 1.52	0.8
Fasting insulin (mIU/ml)	24.47 ± 73.15	13.4 ± 16.54	0.7
Fasting C- Peptide (pM/ ml)	180.81 ± 357.08	279.83 ±281.38	0.5
HOMA - B (%)	57.41 ± 153.18	44.74 ± 56.24	-0.25
HOMA -IR	13.50± 42.83	5.68 ± 6.90	0.6

of hepatic handling of HDL and CHO metabolism and lack of hyperinsulinemia-insulin resistance in the peripheral bed.

In view of the low prevalence of macrovascular diseases as well as lean habitus it was imperative to evaluate nutritional, non-lipid and independent risk factors which are supposed to be markers for atherosclerosis, CAD in particular. We undertook an evaluation of the serum levels of homocysteine - an independent marker/risk factor of macrovascular disease.[38, 39] The analysis of samples was done in the USA and the data are presented in Table 8. Surprisingly, but on a par with our clinical, hormonal and other biochemical observations, it was found that homocysteine levels were significantly lower ($p < 0.05$) in the lean Type 2 DM when compared with healthy controls and definitely lower than both standard weight and obese Type 2 DM.[40]

Interestingly, we observed that proteinuria in the lean Type 2 DM was more related to poor glycemic control rather than a predictor for developing further deteriorating nephropathy.[6] With tight metabolic control there was a lowering of 24-hour urine protein levels, suggesting an improvement in the endothelial cell dysfunction that had originated as a result of poor glycemic state.[41]

Table 8 : Serum homocysteine levels in Lean, Standard- weight and Obese Type 2 DM (mean ± SD)

	Healthy Controls	Lean	Standard Weight	Obese
BMI	23.87±3.42	17.45±1.16	21.7±1.28	28.3±2.25
FBG (mg^{-1})	82.8±10.3	181.1±105.7	110.0±34.78	122.8±38.0
Homocysteine (mmol^{-1})	9.77±3.37	6.39±3.18*	7.36±3.94	8.42±4.43

*$p < 0.05$.
+ Data fromDas et al. [40].

Beta-Cells and Autoimmune Status

The emergence of late autoimmune diabetes in adults (LADA) and earlier postulations that LB Type 2 DM/ Type 2 DM-Lean could be adult counterparts of MRDM/MMDM necessitated not only evaluation of the functional status of beta-cells, i.e. insulin and C-peptide reserve, but also an estimation of the titers of immunological markers testifying autoimmune beta-cell destruction.[1, 8, 9, 37] Prospective studies done on such patients, along with standard or intermediate body weight and obese Type 2 DM from Chennai (Madras) in collaboration with Lucknow and the International Diabetes Institute, Australia, had revealed that islet cell antibodies (ICA) were absent in the serum of Type 2 DM-Lean, while even obese Type 2 DM revealed 7.5% ICA positivity [Table-9]. Similarly, the levels of antibodies to glutamic acid decarboxylase (GAD) were comparable and without statistical difference in all these three groups of Type 2 diabetics. Subsequent studies by Unnikrishnan et al tried to segregate Lean Type 2 diabetics into two groups ie. GAD65 positive and negative.[42] This study was based on the concept that all GAD 65 positive diabetics were evolving Type 1 diabetics.

Considering only one immunological marker (GAD 65 ab) is not sufficient to decide on the immune pathogenesis of these diabetics in our recent study, we assesed both GAD65ab and IA2 antibodies directed against tyrosine phosphate antigen in Type 2 diabetics with ideal as well as low body weight (Table-9).[37] In our study, all the patients were negative for anti GAD Ab while only 4% of LB and 10% NW Type 2 DM respectively were positive for IA-2 (Table 9). Studies done by Mohan et al on patients from Chennai had shown an incidence of 9.6% and 5.1% anti GAD

Table 9 : Incidence of anti GAD Ab and anti ICA/ IA_2 Ab in Asian Indians with low body weight (lean) Type 2 DM

		Mohan et al Ref. 9 (n)	(%)	Das et al Ref. 37 (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		

Ab positivity in their subjects with lean and ideal body weight Type 2 diabetic subjects respectively, but none of their lean subjects were positive for ICA as against 13.3% positivity in ideal weight Type 2 DM. Observations in the current study is very much comparable with the publication by Mohan, Vijayaprabha, Zimmet et al with regards to prevalence of autoimmune markers in LB Type 2 diabetics.

Unnikrishnan, Singh and Sanjeevi had shown that more than 74% of lean subjects with adult onset diabetes were anti GADA negative, which was slightly lower than that reported by Mohan et al.[9 & 42] Unnikrishnan et al had not studied other autoimmune markers in these lean patients with diabetes but evaluated both HOMA-IR and HOMA-B in patients either positive or negative for GADA. Comparison of HOMA-B, HOMA-IR in GAD antibody negative Low bodyweight diabetics of Unnikrishnan et al and the current study (Table-10) did not reveal any statistical difference either in the mean age, BMI, FBG, fasting insulin, HOMA-IR and HOMA-B values respectively. This suggests that the lean diabetics selected from Northern India (Varanasi) and Southern India (Cochin) as evaluated by Unnikrishnan, Singh and Sanjeevi were comparable to our subjects with Type 2 DM-lean who belong to Eastern India.

Comparing the data of anti GADA negative group of diabetic patients of Unnikrishnan et al with that of the present set of type 2 DM-Lean (Table-10) revealed that these lean subjects with diabetes have good beta cell function, insulin resistance but express severe hyperglycemia despite

Table 10 : Comparison of autoimmunity, HOMA - B, HOMA- IR in GADA Ab negative low body weight cases of Unnikrishnan et al and current study

	Unnikrishnan et al[42] (n = 62)	Das et al,[37] (n = 23)	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
Fasting insulin (mIU/ml)	35.1 ± 19.20	24.47 ±73.15	0.3
HOMA – IR	21.83 ± 13.92	13.50 ±42.83	0.2
HOMA – B (%)	92.62 ± 114.64	57.41 ± 153.18	0.3

adequate serum insulin levels. Presence of good beta cell function for insulin and insulin resistance, all these lean subjects are phenotypical variants of Type 2 DM.

Studies on incidence of autoimmune markers were very different from data observed in patients with Type 1 DM in the same population (Table 11). This supports the conclusion that Type 2 DM=-Lean is a genuine variant of Type 2 DM and not a late-onset legacy of autoimmune beta-cell destruction/ Type 1 DM. The cause or mechanism behind low circulating levels of insulin is not similar to that of Type 1 DM.

Mere presence of antibodies against islet-cell or any of its component per se doesnot mean that the subjects are cases of Type 1 DM.[43,44] Approximately 10 per cent of NIDDM patients were positive for cytoplasmic islet-cell antibodies (ICA), as reported in earlier studies, whereas the ICA frequency of nearly 70 per cent is observed in newly diagnosed subjects with Type 1 DM. 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-11). In contrast to anti GAD Ab, the frequency of IA-2 antibodies, directed against antigen tyrosin phosphatase are infrequent in Type 2 diabetics. Anti GAD antibody have the advantage because their titer remains relatively stable over a period of time and that they can be detected by radio-immunoassay which uses recombinant antigen, thus value have less variation between

Table 11 : Prevelence of autoantibody positivity in different type of diabetics and various population groups (in per cent)

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			
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	

laboratories. Anti GAD antibody has been proposed to be a better predictor of insulin requirement than other clinical (low BMI) or biochemical (C-peptide levels) parameters in Asian context.

Beta-Cell Function and Insulin Resistance

The previous observations from different centres, as given in Tables 5 and 6, had revealed good Beta-cell function in the Lean type 2 diabetics but did not asses such reserve using any accepted mathematical model as done by others.[42] In our current study, assessment of beta cell function and insulin resistance was done using homeostatic assessment models ie.HOMA-B and HOMA-IR respectively.[37] It showed a strong positive correlation between HOMA-IR and HOMA-B in both LB and NW Type 2 diabetics, suggesting that they were typical cases of Type 2 DM (Table 7). Lean physique does not reflect either poor Beta-cell function nor loss

Table 12: Correlation between BMI, WHR, HOMA - IR and HOMA – B in patients of LB and NW Type 2 DM

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

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 of classical Type 2 diabetics since anthropometric parameters like BMI and WHR did not reveal any correlation with insulin resistance and therefore needs further evaluation (Table 12).

However, BMI with WHR showed significant positive correlation only in NW Type 2 diabetics but not in LB Type 2 DM. Therefore neither BMI nor WHR is appropriate anthropometric indicator of insulin resistance in these subjects of Type 2 diabetes who have lean habitus. This is likely to be an inherent characteristic of these diabetics.

Summary

Low Body weight Type 2 DM / Type2DM-Lean are neither LADA nor former fruste of Type 1 DM but variants of classical Type 2 DM having absence of markers for autoimmune destruction of Beta-cells and good insulin C-peptide reserve for a prolonged period of life. They constitute an independent variant of Type 2 DM with inherent peculiarities in insulin kinetics in the liver along with altered profile and behavior of key enzymes related to CHO metabolism which are marked by excess extraction of insulin in hepatic bed, hyperactive cytochrome system and non-suppressible glucokinase activity. These peculiarities are reflected in the peripheral circulation as states of hypoinsulinemia,

hyperglycemia, dyslipidemia without low HDLc, raised triglycerides and fewer other markers for atherosclerosis which make diabetics less prone to develop macrovascular disease. Peripheral neuropathy and the consequences of hyperglycemia like infections and proteinuria dominate the clinical picture. In view of more of infective complications and coexistent severe hyperglycemia many of these diabetics may not adequately respond to OHA at the initiation of therapy . However, due presence of insulin resistance and good Beta-cell reserve for insulin, despite of lean habitus, most of them respond well to OHA for long periods of life as may be comparable with any other phenotype of Type 2 diabetes. The insulin resistance observed in Type 2 DM-lean is not related to anthropometric parameters like central obesity and WHR and requires further investigation.

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