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LOW BODY WEIGHT TYPE 2 DIABETES MELLITUS

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ABSTRACT

Non-insulin dependent diabetes mellitus (NIDDM) is the most prevalent form of diabetes mellitus (DM) in India. Currently the nomenclature is type 2 diabetes mellitus (Type 2 DM). About one fourth of these diabetics have a body mass index (BMI) below 19 Kg/m^2, i.e. low body weight Type 2 DM (LB Type 2 DM). They are neither protein deficient nor belong to poor socio-economic class. LB Type 2 DM more often presents with peripheral neuropathy and infections than coronary artery disease (CAD), hypertension or nephropathy. They achieve good glycemic control with sulphonylurea therapy. The leading causes of death are infection, coma, renal failure and cerebrovascular accident. LB Type 2 DM patients have severe basal hyperglycemia with low circulating levels of insulin while C-peptide levels are similar to those of patients with classic type 2 DM. Studies on hepatic glucokinase levels and hepatic-microsomal enzyme systems (mixed function oxidase and cytochrome P450) using antipyrine and lidocaine as in vivo probes revealed hyperactivity with increased futile cycles of carbohydrate metabolism in the LB Type 2 DM patients. These hepatic metabolic features are likely to be responsible for excess insulin utilization and extraction during first pass in the liver, leading to low peripheral circulating levels. Homocysteine levels are also low suggesting efficient metabolic status. Autoimmune destruction of beta-cells is not the cause of hypoinsulinemia as levels of islet cell antibody (ICA) and anti-glutamic acid decarboxylase (GAD) antibodies are similar to those in patients with classical type 2 DM and much lower than those in type 1 DM. The metabolic profile reveals normal high density lipoprotein (HDL) cholesterol levels with type-IV hyperlipoproteinemia in glycemic uncontrolled states. Proteinuria found in uncontrolled metabolic states often reverses, suggesting endothelial cell dysfunction.

KEY WORDS: Lean diabetes mellitus; Low body weight type 2 diabetes; Hepatic metabolism; Metabolic and clinical profile.

INTRODUCTION

Diabetes mellitus (DM) is the most prevalent metabolic and one of the most important non-communicable diseases. There has been a visible rise in its prevalence in developing countries. The impact is worst in neo-affluent and neo-urbanized societies. 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).

Non-insulin dependent DM (NIDDM) - currently the nomenclature is type 2 DM (2) - is the most prevalent form of DM seen in India and constitutes more than 95% of the diabetic population (3). In a recent survey conducted at Cuttack, the prevalence was found to be 6.7% in the general population (aged above 15 years), while similar studies done in the 1970s had shown the prevalence to be 2.1% in the same city [4]. This emphasizes the increasing magnitude of the problem. 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 body weight, i.e. more than 20% below the ideal body weight for height and sex. 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 Kg/m^2, or in other words were low body weight/lean (LB). Analysis of data from the 9 centers spread over India, which included three metropolises viz. Delhi, Calcutta and Chennai, indicated that the prevalence of LB Type 2 DM varied from 11 to 25%. This characteristic persisted even at the end of the study period of five years (1985-90), indicating that leanness was the inherent characteristic and not related to the diabetic state (3). Furthermore, lower socio-economic status

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was not a sine qua non of LB Type 2 DM as more than 80% of these types of diabetic were from the middle socio-economic class. Analysis of dietary intake revealed that they were not protein deprived as the mean daily intake was over 50g (5). Recent data on LB Type 2 DM 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). Decades later, there have been changes in the profile and presentation of diabetes on the whole, yet LB Type 2 DM 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 LB Type 2 DM both at different places and situations. This striking peculiarity in the type 2 DM population is bound to influence the natural history of DM.

Table 1: Prevalence of LB Type 2 DM/ Lean Type 2 DM and other Type 2 DM at Different Centers (in percent).

	Obese	Standard Body Weight	LB
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

LB-Low body Weight diabetes

PECULIARITIES IN CLINICAL PROFILE AND MORTALITY

Anthropometry is not the only criterion that distinguishes these subjects with type 2 DM as a distinct entity. Our observation of a group of randomly selected, 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 Kg/m^2) type 2 DM (10). These observations were on a par with many previous publications on such lean subjects (erroneously titled undernourished NIDDM or UND in the past) where infection and PN were the visibly prevalent clinical presentations in LB Type 2 DM (4, 10).

Table-2: Prevalence of Complications in LB Type 2 DM at Different Places versus Pooled Data on Type 2 DM of all Types (in percent)

	Low Body Weight				ICMR
	Cuttack[a]	Jaipur[b]	Madras[c]		data[d] on NIDDM
			Males	Females	
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	-	-	-	-

[a]Source : Das, 1998 [6]. [b]Source : Nigam, 1995[7]. [c]Mohan et al, 1997[9]. [d]Ahuja, 1993[11].

The clinical presentation and profile of associated complications are visibly different in LB Type 2 DM and differs from those described in books or even when compared with type 2 DM subjects as a whole (Table 2). The complications in type 2 DM as a whole were pooled from the data obtained from nine centers (Delhi, Udaipur, 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 LB Type 2 DM patients had a marked lower incidence of hypertension, CAD, nephropathy vis-à-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 paucity of CAD, HTN and other macrovascular diseases with a relatively lesser prevalence of microvascular complications form the typical natural history of these diabetics. Many independent studies on such LB Type 2 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 in the subcontinent, so different from what is depicted in classical books on DM, cannot be chance but must serve as a clinical marker for LB Type 2 DM. Most interestingly, on post-counseling follow-up of these diabetics, it was found that 80.5% of LB Type 2 DM patients were well controlled on oral hypoglycemic

agents (OHA) while only 16% were secondary failures and 4.5% required combination therapy (insulin and OHA). We have repeatedly published that LB Type 2 DM patients have good beta-cell reserve for insulin and are sulphonylurea responsive (4, 13). Thus, these patients suffer from type 2 DM and should not be confused with either those with type 1 or malnutrition related diabetes mellitus (MRDM) (3, 8, 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).

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 Kg/m^2 and over 30 Kg/m^2 (4). In a prospective study we reported that infection, nephropathy, CVA and coma are more important causes of death than CAD (15). This experience was obviously different from that reported from the Joslin Clinic (Table 3) (3, 4).

Table 3: Causes of Death in Type 2 DM

	Place (Year of Report)				
	Joslin's Clinic	Cuttack		Delhi	Pune
	1979	1978	1988	1977	1977
Coma	1.2	21.0	20.2	21.7	17.8
CAD	54.5	20.0	30.0	21.2	32.4
CVA	11.1	21.0	32.5	12.6	15.0
Nephropathy	5.4	17.0	35.0	22.6	16.7
Infections	4.3	6.0	33.7	-	83.0

GLYCEMIC STATUS AND HEPATIC CARBO-HYDRATE METABOLISM

LB Type 2 DM patients have moderately severe to severe basal hyperglycemia (13, 16). Levels of glycosylated hemoglobin (GHb) are significantly higher than in the classic type 2 DM at diagnosis (3). Treatment paradoxically included the advice to increase calorie intake (males: 1548 to 1998 kcal/day; and females: 1473 to 1818 kcal/day) as the daily intake was lower than desirable. Proper exercise and sulphonylurea in the majority revealed a significant decrease in levels of GHb from 10.1 $\pm$ 2.4 to 6.36 $\pm$ 0.9% in males and from 10.9 $\pm$ 2.4 to 6.3 $\pm$ 1.5% in females respectively after a follow-up of two years. 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 sexes (6, 7, 9). In order to investigate if BMI had any bearing on glycemic status in patients with type 2 DM, a statistical correlation was worked out. In the obese there was a positive correlation (+ 0.051), i.e. a worse glycemic status with a higher BMI, suggesting the possible role of insulin resistance, while a negative value (- 0.02) in the lean not only negated the likely possibility of insulin resistance in the peripheral tissue but envisaged some hitherto unknown mechanism responsible for such hyperglycemia (6, 16). In view of this, glucose handling by the liver in type 2 DM, particularly in those with LB, demands special attention.

Basal hyperglycemia reflects hepatic glucose output. It is an established fact that patients with Type 2 DM have an increased hepatic glucose output (HGO) (17). In classical type 2 DM such hyperglycemia follows the repression of key hepatic glycolytic enzymes and the depression of gluconeogenic enzymes (18). 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 (18, 19). Insulin stimulates glycolysis by causing an increase in the synthesis of glucokinase, phosphofructokinase and pyruvate kinase, 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 (19). 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 4) and observed that they were higher in LB Type 2 DM ($p < 0.01$) as compared to other type 2 DM (20). In healthy controls, there was a negative correlation between values of fasting blood glucose (FBG) and glucokinase ($r = -0.66$, $p < 0.05$) as expected, while no such relationship was established in LB Type 2 DM, suggesting that hepatic enzymes concerned with CHO cycles operate differently and at higher levels. This increase in levels of glucokinase

could be an inherent characteristic of LB Type 2 DM.

Table 4: Fasting Serum Levels of Glucokinase in Healthy Controls LB and other Type 2 DM (mean ± SD).

	BMI	FBG (mg/dl)	Glucoki-nase (IU/L)
Healthy Controls	23.8 ± 3.4	82.8 ± 10.3	36.5 ± 5.6
LB Type 2 DM	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	-
LB Type 2 DM vs.			
Other Type 2 DM	p <0.01	p <0.01	p <0.01

HEPATIC MICROSOMAL ENZYME SYSTEM AND GLYCEMIC STATUS

Current knowledge reveals that hepatic glucose uptake is normal in type 2 DM, while HGO is high owing to hepatic insulin resistance vis-à-vis hyperglucagonemia and increased flux of gluconeogenic precursors from the peripheral bed (17). Studies from the west have 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 less trapping of insulin by the liver and consequential occurrence of peripheral hyperinsulinemia (21). Low circulating levels of insulin are a universal observation in LB Type 2 DM (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 (21). 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 (21). As there is polymorphism of drug oxidation, more than one drug is required to study the MFO system. Antipyrine, the gold standard, is 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 LB, from our centre and in Finland as part of the Indo-Finnish collaborative study on liver metabolism in Type 2 DM (6, 22). The results are presented in Table 5. Antipyrine $t^1/_2$ was markedly low ($p < 0.01$) in the LB Type 2 DM 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 LB Type 2 DM. A Lidocaine study also revealed that metabolite production was dependent on gross functional status of hepatocytes in the obese while it was independent in LB Type 2 DM. Interestingly, the interrelationship between the metabolism of the two drugs revealed an interdependence in the obese Type 2 DM but not in LB Type 2 DM. 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, 22).

Table 5: Results of Antipyrine Clearance and Lidocaine Metabolic (MEGX) Conversion Study in Indian and Finnish Type 2 DM Patients

	Indian		Finnish	
	LB	Obese	Obese	Healthy Controls
BMI	15.6 ± 1.5	28.4 ± 2.8	29.0 ± 4.1	26.7 ± 2.6
FBG (nmol/ L)	17.9 ± 4.2	8.6 ± 1.4	7.9 ±1.7	-
Serum ALT (IU/L)	33.6 ± 16.9	32.4 ± 21.3	-	-
MEGX (IU/L)	43.5 ± 18.1	45.4 ± 30.4	57.9 ± 35.9	35.9 ± 11.0
Antipyrine; $t^1/_2$	8.2 ± 3.5**	14.2 ± 0.9	17.5 ± 4.3	11.1 ± 6.1

***Significantly lower compared to other types of diabetes*

HORMONAL PROFILE AND RESPONSE

Circulating levels of insulin (IRI) have been found to be lower in LB Type 2 DM in all situations, whether fasting or fed, and in all studies as compared to classic type 2 DM. Persistence of lower insulin levels has provoked many 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 LB Type 2 DM subjects from two different centers are presented in Table 6.

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, glucagons and catecholamines (24). Even by eating a non-CHO diet or a mixed meal, which act as insulin secretagogues in diabetes, one can evaluate the beta-cell reserve for insulin in different types of diabetic (25, 26). This was studied in LB Type 2 DM along with patients suffering from MRDM and healthy controls for comparison. They were fed with oral glucose and a diet containing low (R and 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 LB Type 2 DM but least in MRDM (13). This not only testified to the significant insulin reserve in LB Type 2 DM but also differentiated LB Type 2 DM from both MRDM and type I DM.

Table 6: Plasma Levels of Insulin in LB, Obese Type 2 DM and MRDM at Basal and Post-Stimulated State: Mean (± SD)

	Plasma Insulin (µu/ml)		
	Basal	**Post-Glucose**	**Post-Glucagon**
Cuttack			
(Reference 13)			
Healthy controls	11.9 (3.5)	30.9 (5.5)	-
LB Type 2 DM	18.5 (4.1)	29.4 (6.9)	-
MDRM	8.1 (4.5)	15.9 (6.3)	-
(Reference 23)			
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)			
LB Type 2 DM	23.2 (14.4)	33.7 (16.2)	-
Obese Type 2 DM	24.4 (21.5)	64.0 (51.6)	-

In our previous studies we 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 LB and obese type 2 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 (29). This again differentiated LB Type 2 DM from MRDM (23, 29).

Table 7: Plasma Levels of C-Peptide in LB, Obese Type 2 DM and Type 1 DM at Basal and post-Stimulated State: Mean (± SD)

	Basal	**Post-Glucose**	**Post-Glucagon**
Madurai			
Reference 12, (ng/ml)			
Healthy controls	-	4.40 (1.68)	-
Type 1 DM	-	0.73 (0.44)	-
LBW Type 2 DMB	-	2.66 (0.55)	-
Obese Type 2 DM	-	3.73 (1.34)	-
Cuttack			
Reference 23, (ng/ml)			
LBW Type 2 DMB	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			
Reference 9, (pmol/ml)			
LBW Type 2 DMB	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			
Reference 44, (ng/ml)	**Basal**	**Post Prandial**	**Percentage rise**
LB Type 2 DM	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%

Further, in order to probe the beta-cell function and reserve in subjects with type 2 DM, both LB 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 LB Type 2 DM at all stages (Table 6) (23, 29). The C-peptide levels were surprisingly similar, 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 7). Studies on insulin and C-peptide levels in LB Type 2 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, including the most recent at Madras (Table 7), have revealed good beta-cell reserve in LB Type 2 DM on a par with other type 2 DM which happens to be complementary to our earlier reports (9, 23). This finding corroborated well with our concomitant observation that LB Type 2 DM patients have hyperactive futile cycles of CHO metabolism in the liver, an excess of glucokinase activity which could be responsible for excess insulin utilization in the liver.

Table 8: Metabolic Milieu: (HbA_{1c}, Lipids and 24 h Urinary Protein in LB Type 2 DM (Mean Values).

	At entry	After 1 year	After 2 years
HbA_{1c} (%)			
Males	10.1	7.2	6.4
Females	10.9	7.1	6.3
Lipids (mg/dl)			
HDL Cholesterol			
Males	46.7	46.0	46.4
Females	53.7	45.9	48.5
Cholesterol			
Males	202.8	196.4	192.3
Females	227.6	197.2	196.0
Triglycerides			
Males	140.9	137.0	118.1
Females	166.7	128.9	134.0
24 h Urinary Protein (mg)			
Males	280	130	90
Females	190	90	80

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 Type 2 DM. These observations point to an important conclusion that insulin kinetics during first pass and hepatic handling of CHO metabolism are probably the two most important denominators that can explain these peculiar characteristics observed in LB Type 2 DM 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 LB Type 2 DM (see Tables 2 and 3) (4, 10, 15, 30, 31). Analyses of the biochemical milieu followed up in two consecutive years, in a prospective study (Table 8), revealed that those patients with type 2 DM did not have hyperlipidemia which may be 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 GHb values above 10%. In our first publication in 1984 we showed that Indian type 2 DM, particularly underweight diabetics (LB type 2 DM); do not have low HDLC (32). 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 (20, 33). 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 (32, 34, 35). Higher levels of Tg in these diabetics were a fact established by us which was duly acknowledged by the international community (36). Type-IV hyperlipoproteinemia is by far the commonest form of dyslipidemia seen in these diabetics, and that too in a glycemic uncontrolled state (37). On the whole, these diabetics have a favorable lipid profile that could be a consequence of hepatic handling of HDL and CHO metabolism and lack of hyperinsulinemia-insulin resistance in the peripheral bed. This is likely to be an inherent characteristic of these diabetics.

At this stage it is imperative to evaluate a non-lipid and independent risk factor marker for atherosclerosis, CAD in particular, as the world literature emphasizes that type 2 DM patients are much more prone to suffer from it than the general population. 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 9. Unbelievably, 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).

Table 9: Serum Homocysteine Levels in Lean Standard Weight and Obese Type 2 DM (Mean± SD).

	Healthy Controls	LB	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 from Das et al. [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 (see Table 8). With tight metabolic control there was a lowering of 24-h urine protein levels, suggesting an improvement in the endothelial cell dysfunction that had originated as a result of poor glycemic state (41)].

BETA-CELLS AND AUTOIMMUNE STATUS

The emergence of late autoimmune diabetes in adults (LADA) and earlier postulations that LB Type 2 DM/lean type 2 DM could be adult counterparts of MRDM/MMDM (malnutrition modulated diabetes mellitus) necessitated not only an 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, 42). Prospective studies done on such patients, along with standard or intermediate body weight and obese type 2 DM from Madras in collaboration with Lucknow and the International Diabetes Institute, Australia, have revealed that islet cell antibodies (ICA) were absent in the serum of LB Type 2 DM, while even obese type 2 DM revealed 7.5% ICA positivity (9, 43) (Table 10). 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. Such results were very different from data observed in patients with type 1 DM in the same population. This supports the conclusion that LB Type 2 DM 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.

Table 10: Prevalence of Autoantibody Positivity in Different Type of Diabetics and Various Population Groups (Percent) [43].

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	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) OHA			9.1
b) insulin			15.2
Controls			4.8
Bhatia et al			
a) Young Type 2		4	25
b) Type 1		22	40
c) PDDM			25

In conclusion, it can be reasonably stated that low body weight/lean type 2 DM are not mere anthropometric variants of classical type 2 DM, but constitute an independent variant of type 2 DM with inherent peculiarities in insulin kinetics in the hepatic bed along with altered profile and behaviour of key enzymes related to CHO metabolism. These peculiarities are reflected in the peripheral circulation as states of hypoinsulinemia, hyperglycemia, dyslipidemia without low HDLC, raised Tg and fewer other markers for atherosclerosis which make diabetics less prone to develop macrovascular disease, while peripheral neuropathy and the consequences of hyperglycemia like infections and proteinuria dominate the clinical picture. One observation from the National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, that "NIDDM in the presence of low BMI is more strongly familial than that at a higher BMI", warrants further

study into the possible genetic factors that modulate the above factors in lean type 2 DM (45).

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