Diabetes in India is becoming a major problem and we are expecting the incidence to rise sharply over the next two decades. Just as we have a wide variety of cultures, languages, communities, we also have a wide variety of types of Diabetes.

We have Malnutrition Modulated Diabetes Mellitus (PDDM, MRDM, KRDY), Type 1 DM, Type 2 DM, Fibrocalculous Pancreatic Diabetes (FCPD), Lean Type 2 DM, as well as other syndromes and secondary diabetes in India.

Anthropometry, insulin levels, lipolysis, ketogenesis, autoimmune status and genetic information are all different in different types of diabetes. Fatty acid metabolism, which was considered secondary to Insulin kinetics, has now assumed an identity of its own with the discovery of adipocytokines and hormones. It is now time to reassess all available facts in the light of new knowledge.

We can take each type of diabetes and see what the status of plasma insulin and lipolysis is in the different Indian diabetics.

**TYPE 1 DM AND MMDM**

In 1971 I started my journey with Insulin and Diabetes under H. Vaishnava in New Delhi. It was an intriguing feature that there were young, thin, malnourished, insulin-dependant severely hyperglycemic diabetic patients who were not going into ketoadidosis despite not being given insulin. It was hypothesized that something must be wrong in their lipolysis at the adipose tissue level that they were ketosis resistant or there must be a hepatic cause for ketosis resistance. This was the puzzle one needed to unravel.

We studied the Plasma Immuno-reactive Insulin (IRI), Serum Free Fatty Acids (FFA) and Blood Ketones in Ketosis Resistant Young Diabetics (now called PDDM or MMDM), and compared them with classical Type 1 diabetics, all being newly diagnosed diabetics (Figs 1 to 3). Patients were kept for 10 days without insulin, if any patient was very ill, insulin was instituted immediately and the patient withdrawn from the study. After an overnight fast the patients and controls were given. Intravenous tolbutamide and blood samples were drawn and tested for glucose (Asatoor and King 1954), Plasma IRI (Double antibody Radioimmunoassay (Hales and Randle 1963)), and serum FFA (Anstall and Trujillo, 1965). During Fasting and 20, 30, 60 and 90 minutes after IV Tolbutamide. Samples for blood ketones (Mayes and Robson, 1957) were taken during fasting.

Plasma IRI levels were lower than controls in the basal as well as post-tolbutamide injection in the MMDM. This suggests residual beta cell function in the MMDM patients. In contrast the Type 1 diabetics had extremely low basal insulin levels with no rise in insulin after tolbutamide, demonstrating total lack of insulin.

Serum FFA levels in MMDM were significantly higher than normal controls but lower than Type 1 diabetics. FFA levels fell after tolbutamide in healthy controls, but to a lesser extent in MMDM, while there was no response in Type 1 DM. Blood Ketone levels were the highest in the Type 1 DM and lowest in the normal controls. In the MMDM (KRD) they were higher than the normal controls but significantly lower than the Type 1DM (KPD).

Fig. 1 shows plasma IRI in normal controls, MMDM and Type 1 DM before and after IV tolbutamide.
Insulin and Lipolysis in the Indian Diabetic — A 30-Year Journey

Fig. 2 shows serum FFA in normal controls, MMDM and Type 1 DM before and after tolbutamide. Catecholamines strongly influence the hormone sensitive lipase through the c-AMP, resulting in lipolysis and release of FFA from the adipose tissue. They also promote ketogenesis in the liver form the FFA. Vaishnava, et al (1973), had shown reduced lipolysis in vitro in the adipose tissue of the KRDY (MMDM) before and after treatment with insulin in contrast to excessive lipolysis in the Ketosis Prone Type 1 DM.

A number of studies in North Indian Ketosis Resistant young diabetics were carried out using epinephrine. Epinephrine injection produced the highest rise in serum FFA and ketones in Type1 DM compared to MMDM, who showed some rise in FFA and much less in the blood ketones. While normal controls had the least rise in FFA and blood ketones.

Subsequently, in continuation of our studies in Delhi, we studied epinephrine as well as salbutamo-induced lipolysis in a similar group of subjects from Jhansi, Uttar Pradesh. Diagnostic criteria for MMDM, at the study undertaken in Jhansi during 1976-1978, were used as per Samal and Tripathy.

Intravenous salbutamol had a similar effect to epinephrine in causing lipolysis. We repeated the study with propranolol pretreatment and with practolol pretreatment being given before salbutamol and found total block of salbutamol induced lipolysis by propranolol and no effect on salbutamol induced lipolysis by practolol, suggesting that the lipolytic response induced by catecholamines is largely a function of the Beta 2 receptors. We did this study on normal individuals as well as young diabetics (Fig. 4).

Evidence of Some Residual Beta Cell Function and Adipose Tissue Dysfunction

It was concluded from these studies that Plasma IRI was significantly lower in MMDM compared to control subjects but substantially above those of Type 1 DM. The levels of insulin and C-Peptide remain similar even 10 years later in these subjects.

There was evidence of reduced lipolysis and reduced ketogenesis in MMDM compared to IDDM, and that there is some dysfunction of the adipose tissue possibly in the lipolysis mediated by insulin and the catecholamine pathways. Other authors had shown similar results.
**Fig. 3:** Fasting Blood ketone levels

**Fig. 4:** Plasma IRI in normal subjects with salbutamol and beta blockade

**Fig. 5:** Blood glucose in normal subjects with salbutamol and beta blockade

**Fig. 6:** Serum FFA in normal subjects with salbutamol and beta blockade

**Fig. 7:** Serum FFA in normal subjects, KRD, KPD with salbutamol

**Fig. 8:** Blood ketones in normal subjects, KRD, KPD with salbutamol
in Indian diabetics, using oral glucose load, and tolbutamide. Serum FFA levels and Blood Ketone levels showed a similar trend in studies done in Delhi and Orissa. Utilization of ketone bodies in KRD has been shown to be normal by Vaishnava, et al as they found no rise in blood ketones on feeding a ketogenic diet.

Since adrenergic hormones have a significant role in lipolysis and ketogenesis through the c-AMP it was also suggested that autonomic neuropathy in diabetics diminishes lipolysis, however there was no evidence of autonomic neuropathy in the patients of Ketosis Resistant Diabetes though they did have peripheral neuropathy, which was partly due to nutritional deficiency.

**Evidence of Insulin Resistance**

Despite detectable plasma IRI the MMDM patients required higher doses of insulin for control of their diabetes viz 1.5 µ/kg body weight compared to 0.5 to 0.8 µ/kg in Type 1, implying the presence of Insulin Resistance. Similar findings have been reported from Rajasthan and Orissa. Low levels of insulin receptors have been reported in MMDM as well as in malnutrition, there are also no antibodies. Pro-insulin levels have not been studied in these patients, and might be worthwhile doing.

It was surmised that the small amount of Insulin available did not allow high degrees of lipolysis or ketogenesis in the MMDM subjects. In our patients of MMDM the levels of serum FFA and blood ketones did not correlate with the amounts of detectable plasma IRI. Thus the adipose tissue remained less responsive, whatever the insulin response in these subjects. Adipocytes are most sensitive to circulating plasma insulin and at very low levels insulin is able to suppress lipolysis, liver and skeletal muscle, come next in their response to insulin. However, in vitro studies on the same subjects showing reduced FFA release from the fat tissue raises further questions (Vaishnava 1973). There is evidence of Insulin resistance in malnutrition, therefore whatever insulin is available has poor peripheral activity. Krishna Ram, et al did in vivo and in vitro studies on the adipose tissue of IDDM and MMDM and found adequate in vitro lipolysis after epinephrine and nor-epinephrine. They also reported no diminution in the response of the liver to glucagons in these subjects. Krishna Ram’s study fails to explain the total absence of ketosis in MMDM either at diagnosis or even during prolonged insulin withdrawal at later follow-up. Ketosis does not occur even with severe hyperglycemia despite the presence of systemic infections. Ethnic differences between black and white subjects have been shown in the responsiveness of adipocyte lipolytic activity to insulin. The adipocytes from black women subjects had low response to insulin in presence of relative insulinopenia and insulin resistance as compared to the adipocytes from white females. We require similar studies on our MMDM patients comparing them with other Indian diabetics as well as other ethnic groups.

The MMDM patients had low BMI but were pot-bellied. Their waist hip ratio was altered and the waist was definitely more than the hip size. Do they have more visceral fat? Do they store whatever fat they can in the abdomen as in the thrifty genotype? Do they have the metabolic syndrome? They did have enlarged livers. Was it a form of what we call as NASH. Liver biopsies from these patients have however shown increased glycogen by majority of the workers, though one experimental work does mention fatty infiltration as a response to protein malnutrition. When these patients’ diabetes was well controlled, they put on some amount of fat, which was largely around the waist, and their ketosis resistance remained despite available fat stores. Current work in fact shows that increased body fat increases insulin resistance rather than reduce it. Thus the reduced lipolysis was not due to emaciation or non-availability of fat depots. There is possibly a FFA bypass of hepatocyte mitochondria and consequent diminished ketogenesis, similar to that shown in FCPD. Is it a protective mechanism developed by nature for survival, by making them ketosis resistant?

Many experts have postulated the mechanism of development of MMDM as a consequence of prolonged under-nutrition in fetal life and during early childhood. The patients come from very poor background, many of them with periods of near starvation. We reported a very high incidence 47% of MMDM in Jhansi, UP which has a very poor rural population. Similar patients have been reported from other places in India. Insulin secretion falls with protein malnutrition. Insulin secretion improves in protein deficient subjects after re-feeding only when the deficiency has been for a short while in adult life. Protein malnutrition in fetal life an early infancy reduces insulin secretion, which is not restored to normal in adult life by feeding normal diet.

Experimental as well as postmortem studies have shown that low protein diet in pregnancy leads to decreased islet cell vascularity, decreased beta cell proliferative capacity, decreased islet cell size, right shift of glucose stimulated insulin release, altered insulin sensitivity in the muscle and diminished metabolic capacity of liver, muscle and adipose tissue.
The fat studied in vitro for lipolysis was taken from different sites in different studies, abdominal in some cases and extremities in others. New data shows that there are regional differences in fat cells and lipolysis. Omental adipocytes are reported to have higher rates of lipolysis and are more sensitive to catecholamines than the subcutaneous adipocytes. There are also gender differences, as well as differences between upper and lower body fat, the upper body having higher rates of lipolysis then lower body subcutaneous fat. Some studies on healthy people have shown higher rates of lipolysis and LPL activity in subcutaneous adipocytes when these values are expressed as a function of cell number, though omental and mesenteric, adipocytes are still more responsive to positive lipolytic stimuli. The fact that omental, and mesenteric adipocytes drain directly into the portal circulation and send their FFA flux to the liver makes even a slight difference more significant. It would be of interest to study visceral, abdominal subcutaneous and peripheral fat in MMDM patients for the effect of epinephrine or other adrenergic agents. The Beta 3-adrenergic receptor has shown higher frequency of mutant alleles in Pima Indians and people homozygous to the allele have onset of diabetes at a much younger age. This kind of study may need to be done in the MMDM patients seen so widely in India, especially in the light of our and other workers who showed insufficient lipolysis in the adipose tissue of this special category of diabetics put under the name of MMDM.

There was no family history of DM in these patients in our studies. Genetic studies done in MMDM have shown them to be different from Type 1 DM. In HLA studies, the MMDM had a higher prevalence of DR7,DQw9 haplotype, while Type 1 DM had a higher prevalence of DRw17 DQw2 haplotype.

There are conflicting reports on immune markers in the studies in MMDM. Some workers showed presence of Islet Cell Antibodies, while most studies did not find any significant presence of ICA or Insulin Autoantibodies. Results would also depend on patient selection for the study.

Majority of the studies on insulin levels, ketogenesis, immune markers and genetics have compared Type 1 DM with MMDM due to the similarity in age, severity of hyperglycemia, and low BMI. The fact that malnutrition induces insulin resistance, as well as the higher requirement of insulin in MMDM puts it closer to Type 2 DM, who have insulin resistance, do not have ketoacidosis and have remnant beta cell function. Is it an early unmasking of a type 2 DM due to fetal and childhood undernutrition. It will be worthwhile to compare the MMDM patients with Type 2 DM and to compare special ethnic groups and do the same genetic studies as done for Type2 DM to further classify these subjects.

Inflamatory markers need to be studied in these subjects. It is possible that in the background of poor nutrition and a plethora of superadded infections of the GI tract and respiratory tract as is well known in this population it may the underlying factor with causes oxidative stress, reduces beta cell function as well as causes insulin resistance and thereby causes DM.

Our study of 1971 and work reported by Vaishnava (1973) and subsequently in 1976 (Kirti and Vaishnava), showed clear evidence of paucity of lipolysis and ketogenesis in MMDM. Current literature makes these findings very relevant, where the focus has shifted to the adipose tissue and FFA themselves are implicated in insulin resistance as well as reduction in insulin secretion. The hypothesis given over 30 years ago holds water now, when adipose tissue dysfunction has been shown to be the basis of the metabolic syndrome and diabetes.

**PUZZLING PROBLEMS OF THE 1970**

- Young thin Insulin Dependent Ketosis Resistant DM
  - Severely malnourished
  - Severe hyperglycemia but no ketoacidosis
  - Detectable plasma insulin, though less than normal
  - Higher doses of insulin required to control DM (Insulin Resistance)
  - Paucity of lipolysis
    - Poor response in suppression of lipolysis by endogenous insulin
    - Poor response to beta adrenergic stimuli epinephrine and salbutamol
  - Adipose tissue resistant to insulin action and adrenergic stimuli action in vivo and in vitro
  - Lipase receptor defect?
  - Small amounts of plasma insulin adequate to protect from lipolysis and ketogenesis, then why insulin resistance?

**Reduced ketogenesis**

Liver enlargement – Glycogen deposition, NASH – no definite evidence—? Malonyl CoA

Pot bellied – probably due to malnutrition, but CT not available so abdominal fat (visceral versus subcutaneous) not known

High prevalence in microvascular complications, no evidence of macrovascular complications.

No evidence of exocrine pancreatic dysfunction.
NEWER PIECES IN THE PUZZLE IN THE YEAR 2006; WHERE DO THEY FIT?

- HLA and immune markers studies show MMDM is different from Type 1
- Adipose tissue now primary site of abnormalities—dystrophic adipose tissue
- Malnutrition and infections lead to production of proinflammatory molecules and adipocytokines, which produce insulin resistance.
- Fetal protein deficiency reduces beta cell function, predisposes to DM in later life.
- Asians have genetic predisposition to abdominal (specially visceral) adiposity, and diabetes at a younger age.
- ? beta3 adrenergic receptor mutation in Pima Indians results in dystrophic adipose tissue and young age of onset of diabetes. Is it so in MMDM?

Considering the magnitude of the problem and the large numbers of such patients being seen all over the country in the rural and semi-rural areas, a number of workers tried to put it as a separate type of diabetes in the WHO classification, which was accepted a number of times as J diabetes, as Protein Deficient DM and then as MMDM in 199739. However, it again got relegated to the background soon after. I would make a case for more study in these patients on the adipocytokines, inflammatory markers and genetic markers, since they are not Type 1, nor Type 2, so that the WHO and the world would give them a due place in the classification of DM. I would like to propose the Asian MMDM phenotype on the same lines as proposed by Mohan, et al (2006)40, for the Asian Type 2 diabetic:

<table>
<thead>
<tr>
<th>Asian Indian phenotype</th>
<th>Asian Indian MMDM phenotype</th>
</tr>
</thead>
</table>
| Greater ethnic/genetic susceptibility | Malnutrition (Fetal/Early life)/?
| To type 2 DM | ethnic ? gene reduced beta
| Lower threshold for BMI | cell function-predis to DM
| for DM | Undernourished, pot bellied,
exocrine pancreas normal
| Inflammatory Markers; CRP, IL6 | Infections;? inflammatory markers,
cytokines
| Abdominal Obesity and Visceral fat | Adipose Tissue Dysfunction
| High Serum Insulin/Insulin Resistance | Low Serum Insulin/Insulin Resistance
| Low Adiponectin | Reduced lipolysis, lower FFA, No Ketosis
| Characteristic Dyslipidemia; Low HDL | Good HDL cholesterol, Normal LDL
| High Triglycerides and sdHDL | Fatty Liver
| | Increased Prevalence of
| | Premature T2DM
| | Lower Prevalence of Diabetic
| | retinopathy and nephropathy
| | Absence of Macrovascular
| | complications
| | Increased Prevalence of
| | Neuropathy, nephropathy and retinopathy

I hope further work on genes and adipocytes is carried out in these subjects to clarify the place of these patients in the world of diabetes.

Now let us discuss the other types of diabetes seen in India in relation to plasma insulin, lipolysis and ketoacidosis:

FIBROCALCULOUS PANCREATIC DIABETES

High incidence observed in Tamil Nadu41, Kerala42, Orissa43, and also in South America44 and parts of Africa45. Ramachandran, Tripathy and Mohan have done extensive work on this. The patients have exocrine pancreatic deficiency. Plasma insulin levels are low but higher than Type 2 DM, depending on the degree of pancreatic involvement. Patients have no insulin resistance. Glucagon levels are also low11. There is a strong genetic basis46, added to that are environmental factors like toxins, oxidants, and poor nutrition which are involved in the pathogenesis of FCPD leading to exocrine pancreatic destruction47. Lipolysis and ketogenesis is similar to Type 1 DM.

LADA

Latent Autoimmune Diabetes in Adults, is where slow destruction of beta cells occurs due to autoantibodies. The patients soon go on to insulin therapy and have positive immune markers. There insulin levels are similar to type 2 DM. They do not have insulin resistance initially though some degree of insulin resistance may develop if they gain excessive weight after insulin treatment. Their biochemical responses are like IDDM48.

LEAN TYPE 2 DM

Majority (>80%) of Type 2 DM in developed countries are obese with a high BMI while in India, Most (>60%) of the Type 2 DM are non obese as per BMI. Many Type 2 Indian diabetics are lean with a BMI of <18.5. Mohan et al reported 3.5% lean type 2 DM among of all type 2 DM at their center in Chennai39. 53% males and 47% females with lean Type 2 were on insulin the remaining being on oral hypoglycemic agents even after a mean duration of diabetes of 9.2+/-. 8.1 years. They did not find significant presence of ICA or GAD
antibodies in these subjects. Patients on OHA had detectable levels of C-peptide. Thus these patients did not qualify as type 1 DM or as LADA. They had more severe diabetes with higher prevalence of proliferative diabetic retinopathy, neuropathy and nephropathy. It may be that these were inadequately controlled type 2 diabetics with poor residual beta cell function.

Indian type 2 patients in general have lower BMI than the Caucasians. The waist hip ratio seems an important marker in Indian diabetics, especially when they get labeled as ‘lean’ diabetics according to BMI.

Type 2 DM

Fasting, as well as stimulated, plasma insulin levels have been measured in Indian Type 2 diabetics by many workers across the country. Adult Indians, diabetics as well as non diabetics, appear to have higher basal as well as glucose mediated plasma insulin response as compared to Caucasian subjects. at a comparable level of blood glucose suggesting that Indians have more insulin resistance than Caucasians. Clamp studies in Indian diabetics in India as well as Indians living abroad have also shown higher degree of insulin resistance at younger ages as well as at any level of truncal fat compared to their Caucasian counterparts. Insulin resistance becomes more pronounced as they get urbanized or migrate to the developed world.

Plasma FFA concentration reflects a balance between release (from intravascular lipolysis of triglyceride-rich lipoproteins and lipolysis of adipose tissue triglyceride stores) and uptake (predominantly re-esterified in adipose tissue and liver and oxidized in muscle, heart, liver and other tissues. Insulin has a potent effect on hormone sensitive lipase, the principal regulator of FFA release from adipose tissue.

Lipolysis and FFA levels have been extensively studied in Indians residing in India as well as migrant Indians in the US and UK. They have higher amounts of body fat than their Caucasian counterparts even at the same BMI. Waist hip ratio is more even at low BMI in Indians. Abdominal fat has now been shown to have higher FFA flux compared to peripheral fat. Of the abdominal fat, the Visceral adipose tissue affects the FFA flux much more compared to the abdominal subcutaneous tissue as it directly drains to the portal circulation. Even among the abdominal subcutaneous tissue it has been shown that the peri-umbilical subcutaneous fat contributes more to plasma FFA and hepatic insulin resistance than the adipose tissue in the other parts of the abdominal wall. Therefore, sagittal abdominal diameter (SAD) has also been added to the list of markers for insulin resistance.

Difference in lipolysis has been shown between the male and female adipose tissue. Upper body adipose tissue has been shown to have higher FFA release compared to lower body adipose tissue, which is more in women. However lot of conflicting data is there on this issue. Central adiposity shows consistent relationship with abnormalities in lipolysis.

Systemic FFA levels are higher in Indians and in Indian origin British and American subjects, and reflect the FFA release from visceral fat depots. There is a positive correlation between FFA levels and fasting hyper-insulinemia and insulin resistance. On glucose administration there was hyperinsulinemia in Asian Indian subjects while the plasma FFA levels were not completely suppressed. Thus suggesting defective insulin action in the adipose tissue.

The adipocytes and its function are of prime importance in the metabolic syndrome. FFA levels and Leptin levels were found to be high in Asians even in non-obese, non-diabetic subjects compared to Caucasians, this was also found in diabetic and non-diabetic Asians with coronary artery disease.

Adiponectin levels in Indian diabetics have been shown to be low and correlated well with the fasting plasma insulin and glucose (HOMA), further emphasizing that adipose tissue abnormalities contribute to the metabolic syndrome in Indians. The levels were much lower than those of Caucasians as well as African Americans.
Interventions that reduce circulating FFA, either due to or independently of weight loss and increased activity, are likely to improve insulin sensitivity, beta cell function and cardiovascular risk.

Radha, et al\(^5^9\) have shown that PPARg gene polymorphism deficiency is related to a large extent with type 2 DM in South Indians, influencing the increase in visceral fat, insulin resistance and thereby development of dm at an early age when environmental influences are added on. Other genes have also shown to be associated with younger onset of diabetes in Indians\(^6^0\).

High prevalence of TCF7L2 gene has been found to be associated with Type 2 DM in South India in Chennai as well as Hyderabad\(^6^1\). Other genetic studies are being published showing genetic predisposition to the metabolic syndrome and triglycerides\(^6^2,6^3\).

Inflammatory pathways are now being implicated in the pathogenesis of the metabolic syndrome and diabetes mellitus\(^6^4\). Inflammatory markers like hsCRP, VCAM-1 and IL-6 were also high in Type 2 Indian diabetics, showed positive correlation to increasing degrees of glucose tolerance, as well as waist hip ratio\(^6^5\).

Yajnik, et al\(^6^6\) and many other workers have shown that protein malnutrition in early life causes early loss of beta cell mass and function, also inducing insulin resistance, and lifestyle changes later in life, like sedentary occupation and over-nutrition then produces diabetes mellitus. Asian newborns have been shown to have a higher percentage of visceral fat, a lesser amount of muscle mass and lower bone mass compared to Caucasian babies. Thus we already have the stage set for insulin resistance at birth.

With the adipose tissue producing its gamut of adipocytokines, the Indian diabetic who has a thrifty gene, deficiency of protective genes like PPARg, excess of pro-diabetic genes, protein deficiency in fetal life, micronutrient deficiency, infections and inflammatory molecules, toxins from the environment, now adds a lifestyle of low physical activity and excess of caloric intake and ultimately takes a shortcut to becoming diabetic at an early age.

Abate and Chandalia\(^6^7\) have, on the basis of their extensive work recently, put forward the concept of Dysfunctional Adipose Tissue as the basis of systemic insulin resistance as opposed to increased adipose tissue mass as seen in obesity. Thus the typical Indian type 2 diabetic has adipose tissue dysfunction, with suppression of lipolysis in adipose tissue, resulting in diversion of FFA flux to non-fat tissues like liver, heart and muscle. This is in keeping with the hypothesis given over 30 years ago by our group Vaishnava 1973\(^2\), Kirti and Vaishnava 1976,\(^1\) as well as workers from Orissa\(^3\) and Chennai\(^4^0\) that adipose tissue is abnormal in MMDM and Type 2 Indian diabetics, and there is abnormal metabolism in the liver and muscles of these diabetics, and that presence of residual insulin in diabetics does not explain all the clinico-biochemical features in Indian diabetics, though there were fewer means to establish this at that time.

REFERENCES


