

# MRDM - Experience from a Public Hospital\*

S. Venkataraman, A. Sundaram, V. Seshiah

## INTRODUCTION

The clinical presentation of diabetes mellitus in tropical countries includes a distinct subset form ing less than 1 per cent of total diabetic population which evades the label of either IDDM or NIDDM. The WHO study group[1] in 1985 recognised the existence of such a distinct type of diabetes mellitus as malnutrition related diabetes mellitus MRDM . MRDM comprises of two varieties, fibro calculous pancreatic diabetes (FCPD) and protein deficient pancreatic diabetes (PDPD). FCPD has been by and large accepted to be a distinct entity, but PDPD still remains controversial as a distinct form of diabetes mellitus. PDPD is being regarded as a forme furste of IDDM, with the clinical behaviour probably being modified by the associated malnutrition or the loss of weight could be due to uncontrolled diabetic state[2].

## HISTORICAL PERSPECTIVES

Hugh-Jones[3] in J'amaica first described the features of 'J' type diabetes which included resistance to the development of ketosis, resistance to action of exogenous insulin, wasting, emaciation and onset of diabetes usually between 15-25 years of age. This subtype is now designated as PDPD. Zuidema[4] described patients with chronic pancreatitis who showed pancreatic calcification and fibrosis, referred to as pancreatic fibrosis calcification syndrome or Zuidema syndrome. Seshiah et al [5] in a study of young diabetic patients in Madras South India, recognised the existence of a category (IRDM) who required insulin for control of hyperglycaemia but who seldom develop ketosis. The WHO Study Group 1985 discarded the terms 'J' type diabetes, 'M' type diabetes, ketosis resistant youth onset diabetes etc and gave the label of MRDM which suggested a uniformity in a clinical entity which is probably more heterogenous.

## EXPERIMENTAL EVIDENCE

Swenne et al[6] studied the effects of malnutrition on rats and documented an impaired insulin response to glucose and non-glucose stimuli. Furugian et al[7] concluded that diabetes may

develop not only during protein deprivation but also after its cessation.

## PREVALENCE OF MRDM

In a study from Bangladesh[8] comprising 498 subjects with the onset of diabetes mellitus below 30 years of age, 177 subjects (about 50 per cent) could be categorised as PDPD while 75 subjects (15 per cent) had pancreatic calcification and were classified as FCPD. A similar high prevalence of MRDM subtypes has been observed by Tripathy et al[9]. Regional differences in the prevalence of the subtypes of MRDM exist. In the series of Ramachandran et al 10 FCPD formed about 1, per cent of all diabetic patients. On the other hand FCPD constituted less than 0.2 per cent of 22,000 diabetic patients recruited in the Dept. of Diabetology, Madras Medical College. Morrison et al[11] observed that FCPD was rare in the caribbeans while PDPD was more common. Geevarghese[12] from Kerala, India and Wiyono[13] from Indonesia have reported that there is a decrease in the incidence of FCPD.

## AETIOPATHOGENESIS

Epidemiological association of 'malnutrition' with this type of diabetes, experimental observations on the interaction of protein energy malnutrition and consumption of the cyanogenic cassava [14] on insulin secretion and glucose tolerance led to an interesting hypothesis to explain the pathogenesis of MRDM. Cyanogen mediated potential injury to the pancreatic beta cells is presumably due to a nutritional lack of the sulphur containing amino acids which results in defective detoxification of cyanogenic. However in many areas where FCPD has been reported there is no history of cassava consumption. Interestingly it has been established that the cyanogen content of cassava is too little to produce any deleterious effects on the pancreatic beta cells[15]. Mngola[16] linked the occurrence of FCPD with the consumption of an alcoholic brew called changaa. Thus dietary factors other than cassava could probably be implicated in the causation of FCPD.

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\* From Department of Diabetology, Madras Medical College & Government General Hospital, Madras, India.

Familial aggregation of cases of FCPD have been observed by Pitchumoni[17] and Mohan et al[18]. In the enthusiasm to arrive at conclusions invoking a possible genetic basis in the causation of FCPD one should be aware that family members more often share the same environment. Kambo et al[19] have established that both HLA DQ-B and the class 3 allele of insulin gene, were increased in FCPD. Abdulkadir et al[20] in a study from Ethiopia have shown MRDM to be associated with DR3 postulating that the genetic basis for susceptibility to MRDM and Type I diabetes could be partially identical in that ethnic group. However Sanjeevi and Seshiah et al[21] concluded that the genetic background of MRDM is different from that of Type 1 diabetes. Yajnik[22] supports the contention that PDPD may be a subtype of IDDM rather than an aetiologically separate entity. This, theory assumes significance in the light of the findings of islet cell antibodies (ICA) in MRDM subjects by Wiyono et al[23] and Hazra et al[24]. In fact in the latter study the ICA positivity in MRDM was similar to that in IDDM. Abu-Bakare et al[25] contended that PDPD subtype of MRDM is a forme fruste of IDDM, at least in a subset of patients.

### **INSULIN PROFILE AND INSULIN RESISTANCE IN MRDM**

Mohan et al[26] classified tropical pancreatic diabetes (TPD) subjects into three categories based on the serum C-peptide responses. Majority of the subjects had low but measurable C-peptide levels, higher than those in IDDM[27]. This indicates relatively preserved endogenous insulin reserve which may be a factor protecting FCPD patients against ketosis. Ahuja et al[28] and Samal et al[29] have also documented endogenous insulin reserve of FCPD patients.

MRDM subjects have been found to have insulin resistance. Rao[30] contends that the insulin resistance in MRDM is not mediated by antibodies to exogenous insulin. Insulin resistance could be either primary or secondary to insulin deficiency. Mohan et al[31] have established that FCPD patients show evidence of insulin resistance similar to that of NIDDM patients.

### **CLINICAL FEATURES**

The clinical features of PDPD variant of MRDM have undergone little modifications subsequent to the original description by Hugh Jones. The commonly suggested criteria[32] lack a specific marker for diagnosis. Features of onset before 30 years of

age, male preponderance, low BMI (<18 kg/m<sup>2</sup>) and moderate to severe hyperglycaemia were observed in our series also. In contrast to PDPD, FCPD subjects have a specific marker in the form of pancreatic calcification. In our series of subjects with FCPD, all had radiological evidence of pancreatic lithiasis, while 80 per cent gave history of severe abdominal pain for a period of two to five years prior to diagnosis of diabetes. Suresh et al[33] have analysed the utility of ultrasonography in the diagnosis of FCPD. Among subjects who did not have calcification, increased echogenicity, heterogenous appearance and ductal dilatation were observed. Endoscopic retrograde cholangio-pancreatography (ERCP) studies have been reported in FCPD subjects by Balakrishnan et al[34]. Patients with pancreatic calculi showed abnormal pancreatograms with marked ductal changes. Yajnik et al[35] have studied the pancreatic exocrine function in Indian diabetics and concluded that more than 90 per cent of FCPD subjects showed a severe diminution in all pancreatic exocrine markers. In an analysis of the spectrum of pancreatic exocrine and endocrine (Beta cell) function in tropical calcific pancreatitis[36] there progressive and parallel decline in exocrine and endocrine markers with deterioration of glucose tolerance lending support to the concept that diabetes in FCPD is secondary to chronic pancreatitis.

### **COMPLICATIONS**

Contrary to earlier contention that vascular complications are rare in FCPD, it has been established that proliferative retinopathy and maculopathy occur in FCPD[37] as well as in PDPD[38]. The occurrence of neuropathy[39] and left ventricular dysfunction[40] has also been adequately documented in FCPD subjects. In our own series of 32 FCPD subjects, nephropathy was present in one subject, retinopathy in one, neuropathy in 6 while one subject had cardiomyopathy (unpublished). Sutjahjo et al[41] have observed a high frequency of autonomic as well as peripheral neuropathy in MRDM subjects. They contend that 'autonomic dysfunction appears to be a new characteristic of MRDM, not mentioned by the WHO study group'.

### **MANAGEMENT**

Majority of FCPD subjects require insulin for the control of hyperglycaemia while a small proportion could be managed with sulphonylureas and diet alone, the therapeutic response being determined by patient's C-peptide status. In our FCPD subjects, the insulin requirement ranged from 1.5 to 2.5

units/kg/day. Steatorrhoea could be alleviated by pancreatic enzymes but abdominal pain, if intractable and severe, might warrant surgical intervention. PDPD subjects require more insulin and they also tend to have a lower BMI compared to FCPD subjects. Our IDDM subjects tended to gain the lost weight after insulin treatment but PDPD subjects did not gain the lost weight despite good metabolic control. It is tempting to speculate that the insulin resistance is probably not restricted to metabolic functions of insulin but also to the growth promoting effects of insulin. A role for somatomedins is also possible.

## CONCLUSION

The clinical entity of MRDM is riddled with many controversies regarding its possible aetiology. Even the existence of a separate subtype (PDPD) is challenged. Abu-Bakare et al contend that the WHO report "automatically legitimises what may yet prove to be a child or children of indeterminate origin". Similarly the initial enthusiasm linking consumption of cassava with FCPD has waned, necessitating further research to identify the possible aetiological factors in the causation of FCPD. Family studies and genetic markers imply that the entity of MRDM might be more heterogenous than originally thought when WHO classified it as a separate form of diabetes mellitus.

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