

# Studies on maturity onset diabetes of the young (MODY) from S. India

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## ABSTRACT

We examined the following aspects of Maturity Onset Diabetes of the Young (MODY): prevalence, vascular complications, insulin secretion in offspring of MODY subjects, insulin resistance and whether MODY can be considered a distinct disease.

We report a higher prevalence of MODY among Asian Indian patients. The prevalence rates of microvascular complications in MODY were found to be the same as in classical NIDDM patients. Glucose stimulated insulin and C-peptide responses were compared with non-diabetic controls. In MODY subjects, C-peptide responses were lower, whereas insulin responses were varied. Insulin secretion in offspring of MODY subjects was similarly evaluated, and abnormalities discovered even in these pre-diabetic subjects. Using the euglycaemic clamp technique, MODY patients were found to be more insulin resistant than classical NIDDM patients. Further lines of evidence are needed to resolve whether MODY can be considered a distinct disease.

## INTRODUCTION

The entity known as Maturity Onset Diabetes of the Young (MODY) was first described by Fajans (1) who first reported youth onset diabetics who were not dependent on insulin. Later Tattersall (2) from the king's College, London, published a report entitled "Mild familial diabetes with dominant inheritance" where he described non-insulin-dependent diabetes presenting in youth. Soon a joint report followed from Tattersall and Fajans (3) where the term "MODY" was used for the first time using the first letters of "Maturity Onset Diabetes of Youth." In this paper they set down the following criteria for the diagnosis of MODY:

1. Age at diagnosis below 25 years
2. Control of fasting hyperglycaemia without insulin for a minimum of 2 years and
3. Absence of ketosis at any time

Tattersall has recently suggested that the period without insulin should be extended to 5 years to completely exclude cases of IDDM who might initially respond to oral agents (4). It has also been suggested (4) that autosomal dominant inheritance should be used as a diagnostic criterion. However most studies in the literature have used the original criteria of Tattersall and Fajans.

## PREVALENCE OF MODY

A number of reports from Europe and U.S.A. (5-8) have confirmed the existence of MODY. However, MODY is not a common form of diabetes among the white population (8). Recently it has been recognised that in certain communities of the world MODY type of diabetes is more common. This has been shown in Pima Indians (9), in the Nauru population (10) and more recently in Asian Indians in South Africa (11) and southern India (12).

The actual prevalence of MODY in different populations still remains unknown. The only study that has examined the prevalence of MODY in the general population (8) found it to be 0.15%. In Tattersall's original report (2), 1 in 200 patients attending the King's College Hospital were found to have MODY type diabetes. In S. Africa, Jialal and co-workers (11) using a cut-off point of 35 years, found that 10% of Indian NIDDM patients had MODY, a figure that was very much higher than in black and white communities living in S. Africa. In southern India we (12) found that 4.8% of our NIDDM patients at Madras had age at diagnosis below 25 years, in 18.5% it was below 35 years and in almost 50% it was below 45 years. Thus, there appears to be a higher prevalence of MODY among Asian Indian patients.

## VASCULAR COMPLICATIONS IN MODY

There is considerable controversy whether patients with MODY are prone to vascular complications. Tattersall (2) in his original report stated that microvascular complications were very uncommon in MODY.

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Based on a large series, Fajans (13) reported that vascular complications occurred in his MODY patients with the same frequency as in classical NIDDM patients. Tattersall (4) then suggested that there could be different subgroups within MODY, such as autosomal dominant MODY and sporadic MODY and that the dominantly inherited MODY were protected from microvascular complications.

During the last 6 years, several reports on microvascular complications in Asian Indian MODY patients have been published and these have been recently reviewed (14-16). At the Diabetes Research Centre, Madras, were registered a very large series of MODY patients (219 patients). This afforded a good opportunity to test the hypothesis that patients of MODY are protected from microvascular complications. We divided our 219 patients into three groups: MODY with definite autosomal dominant inheritance which included vertical transmission of diabetes through three or more generations; MODY patients who had a first degree relative with diabetes but in whom the dominant inheritance was not definite and finally a group of MODY with no family history of diabetes; sporadic or non-hereditary MODY.

Table 1 shows the occurrence of vascular complications in the three subgroups of MODY. It can be seen that microvascular complications were

equally common in all three subgroups of MODY including those with autosomal dominant inheritance (12). In a more recent study (17) we looked at vascular complications in 85 MODY patients who were watched for duration of diabetes with a group of classical NIDDM patients. It was found that there was no significant difference between the MODY and the classical NIDDM patients in prevalence rates of microvascular complications. Macrovascular complications, on the other hand, were less common among the MODY patients but this is hardly surprising considering their younger age. We therefore concluded that MODY were prone to microvascular complications just like the patients with classical NIDDM. Similar findings have been reported by Jialal et al from S. Africa (18).

### INSULIN SECRETION IN MODY

Considerable heterogeneity has been described with respect to insulin responses to an oral glucose load in MODY (13). Thus families with normal as well as high insulin responses to glucose load have been described. Since it is known that approximately 50% of insulin undergoes extraction in the liver whereas the extraction of C-peptide is negligible, C-peptide assay gives us a better index of pancreatic beta cell secretion and simultaneous assay of insulin and C-peptide gives information regarding pancreatic beta cell secretion as well as the peripheral

**Table 1. Percentage distribution of vascular complications in MODY\***

	< 15 yr duration			> 15 yr duration		
	Definite autosomal dominant MODY (n=43)	Possible autosomal dominant MODY (n=82)	Non-hereditary MODY (n=34)	Definite autosomal dominant MODY (n=16)	Possible autosomal dominant MODY (n=35)	Non-hereditary MODY (n=9)
BDR	2	11	6	25	41	44
Proliferative retinopathy	2	2	3	6	6	11
Nephropathy	7	5	6	6	23	33
Neuropathy	2	12	6	31	49	55
IHD	0	4	0	6	14	0

\*Ref 12-Mohan et al. Diabetes Care 1985; 8: 371-74.

BDR = Background Diabetic Retinopathy

IHD = Ischemic Heart Disease;

Difference between the three groups of MODY: not significant (Fischer's exact probability test)

metabolism of insulin. We therefore performed simultaneous studies of insulin and C-peptide responses to glucose load in subjects with MODY and matched groups of control non-diabetic subjects. We found that C-peptide responses to glucose load were lower in MODY subjects, thereby providing evidence for decreased beta cell function in MODY (19). The insulin responses were varied, with some patients having normal responses and others low responses. This suggests that there could be an additional defect in the peripheral metabolism of insulin, most likely at the hepatic level. This could be a compensatory mechanism to maintain higher physiological circulating levels of insulin in the face of defective pancreatic beta cell function. Recent studies from S. Africa (20, 21) have confirmed our observations regarding defective beta cell secretion in MODY.

### **INSULIN SECRETION IN OFFSPRING OF MODY SUBJECTS**

Having established that defective pancreatic beta cell secretion is a feature of MODY patients, our next objective was to see whether this defect in beta cell secretion precedes the onset of diabetes and if so, whether this could be used as an early biochemical marker for diabetes in MODY families. This is particularly relevant because in a disease with autosomal dominant inheritance only 50% of the offspring eventually develop diabetes if only one of the parents has the disease. It would therefore be useful if an early biochemical marker for diabetes could be found in these families.

We studied offspring of MODY subjects (O-MODY) at a stage when they had normal glucose tolerance tests and examined their insulin and C-peptide responses to a glucose load. We were able to find evidence of abnormalities of insulin secretion even in these prediabetic subjects, suggesting that biochemical defects in MODY may be identifiable years before the onset of clinical diabetes.

### **INSULIN RESISTANCE IN MODY**

Earlier studies on insulin resistance in MODY have produced conflicting results (23, 24). The euglycaemic clamp technique is widely recognised as one of the best ways of assessing insulin resistance (25). Mohan et al (26) performed euglycaemic clamps in MODY patients and healthy non-diabetic control subjects. The results showed that despite their younger age, MODY patients were more insulin resistant than classical NIDDM patients. It was therefore concluded that insulin resistance is a feature of MODY patients and this could be one of the

factors responsible for the younger age at onset of diabetes that was observed in them.

### **IS MODY A DISTINCT DISEASE?**

There are several lines of evidence to suggest that MODY is a distinct disease. Firstly MODY is the only form of diabetes today where a definite mode of inheritance has been worked out (27). It is also the only type of diabetes for which a monogenic inheritance has been proposed. The prevalence of MODY varies in different ethnic groups. This is also suggestive of a distinct disease that has varying prevalence rates in different communities.

There is also evidence to suggest that MODY could be just one end of the spectrum of NIDDM. The clinical features of MODY and the biochemical and hormonal characteristics do not show any differences from classical NIDDM. Genetic studies on MODY (10, 28) have drawn a blank so far, though admittedly these have been done on Caucasian subjects MODY. Very recently, in collaboration with Dr. Graham Hitman of the Royal London Hospital, Whitechapel, London, we (29) have looked at various gene markers in MODY. The results showed that there was a strong association with the class 3 allele of the insulin gene but the results were not different from that seen in classical NIDDM patients. Obviously more studies need to be done to resolve whether MODY is a separate disease or merely a continuum of NIDDM.

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