

Abnormalities in Insulin Secretion in Healthy Offspring of Indian Patients with Maturity-Onset Diabetes of the Young

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Serum C-peptide (CP) and immunoreactive insulin (IRI) responses were studied in 47 euglycemic offspring of patients with maturity-onset diabetes of the young (MODY). Mean IRI responses were not significantly different in nonobese offspring of MODY patients (O-MODY) but they were lower in obese O-MODY than in respective controls. Mean CP responses were low in both groups, the change being more pronounced in obese O-MODY. These findings indicate that alterations of secretion and metabolism of insulin can be detected even before glucose intolerance is seen in O-MODY. *DIABETES CARE* 1986; 9:53-56.

Maturity-onset diabetes of the young (MODY) is a well-documented subgroup of non-insulin-dependent diabetes mellitus (NIDDM) with onset at a young age.^{1,2} Genetically, MODY is characterized by autosomal dominant inheritance.^{3,4} According to autosomal dominant inheritance, if one parent is diabetic, 50% of the offspring ultimately develop diabetes.⁵ Since abnormalities in glucose tolerance tests are seen relatively late even in those with dominantly inherited diabetes,⁶ it is difficult to predict the individuals with the diabetic genotype in a particular family. No early marker has as yet been identified to detect the prediabetic stage of MODY.⁶ A marker would be useful in helping to identify the "prediabetic" individuals in a family.

It is well known that in the prediabetic stage, insulin responses to glucose stimulation are quite heterogeneous and may be high,⁷ normal,⁸ or low.^{9,10} Serum C-peptide (CP) is a more specific index of pancreatic beta cell function¹¹ because, unlike insulin, it does not undergo a significant amount of extraction in the liver.¹² By simultaneous measurement of immunoreactive insulin (IRI) and CP in peripheral circulation, information about pancreatic beta cell secretion as well as the hepatic extraction of the hormone may be obtained.¹³⁻¹⁶

In this study, we have estimated serum CP and IRI responses to glucose load in offspring of MODY (O-MODY) at the stage when they have normal glucose tolerance to determine whether any changes in beta cell function could be detected.

MATERIALS AND METHODS

The study group was composed of 47 O-MODY from families with definite autosomal dominant inheritance of diabetes. The criteria for autosomal dominant inheritance was that of Fraser-Roberts,⁵ which includes vertical transmission of diabetes through three or more generations. Twenty-five age-, sex-, and weight-matched subjects with no family history of diabetes formed the control group. All individuals selected for the study had normal glucose tolerance according to the criteria of the WHO Expert Committee on Diabetes.¹⁷

Oral glucose tolerance tests (OGTT) were done using a 75-g glucose load. Plasma samples collected during the OGTT were kept frozen at -20°C and assayed using the procedure of Heding.¹⁸ The antiserum used was M1230. The sensitivity of the assay was 0.02 pmol/ml and the intra- and interassay coefficients of variation were 5.6% and 9.8%, respectively. Insulin assay was done by the method of Herbert et al.¹⁹ The sensitivity of the assay was 2 $\mu\text{U}/\text{ml}$ and intra- and interassay coefficients of variation were 6.0% and 7.9%, respectively. Plasma glucose was estimated by the O-toluidine method. Coefficients of variation of assays within day and between days were $<5\%$.

The areas under the CP and IRI curves were calculated by adding the values obtained during the OGTT. The values for obese and nonobese O-MODY were compared with those of weight-matched control subjects.

Body mass index (BMI) was calculated by the following formula: $\text{wt}(\text{kg})/\text{ht}^2(\text{m})$. Women with BMI ≥ 25 and men with BMI ≥ 27 were considered obese.

TABLE 1
Clinical details of study groups

	N	Mean age (yr)	BMI	Plasma OGTT (mg/dl)				
				0 min	30 min	60 min	90 min	120 min
Nonobese								
Control	15	26 ± 8	22.0 ± 3	87 ± 11	124 ± 14	117 ± 20	102 ± 21	79 ± 20
O-MODY	39	26 ± 9	22.0 ± 2	85 ± 12	118 ± 10	120 ± 12	108 ± 16	80 ± 18
Obese								
Control	10	28 ± 10	29.1 ± 1.3	89 ± 11	133 ± 18	141 ± 18	125 ± 13	111 ± 9
O-MODY	8	27 ± 8	30.5 ± 2.0	90 ± 12	140 ± 16	142 ± 17	121 ± 12	100 ± 10

All values are mean ± SD.

The Mann-Whitney U-test was used to calculate the significance of the changes in IRI and CP values in O-MODY in comparison with controls.

RESULTS

The clinical details of the study groups are shown in Table 1. The 47 individuals in this study were from 40 different diabetic families. Comparison of mean plasma Σ IRI and Σ CP values in O-MODY and controls is shown in Table 2. Results are presented separately for nonobese and obese groups. The mean IRI value in nonobese O-MODY was not significantly different from the control value, whereas obese O-MODY had lower mean IRI values than controls. The Σ CP values were significantly low in both groups of O-MODY.

Table 3 shows the mean IRI and CP values at the individual time points during the OGTT. In nonobese O-MODY the IRI values were not significantly different from those of the control group. In obese O-MODY the IRI values were lower at 30, 60, 90, and 120 min (5% level). Serum CP values were significantly lower than control values in nonobese O-MODY at 0 and 30 min (5% level). In obese O-MODY the reduction in CP was more marked at all time points of the OGTT (1% level).

A dissociation between fasting and peak IRI and CP values was observed in many O-MODY patients, and this was particularly so for the CP values.

DISCUSSION

MODY patients may exhibit either a high, normal, or low IRI response to glucose load.²⁰ Using the CP assay, we have shown recently that beta cell secretion in MODY is more homogenous and 75% of patients have a low CP level.²¹ Thus when CP is used, MODY patients seem to have lower beta cell response than do control subjects. The normal IRI values could be due to decreased hepatic extraction of insulin commonly seen in NIDDM patients.¹⁶ This study demonstrates that low CP levels are seen even in euglycemic O-MODY and is the first report on CP levels in O-MODY. Only long-term follow-up will show whether the individuals with low CP levels are the ones who ultimately develop diabetes.

It is known that a diminished pancreatic beta cell reserve can be inherited as a genetic trait.²⁰ We have shown recently that the offspring of conjugal diabetic parents in India, who are at increased risk of developing diabetes, have low mean CP levels.²² Interestingly, Bonora et al.,²³ studying a similar group of European subjects, did not find evidence of any defect in pancreatic beta cell response in offspring of conjugal diabetic patients or in those with one diabetic parent.²⁴ This finding may be related to ethnic differences in the genetic factors operating in Indian patients. Further evidence for this hypothesis comes from the observation that the prevalence of diabetes in offspring of conjugal Indian diabetic parents is much higher than that reported in any European population.²⁵ Finally, we²⁶ and others²⁷ have reported that MODY itself is more common in Indians than in Europeans. These studies seem to suggest that genetic influences are stronger in Indian patients. Our finding of low CP levels in Indian O-MODY patients suggests that defects in pancreatic beta cell secretion can be identified years before onset of overt diabetes.

The fact that in the majority of these individuals, the peripheral insulin concentration is maintained at a normal level suggests that there may be alterations in the peripheral metabolism of insulin, the more likely mechanism being a decreased hepatic extraction of insulin, which could be a compensatory mechanism for the low pancreatic beta cell reserve.

In summary, changes in beta cell secretion and insulin metabolism are identifiable in Indian O-MODY patients.

TABLE 2
Insulin and C-peptide secretion during OGTT in O-MODY

	Σ IRI (μ U/ml)	Σ CP (pmol/ml)
Nonobese		
Control (N = 15)	255 ± 70	5.16 ± 1.0
O-MODY (N = 39)	307 ± 148	4.23 ± 1.35
Significance	NS	5% level
Obese		
Control (N = 10)	832 ± 221	9.72 ± 3.0
O-MODY (N = 8)	552 ± 286	4.98 ± 2.15
Significance	5% level	5% level

All values are mean ± SD.

TABLE 3
Insulin and C-peptide responses during individual time points of OGTT in O-MODY

	IRI ($\mu\text{U/ml} \pm \text{SD}$)					CP ($\text{pmol/ml} \pm \text{SD}$)				
	0 min	30 min	60 min	90 min	120 min	0 min	30 min	60 min	90 min	120 min
Nonobese										
Control (N = 15)	13 \pm 6	58 \pm 28	81 \pm 30	65 \pm 23	38 \pm 15	0.61 \pm 0.19	1.11 \pm 0.23	1.41 \pm 0.57	1.56 \pm 0.56	1.35 \pm 0.3
O-MODY (N = 39)	12 \pm 6	94 \pm 69	87 \pm 48	82 \pm 45	50 \pm 38	0.35 \pm 0.2*	0.7 \pm 0.22*	0.94 \pm 0.4	1.31 \pm 0.66	1.0 \pm 0.42
Obese										
Control (N = 10)	28 \pm 12	173 \pm 46	274 \pm 91	210 \pm 83	157 \pm 94	0.98 \pm 0.54	2.72 \pm 1.07	4.11 \pm 1.15	3.23 \pm 1.19	2.77 \pm 1.2
O-MODY (N = 8)	19 \pm 15	93 \pm 52*	138 \pm 74*	124 \pm 95*	73 \pm 56*	0.43 \pm 0.25	0.77 \pm 0.21	1.13 \pm 0.47	1.37 \pm 0.61	1.12 \pm 0.4†

*Significant at 5% level.

†Significant at 1% level at all time points.

The defect is greater in obese individuals, suggesting that early intervention by weight reduction and physical training could be attempted in these individuals to determine whether the ultimate development of diabetes can be prevented. Such a study is now in progress.²⁸

ACKNOWLEDGMENT: We thank Novo Industri A/S, Denmark, for kindly supplying C-peptide kits.

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