C-Peptide Responses to Glucose Load in Maturity-Onset Diabetes of the Young (MODY)

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Pancreatic beta cell responses were measured in obese and nonobese maturity-onset diabetes of the young (MODY) patients by estimating serum immunoreactive insulin (IRI) and C-peptide (CP) during oral glucose tolerance testing (OGTT). The serum CP responses were generally low in MODY patients and more pronounced in obese patients. The IRI responses were heterogenous; some patients had normal and others low responses. It was observed that in several patients there was a relatively higher IRI concentration in comparison with the CP values, as indicated by low CP and normal IRI values. This is suggestive of altered metabolic fates of insulin and CP in the MODY patients. DIABETES CARE 1985; 8:69–72.

The status of maturity-onset diabetes in the young (MODY) as a distinct form of non-insulin-dependent diabetes mellitus (NIDDM) is fairly well established.[1–3] It has been shown that heterogeneity exists even among MODY.[3,4] This is particularly so with reference to insulin response to glucose stimulus.[5–8] Some individuals with MODY have been shown to exhibit high insulin response, while others have low insulin response to glucose.[5–10] The former group does not progress to insulin-dependent diabetes (IDDM), while the latter has been found to do so over a period of time.[5,9]

It is well known that a considerable proportion of insulin undergoes extraction in the liver.[11–15] Hence, the circulating level of immunoreactive insulin (IRI) does not accurately reflect the pancreatic beta cell secretion. Measurement of serum C-peptide (CP) gives better information about the beta cell function. There is only one report on the CP levels in MODY patients.[16] In this study, we have done simultaneous assessment of serum IRI and CP in MODY to study the beta cell secretion and metabolism of insulin in these patients.

MATERIALS AND METHODS

The following groups of patients were studied:

Controls. Nonobese and obese healthy nondiabetic controls with no family history of diabetes. All had normal glucose tolerance.

MODY. Nonobese and obese diabetic patients. All patients designated as MODY satisfied the criteria of Tattersall and Fajans:[2] (1) age at onset of diabetes was <25 yr; (2) correction of fasting hyperglycemia was possible for a minimum period of 2 yr without insulin. No patient in this study was treated with insulin; and (3) all MODY patients in this study had autosomal dominant inheritance with vertical transmission of diabetes through three generations. All probands were drawn from separate families.

The body mass index (BMI) was calculated according to the formula: weight (kg) ÷ height (m^2). Those with BMI values of ≥27 were classified as obese. The IRI and CP responses in the obese and nonobese groups were analyzed separately because of the well-known influence of obesity on these parameters.

Liver and kidney function tests were normal in all patients, as shown by normal blood urea, serum creatinine, SGOT, SGPT, serum proteins, A:G ratio, creatinine clearance, and 24-h proteinuria.

OGTT was performed with 75 g glucose load. All antidiabetic drugs were withdrawn ≥3 days before the OGTT. The National Diabetes Data Group criteria were used for diagnosis of diabetes.[17] Plasma glucose was estimated by the O-toluidine method. Glycosylated hemoglobin (HbA_1) was estimated by the colorimetric procedure of Eross et al.[18] Serum samples were kept frozen at −20°C until the hormone assays were done. IRI was estimated by the method of Herbert et al.[19] Intra- and interassay coefficients of variation of the assay

TABLE 1
Clinical details of the study groups

Groups (no.)	Sex (M/F)	Age (in yr) (mean ± SEM)	Duration of diabetes (in yr) (mean ± SEM)	Body mass index (mean ± SEM)	Plasma glucose (mg/dl ± SEM)					HbA_1 (%) (mean ± SEM)
					Fasting	30 min	60 min	90 min	120 min	
Control										
Nonobese (15)	9/6	26.2 ± 1.8	—	21.5 ± 0.6	88 ± 3	126 ± 4	120 ± 5	106 ± 6	82 ± 8	7.4 ± 0.3
Obese (10)	6/4	22.3 ± 1.6	—	30.1 ± 0.8	89 ± 4	136 ± 6	146 ± 6	125 ± 4	114 ± 3	7.3 ± 0.3
MODY										
Nonobese (15)	10/5	23.2 ± 1.3	7.4 ± 1.8	20.8 ± 0.8	217 ± 21	285 ± 25	337 ± 25	351 ± 27	343 ± 24	11.1 ± 0.8
Obese (11)	6/5	22.6 ± 1.0	6.38 ± 1.3	30.6 ± 0.8	117 ± 19	256 ± 21	316 ± 19	328 ± 25	316 ± 25	10.9 ± 0.7

were 5.6% and 9.8%, respectively. The lower detection limit of the assay was 2 μU/ml. The antibody used in the assay had 67% crossreactivity with proinsulin. C-peptide was estimated by the method of Heding[20] using M-1230 antiserum (Novo Industri, Bagsvaerd, Denmark). The detection limit of the C-peptide assay was 0.02 pmol/ml. The intra- and interassay coefficients of variation were 5.8% and 8.6%, respectively. The area under the IRI (ΣIRI) and CP (ΣCP) curves were obtained by adding the values at the five time intervals of OGTT.

As the IRI and CP values did not show Guassian type of distribution, the Mann-Whitney U-test was applied for comparison of the results.

RESULTS

Table 1 shows the clinical details of the study groups. The plasma glucose and HbA_1 values were comparable in the obese and nonobese MODY during the OGTT. Figure 1 shows the mean IRI and CP values in the obese and nonobese patients in comparison with the weight-matched controls. The IRI values in the

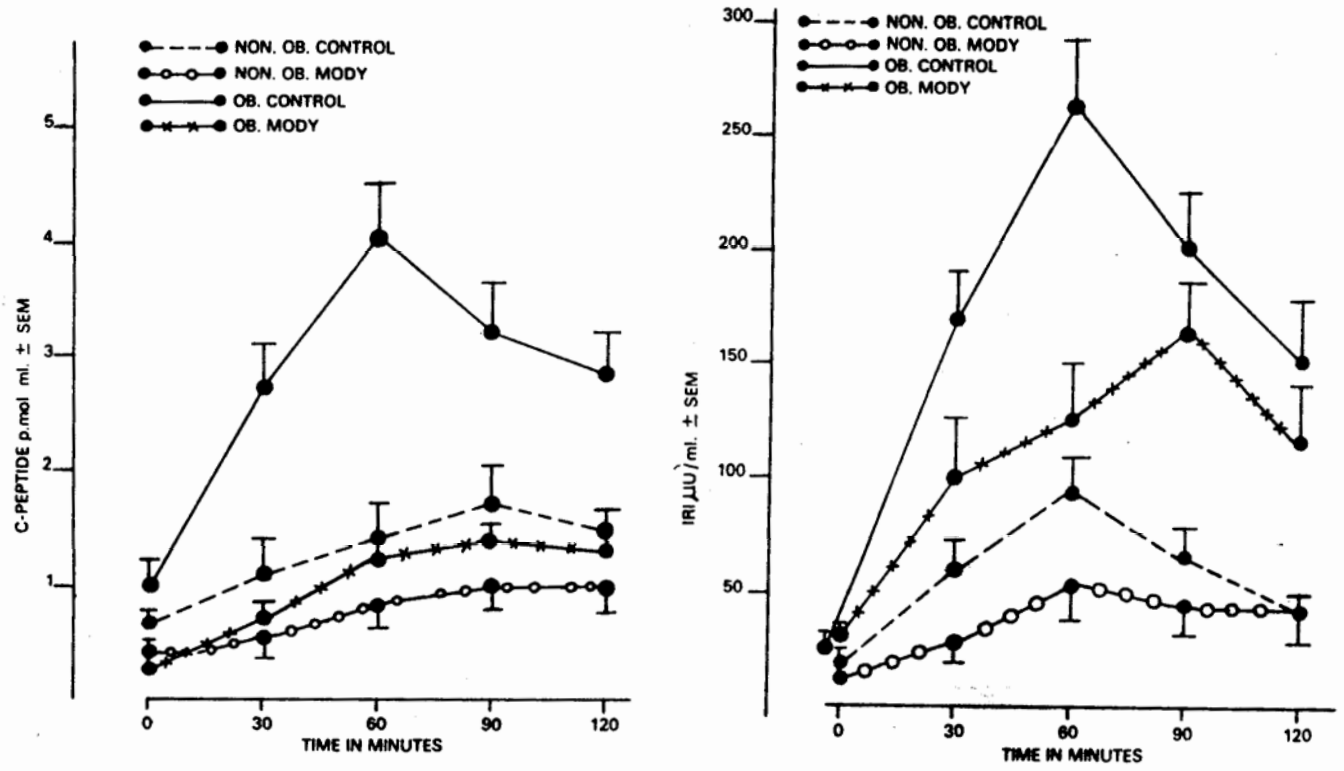

FIG. 1. IRI and CP responses in nonobese and obese MODY patients in comparison with weight-matched controls.

TABLE 2
ΣIRI and ΣCP in the study groups

	ΣIRI (μU/ml) (mean ± SEM)	ΣCP (pmol/ml) (mean ± SEM)
Nonobese		
Control	280 ± 24	5.2 ± 0.28
MODY	172 ± 27	3.23 ± 0.45
	$P < 0.01$	$P < 0.01$
Obese		
Control	825 ± 89	13.63 ± 0.85
MODY	520 ± 108	3.93 ± 0.7
	$P < 0.05$	$P < 0.01$

obese and the nonobese MODY were significantly low ($P < 0.01$ at 30, 60, and 90 min). The CP concentrations were decreased significantly ($P < 0.01$ at all time intervals) in both groups of MODY.

Table 2 shows the ΣIRI and ΣCP values in the different study groups. In the nonobese and obese MODY the ΣIRI was found to be low ($P < 0.01$ and $P < 0.05$, respectively). ΣCP was also lower in both MODY groups ($P < 0.01$). The decrease in the obese group is more marked than in the nonobese group. The ΣIRI was found to be low in 53% of nonobese MODY; the other 47% had normal ΣIRI. In the same group 67% had low ΣCP. In the obese patients, 64% had low ΣIRI and 90% had low ΣCP.

DISCUSSION

Serum CP concentrations are found to be generally low in the MODY patients. Sixty-seven percent of the nonobese and 90% of the obese MODY have poor and the remaining patients have normal CP responses to glucose load. The insulin responses, however, are different. In 14% of the nonobese and 26% of the obese patients, the IRI values were normal, despite low CP concentrations. This relatively higher concentration of insulin in circulation could theoretically be due to (1) decreased extraction of insulin by the liver[21]; (2) decreased degradation of insulin at the receptor level; (3) the presence of greater proportion of proinsulin in circulation, which crossreacts with insulin antibody; or (4) altered metabolism of CP. An enhanced metabolism of CP is unlikely to be the contributing factor since the patients studied have no renal complications and their glomerular filtration rate (GFR) values were also within the normal limits. Faber et al.[22] have shown by a constant infusion study that the metabolic clearance rate of CP does not vary at different concentrations.

Studies by Rossell et al.[23] have demonstrated that the proinsulin/insulin ratios are normal in obese individuals with impaired IRI/CP ratios. However, the contribution of proinsulin to the elevated IRI values may vary in diabetes, and warrants direct assay of proinsulin. Because insulin is a hormone degraded mainly at the hepatic level, an alteration in the handling of insulin at the hepatic level in diabetic patients is also a possibility.[20–25] The role of insulin receptors in regulating insulin level has also been recently recognized.[26,27]

The insulin concentrations in obese controls in this study are higher than those reported in Caucasian populations, but are comparable with those seen in the Pima Indians.[28] With regard to insulin responses in MODY, we noticed only two types of responses; i.e., normal and low. The absence of high insulin responses as observed by Fajans et al.[5] is probably due to the more severe glucose intolerance present in our patients. This is because our patients were all diabetic and satisfied the higher plasma glucose criteria recommended by the National Diabetes Data group for diagnosis of diabetes, whereas the study group of Fajans consisted of individuals with "chemical" diabetes. Most of his patients would be classified under the category of impaired glucose tolerance by the above classification.

In this study the CP values in MODY are found to be decreased, but these changes are not always reflected in the IRI values. Ikeda et al.[16] have also reported that the mean ΣCP in nonobese MODY is lower than the control values. But in their study, serum IRI was not estimated. Simultaneous measurement of insulin and CP in blood is found to be more useful because it gives a better idea of the pancreatic beta cell secretion and the metabolism of insulin. The explanation for the differences in the IRI and CP levels can come only from direct metabolic clearance studies.

To summarize, while insulin levels in MODY may be either normal or low, the CP levels appear to be generally low in most patients with this form of diabetes.

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