

## ABNORMALITIES IN INSULIN RESPONSE TO INTRAVENOUS GLUCOSE IN OFFSPRING OF CONJUGAL (TYPE 2) DIABETIC PARENTS

A Ramachandran\*, C Snehalatha\*\*, V Mohan\*, M Viswanathan\*\*\*

### SUMMARY

Glucose and insulin responses were measured during intravenous glucose tolerance test in 12 normal controls and 16 normoglycaemic adult offspring of conjugal diabetic parents. The glucose response curve and the glucose disposal rate in the offspring were not different from the normal pattern. These subjects elicited a lower first phase insulin (0-10 minutes area under the curve,  $p = 0.04$ ), lower peak immunoreactive insulin response ( $p = 0.032$ ) and also showed a delay in the first phase ( $p = 0.037$ ) compared to control values. The second phase of insulin (11-120 minutes area) was not significantly different in the two groups.

These changes could serve as early markers of diabetes in offspring of conjugal diabetic parents.

**Key Words:** Intravenous glucose tolerance, biochemical markers.

### INTRODUCTION

Earlier studies from our centre have shown that the prevalence of diabetes among the offspring of conjugal diabetic parents (OCDP) in southern India is much higher than that reported in Europeans.<sup>1</sup> Studies on normoglycemic OCDP using oral glucose load showed abnormalities in pancreatic beta cell responses.<sup>2</sup> Intravenous glucose tolerance test (IVGTT) has certain advantages over oral glucose stimulation because of the absence of confounding influences of the gastrointestinal hormones.<sup>3</sup> Earlier workers have used this technique to study European 'prediabetic' individuals.<sup>4-6</sup> In this paper, we report the findings on insulin responses to IVGTT in a group of Indian OCDP subjects.

### MATERIAL AND METHODS

Standard IVGTT was done in 12 normal controls with no known family history of diabetes and 16 normoglycemic adult OCDP. In every instance, both parents had NIDDM. All OCDP underwent an oral GTT with 75 g glucose load 2-3 days prior to the IVGTT. All had normal glucose values according to the WHO Study Group criteria.<sup>7</sup> All subjects reported to the clinic in the morning after an overnight fast of 10 to 12 hours. An indwelling cannula was inserted into the antecubital vein and the subject remained in bed throughout the test. Blood samples were drawn from the indwelling cannula at - 10, 0, 1, 2, 3, 5, 7, 10, 15, 20, 25, 30, 40, 50, 60, 90 and 120 minutes for analysis of plasma glucose and immunoreactive insulin (IRI). A glucose load of 0.5 g/kg body weight was infused after the basal samples were drawn from the antecubital vein of the opposite arm. The glucose disposal ( $K_G$ ) was calculated using the formula  $K_G = 69.3 \div t/2$ .<sup>8</sup> The time in minutes required for the

plasma glucose to decrease from the peak to half the value was designated as  $t/2$ . Samples were collected in EDTA. Plasma glucose was estimated by glucose oxidase-PAP method (Boehringer Mannheim, West Germany). IRI was estimated by a modified method of Herbert *et al*,<sup>9</sup> using the RIA kit supplied by the Bhabha Atomic Research Centre, Bombay. The intra and inter assay coefficients of variations were 6.5% and 8.2% respectively.

The area under the insulin curve between 0 and 10 minutes was obtained by summing up the insulin values (0 minute value = mean of - 10 and zero minute) and was designated as phase 1. The remaining values were summed up and designated as phase 2.

### STATISTICAL ANALYSIS

Values are represented as mean  $\pm$  SEM. Wilcoxon's rank sum test was used to calculate the difference between the group means.

### RESULTS

Fig. 1 shows the plasma glucose and the IRI responses in the controls and the OCDP. The glucose response were not significantly different in the two groups. The glucose disposal constant,  $K_G$ , was normal in all OCDP. The mean  $K_G$  values in the controls and OCDP were  $2.34 \pm 0.26$  and  $2.1 \pm 0.2$  respectively.

OCDP elicited a lower first phase IRI response (Table). The peak IRI response was lower and delayed in the OCDP. The second phase of IRI response was not significantly different in the OCDP compared to controls, Fig. 2 shows the scatter of  $\Sigma$  IRI-1 and  $\Sigma$  IRI-2 in the controls and OCDP.

### DISCUSSION

The insulin secretion and glucose disposal rate in response to intravenous glucose administration were studied in adult offspring of conjugal diabetic (NIDDM) parents. The glucose disposal ( $K_G$ ) was not significantly different in OCDP compared to normal controls. But the

\*Deputy Director; \*\*Head, Department of Biochemistry; \*\*\*Director, Diabetes Research Centre and MV Hospital for Diabetes, Madras.

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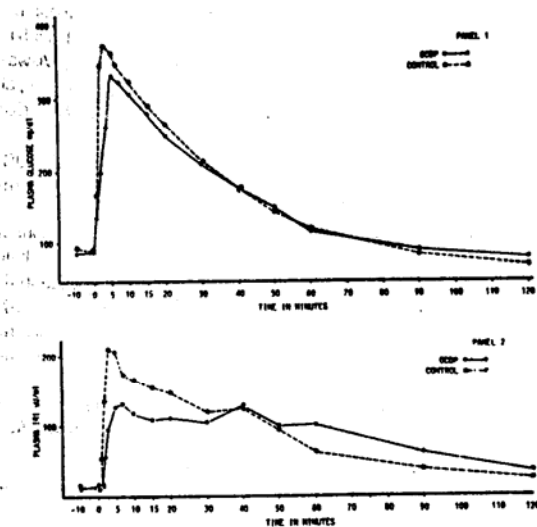


Fig 1: Mean glucose (Panel 1) and IRI responses (Panel 2) during IVGTT in OCDP in comparison with controls.

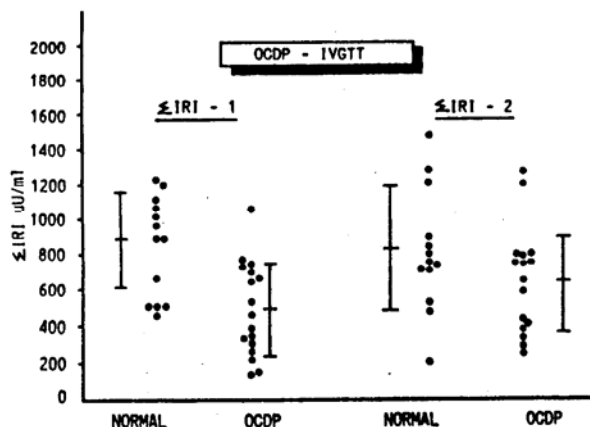


Fig 2: Scatter of  $\Sigma$  IRI values in the first ( $\Sigma$  IRI-1) and second ( $\Sigma$  IRI-2) phase during IVGTT in normal individuals and OCDP.

insulin responses were lower. The acute phase (Phase 1) of insulin secretion was both delayed and diminished significantly. The second phase of insulin secretion did not show any statistically significant deviations from the normal.

Although delayed insulin peak in response to intravenous glucose has been demonstrated among European 'prediabetics'<sup>4-6</sup> the results of the present study is significant because of the higher risk of diabetes in Indian OCDP compared to the Europeans.<sup>1</sup> In our earlier study<sup>1</sup> in 580 OCDP, 62% had evidence of carbohydrate intolerance and this is the highest figure reported compared to identical study subjects from other ethnic groups. The insulin secretion in response to oral glucose load in normoglycaemic

Table: Clinical and Biochemical Parameters in the Study Groups

	Controls	OCDP	P value
M:F	7:5	11:5	
Age (years)	26 ± 2.1	29 ± 1.8	NS
BMI (kg/m <sup>2</sup> )	26 ± 2.1	27.1 ± 2.0	NS
K <sub>a</sub>	2.34 ± 0.26	2.1 ± 0.2	NS
Phase 1 (0-10')			
$\Sigma$ IRI (uU/ml)	876 ± 80	543 ± 67	0.04
Peak time (min)	4.2 ± 0.7	7 ± 0.8	0.037
Peak IRI (uU/ml)	254 ± 27	164 ± 24	0.032
Phase 2 (11-120')			
$\Sigma$ IRI (uU/ml)	832 ± 102	713 ± 103	NS
Peak time (min)	25 ± 3.5	35 ± 2.7	NS
Peak IRI (uU/ml)	197 ± 34	164 ± 24	NS

All values are mean ± SEM.

lycaemic OCDP also showed abnormal beta cell function compared to weight-matched controls.<sup>2</sup> More interestingly recent work from our centre showed abnormalities in insulin binding to erythrocytes in normoglycaemic OCDP.<sup>10</sup> Thus it is reasonable to conclude that normoglycaemic OCDP have not only beta cell secretory defect but also abnormal peripheral insulin action. These abnormalities precede the development of carbohydrate intolerance. Impaired first phase insulin response to glucose has been demonstrated several years prior to onset of Type I diabetes also, which further shows that insulin secretory defect may be a prerequisite for the development of diabetes.<sup>11</sup>

The first phase peak IRI response in normal controls was also slightly delayed compared to the reported value by Konec *et al.*<sup>6</sup> This could also be an ethnic difference similar to that noted in the IRI response to oral glucose load in Indians compared to Europeans.<sup>12</sup> The loss of first phase insulin secretion by infusion of somatostatin produced lowered glucose tolerance and blunted glucose induced thermogenesis in normal volunteers<sup>13</sup>. Ferner *et al.*<sup>14</sup> have demonstrated that hyperglycaemia *per se* influences insulin secretion during IV glucose infusion. In our study there was no significant difference in the serum glucose concentrations between controls and OCDP and therefore the difference in the IRI responses could not have been influenced by the plasma glucose concentration.

The abnormal first phase of insulin demonstrated in the normoglycaemic OCDP in this study shows that insulin secretory defect probably precedes other abnormalities in the causation of diabetes. This could serve as an early marker of diabetes in them.

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