

## PANCREATIC BETA CELL FUNCTION IN NORMOGLYCAEMIC OFFSPRING OF DIABETIC PARENTS

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

### ABSTRACT

The aim of the study was to look for any time-related fluctuation in the pancreatic beta cell function in normal offspring of diabetic parents, over a period of three years. Serum insulin (IRI) and C-peptide (CP) responses to oral glucose were reevaluated three years after the initial study in 25 normoglycaemic offspring of conjugal Type 2 diabetic parents. The mean area under the curve of IRI (AUC IRI) response was higher than normal control value in the offspring at both time points ( $P < 0.01$ ) and the two values did not differ much. The 2 hr IRI was also significantly higher ( $P < 0.05$ ) than the control value. CP responses at both time points in the offspring did not differ from the mean control value. Wide fluctuations in the individual IRI were noted on follow-up despite similar plasma glucose response. Follow-up IRI was higher in 6, lower in 5 ( $\pm 25\%$  of the initial) and remained unaltered in the other 4 offspring. The corresponding CP showed increased values in 3, decreased values in 5 and no change in 7 offspring. The fluctuations were nonuniform in nature among the individuals studied. Disparity between the IRI and CP responses were present in 5 offspring during the follow-up. This study thus shows that wide fluctuations in insulin responses occur even in the normoglycaemic offspring of diabetic parents.

### INTRODUCTION

Study of the beta cell responses in normoglycaemic offspring of diabetic parents is important to understand the natural history of diabetes. Results of such studies have been inconsistent. Normal,<sup>1-3</sup> low<sup>4-6</sup> and high<sup>7-12</sup> insulin (IRI) responses have been demonstrated by different groups of workers. Similarly, while a high IRI response is considered to be predictive of diabetes by some,<sup>12-14</sup> others believe low response to be the forerunner of the disease.<sup>15</sup> Although ethnic variations play a significant role in producing different findings, they cannot explain the spectrum of changes demonstrated in the above reports.

Low C-peptide (CP) response with higher than normal IRI values have been noted by us in the offspring suggesting the possibility of peripheral metabolic alterations which produce higher proportions of circulating IRI.<sup>7,8,16</sup>

The aim of the present study was to find out whether IRI and CP responses showed time-related alterations in normoglycaemic offspring of diabetic parents. Therefore, we reevaluated CP and IRI responses during oral glucose tolerance test (OGTT) in these subjects, 3 years after an initial assessment. We chose offsprings of Type 2 diabetic parents because of

their strong genetic predisposition to diabetes.<sup>17</sup>

### MATERIAL AND METHODS

Twenty seven offsprings from 26 families who had normal glucose tolerance (2 hr standard OGTT with 75 gm glucose load) were available for a 3 year review between October 1989 to July 1990. The clinical details are shown in Table 1. None of the offspring was obese (BMI  $\geq 25$  kg/m<sup>2</sup> for female and BMI  $\geq 27$  kg/m<sup>2</sup> for male); all were in good health and did not take any medication. The dietary habits were almost similar in all of them. In every case, both parents had Type 2 diabetes. Based on a retest with 2 hr OGTT, using the WHO study group report recommendations,<sup>18</sup> 15 offspring were found to have normal glucose tolerance. Three had developed diabetes, 6 had impaired glucose tolerance and 3 others had very early glucose intolerance with only an elevated peak glucose response. Only the results in 15 offspring with normal glucose tolerance were analysed.

During the initial and follow-up GTT, fasting and halfhourly post-glucose plasma samples were collected in EDTA for the estimation of glucose (glucose oxidase, Boehringer Mannheim reagents), IRI and CP measurements. IRI was estimated by a modified method of Herbert *et al*<sup>19</sup> using a double antibody procedure (kit from Bhabha Atomic Research Centre, Bombay). The sensitivity, intra and interassay coefficients of variations of the assay were 2 uU/ml, 4.8% and 7.5% respectively. CP measurement was done using the RIA kit of Diagnostic Products Corporation, U.S.A. The sensitivity of the assay was 0.03 nmol/l and the intra and interassay coefficients of variations were 5.2% and 7.6%.

The AUC of glucose, IRI and CP were calculated using Haffner's formula.<sup>10</sup> IRI to glucose ratios were calculated by dividing the AUC of IRI (uU/ml) by the corresponding AUC of glucose (mg/dl).

Fifteen healthy volunteers, with no family history of diabetes, matched for age, the body mass index (BMI = kg/m<sup>2</sup>) and dietary habits were also studied. All the controls and offsprings were non-obese and all of them had normal glucose tolerance during a standard OGTT with 75 gm glucose load.

Statistical comparisons were made using 't' tests: non-paired

\*Head, Dept of Biochemistry; \*\*Research Assistant; \*\*\*Deputy Director; \*\*\*\*Director, Diabetes Research Centre & MV Hospital for Diabetes, 5, Main Road, Royapuram, Madras - 600 013. Received: 3.3.1992.

Table 1: Clinical and Biochemical Details of the Offspring in Relation to the Control Group

	Control (n = 15)	Initial (n = 15)	Follow-up (n = 15)
M : F ratio	8:7	9:6	9:6
Age (years)	31.2 ± 8.6	32.4 ± 9.5	35.4 ± 9.5
BMI (kg/m <sup>2</sup> )	23.6 ± 3.0	23.5 ± 2.7	25.0 ± 4.6
<b>Glucose (mg/dl)</b>			
Fasting	85 ± 11	90 ± 15	94 ± 16
2 hr	94 ± 13	96 ± 12	107 ± 17
AUC	222 ± 17	233 ± 31	250 ± 28
<b>IRI (uU/ml)</b>			
Fasting	13 ± 6	14 ± 10	18 ± 11
2 hr	38 ± 15	89 ± 99**	94 ± 63
AUC	112 ± 32	202 ± 131*	190 ± 129
<b>I/G ratio</b>			
CP (nmol/l)	0.5 ± 0.15	0.85 ± 0.51**	0.87 ± 0.6
Fasting	0.61 ± 0.2	0.58 ± 0.26	0.60 ± 0.2
2 hr	1.65 ± 0.55	1.48 ± 1.0	1.36 ± 0.96
AUC	2.5 ± 0.47	2.52 ± 1.25	2.32 ± 1.16

\*P < 0.01; \*\*P < 0.05 compared with controls  
All values are mean ± SD.

for comparison of the controls vs offspring and paired for comparison of the two values in offsprings.

## RESULTS

Table 1 shows the results in the controls and the offsprings.

### Initial values :

The initial mean AUC IRI in the offspring was significantly higher ( $P < 0.01$ ) than the control value, despite the AUC glucose being similar in both the groups. The I/G ratio in the offspring was therefore higher ( $P < 0.05$ ) than the control value. The fasting IRI value in the offspring did not differ from the control value; but the 2 hr IRI was significantly higher ( $P < 0.05$ ). CP response in the offsprings did not differ from the mean control value.

### Follow-up results

There was no significant change in the BMI of the offspring during the follow up period. The maximum gain or loss of weight noted was 4 kg, and these changes had no correlation with the changes in IRI or CP values. Comparison of the mean values at the 1st and 2nd testing showed no significant changes in the various biochemical parameters. The fasting IRI value was slightly higher on follow up; but the difference was statistically non-significant. However when the initial and follow up values of individual offsprings were compared, significant variations were observed in the IRI and CP patterns. The results are shown in figure 1. On account of wide individual variations in the IRI values in the offspring and their significant difference from the mean control values, the follow-up changes in the offspring could not be evaluated in comparison with the control values. An arbitrary cut off point was therefore chosen based on the initial values in each offspring. If the follow-up value differed from the initial value by  $\pm 25\%$  (a quartile), it was considered to be different. The follow-up IRI was higher in 6, lower in 5 and remained unaltered in 4 offsprings. Reduction in IRI was noted only in those who had higher than normal values initially. The corresponding CP showed increased values in 3, decreased values in 5 and no change in 7 offspring. Disparity between the IRI and CP responses was noted in 5 off-

spring on follow-up (Figure 2).

The changes in IRI responses and I/G ratios showed an identical pattern as shown in the panels 1 and 3 of the figure. The mean I/G ratios at the two periods of study were also similar ( $0.85 \pm 0.51$  and  $0.87 \pm 0.6$ ).

## DISCUSSION

Widely varied IRI responses have been reported in nondiabetic offsprings of diabetic parents. Offsprings of two diabetic parents have been chosen for the study as they are found to be having a high risk of developing diabetes.<sup>17</sup> Our earlier observation that the mean IRI response to glucose stimulation is higher in the offsprings is confirmed in this study also.<sup>7,8,14</sup> In this study, we have analysed the CP and IRI responses in normoglycaemic offsprings at two intervals of time. In response to similar plasma glucose values, IRI and CP responses in the same individual show wide fluctuations and a nonuniform pattern is seen among different offsprings. Moreover, in some offsprings, dissociation between CP and the corresponding IRI responses is observed indicating the possibility of alterations in the peripheral metabolism of these peptides. Evidence for such metabolic alterations in insulin have been reported by some workers.<sup>16</sup> The I/G ratios change in the same fashion as the insulin ruling out the possibility of any fluctuation in glucose being the cause for the changes in IRI response.

High or low IRI concentrations have been demonstrated in the same person at different stages of diabetes.<sup>20</sup> Fluctuating beta cell responses in normoglycaemic state have not been reported so far. The

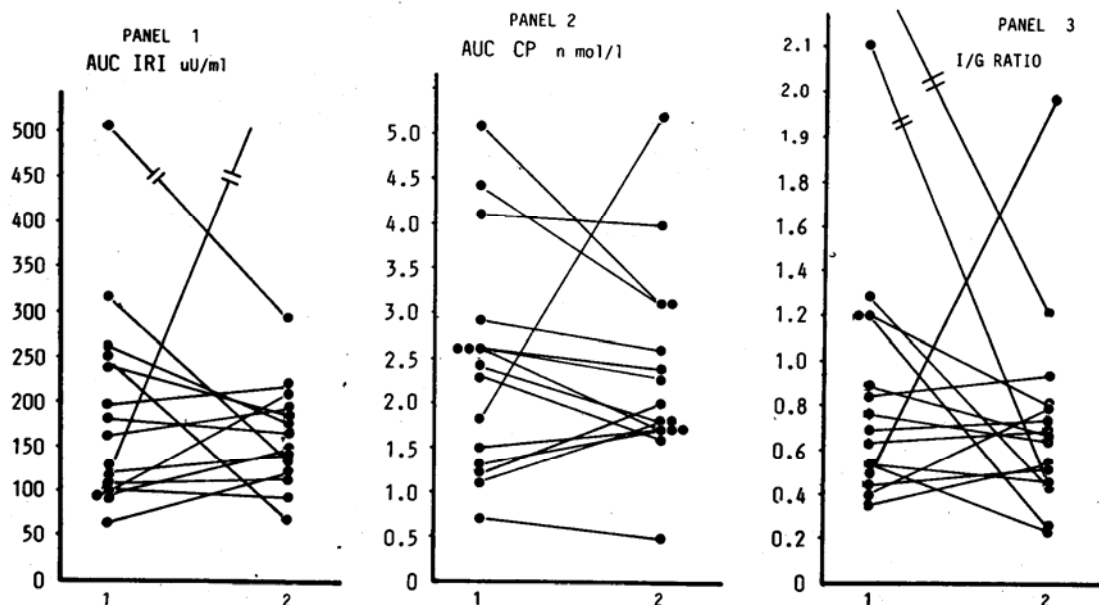


Fig. 1: Panel 1 Shows the AUC IRI in each offspring, during the 1st and 2nd analysis. Panel 2 Shows the changes in AUC CP during the two time periods of study. Panel 3 Shows the corresponding changes in I/G ratios in the same individuals. X axis - 1. Initial 2. Follow-up, Y axis shows the values of corresponding parameters.

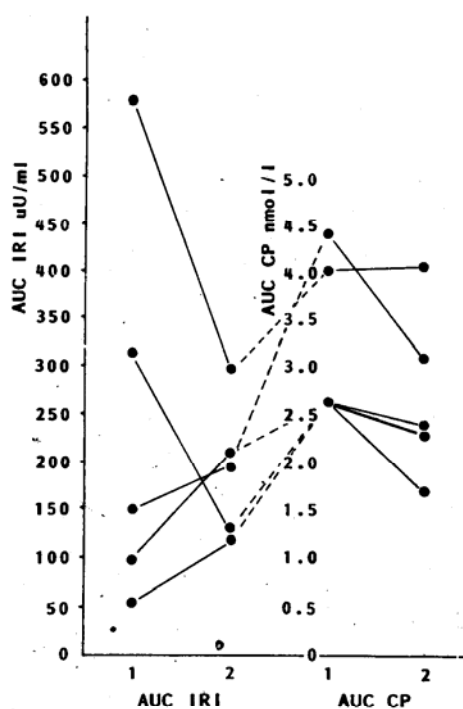


Fig. 2: AUC IRI and AUC CP values in 5 individuals, during the initial follow-up assessments. The IRI and CP values are joined by dotted line so that the individual patterns can be identified.

x axis - 1. Initial 2. Follow-up

reasons for the fluctuations are speculative. It may be due to the development of insulin resistance or due to the beta cell inefficiency. However it is important to consider the fact that, in a prediabetic individual, a normal glucose concentration could produce widely varied IRI responses at different periods and this may probably be an important reason for the inconsistent findings on IRI responses in cross-sectional studies conducted in such individuals. Serial estimations of IRI and CP values are required in the offspring in order to understand the sequence of changes occurring in these individuals. A random estimation may be of limited value.

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## ANNOUNCEMENT

**International Esophageal Motility Workshop** will be held from November 18-20, 1994.

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