

IMMUNO REACTIVE INSULIN RESPONSES TO GLYCEMIC STIMULUS IN MATURITY ONSET DIABETICS EFFECT OF SEVERITY AND BODY WEIGHT

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SUMMARY Immuno Reactive Insulin (IRI) responses to oral glucose load were measured in 77 newly detected maturity onset diabetics. The IRI responses were studied with respect to two parameters viz. severity of diabetes and body weight. The study subjects were divided into mild, moderate and severe diabetics according to the severity of hyperglycemia. In general the mild and moderate diabetics showed a higher than normal IRI output. The insulin response became flat with increasing severity of the disease.

Obesity had a significant impact on IRI response. Mild and moderate diabetics with obesity exhibited hyperinsulinism in comparison with the patients with ideal body weight. In severe diabetics, obesity had no impact on insulin secretion.

The IRI patterns were further classified into flat, low, normal and exaggerated type based on the peak concentration. While flat response was commoner in severe diabetics and exaggerated response in mild diabetics, there were a lot of intra-group variations.

INTRODUCTION

The development of radioimmunoassay has provided a sensitive and specific method of measuring the plasma insulin levels. There have been a few studies on

Immuno Reactive Insulin (IRI) levels in Indian diabetics.¹⁻⁴ It has been recognised that diabetes in India differs from that seen elsewhere in certain aspects like its milder clinical course, low incidence of obesity and relative infrequency of ketosis^{5, 6} This paper presents the results of a study of the correlation between IRI responses and severity of diabetes and also the body weight of the individual.

MATERIAL AND METHODS

The study group comprised of 77 newly detected maturity onset diabetics attending the Diabetes Research Centre, Madras. A group of twenty normal volunteers served as controls. There were 55 men and 22 women patients in the age group of 30-70 years. None of the subjects were receiving oral hypoglycemic agents at the time of the study and none of them had ever been treated with insulin.

Standard oral G.T.T. was performed in all the patients. Patients were given glucose loads of 50, 75 or 100 gms depending whether they were lean, of ideal body weight or obese. Blood sugar was estimated by the method of Somogyi.⁷ Diagnosis of diabetes was made using the criteria of Fajans.⁸

Radioimmunoassay of insulin was performed by the method of Herbert *et al*⁹ using dextran coated activated charcoal to separate the free and bound insulin. The Radio Immuno Assay Insulin Kit supplied by the Bhabha Atomic Research Centre, Bombay, was used.

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GROUPING OF PATIENTS

(a) *Severity of diabetes:* Diabetics were classified into three groups based on the fasting blood sugar levels as follows:

Mild	< 120 mgs/100 ml
Moderate	121 to 180 mgs/100 ml
Severe	> 181 mgs/100 ml

(b) *Body weight:* The ideal body weight was determined from the chart supplied by the Life Insurance Corporation, India. Subjects with 115% of ideal body weight or more were classified as obese and those below 85% as lean.

(c) *Insulin response:* A classification was adopted by us to grade insulin response using the peak value of insulin as follows:

Flat	< 25 μ u/ml
Low	25-50 μ u/ml
Normal	51-160 μ u/ml
Exaggerated	> 160 μ u/ml

RESULTS

In the control group, the fasting insulin level varied between 4-30 μ u/ml with a mean value of 13.5 ± 2.3 (S.E.M.) μ u/ml. The peak concentration was 85.6 ± 1.6 (S.E.M.) μ u/ml and was obtained either at 30' or 60'. The insulin concentration dropped gradually to basal levels by two hours.

Severity of diabetes and serum insulin: There were 32 mild, 29 moderate and 16 severe diabetics in the study group. Table 1 details the mean fasting blood sugar and mean IRI values obtained during G.T.T. in the normal volunteers and the three groups of diabetics. Figure 1 represents the same data graphically.

The mild and moderate groups of diabetics showed an overall higher output of insulin in comparison with the control group. In both these groups the 2 hour

TABLE 1.—Fasting Blood Sugar and Serum Insulin Response in the Study Group

Study group	Total Number	Fasting blood sugar mg% (SEM)	Fasting	IRI μ U/ml \pm S.E.M.		
				30'	60'	90'
Control	20	82.8 ± 3.0	13.5 ± 2.3	74.8 ± 7.5	85.6 ± 1.6	47.9 ± 5.7
Mild Diabetics	32	95.0 ± 2.3	11.4 ± 1.3	53.3 ± 8.2	84.3 ± 9.9	$83.3 \pm 10.4^*$
Moderate Diabetics	29	154.8 ± 23.9	17.9 ± 2.0	35.3 ± 4.8	75.1 ± 17.7	73.7 ± 15.5
Severe Diabetics	16	206.3 ± 9.4	11.7 ± 2.0	$17.7 \pm 4.5^{**}$	$27.9 \pm 6.3^{**}$	29.1 ± 7.5
						$68 \pm 10.7^{**}$
						$69.8 \pm 15.0^{**}$
						25.3 ± 6.9

*P < 0.01 with reference to the control group.

**P < 0.001 with reference to the control group.

Level of significance was negligible at other intervals.

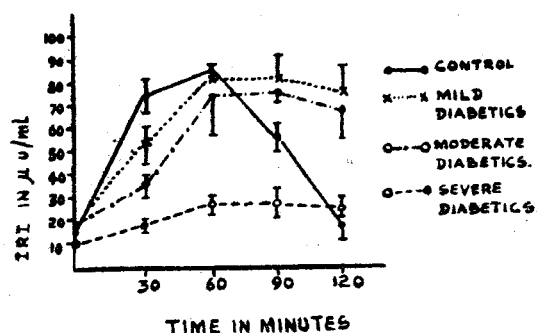


Fig. 1. Serum Insulin Responses in Mild, Moderate and Severe Diabetics.

IRI values were considerably higher than in the controls. ($P < 0.001$). In the severe diabetics the insulin output was low, the mean peak value being 29.1 ± 7.5 (S.E.M.) μ u/ml. The fasting insulin values remained within normal limits in all the three groups. No correlation was seen between the fasting insulin and the fasting blood sugar concentration.

Table 2 shows the analysis of the IRI levels in relation to the two hour post glucose levels (P.G.). Patients with 2 hour P.G. values below 250 mg% exhibited higher output of IRI than the normal controls. Thereafter a gradual lowering in insulin concentration was noted. The level became negligible with 2 hour P.G. values above 350 mg%.

Obesity and insulin response: The study group consisted of 62 subjects with ideal body weight, 12 obese and 3 lean subjects. Mean insulin values of individual groups are shown in Table 3. The same data is shown diagrammatically in Figure 2.

The obese diabetics in general showed a significantly higher insulin output than the other two groups. All the lean diabetics showed flat insulin response to glucose stimulus but the data could not be analysed statistically due to the small number in this group.

Combined effect of severity and body

TABLE 2.—Insulin Response in Relation to the 2 Hour Post Glucose Blood Sugar Value

P.G. Blood sugar value	No. of patients	Fasting	IRI μ U/ml \pm S.E.M.			
			30'	60'	90'	120'
< 120 mg%	14	8.3 ± 2.1	60.0 ± 11.5	68.8 ± 12.1	60.8 ± 10.0	34.6 ± 9.6
121-150 mg%	11	12.7 ± 2.1	72.5 ± 18.6	115.6 ± 23.1	72.3 ± 24.6	62.9 ± 22.5
151-200 mg%	17	11.5 ± 1.7	40.0 ± 5.2	73.4 ± 9.3	99.1 ± 17.0	84.2 ± 16.5
200-250 mg%	13	24.3 ± 6.3	40.0 ± 9.2	106.6 ± 36.3	76.2 ± 34.2	83.0 ± 32.3
250-300 mg%	11	13.3 ± 1.4	27.8 ± 5.8	42.8 ± 10.0	48.2 ± 12.8	49.6 ± 13.3
300-350 mg%	6	13.3 ± 9.7	26.1 ± 10.4	44.0 ± 10.8	47.5 ± 16.6	44.4 ± 13.3
> 350 mg%	5	13.6 ± 3.2	17.8 ± 2.6	21.2 ± 2.8	25.8 ± 3.3	22.0 ± 6.2

TABLE 3.—Insulin Responses in Ideal Body Weight, Obese and Lean Diabetics

Group of Diabetics	Number of patients	Fasting	Insulin values in $\mu\text{U/ml} \pm \text{S.E.M.}$			
			30'	60'	90'	120'
Ideal body weight	62	12.2 \pm 1.1	35.9 \pm 6.2	64.8 \pm 10.0	62.9 \pm 8.8	54.2 \pm 11.4
Obese	12	24.3 \pm 1.9	61.4 \pm 9.6	125.0 \pm 35.1	123.3 \pm 32.8	109.8 \pm 33.7
Lean	3	13.3 \pm 1.1*	9.8 \pm 3.5***	14.0 \pm 3.9*	18.3 \pm 8.2*	17.7 \pm 3.61***

***P<0.05 in comparison with the ideal body weight.

*P<0.01 in comparison with the ideal body weight.

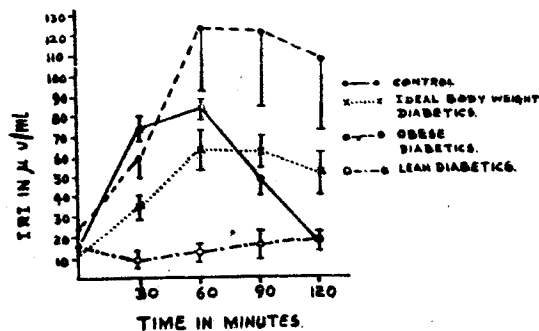


Fig. 2. Insulin Responses in Ideal Body Weight, Obese and Lean Diabetics.

weight: The mild, moderate and severe diabetics were further subdivided based on their body weight. Table 4 and Figure 3 show the break-up of these groups accordingly. Obesity caused an increase in insulin response in the mild and moderate diabetics but failed to do so in severe diabetics. The moderate diabetics with obesity in this study, exhibited markedly elevated insulin response and even the fasting insulin level was found to be elevated.

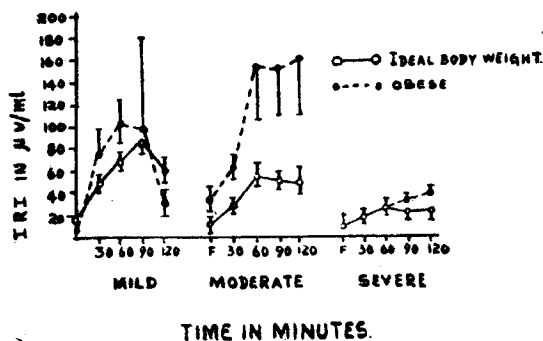


Fig. 3. Insulin Responses—Combined Effect of Severity of Diabetes and Body Weight.

An analysis of data was done based on the insulin response using the criteria described earlier. The four types of response which were obtained namely, flat, low, normal and exaggerated were then correlated with the severity of diabetes.

TABLE 4.—Insulin Response—Effect of Obesity in the Different Groups of Diabetics

Group of diabetics	Body weight	No. of patients	Fasting	Insulin values in $\mu\text{U/ml} \pm \text{S.E.M.}$			
				30'	60'	90'	120'
Mild	Ideal body weight	29	11.8 \pm 1.3	49.9 \pm 8.7	79.0 \pm 10.6	89.9 \pm 10.6	60.0 \pm 13.2
	Obese	3	7.3 \pm 1.9	76.7 \pm 20.8	105.0 \pm 22.8	103.3 \pm 85.8	33.8 \pm 13.8
Moderate	Ideal body weight	22	12.3 \pm 0.9	28.8 \pm 3.8	58.0 \pm 13	52.2 \pm 8.6	53.6 \pm 11.5
	Obese	7	35.3 \pm 77**	65.5 \pm 10.8**	161.3 \pm 54**	158.3 \pm 47**	162.9 \pm 48.2**
Severe	Ideal body weight	14	12.6 \pm 3.5	18.6 \pm 5.0	29.4 \pm 7.0	26.1 \pm 9.2	23.4 \pm 7.8
	Obese	2	12.5 \pm 4.9	17.5 \pm 7.2	28.0 \pm 0	31 \pm 0.7	38.5 \pm 1.1

**P<0.001 in comparison with the ideal body weight group.

P values are not calculated in the other groups due to the small number of patients in each sub group.

Though a gradual transition from an exaggerated insulin response in mild diabetics to a flat response in severe diabetics was seen, wide variations in insulin patterns were seen in each group.

DISCUSSION

The present study has brought out the complexity of the relationship between insulin response and glucose stimulus. In general, great variability in the individual insulin responses is seen as shown by the large standard errors. This point has been stressed by Berson and Yalow¹⁰ and Reaven and Miller¹¹ also.

Amongst a variety of factors regulating the level of circulating insulin, the primary and the critical determinant is the glucose tolerance. This is confirmed by the inverse relationship observed between glucose intolerance and the insulin secretion, in this study. Others workers also have noted that the insulin response becomes weaker with increasing degree of glucose intolerance.¹²⁻¹⁴

In this study, correlation of IRI levels with the 2 hour P.G. values reveal findings similar to those described by Savage *et al.*¹⁴ Patients with 2 hour P.G. values below 250 mg% show exaggerated IRI responses which gradually decrease with increasing sugar values. The difference between the fasting and peak levels of IRI becomes negligible with 2 hour P.G. values above 350 mg%. These observations thus suggest a gradual decrease in the sensitivity of the beta cells of pancreas to glycemic stimulus.

The delayed insulin peak characteristic of diabetes¹²⁻¹⁵ is a prominent feature of all the three groups of patients described. The delayed response is indicative of an elevated stimulatory threshold to insulin for glucose. It is still controversial

whether this implies a defect in the synthesis or the release of insulin.

Obesity has been shown to be an important factor in determining the magnitude of plasma insulin rise after glucose intake.^{1,3,16,18} The higher mean insulin response observed in the obese diabetics in this study confirms this point. This is manifested clearly in the mild and moderate group of diabetics. In the severe group of diabetics, in this study, the beta cells appear to be completely exhausted and hence is uninfluenced by any of the factors influencing insulin secretion. The lean diabetics showed that insulin response to glycemic stimulus in accordance with the earlier reports.^{10,20}

Variations in the insulin response in diabetics with similar glucose tolerance projects the heterogenous nature of IRI secretion. This observation clearly implies the interplay of many factors in determining the insulin concentration in response to glucose stimulus.

The results of the present study are in agreement with those of the Indian and Western reports.^{1,2,14,16-21} Hence it appears that the overall IRI responses do not reflect the variations in the clinical manifestations in Indian diabetics. Regional and geographic differences in the epidemiological and dietary patterns of the population may be contributory factors for these variations.

In view of the apparent puzzle of insulin secretion in diabetes, it is difficult to generalise that hypoinsulinaemia characterises severe diabetes and hyperinsulinaemia is the rule in mild diabetes. Hence measurement of IRI may not help to assess the severity of diabetes.

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