INSULIN ANTIBODIES IN DIABETIC PATIENTS

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INTRODUCTION :

Circulating antibodies to insulin is one of the chief factors responsible for poor response to insulin in diabetes. At the Diabetes Research Centre, Madras, it has been frequently noticed that several diabetic patients responding poorly to insulin show good control of hyperglycaemia when treated with the combination therapy of high carbohydrate diet and oral drugs. (Viswanathan, 1973; Viswanathan et al, 1978). This prompted us to measure the insulin antibody levels in a group of poor-responders to insulin in order to evaluate their role in causation of insulin resistance. Follow-up study of the patients was carried out to assess the variation of the antibody titres in these patients.

MATERIAL AND METHODS :

Insulin antibody levels were measured in 104 diabetic patients selected at random and responding poorly to insulin. There were 65 males and 39 females in this group. Their age distribution is shown in Table 1.

In this study, 57 patients were receiving lente insulin only, 6 patients were receiving plain insulin and the other 41 patients were on combination of lente and plain insulins. The patients were selected at random and the dose of insulin used varied widely, and hence no attempt was made in this study to relate the antibody titre to the dose of insulin. All the patients received 80 U or more of insulin/day and it exceeded 120 U/d in a few patients. The distribution of patients according to the duration of insulin therapy is shown in Table 2.

TABLE 1
SHOWS AGE DISTRIBUTION OF PATIENTS

Age	<30 years	30-50 years	>50 years
Number	5	44	55

TABLE 2
SHOWS DURATION OF INSULIN THERAPY

Period	<1 year	1-5 years	>5 years
No. og patients	19	32	53

Measurement of insulin antibodies was made by the radio-immunoassay method of Sebriakova and Little (1973). In this procedure, the antibody titre is referred to as the antibody index which is arbitrarily calculated using the amount of insulin standard required to displace 25 per cent of the bound labelled insulin. This, in other

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words, is the amount of insulin required to reduce the counts per minute (Cpm) of bound radio-active insulin to 75 per cent of its total binding. In this proceedure the therapeutic preparation of insulin used by the patients is used as the standard insulin and hence, the variations in the binding due to species specificity are ruled out. The result is expressed in μU of insulin antibody/ml of serum. This is not the absolute amount of insulin antibody in serum, but indicates a relative, quantitative immunologic response of the patient to insulin. This method is found to be reliable and reproducible for measurement of insulin antibodies.

Serum samples for the assay of insulin antibody index (Ab index) were collected in the fasting state, after withdrawing, insulin injection for 24 hours. The serum was kept at — 20°C till the assays were performed.

94 patients were available for follow-up for periods of 1 to 6 months. The control of diabetes was assessed by measuring the fasting and post-prandial blood sugar values. The details of the treatment is dealt with later.

RESULTS :

Duration of therapy : The antibody index was studied in relation to the duration of insulin treatment. The results are given in Table 3.

There was no correlation between the duration of insulin therapy and the mean antibody index. This is better seen from the wide range of values in each of the 3 groups.

We separately analysed the antibody index of the 57 patients receiving lente insulin alone, and this is shown in Table 4.

In this study, in patients receiving lente insulin alone, there appeared to be an increase in the mean antibody index with

TABLE 3

INSULIN ANTIBODY INDEX IN RELATION TO THE DURATION OF THERPY

Duration in years	<1 year	1 to 5 years	>5 years
Number of patients	16	32	52
Insulin Ab Index μU/ml (Mean)	3016	4905	4382
Insulin Ab Index μU/ml (Range)	5....7999*	16... 44280	0....37314**

* 3 cases with an antibody index of over 1 lakh μU/ml excluded from calculation.
** 1 case with and antibody index of 2,19315 μU/ml excluded from calculation.

TABLE 4

SHOWS INSULIN ANTIBODY INDEX AND DURATION OF INSULIN THERAPY IN PATIENTS TREATED WITH LENTE INSULIN

Duration in years	<1 year	1 to 5 years	>5 years
Number of patients	10	16	30*
Ab Index μU/ml (Mean)	1650	5203	6007
Ab Index μU/ml (Range)	16...6182	156...21939	0...37314

* 1 patient with Ab index of 2,19315 μU/ml excluded from the calculation.

duration of treatment. However, even here the intragroup variations were very wide.

The wide variation in antibody index is better illustrated in Table 5.

TABLE 5

SHOWS ANTIBODY INDEX IN 8 PATIENTS RECEIVING LENTE INSULIN.

Duration in years	Insulin antibody index (μU/ml)
10	434
10	1028
10	15670
10	Negligible
13	9244
13	330
15	Negligible
16	54

This table shows the antibody index in 8 patients receiving nearly the same dose of lente insulin (80 units) for almost the same length of time, viz., 10 to 15 years. It is seen that a few patients have circulating antibody titres as high as 15,000 while a few others have negligible amount of antibodies. Similar variations were observed in patients on combination of insulins also.

RESPONSE TO TREATMENT AND FOLLOW-UP STUDY :

After the estimation of antibody titre, all the patients were put on a proper diet (High Carbohydrate, high fibre diet) and a combination of glybenclamide and phenformin. Out of the total of 94 patients who were available for follow-up, 54 responded to diet and oral drugs, 26 patients could be controlled by addition of conventional insulin to oral drugs. The rest of the 14 patients did not respond to any of the above regimens and they responded to Monocomponent Insulins (Novo Industri — Denmark). The mean initial antibody titre of these patients is given in Table 6.

TABLE 6

SHOWS ANTIBODY INDEX IN PATIENTS ON VARIOUS THERAPIES

Mode of therapy	Number of patients	Percentage	Ab titre μU/ml
Oral drugs	54	57.5	7538
Insulin + Oral drugs	26	27.7	1776
Monocomponent Insulin	14	14.8	3174

More than 50 per cent of patients who originally came to us with history of insufficient response to large dose of insulin responded to oral drugs and only 14 per cent required monocomponent insulin. As seen from the above table, there was no correlation between the initial antibody titre and the subsequent response of the patients to various modes of therapy. Thus a random single estimation of insulin antibody titre does not seem to help in planning the subsequent therapy also.

DISCUSSION :

Anti-insulin antibodies are developed in insulin-treated patients within a few months. In most patients where the concentration of the antibodies is only moderate, they have little clinical significance. (Taylor, 1968).

In this study, it is noted that the antibody levels show wide individual variations in patients who were on conventional insulin, and no correlation is observed between the duration of insulin therapy and the antibody index. However, the antibodies

for porcine and bovine insulin has not been studied separately.

It is particularly interesting that many of the patients who have not been responding to insulin, responded well to proper diet and a combination of oral drugs. The degree of response in these patients was unrelated to the amount of insulin antibodies in serum. Probably this could be attributed to the effect of an improved dietary adherence. These patients may have enough endogenous secretion of insulin which is being made available to the tissues either by increased tissue sensitivity and/or by an augmentation of the insulin output. Monocomponent insulin was useful to obtain control of diabetes in those who did not respond to any other modality of therapy and in these patients, immunogenic insulin resistance could have been responsible for the initial lack of response. The experience of monocomponent insulin in this Centre in a larger series of diabetics has proved its value in the treatment of insulin resistant cases. (Viswanathan et al, 1980).

The antigenicity of the insulins are known to vary with the source and type of insulin preparation (Little et al, 1977). It is also demonstrated that the same insulin preparation can give rise to antibodies with different avidity (Little et al, 1977 and Dixon, Exon and Hughes, 1977). Hence the quantum of antibody index alone does not reflect the actual immunologic potency of the antibodies. Small amounts of antibodies with greater avidity for insulin have been demonstrated in diabetic patients in the labile group (Dixon, Exon and Hughes, 1972). Hence, we feel, an interplay of several variable factors influence the quantity and quality of the antibodies.

In view of the present knowledge regarding the biological actions of insulin, it is essential to consider the role of insulin receptors in deciding the biological potency of Insulin. A number of reports of insulin receptor defects and insulin insensitivity have appeared recently. (Flier et al, 1975; Olefsky, 1976; Baldwin et al, 1979; Kahn and Rosenthal, 1979; Skyler, 1979). Hence, in patients with low titre of insulin antibodies, presenting with insulin resistance, the status of insulin receptors needs to be looked into.

This preliminary study indicates that random estimation of insulin antibodies in diabetic patients is of limited value. However, serial estimation of insulin antibody index may yield useful information.

SUMMARY

Circulating antibodies to insulin were measured in 104 maturity onset diabetics receiving insulin for varying periods and who showed poor response to treatment. The data was analysed to study the relation between the insulin antibody index and insulin resistance. The Antibody Index was determined by the radioimmunoassay of Sebriakova and Little (1973).

The antibody index varied widely among individuals receiving similar dose and type of insulin for similar periods, some patients had markedly elevated insulin antibody indices. There was no correlation between the duration of insulin therapy and the antibody index. It was also noticed that in a few patients with severe resistance to insulin, the antibody titre was low.

94 patients were available for follow-up for periods ranging from 1 month to 6 months. Of these 54 patients responded to diet and oral drugs. 26 patients responded to diet and oral drugs plus conventional insulin. 14 patients responded to Monocomponent Insulin (Actrapid M.C. NOVO) in much smaller doses.

No correlation was seen between the antibody index and the nature of response to treatment in any of the above groups. Parameters other than the insulin antibody titre, like the avidity of the antibody, sensitivity of insulin receptors etc. appear to play important role in determining the response to the various therapies in diabetic patients.

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