CHANGES IN PERIPHERAL INSULIN CONCENTRATIONS IN NON INSULIN DEPENDENT DIABETES DURING TREATMENT
Assessment by Mathematical Applications

A Ramachandran*, C Snehalatha**, V Mohan**, H Timothy,+ M Viswanathan#

SUMMARY

Serum immunoreactive insulin responses to meal stimulus were studied in 20 newly detected non insulin dependent diabetes mellitus patients, following one week of treatment with high carbohydrate, high fibre diet and glibenclamide. Ten patients showed "rapid glycaemic response" i.e. the glycaemic response was good within a week. The rest of them were called "slow responders". The insulin responses were heterogenous. Mathematical calculations using the glucose and insulin responses showed improved beta cell function and peripheral action of insulin in rapid responders. On the other hand, the slow responders showed only slightly improved beta cell function with no change in peripheral action of insulin.

The second phase of the study constituted follow-up studies upto 6 months. The corrected insulin response (CIR) increased initially in several patients. The peripheral insulin action improved in all patients with longer duration of treatment and lower insulin concentrations were required to maintain normoglycaemia at this stage

The results of the study indicate that a) multiple factors influence glucoregulation, b) even short term effects of the drug appear to be mediated by extra pancreatic mechanisms, and c) the extrapancreatic action improves significantly on long term use of the drug.

KEY WORDS: Diabetes mellitus, beta cell function, glibenclamide.

INTRODUCTION

Patients with non insulin dependent diabetes mellitus (NIDDM) could have defects at multiple sites involving the synthesis and/or action of insulin.[1-3] Pancreatic beta cell responses are heterogenous in patients with NIDDM and are influenced by a variety of factors including body weight and degree of hyperglycaemia.[4] Measurement of immunoreactive insulin (IRI) response to glucose stimulus alone does not assess the beta cell secretion as it is highly variable and is not linearly related to the blood glucose concentration. Better assessment of the insulin secretion in relation to the glucose concentration and the peripheral action of insulin can be made using certain mathematical derivations involving the plasma glucose and IRI values.[5,6] The application of the formulae helps to evaluate the pancreatic function during an oral glucose tolerance test independent of the glucose level. This makes it possible to compare the same individual under different conditions or different individuals under identical circumstances. They also help to separate the contributions of the beta cell function and peripheral insulin resistance to the plasma glucose response obtained with glucose load. However, the application of these formulae at the fasting state is not advised as the interplay of several regulating factors at that state leads to a large percentage of error.

Sulphonylurea compounds are widely used in treating NIDDM patients and considerable work has been done to elucidate their mode of action. The postulated mechanisms include effects on synthesis and/or release of insulin, as well as extrapancreatic actions on the insulin receptor and post-receptor sites.[7-9] Insulin sensitivity may also be influenced by diet treatment.[10-12]

In this study, we have measured the changes in IRI responses during treatment of Indian NIDDM patients with diet and glibenclamide. The corrected insulin response and the peripheral insulin sensitivity have also been assessed using the mathematical calculations of Sluiter *et al*[5,6]

MATERIAL AND METHODS

Twenty newly diagnosed non-obese NIDDM patients who had not received any treatment were taken up for the study. The diagnosis of NIDDM was made according to the WHO criteria[13] (fasting plasma glucose ≥ 140 mg/dl, or ≥ 200 mg/dl 2 hr after 75 g glucose load). There were 12 men and 8 women with a mean age of 45 ± 1.1 years. The mean body mass index (BMI) was 23.2 ± 3.0 kg/m^2. Fasting and post-prandial (90 min) venous blood samples were collected for estimation of plasma glucose, and insulin (IRI) during the initial visit. A standard breakfast of 400 Kcal with 65% carbohydrate, 20% protein and 15% fat was used for studying meal-stimulated IRI. All patients were then given a high carbohydrate, high fibre (HCHF) diet, distributed into

*Deputy Director, **Head, Department of Biochemistry, # Director, + Research Student, Diabetes Research Centre and MV Hospital for Diabetes, Madras.

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four feeds containing 20%, 35%, 10% and 35% respectively of the total calories intake.[14] Refined sugars were totally prohibited. The calorie allowance varied from 1500-2000 Kcal per day depending on individual needs. Patients were given glibenclamide, the initial dose of which was 10 mg/day given in two equal divided doses, in the morning and night before food.

In the first phase of the study, patients were reviewed after one week. The fasting and post-prandial (PP) blood samples were collected for reassessing plasma glucose and IRI. The post-prandial samples on follow-up were taken with the prescribed dose of drugs. Those who responded (PP plasma glucose < 160 mg/dl) within one week were classified as "rapid responders" (RR) and the remaining as "slow responders" (SR).

In the second phase of the study, long term follow-up was taken up. The biochemical parameters were repeated at the end of 1 month, 3 months and 6 months of therapy in available patients. Discrimination based on the plasma glucose values was not made in this phase of the study.

Plasma glucose was estimated by ortho-toluidine method and immunoreactive insulin (IRI) by the radioimmunoassay procedure of Herbert *et al.*[15]

The corrected insulin response (CIR) and the peripheral action of insulin (A) were calculated using the IRI and glucose values applying the mathematical formulae given below.[5,6] We have used the IRI and glucose values at 90 min after stimulation, for the calculations.

$$CIR = \frac{\text{Insulin (uU/ml) X 100}}{\text{plasma glucose (plasma glucose - 70 (mg/dl)}}$$

$$A = \frac{10000}{\text{IRI (uU/ml) X glucose (mg/dl)}}$$

Body mass index (BMI) was calculated using the formula: weight in kg divided by height in square metres. Only those with ideal body weight i.e. women with BMI of 18-25 and men with BMI of 18-27 were included in the study.

Mann Whitney U test was used for statistical analysis.

RESULTS

First phase

Table 1 shows the biochemical parameters in the patients during 1 week follow-up. Rapid response was seen in 10 of 20 patients (50%). The initial plasma glucose values were significantly higher in slow responders ($P < 0.01$ for fasting and $P < 0.05$ for postprandial glucose). There was no significant difference in the fasting and stimulated IRI between slow responders and rapid responders. The mean BMI values in the rapid responders and slow responders were similar (23.6 ± 3.1 and 24 ± 2.8 respectively).

The fasting IRI values did not change significantly in both the groups. The stimulated insulin response increased in both groups, but the change was not statistically significant.

Significant improvement was seen in the corrected insulin response (CIR) and peripheral insulin activity (A) in the rapid responders ($P < 0.001$) (Table 1). In the slow responders an increase in CIR was noted and this was significantly lower compared to that in rapid responders ($P < 0.001$).

Second phase

The metabolic control was sustained during longer periods of follow-up. Of the 20 patients, 15 patients were available for one month review and they had a mean PP plasma glucose of 155 ± 10 mg/dl. The dose of glibenclamide was decreased from 10 mg to 5 mg, in divided doses, in 10 of the 15 patients because of hypoglycaemic symptoms. In 12 patients, follow-up studies were done at 3 months and 6 months. Table 2 shows the mean PP plasma glucose and the IRI in the patients during the different periods of study.

The figure shows the mean CIR (90 min) and A values during the follow-up. The CIR value was very

Table 1: **Biochemical Parameters – 1 week follow-up**

	Plasma Glucose mg/dl		IRI uU/ml		CIR (90 min)	A (90 min)
	F	90 min	F	90 min		
Rapid Responders (n = 10)						
Initial	120 ± 12	324 ± 27	22 ± 9	49 ± 9	0.07 ± 0.02	0.94 ± 0.17
Follow-up	116 ± 8	145 ± 8* P < 0.001	20 ± 8	66 ± 15	0.97 ± 0.21* P < 0.001	1.59 ± 0.32* P < 0.001
Slow Responders (n = 10)						
Initial	178 ± 11** P < 0.01	396 ± 21** P < 0.05	20 ± 7	42 ± 7	0.04 ± 0.1	0.8 ± 0.21
Follow-up	168 ± 12	206 ± 7* P < 0.001	22 ± 11	66 ± 8	0.25 ± 0.04*,** P < 0.001	0.84 ± 0.1

* Compared to initial value; ** Compared to Rapid Responders.
Values as mean ± SEM

Table 2: Initial and Follow-up Values of Postprandial Plasma Glucose and IRI in the study subjects

...er	Initial	1 week	1 month	3 months	6 months
...ma glucose	359 ± 19	176 ± 9*	155 ± 10*	176 ± 10*	168 ± 5*
mg/dl ± SEM	(20)	(20)	(15)	(12)	(12)
IRI uU/ml ± SEM	45 ± 6	66 ± 8**	61 ± 9**	70 ± 9**	52 ± 8

* $P < 0.001$ compared to the initial value
** $P < 0.01$ compared to the initial value
Figures in brackets show number of subjects

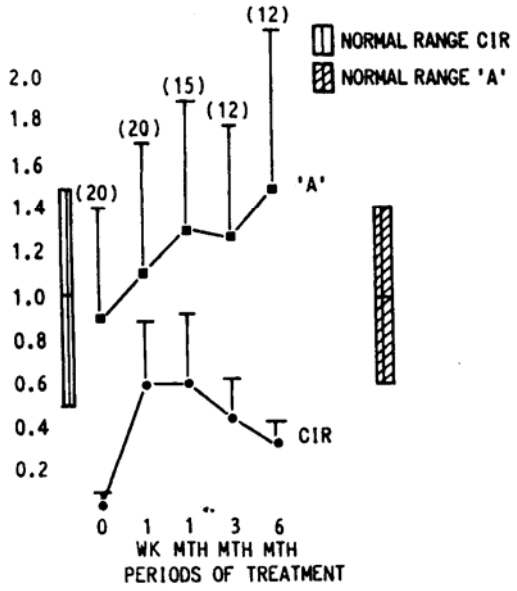

Fig.: Changes in the CIR and A values in the diabetic subjects on follow-up. The evaluations were done at the end of 1 week, 3 months and 6 months. Numbers in brackets show the number of subjects studied.

low at the beginning of the study, improved within one week and was maintained at that level for a month. With longer duration of treatment, mean CIR decreased and at 6 months, the mean value was even lower than the normal value. The mean value for A improved steadily throughout the study period.

DISCUSSION

Achievement of optimal metabolic regulation in NIDDM patients is accompanied by changes in insulin secretion and action. Estimation of peripheral IRI, however, does not reflect the actual metabolic changes. By applying the calculations[5,6] using the glucose and IRI values obtained during the study, we were able to differentiate the two functions, namely, the insulin secretion and action.

In the first phase of the study, the subjects were classified into "rapid responders" and "slow responders" according to the glycaemic regulation attained. The mathematical calculations employed have helped to show the differences between these two groups. In the "rapid responders" there was significant improvement both in insulin secretion and peripheral insulin action as indicated by changes in CIR and A respectively. On the other hand in the "slow responders", while the insulin secretion (CIR) showed significant improvement, the peripheral action of insulin (A) failed to change significantly and this may be responsible for the "slow response". It seems feasible to conceive thus that both these factors are important in achieving optimal glycaemic regulation in the early phase therapy in NIDDM.

The follow-up for longer periods of time showed the changes occurring on long term therapy. The initial CIR values (index of insulin secretion) were low in all patients, which indicated subnormal insulin secretion. During therapy, the CIR increased in many, indicating improved insulin secretion and at the end of 3 months, 50% had normal CIR. However, at the end of 6 months, there was a reversal of this phenomenon and 83% showed low CIR, while maintaining normoglycaemia. The peripheral action (A), on the other hand, showed improvement in all by the first week and this was sustained throughout the study period. At the end of 6 months, all showed normal peripheral insulin action. These results suggest that only some patients show an increase in IRI response during treatment but a more marked effect is seen in the peripheral action of the hormone. The enhancement of peripheral action of insulin increased with duration of the treatment as evidenced by the lower CIR required for the maintenance of euglycaemia at the end of 6 months of therapy. Kolterman *et al*[7] noted that glyburide produced glycaemic control both by increasing the IRI response and by extrapancreatic actions. The minimum period of study was 3 months and the major extrapancreatic effect noted by them was suppression of basal hepatic glucose output. A decrease in IRI concentration with further improvement in its peripheral action was observed only by the 18th month of treatment. Lebovitz and Feinglos[16] showed that both insulin secretion and action improved in 6 weeks of glipizide therapy.

In this study, in a proportion (9/20) of the patients, the absolute insulin concentrations after 1 week of therapy were lower than the pretreatment value; but their corrected responses were higher than the original values. This indicates that the pancreatic effect of the drugs produces an appropriate response for the ambient glucose concentration. Significant improve-

ment in the peripheral action (A) was seen simultaneously and this function predominated with longer period of treatment. Several authors[9,16,17] have shown similar actions of sulphonylurea drugs only on prolonged therapy. In the present study, we were able to achieve both the effects, viz. a better beta cell function and enhanced peripheral action of insulin even within a week. This has been corroborated by another recent study which showed improvement in insulin binding to erythrocyte receptors in NIDDM within this period.[18] The HCHF diet used in our patients could also have contributed to the improvement in the insulin sensitivity. Our study[10] as well as those of other workers have shown that the HCHF diet improves the peripheral sensitivity to insulin.[11,12] This shows the rapid improvement in the peripheral insulin sensitivity with therapy in NIDDM.

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