RAPID IMPROVEMENT IN INSULIN SENSITIVITY DURING GLYCAEMIC REGULATION IN NIDDM SUBJECTS

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SUMMARY

Insulin tolerance test (ITT) was performed in 16 newly diagnosed non-insulin dependent patients and insulin sensitivity was calculated as K_{ITT} from the glucose disposal rate. The patients were then treated with diet and glibenclamide. All patients showed reduction in hyperglycaemia (post prandial glucose < 200 mg/dl) within ten days, ITT was repeated in all between 2 to 10 days (mean 5± 3 days).

The mean fasting plasma glucose decreased from 205± 42 mg/dl to 139± 29 mg/dl ($p < 0.001$) in 5±3 days. The K_{ITT} value improved from 1.26± 1.06 to 2.64± 1.6 ($p < 0.001$). Both the K_{ITT} values were significantly lower than the control value of 5.49± 1.9 ($p < 0.001$). There was an inverse correlation between K_{ITT} and the fasting plasma glucose values ($r=0.59$, $P = 0.0024$).

This study shows that in NIDDM patients, the insulin sensitivity could improve within a few days of treatment with oral hypoglycaemic agents.

Key Words: Insulin Tolerance Test; Glucose Disposal Rate; Glibenclamide; NIDDM

INTRODUCTION

Non-insulin dependent diabetes is characterised by defects of insulin synthesis, release and action[1]. One of the major abnormalities described is defective insulin action at the target tissues[2].

Peripheral insulin resistance is measured by the euglycaemic clamp technique. Here a continuous, fixed rate insulin infusion is given along with a variable dextrose infusion to maintain steady state plasma glucose levels[3]. A simpler technique is to calculate the glucose disposal rate measured as K_{ITT} by the intravenous insulin tolerance test (ITT) which also provides a measure of peripheral insulin sensitivity in vivo. Good correlation has been observed between the two techniques[5]. It is well known that improvement in peripheral insulin sensitivity accompanies metabolic control of diabetes. However, most of the earlier studies have shown improvement in insulin sensitivity only after chronic treatment[6-8]. This study assesses the peripheral insulin sensitivity using ITT in NIDDM patients after short treatment with conventional therapeutic measures.

MATERIAL AND METHODS

The study group comprised of 16 newly diagnosed non-obese NIDDM patients. All were of ideal body weight. Diagnosis of diabetes was done by oral GTT using the criteria of the WHO study group report on diabetes mellitus[9]. Glycosylated haemoglobin (HbAl) was estimated during GTT in all cases. None had received any antidiabetic treatment prior to the study. All patients were hospitalised for the study. The day after admission, insulin tolerance test was performed. Informed consent was obtained from all the patients. They were given high calorie high fiber (HCHF) diet and 10 mg of glibenclamide in two divided doses. When the post prandial plasma glucose decreased to <200 mg/dl (between 2 to 10 days with a mean of 5± 3 days), the ITT was repeated.

Insulin sensitivity was assessed by insulin tolerance test as described by Alford *et al*[4]. After an overnight fast, a polyethylene catheter was inserted into a forearm vein. Blood samples were drawn at -5 min and at 0' intervals for the basal plasma glucose estimation. The average of the two values was taken as the basal value. Thereafter, 0.1 U/Kg of purified porcine insulin (Actrapid MC Novo) was injected IV over a period of 2 minutes. Blood samples were drawn at 5' intervals for 90' for estimation of glucose. The test was terminated before 90' if hypoglycaemic symptoms occurred. The K_{ITT} was derived from the slope of the linear portion of the regression line of the natural logarithm of the glucose versus time[4]. The formula used was $K_{ITT} = 0.693 \times 100$ where t 1/2 represents the half life of plasma glucose decay. The half life of plasma glucose was obtained by plotting the plasma glucose concentrations against time on a semilogarithmic graph paper. The rate of glucose decline between 10 to 40 minutes interval was used, as the onset of insulin action takes 5 to 10 minutes. The K_{ITT} values obtained on 18 normal non-obese subjects acted as control.

Plasma glucose was estimated by the glucose oxidase method and HbAl by the colorimetric method of Eross *et al*[10]. Statistical comparisons were made using the paired *t* test and the correlation coefficient tests.

RESULTS

The initial mean fasting plasma glucose (FPG) and HbAl values in the study group were 205 ± 42

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mg/dl and 10.0 ± 1.7% respectively (Table 1). The initial KITT value was 1.26 ± 1.06. The control value was 5.49 ± 1.9 ($p < 0.001$) (Table 2). The individual values are shown in Figure 1. Following treatment, the mean FPG in study group decreased to 139 ± 29 mg/dl. The KITT value improved to 2.64 ± 1.06 ($p < 0.01$ compared to the initial value). The changes in individual values are shown in Figure 2.

An inverse correlation was observed between the FPG and KITT value ($r = -0.59$, $p = 0.0024$).

Table 1: Details of the study groups

	M:F	Age	BMI	FPG	HbAI (%)
Controls	10:8	38.9 ± 6.3	22.9 ± 1.6	84.2 ± 2	7.3 ± 0.5
NIDDM	10:6	51.0 ± 8.9	23.0 ± 1.7	205 ± 42	10.0 ± 1.7

BMI = Body mass index FPG = Fasting plasma glucose
Values are mean ± SD.

Table 2: Improvement in insulin resistance

	KITT		FPG mg/dl
	Controls	NIDDM	
Initial	5.49 ± 1.9	1.26 ± 1.06* P < 0.001	205 ± 42
Follow-up	—	2.64 ± 1.6** P < 0.01	139 ± 29** P < 0.001

*Compared to controls **Compared to initial value
FPG = Fasting plasma glucose

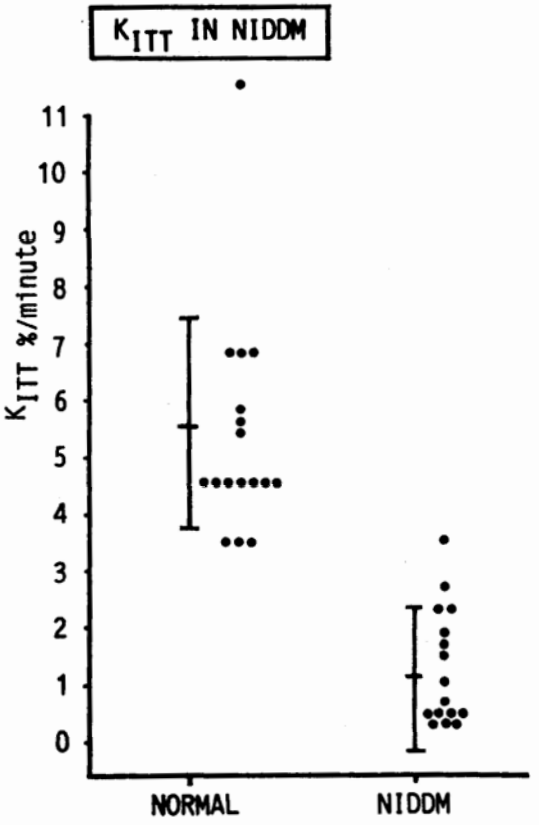

Fig.1: KITT values in the control and NIDDM patients, at the start of the study.

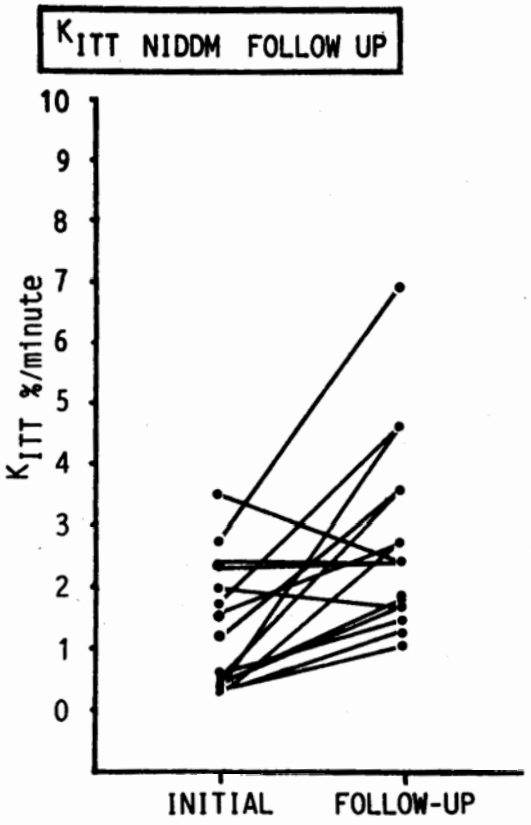

Fig.2: Changes in KITT in individual patients.

DISCUSSION

The pathophysiology of NIDDM involves multiple defects at several sites[1]. The severity of diabetes depends on the beta cell insulin secretory defect as well as the degree of peripheral insulin resistance at the target tissue. In a given individual, peripheral insulin resistance could in turn vary depending on body weight and level of hyperglycaemia. Recent studies have focussed the role of receptors in peripheral insulin re-

sistance. Most recent studies show that post receptor defects are more important than defects at the receptor site[11]. Peripheral insulin resistance is thus ideally assessed by in vivo studies. The euglycaemic clamp technique is one of the best methods of assessing peripheral insulin sensitivity[3]. However, the insulin concentrations required during clamp technique to achieve steady state plasma glucose are usually much higher than physiological concentrations of insulin. Moreover, 300 - 400 ml of blood is needed to perform the test. On the other hand, ITT is comparatively a simple procedure and gives equally good assessment[5]. We, therefore, used ITT to assess peripheral insulin resistance in NIDDM patients. None of the patients were obese, obviating the effect of obesity on insulin action.

The peripheral insulin resistance as measured by the ITT is a net result of resistance to insulin action at different sites. These sites include the hepatic level and the target tissue level which consists of receptor and post receptor abnormalities. Earlier studies have reported improvement in insulin binding to target cells after prolonged treatment with sulphonylurea compounds[6-8] as well as with HCHF diets[12]. Most of these studies have shown improvement only after chronic therapy. To the best of our knowledge, this is the first study where significant improvement in KITT has been demonstrated after a few days of conventional therapy. The mechanisms involved in such a rapid improvement may be multiple. It has been demonstrated that reduction in hyperglycaemia can decrease insulin resistance in IDDM patients[13]. Similar observations are reported in obesity and NIDDM patients[14].

Our own studies in NIDDM patients have shown rapid improvement in insulin binding to erythrocyte insulin receptors within a few days[15]. Although measurement of insulin resistance by ITT has certain limitations, it does clearly indicate that the insulin sensitivity in NIDDM patients improves rapidly, with conventional modes of therapy.

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NEWS

The Western Chapter of Indian Society of Nephrology has been formed. This includes the state of Maharashtra, Bombay, Gujarat and Diu, Daman and Goa. Members of the Indian Society of Nephrology and other nephrologist are kindly requested to send their names with full address to the Secretary, Dr. Pradeep Pandya, Opp. Sardar Bhavan, Baroda 390 001, Gujarat.