

HYPER INSULINISM AND DECREASED INSULIN SENSITIVITY IN NON-OBESE HEALTHY OFFSPRING OF CONJUGAL DIABETIC PARENTS AND INDIVIDUALS WITH IGT AND NIDDM

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Abstract : Insulin sensitivity was measured by insulin tolerance test using K_{ITT} as an index of insulin mediated glucose metabolism in 9 non-obese healthy offspring of conjugal diabetic parents (OCDP) and 9 non-obese NIDDM patients. The mean K_{ITT} value in the offspring of conjugal diabetic parents was $3.85 \pm 1.64 \text{ min}^{-1} \times 100$ which was lower ($P < 0.05$) than the value of $5.49 \pm 1.9 \text{ min}^{-1} \times 100$ in the control subjects. While, the mean K_{ITT} value in NIDDM patients was $1.85 \pm 0.9 \text{ min}^{-1} \times 100$ which was significantly lower ($P < 0.001$) than that in the control subjects.

Estimation of plasma immunoreactive insulin (IRI) and C-peptide in these subjects and in subjects with impaired glucose tolerance (IGT) showed significantly higher levels of insulin than that in the control subjects but there was no corresponding increase in the C-peptide levels. The mean area under the insulin curve (IRI) was $242 \pm 69 \mu\text{U/ml}$ in the control subjects versus $527 \pm 206 \mu\text{U/ml}$ in IGT ($P < 0.001$), $648 \pm 215 \mu\text{U/ml}$ in NIDDM ($P < 0.001$) and $466 \pm 130 \mu\text{U/ml}$ in OCDP ($P < 0.001$).

These results suggest that 1) healthy offspring of two type II diabetic parents have decreased insulin sensitivity and insulin resistance is present in all the NIDDM patients, 2) peripheral hyperinsulinism is a common feature in healthy offspring of conjugal diabetic parents, and in subjects with IGT and mild NIDDM and this hyperinsulinism is not due to increased B-Cell secretion but due to some metabolic alterations of insulin occurring at the extra pancreatic levels.

Key words : insulin sensitivity
hyperinsulinism

insulin tolerance test
insulin resistance

INTRODUCTION

It is now clear that simple insulin deficiency does not entirely account for the diabetic syndrome, in patients with Non insulin dependent diabetes mellitus (NIDDM), because insulin deficiency does not exist in many patients with NIDDM (1). Patients with mild

diabetes will have normal or even increased levels of plasma insulin following an oral glucose challenge (2). This combination of glucose intolerance in the face of normal or hyperinsulinemia clearly indicates an insulin resistant state. Insulin resistance is one of the major pathogenic factors in individuals with NIDDM and impaired glucose tolerance (IGT).

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The pathophysiological mechanism relating the high insulin concentration in peripheral circulation and insulin resistance in mild glucose intolerance has not been clearly elucidated.

The offspring of diabetic couples has long been thought to have a high risk of developing diabetes (3). Earlier studies have shown a high prevalence of type II diabetes among the offspring of conjugal type II diabetic parents (4). Healthy adult offspring of conjugal diabetic parents are therefore ideal subjects to look for early abnormalities of insulin sensitivity. But there are very few reports on insulin sensitivity in these individuals (5, 6).

This study was thus carried out to a) evaluate the degree of insulin resistance in the healthy offspring of diabetic couples, individuals with IGT and NIDDM and b) to assess whether the associated hyperinsulinism is pancreatic in origin or due to metabolic alterations occurring in the periphery. To obviate the effect on obesity on beta cell function, only non-obese individuals were selected for this study.

METHODS

Nine healthy offspring of conjugal diabetic parents (OCDP), twelve individuals with IGT and nine NIDDM patients (with 2 hr plasma glucose 200-250 mg/dl) were selected for this study. The individuals were classified into IGT and NIDDM, according to the WHO Expert Committee criteria (7), after an oral Glucose tolerance test (GTT) with 75 gm glucose. The clinical details of the study subjects are given in Table I. Plasma glucose was estimated by Ortho-toluidine method (8). Plasma samples were collected in EDTA, in fasting and every 30 min upto 2 hrs after glucose intake for the estimation of immunoreactive insulin (IRI) and C-peptide. The samples were kept frozen at -20°C till the assay. IRI was estimated by radioimmuno assay procedure of Herbert et al (9) with some modifications. Plasma C-peptide was estimated by RIA method of Heding (10) with NOVO (Denmark) C-peptide kit. Δ Glucose (n./dl), Δ IRI ($\mu\text{U/ml}$) and Δ C-peptide (pmol/ml) values were calculated by adding the respective

four half-hourly values obtained after glucose intake, during the GTT.

Insulin response to glucose was assessed by calculating the ratio of area under curve (AUC) after glucose intake for insulin to AUC for glucose (I/G ratio).

TABLE I: Clinical details of the study groups.

Group	Sex M:F	Age (years)	Duration (years)	Body mass index (BMI)
Controls	10:5	38.9 \pm 6	—	23 \pm 1.6
IGT	10:2	39 \pm 9	1 month- 2 years	23 \pm 2
NIDDM	7:2	37 \pm 9	1.6 \pm 1	23.4 \pm 3
OCDP	5:4	37 \pm 10	—	23 \pm 1

Δ IRI mU/L

I/G ratio = -----

Δ glucose mM/L

Insulin sensitivity was measured in the offspring of conjugal diabetic parents, NIDDM patients and the control subjects. They were all of ideal body weight.

Insulin sensitivity was measured by insulin tolerance test (ITT) described by Alford et al (11) using K_{ITT} as an index of insulin mediated glucose metabolism, as glucose clamp technique was not available. 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 μkg of purified porcine insulin (Actrapid M.C. Novo) was injected intravenous over a period of 2 min. Blood samples were drawn at 5' intervals for 90' for estimation of glucose. The test was terminated before 90', if hypoglycemic 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 (11). The formula used was (12)

$$K_{ITT} = \frac{0.693 \times 100}{t_{1/2}}$$

where $t_{1/2}$ represents the half life of plasma glucose decay. The half life of plasma glucose was obtained by plotting plasma glucose concentrations and time on semilogarithmic graph paper. The rate of glucose decline between 10 to 40 min interval was used as the onset of insulin action takes 5 to 10 min. The K_{ITT} values obtained were compared to that in the normal non-obese control subjects.

Mann Whitney-U test was used for statistical analysis. Pearson's correlation test was also done.

RESULTS

Table II shows the plasma glucose, IRI and C-peptide levels in the different groups of the study subjects.

Insulin response : Offspring of conjugal diabetic parents (OCDP), individuals with IGT and NIDDM showed significantly higher levels of insulin than the control subjects (Table II). The individual Δ IRI values in all the groups are shown in Fig. 1.

C-peptide response : The mean Δ C-peptide value in the individuals with IGT was slightly lower and in the OCDP and NIDDM, it was slightly higher than the control value, but the differences were not statistically significant (Table II). The individual Δ C-peptide values are shown in Fig. 2. In 55% of the OCDP, 67% of the individuals with IGT and 33% of NIDDM patients, the C-peptide levels were not high, although the corresponding IRI values were higher than normal.

Insulin/Glucose ratios : The Δ IRI/ Δ glucose ratios in the three groups were higher than in controls (Table II). No correlation was observed between 2 hr plasma glucose and Δ IRI in IGT subjects and in OCDP. A negative but not statistically significant correlation was observed between 2 hr plasma glucose and Δ IRI in NIDDM patients, $r = -0.28$, $P > 0.1$.

Insulin sensitivity : Insulin sensitivity measured as the glucose disposal rate (K_{ITT}) was significantly lower in the NIDDM patients ($P < 0.001$) and also in the OCDP ($P < 0.05$) compared with the control value, suggesting decreased insulin sensitivity (Table III). The K_{ITT} values were low in all the NIDDM patients and in 50% of the OCDP (Fig. 3).

DISCUSSION

Hyperinsulinemia both in the basal state and after stimulation of the beta cell is commonly observed in obesity (13). In non-obese individuals, hyperinsulinism develops only when insulin resistance sets in (14).

This study shows that the hyperinsulinemia observed in OCDP, IGT, and mild NIDDM is not due to increased beta cell secretion as there was no corresponding increase in C-peptide concentration in all the three groups. So the peripheral hyperinsulinism is probably due to some compensatory mechanism, either at the hepatic level or at the level of receptor mediated enzymatic degradation of insulin. Bonora et al (15) have reported hyperinsulinism with low hepatic insulin extraction and hyper secretion of beta cells in mild glucose intolerance

TABLE II : Plasma glucose, IRI and C-peptide responses.

Group	Plasma glucose mg/dl		Δ IRI μ U/ml	Δ C-peptide pmol/ml	Δ IRI/ Δ Glucose
	Fasting	Δ Glucose			
Controls (n=15)	89 \pm 8	446 \pm 38	242 \pm 69	5.37 \pm 0.94	9.8 \pm 2.73
IGT (n=12)	105 \pm 15	687 \pm 78	527 \pm 206*	4.3 \pm 2.4	14 \pm 5.5**
NIDDM (n=9)	111 \pm 20	849 \pm 77	648 \pm 215*	7.2 \pm 3.8	14 \pm 4.6**
OCDP (n=9)	98 \pm 16	516 \pm 73	466 \pm 130*	6 \pm 2.7	15.3 \pm 4.5*

* $P < 0.001$; ** $P < 0.05$ compared with controls.

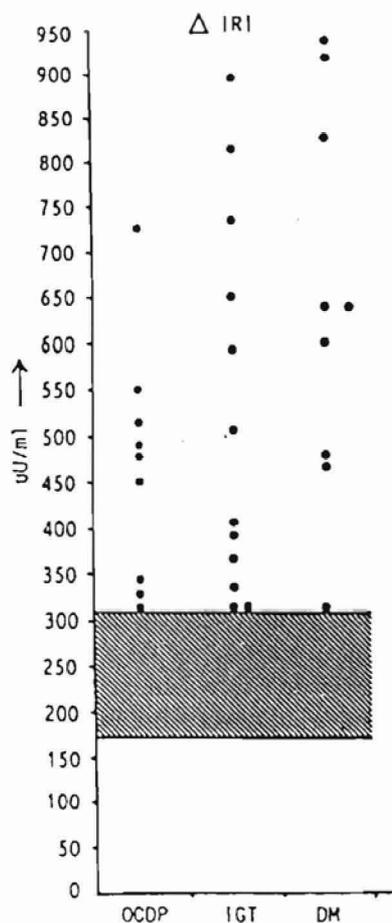


Fig. 1 : Distribution of Δ IRI in OCDP, IGT and NIDDM subjects. The shaded block indicates the normal range (mean \pm 1 SD) for controls.

TABLE III : PK_{ITT} values.

Group	K_{ITT} ($min^{-1} \times 100$)
Controls	5.49 ± 1.9
NIDDM	$1.85 \pm 0.9^*$
OCDP	$3.85 \pm 1.64^{**}$

*($P < 0.001$; ** $P < 0.05$ compared with control subjects).

and obese subjects. But, in our study, IGT subjects showed lower or near normal beta cell secretion which proves that the peripheral hyperinsulinemia is not due to increased beta cell secretion. In these individuals, the metabolic clearance rate of insulin might have

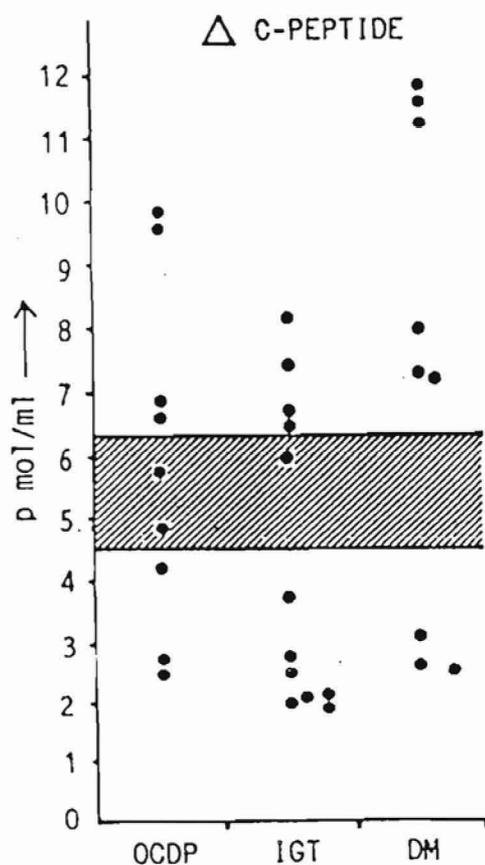


Fig. 2 : Distribution of Δ C-peptide in OCDP, IGT and NIDDM subjects. The shaded block indicates the normal range (means \pm 1SD) for controls.

been altered. Most of the insulin degradation has been demonstrated to follow hormone receptor binding (16). Reduced binding of insulin to its receptors is reported in mild glucose intolerance (17). So, the hyperinsulinemia in IGT individuals could be due to either decreased hepatic extraction of insulin and/or decreased number of insulin receptors, resulting in decreased insulin binding and lowered insulin degradation. In NIDDM patients and OCDP subjects also the results are similar showing that the hyperinsulinism is not due to increased beta cell secretion, but due to alterations in the insulin metabolism at the periphery. Coscelli et al (18) have reported that both in normal

reported decreased insulin binding to its receptors and decreased affinity of the receptors in both non-obese and obese OCDP subjects with normoglycemia. Results of this study also suggest that, there could be insulin receptor abnormalities in OCDP which could be the reason for insulin resistance in these subjects.

In summary, the data presented in this paper suggest that, peripheral hyperinsulinism observed in OCDP, individuals with IGT and NIDDM, is not pancreatic in origin, but due to some alterations in the insulin metabolism. The insulin resistance measured by ITT is present in all the NIDDM patients, and in 50% of the OCDP.

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