

GLUCAGON RESPONSE TO GLUCOSE LOAD IN OFFSPRING OF CONJUGAL TYPE 2 DIABETIC PARENTS IN SOUTH INDIA

C Snehalatha*, PK Bhattacharya**, V Mohan***, A Ramachandran***, M Viswanathan****

SUMMARY

Immunoreactive glucagon responses were measured in 21 normoglycaemic adult offspring of non-insulin dependent (Type 2) diabetic parents, in the fasting state and during an oral glucose tolerance test. In 7 of the 21 offspring, the mean fasting immunoreactive glucagon value was significantly lower than the control value ($p < 0.001$). In this group, glucose stimulation did not produce inhibition of immunoreactive glucagon secretion. The insulin response in this group was not significantly different from the values in the other study groups. In the other 14 offspring, the pattern of glucagon response to glucose stimulation was similar to controls.

It is likely that this non-suppressive effect of glucose on immunoreactive glucagon in some of the "prediabetic" individuals is an early change in the alpha cell function during the natural history of non-insulin dependent diabetes in Asian Indian subjects.

Key words: Immunoreactive glucagon, pancreatic alpha cell function.

INTRODUCTION

Glucose homeostasis is maintained mainly by the reciprocal secretion of the two major pancreatic hormones, insulin and glucagon. Although the metabolic aberrations in diabetes are attributed to deranged insulin metabolism, there are sufficient manifestations of defective glucagon metabolism also in non-insulin dependent Type 2 diabetes.¹ Changes in beta cell function have been demonstrated in normoglycaemic offspring of Type 2 diabetic parents, in several ethnic groups, suggesting a genetic predisposition to these changes.²⁻⁹ Offspring of Type 2 diabetic parents have been shown to be a high risk group for the disease, in south India.¹⁰ Hence, they form an ideal group to look for early metabolic and hormonal changes occurring in "prediabetic" stages. Our earlier studies have shown that the non-obese normoglycaemic offspring of two Type 2 diabetes patients have higher than normal insulin responses to glucose,^{7,8} and they also show a dissociation in the molar ratio of insulin/C-peptide in peripheral circulation.⁷

As there are only a few reports on the functional status of the alpha cells in these "prediabetic" individuals,^{3,5,11} this study was taken up to assess the glucagon response to glucose stimuli in normoglycaemic offspring of Type 2 diabetic parents.

MATERIAL AND METHODS

Twenty one offspring (11 men and 10 women, aged 26 to 51 years, mean 35.7 ± 7.3 SD) from different families were studied. In all families, both the parents had Type 2 diabetes. All the offspring had normal glucose tolerance according to the WHO criteria.¹² They were not on any medication for diabetes and were free from any other illness. Their mean body mass index

was 25 ± 4.5 kg/m². Ten normal volunteers (6 men, 4 women, age 34.2 ± 4.3 years and BMI 23.4 ± 3.2 kg/m²) were also tested for comparison.

Plasma samples were collected during the 2-hour oral glucose tolerance test with 75 g glucose load, for the estimation of immunoreactive insulin (IRI) and immunoreactive glucagon (IRG). Blood samples were collected in tubes containing 1000 KIU of trasylol and 1.2 mg of EDTA per ml of blood. The plasma was separated immediately and stored at -20°C. IRI was estimated by a modified procedure of Herbert *et al*¹³ and IRG using the kit supplied by Diagnostic Products Corporation, USA. The antiserum is specific for human pancreatic glucagon of mol wt 3500 and its sensitivity is 5 pmol/l. Intra assay coefficient of variation (CV) was 5.8% and inter assay CV was 9.8%.

Plasma glucose was estimated by the glucose oxidase method (GOD-PAP, Boehringer Mannheim). Statistical comparisons were done using ANOVA.

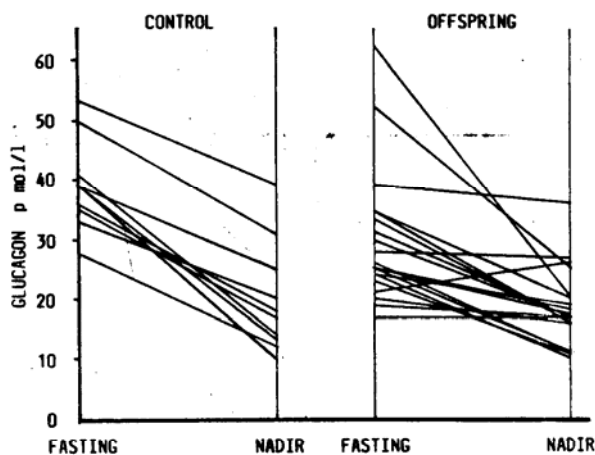


Fig 1: Fasting and nadir concentrations of plasma glucagon obtained during the GTT in controls and offspring. In seven offspring, there was negligible decrease in the fasting glucagon value following glucose ingestion.

*Head, Department of Biochemistry, **Research Student, ***Deputy Director, ****Director, Diabetes Research Centre & MV Hospital for Diabetes, S Main Road, Royapuram, Madras 600 013. Received: 20.10.1990 Accepted: 15.3.1991

Table 1: Plasma Glucose, Insulin and Glucagon responses in the study groups

Time (min)	Control (n=10)					Offspring									
	0	30	60	90	120	Group A (n=7)					Group B (n=14)				
	0	30	60	90	120	0	30	60	90	120	0	30	60	90	120
Plasma Glucose (mg/dl)	96	134	123	114	96	95	143	147	125	111	96	139	147	129	109
	6	16	19	22	17	6	23	21	18	15	6	22	23	20	13
Insulin (uU/ml)	12	82	101	86	50	6	85	132	115	77**	18	83	120	96	67
	8	40	59	27	24	8	36	56	60	43	13	69	68	66	45
Glucagon (pmol/l)	39	34	23	35	34	25*	24	25	25	28	30	25	21	23	23
	8	10	10	11	18	7	7	11	11	14	10	10	10	9	11

*p < 0.001; **p < 0.002 compared to control value. Values are Mean ± SD.

RESULTS

The Table shows the mean values of plasma glucose, IRI and IRG responses in the offspring in comparison with the controls. The glucose values were similar in the offspring and controls.

Glucose produced a suppression of glucagon secretion in normal individuals, the percentage of suppression ranging from 21 to 74% of the fasting value (mean 58.6% ± 17.7% SD) (Fig 1). In seven offspring (group A) this suppressive effect was absent. In this group, the mean fasting value of glucagon was significantly lower (p < 0.001) than the control value. In the other 14 offspring (group B), glucose produced a suppression of glucagon secretion ranging from 22 to 68% (48.4 ± 16.8%).

The fasting IRI values and the values in response to glucose stimulation were slightly higher in offspring in groups A and B. Statistical significance was observed only in the 2-hour value in group A (p < 0.002). The mean IRI responses of offspring in group A and group B were similar.

DISCUSSION

Several studies have attempted to analyse the early changes occurring in the natural history of diabetes by assessing the beta cell function²⁻⁹ and insulin sensitivity¹⁴⁻¹⁶ in offspring of diabetic parents. Altered insulin metabolism⁵⁻⁷ and lowered insulin sensitivity¹⁴⁻¹⁶ have been demonstrated in these individuals, genetically prone to diabetes. The few reports^{3,5,11} on the glucagon response in "prediabetic" subjects have shown varied results. Johansen *et al*³ reported higher fasting values of glucagon in unaffected twins of diabetic subjects. In a recent study on offspring having one type 2 diabetic parent, higher basal plasma glucagon values were observed.⁵ Johnston *et al*¹¹, on the contrary, observed normal glucagon responses in offspring of two type 2 diabetic parents to both glucose and arginine stimulation.

The study subjects in this report form a homogeneous group with high risk of diabetes.¹⁰ Our results on glucagon responses are at variance from the reports mentioned above.^{3, 5, 11} The fasting glucagon values in many offspring were lower than the control value. In 33% of the offspring, the suppressive effect of glucose on the secretion of glucagon was lacking. This may be an early change occurring in the alpha cell

function in these individuals. Ethnic differences may be responsible for the different results observed in Asian Indians. It is possible that the secretory functions of the alpha and beta cells go through a series of changes in the natural history of diabetes. We had observed an enhanced glucagon secretion in the NIDDM patients in response to glucose stimulation in contrast to patients with fibrocalculous pancreatic diabetes where the glucagon response was absent.¹⁷ Serial assessment of glucagon and insulin secretion will be needed to study functional changes occurring both in the alpha and beta cells of the pancreas during the natural history of diabetes.

ACKNOWLEDGEMENT

We gratefully acknowledge the grant-in-aid from the Board of Research in Nuclear Science, Bombay, for this study which formed a part of the project no.35/2/87-G.

REFERENCES

- Gerich JE. Abnormal glucagon secretion in Type 2 (non-insulin dependent) diabetes mellitus: Causes and consequences. In: Creutzfeldt W, Lefebvre P, Eds. *Diabetes Mellitus: Pathophysiology and Therapy*, Berlin: Springer-Verlag, 1989: 127-33.
- Cerasi E, Efendic S, Luft R. Dose response relation between plasma insulin and blood glucose levels during oral glucose loads in prediabetic and diabetic subjects. *Lancet* 1973; i: 794-7.
- Johansen K, Soeldner JS, Gleason RE. Insulin, growth hormone and glucagon in prediabetes mellitus: A review. *Metabolism* 1974; 23: 1185-99.
- Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Decreased insulin concentrations in non-diabetic offspring of diabetic parents. *N Engl J Med* 1988; 319: 1297-301.
- Leslie RDG, Volkman HP, Poncher M, Hanning I, Orskov H, Alberti KGMM. Metabolic abnormalities in children of non-insulin dependent diabetics. *Br Med J* 1986; 293: 840-2.
- O'Rahilly S, Turner RC, Methews DR. Impaired pulsatile secretion of insulin in relatives of patients with non-insulin dependent diabetes. *N Engl J Med* 1988; 318: 1225-30.
- Snehalatha C, Mohan V, Ramachandran A, Jayashree R, Viswanathan M. Pancreatic beta cell function in offspring of conjugal diabetic parents: Assessment by IRI and C-peptide ratio. *Horm Metab Res* 1984; 16 (Suppl): 142-4.
- Snehalatha C, Ramachandran A, Mohan V, Viswanathan M. Insulin response in obese and non-obese offspring of conjugal Indian diabetic parents with increasing glucose intolerance. *Pancreas* 1986; 1: 139-42.
- Savage PJ, Bennett PH, Gordon P, Miller M. Insulin responses to oral carbohydrate in true prediabetes and matched controls. *Lancet* 1975; i: 300-2.
- Viswanathan M, Mohan V, Snehalatha C, Ramachandran A.

- High prevalence of Type 2 (non-insulin dependent) diabetes among the offspring of conjugal Type 2 diabetic parents in India. *Diabetologia* 1985; 28: 907-10.
11. Johnston C, Ward WK, Beard JC, McKnight B, Porte D Jr. Islet function and insulin sensitivity in the non-diabetic offspring of conjugal Type 2 diabetic parents. *Diabetic Medicine* 1990; 7: 119-25.
 12. WHO Expert committee: Second report on Diabetes Mellitus. WHO Tech Re Ser 646, Geneva, 1980.
 13. Herbert V, Lau KS, Gottlieb CW, Bleicher SJ. Coated charcoal immunoassay of insulin. *J Clin Endocrinol Metab* 1965; 25: 1375-84.
 14. Bogardus C, Lillioja S, Foley J, *et al*. Insulin resistance predicts the development of non-insulin dependent diabetes mellitus in Pima Indians. *Diabetes* 1987; 36: 47A.
 15. Leslie RDG, Ganesh A, Volkman HP, Alberti KGMM. Insensitivity to insulin in offspring of non-insulin dependent diabetic parents. *Diab Nutr Metab* 1988; 3: 235-7.
 16. Ramachandran A, Snehalatha C, Mohan V, Bhattacharyya PK, Viswanathan M. Decreased insulin sensitivity in offspring whose parents both have Type 2 diabetes. *Diabetic Medicine* 1990; 7: 331-4.
 17. Mohan V, Snehalatha C, Ramachandran A, Chari S, Madanagopalan M, Viswanathan M. Plasma glucagon responses in tropical fibrocalculous pancreatic diabetes. *Diab Res Clin Pract* 1990; 9: 97-101.
-