The Korean Journal of Internal Medicine
Vol. 1, No. 1, January, 1986

Postprandial 2-hr C-peptide Concentration as a Guide for Insulin Treatment in Patient with NIDDM

Rhee Sook Kim, M.D., In Myung Yang, M.D., Jin Woo Kim, M.D.,
Young Seol Kim, M.D., Kwang Won Kim, M.D., Sun Woo Kim, M.D.
and Young Kil Choi, M.D.

Department of Internal Medicine, Kyung Hee University Hospital, Seoul, Korea

To determine the usefulness of postpradial-2hr serum C-peptide as a guide for insulin treatment in NIDDM, the 67 NIDDM patients admitted in Kyung Hee University Hospital from Nov. 1981 to May 1984 were classified according to postprandial 2-hr insulin, C-peptide levels and 24-hr urine C-peptide levels.

The patients were divided into 3 groups according to the level of insulin or C-peptide in normal persons reported previously.[9]

In 22 patients with postprandial 2-hr values of more than 5.8 ng/ml for C-peptide, 12 patients (55%) were diet controllable and only 5 patients (22%) required insulin treatment. On the other hand, in the classification according to postprandial 2-hr insulin or 24-hr urine C-peptide levels, higher response groups should be controlled by diet alone, but 9 of 18 patients (50%) for insulin, 8 of 14 patients (57%) for 24-hr urine C-peptide required insulin treatment.

The classification according to postprandial 2hr C-peptide levels was a more sensitive guide for insulin treatment than that with postprandial 2hr insulin level or 24hr urine C-peptide level.

Key Words: *Postprandial 2-hr serum C-peptide, Guide for insulin treatment, NIDDM*

INTRODUCTION

In the past decades it had been asserted that glucose intolerance in NIDDM patients can arise from several causes. Numerous accumulated evidences support the notion that insulin resistance and decrease of insulin secretory capacity are the major causes of glucose intolerance in NIDDM.[1-5]

Although the majority of NIDDM patients has normal or increased serum insulin concentration and 24-hour urinary C-peptide excretion,[6] many of them require insulin therapy in practice without any improvement by diet therapy and oral hypoglycemic agents. Many factors are taken into consideration to use insulin such as degree of blood glucose elevation, history of actual ketosis, relative body weight, complications, duration of disease, success or failure of the previous treatment modalities. However, there has been no useful criteria for the insulin therapy before one begin to start diet therapy and oral hypoglycemic agents.

Turkington et al.[7] reported that the patients with peak value of less than 60μU/ml for serum insulin concentration or less than 6.0 ng/ml for serum C-peptide concentration during oral glucose tolerance test did not normalize the blood glucose concentration after weight reduction and required an additional oral hypoglycemic agent or insulin. Rendell et al.[8] advocated that patients with fasting and glucose stimulated plasma C-peptide values similar to those in normal subjects were diet-controlable diabetes.

To determine whether postprandial 2hr serum C-peptide level is useful indicator for insulin treatment in NIDDM, we performed the retrospective analysis of several clinical characteristics according to the classification by postprandial 2hr serum insulin, C-

Address reprint requests: Young Kil Choi M.D., Department of Internal Medicine in Kyung Hee University Hospital, Hoekidong Seoul 131, Korea

peptide level and 24-hour urinary C-peptide excretion.

SUBJECTS AND METHODS

Subjects were 67 patients (37 male and 30 female) with NIDDM admitted from February, 1981 to May, 1984, in Kyung Hee University Hospital.

They were aged from 31 to 76 years and free from renal failure. Blood glucose was measured by glucose oxidase method, HbA_1c by column method and plasma insulin and C-peptide were measured by radioimmunoassay (Daiichi radioisotope laboratories). All patients were classified in three ways by serum insulin, C-peptide, 24-hr urine C-peptides and reclassified into 3 groups (Table 2) on the basis of normal values which we reported previously (Table 1).[9] Group 1 of each classification had values above 1 S.D of mean and group 3 had values below 1 S.D of mean.

Table 1. Serum insulin, serum C-peptide and 24hr urinary C-peptide in normal subjects (n=11)*

	Serum insulin (μU/ml)		Serum C-peptide (ng/ml)		24hr urine C-peptide (μg/gm.Cr.)
	Basal	pp2hr	Basal	pp2hr	
Normal	13±5	36±18	2.0±0.7	4.7±1.1	52±18

Table 2. Grouping of the subjects according to the level of serum insulin, serum C-peptide and 24hr urinary C-peptide

	Group
Serum Insulin (μU/ml)	Group I_1>54
	Group I_2 18~54
	Group I_3<18
Serum C-peptide (ng/ml)	Group C_1>5.8
	Group C_2 3.6~5.8
	Group C_3<3.6
24 hr-urine C-peptide (μg/gm. Cr.)	Group U_1>70
	Group U_2 34~70
	Group U_3<34

RESULTS

1. Clinical and laboratory findings

1) In each group classified according to the postprandial 2-hr serum insulin level (Table 3), The higher response group of insulin (group I_1) was more obese than the lower response group (group I_3). Their weight indices were 1.13±0.14, 0.98±0.12 respectively. Fasting blood sugar and HbA_1c were low in group I_1 significantly. ($p<0.005$) The incidence of diabetic complica-

Table 3. Clinical and laboratory findings in each group classified according to the postprandial 2-hr serum insulin level

	Group I_1	Group I_2	Group I_3
N	18	32	17
Age(Yr.)	54.0±11.2	52.2±14.9	53.1±9.2
BMI*	24.6± 3.2	24.6±10.0	21.4±2.6*
Weight index**	1.13±0.14	1.05±0.11	0.98±0.12*
Duration (Yr.)	4.5 ± 4.6	4.3 ±3.9	5.0 ±3.4
Blood glucose (mg/dl)			
Fasting	183.8±67.2	216.5±73.9	302.5±80.1
pp2 hr	338.6±27.5	309.6±75.6	409.0±109.9
HbA_1c(%)	10.0± 2.0	10.7± 2.3	13.0± 1.8*
Complication	4(13%)	13(43%)	13(43%)
Retinopathy	3	8	8
Neuropathy	1	3	5
Nephropathy	0	2	0

*BMI: Body mass index = Weight (kg)/Height^2(m)

**Weight index: Weight/Ideal body weight *: -<0.005

tions was lower in group I_1 (13%) than in group I_3 (43%).

2) In the classification according to the level of postprandial 2-hr serum C-peptide (Table 4). There were similar results to the classification according to insulin level but more significant discrimination between two groups. (group C_1, C_3).

3) In the classification according to the level of 24-hr urine C-peptide (Table 5). The higher response group (group U_1) was more obese than the lower response group (group U_3). ($p<0.005$). Their weight indices were 1.13 ± 0.15, 0.97 ± 0.12 respectively. Fasting blood sugar was lower in group U_1 (188.5 ± 85.6) than in group U_3 (272.9 ± 81.5 mg/dl). The incidence of diabetic complications was lower in group U_1 (9%) than in group U_3 (62%). When these results were compared with the above results by the classification according to the level of postprandial 2-hr serum C-peptide, the incidence of diabetic complications had no difference but fasting blood sugar and HbA_1c presented more significant difference in the classification according to postprandial 2-hr serum C-peptide level.

2. Changes in the mode of treatment during the initial and final phase of the admission in each group.

1) In the classification according to the level of postpradial 2-hr serum insulin (Table 6). Diet-

Table 4. Clinical and laboratory findings in each group classified according to the postprandial 2-hr serum C-peptide level

	Group C_1	Group C_2	Group C_3
N	22	13	31
Age(Yr.)	50.7 ± 11.7	57.7 ± 7.9	53.0 ± 13.2
BMI	24.4 ± 3.0	23.9 ± 2.4	21.4 ± 2.7*
Weight index	1.10 ± 0.13	1.10 ± 0.11	1.00 ± 0.13*
Duration (Yr.)	2.3 ± 3.4	4.3 ± 3.9	5.0 ± 3.4
Blood glucose (mg/dl)			
Fasting	167.5 ± 61.5	222.3 ± 45.5	273.2 ± 87.2*
pp2hr	291.1 ± 85.8	362.6 ± 86.8	356.4 ± 108.0
HbA_1c(%)	9.7 ± 1.6	11.0 ± 2.1	$12. \pm 2.6$*
Complication	2(7%)	8(26%)	20(67%)
Retinopathy	2	6	11
Neuropathy	0	2	7
Nephropathy	0	0	2

* $p<0.005$

Table 5. Clinical and laboratory findings in each group classified according to the 24-hr urinary C-peptide level

	Group U_1	Group U_2	Group U_3
N	14	11	20
Age(Yr.)	53.1 ± 9.4	50.2 ± 12.2	55.2 ± 11.0
BMI	24.8 ± 3.4	24.3 ± 1.5	21.2 ± 2.6*
Weight index	1.13 ± 0.15	1.05 ± 0.12	0.97 ± 0.12*
Duration (Yr.)	2.4 ± 3.0	3.6 ± 3.4	6.1 ± 5.0
Blood glucose (mg/dl)			
Fasting	183.5 ± 85.6	232.0 ± 39.6	272.9 ± 81.5**
pp2 hr	310.5 ± 73.8	391.1 ± 21.0	268.2 ± 96.6
HbA_1(%)	10.4 ± 2.0	11.3 ± 1.5	12.2 ± 1.6
Complication	4(9%)	6(29%)	13(62%)
Retinopathy	1	4	7
Neuropathy	1	2	5
Nephropathy	0	0	1

* $p<0.005$ ** $p<0.01$

controllable diabetic patients (pp2hr blood sugar; less than 200 mg/dl) were 6 (33%) in group I_1 but zero in group I_3. Remarkably, one patient in group I_1 was receiving insulin on admission but was able to control by diet, only on discharge. The patients receiving insulin on discharge were 9 (50%) in group I_1, 17 (100%) in group I_3.

2) In the classification according to the level of postprandial 2-hr serum C-peptide. (Table 7). Diet-controllable diabetics were 12 (55%) in group C_1 but zero in group C_3. The Diabetics receiving insulin on discharge were 5 (22%) in group C_1, 29 (97%) in group C_3.

Table 6. Changes in the mode of treatment during the initial and final phase of admission in each group, classified according to the level of postprandial 2-hr serum insulin

Treatment Initial	Treatment Final	Group I_1	Group I_2	Group I_3
None	Diet	5	7	—
Oral*	Diet	—	1	—
Insulin	Diet	1	—	—
None	Oral	2	1	—
Oral*	Oral	1	3	—
None	Insulin	3	5	7
Oral*	Insulin	2	8	6
Insulin	Insulin	4	6	4
Total Number		19	31	17

*Oral: Oral hypoglycemic agent

Table 7. Changes in the mode of treatment during the initial and final phase of admission in each group, classified according to the level of postprandial 2-hr serum C-peptide

Treatment Initial	Treatment Final	Group C_1	Group C_2	Group C_3
None	Diet	10	1	—
Oral*	Diet	1	—	—
Insulin	Diet	1	—	—
None	Oral	2	1	—
Oral*	Oral	3	—	—
None	Insulin	2	4	10
Oral*	Insulin	1	—	9
Insulin	Insulin	2	3	10
Total Number		22	9	30

*Oral: Oral hypoglycemic agent

3) In the classification according to the level of 24-hr urine C-peptide (Table 8). Diet-controllable diabetics were 4 (29%) in group U_1 but none in group U_3. The diabetics receiving insulin on discharge were 8 (57%) in group U_1, 19 (95%) in group U_3.

At the point, diet-controllable diabetics may be present higher response (such as group I_1, C_1, U_1) than diabetics requiring additional treatment one would think that the classification according to the level of postprandial 2-hr serum C-peptide is a more sensitive index for insulin treatment than other classifications.

DISCUSSION

Diabetes consisted of juvenile-onset diabetes and adult-onset diabetes in past years, but several inconsistencies were indicated in this classification.

At present, diabetes are classified into three groups; IDDM, NIDDM, secondary diabetes according to the propose by national diabetes Data group in 1973.[10]

IDDM is almost always characterized by a nearly total absence of endogenous insulin secretion from pancreatic β-cells and caused by an inflammatory process, so called insulitis.

Genetics[11-13] and viral infections[14-15] are thought to play important etiologic roles in its pathogenesis. Therefore, all insulin dependent diabetics require insulin to sustain life because of proneness to ketosis and severe hyperglycemia.

In contrast, NIDDM has no defects in insulin

Table 8. Changes in the mode of treatment during the initial and final phase of admission in each group, classified according to the level of postprandial 2-hr urinary C-peptide

Treatment Initial	Treatment Final	Group U_1	Group U_2	Group U_3
None	Diet	2	2	—
Oral*	Diet	1	—	—
Insulin	Diet	1	—	—
None	Oral	2	1	—
Oral*	Oral	—	1	1
None	Insulin	5	4	6
Oral*	Insulin	2	2	5
Insulin	Insulin	1	1	8
Total Number		14	11	20

*Oral: Oral hypoglycemic agent

secretion from pancreatic β-cell and may results from a specific receptor or post-receptor defect namely, insulin resistance in target tissues of insulin.

Since Yallow et al.[17] reported the methods employed in the immunoassay of endogenous insulin in 1960, these facts become more clear. Therefore, the principle of treatment is a removal of the causes of insulin resistance. For the treatment of diabetes, it has no disagreement that insulin therapy is mandatory for the treatment of IDDM. Because the pathogenic mechanism of NIDDM is insulin resistance and level of insulin in patients with NIDDM are normal or increased, the patients with NIDDM do not need insulin for treatment theoretically. However, many patients are treated with insulin in practice. A few modalities for treatment are applied to patients with NiDDM, diet only, diet and oral hypoglycemic agent, diet and insulin.

And yet, diet therapy remains the most important method for treatment of NIDDM because weight reduction by diet improves insulin resistance and restores the sensitity of tissues to insulin. In practice, a physician has to use insulin in the patient whose blood sugar has not been controlled by diet therapy and oral hypoglycemic agents.

Therefore, there occurs a question how we predict one to need the insulin thereapy before starting diet therapy and oral hypoglycemic agent. Turkington et al.[7] published that patients with peak values of less than 60 μU/ml for insulin or less than 6.0 ng/ml for C-peptide induced during oral glucose tolerance testing did not normalize the blood sugar concentration after weight reduction and required additional oral hypoglycemic agent or insulin. Rendell et al.[8] advocated that patients with fasting and glucose-stimulated plasma C-peptide values similar to those in normal subjects were diet-controllable diabetes and others needed oral hypoglycemic agents or insulin. In another study,[18] they reported that insulin secretory capacity was measured by C-peptide responsle during a standard oral glucose tolerance test in patient who achieved normalization of plasma glucose level only by dietary regimen.

Summed C-peptide levels of the diabetics controlled by diet therapy was higher than for normal weight, nondiabetic volunteers. Beischer et al.[19] asserted that the response of immunoassayable C-peptide to an intravenous glibenclamide-glucose load in diabetics was useful index in order to predict which patients would be manageable with glibenclamide tablets and which would require insulin. Madsbad et al.[20] contended that serum C-peptide concentration measured 6 minutes after an I.V. injection of 1 mg glucagon seemed to be of value in the out patient clinic to discriminate non-insulin dependent from insulin-dependent patients.

The above reporters performed prospective study but we did a retrospective study and discovered similar results with them. We measured the postpradial 2-hr response of insulin or C-peptide because diabetics present the peak response about 2-hr after meal, which is different from peak respnse about 30-60 min in normal subjects.[21] In addition, we measured the 24-hr urine C-peptide in order to determine a more precise index for insulin treatment.

In the classification according to the level of postprandial 2-hr serum C-peptide and 24-hr urine C-peptide, (Table 7, 8) diet-controllable diabetics were 12 (55%), 4 (29%) in higher group (C_1 U_1) respectively and insulin needed diabetics were 29 (97%), 19 (95%) in lower group (C_3, U_3) respectively. 12 (55%) in the higher response group (C_1) was controlled by diet. Especially, one who was diagnosed as CVA was controlled by insulin transiently after admission and then, by diet after discharge. It was believed that CVA, one acute stress could aggravate glucose intolerance transietly in this patient. Nondiet-controllable diabetics in group C_1 were 10 (45%), 5 of them required insulin therapy. By previous reports[7,8] they should be controlled by diet only. One had pulmonary tuberculosis. Two had no specific diseases and required daily 30 U, 40 U of insulin on admission and reduced to 20 U, 12 U 3 months, 5 months later respectively. Rest one was a patient with CVA and required 60 U of insulin on admission. But we also expect that the dose of insulin will be decreased in near future. Therefore, we could get the result that the classification according to postprandial 2-hr serum C-peptide is a more sensitive indicator for the requirement of insulin therapy than that according to 24-hr urine C-peptide. The reason why the 24-hr urinary C-peptide was less sensitive may arise from the fact that postprandial 2-hr serum C-peptide reflects secretory response of insulin newly synthesized from pancreatic β-cell after mixed meal, but 24-hr urine C-peptide reflects the total insulin secretory capacity of pancreatic β-cell throughout meal, emotional stress, and other during all the day.

Turkington et al.[22] published the results of their study as follows: In glucose tolerance test (100g) characterized by measurement of induced insulin secretion, diabetic complication of retinopathy, sensory neuropathy and renal disease developed only in the group of patients that the induced serum insulin peak fell below 60μU/ml and who showed

greater than this were not associated with development of these complications. They suggested that a critical amount of insulin secretory reserve could distinguish the qualitatively distinct clinical syndrome, true diabetes from the syndrome of pure resistance to insulin. Our results were similar to theirs.

Most diabetics needed insulin therapy had more frequent diabetic complications and lower level of postprandial 2-hr serum insulin, C-peptide and 24-hr urine C-peptide. In conclusion, to predict the diabetics need insulin therapy, the duration of diabetes mellitus, presence of diabetic complications, degree of sugar elevation, and failure of previous treatment modalities are important factors but the level of postprandial 2-hr serum insulin and C-peptide, 24-hr urine C-peptide are more important factors. Among them, the classification according to postprandial 2-hr C-peptide level is a most sensitive guide for insulin treatment.

REFERENCES

1. Himsworth H: *The syndrome of diabetes mellitus and its cause. Lancet 1:465, 1949*
2. Bolinder J, Ostman J, Arner P: *Postreceptor defects causing insulin resistance in normoinsulinemic noninsulin dependent diabetes mellitus. Diabetes 31:911, 1982*
3. Olefsky JM, Reaven GM: *Insulin binding in diabetes. Relationships with plasma insulin levels and insulin sensitivity. Diabetes 26:680, 1977*
4. Olefsky JM, Kolterman OG: *Machanisms of insulin resistance in obesity and noninsulin dependent (type II) diabetes. Am J Med 70:151, 1980*
5. Rizza R, Mandarino L, Gerich J: *Mechanisms of insulin resistance in man: Assessment using the insulin dose-response curve in conjunction with insulin receptor binding. Am J Med 70:169, 1981*
6. Reaven GM: *Insulin-independent diabetes millitus: Metabolic characteristics. Metabolism 29:445, 1980*
7. Turkington RW, Estkoski A, Link M: *Secretion of insulin or connecting peptide. A predictor of insulin dependence of obese diabetics. Arch Intern Med 142:1102, 1982*
8. Rendell M: *C-peptide levels as a criteirion in treatment of maturity onset dabetes. J Clin endocrinol Metab 57:1198, 1983*
9. Kim SY, Lee TW, Kim JW, Kim YS, Cho KS, Kim KW, Kim SW and Choi YK: *The urinary C-peptide excretion in diabetic patient. J Korean Diabetes Association, 7:5, 1982.*
10. National diabetes data group: *Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039, 1979*
11. Christy M, Green A, Christau B: *Studies of the HLA system and insulin-dependent diabetes mellitus. Diabetes Care 2:209, 1979*
12. Ginsherg-Fellner F, Dobersen MJ, Witt ME: *HLA antigens, cytoplasmic islet cell antibodies and carbohydrate tolerance in families of children with insulin dependent diabetes mellitus. Diabetes 31:292, 1982*
13. Sakurami T, Ueno Y, Nagaoka K: *HLA-DR specifications in Japanese with juvenile onset insulin-dependent D.M. Diabetes 31:105. 1982*
14. Craighead JE: *Viral diabetes mellitus in man and experimental animals. Am J Med 70:127, 1981*
15. Gamble DR, Kinsley ML, Fitzgerald MG. *Viral antibodies in diabetes mellitus. Br Med J 3:627. 1969*
16. Menser MA, Forrest JM, Bransby RD: *Rubella infection and diabetes mellitus. Lancet 1:57. 1978*
17. Yalow RS, Berson SA: *Immunoassay of endogenous plasma insulin in man. J Clin Invest 39:1157. 1960*
18. Rendell M, Ross DA, Dreq HM: *Endogenous insulin secretion measure by C-peptide in maturity onset diabetes controllable by diet alone. Arch Intern med 141:1617. 1981*
19. Beischer W, Kerner L, Pfeiffer EF: *Insulin therapy in relation to circulating C-peptide levels. Diabetes (Suppl 1) 27:235, 1978*
20. Madshad S, Krarup T, McNair P: *Practical clinical value of the C-peptide respnse to glucagon stimulation in the choice of treatment in diabetes mellitus. Acta Med Scand 210:153, 1981*
21. DeGroot LJ, Winegrad AL: *Diabetes Mellitus. Endocrinology 2:1010, 1979*
22. Turkington RW, Weindling HK: *Insullin secretion in the diagnosis of adult-onset diabetes mellitus. JAMA 240:833, 1978.*