C-Peptide in NIDDM

Follow-up for 4–6 yr

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OBJECTIVE— To study whether fasting and 1-h postbreakfast C-peptide levels in NIDDM stabilize with time in individual patients.

RESEARCH DESIGN AND METHODS— Within the period of 4–6 yr, 49 NIDDM patients had repeated tests of fasting and 1-h postprandial levels of plasma glucose and C-peptide with the aim of determining their individual qualitative patterns. Throughout the follow-up period, 13 patients were treated with insulin, 21 with oral sulfonylureas, and 15 were switched from oral drugs to insulin, with the tests done in both treatment periods.

RESULTS— The group as a whole demonstrated no changes in mean fasting or postprandial C-peptide within 4–6 yr of observation, irrespective of the mode of therapy or its changes. Glycemic and C-peptide response to breakfast was qualitatively typical for each patient with the correlation between plasma glucose and C-peptide. However, the response was vastly different from patient to patient, and the cross-sectional data showed no correlation between postprandial changes in glycemia and C-peptide, nor between glycemic response to breakfast and fasting plasma glucose or C-peptide. In spite of high fasting glycemia, 25% of the patients showed remarkable tolerance to breakfast with only small increases in plasma glucose. In many other patients, however, in spite of similar increase in C-peptide, plasma glucose rose sharply after the meal.

CONCLUSIONS— In our group, no deterioration of the insulin secretory function was observed within 4–6 yr of follow-up. Qualitative patterns of the glycemic and C-peptide responses to breakfast were typical for each patient but vastly different between patients. We see in NIDDM a syndrome with few common characteristics and recommend further work for its subclassification into forms with different pathogenesis.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; TSH, THYROTROPIN; BMI, BODY MASS INDEX; WHR, WAIST-TO-HIP RATIO; CI, CONFIDENCE INTERVAL.

NIDDM is a syndrome of hyperglycemia without tendency to ketosis. These features are hardly enough to consider it a disease, and this can explain the lack of universally accepted unified theory of its pathogenesis, be it insulin insufficiency, insulin receptor or postreceptor (black box) defect, or an insulin-independent abnormality. Even its differentiation from IDDM is unsatisfactory in clinical practice (1). The approach to therapy of this syndrome is purely empyrical, and its results more often than not are mediocre at best.

It was claimed that persistent hyperglycemia leads, in the long run, to the exhaustion of pancreatic β-cells and ultimately to absolute insulin deficiency (2). This was found in several highly endogamous groups, but extrapolation from these observations to heterogeneous Caucasian populations is unwarranted. Indeed, Pima Indians are much more insulin resistant than Caucasians, even when matched for other factors (3); and significant differences in insulin and C-peptide secretion were reported, for example, between Caucasians and Gudjeratis in the same location (4).

In initiating this work, we hypothesized that NIDDM in Caucasians is a syndrome of diverse pathogenesis, that only a small minority of these patients become insulin dependent with time, and that in the great majority of patients, diabetes control is independent of endogenous insulin secretion. We have tried to verify this hypothesis by following a group of NIDDM patients for 4–6 yr.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS— Forty-nine Caucasian patients (23 men, 26 women) were seen in the clinic by the same physician 6–10 times/yr and had the characteristics shown in Table 1. None suffered from renal failure or conditions likely to affect gastric emptying or intestinal absorption. They did not know of any case of IDDM in their immediate families. Six patients suffered from primary hypothyroidism (2

Table 1—*Clinical characteristics of NIDDM patients*

AGE (YR)	59 ± 9.1 (37–73)	
DURATION OF DIABETES (YR)	8 ± 6.3 (<1–24)	
BMI (KG/M^2)	30.7 ± 6.5 (19.6–47.6)	
WHR	0.96 ± 0.08 (0.77–1.28)	
TOTAL CHOLESTEROL (MG/DL)	201 ± 46 (105–346)	
TRIGLYCERIDES (MG/DL)	261 ± 180 (63–1023)	
	FIRST TEST	LAST TEST
FASTING GLYCEMIA (MM)	12.6 (7.4–20.3)	11.3 (5.8–17.9)
GLYCEMIA 1 H AFTER MEAL (MM)	15.9 (8.4–23.5)	15.5 (8.5–22.3)
INDIVIDUAL CHANGES AFTER MEAL (MM)	3.3 (−0.7–7.2)	4.0 (0.4–7.9)
FASTING C-PEPTIDE (NM)	0.87 (0.33–2.43)	0.67 (0.30–2.50)
C-PEPTIDE 1 H AFTER MEAL (NM)	1.47 (0.50–2.93)	1.05 (0.30–3.33)
INDIVIDUAL CHANGES AFTER MEAL (NM)	0.45 (0–1.23)	0.33 (−0.38–1.20)

Values for age, duration of diabetes, BMI, WHR, total cholesterol, and triglycerides are means ± SD (range); values for glycemia and C-peptide are means (95% CI).

of them after thyroidectomy), without the presence of thyroid antibodies. Hypothyroidism was well controlled with thyroxin; blood levels of thyroxin and TSH were assayed twice a year. Ten patients suffered from hypertension and 10 from symptomatic coronary disease (of them 4 had both conditions). We could not discern any effect of these diseases on the parameters studied, nor effects of the medications (mostly, angiotensin-converting enzyme inhibitors and/or Ca channel blockers).

The first tests were done in 1984–1987. After an overnight fast, each patient gave a sample of blood for glucose and C-peptide, and then ate a breakfast of 500 cal with 50 g carbohydrates (5); 1 h later, blood tests were repeated. In the following years, fasting levels of C-peptide and the breakfast tolerance test were repeated several times, the last one in late 1991.

At the time of the first test, 36 patients were treated with sulfonylureas (glibenclamide or glipizide) and 13 with insulin. Later, 15 patients were switched from oral agents to insulin. The indication for this was only persistent hyperglycemia >11–14 mM, irrespective of the C-peptide values. However, another factor was willingness of the patients to take insulin; quite a few of them flatly refused, and we cannot say that the patients who started on insulin had higher glycemia than those who stayed on sulfonylureas. In the insulin-treated patients, 20 of 28 received one injection a day of a long-acting preparation, and 8 of 28 received two such injection a day. In the latter group, the evening injection was not omitted before the tests.

C-peptide was determined in the Nichols Institute (San Juan Capistrano, CA); antibodies used for its determination have negligible cross-reactivity with proinsulin.

Statistical evaluation was done by both parametric and, when the data distribution was nonnormal, by nonparametric methods: Mann-Whitney test for the group differences and the Spearman rho for correlations. Intraindividual differences were analyzed by the paired Student's *t* test. We used STATGRAPHICS 4.0 (STSC, Rockville, MD) for computations.

RESULTS — The characteristics of the patients are presented in Table 1. The group as a whole showed no correlation between fasting levels of plasma glucose and C-peptide, nor between their fasting and postprandial levels, or between their respective changes after breakfast. Results of the first test are presented in Table 1, and all the following ones were qualitatively similar in this respect.

Within 4–6 yr of observation, intraindividual plasma glucose and C-peptide values fluctuated widely, although no changes occurred in the group as a whole: neither fasting nor postprandial glycemic values nor the corresponding C-peptide levels differed significantly between the first and the last tests. A significant but rather weak correlation (by the Spearman rho) was noted between the individual first and last tests in relation to glycemic ($r = 0.4165$, $P = 0.0043$) and C-peptide ($r = 0.4070$, $P = 0.0053$) responses to the meal. Age, duration of diabetes, BMI, WHR, total cholesterol, and triglycerides did not correlate significantly with any of the studied parameters. Statistical adjustment for fasting glycemia was made to evaluate its possible relationship with plasma glucose or C-peptide. No such correlations were found.

To determine whether glycemic effect of the meal stood in any relation to the C-peptide, we divided the group into quartiles according to their increase in glycemia after the meal (Table 2). Most striking was quartile I, four of the patients in this subgroup showed a decrease of plasma glucose 1 h after breakfast. No differences were observed between these subgroups in relation to any other parameter. Nor did these subgroups differ in the number of patients switched from sulfonylureas to insulin because of poor diabetes control (Table 2). In all, there were 16 such patients. As a result of the change in therapy, their mean fasting plasma glucose decreased from 15.2 ± 4.6 to 11.2 ± 4.5 mM, with the average individual decrease of 3.9 mM ($P = 0.0023$). However, increase in plasma glucose after breakfast remained the same on insulin as it had been on oral drugs, correspondingly 4.0 ± 2.0 vs. 4.2 ± 1.5 mM. In addition, change of therapy and better control of diabetes did not affect the mean fasting C-peptide (1.08 ± 0.67 vs. 0.98 ± 1.02 nM) or its increase after breakfast (by 0.49 ± 0.51 vs. 0.41 ± 0.67 nM).

Table 2—*Independence of postprandial increase in plasma glucose from fasting glycemic level and from postprandial increase in C-peptide secretion*

	Quartiles of postprandial glycemic response			
	I	II	III	IV
Sex (men/women)	4/8	6/6	7/6	6/6
Age (yr)	56 (40–73)	59 (51–70)	61 (49–71)	61 (41–68)
Duration of diabetes (yr)	5 (1–16)	10 (2–24)	6 (1–15)	11 (1–24)
BMI (kg/m^2)	33.9 ± 2.1	31.0 ± 2.0	29.8 ± 1.1	27.5 ± 1.9
WHR	0.94 ± 0.03	0.96 ± 0.04	0.92 ± 0.03	0.97 ± 0.01
Treatment (sulfonylyreas/insulin)				
1984–1986	10/2	7/5	10/3	9/3
1991	6/6	4/8	6/7	5/7
Fasting glycemia (mM)	13.6 ± 1.4	13.3 ± 1.3	11.8 ± 0.9	12.7 ± 1.6
Increase in glycemia after breakfast (mM)	0.1 ± 0.4	2.7 ± 0.1	4.3 ± 0.2	6.4 ± 0.3
As % of fasting	0.4	20.3	36.8	50.4
Fasting C-peptide (nM)	1.03 ± 0.14	1.36 ± 0.16	1.10 ± 0.21	0.92 ± 0.20
Increase in C-peptide after breakfast (nM)	0.47 ± 0.11	0.54 ± 0.11	0.60 ± 0.15	0.56 ± 0.11
As % of fasting	45.6	39.7	54.5	60.9
Postprandial increase in plasma glucose (mM)	1.94	2.17–3.28	3.33–5.16	5.28–7.89

Values for age and duration of diabetes are mean (range); the values for BMI, WHR, glycemia, and C-peptide are means ± SD.

In this group, typically heterogeneous, no correlation was noted between glycemia and C-peptide. However, this general rule obscures remarkable intraindividual relations between these two parameters. Figure 1 and examples presented in Fig. 3 show that in every individual the patterns of response to breakfast persisted, but the absolute values of fasting C-peptide did correlate with the fasting level of glycemia.

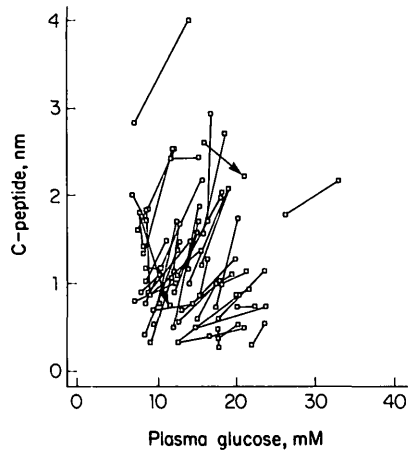

Figure 1—*Effect of breakfast on glycemia and C-peptide in NIDDM. The lines connect results of the same individual before and after breakfast. C-peptide after breakfast increased in all patients except 2 (arrows).*

CONCLUSIONS — Our approach was based on clinical considerations: the breakfast test is a physiological one and more relevant to real life than intravenous glucose load (6–8). C-peptide assay, in spite of its limitations (9), is at least as acceptable as that of insulin for evaluating β-cell function (10,11). Because some of our patients were treated with insulin, in any case, only C-peptide assay could be used. Peripheral C-peptide also may be a more reliable index of insulin resistance than peripheral insulin (12). Although a single postmeal value could not provide detailed information, for the purpose of this study, we were satisfied that maximum levels of both insulin and C-peptide are reached 1 h after a meal (13). This, however, is not necessarily true for all NIDDM patients, and it is possible that a more detailed postmeal evaluation with many time points would give slightly different results. We believe, however, that qualitatively, this simple test is clinically acceptable.

Our initial hypothesis was that because NIDDM is a non–insulin-dependent condition, insulin secretion in such patients should remain rather stable with time, and that plasma glucose would not correlate with endogenous insulin secretion. The results in general support this hypothesis. The group did not demonstrate a decrease in C-peptide after 4–6 yr of observation. When we compared the postmeal changes in C-peptide, the distribution of the differences between the first and last tests was Gaussian, pointing to their random nature. The lack of correlation between C-peptide and plasma glucose, reported earlier (5), held true also after 4–6 yr.

Hyperglycemia leads to glucosuria, and even in elderly people with a high renal threshold to glucose, this factor may play a significant role in diminishing postprandial increase in plasma glucose. However, in our patients, no negative correlation was observed be-

tween fasting plasma glucose and its increase after the meal.

The idea of primary insulin resistance in NIDDM partially compensated by increased insulin secretion was approached by comparing the quartiles of plasma glucose changes after breakfast. If the defect was insufficient insulin secretion, we would expect the lowest C-peptide in the quartile with the highest plasma glucose increase after the meal. Had insulin resistance played a decisive role, we would expect the highest plasma glucose increase after the meal accompanied also by the highest C-peptide response. Neither turned out to be true, and the groups of the lowest and highest increases of plasma glucose after breakfast did not differ in their absolute or meal-stimulated C-peptide secretion.

It is, however, quite plausible that some NIDDM patients might, with time, develop absolute insulin deficiency by an autoimmune mechanism, and thus represent slowly progressing IDDM (14–16). Although no such patients were in this group, it might be because the observation time was too short or, more likely, that the duration of diabetes in most patients was already significant at the beginning of the study. In other words, those destined to develop IDDM had already done so. Whatever it might be, our patients with relatively long-standing NIDDM demonstrated both persistency of their individual patterns of C-peptide secretion and its relative stability, and C-peptide did not correlate negatively with the duration of the disease.

The lack of a common pathogenetic denominator in NIDDM became obvious when we turned to the individual data: virtually every patient preserved qualitatively the same pattern of response to breakfast. In a crude way, it could be described as the slope of the curve. Wide diversity of patterns of the individual responses of C-peptide and plasma glucose (Figs. 2,3) shows how futile it would be to consider the patients as sharing common pathogenesis. Individual data support the view of the existence of broad insulin-sensitive and insulin-resistant forms of NIDDM reported in blacks (17). In the latter group, absolute insulin responses to oral glucose and glucagon were normal (17).

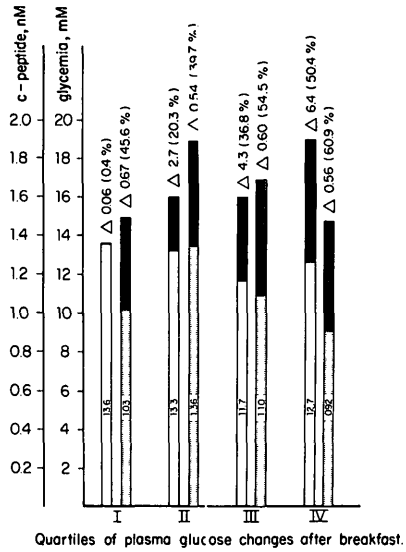

Figure 2—*Quartiles of plasma glucose increase after breakfast. Fasting plasma glucose (□), increase in plasma glucose after breakfast (■). Correspondingly fasting C-peptide (▤) and its increase after breakfast (▩). Figures above the bars show the median absolute increases and (in parenthesis) the same as the percentage of the fasting. Increase in plasma glucose in quartile I is barely visible.*

When individual results were analyzed according to glycemic response to the meal, several distinct patterns became obvious. Patients of quartiles I and II demonstrated normal breakfast tolerance with almost no increase (in rare cases, even decrease!) of plasma glucose. It was striking to see many highly hyperglycemic patients were remarkably breakfast tolerant. In these patients, an increase in insulin secretion is sufficient to prevent a high rise in plasma glucose. It looks like their glucostat is set to high values, and that their β-cells completely retain their function. The obvious conclusion is that fasting glycemia in these patients is not determined by insulin. The likely defect could conceivably lie in hepatic glucose-regulated release of glucose, the main process supplying glucose to the circulation in the postabsorptive state, the importance of which has been stressed repeatedly (18–21). Being insulin-independent, this process is by definition insulin resistant, and it acts independently of the other, much better understood mechanism, that of blocking hepatic glucose release by insulin. The latter is the main mechanism operating postprandially.

Meal tolerance, as contrasted with fasting plasma glucose, merits much greater attention than usually accorded. We see the counterpart of our data in the experiments in which well-controlled NIDDM patients received glucose infusion to sustain the glycemic level of 20 mM. With continuing glucose infusion, they then were given a meal, and their glycemia decreased; whereas C-peptide increased to a much greater degree than after an identical meal given against the background of glycemia of 6 mM (22). Clearly, C-peptide response was potentiated by acute hyperglycemia. However, another factor probably plays a major role, that is, secretion of incretin after the meal load. It is likely that hyperglycemia is necessary for the incretic effect.

The subgroup of quartile IV showed the highest elevation of plasma glucose after breakfast. These patients did not have higher fasting hyperglycemia than those of the first quartile, and their C-peptide response to the meal was of the same magnitude. Probably, either their tissues were much less sensitive to insulin or another mechanism altogether was involved. Quartile II lay in between, and their breakfast tolerance was only marginally abnormal.

In general, the group demonstrated that even extremely high fasting hyperglycemia did not prevent efficient disposal of the meal in many patients. In other words, in many NIDDM patients (our quartile I and probably quartile II), the problem is fasting hyperglycemia, not decreased meal tolerance. Our re-

much larger one is needed to find out whether the pattern of the C-peptide response to a meal could serve as a predictor of the more successful therapy (sulfonylureas versus biguanides versus insulin).

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