The Classification of Diabetes by Clinical and C-Peptide Criteria

A prospective population-based study

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OBJECTIVE — To evaluate both the concordance in the classification of diabetes by clinical and C-peptide criteria and, prospectively, the consistency of the classification by C-peptide.

RESEARCH DESIGN AND METHODS — Individuals with diabetes who were enlisted in the prospective epidemiological study of diabetic neuropathy (Rochester Diabetic Neuropathy Study [RDNS]) were classified clinically by National Diabetes Data Group (NDDG) criteria to IDDM and NIDDM at entry to the study. In addition, C-peptide response to 1 mg glucagon was measured at entry for the classification to IDDM (basal C-peptide, <0.17 pmol/ml; increment above basal, <0.07 pmol/ml) and NIDDM (all other responses) and for concordance with the clinical classification made. The consistency of the C-peptide response was assessed every 2 years for up to 8 years.

RESULTS — Among 346 individuals with diabetes, 84 were classified as IDDM and 262 as NIDDM by clinical algorithm. Concordance with the C-peptide response occurred in 89% of the patients and remained consistent during 8 years of follow-up. Among the 37 patients with discordant clinical and C-peptide classification, those considered clinically to have NIDDM had a consistent IDDM C-peptide response during follow-up, and most of those considered to have IDDM clinically eventually showed an IDDM C-peptide response during follow-up.

CONCLUSIONS — Clinical criteria for the classification of diabetes are highly correlated with the assessment of insulin secretory reserve. A small number of individuals considered to have NIDDM clinically or by C-peptide have or develop an IDDM peptide response.

The two major classes of diabetes, IDDM and NIDDM, were characterized by the National Diabetes Data Group (NDDG) primarily by clinical features (1). The qualitatively expressed discriminant relating to insulin secretory reserve (insulinopenia in IDDM or preserved insulin secretion in NIDDM) (1) has, over succeeding years, evolved to a quantitative corroboration of these classes on the basis of C-peptide concentrations. Various criteria for basal and stimulated C-peptide concentrations have been reported for the classification of diabetes (2–21). There are scant epidemiological data regarding the concordance of classification by clinical and C-peptide criteria (13,15,19–21) or the prospective assessment of the consistency of C-peptide concentrations, especially in a population-based study (21). We had the opportunity to address these issues in the course of determining the epidemiological and demographic features of neuropathy in persons with diabetes under the aegis of the Rochester Diabetic Neuropathy Study (RDNS) (22).

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DCCT, Diabetes Control and Complications Trial; NDDG, National Diabetes Data Group; RDNS, Rochester Diabetic Neuropathy Study.

RESEARCH DESIGN AND METHODS

— Using the unique database that is available from the common medical record system of the Mayo Clinic and accessing the medical records of other medical care providers in the area who serve the local population, we identified all Rochester residents known to have diabetes and living within the geographic boundaries of the city on 1 January 1986. Residents who developed diabetes after this date were excluded.

Diabetes was confirmed by the satisfaction of NDDG criteria (1) and its classification was accomplished by the application of a clinical algorithm based on NDDG criteria (Fig. 1) (1).

The classification to IDDM and NIDDM by the clinical algorithm was compared with a classification based on basal and stimulated (6 minutes after 1 mg i.v. glucagon) C-peptide concentrations. C-peptide was measured by radioimmunoassay (23). Using previously published criteria for the characterization of IDDM and NIDDM as a guide, we arbitrarily segregated basal and the increment above basal C-peptide into three responses: <0.07, 0.07–0.17, and >0.17 pmol/ml. The various permutations and combinations of responses are shown in Table 1. Basal and stimulated C-peptide responses were assessed biannually over the succeeding years of follow-up.

RESULTS

At entry

Of the total cohort of 381 patients enrolled in the RDNS, 346 had C-peptide responses to intravenous glucagon measured at entry to the study: 227 at year 2, 207 at year 4, 153 at year 6, and 35 at year 8. The clinical features of these patients classified by the clinical algorithm at entry to the study are shown in Table 2. Among the patients who had C-peptide measured at entry, 84 were classified by the clinical algorithm as IDDM and 262 as NIDDM. The concordance in classification between the clinical algorithm and C-peptide occurred in 67 IDDM and 242 NIDDM. Twenty patients

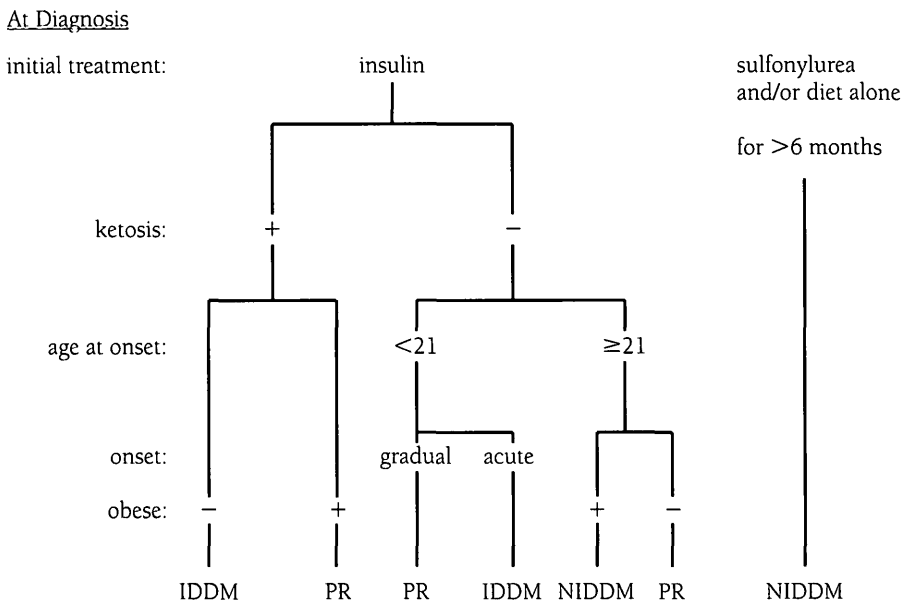

Figure 1—*An algorithm for the classification of diabetes. Ketosis was defined as an episode of ketoacidosis or ketonuria or more than trace ketonuria; gradual onset was characterized by premorbid plasma glucose concentrations >100 and <140 mg/dl for months or years; acute onset was characterized by abrupt onset of hyperglycemia and associated symptoms without prolonged premorbid borderline hyperglycemia; obesity was defined as >120% ideal body weight as defined by Metropolitan Height and Weight Tables (Build Study, Society of Actuaries and Association of Life Insurance Medical Directors of America, 1979). PR, physician review.*

Table 1—*Potential patterns of C-peptide response to intravenous glucagon*

C-peptide (pmol/ml) Basal	Increment above basal at 6 min	Pattern designation
<0.07	<0.07	A
≥0.07 <0.17	<0.07	B
<0.07	≥0.07 <0.17	C
≥0.17	≥0.17	D
≥0.07 <0.17	≥0.17	E
≥0.07 <0.17	≥0.07 <0.17	F
<0.07	≥0.17	G
≥0.17	<0.07	H
≥0.17	≥0.07 <0.17	I

Responses A and B were considered to be indicative of IDDM; all other patterns of response were considered to be compatible with NIDDM.

classified by clinical algorithm as NIDDM and 17 classified by clinical algorithm as IDDM at entry were discordant in classification by C-peptide. The C-peptide patterns of response are shown in Table 3.

Follow-up

Among the 67 IDDM patients concordant by clinical algorithm and C-peptide at entry, C-peptide responses were reassessed at 2 years in 34 patients, at 4 years in 37, at 6 years in 25, and at 8 years in 10. None of these patients who had follow-up C-peptide measurements showed sustained responses consistent with NIDDM (patterns D to I) on the last two consecutive testing periods (years 2 and 4, 4 and 6, or 6 and 8). Three patients had a response consistent with NIDDM on one occasion and one on two occasions.

Among the 242 NIDDM patients concordant by clinical algorithm and C-peptide at entry, C-peptide responses were reassessed at least once in 195 patients: at 2 years in 165 patients, at 4 years in 141, at 6 years in 105, and at 8 years in 21. The consistency of the NIDDM response pattern during follow-up was observed in 167 patients. An IDDM response pattern was observed on one occasion during follow-up in 33 patients. When the criterion for the conversion to IDDM of having pattern A or B on the last two consecutive testing periods (years 2 and 4, 4 and 6, or 6 and 8) was employed, only one patient qualified.

Among the 20 patients classified as NIDDM by clinical algorithm, who had a discordant C-peptide response at entry, 14 had a C-peptide response of pattern A and 6 of pattern B. At entry to the study, all of these patients were insulin treated. C-peptide responses were reassessed at 2 years in 15 patients, at 4 years in 15, at 6 years in 13, and at 8 years in 2. Among these patients, only two had an NIDDM C-peptide response on one occasion during follow-up.

No patient, therefore, showed a conversion to an NIDDM-type C-peptide response (pattern D to I in the last two successive testing periods). The discordance between the classification by clinical algorithm and C-peptide in these patients points to a deficiency in the algorithm or its interpretation since all were reassessed at entry.

Among the 17 patients classified as IDDM by clinical algorithm who had a discordant C-peptide response at entry, 2 had pattern D, 2 had pattern E, 7 had pattern F, 3 had pattern H, and 3 had pattern I. C-peptide responses were reassessed at 2 years in 13 patients, at 4 years in 14, at 6 years in 10, and at 8 years in 2. Only two patients had consistent NIDDM.

C-peptide responses during follow-up. Six patients converted to consistent IDDM-type C-peptide responses (all were pattern A during last two successive testing periods). The remaining patients showed variable (NIDDM and IDDM) responses during follow-up.

Table 2—*Demographic features of patients who had C-peptide measured at entry*

Classification by clinical algorithm	*n*	M/F	Age at onset of diabetes (years)	Duration of diabetes at entry (years)	BMI at entry (kg/m²)
Concordant					
IDDM	67	32/35	19.2 (4–49)	17.9 (1.3–63.5)	25.0 (19.6–39.1)
NIDDM	242	120/122	55.1 (14–82)	10.0 (1.1–71.7)	30.8 (18.7–60.1)
Discordant					
IDDM	17	13/4	33.0 (6–63)	9.3 (0.7–33.0)	25.6 (21.0–33.2)
NIDDM	20	8/12	41.5 (17–62)	12.9 (2.1–32.4)	24.6 (20.7–32.3)

Data are median (range), unless otherwise indicated. Concordant, agreement in the classification by clinical algorithm and C-peptide; discordant, disagreement in the classification by clinical algorithm and C-peptide.

Table 3—*The classification by clinical algorithm*

	IDDM (n = 84)		NIDDM (n = 262)	
C-peptide pattern	n	Percentage	n	Percentage
A	57	68	14	5
B	10	12	6	2
Subtotal	67	80	20	7
C	0	0	0	0
D	2	2	204	78
F	7	8	5	2
G	0	0	0	0
H	3	4	13	5
I	3	4	12	5
Subtotal	17	20	242	93
Total	84	100	262	100

Data are n or %. Responses A and B were considered to be indicative of IDDM; all other patterns of response were considered to be compatible with NIDDM.

CONCLUSIONS — Our selection of C-peptide criteria for the classification of diabetes, although arbitrary, was based on an interpretation of the literature extant about a decade ago when the present study was being designed. Our choice of basal C-peptide <0.17 pmol/ml for IDDM is consistent with the Diabetes Control and Complications Trial (DCCT) criterion of <0.2 pmol/ml (24) and that of the VA Cooperative Study of NIDDM, which used an exclusion criterion of <0.21 pmol/ml (25). Unlike the DCCT, in which two absolute levels of stimulated C-peptide (primary prevention, <0.5 pmol/ml; secondary intervention, <0.2 pmol/ml) were used, and the VA Cooperative Study where the response to β-cell stimulus was not assessed, we reasoned that the ability to augment C-peptide concentrations would be a preferred way to assess β-cell reserve. Consequently, we examined the increment above baseline C-peptide as <0.07, 0.07–0.17, and >0.17 pmol/ml. Other investigators who have taken a diametrically opposite approach to ones in which C-peptide concentrations (whether basal or stimulated) were the independent variable and clinical characteristics the dependent variable observed ~90% accuracy when cutoff values of C-peptide of 0.16 pmol/ml (13,20) and 0.08 pmol/ml (19) were used to classify IDDM and NIDDM. These criteria are remarkably close to the ones reported here.

At entry to the study, the concordance between the two systems of classification, clinical algorithm and C-peptide, occurred in 89% of the 346 patients. There was a high degree of consistency of the C-peptide response over the subsequent years of follow-up, up to 8 years in some patients. No IDDM patient showed a sustained NIDDM-type C-peptide response, and only one NIDDM patient showed a sustained IDDM-type C-peptide response. Of the patients classified as NIDDM by the clinical algorithm, 14% showed an IDDM C-peptide response on at least one occasion, which suggests failing β-cell reserve but not to the IDDM level. Repeated fasting C-peptide concentrations after a 12-month interval in 215 insulin-treated individuals with diabetes on the island of Falster, Denmark, showed a high degree of consistency of response when the initial C-peptide concentration was <0.2 pmol/ml (21).

The discordance in classification among 20 patients allocated to NIDDM by the clinical algorithm, all of whom had IDDM-type C-peptide responses at entry and almost consistently during follow-up, is not readily explained. At entry to the study, all were treated with insulin. Since four patients had a duration of diabetes <5 years at entry to the study, the prolonged duration with a concomitant waning β-cell function cannot be the sole mechanism. It appears that one or more characteristics of the clinical algorithm misdirected the classification in these patients. The initial treatment with diet or sulfonylureas in 12 patients and obesity in 2 additional patients may have been misleading. Among the 17 patients classified as IDDM by clinical algorithm but NIDDM by C-peptide response, only 2 patients showed consistent NIDDM-type C-peptide responses during follow-up: >0.17 pmol/ml basal and increment above basal. The remainder converted to consistent IDDM responses or showed variable responses during follow-up. The majority of these patients, therefore, could be considered to have IDDM in evolution. Although these patients had an NIDDM-type C-peptide response at entry, most had a blunted increment of C-peptide above basal at entry to the study. A limited response of C-peptide (e.g., <0.17 pmol/ml), regardless of the basal concentration of C-peptide, may be a forebear of IDDM.

Are there clinical characteristics that suggest a measurement of insulin secretory reserve to classify a patient properly? This study does not identify any. One could argue that a ~90% concordance between the clinical and C-peptide criteria for classification is better than might be expected.

We offer the following conclusions: *1*) the clinical criteria for the classification of diabetes, although arbitrary and sometimes difficult to apply, nevertheless show a high degree of correlation with the assessment of insulin secretory reserve; *2*) the clinical criteria for the classification of diabetes appear to be better at predicting IDDM (once classified as IDDM, it can be confirmed immediately or later by the assessment of insulin secretory reserve); and *3*) the clinical criteria for NIDDM are good, but one should allow for the inclusion of some IDDM patients (~10%), which is consistent with the studies that show ~10% ICA-positivity in individuals who are considered clinically to be NIDDM.

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References

1. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1052, 1979
2. Heding LG: Specific and direct radioimmunoassay for human proinsulin in serum. *Diabetologia* 13:467–477, 1977
3. Faber OK, Binder C: C-peptide response to glucagon: a test for the residual β-cell function in diabetes mellitus. *Diabetes* 26:605–610, 1977
4. Heding LG: Insulin C-peptide and proinsulin in nondiabetics and insulin-treated diabetics: characterization of the proinsulin in insulin-treated diabetics. *Diabetes* 27 (Suppl. 1):178–183, 1978

5. Madsbad S, Faber OK, Binder C, McNair P, Christiansen C, Transbol I: Prevalence of residual β-cell function in insulin-dependent diabetics in relation to age at onset and duration of diabetes. *Diabetes* 27 (Suppl. 1):262–264, 1978
6. Mirel RD, Ginsberg-Fellner F, Horwitz DL, Rayfield EJ: C-peptide reserve in insulin dependent diabetes: comparative response to glucose, glucagon and tolbutamide. *Diabetologia* 19:183–188, 1980
7. Madsbad S, Krarup T, McNair P, Christiansen C, Faber OK, Transbol I, Binder C: Practical clinical value of the C-peptide response to glucagon stimulation in the choice of treatment in diabetes mellitus. *Acta Med Scand* 210:153–156, 1981
8. Welborn TA, Garcia-Webb P, Bonser AM: Basal C-peptide in the discrimination of type I from type II diabetes. *Diabetes Care* 4:616–619, 1981
9. Garcia-Webb P, Bonser A, Welborn TA: Correlation between fasting serum C-peptide and beta-cell insulin secretory capacity in diabetes mellitus (Letter). *Diabetologia* 22: 296, 1982
10. Werther GA, Turner RC, Jenkins PA, Baum JD: Twenty-four hour profiles of plasma C-peptide type I (insulin-dependent) diabetic children. *Diabetologia* 22:245–249, 1982
11. Goldstein DE, Parker KM, England JD, England JE, Wiedmeyer H-M, Rawlings SS, Hess R, Little RR, Simonds JF, Breyfogle RP: Clinical application of glycosylated hemoglobin measurements. *Diabetes* 31 (Suppl. 3):70–78, 1982
12. Dauzat J, Moinade S, Gaillard G, Glanddier Y, Gachon AM: La réserve insulinique du diabétique insulinodépendant: rôle du peptide C dans l'équilibre du diabète. *Presse Med* 12:1983–1987, 1983
13. Welborn TA, Garcia-Webb P, Bonser A, McCann V, Constable I: Clinical criteria that reflect C-peptide status in idiopathic diabetes. *Diabetes Care* 6:315–316, 1983
14. Laakso M, Sarlund H, Pyorala K: Prevalence of insulin deficiency among initially non-insulin-depedent middle-aged diabetic individuals. *Diabetes Care* 9:228–231, 1986
15. Koskinen P, Viikari J, Irjala K, Kaihola HL, Seppala P: Plasma and urinary C-peptide in the classification of adult diabetics. *Scand J Clin Lab Invest* 46:655–663, 1986
16. Clarson C, Daneman D, Drash AL, Becker DJ, Ehrlich RM: Residual lo-cell function in children with IDDM: reproducibility of testing and factors influencing insulin secretory reserve. *Diabetes Care* 10:33–38, 1987
17. Damsgaard EM, Faber OK, Frøland A, Green A, Hauge M, Holm NV, Iversen S: Prevalence of fasting hyperglycemia and known non-insulin-dependent diabetes mellitus classified by plasma C-peptide: Fredericia survey of subjects 60–74 years old. *Diabetes Care* 10:26–32, 1987
18. Gjessing HJ, Matzen LE, Faber OK, Frøland A: Fasting plasma C-peptide, glucagon stimulated plasma C-peptide, and urinary C-peptide in relation to clinical type of diabetes. *Diabetologia* 32:305–311, 1989
19. Prior MJ, Prout T, Miller D, Ewart R, Kumar D: C-peptide and the classification of diabetes mellitus patients in the Early Treatment Diabetic Retinopathy Study. *Ann Epidemiol* 3:9–17, 1993
20. Laakso M, Sarlund H, Pyorala K: Clinical characteristics in the discrimination between patients with low or high C-peptide levels among middle-aged insulin-treated diabetics. *Diabetes Res* 4:95–99, 1987
21. Nielsen NV, Tronier B: C-peptide in diabetes mellitus treated with insulin: a 3-year epidemiological study on the island of Falster, Denmark. *Diabetes Res* 3:475–478, 1986
22. Dyck PJ, Kratz KM, Lehman KA, Karnes JL, Melton LJ, O'Brien PC, Litchy WJ, Windebank AJ, Smith BE, Low PA, Service FJ, Rizza RA, Zimmerman BR: The Rochester Diabetic Neuropathy Study: design, criteria for types of neuropathy, selection bias, and reproducibility of neuropathic tests. *Neurology* 41:799–807, 1991
23. Heding LG: Radioimmunological determination of human C-peptide in serum. *Diabetologia* 11:541–548, 1975
24. The DCCT Research Group: The Diabetes Control and Complications Trial (DCCT): design and methodologic considerations for the feasibility phase. *Diabetes* 35:530–545, 1986
25. Abraira C, Emanuele N, Colwell J, Henderson W, Comstock J, Levin S, Nuttall F, Sawin C, VA Cooperative Study Group: Glycemic control and complications in type II diabetes: design of a feasibility trial. *Diabetes Care* 15:1560–1571, 1992