Distinct Diagnostic Criteria of Fulminant Type 1 Diabetes Based on Serum C-Peptide Response and HbA_{1c} Levels at Onset

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OBJECTIVE — Diagnostic criteria in fulminant type 1 diabetes, a novel subtype of type 1 diabetes, remain unclear.

RESEARCH DESIGN AND METHODS — We analyzed basal and longitudinal changes of serum C-peptide levels during a 75-g oral glucose tolerance test (OGTT) in 125 consecutively recruited patients with type 1 diabetes including fulminant type 1 diabetes ($n = 25$) and acute-onset type 1 diabetes ($n = 100$). Discriminating criteria of fulminant type 1 diabetes were examined using receiver-operating characteristic curve analysis and multiple logistic regression analysis.

RESULTS — The integrated values of serum C-peptide response during OGTT (ΣC-peptide) in fulminant type 1 diabetes at onset, 1 year, and 2 years after onset were markedly lower than those in acute-onset type 1 diabetes. None of the patients with fulminant type 1 diabetes had improvement of C-peptide response to OGTT. Fasting C-peptide values at onset in fulminant type 1 diabetes were significantly lower than those in acute-onset type 1 diabetes. We established diagnostic criteria of serum C-peptide and HbA_{1c} levels at onset that discriminate fulminant type 1 diabetes from acute-onset type 1 diabetes with high sensitivity and specificity: a criterion in which the levels of both the fasting C-peptide is $\leq$0.033 nmol/l and HbA_{1c} is $\leq$8.0% or a criterion in which the levels of both the ΣC-peptide is $\leq$0.540 nmol/l and HbA_{1c} is $\leq$8.0%.

CONCLUSIONS — Fulminant type 1 diabetes has extremely low β-cell function at onset that rarely recovers after onset. Sensitive and specific diagnostic criteria were established for detection of fulminant type 1 diabetes based on serum C-peptide and HbA_{1c} levels at onset.

Diabetes Care 27:1936–1941, 2004

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Received for publication 24 November 2003 and accepted in revised form 16 May 2004.

Abbreviations: AUC, area under receiver-operating characteristic curve; GADAb, GAD autoantibody; IAA, insulin autoantibody; IA-2Ab, insulinoma-associated protein 2/islet cell antigen 512 autoantibody; ICA, islet cell antibody; OGTT, oral glucose tolerance test; ROC, receiver-operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

In 1988, a study suggested that there might be a novel subtype of type 1 diabetes that was called the "fulminant form of type 1 diabetes" (1,2). In 2000, this subtype, which had the same characteristics as the subtype discussed in the 1988 study, was described and named "fulminant type 1 diabetes" (3–6). The characteristic features at onset of this subtype of type 1 diabetes (1–6) include: *1*) abrupt onset of diabetes with fulminant symptoms including marked hyperglycemia, severe diabetic ketoacidotic coma, and normal or near-normal HbA_{1c} levels; *2*) absence of autoantibodies against islet cells including islet cell antibodies (ICA), GAD autoantibodies (GADAb), insulinoma-associated protein 2/islet cell antigen 512 autoantibodies (IA-2Ab), and insulin autoantibodies (IAA); and *3*) involvement of exocrine pancreas as well as pancreatic islets with elevated serum levels of pancreatic enzymes. The key issue for the diagnosis in this new subtype of type 1 diabetes is absence of autoantibodies against islet cells. However, the measurement of pancreatic autoantibodies including GADAb, ICA, IA-2Ab, and IAA is in the process of being standardized (7), and these autoantibodies can be measured in a limited number of laboratories. Data on longitudinal changes of serum C-peptide levels as well as the basal values in newly diagnosed patients with type 1 diabetes, including fulminant type 1 diabetes and classical type 1 diabetes, were obtained prospectively. We tried to establish sensitive and specific criteria for clinical diagnosis of fulminant type 1 diabetes at onset based on serum C-peptide concentration.

RESEARCH DESIGN AND METHODS

— A total of 126 newly diagnosed type 1 diabetic patients (onset age 34 ± 15 years [mean ± SD]; age range 2–71; 70 men, 56 women) were consecutively recruited in the "Toranomon Prospective Study on Type 1 Diabetes" from

1980 to 2001 (5,8–13). All patients met the American Diabetes Association criteria for type 1 diabetes (14). The duration from onset of diabetes symptoms to hospitalization was within 90 days in all case subjects. The exclusion criteria were the presence of mitochondrial DNA mutation (A/G) at 3,243 bp and/or hepatocyte nuclear factor-1α gene mutation. One patient was excluded because of the presence of mitochondrial DNA mutation (A/G) at 3,243 bp. According to the tentative criteria in previous studies (3,5), 25 patients who were negative for autoantibodies against pancreatic antigens (including ICA, GADAb, IA-2Ab, and IAA) and had normal or near-normal HbA_{1c} levels (≤8.3%) at onset of diabetes were diagnosed as having fulminant type 1 diabetes. The remaining 100 patients were subdivided as acute-onset type 1 diabetes. Residual β-cell function of the total 125 patients, including 25 patients with fulminant type 1 diabetes and 100 patients with acute-onset type 1 diabetes, was analyzed in this study.

At onset of overt diabetes, all patients were hospitalized. Their clinical characteristics were recorded, and plasma glucose, HbA_{1c}, arterial pH, serum elastase 1, serum amylase, and serum lipase were measured within 2 days after initial diagnosis. HbA_{1c} levels were measured by a high-performance liquid chromatography method calibrated with Japan Diabetes Society Calibrator Lot 2 (15). This method for HbA_{1c} assay was standardized by the Japan Diabetes Society/Japanese Society of Clinical Chemistry and established a firm and reproducible link to the method of the International Federation of Clinical Chemistry (15). In all patients with type 1 diabetes, blood samples for the assay for pancreatic autoantibodies were obtained at least twice within 10 and 30 days after the diagnosis of diabetes. All serum samples for autoantibody and C-peptide assays were kept at −80°C until assay.

Diabetes-related autoantibodies (including ICA, GADAb, IA-2Ab, and IAA) were assayed as previously described (8,16–18). Our laboratory participated in the second through fifth International Workshop on Standardization of the ICA Assay, in which we established the quality of our ICA assay as follows: a cutoff point of 5 Juvenile Diabetes Foundation units, sensitivity of 90%, and specificity of 92% (16). The sensitivity and specificity of the GADAb assay were 80 and 100%, respectively, in the second International GADAb Workshop (16). The IA-2Ab assay was evaluated in the third proficiency IA-2Ab test organized by the Research Institute for Children, and the results showed 100% sensitivity and 100% specificity (17). The sensitivity and specificity of the IAA assay were both 100% in the fourth International IAA Workshop (18). After obtaining written informed consent, detection of mitochondrial DNA mutation (A/G) at 3,243 bp and hepatocyte nuclear factor-1α gene mutation was performed as previously described (19,20). Serum C-peptide levels were measured as previously described (9). The assay quality was checked using recombinant human C-peptide of World Health Organization standards (ampoules coded 84/510) (21) and two control samples (Daiichi Pharmaceutical, Tokyo, Japan). At the C-peptide concentration of 0.760 and 0.056 nmol/l, the intra-assay coefficient of variation (CV) values (10 replicates) were 3.4 and 9.5%, respectively. The interassay CV values (10 occasions) at concentrations of C-peptide of 0.760 and 0.056 nmol/l were, respectively, 8.1 and 14.2%. The minimal detection limit of C-peptide concentration was 0.017 nmol/l (9). C-peptide levels <0.017 nmol/l were regarded as 0.000 nmol/l in this study. Samples from each subject were in the same assay run. Patients were tested using a 75-g oral glucose tolerance test (OGTT) at onset ($n = 125$), at 1 year ($n = 66$), and at 2 years ($n = 60$) after onset. OGTT at onset was performed for each patient after obtaining steady glycemic control by insulin therapy (3–4 weeks). The response of serum C-peptide during OGTT was quantified as the integrated value of the serum C-peptide levels obtained during OGTT at 0, 30, 60, 90, and 120 min: ΣC-peptide. The improvement of residual β-cell function was defined as increments of ΣC-peptide values >0.331 nmol/l (1.0 ng/ml) when compared with the values at onset during the follow-up period.

Statistical analysis

The Mann-Whitney *U* test and the Fisher's exact test were applied to compare the values of clinical features among the different subgroups of type 1 diabetes. The Wilcoxon's signed-rank test was used to compare the longitudinal changes of the ΣC-peptide values of each subtype of type 1 diabetes. Frequencies of subjects who had their improvement of residual β-cell function in different subgroups of type 1 diabetes were compared using Fisher's exact test. Receiver-operating characteristic (ROC) curves were analyzed to define the optimal cutoff values of clinical and laboratory findings at onset for discrimination of fulminant type 1 diabetes from acute-onset type 1 diabetes (22). Each discriminating criterion of clinical or laboratory finding at onset was devised based on the corresponding cutoff value. The areas under ROC curves (AUCs), which indicate the accuracy of the tests, were calculated and compared (23). A multiple logistic regression analysis was performed to identify independent factors for prediction of fulminant type 1 diabetes. The following variables of clinical and laboratory findings at onset were included in the multiple regression analysis: age at onset, sex, BMI, duration of hyperglycemic symptoms before diagnosis, plasma glucose levels, arterial pH, serum amylase levels, serum lipase levels, serum elastase 1 levels, ΣC-peptide values, and fasting C-peptide levels. Continuous variables were dichotomized based on whether they met or did not meet the discriminating criteria, which were devised by the optimal cutoff values as mentioned above, and then these variables were included in multiple regression analysis. A multiple regression model for predicting diagnosis of fulminant type 1 diabetes was devised and evaluated on our study population. The model was constructed by stepwise selection with $P = 0.05$ used as the criterion for both entry into and retention in the model. We used JMP software (version 5) and MedCalc software (version 7) for statistical analyses. All data except for AUCs were expressed as mean ± SD. The protocol of the Toranomon Prospective Study on Type 1 Diabetes was approved by the Ethical Committee of Toranomon Hospital.

RESULTS

Clinical features at onset of diabetes in patients with fulminant type 1 diabetes

Twenty-five patients with fulminant type 1 diabetes had significantly shorter duration of hyperglycemic symptoms before diagnosis (mean 4 ± 3 days, range 1–10, $P < 0.0001$) versus acute-onset type 1 diabetes (mean 48 ± 32 days, range 1–90, $n = 100$). Plasma glucose levels at onset of

diabetes in patients with fulminant type 1 diabetes (47.4 ± 20.4 mmol/l [16.9–102.0]) were significantly higher than those in patients with acute-onset type 1 diabetes (26.7 ± 12.8 mmol/l [11.3–71.1]) ($P < 0.0001$). In contrast, the levels of HbA_{1c} at onset of diabetes in patients with fulminant type 1 diabetes (6.5 ± 1.1% [4.3–8.3]) were significantly lower than those in patients with acute-onset type 1 diabetes (11.3 ± 2.7% [5.1–19.1]) ($P < 0.0001$). The degree of acidosis in patients with fulminant type 1 diabetes (arterial blood pH 7.11 ± 0.14 [6.91–7.34]) was more severe than that in patients with acute-onset type 1 diabetes (7.28 ± 0.09 [7.02–7.39]) ($P < 0.0001$). BMI at onset of patients with fulminant type 1 diabetes (20.5 ± 2.5 kg/m^2 [16.7–28.7]) was significantly higher than that of patients with acute-onset type 1 diabetes (18.7 ± 2.4 kg/m^2 [13.8–26.7]) ($P = 0.0009$). Ninety-six percent (24/25) of patients with fulminant type 1 diabetes had elevated levels of serum pancreatic enzymes. Age at onset (37 ± 14 years [21–65]) and sex (16 men, 9 women) in patients with fulminant type 1 diabetes were not significantly different from those in patients with acute-onset type 1 diabetes (age at onset 33 ± 15 years [2–71], 54 men, 46 women). Among 100 patients with acute-onset type 1 diabetes, ICA was positive in 74% (74/100), GADAb in 69% (69/100), IA-2Ab in 61% (61/100), and IAA in 15% (15/100). All patients with fulminant type 1 diabetes were negative for ICA, GADAb, IA-2Ab, and IAA. All features of patients with fulminant type 1 diabetes are compatible with those in previously reported studies (1–6).

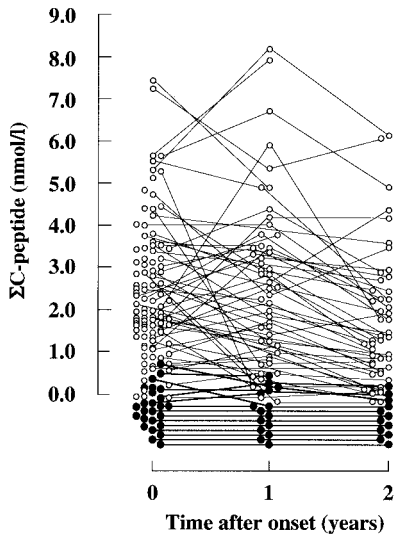

Figure 1—*Longitudinal changes of residual β-cell function in type 1 diabetes. The mean integrated values of serum C-peptide levels obtained during OGTT (ΣC-peptide) in patients with fulminant type 1 diabetes (●) were 0.087 ± 0.190 nmol/l at onset* (n = *25), 0.083 ± 0.157 nmol/l at 1 year after onset* (n = *15), and 0.025 ± 0.078 nmol/l at 2 years after onset* (n = *12). The mean values in patients with acute-onset type 1 diabetes (○) were 2.443 ± 1.550 nmol/l at onset* (n = *100), 2.611 ± 1.970 nmol/l at 1 year after onset* (n = *51), and 1.791 ± 1.548 nmol/l at 2 years after onset* (n = *48).*

Longitudinal changes of residual β-cell function and diagnostic criteria in patients with fulminant type 1 diabetes

Residual β-cell function. The values of ΣC-peptide in patients with fulminant type 1 diabetes were markedly lower than those in patients with acute-onset type 1 diabetes at onset ($P < 0.0001$), 1 year after onset ($P < 0.0001$), and 2 years after onset ($P < 0.0001$) (Fig. 1). The ΣC-peptide values in patients with fulminant type 1 diabetes remained unchanged during a 2-year period after onset (Fig. 1). None of the patients with fulminant type 1 diabetes had improvement of their ΣC-peptide values during a 2-year period after onset. In contrast, in patients with acute-onset type 1 diabetes, the ΣC-peptide values at 2 years after onset were significantly lower than those at onset ($P < 0.0001$) and 1 year after onset ($P < 0.0001$), although there was no significant change between the ΣC-peptide values at onset and 1 year after onset. Furthermore, 39% (20/51) of patients with acute-onset type 1 diabetes had improvement of their ΣC-peptide values at 1 year after onset ($P = 0.0030$ vs. fulminant type 1 diabetes). Fasting serum C-peptide values at onset (mean 0.009 ± 0.021 nmol/l, $n = 25$) as well as ΣC-peptide values in fulminant type 1 diabetes were significantly lower than those in acute-onset type 1 diabetes (0.243 ± 0.139 nmol/l, $n = 100$, $P < 0.0001$).

ROC curve analysis. The AUCs for ΣC-peptide values (0.974 ± 0.013 [mean ± SE]) and fasting C-peptide levels (0.973 ± 0.013) were significantly greater than AUCs for serum amylase levels (0.877 ± 0.046, $P = 0.034$ and $P = 0.038$, respectively), arterial pH (0.841 ± 0.037, $P < 0.001$ and $P = 0.001$, respectively), plasma glucose levels (0.827 ± 0.053, both $P = 0.006$), serum lipase levels (0.797 ± 0.056, $P = 0.002$ and $P = 0.001$, respectively), BMI (0.715 ± 0.062, both $P < 0.001$), and onset age (0.555 ± 0.066, both $P < 0.001$) (Fig. 2*A–D*). The AUCs for HbA_{1c} levels (0.969 ± 0.014) and duration of hyperglycemic symptoms (0.944 ± 0.020) were significantly greater than AUCs for arterial pH ($P = 0.001$ and $P = 0.004$, respectively), plasma glucose levels ($P = 0.009$ and $P = 0.021$, respectively), serum lipase levels ($P = 0.003$ and $P = 0.011$, respectively), BMI (both $P < 0.001$), and onset age (both $P < 0.001$). The AUC for serum elastase 1 levels (0.918 ± 0.039) was significantly greater than AUCs for serum lipase levels ($P = 0.041$), BMI ($P = 0.006$), and onset age ($P < 0.001$). There was no significant difference among AUCs for ΣC-peptide values, fasting C-peptide levels, HbA_{1c} levels, duration of hyperglycemic symptoms, and serum elastase 1 levels.

Table 1 indicated discriminating criteria devised from the optimum cutoff values based on ROC curve analysis of clinical and laboratory findings at onset of diabetes and sensitivities, specificities, positive predictive values, and negative predictive values for these criteria. Sensitivities and specificities of the discriminating criteria of ΣC-peptide values and fasting C-peptide levels were >90%. Positive predictive values of the discriminating criteria of ΣC-peptide values and fasting C-peptide levels were both 80%, whereas those of the discriminating criteria of the other variables were <70%.

Multiple logistic regression analysis. Based on a multiple logistic regression analysis, ΣC-peptide values at onset ≤0.540 nmol/l and HbA_{1c} levels at onset ≤8.0% were recognized as independent variables for discriminating fulminant type 1 diabetes from acute-onset type 1 diabetes; the odds ratio of ΣC-peptide was 16.2 (95% CI 4.0–65.1; $P < 0.0001$), and the odds ratio of HbA_{1c} was 11.5 (2.8–47.4; $P = 0.0007$). Using the criterion where patients whose ΣC-peptide values at onset were ≤0.540 nmol/l and HbA_{1c} levels at onset were ≤8.0% were diagnosed as fulminant type 1 diabetes, sensitivity and specificity were 92.0% (23/25 [95% CI 74.0–99.0]) and 99.0% (99/100 [94.6–100.0]), respectively, and positive and negative predictive values were 95.8% (23/24 [78.9–

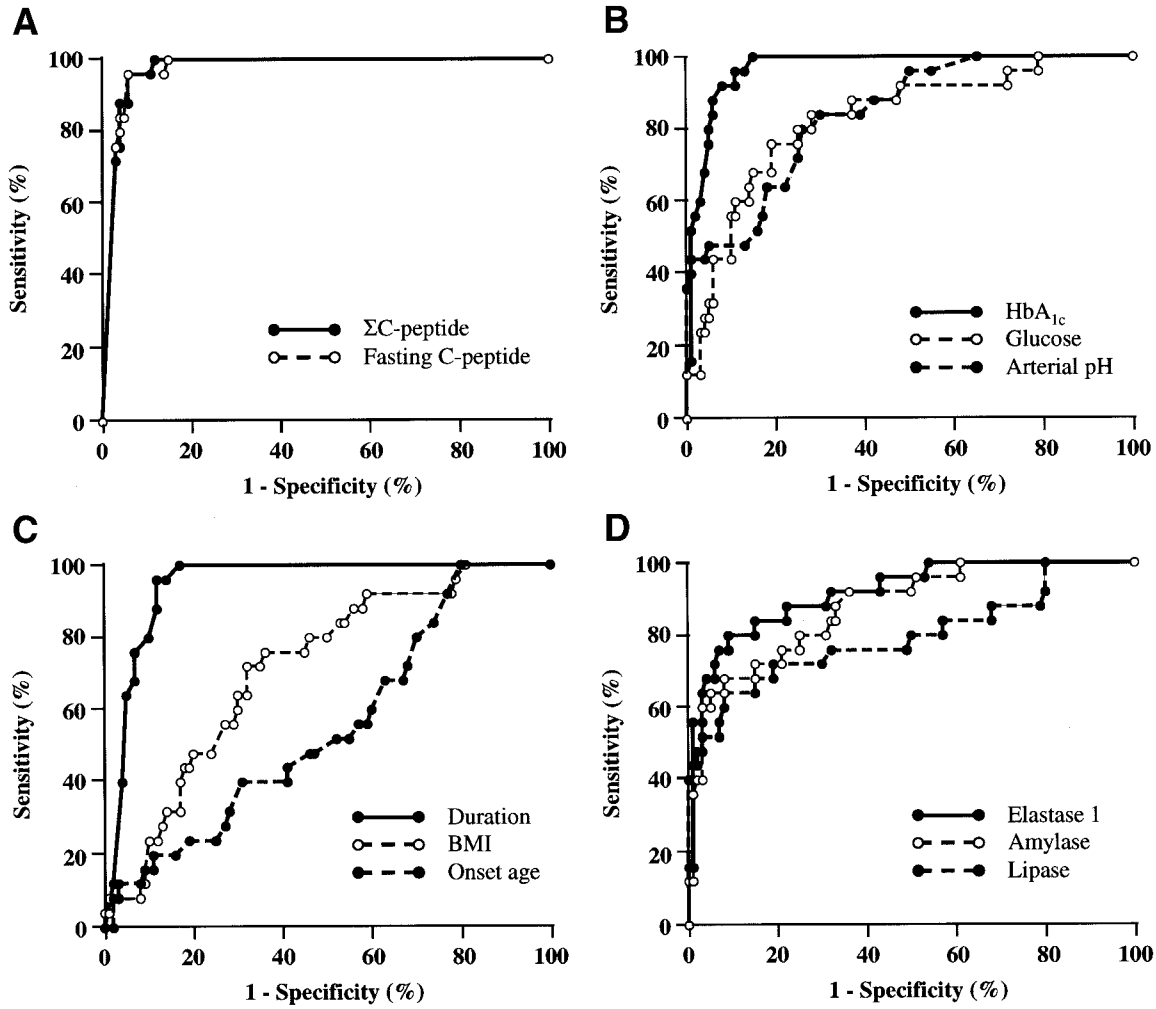

Figure 2—*ROC curves for clinical and laboratory findings at the onset of diabetes, discriminating between fulminant type 1 diabetes and acute-onset type 1 diabetes.* A*: ROC curves for* Σ*C-peptide values and fasting serum C-peptide levels.* B*: ROC curves for HbA_{1c} levels, plasma glucose levels, and arterial pH. C: ROC curves for duration of hyperglycemic symptoms before diagnosis, BMI, and onset age of diabetes.* D*: ROC curves for serum elastase 1 levels, serum amylase levels, and serum lipase levels.*

99.9]) and 98.0% (99/101 [93.0–99.7]), respectively.

To assess which variables are significant independent ones in the absence of ΣC-peptide values, which were sometimes hard to obtain in clinical practice, a further multiple logistic regression analysis was done after excluding ΣC-peptide values. In this case, fasting C-peptide levels at onset ≤0.033 nmol/l and HbA_{1c} levels at onset ≤8.0% were recognized as independent variables; the odds ratio of fasting C-peptide was 11.4 (95% CI 3.4–38.4; $P = 0.0001$), and the odds ratio of HbA_{1c} was 7.7 (2.2–26.7; $P = 0.0013$). Using the criterion where patients whose fasting C-peptide levels at onset were ≤0.033 nmol/l and HbA_{1c} levels ≤8.0% were diagnosed as fulminant type 1 diabetes, sensitivity, specificity, positive predictive value, and negative predictive value were 92.0% (23/25 [95% CI 74.0–99.0]), 98.0% (98/100 [93.0–99.8]), 92.0% (23/25 [74.0–99.0]), and 98.0% (98/100 [93.0–99.8]), respectively.

CONCLUSIONS — In previous studies (3,5), the diagnosis of fulminant type 1 diabetes was based on negative findings of type 1 diabetes–related autoantibodies, including ICA, GADAb, IA-2Ab, and IAA, and aggressive mode of onset. However, type 1 diabetes–related autoantibodies in classical acute-onset type 1 diabetes are sometimes negative even at onset of diabetes (24–26). Very few hospital laboratories can assay diabetes-related autoantibodies, including ICA, GADAb, IA-2Ab, and IAA. Measurement of C-peptide levels can be easily carried out during routine practice. In the present study, we clearly demonstrate that the measurement of serum C-peptide values at onset is highly effective for diagnosis of fulminant type 1 diabetes without measuring pancreatic autoantibodies. The serum C-peptide values at onset were also highly predictive for further change of serum C-peptide levels. Low serum C-peptide levels at onset (fasting C-peptide ≤0.033 nmol/l or ΣC-peptide ≤0.540 nmol/l) can discriminate fulminant type 1 diabetes from acute-onset type 1 diabetes with high sensitivity and specificity (Table 1). Because acute-onset type 1 diabetes is much more common than fulminant type 1 diabetes, the possibility cannot be

Table 1—*Discriminating criteria of fulminant type 1 diabetes from acute-onset type 1 diabetes and the sensitivity, specificity, positive predictive value, and negative predictive value for each discriminating criterion*

Discriminating criterion*	Sensitivity	Specificity	Positive predictive value	Negative predictive value
ΣC-peptide ≤0.540 nmol/l	96.0 (79.7–99.9)	94.0 (87.4–97.8)	80.0 (61.4–92.3)	98.9 (94.3–100.0)
Fasting serum C-peptide ≤0.033 nmol/l	96.0 (79.7–99.9)	94.0 (87.4–97.8)	80.0 (61.4–92.3)	98.9 (94.3–100.0)
Age at onset >20 years	100.0 (86.2–100.0)	20.0 (12.7–29.2)	23.8 (16.0–33.1)	100.0 (83.2–100.0)
BMI >19.1 kg/m^2	76.0 (54.9–90.6)	64.0 (53.8–73.4)	34.5 (22.2–48.6)	91.4 (82.3–96.8)
Duration ≤8.0 days	96.0 (79.7–99.9)	88.0 (80.0–93.6)	66.7 (49.0–81.4)	98.9 (93.9–100.0)
Glucose >33.6 mmol/l	76.0 (54.9–90.6)	81.0 (71.9–88.2)	50.0 (33.9–66.6)	93.1 (85.6–97.4)
HbA_{1c} ≤8.0%	96.0 (79.7–99.9)	89.0 (81.2–94.4)	68.6 (50.7–83.2)	98.9 (94.0–100.0)
Arterial pH ≤7.21	84.0 (63.9–95.4)	74.0 (64.3–82.3)	44.7 (30.2–59.9)	94.9 (87.4–98.6)
Amylase >345 IU/l	68.0 (46.5–85.1)	92.0 (84.8–96.5)	68.0 (46.5–85.1)	92.0 (84.8–96.5)
Lipase >173 U/l	64.0 (42.5–82.0)	92.0 (84.8–96.5)	66.7 (44.7–84.4)	91.1 (83.8–95.8)
Elastase one >231 ng/dl	80.0 (59.3–93.2)	91.0 (83.6–95.8)	69.0 (49.2–84.7)	94.8 (88.3–98.3)

Data are percent (95% CI). *Discriminating criterion of fulminant type 1 diabetes (n = 25) from acute-onset type 1 diabetes (n = 100) was devised from the optimum cutoff value obtained using ROC curve analysis of each clinical or laboratory finding at onset of diabetes. Normal range of amylase, 111–336; normal range of lipase, 25–170; normal range of elastase 1, 22–221.

ruled out that our criteria based only on serum C-peptide give a fair number of false positives in acute-onset type 1 diabetes. Recently, Maldonado et al. (27) reported an association of ketosis-prone and ICA-negative diabetes with diminished fasting C-peptide levels at mean values of 0.08 nmol/l in the U.S. population. This value is similar to the cutoff value of fulminant type 1 diabetes in our study (Table 1).

Our study, using multiple logistic regression analysis, demonstrates that the diagnostic criteria consisting of the combination of serum C-peptide levels at onset and HbA_{1c} levels at onset (a criterion where the level of fasting C-peptide is ≤0.033 nmol/l and HbA_{1c} ≤8.0% or where the level of ΣC-peptide is ≤0.540 nmol/l and HbA_{1c} ≤8.0%) increased positive predictive values without changing other properties of the criteria, including sensitivities, specificities, and negative predictive values, when compared with those of criteria consisting only of serum C-peptide levels. Therefore, criteria taking into account both serum C-peptide levels at onset and HbA_{1c} levels at onset improve the diagnostic accuracy of fulminant type 1 diabetes without the measurement of islet cell autoantibodies.

We have prospectively demonstrated that patients with fulminant type 1 diabetes had extremely low C-peptide response during OGTT at onset, at 1 year after onset, and at 2 years after onset when compared with patients with acute-onset type 1 diabetes. Characteristically, none of patients with fulminant type 1 diabetes had improvement of ΣC-peptide values, i.e., >0.331-nmol/l (1.0 ng/ml) increase of ΣC-peptide values after onset (1 year and 2 years) when compared with the values at onset. In contrast, in more than one-third of acute-onset type 1 diabetic patients, improvement of ΣC-peptide values as demonstrated by OGTT at 1 year after onset was recognized. These findings are in line with previous reports that a high C-peptide level at diagnosis has been associated with a higher C-peptide level during the first year of follow-up (28,29). No recovery of residual β-cell function after onset is another characteristic feature of fulminant type 1 diabetes. An inverse correlation has been reported between residual β-cell function and the degree of glycemic instability (30). We previously demonstrated that a negative relationship between preserved β-cell function and progression of diabetes complications exists (12). This indicates that patients with fulminant type 1 diabetes have higher risks of developing diabetes complications than patients with acute-onset type 1 diabetes. Therefore, fulminant type 1 diabetic patients might have a need for accurate diagnosis followed by intensive insulin therapy to attain good and stable glycemic control.

Acknowledgments— This study is the fifth of the Yamanashi Diabetes Research Group (since 2002). This study was partly supported by grants from the Ministry of Education, Science, Sports and Culture, Japan, and the Japan Diabetes Foundation.

We thank T. Hughes for editorial assistance.

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