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Islet cell antibodies are associated with β-cell failure also in obese adult onset diabetic patients

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Abstract. To clarify the utility of islet cell antibodies (ICA) to correctly classify and predict insulin treatment in newly diagnosed diabetic subjects, ICA, body mass index (BMI), glycated hemoglobin (HbA_{1c}), and fasting plasma C-peptide values were evaluated at and 3 years after diagnosis in 233 new, consecutively diagnosed, adult diabetic patients classified as obese or nonobese (National Diabetes Data Group, NDDG criteria). Among the 233 patients, 31 were nonobese ICA-positive (mean age at diagnosis 43 ± 3 years), 55 nonobese ICA-negative (mean age at diagnosis 58 ± 2 years), 7 obese ICA-positive (mean age at diagnosis 57 ± 5 years), and 139 obese ICA-negative (mean age at diagnosis 58 ± 1 years). Fasting C-peptide decreased ($P < 0.05$) in nonobese ICA-positive patients who after 3 years showed lower BMI (22.6 ± 0.6 versus 24.5 ± 0.4; $P < 0.05$), lower fasting C-peptide (0.14 ± 0.06 nmol/l versus 0.71 ± 0.07 nmol/l; $P < 0.001$), and higher frequency of insulin treatment [28/31 (90%) versus 6/45 (13%); $P < 0.001$] than nonobese ICA-negative patients. In obese ICA-positive patients, fasting C-peptide also decreased (Δ C-peptide 0.17 ± 0.04 nmol/l; $P < 0.05$) after diagnosis, and 3 years after diagnosis, obese ICA-positive patients showed lower BMI (25.7 ± 1.2 versus 29.8 ± 0.4; $P < 0.01$) and fasting C-peptide (0.08 ± 0.04 nmol/l versus 1.06 ± 0.05 nmol/l; $P < 0.001$) and higher HbA_{1c} values ($9.92\% \pm 0.68\%$ versus $7.39\% \pm 0.21\%$; $P < 0.01$) and a higher frequency of insulin treatment [7/7 (100%) versus 5/121 (4%); $P < 0.001$] than obese ICA-negative patients. Therefore, ICA detected at diagnosis of diabetes in both obese and nonobese adult patients indicate β-cell dysfunction, high HbA_{1c} levels, and progression to insulin dependency.

Key words: Fasting C-peptide – Autoimmunity – Islet cell antibody

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Introduction

The diagnosis of type 2 (non-insulin-dependent) diabetes mellitus in adult patients is mostly based upon clinical criteria such as mature age and obesity [1]. Type 1 diabetes may occur in elderly subjects [2, 3], however, and not all type 2 diabetic patients are obese [2, 4]. Accordingly, one of every four newly diagnosed adult diabetic patients may be misclassified [5, 6]. The WHO classification of diabetes distinguishes two forms of type 2 diabetes (with and without obesity [7]), but the diagnosis of type 2 diabetes is also complicated by the fact that an autoimmune subtype of type 2 diabetes featuring islet cell antibodies (ICA) has been described [8, 9]. ICA have been detected in 10%–23% of adult patients classified as type 2 diabetic [10–16] and are associated with progressive β-cell dysfunction [14, 17, 18] and insulin dependency [10–14, 18]. Type 2 diabetic patients with ICA at diagnosis often have a low body mass index (BMI) [14, 15, 18], but ICA may be detected in obese diabetic patients examined up to 2 years after diagnosis [11]. The role of ICA at diagnosis of type 2 diabetes in obese subjects is not well established, however.

To clarify the clinical utility of ICA to establish the correct type of diabetes and, consequently, to facilitate the institution of correct treatment in newly diagnosed adult diabetic subjects, ICA and the degree of obesity were assessed at diagnosis of diabetes in 233 adult patients followed prospectively for 3 years. The aims of the current study were to relate ICA and obesity at diagnosis of diabetes to impairment in β-cell function and the need for insulin treatment 3 years thereafter, when the true type of diabetes should be evident.

Materials and methods

Subjects

Between September 1985 and August 1987, all new, consecutively diagnosed, adult (≥15 years of age) diabetic patients [$n = 233$, 24 (10%) 15–34 years of age] in the city of Malmö (230056 inhabi-

tants, 197848 ≥ 15 years of age 1986), Sweden, were tested for ICA [15, 18]. BMI at diagnosis was used to classify the patients as obese or nonobese according to the National Diabetes Data Group (NDDG) criteria (BMI > 27 kg/m^2 in men and BMI > 25 kg/m^2 in women defines obesity [19]). The 233 patients could be divided into four groups: 31 nonobese ICA-positive patients (mean age at diagnosis 43 ± 3 years), 55 nonobese ICA-negative patients (mean age at diagnosis 58 ± 2 years), 7 obese ICA-positive patients (mean age at diagnosis 57 ± 5 years), and 139 obese ICA-negative patients (mean age at diagnosis 58 ± 1 years); BMI was missing in one ICA-negative patient. Three years after the initial diagnosis and classification, the type of treatment could be established in 204/212 (96%) of the surviving patients and related to current BMI, glycated hemoglobin (HbA_{1c}) and fasting C-peptide values, as well as to the initial classification and test results. Patients were treated by experienced clinicians who, without knowledge of the ICA and fasting C-peptide results, instituted insulin when needed a judging from their clinical experience.

The study was approved by the Ethical Committee at the University of Lund, Sweden. Informed consent was obtained from all subjects.

Analytical methods

BMI was calculated as weight in kilograms/(height in m)^2. Treatment and mortality data were obtained from the patient records.

Samples for HbA_{1c} and C-peptide determination were collected in tubes with ethylene diamine tetra-acetic acide (EDTA). HbA_{1c} samples were kept at +4 °C until analysis by a high-performance liquid chromatography method [20]. Reference values of healthy individuals were 3.90%–5.30%. The intra-assay coefficient of variation was 1% and the interassay, 2%. Samples for fasting C-peptide were centrifuged and kept at −20 °C until assayed by radioimmunoassay [21]. The lower detection limit was 0.10 nmol/l, and intra- and interassay coefficients of variation were 7% and 9%, respectively. Reference values were 0.25–0.75 nmol/l [22].

ICA were assayed by an indirect two-colour immunofluorescence test incubating patient sera with frozen sections of human blood group "0" pancreas [23, 24]. ICA was quantified by diluting sera until ICA could not be detected. Titers were converted to Juvenile Diabetes Foundation (JDF) units, by a standard curve based on the international JDF reference serum sample [25]. The detection limit for the ICA assay was 3 JDF units for the pancreas used.

Statistics

When testing group differences, the Kruskal-Wallis variance test was conducted, and if significant, possible differences between two groups were evaluated with the Mann-Whitney U-test. Differences between two test occasions within groups were evaluated with the Wilcoxon signed-rank test and differences in frequency, with the chi-square test. All tests were two-tailed, and $P < 0.05$ was considered significant. Results are presented as mean ± SEM.

Results

Nonobese patients

At diagnosis, nonobese ICA-positive patients ($n = 31$) were significantly younger (43 ± 3 years versus 58 ± 2 years; $P < 0.01$), showed higher HbA_{1c} ($P < 0.01$; Fig. 1), lower BMI ($P < 0.01$; Fig. 2), and lower fasting C-peptide ($P < 0.001$; Fig. 3) than nonobese ICA-negative patients ($n = 55$). Though fasting C-peptide decreased (Δ C-peptide 0.10 ± 0.05 nmol/l; $P < 0.05$) and BMI was unchanged during the first 3 years after diagnosis, HbA_{1c}

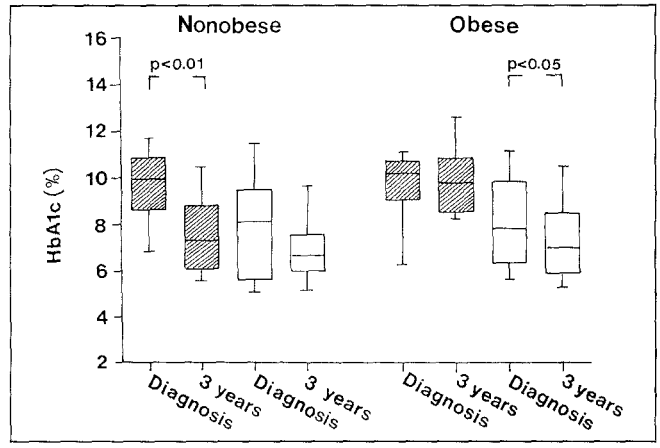

Fig. 1. Glycosylated hemoglobin (HbA_{1c}) at and 3 years after diagnosis in nonobese ICA-positive (▨; $n = 31$), nonobese ICA-negative (□; $n = 55$), obese ICA-positive (▨; $n = 7$), and obese ICA-negative (□; $n = 139$) patients. Box plots display the 10th, 25th, 50th, 75th, and 90th percentiles

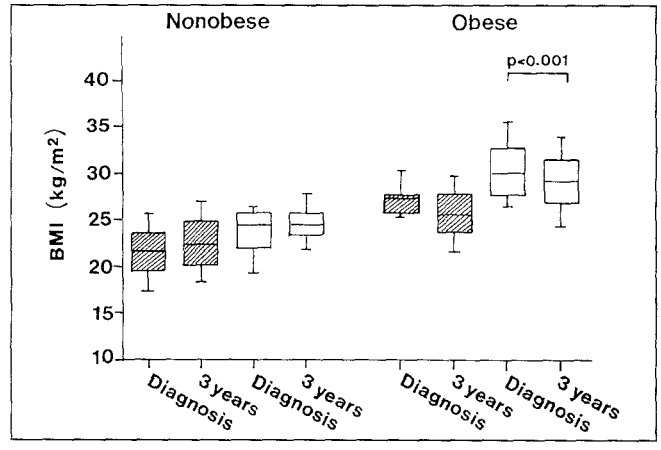

Fig. 2. Body mass index (*BMI*) at and 3 years after diagnosis in nonobese ICA-positive (▨; $n = 31$), nonobese ICA-negative (□; $n = 55$), obese ICA-positive (▨; $n = 7$), and obese ICA-negative (□; $n = 139$) patients. Box plots display the 10th, 25th, 50th, 75th, and 90th percentiles

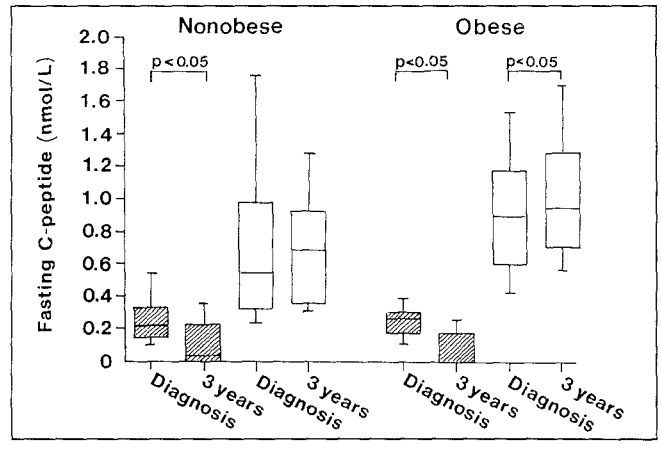

Fig. 3. Fasting C-peptide at and 3 years after diagnosis in nonobese ICA-positive (▨; $n = 31$), nonobese ICA-negative (□; $n = 55$), obese ICA-positive (▨; $n = 7$), and obese ICA-negative (□; $n = 139$) patients. Box plots display the 10th, 25th, 50th, 75th, and 90th percentiles

improved significantly (Δ HbA_{1c} 1.78% ± 0.51%; $P < 0.001$) in nonobese ICA-positive patients and did not differ from HbA_{1c} in nonobese ICA-negative patients 3 years after diagnosis. Nonobese ICA-positive patients showed a significantly ($P < 0.001$) higher frequency of insulin treatment than nonobese ICA-negative patients at diagnosis [18/31 (58%) versus 7/55 (13%)], but this frequency had increased further to 28/31 (90%) after 3 years, when the frequency of insulin treatment was still low in ICA-negative patients [6/45 (13%)]. Five nonobese ICA-positive patients lost ICA during the first 3 years after diagnosis. In nonobese ICA-positive patients, ICA levels at and 3 years after diagnosis were similar (60 ± 3 JDFU and 33 ± 3 JDFU, respectively) and did not correlate with HbA_{1c} or fasting C-peptide levels.

In nonobese ICA-negative patients, BMI, HbA_{1c}, and fasting C-peptide were unchanged during the first 3 years after diagnosis, and ICA did not develop in any patient. In nonobese patients (all; $n = 86$), fasting C-peptide at diagnosis correlated inversely (r −0.28; $P < 0.05$) with HbA_{1c} at diagnosis and directly ($r = 0.74$; $P < 0.001$) with fasting C-peptide 3 years after diagnosis.

Obese patients

At diagnosis, obese ICA-positive patients ($n = 7$) showed significantly lower BMI ($P < 0.05$; Fig. 2) and fasting C-peptide ($P < 0.001$; Fig. 3) than obese ICA-negative patients ($n = 139$). BMI and HbA_{1c} were unchanged during the first 3 years after diagnosis in obese ICA-positive patients, but decreased (improved; $P < 0.001$ and $P < 0.05$, respectively) in obese ICA-negative patients (Figs. 1, 2). As in nonobese ICA-positive patients, fasting C-peptide decreased significantly ($P < 0.05$; Fig. 3) during 3 years in obese ICA-positive patients, whereas it increased ($P < 0.05$; Fig. 3) in obese ICA-negative patients. Three years after diagnosis, the frequency of insulin treatment in obese ICA-positive patients was significantly higher than in obese ICA-negative patients [7/7 (100%) versus 5/121 (4%); $P < 0.001$], as compared with 2/7 (29%) versus 4/139 (3%; NS, $P = 0.053$) at diagnosis. In obese ICA-positive patients, ICA levels at and 3 years after diagnosis were similar (85 ± 4 JDFU and 28 ± 3 JDFU, respectively) and did not correlate with HbA_{1c} or fasting C-peptide levels. Three years after diagnosis, one obese ICA-positive patient had lost ICA, whereas three obese ICA-negative women 52–57 years of age, had developed ICA; fasting C-peptide range was 0.36–1.27 nmol/l and HbA_{1c} range 6.01%–6.63% in these three still non-insulin-requiring patients.

ICA-positive patients; nonobese versus obese

At diagnosis, no significant differences in HbA_{1c} and fasting C-peptide were found between nonobese and obese ICA-positive patients (Figs. 1, 3). Three years later, however, nonobese ICA-positive patients showed significantly lower HbA_{1c} than obese ICA-positive patients (7.55% ± 0.57% versus 9.92% ± 0.68%; $P < 0.01$).

ICA-negative patients; nonobese versus obese

Both at diagnosis ($P < 0.01$) and 3 years later ($P < 0.001$), nonobese ICA-negative patients showed significantly lower fasting C-peptide than obese ICA-negative patients; however, when fasting C-peptide was related to BMI (ratio of fasting C-peptide/BMI), no differences were found between ICA-negative nonobese und obese patients, either at diagnosis (0.03 ± 0.01 versus 0.03 ± 0.01 nmol/l) or 3 years later (0.03 ± 0.01 versus 0.03 ± 0.01 nmol/l).

ICA positivity and age

Among all ICA-positive patients (38/233; 16%), those over 40 years of age ($n = 21$) showed a significantly lower frequency of insulin treatment at diagnosis than those under 40 years of age [$n = 17$, 6/21 (29%) versus 14/17 (82%); $P < 0.01$], whereas fasting C-peptide levels at diagnosis were similar (0.29 ± 0.04 and 0.23 ± 0.03 nmol/l, respectively) in both age groups. Three years after diagnosis, however, there was no significant difference in the frequency of insulin treatment [18/21 (86%) and 17/17 (100%), respectively] between ICA-positive patients over and under 40 years of age at diagnosis.

Prediction of insulin dependency

Sensitivity, specificity, positive and negative values regarding prediction of insulin treatment 3 years later were calculated for patient age <40 years, lack of obesity, different cut-off fasting C-peptide levels (FCp), and ICA analysis at diagnosis of diabetes. ICA analysis showed the best utility to predict insulin treatment when sensitivity, specificity, and positive and negative predictive values were considered (Table 1).

Table 1. Sensitivity, specificity, positive and negative predictive values for patient age <40 years, lack of obesity, fasting C-peptide levels (FCp) <1.64 SD in healthy controls [22] (95% of the population with one-tailed tests), FCp below reference interval, and islet cell antibody (ICA) analysis at diagnosis of diabetes regarding prediction of insulin treatment 3 years later

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Age <40 years	48	92	59	87
Lack of obesity	74	72	47	90
FCp <1.64 SD in controls (<0.21 nmol/l)	35	98	83	83
FCp below reference interval (<0.25 nmol/l)	53	96	82	87
ICA present	76	98	92	93

Discussion

Our prospective and population-based study showed that ICA could be found in 16% (38/233) of new consecutively diagnosed, adult diabetic patients, 36% (31/86) in nonobese and 5% (7/146) in obese. The ICA frequency in adult patients was, as expected, considerably lower than in consecutively diagnosed Swedish children [26] and young (15–34 years of age) adults [16]. When examined three years after diagnosis, it was obvious that ICA at diagnosis, also in obese patients, predicted a future need of insulin treatment; 92% (35/38) [90% (28/31) nonobese, 100% (7/7) obese] of ICA-positive patients were receiving insulin 3 years after diagnosis as compared with only 7% (11/166) of ICA-negative patients.

Higher body weight is associated with a lower risk of progression to insulin dependency [27–29] and preserved β-cell function [30] in middle-aged diabetic patients. In this context, our finding that ICA may be detected at diagnosis of diabetes also in obese patients, confirming previous observations by Irvine et al. [11], is important and indicates that ICA-associated progressive β-cell dysfunction is a potential problem also in obese patients. Previous observations of ICA in adult type of diabetic patients suggested that ICA are confined to nonobese patients [14, 15, 18]. The current study shows, however, that ICA in obese subjects also are associated with low C-peptide values that, as in nonobese ICA-positive subjects, deteriorate after diagnosis, leading to a more severe metabolic disturbance in comparison with ICA-negative obese patients after 3 years, although insulin therapy had been instituted in all obese ICA-positive patients. That HbA1c decreased after insulin treatment in nonobese, but not in obese, ICA-positive patients might be attributed to a difference in insulin resistance.

In our prospective study, both nonobese and obese ICA-negative patients showed unchanged and preserved β-cell function 3 years after diagnosis, in accordance with other prospective studies of β-cell function in type 2 diabetes showing persistence of insulin secretion during the first 5 years after diagnosis [31, 32], but in contrast to the decrease in β-cell function reported 10 years after diagnosis of type 2 diabetes in a cross-sectional study [4]. Further follow-up will reveal if such a decrease in β-cell function occurs in our patients. Anyhow, if type 2 diabetic patients are to be classified with respect to β-cell function, a classification based on the presence or absence of ICA is more relevant than the WHO classification [7] based upon the presence or absence of obesity.

In our study ICA were found in patients of all ages, but elderly (>40 years of age) ICA-positive patients commenced insulin therapy more seldomly at diagnosis than younger (<40 years of age) ICA-positive patients. The choice of insulin therapy to control diabetes in our patients was of course dependent on the individual physician's attitude, but this prospective follow-up demonstrated that ICA indicated both β-cell dysfunction and institution of insulin treatment upon clinical grounds among ICA-positive patients of all ages.

HbA_{1c} decreased significantly during the first 3 years after diagnosis in insulin-treated, nonobese ICA-positive patients and in obese ICA-negative patients, whereas it remained unchanged in other groups, including nonobese ICA-negative subjects. This lack of a treatment effect on HbA_{1c} among nonobese ICA-negative patients raises the question of whether insulin treatment would have had a favourable influence on metabolic control also in nonobese ICA-negative patients with preserved β-cell function 3 years after diagnosis. Differences in metabolic control can of course also be attributed to differences in patient compliance with diet and exercise; as the decrease in HbA_{1c} in obese ICA-negative patients was associated with a corresponding decrease in BMI, improvement of metabolic control might have been a consequence of the reduction in the degree of insulin resistance.

Newly diagnosed diabetic patients might be in a catabolic state with a loss of body weight before diagnosis. Hence, BMI values recorded at diagnosis might not be representative, and the BMI might be expected to increase after diagnosis as a result of institution of adequate diabetes treatment. In this study, however, a significant change in BMI during the first 4 years after diagnosis was seen only in obese ICA-negative patients, in whom BMI decreased (improved), presumably as a result of diet treatment and patient education. Hence, it appears that BMI at diagnosis is representative or that a prediagnostic loss of body weight will not be restituted in nonobese subjects.

The hyperglycaemic state present at diagnosis of diabetes has been reported to potentiate β-cell responses [33, 34], resulting in inappropriately high C-peptide values at diagnosis, although other investigators have found that chronic hyperglycaemia results in desensitization of human islets to further acute stimulation with glucose [35, 36]. In nonobese patients in this study, however, fasting C-peptide values at the diagnosis of diabetes correlated with HbA_{1c} at diagnosis as well as with fasting C-peptide 3 years after diagnosis. This suggests that the prevailing degree of β-cell function at diagnosis is important for the degree of glycaemic control at diagnosis, as well as for β-cell function 3 years thereafter in nonobese adult patients with diabetes mellitus.

Finally, it has to be clarified whether ICA correctly predicted the type of diabetes as well as the need for insulin 3 years after diagnosis of diabetes. Among ICA-positive patients, 28/31 nonobese and 7/7 obese were receiving insulin treatment after 3 years, i.e., 92% (35/38) were insulin-treated after 3 years as compared with 53% (20/38) at diagnosis. Most likely, these ICA-positive patients had type 1 diabetes. In addition, the remaining three ICA-positive subjects (fasting C-peptide range 0.24–0.42 nmol/l at diagnosis and 0.36–0.37 nmol/l 3 years after diagnosis) may also be considered as type 1 diabetic patients. Among the surviving ICA-negative patients, 7% (11/166) was receiving insulin treatment after 3 years, of whom 5 (4/6 nonobese and 1/5 obese according to low C-peptide values; Table 2) may be considered to have type 1 diabetes. Hence, altogether 21% (43/204) of surviving patients who could be followed up in this study might be considered to have type 1 and 79% (161/204) to have type 2 diabetes.

Table 2. ICA-negative patients insulin-treated 3 years after diagnosis of diabetes. Sex, age (years), fasting C-peptide (FCp; nmol/l), body mass index (BMI), glycosylated hemoglobin (HbA_{1c}; %), and insulin treatment at diagnosis (0 year) and 3 years later (3 years)

	Sex	Age	BMI		HbA_{1c}		FCp		Insulin treatment	
			0 year	3 years	0 year	3 years	0 year	3 years	0 year	3 years
Nonobese										
	Male	30	19.1	–	12.17	–	0.10	–	+	+
	Male	33	19.6	21.8	–	4.14	–	0.18	0	+
	Male	26	23.9	24.1	11.07	6.24	0.37	0.56	+	+
	Female	65	22.3	–	11.90	–	0.53	–	0	+
	Female	22	23.6	21.5	6.62	9.08	0.27	0.36	+	+
	Female	39	14.8	20.8	9.10	5.49	0.24	–	+	+
Obese										
	Male	44	33.0	36.3	8.59	10.51	0.95	0.40	0	+
	Male	62	27.9	29.4	11.78	6.03	0.78	0.74	+	+
	Female	66	43.6	40.6	8.92	8.41	1.47	1.49	0	+
	Female	41	26.3	–	14.75	10.47	1.48	0.70	0	+
	Female	20	37.3	34.6	7.61	7.55	1.28	1.83	0	+

In conclusion, ICA are detected at diagnosis of diabetes in obese as well as in nonobese adult patients, indicating β-cell dysfunction, high HbA_{1c} levels, and progression to insulin dependency. To accomplish an appropriate classification and adequate treatment of diabetes, adult onset diabetic patients should be subjected to ICA analysis upon diagnosis of diabetes.

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References

1. West KM, Kalbfleisch JM, Influence of nutritional factors on prevalence of diabetes. Diabetes 20:99–108, 1971
2. Melton J, Palumbo P, Chu-pin C, Incidence of diabetes mellitus by clinical type. Diabetes Care 6:75–86, 1983
3. Laakso M, Pyörälä K, Age of onset and type of diabetes. Diabetes Care 8:114–117, 1985
4. Eriksson J, Forsén B, Häggblom M, Teppo A-M, Groop L, Clinical and metabolic characteristics of type 1 and type 2 diabetes: an epidemilogical study from the Närpes community in western Finland. Diabetic Med 9:654–660, 1992
5. Hother-Nielsen O, Faber O, Sørensen NS, Beck-Nielsen H, Classification of newly diagnosed diabetic patients as insulin-requiring or non-insulin-requiring based on clinical and biochemical variables. Diabetes Care 11:531–537, 1988
6. MacIver D, McNally P, Shaw D, Hearnshaw J, Predicting future treatment of diabetes mellitus from characteristics available at presentation. Diabetic Med 5:766–770, 1988
7. WHO Study Group, Report of diabetes mellitus technical report series no. 727. WHO, Geneva, 1985
8. Groop LC, Eriksson J, Ekstrand A, Franssila-Kallunki A, Saloranta C, Miettinen A, Metabolic characteristics of autoimmune diabetes in adults. Diabetologia 34:46–51, 1991
9. Kobayashi T, Tamemoto K, Nakanishi K, Kato N, Okubo M, Kajio H, Sugimoto T, Murase T, Kosaka K, Immunogenetic and clinical characterization of slowly progressive IDDM. Diabetes Care 16:780–788, 1993
10. Irvine WJ, McCallum CJ, Gray RS, Cambell CJ, Duncan LJP, Farquhar JW, Vaughan H, Morris PJ, Pancreatic islet cell antibodies in diabetes mellitus correlated with the duration and type of diabetes, coexistent autoimmune disease and HLA-type. Diabetes 26:138–147, 1977
11. Irvine WJ, Sawers JSA, Feek CM, Prescott RJ, Duncanc JP, The value of islet cell antibody in predicting secondary failure of oral hypoglycemic agent therapy in diabetes mellitus. J Clin Immunol 2:23–26, 1979
12. Di Mario U, Irvine WJ, Borsey DQ, Kyner JL, Weston J, Galfo C, Immune abnormalities in diabetic patients not requiring insulin at diagnosis. Diabetologia 25:392–395, 1983
13. Gleichmann H, Zörcher B, Greulich B, Gries FA, Henrichs HR, Bertrams J, Kolb H, Correlation of islet cell antibodies and HLA-DR phenotypes with diabetes mellitus in adults. Diabetologia 27:90–92, 1984
14. Groop LC, Bottazzo GF, Doniac D, Islet cell antibodies identify latent type 1 diabetes in patients aged 35–75 years at diagnosis. Diabetes 35:237–241, 1986
15. Landin-Olsson M, Nilsson K-O, Lernmark Å, Sundkvist G, Islet cell antibodies and fasting C-peptide predict insulin requirement at diagnosis of diabetes mellitus. Diabetologia 33:561–568, 1990
16. Landin-Olsson M, Karlsson F, Lernmark Å, Sundkvist G, The DISS group, Islet cell and thyrogastric antibodies in 633 consecutive 15- to 34-yr-old patsients in the diabetes incidence study in Sweden. Diabetes 41:1022–1027, 1992
17. Kobayashi T, Itoh T, Kasaka K, Sato K, Tsuji K, Time course of islet cell antibodies and β-cell function in non-insulin-dependent stage of Type 1 diabetes. Diabetes 36:510–517, 1987
18. Gottsäter A, Landin-Olsson M, Fernlund P, Lernmark Å, Sundkvist G, β-cell function in relation to islet cell antibodies (ICA) during the first three years after the clinical diagnosis of diabetes in non-insulin-dependent (type II) diabetic patients. Diabetes Care 16:902–910, 1993
19. National Diabetes Data Group (NDDG), Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039–1057, 1979
20. Jeppsson J-O, Jerntorp P, Sundkvist G, Englund H, Nylund V, Measurement of hemoglobin A1c by a new liquid-chromatographic assay: methodology, clinical utility, and relation to glucose tolerance evaluated. Clin Chem 32:1867–1872, 1986
21. Heding L, Radioimmunological determination of C-peptide in serum. Diabetologia 11:541–548, 1975
22. Gottsäter A, Landin-Olsson M, Fernlund P, Gullberg B, Lernmark Å, Sundkvist G, Pancreatic beta-cell function evaluated by intravenous glucose and glucagon stimulation. A compari-

son between insulin and C-peptide to measure insulin secretion. Scand J Clin Lab Invest 52:631–639, 1992
23. Madsen OD, Landin-Olsson M, Bille G, Sundkvist G, Lernmark Å, Dahlquist G, Ludvigsson J, A two-colour immunofluorescence test with a monoclonal human proinsulin antibody improves the assay for islet cell antibodies. Diabetologia 29:115–118, 1986
24. Landin-Olsson M, Sundkvist G, Lenmark Å, Prolonged incubation on the two-colour immunofluorescent test increases the prevalence and titres of islet cell antibodies in Type 1 (insulin-dependent) diabetes mellitus. Diabetologia 30:327–332, 1987
25. Boitard C, Bonifacio E, Bottazzo GF, Gleishmann H, Molenaar J, Immunology and diabetes workshop: report on the third international (stage 3) workshop on the standardisation of cytoplasmic islet cell antibodies. Diabetologia 31:451–452, 1988
26. Landin-Olsson M, Karlsson A, Dahlquist G, Blom L, Lernmark Å, Sundkvist G, Islet cell and other organ-specific autoantibodies in all children developing Type 1 (insulin-independent) diabetes mellitus in Sweden during one year and in matched controls. Diabetologia 32:387–395, 1989
27. Lyons TJ, Kennedy L, Atkinson AB, Buchanan KD, Hadden DR, Weaver JA, Predicting the need for insulin therapy in late onset (40–69 years) diabetes mellitus. Diabetic Med 1:105–107, 1984
28. Pontiroli AE, Calderara A, Capra F, Fattor B, Illeni MT, Pozza G, HLA phenotype and secondary failure to oral hypoglycaemic agents. Diabetologia 30:824–825, 1987
29. Pontiroli AE, Calderara A, Maffi P, Bonisolli A, Carenini PM, Piatti PM, Monti LD, Gallus G, Pozza G, Illeni MT, Secondary failure to oral hypoglycaemic agents in non-obese patients with non-insulin-dependent diabetes is related to reduced insulin release. Diabete Metab 15:79–84, 1989
30. Laakso M, Rönnemaa T, Sarlund H, Pyörälä K, Kallio V, Factors associated with fasting and postglucagon plasma C-peptide levels in middle-aged insulin-treated diabetic patients. Diabetes Care 12:83–88, 1989
31. Niskanen LK, Uusitupa MI, Sarlund H, Siitonen O, Pyörälä K, Five-year follow-up study on plasma insulin levels in newly diagnosed NIDDM patients and nondiabetic subjects. Diabetes Care 13:41–47, 1990
32. Niskanen L, Karjalainen J, Sarlund H, Siitonen O, Uusitupa M, Five-year follow-up of islet cell antibodies in type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 34: 402–408, 1991
33. Arnold-Larsen S, Madsbad S, Kühl C Reproducibility of the glucagon test. Diabetic Med 4:299–303, 1987
34. Gjessing HJ, Reinholdt B, Pedersen O, The plasma C-peptide and insulin responses to stimulation with intravenous glucose and a mixed meal in well controlled type 2 (non-insulin-dependent) diabetes mellitus: dependency on acutely established hyperglycaemia. Diabetologia 32:858–863, 1989
35. Davalli AM, Ricordi C, Socci C, Braghi S, Bertuzzi F, Fattor B, Di Carlo V, Pontiroli AE, Pozza G, Abnormal sensitivity to glucose of human islets cultured in a high glucose medium: partial reversibility after an additional culture in a normal glucose medium. J Clin Endocrinol Metab 72:202–208, 1991
36. Davalli AM, Pontiroli AE, Socci C, Bertuzzi F, Fattor B, Braghi S, Di Carlo V, Pozza G, Human islets chronically exposed in vitro to different stimuli become unresponsive to the same stimuli given acutely: evidence supporting specific desensitization rather than β-cell exhaustion. J Clin Endocrinol Metab 74:790–794, 1992

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