A Clinical Screening Tool Identifies Autoimmune Diabetes in Adults

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OBJECTIVE — Latent autoimmune diabetes in adults (LADA) is defined as adult-onset diabetes with circulating islet antibodies but not requiring insulin therapy initially. Diagnosing LADA has treatment implications because of the high risk of progression to insulin dependency. Currently, there are no recommendations for islet antibody testing in adult-onset diabetes. In this study, we aimed to develop a clinical screening tool to identify adults at high risk of LADA who require islet antibody testing.

RESEARCH DESIGN AND METHODS — Subjects with LADA ($n = 102$, GAD antibody [GADA]+) and type 2 diabetes ($n = 111$, GADA−) (aged 30–75 years) were interviewed retrospectively. The clinical features documented were age of onset, acute symptoms of hyperglycemia, BMI, and personal and family history of autoimmune disease. Any clinical feature that was significantly more frequent in LADA was designated as a distinguishing clinical feature. In each subject, a "LADA clinical risk score," based on the total number of distinguishing features, was calculated. A prospective study of adults with newly diagnosed diabetes ($n = 130$) was used to determine whether the LADA clinical risk score could identify LADA.

RESULTS — In the retrospective study, five clinical features were more frequent in LADA compared with type 2 diabetes at diagnosis: *1*) age of onset <50 years ($P < 0.0001$), *2*) acute symptoms ($P < 0.0001$), *3*) BMI <25 kg/m^2 ($P = 0.0004$), *4*) personal history of autoimmune disease ($P = 0.011$), and 5) family history of autoimmune disease ($P = 0.024$). In the prospective study, the presence of at least two of these distinguishing clinical features (LADA clinical risk score ≥2) had a 90% sensitivity and 71% specificity for identifying LADA and a negative predictive value for a LADA clinical risk score ≤1 of 99%.

CONCLUSIONS — At least two distinguishing clinical features are found in a majority of patients with LADA at diagnosis and can be used to identify adults with diabetes at higher risk for LADA.

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Latent autoimmune diabetes in adults (LADA) is a form of type 1 diabetes characterized by adult-onset diabetes (usually age >30 years), circulating islet antibodies, most commonly to GAD, and, initially, lack of requirement for insulin treatment (1,2). Based on findings in the U.K. Prospective Diabetes Study (UKPDS), ~10% of adults with diabetes have LADA (3). LADA is believed to be a slowly progressive form of autoimmune β-cell destruction, given that people with LADA have evidence of islet autoimmunity, namely circulating islet antibodies and type 1 diabetes susceptibility HLA class II alleles DQ2 and/or DQ8 (1). Tissue immunofluorescence islet cell antibodies and GAD antibodies (GADAs) are common in LADA, whereas antibodies to tyrosine phosphatase–like insulinoma antigen 2 (IA-2A) and insulin (IAAs) are not common (4). Patients with LADA typically present with more preserved β-cell function than those with classic type 1 diabetes but usually experience marked loss of β-cell function within 3 years of diagnosis, which eventually results in insulin dependence (5).

Detection of islet autoimmunity in adult-onset diabetes has prognostic and treatment implications. In the UKPDS, a majority of adults with diabetes, who had detectable GADAs, required insulin treatment within 6 years of diagnosis (3). We believe that physicians need to be aware that patients with LADA are prone to insulin deficiency and often require rapid escalation of oral hypoglycemic treatment or commencement of insulin earlier than islet antibody–negative patients.

Despite the frequency of LADA, there are no universal recommendations regarding testing for islet antibodies in adult-onset diabetes. Currently, many physicians test for islet antibodies only if they suspect LADA, generally on the basis of body weight. Overweight adults with diabetes are presumed to have type 2 diabetes and are not tested, whereas normal-weight adults are considered to potentially have LADA and may be tested (6,7). However, this approach neglects the many studies (8–12) in which LADA has been documented with mean BMI in the overweight or even obese category. Moreover, with increasing obesity in adults worldwide (13), it will become even more difficult to distinguish LADA from type 2 diabetes based on BMI. A reliable clinical strategy is required to identify which adults with diabetes have a high likelihood of LADA and need testing for islet antibodies. Thus, we aimed to identify clinical features that distinguished LADA in adults presenting with diabetes and to establish a clinical screening tool that would improve the detection of LADA and ultimately the management of patients with LADA.

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Abbreviations: AUC, area under the curve; GADA, GAD antibody; IA-2A, tyrosine phosphatase–like insulinoma antigen 2; IAA, insulin autoantibody; LADA, latent autoimmune diabetes in adults; ROC, relative operating characteristic; UKPDS, U.K. Prospective Diabetes Study.

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

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RESEARCH DESIGN AND METHODS

Retrospective study

Patients with LADA ($n = 102$) and type 2 diabetes ($n = 111$) were recruited from metropolitan Melbourne by referral from diabetes educators in community centers and treating physicians and through the Royal Melbourne Hospital diabetes clinics. A majority (97%) of the subjects were Caucasian. All patients (aged 30–75 years) had diabetes according to World Health Organization criteria (14). Patients with LADA were distinguished from type 1 diabetic patients because they had no requirement for insulin at diagnosis and for a minimum of 6 months after diagnosis. Subjects with LADA were distinguished from type 2 diabetic patients because they were serum GADA+, whereas type 2 diabetic subjects were GADA−. Other islet autoantibodies, namely IAAs and IA-2As, were not tested for at entry into the study because of their reported low frequency in LADA. Subjects known to have secondary forms of diabetes were excluded. All subjects underwent a structured interview (APPENDIX) to retrospectively determine the clinical features of presentation. The study was approved by the Royal Melbourne Hospital Human Research and Ethics Committee and subjects participating provided written informed consent.

Prospective study

Subsequently, a prospective study was performed on 130 subjects (aged 30–75 years) with recently diagnosed (<2 months) diabetes according to World Health Organization criteria who did not require insulin treatment. Subjects were recruited from a national diabetes register, the National Diabetes Services Scheme, which is managed by Diabetes Australia. Subjects registering with the National Diabetes Services Scheme have the option of agreeing to be contacted for the purpose of research. All subjects eligible for the study (i.e., aged 30–75 years, who did not require insulin at diagnosis) were sent a letter inviting them to participate in the study. Subjects who agreed to participate in the study provided written consent. After a structured interview, patients had blood taken to determine GADAs. The study was approved by the Royal Melbourne Hospital Clinical Research and Ethics Committee.

GADA assay

GADAs were measured by precipitation of in vitro–transcribed and –translated [^{35}S]methionine-labeled GAD65. The assay has had good sensitivity and specificity in International Workshops and Standardization Programs conducted by the Immunology of Diabetes Society (e.g., in ref. 15). Specificity and sensitivity in the 2003 Diabetes Antibody Standardization Program were 97 and 80%, respectively. The threshold for GADA positivity was established as the 97th percentile of unselected healthy schoolchildren at 5 units/ml.

Clinical assessment

All subjects were interviewed by the same endocrinologist (S.F.) to determine the age at diabetes onset, presence of acute symptoms before diagnosis (polydipsia, polyuria, and unintentional loss of weight), weight and height at diagnosis, family history of diabetes, family or personal history of any HLA DR3/DQ2- and/or DR4/DQ8-associated autoimmune disease, i.e., autoimmune thyroid disease (16), celiac disease (17), Addison's disease (18), vitiligo (19), rheumatoid arthritis (20), pernicious anemia (21), and autoimmune hepatitis (22). Details of the specific interview questions are provided in the APPENDIX. Metabolic markers such as ketonuria, blood glucose level, and HbA_{1c} (A1C) at diagnosis were not studied, as they were not routinely documented in these subjects.

Statistics

Differences in age and BMI were analyzed with an unpaired *t* test. Differences in age at diagnosis according to decade category, BMI according to weight category, acute symptoms, personal and family history of autoimmune disease, and family history of diabetes were analyzed with Fisher's exact tests. Statistical analyses were performed with GraphPad PRISM version 3.0 software.

The ability of a "LADA clinical risk score" to predict LADA was analyzed by a relative operating characteristic (ROC) plot using two different methods. The first method calculated a LADA clinical risk score based on the total number of "distinguishing" clinical features present in each subject. A distinguishing clinical feature was defined as a feature that was significantly more frequent in LADA compared with type 2 diabetes in the retrospective study. One point was scored for the presence of each distinguishing clinical feature, with a LADA clinical risk score of 5 being the maximum. In the second method, a LADA clinical risk score was calculated on the basis of a multivariate analysis of the distinguishing clinical features. Each clinical feature independently associated with LADA was weighted according to its odds ratio (OR) coefficient derived from a logistic regression model. The ability of the two clinical risk scores to predict LADA was assessed by calculating the area under the curve (AUC). Also, cutoff points with optimal sensitivity and specificity for both clinical scoring methods were determined to ascertain their ability to predict LADA in the prospective study.

RESULTS — In the retrospective study, subjects with LADA were significantly younger than type 2 diabetic subjects (median age 46.2 vs. 60.8 years, $P < 0.0001$) with a majority (64%) having diabetes diagnosed before the age of 50 (Table 1). The median BMI was lower in subjects with LADA compared with type 2 diabetic subjects, but a majority of both subjects with LADA and type 2 diabetes were in the overweight or obese category (BMI ≥25.0 kg/m^2) (Table 1). Acute symptoms (polydipsia and/or polyuria and/or weight loss) were present in a majority of subjects with LADA, being significantly more frequent than in type 2 diabetic subjects (67 vs. 28%, $P < 0.0001$). A family history of type 1 diabetes was more common in subjects with LADA, whereas a family history of type 2 diabetes was similar in subjects with LADA and type 2 diabetes. A family or personal history of DR3- and/or DR4-related autoimmune diseases was more common in LADA. The most common associated autoimmune disease in patients with LADA was thyroid autoimmune disease and in relatives was type 1 diabetes (Table 1).

On the basis of these findings, five distinguishing clinical features were significantly more frequent in subjects with LADA than in subjects with type 2 diabetes at diagnosis (Fig. 1). These were *1*) age of diabetes onset <50 years, *2*) acute symptoms of polydipsia and/or polyuria and/or unintentional weight loss before diagnosis, *3*) BMI <25 kg/m^2, *4*) a personal history of DR3- and/or DR4-related autoimmune disease, and *5*) a family history of DR3- and/or DR4-related autoimmune disease. A majority (75%) of subjects with LADA and a minority (24%) of type 2 diabetic subjects had at least two

Table 1—*Retrospective study: clinical features at diagnosis*

Clinical features	LADA	Type 2 diabetes	*P*
n	102	111	
Age (years)			
Median	46.2 (39.1–54.3)*	60.8 (35.9–67.6)	<0.0001
30.0–39.9	30 (30)†	5 (5)	<0.0001
40.0–49.9	34 (34)	14 (16)	0.0022
50.0–59.9	25 (25)	29 (32)	0.64
60.0–69.9	9 (9)	34 (38)	<0.0001
70.0–80.0	4 (4)	18 (20)	0.001
Sex (male/female)	50/52	55/56	0.999
BMI (kg/m^2)			
Median	27.9 (24.6–32.5)	30.8 (27.3–34.6)	0.0034
Lean (BMI <25)	31 (32)	11 (13)	0.0004
Overweight (BMI 25.1–30.0)	26 (27)	30 (33)	0.65
Obese (BMI ≥30)	42 (43)	59 (65)	0.0045
Symptoms			
Acute symptoms	66 (67)	25 (28)	<0.0001
Polyuria and/or polydipsia	60 (61)	23 (26)	<0.0001
Unintentional weight loss	36 (37)	5 (5)	<0.0001
Personal history autoimmune disease			
Any autoimmune disease	25 (25)	11 (12)	0.011
Autoimmune thyroid disease	19 (10)	6.3 (7)	0.007
Rheumatoid arthritis	2.0 (2)	2.7 (3)	0.999
Celiac disease	0.9 (1)	0.9 (1)	0.999
Other autoimmunity	2.9 (3)	2.7 (3)	0.48
Family history autoimmune disease			
Any autoimmune disease	46 (47)	31 (34)	0.024
Type 1 diabetes	24 (24)	9.9 (11)	0.0092
Autoimmune thyroid disease	20 (20)	9.9 (11)	0.053
Rheumatoid arthritis	9.8 (10)	6.3 (7)	0.45
Celiac disease	2.9 (3)	4.5 (5)	0.72
Other autoimmune disease	1.9 (2)	5.4 (6)	0.28
Family history type 2 diabetes	57 (58)	55 (61)	0.78

Data are median (25th–75th percentile) (range) or *n* (%).

distinguishing clinical features (LADA clinical risk score ≥2).

A multivariate analysis confirmed that age of diabetes onset <50 years (OR 1.85, $P < 0.0001$), acute symptoms (1.34, $P < 0.0001$), BMI <25 kg/m^2 (1.29, $P < 0.003$), and a personal history of autoimmune disease (1.14, $P = 0.0143$) were independently associated with a diagnosis of LADA. In this form of analysis, family history of autoimmune disease was not independently associated with LADA. A multivariate LADA clinical risk score was determined based on the OR coefficients from the logistic regression model. The formula for calculating the multivariate LADA clinical score was [1.85 (if age of onset <50 years) + 1.29 (if BMI <25 kg/m^2) + 1.37 (for the presence of acute symptoms) + 1.14 (for the presence of a personal history of autoimmune disease)]. The multivariate LADA clinical risk score was compared with the original five-point LADA clinical risk score using a ROC plot (Fig. 2). The performance of the clinical risk scores was similar (five-point LADA clinical risk score AUC = 0.81 vs. multivariate LADA clinical risk score AUC = 0.84). The optimal cutoff point for the five-point LADA clinical risk score was ≥2 (sensitivity of 75% and specificity of 77%), and for the multivariate LADA the clinical risk score was ≥1.37 (sensitivity of 76% and specificity of 77%).

Table 2—*Prospective study: prediction summary*

LADA clinical risk score*	LADA (GADA+)	Type 2 diabetes (GADA−)	Total
≥2	9	34	43
≤1	1	86	87
Totals	10	120	130

Score is based on the number of distinguishing clinical features for LADA (see Fig. 1).

In the prospective study, a majority (86 of 130) of subjects had none or one distinguishing clinical feature (Table 2). The presence of two or more distinguishing clinical features (LADA clinical score risk ≥2) had a 90% sensitivity and 71% specificity for detecting LADA (Table 2). A LADA clinical risk score ≥2 identified 9 of 10 subjects with LADA and a LADA clinical risk score of ≤1 prospectively identified 86 of 120 GADA− type 2 diabetic subjects (Table 2). Also, a LADA clinical risk score ≤1 was highly reliable for excluding LADA, with 86 of 87 patients who had a LADA clinical score of ≤1 being GADA− (negative predictive value 99%). The multivariate LADA clinical risk score (cutoff ≥1.37) had a similar sensitivity of 90% but lower specificity of 56% for detecting LADA.

CONCLUSIONS — A retrospective study of clinical parameters at diagnosis in adult-onset diabetes revealed that a majority of subjects with LADA had at least two of five distinguishing clinical features (age of onset <50 years, acute symptoms, BMI <25 kg/m^2, personal history of autoimmune disease, or family history of autoimmune disease) compared with a minority of type 2 diabetic subjects. In a prospective validation study, the presence of at least two distinguishing clinical features (LADA clinical risk score ≥2) at diagnosis had 90% sensitivity and 71% specificity for detecting LADA. Furthermore, the presence of less than two distinguishing clinical features (LADA clinical risk score ≤1) was a highly reliable method for excluding LADA (negative predictive value 99%). This clinical screening method is superior to the current popular clinical practice of only screening patients with a BMI <25 kg/m^2 for GADAs. Using this normal BMI cutoff as the sole criterion in the prospective study would result in a 30% sensitivity, because a majority of subjects with LADA are overweight or obese.

This is the first report of a clinical screening tool to distinguish LADA from type 2 diabetes in adults presenting with diabetes. We carefully dissected clinical

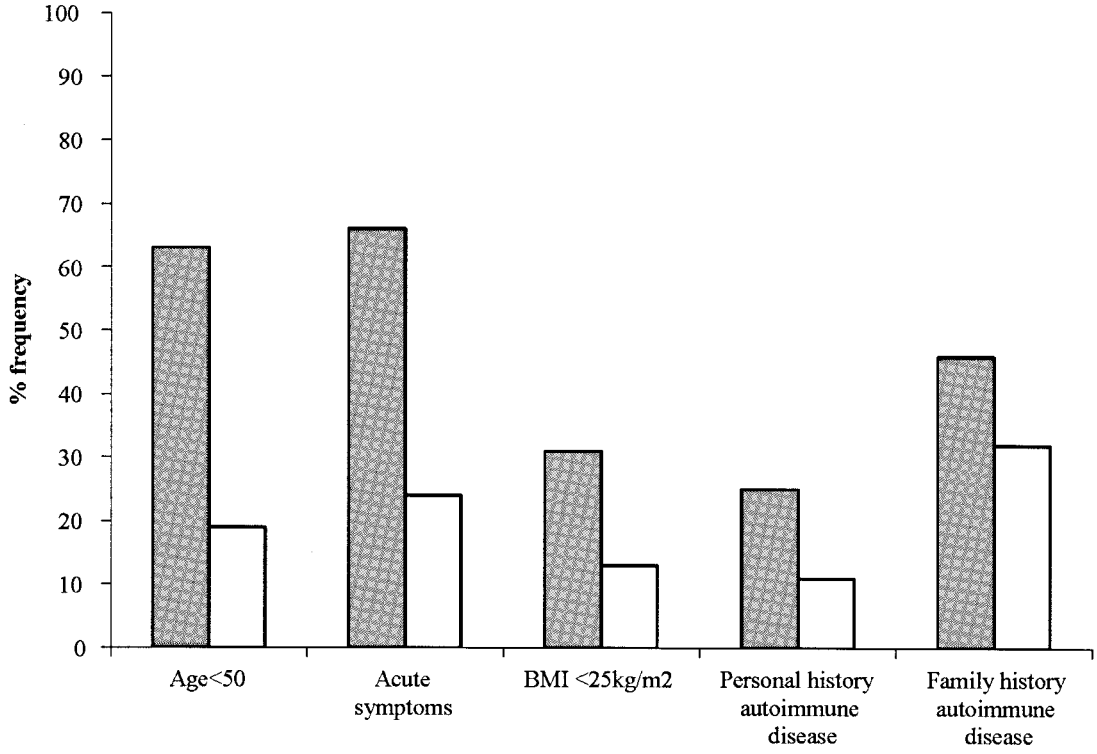

Figure 1— *Retrospective study: distinguishing clinical features at diagnosis in LADA (■) versus type 2 diabetes (□) (age of onset <50 years [P < 0.0001], acute symptoms of polydipsia and/or polyuria and/or unintentional weight loss before diagnosis [P < 0.0001], BMI <25.0 kg/m^2 [P = 0.0004], personal history of HLA DR3- and/or DR4-related autoimmune disease [P = 0.011], and family history of HLA DR3- and/or DR4-related autoimmune disease [P = 0.024]).*

features at presentation of diabetes in adults, given that previous reports of clinical features suggested that there is no one consistent distinguishing clinical feature that discriminates LADA from type 2 diabetes. An earlier age of onset in LADA compared with type 2 diabetes was documented in a large study (1) but not in other smaller studies (23–26). BMI was lower in LADA compared with type 2 diabetes in the UKPDS cohort (3) as well as in several other studies (1,9,11,23,26–28), but this difference was not seen in smaller studies (10,12,24). Presentation with acute symptoms was investigated in one study (23), which showed that they were more frequent in subjects with LADA than in those with type 2 diabetes. Addressing family history of diabetes, another study showed no difference in either type 1 diabetes or type 2 diabetes in subjects with LADA compared with type 2 diabetic subjects (1). It was interesting that a family history of type 2 diabetes did not necessarily signify that an individual had type 2 diabetes, given that a majority (57%) of our subjects with LADA had a family history of type 2 diabetes with an overall frequency similar to that of the type 2 diabetic subjects (55%). There have been no reports on the frequency or family history of DR3- and/or DR4-related autoimmune disease in LADA. Thus, what seems clear from previous studies is that no one clinical feature reliably discriminates LADA from type 2 diabetes.

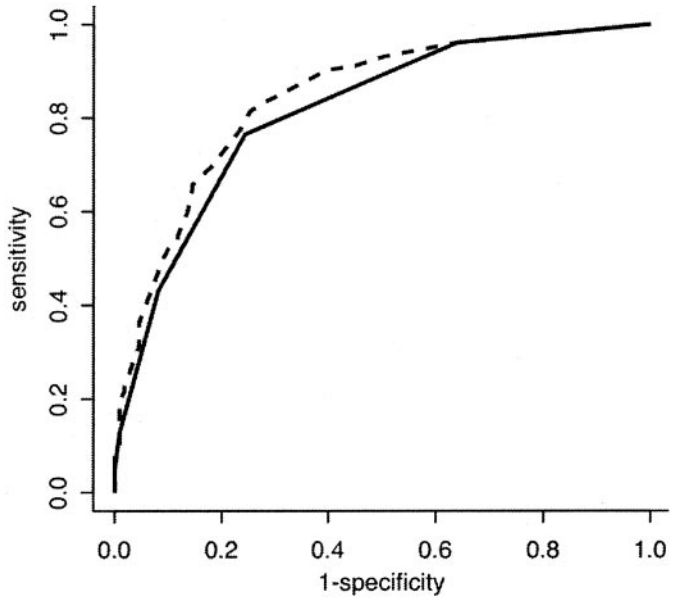

Figure 2— *ROC analysis comparing the five-point LADA clinical risk score (solid line) versus the multivariate LADA clinical risk score (dashed line).*

Our findings suggest that assessing multiple clinical features of presentation enables adults with diabetes to be triaged into two groups: lower risk for LADA (LADA clinical risk score ≤1) and higher-

risk for LADA (LADA clinical risk score ≥2). The benefits of this screening tool approach for LADA are several. First, it assists in identification and management of patients with LADA. Physicians dealing with a patient who has a higher risk for LADA and who has suboptimal glycemic control should have an increased level of suspicion that the lack of control may be due to insulin deficiency secondary to autoimmune β-cell pathologic changes. With such a patient, it would be logical to perform islet antibody testing to exclude autoimmune diabetes. Our experience is that suboptimal glycemia in such patients is frequently prolonged because it is not attributed to autoimmune diabetes and insulin deficiency. Second, this simple clinical screening tool is practical and cost-effective. LADA can be excluded in a majority of adults with diabetes, e.g., approximately two-thirds (84 of 120) in the prospective study, on the basis of a clinical risk score ≤1. Finally, this screening tool could be used to identify subjects with LADA for inclusion in intervention trials. LADA populations are attractive candidates for autoimmune diabetes intervention trials because they have slowly progressive loss of β-cell function and therefore potentially a wider therapeutic window than in classic type 1 diabetes.

We have pragmatically adopted the five-point LADA clinical risk score over the multivariate scoring method to determine which patients should be tested for GADAs because it is simple to use and has better specificity in the prospective study. The use of the tool in clinical practice will depend on the reliability of the patient's history, which can be influenced by language and culture, inaccurate reporting of acute symptoms, and lack of awareness of the family medical history. Diabetes in relatives of patients with LADA may also be misclassified, i.e., relatives with LADA may be diagnosed as having type 2 diabetes. Misclassification of diabetes in relatives could only be excluded by testing for islet antibodies. The ability of the LADA clinical risk score to predict LADA in the prospective study, a homogeneous source of diabetic patients, confirms the utility of the clinical screening tool. The applicability of our findings to LADA cohorts from other nations and ethnicities will be important to establish. Finally, testing for other islet antibodies in patients with high-risk LADA clinical risk scores ≥2 could potentially enhance our prediction of autoimmune diabetes, as some of these patients may be GADA− but IA-2A+ and/or IAA+.

In summary, a majority of patients with LADA have at least two of five distinguishing clinical features (age of onset <50 years, acute symptoms before diagnosis, BMI <25 kg/m^2, personal history of autoimmune disease, or family history of autoimmune disease) at diagnosis of diabetes. The presence of at least two of these clinical features (LADA clinical risk score ≥2) in adults with diabetes justifies GADA testing. This clinical screening tool should increase the identification of autoimmune diabetes in adults and hopefully improve clinical management of their disease.

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APPENDIX

Interview questions

Did you have any acute (recent-onset, i.e., <6 months) symptoms of excessive thirst, frequent urination, or unintentional weight loss before diagnosis?

(*The presence of symptoms such as fatigue, infection, and blurred vision were not included because they were deemed to be more subjective.*)

What was your weight (to the nearest kilogram) at diagnosis?

What is your height (to the nearest centimeter)?

Do you have a family history of diabetes (first- and second-degree relatives)? If yes, is it type 1 (insulin-dependent or juvenile-onset) diabetes or type 2 (non–insulin-dependent or adult-onset) diabetes?

(*Relatives with adult-onset diabetes who commenced insulin treatment within 6 months of diagnosis were classified as having type 1 diabetes.*)

Do you or any of your relatives (first- and second-degree relatives) have autoimmune thyroid disease (i.e., an over- or underactive thyroid gland also known as Graves' or Hashimoto's disease), celiac disease (gluten allergy or intolerance), Addison's disease, pernicious anemia (vitamin B_{12} deficiency), vitiligo, alopecia, rheumatoid arthritis, Sjögren's disease, or autoimmune hepatitis?

(*If patients were unsure or not aware, these conditions were recorded as not being present.*)

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