Individuals Fulfilling Criteria for Type 2 Diabetes Rather Than LADA Display Transient Signs of Autoimmunity Preceding Diagnosis With Possible Clinical Implications: The HUNT Study

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Latent autoimmune diabetes in adults (LADA) is classified as type 1 diabetes because of autoantibody positivity. In contrast, individuals classified as having type 2 diabetes are by definition autoantibody negative. However, autoantibodies may fluctuate (1). We therefore examined whether some individuals have transient evidence of autoimmunity preceding a diagnosis of type 2 diabetes and whether their clinical characteristics differ from those of other individuals classified as having type 2 diabetes.

The study was performed among participants of the second (HUNT2, 1995–1997) and third (HUNT3, 2006–2008) surveys of the Nord-Trøndelag Health Study (HUNT) in Norway. Details about HUNT are available elsewhere (2,3). Participants with self-reported diabetes in HUNT3 ($n = 2,264$) were given a detailed diabetes-related questionnaire and invited to a follow-up clinical investigation that included measurements of hemoglobin A_{1c} (HbA_{1c}), fasting glucose, C-peptide, and the autoantibodies GADA and islet antigen-2 (IA-2A).

We investigated participants with incident type 2 diabetes between HUNT2 and HUNT3 ($n = 965$), defined as diabetes without GADA and IA-2A in HUNT3 and no insulin treatment within 1 year after diagnosis. Among them, 171 participants were excluded due to lack of serum samples or possible unknown diabetes at HUNT2, as indicated by nonfasting serum glucose >11.0 mmol/L in HUNT2. Serum samples that were collected during the HUNT2 baseline examination were used for measurements of four autoantibodies: GADA, IA-2A, zinc transporter 8 (ZnT8A), and insulin (IAA). Participants who tested positive for one or more autoantibodies at HUNT2 were also tested in serum samples collected in HUNT3 for ZnT8A and IAA positivity.

All four autoantibodies were assayed at the Hormone Laboratory, Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway, using in-house and mainly manually immunoprecipitation methods. Autoantibody positivity was defined as GADA >0.05 autoantibody index (ai), IA-2A >0.07 ai, ZnT8A >0.05 ai, and IAA >0.04 ai. Based on the laboratory's participation in the Islet Autoantibody Standardization Program in 2016, cutoff for autoantibody positivity was set for a specificity for autoimmune diabetes of >97.5%, which entailed a sensitivity of 62%, 70%, 50%, and 16%, respectively.

Among 794 participants with incident type 2 diabetes, 26 participants (3.3%) were positive for autoantibodies before diagnosis (at HUNT2). All were single positive; 2 were positive for GADA, 2 for IA-2A, 7 for ZnT8A, and 15 for IAA. Only one prediagnostic autoantibody–positive participant was positive (for ZnT8A) both before and after diagnosis of diabetes; excluding this participant did not change the results. Characteristics of our study population are given in Table 1. Prediagnostic autoantibody–positive participants were markedly younger at the time of diagnosis than autoantibody-negative participants (median 53 vs. 61 years of age, $P < 0.001$ for difference). The prediagnostic autoantibody–positive participants also displayed directionwise characteristics compatible with reduced β-cell function (fasting C-peptide median 861 vs. 1,006 pmol/L, HOMA2-%B median 60.8 vs. 78.1), worse metabolic control (HbA_{1c} median 7.1% vs. 6.7%), and more symptoms at diagnosis. However, differences were not statistically significant for these differences and borderline only for symptoms ($P = 0.054$).

We report evidence of transient autoimmune activity prior to diagnosis of type 2 diabetes as classified by current

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Table 1—Clinical characteristics of prediagnostic autoantibody (Ab)-negative versus Ab-positive participants with incident type 2 diabetes at HUNT3

	Ab-negative HUNT2		Ab-positive HUNT2		
	N		*N*		*P* value
Age at participation (years)	768	65 (58–73)	26	58 (53–66)	0.001
Sex (male)	768	380 (49.5)	26	16 (61.5)	0.226
Waist/hip ratio	762	0.97 (0.92–1.02)	26	0.98 (0.94–1.03)	0.266
Waist circumference (cm)	762	103 (95–111)	26	104 (97–109)	0.849
BMI (kg/cm^2)	763	29.9 (27.1–33.3)	26	30 (27.3–31.9)	0.775
Diastolic blood pressure (mmHg)	767	75 (68–82)	26	75 (65–80)	0.700
Systolic blood pressure (mmHg)	767	136 (126–150)	26	131 (123–147)	0.342
Nonfasting glucose (mmol/L)	746	7.5 (6.0–9.8)	25	8.3 (6.5–11.8)	0.295
Fasting glucose (mmol/L)	368	7.3 (6.5–8.7)	9	7.7 (6.6–9.7)	0.684
Total cholesterol (mmol/L)	746	5 (4.2–5.7)	25	4.9 (4.4–5.7)	0.814
HDL cholesterol (mmol/L)	746	1.1 (1.0–1.3)	25	1.1 (0.9–1.4)	0.299
Triglycerides (mmol/L)	763	2.0 (1.4–2.7)	26	2.1 (1.5–2.9)	0.407
Fasting C-peptide (pmol/L)	500	1,006 (710–1,254)	12	861 (614–1,112)	0.254
HbA_{1c} (mmol/mol)	517	50 (43–61)	21	54 (44–65)	0.250
HbA_{1c} (%)	517	6.7 (6.1–7.7)	21	7.1 (6.2–8.1)	0.255
Diabetes duration (years)	768	3.8 (1.9–6.6)	26	4.2 (3.1–7.3)	0.195
Age at onset (years)	768	61 (53–69)	26	53 (47–58)	<0.001
HOMA2-%B (β-cell function)	350	78.1 (54.6–105.1)	9	60.8 (45.6–88.0)	0.288
HOMA2-%S (insulin sensitivity)	350	40.6 (31.4–57.6)	9	42.2 (32.2–70.2)	0.619
HOMA2-IR (insulin resistance)	350	2.5 (1.7–3.2)	9	2.4 (1.5–3.2)	0.631
Current daily smoker	743	99 (13.3)	26	6 (23.1)	0.155
First degree family history of diabetes	767	467 (60.9)	26	17 (65.4)	0.521
Second degree family history of diabetes	763	427 (56.0)	26	11 (42.3)	0.168
Symptoms when diagnosed	701	236 (33.7)	25	13 (52.0)	0.058
GADA (ai)	768	<0.01 (0.04)	26	<0.01 (0.09)	<0.001
IA-2A (ai)	768	<0.04 (0.07)	26	<0.04 (0.11)	<0.001
ZnT8A (ai)	768	<0.01 (0.05)	26	<0.01 (0.32)	<0.001
IAA (ai)	768	<0.05 (<0.05)	26	0.05 (0.08)	<0.001

Data are median (interquartile range), median (range) for autoantibodies, or *n* (%) unless otherwise indicated. *N* = number of participants included in the analysis. *P* values were calculated by Mann-Whitney *U* test for continuous variables and by χ^2 test or Fisher exact test for categorical variables.

criteria. Furthermore, transient autoantibody positivity associates with earlier onset of type 2 diabetes. To our knowledge, evidence of transient autoimmune activity prior to type 2 diabetes diagnosis has not previously been demonstrated. Notably, the nomenclature used in some previous publications could indicate otherwise; however, in those studies the term type 2 diabetes also included LADA (4,5). In addition, a previous study highlights the impact of fluctuating autoimmunity since some adolescents and young adults can be autoantibody negative at diabetes diagnosis but positive later with a resulting negative effect on C-peptide (6).

Our results indicate that ~3% of individuals classified as type 2 diabetes may have signs of transient autoimmunity, a prevalence that is similar to maturity-onset diabetes of the young (MODY). The prevalence is sufficiently large to substantially contribute to the recognized phenotypic heterogeneity in type 2 diabetes.

One might ask whether the patients characterized here with "hidden autoimmunity" fit into any of the five clusters of adult-onset diabetes recently described (7). However, no obvious resemblance with any of the clusters seems apparent. In particular, a GADA-negative and β-cell–deficient cluster was, in contrast to our patients, characterized by comparatively low BMI.

A limitation of our study is that we only measured the autoantibodies in a single sample collection and we only have a 10-year interval for sample collection. Hence, we could not detect at which time point the participant turned autoantibody positive or when they later became negative. In addition, the relatively low response rate regarding fasting blood sampling among the participants with diabetes left us with a low number of samples to analyze differences in C-peptide.

In conclusion, we demonstrate signs of transient, prediagnostic evidence of autoimmune activity in patients later diagnosed and classified as having type 2 diabetes. Compared with other participants with type 2 diabetes, this subgroup had earlier onset of diabetes and may have lower β-cell function with possible clinical implications.

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