

# Screening for coeliac disease in adult insulin-dependent diabetes mellitus

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**Abstract.** Sjöberg K, Eriksson KF, Bredberg A, Wassmuth R, Eriksson S (University of Lund, University Hospital, Malmö, Sweden; and University of Erlangen-Nürnberg, Erlangen, Germany). Screening for coeliac disease in adult insulin-dependent diabetes mellitus. *J Intern Med* 1998; **243**: 133–40.

**Objectives.** To study, by sequential screening for gliadin antibodies (GA) and endomysial antibodies (EMA), the prevalence and clinical characteristics of coeliac disease (CD) in adult IDDM patients.

**Subjects and measurements.** A series comprising 1664 diabetes patients [848 with IDDM, 745 with non-insulin-dependent diabetes (NIDDM) and 71 with secondary diabetes] were screened for GA. IgA- or IgG-GA positive sera were analysed for EMA.

**Results.** IgA-GA were more frequent in all the diabetes subgroups (13.7% in IDDM, 12.3% in NIDDM and 23.9% in secondary diabetes,  $P < 0.001$  in all three cases) than among healthy blood donors (4.7%). Two patients with NIDDM had CD. Of the

IDDM group ( $n = 848$ ), 8 had previously diagnosed CD and 14 more (of whom 7 could be biopsied) were EMA positive. All had villous atrophy. The minimum prevalence of CD (including probable cases) in IDDM was 2.6% (22/848). Patients with previously known CD had more symptoms ( $P < 0.001$ ), more deficiency states ( $P < 0.001$ ) and more autoimmune diseases ( $P < 0.04$ ) than those identified by screening. IDDM patients with a diabetes duration of 31–40 years were characterised by a higher prevalence of CD than patients with a duration of less than 30 years (6.7% vs. 1.7%;  $P < 0.02$ ).

**Conclusions.** Serial analysis of GA and EMA confirmed a high prevalence of CD in adult IDDM (2.6%). False-positive IgA-GA test results are frequent in patients with diabetes, irrespective of type. EMA analysis is the preferable screening tool for CD in diabetes.

**Keywords:** coeliac disease, diabetes mellitus, endomysial antibodies, gliadin antibodies, IDDM, prevalence.

## Introduction

Insulin-dependent diabetes mellitus (IDDM) is an autoimmune disease characterised by beta-cell destruction resulting in glucose intolerance and finally insulin dependence. IDDM has also been reported to be characterised by increased prevalences of various autoantibodies, and of manifest autoimmune diseases such as chronic thyroiditis, atrophic gastritis and coeliac disease (CD) [1, 2].

Both the incidence and prevalence of IDDM are high in Scandinavia, where they manifest an increase from south to north. The prevalence is 148 per 100000 in Sweden, and that in Finland 191 per 100000, which is the highest in the world [3].

Several studies have shown CD to be a condition sometimes occurring in association with IDDM. Reported figures for the prevalence of CD in IDDM range from 1–4% among children [4–7] to 2–4.6% among adults [8–11], and are thus higher than in the general population, recently estimated to be 0.26–0.38% [12–14].

Increasing awareness and recognition of milder, less symptomatic forms of CD without overt signs of classic malabsorption may have contributed to the increase in the figures reported for the prevalence of CD. However, these milder cases may also present diagnostic difficulties. In patients with a metabolic disorder such as IDDM, in whom gastrointestinal neuropathy and weight changes may be characteris-

tic clinical features the diagnosis of CD may be even more difficult to establish. The serum concentration of gliadin antibodies (GA) has been used as a variable in screening for CD [6, 15–17]. However, with sensitivity and specificity levels of around 80%, a positive GA test is insufficient for CD diagnosis [16]. In blood donors we found the predictive value of GA positivity to be low, CD being present in only 4.5% (1/22; 13 biopsied) of those with positive IgG + IgA-GA tests [15]. In another earlier investigation, comprising patients with different chronic liver diseases, we found the variable to manifest a better predictive value, 26% (5/19) of IgA- and IgG-GA positive patients having CD, though the false-positive rate was still high [18].

The serum level of endomysial antibodies (EMA) has a higher sensitivity of 80–90% and a specificity approaching 100% for CD diagnosis [17, 19], but testing is relatively expensive and time-consuming and therefore less suitable for screening larger populations.

The aims of the present investigation were twofold: to determine the frequency of gliadin antibodies (IgA and IgG) in a large group of adult patients with IDDM, NIDDM or secondary diabetes; and, based on stepwise analysis of GA followed by EMA in GA-positive patients, to determine the prevalence of CD and identify clinical features in a series of adult diabetes patients representing the majority of cases of IDDM in a well defined population.

## Patients and methods

### *The diabetic population*

In Malmö, a city with a population of 240000, most

(approx. 80%) IDDM patients and patients with complicated NIDDM undergo an annual check-up at a special diabetes out-patient clinic at the Dept. of Endocrinology. The present series (Table 1) consisted of all diabetic patients in Malmö invited for their regular annual check-up during a 21-month period between 1989 and 1991. The series as a whole comprised 1664 patients: 848 (400 women, 448 men) with IDDM, mean age 46.1 years (range 17–86); 745 (352 women, 393 men) with NIDDM, mean age 61.7 years (range 24–92); and 71 (seven women, 63 men) with secondary diabetes, mean age 53.9 years (range 33–77).

### *Diagnostic criteria of diabetic subtypes*

All of the 1664 diabetic patients were classified primarily according to the WHO criteria [3, 20–22]. As 312 patients were initially diagnosed as having NIDDM but later developed insulin dependence, their diabetes was re-evaluated and diagnosed as IDDM if at least two of the following conditions were fulfilled: age at diabetes onset below 35 years, an interval of less than three years between diabetes onset and insulin requirement, or a (body mass index) BMI below 25 for women and below 27 for men. Patients positive for islet cell antibodies (ICA), with subnormal serum C-peptide concentrations or manifesting evidence of multiple autoimmunity were also diagnosed as having IDDM. In most cases, secondary diabetes was due to pancreatic insufficiency resulting from alcohol abuse.

### *Clinical characteristics*

In the IDDM group, the subgroup with previously

**Table 1** Characteristics of the diabetes series as a whole ( $n = 1664$ )

n =	IDDM 848			NIDDM 745			Secondary 71		
	Q1	Med	Q3	Q1	Med	Q3	Q1	Med	Q3
Age	33	44	59	55	62	70	47	53	61
Diabetes duration	8	17	27	3	9	14	1	6	11
IgA-GA (AU)	1.7	3.0	4.9	1.7	3.2	5.4	3.1	4.4	7.2
IgG-GA (AU)	23	35	84	23	26	61	23	27	54
BMI ( $\text{kg m}^{-2}$ )	22	23	25	25	28	31	20	23	26
*N =		402			360			27	
HbA1c (%)	6.8	7.9	9.0	7.3	8.5	10	7.3	8.6	9.5
*N =		360			303			28	

GA, denotes gliadin antibodies, BMI, denotes body mass index. The values given are 1st and 3rd quartiles and the median. \*As data for BMI and HbA1c were not available for all patients the numbers for whom such data were available are given below the values of BMI and HbA1c.

known CD were compared to the subgroup with CD identified at screening, with respect to clinical presentation, associated autoimmune disease, age at onset of diabetes, age at CD diagnosis, and the following laboratory variables: haemoglobin, the serum levels of iron, calcium, and albumin, and the blood-folate level. In the IDDM subgroup ( $n = 848$ ), GA titres and the prevalence of CD were checked for correlation to diabetes duration.

#### Identification of coeliac disease patients with diabetes

The diagnostic registries of the Depts. of Medicine and Endocrinology (coded according to the ICD system) were checked for cases of previously identified CD within the diabetes population.

#### Serological markers used in screening for coeliac disease

We analysed the patient cohort using a recently proposed stepwise procedure [23]. In the first step, all patients were analysed for GA. In the second step, all patients manifesting either IgA- or IgG-GA were analysed for EMA. The diagnostic procedure is outlined in Fig. 1.



Fig. 1 Results of gliadin and endomysial antibody screening and small bowel biopsy in 848 IDDM patients.

#### Gliadin antibody analysis

GA titres were measured with an enzyme-linked immunosorbent assay as previously described [15]. A positive test result was defined as a titre above 8.5 arbitrary units for IgA-GA, and above 330 arbitrary units for IgG-GA. In patients with untreated CD compared with inflammatory bowel disease or irritable bowel syndrome, GA analysis has a sensitivity of 92% and a specificity of 86%, if the occurrence of either IgA- or IgG-GA is regarded as a positive test result [15].

The prevalence of GA positivity in the diabetic subgroups was compared with that in a group of 1537 healthy blood donors (420 women, 1117 men), mean age 38 years (range 19–70), previously described [15].

#### Endomysial antibody analysis

All IgA- or IgG-GA positive patients were tested for EMA with indirect immunofluorescence analysis [24], using commercially available fixed sections of the distal third part of monkey oesophagus (BioSystems, Barcelona, Spain) as the antigen substrate [25]. Patient serum was diluted 1/5 in phosphate-buffered saline, pH 7.6, and 1% bovine serum albumin. Endomysium-specific IgA was detected with an FITC-labelled anti-human IgA conjugate (BioSystems). Positive sera were end-point titrated, the result being expressed as the highest dilution factor giving a positive fluorescence pattern. All sera manifesting fluorescence (titre  $\geq 5$ ) were considered to be EMA positive. In house positive controls are routinely included in every analysis. The Department of Microbiology, where this analysis was carried out, also takes part in the UKNEQAS international quality assessment scheme.

In order to determine the diagnostic accuracy of EMA analysis, we analysed sera from four cohorts: 25 patients (20 women, 5 men) with newly diagnosed, untreated CD, mean age 48 years (range 21–76); 36 patients (20 women, 16 men) with Crohn's disease, mean age 38 years (range 20–72); 24 patients (9 women, 15 men) with ulcerative colitis, mean age 50 years (range 24–85); and 46 patients (33 women, 13 men) with irritable bowel syndrome, mean age 54 years (range 16–66). Of the 25 patients with newly diagnosed CD, 21 had a positive EMA test result (4 false negatives), corresponding to a sensitivity of 84%. None of the patients with

Crohn's disease or ulcerative colitis manifested EMA. One patient with the initial diagnosis irritable bowel syndrome had a positive EMA test and partial villous atrophy. Of 29 EMA-positive patients (20 women, 9 men), mean age 45.9 years (range 19–79), investigated because of suspected CD, all had villous atrophy - i.e. showing EMA analysis to have a specificity of 100%.

#### *Small bowel biopsy*

All EMA-positive diabetic patients were offered a small bowel biopsy (Watson capsula or gastroscopy). The specimens were examined at the Department of Pathology, according to Marsh's criteria [26].

#### *Statistical analysis*

The non-parametric Wilcoxon two sample test was used to investigate differences in GA titres dependent on sex. Spearman correlation was used to check for relation between GA titres and age. Odds ratios, calculated as the products of  $2 \times 2$  contingency tables, according to Woolf [27], were used in comparing the IDDM group to the normal blood donors with regard to the prevalence of GA positivity and the prevalence of CD as well as in comparisons of subnormal laboratory values in the group with previously known CD and the group with CD identified at screening. The chi squared test with Yates' correction was used to assess levels of significance, a *P*-value below 0.05 being considered significant. Fisher's exact test was used for comparison of the previously known CD and screening-identified CD subgroups with regard to the proportion of symptomatic cases. The Mann–Whitney *U*-test was used for subgroup comparisons with regard to age at IDDM onset and age at

CD diagnosis. Relationship between GA titres and diabetes duration was assessed with Spearman correlation in the IDDM group as a whole ( $n = 848$ ). To see if there was any change in IgA- or IgG-GA titre on an individual basis samples from 1989 and 1991 were compared with a paired *t*-test after age adjustment in 48% (410/848) of the IDDM patients for whom samples were available from both years. The Mantel–Haenszel chi-squared test was used to assess the relationship between diabetes duration and the prevalence of CD.

## Results

#### *Characteristics of the diabetes population*

Mean IgA-GA titres were 4.6 (5.2), 4.5 (4.8) and 6.4 (5.6), respectively, for the IDDM, NIDDM and secondary diabetes groups, as compared to 2.8 (3.0) for the blood donor group, and mean IgG-GA titres were 79 (112), 67 (102) and 72 (132), respectively, in the IDDM, NIDDM and secondary diabetes groups, as compared to 84 (123) for the blood donor group, none of the group differences either in IgA- or IgG-GA titres being significant. Since neither IgA-GA nor IgG-GA titres were normally distributed, the demographic and baseline characteristics of the diabetic series as a whole are presented in terms of medians and 1st and 3rd quartile values (Table 1).

#### *Prevalence of GA positivity*

The prevalences of GA positivity in the different groups are given in Table 2 and Fig. 2.

Of the diabetic series as a whole ( $n = 1664$ ), 2.0% (33) were IgA- and IgG-GA positive, and 15.5% (258) were either IgA-GA and/or IgG-GA positive

**Table 2** Occurrence of gliadin antibodies among diabetes patients, as compared with healthy blood donors

	IgA-GA	<i>P</i>	IgG-GA	<i>P</i>	IgA + G-GA	<i>P</i>	EMA	CD
IDDM ( $n = 848$ )	116	<0.001	37	NS	19	NS	20	15
%	13.7		4.4		2.2			
IDDM ( $n = 745$ )	92	<0.001	26	NS	11	NS	1	2
%	12.3		3.5		1.5			
Sec. ( $n = 71$ )	17	<0.001	3	NS	3	NS	0	0
%	23.9		4.2		4.2			
Blood donors ( $n = 1537$ )	72		75		22		nd	1
%	4.7		4.9		1.4			

GA, gliadin antibodies; EMA, endomysial antibodies; CD, coeliac disease; *P* = levels of significance, as compared with blood donors; NS, non-significant; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; Sec, secondary diabetes; nd, not determined.

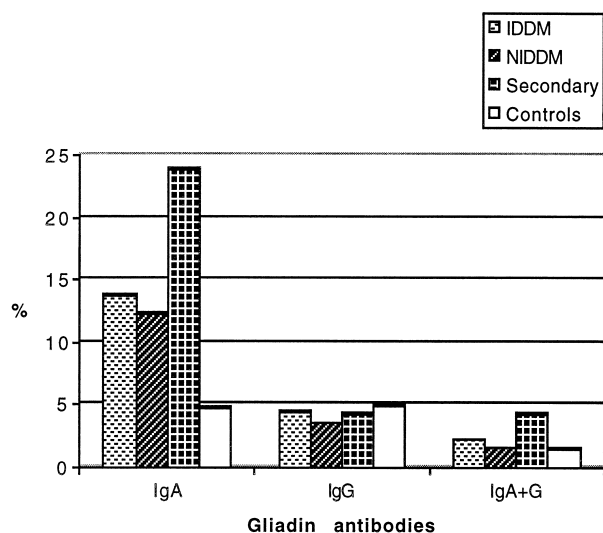


Fig. 2 Prevalence of gliadin antibody positivity in diabetic groups and healthy blood donors (controls).

[13.5% (225) being IgA-positive, and 4.0% (66) IgG-GA positive].

Of the 33 patients who were both IgA- and IgG-GA positive, 19 had IDDM, 11 had NIDDM, and three had secondary diabetes. Of the 19 IDDM patients, all 17 who were available for further investigation had sub-normal C peptide concentrations (<0.10 nmolL<sup>-1</sup>).

IgA-GA titres were higher in men than in women ( $P = 0.004$ ), both among diabetics (irrespective of diabetes type), and among blood donors ( $P < 0.01$ ). IgG-GA titres decreased with age both among diabetics and among blood donors (-0.11 and -0.16, respectively;  $P < 0.001$  in both cases). There was no correlation between IDDM duration and GA titres ( $r$  for IgG-GA = 0.001, for IgA-GA = 0.007; NS), not even in the subgroup with CD ( $r$  for IgG-GA = 0.16, for IgA-GA = -0.13; NS).

Table 3 IDDM patients with coeliac disease

Age	Sex	Age at IDDM onset	Age at diagnosis of CD	Symptoms before screening	IgA-GA	IgG-GA	EMA	Hb	S-Fe	B-Folate	S-Ca	S-Alb	Other autoimmune diseases and comments
Group 1													
74	F	48	58	Anaemia	+	-	-	<u>109</u>	<u>7.5</u>	<u>16</u>		<u>33</u>	
54	M	11	39	Diarrhoea	+	-	-	<u>117</u>	<u>5</u>		<u>2.0</u>		
63	F	11	42	..	+	-	+	126	<u>4</u>	<u>120</u>	<u>2.15</u>	37	
27	F	19	20	..	+	-	+	<u>114</u>	11	546			Ulcerative colitis
45	M	3	42	..	+	-	+	133	13	217	<u>2.16</u>	<u>28</u>	
61	F	18	43	Anaemia	+	+	+	<u>109</u>	10		<u>1.95</u>	<u>33</u>	Chronic thyroiditis, sarcoidosis
55	F	29	44	..	+	+	+	<u>110</u>	<u>7</u>	<u>18</u>	<u>2.15</u>	<u>33</u>	Chronic thyroiditis #, sarcoidosis
55	F	11	45	..	+	+	+	<u>110</u>	<u>4</u>	184	<u>2.05</u>	<u>24</u>	Goitre
Group 2													
50	F	9	47		+	+	+	142	<u>5</u>	277	2.32	<u>37</u>	
28	F	5	28		+	+	+	115	<u>3</u>	318	<u>2.16</u>	<u>31</u>	
48	M	33	45		+	+	+	138	<u>6</u>	543	2.51	<u>38</u>	Dermatitis herpetiformis
24	F	24	24		+	+	+	125	10	258	2.39	41	
62	M	41	62		+	-	+	146	21	358	2.56	45	
53	F	38	53		+	-	+	141	<u>7</u>	<u>97</u>	2.51	42	
49	M	13	49		+	-	+	160	22	400	2.31	<u>35</u>	
Group 3													
59	M	20	—		+	-	+	161	18	18.7*	2.50	49	Hyperparathyroidism
46	F	13	—		+	-	+	153	19	140	2.54	48	
61	M	38	—		+	-	+	148	26	<u>4.0*</u>	2.44	41	
57	F	9	dead	Dysregulation	+	-	+	120	12	5.9*	2.45	37	Chronic thyroiditis #, AMI†
72	F	40	dead		+	-	+	127	15	9.7*	2.27	<u>36</u>	AMI†
77	F	69	dead		+	-	+	154	23	12.0*	2.49	44	Suicide†
49	M	5	dead		+	-	+	<u>125</u>	<u>9</u>	52.4*	2.38	<u>38</u>	AMI†

Group 1, previously known coeliac disease; Group 2, additional patients diagnosed by antibody screening and small bowel biopsy; Group 3, EMA-positive patients, not biopsied; M, male; F, female; #, ophtalmopathy; AMI, acute myocardial infarction; †, cause of death (for these patients age at death is stated); Dysregulation, poor glucose control; GA, gliadin antibodies; EMA, endomysial antibodies; Hb, haemoglobin (115–147 g L<sup>-1</sup> for women, 131–163 g L<sup>-1</sup> for men); S-Fe, serum iron (10–28 μmol L<sup>-1</sup> for women; 13–35 μmol L<sup>-1</sup> for men; B-Folate (125–500 nmol L<sup>-1</sup>); \*, serum folate (5–30 nmol L<sup>-1</sup>); S-Ca, serum calcium (2.2–2.6 mmol L<sup>-1</sup>); S-Alb, serum albumin (<50 years 40–51 g L<sup>-1</sup>, >50 years 37–48 g L<sup>-1</sup>); Underlined values are subnormal.

**Table 4** Numbers of CD patients in the IDDM group with increasing duration of diabetes

Duration (years)	0–10	11–20	21–30	31–40	≥41
CD, (n)	4	6	2	7	3
IDDM, (n)	253	252	170	98	53
% with CD	1.6	2.3	1.2	6.7	5.4

Duration is the time from diabetes onset in years.

#### *Prevalence of coeliac disease in NIDDM and secondary diabetes*

One NIDDM patient had previously diagnosed CD and one more was EMA-positive, corresponding to a CD prevalence of 0.27% (2/745). In the secondary diabetes group, three patients were both IgA- and IgG-GA positive, but none was EMA positive, and none had previously diagnosed CD.

#### *Prevalence of EMA and CD in IDDM*

Figure 1 shows the number of patients found in each diagnostic step, and Table 3 the patients with CD and/or EMA positivity.

Of the eight patients with previously diagnosed CD, five were IgA-GA positive but had normal IgG-GA titres, and three were both IgA- and IgG-GA positive.

Of the fourteen new CD patients identified by EMA analysis, seven had villous atrophy, four died during the interval between blood sampling and analysis, and three refused biopsy. Of the seven patients with villous atrophy, four were both IgA- and IgG-GA positive, and the remaining three IgA-GA positive.

Although the prevalence of CD in the healthy Swedish population has been reported to be high, a rate of 0.38% (7/1866) having been detected by GA analysis in one study [12], the prevalence in the present IDDM group was much higher, being at least 1.8% (15/848) or as much as 2.6% (22/848) if all EMA positive patients are included.

In all cases of CD, its diagnosis was preceded by onset of IDDM, the mean interval between the two being 23 years (range 1–39; Table 3). Accordingly, there was a significant increasing trend with duration ( $P = 0.018$ ; Table 4).

#### *Clinical and laboratory findings*

All eight patients with previously known CD had had clinical symptoms, as opposed to only one of the fourteen whose CD was detected at screening ( $P < 0.001$ , Table 3). In the latter group, three patients

admitted in response to specific questioning having had minor gastrointestinal complaints they had ignored. Of the eight patients with previously known CD, four had autoimmune diseases, as compared to only one of the fourteen whose CD was detected at GA or EMA screening ( $P < 0.04$ ). Mean age at onset of diabetes was 18.8 years in the group with known CD and 20.4 years in the group whose CD was detected at screening, the respective mean ages at CD diagnosis being 41.6 and 44 years (NS). In the group with previously known CD, 76% (26/34) of laboratory analyses yielded abnormal values, *e.g.* for haemoglobin, and blood folate and serum iron, calcium and albumin concentrations), as compared to only 21% (15/70) in the screening-detected CD group ( $P < 0.001$ ).

## Discussion

As the University Hospital, Malmö, is the sole tertiary level facility serving the city, almost all patients with IDDM in the city are seen at the out-patient clinic where the screening took place. In the Malmö population ( $n = 240\ 000$ ) the prevalence of IDDM among 48-year-old men has been shown to be 0.45% [28]; and thus our IDDM group may be considered to constitute the majority (?78%) of IDDM cases in the city [*i.e.* 0.35% (848/240 000)].

The predictive value of GA for CD detection in a healthy population is known to be limited. In a previous investigation comprising healthy blood donors, we found one case of CD among 22 persons (*i.e.* 4.5%; 13 biopsied) both IgA- and IgG-GA positive [15]. In the present study of patients with IDDM the predictive value of GA was higher: 21% (4/19; 12 biopsied) of those who were IgA- and IgG-GA positive had previously unknown CD [36.8% (7/19), if the three with known CD and IgA- and IgG-GA are also included]. Despite the improved predictive value of combined IgA- and IgG-GA positivity, there was a high false-positive rate for IgA-GA. The fact that gliadin is first encountered by the immune system in

the gastrointestinal tract might explain the selective increase in IgA-GA, as compared with IgG-GA. However, we also found a high prevalence of IgA-GA positivity in the NIDDM and secondary diabetes groups, *i.e.* diseases not normally associated with autoimmunity. However, the higher prevalence of IgA-GA positivity in NIDDM and secondary diabetes was not correlated with the presence of EMA positivity consistent with CD. In view of the high specificity of EMA analysis, these findings suggest that in patients with diabetes in general, but in those with NIDDM or secondary diabetes in particular, EMA is a better screening variable than GA. The high prevalence of persistent positive serological markers (GA and EMA) among previously known cases of CD in the IDDM subgroup probably reflects the difficulties for these diabetic subjects to adhere to two different dietary regimens.

In the two-step screening procedure used [23], the ideal is to optimise sensitivity in the first step and specificity in the second, thus enabling identification of the majority of patients with CD with a minimum of falsely sero-positive individuals. Accordingly, we screened the population with GA, a quick and cheap method. In a second step we used EMA analysis with specificity of 100%. In view of the high specificity of EMA analysis, in all likelihood CD is also present in the three patients not yet investigated, and was probably present in the four who died. The prevalence of CD in IDDM might thus be 2.6% (22/848). Moreover, this figure probably represents a minimum, since the sensitivity in both the first step (GA) and the second step (EMA) is around 90% for the detection of CD. The prevalence of CD found in IDDM in Malmö is thus comparable to figures reported for adults from other European countries [8–11].

Despite the lack of correlation between GA-titres and diabetes duration, the prevalence of CD was found to vary with the duration of diabetes. After 30 years diabetes duration, the prevalence of CD was > 6% (Table 4). In a study comprising 238 children and adolescents with IDDM, Mäki and co-workers identified five patients with CD within one year after onset of diabetes and found nine more cases during follow-up. The mean interval between onset of diabetes and detection of reticulín antibody positivity, used for screening in that study, was only 13 months [29]. Although we have not followed our adult population with repeated antibody tests, the interval found in our study between diabetes onset and CD-

diagnosis suggests that Mäki and colleagues might well have found the interval between the two diagnoses to be longer had they too studied an adult population.

Using the anti-reticulín antibody titre as the screen variable, Collin and colleagues found eight patients with CD among 195 with IDDM (4.1%). None of the CD patients manifested signs of malabsorption or significant abdominal complaints [8]. Using EMA analysis, Sategna-Guidetti and co-workers found the prevalence of CD to be 2.6% (10/383). Only one patient had gastrointestinal complaints but all had iron deficiency [9]. Page and co-workers, who screened 1789 patients (43% IDDM and 57% NIDDM) with IgA-GA analysis, found the prevalence of CD to be 1.8% (14/767) in the IDDM subgroup and 0.3% (1/340) in the NIDDM subgroup [10]. In Sweden, the prevalence of CD in a group of 459 IDDM patients aged 2–21 was found to be 4.6% [11]. Of the 15 newly detected CD patients in that study, only one had unequivocal gastrointestinal symptoms. In the present study, the eight previously diagnosed CD patients came to our attention because of diarrhoea and/or different deficiency states, whereas the seven verified and the seven probable CD patients diagnosed by screening lacked gastrointestinal symptoms. Gastrointestinal symptoms in CD can be few, and when present may, considering the long diabetes duration, be misinterpreted as due to autonomic neuropathy.

CD is more prevalent in women. Of the 22 patients with verified or probable CD in the present study, 14 were women. This male:female ratio of 1:1.75 (8:14) is consistent with several previous reports. Bodé and co-workers, who reviewed nine studies in 1996, found reported figures for the male:female ratio to range from 1:1 to 1:2.8 [30]. In contrast, IgA-GA titres were higher in men than in women in all types of diabetes, a finding providing support for the hypothesis that IgA-GA positivity is often a marker of something other than CD.

To sum up, we confirmed the high prevalence of CD in adult IDDM [8–11]. We also observed a very high frequency of false-positive IgA-GA test results, both in IDDM and in other types of diabetes. The reasons for IgA-GA development in disorders regarded as not HLA associated and lacking autoimmune background remain to be explained. In all cases of CD, its diagnosis was preceded by the onset of IDDM, in some cases by several decades. Since many

patients appear to have CD in an oligosymptomatic or even asymptomatic form, routine serological screening for CD in the follow-up of IDDM patients might be of value. Our findings indicate EMA analysis to be superior to GA analysis as a screening tool.

## Acknowledgements

We thank Birgitta Tenngart and Birgitta Lindholm for skilful technical assistance, Jan-Åke Nilsson for expert statistical guidance and Stefan Lindgren for valuable advice. This investigation has been supported by the Ernhold Lundström, Albert Pålsson and Alfred Österlund Foundations, the Funds of the Medical Faculty and of Malmö Sjukvårdsförvaltning, and the Swedish Medical Association.

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Received 28 May 1997; accepted 19 August 1997.

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