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Prevalence of Thyroid Disorders in Untreated Adult Celiac Disease Patients and Effect of Gluten Withdrawal: An Italian Multicenter Study

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OBJECTIVES: Many afflictions have been associated with celiac disease, but chance associations may exists. The aim of this study was to establish, by means of a multicenter prospective study, the prevalence of thyroid impairment among adult patients with newly diagnosed celiac disease and to evaluate the effect of a 1-yr gluten withdrawal on thyroid function.

METHODS: A total of 241 consecutive untreated patients and 212 controls were enrolled. In 128 subjects a thorough assessment, including intestinal biopsy, was repeated within 1 yr of dietary treatment. Thyroid function was assayed by measuring the levels of TSH, free T3, free T4, thyroperoxidase, and thyroid microsome antibodies.

RESULTS: Thyroid disease was 3-fold higher in patients than in controls ($p < 0.0005$). Hypothyroidism, diagnosed in 31 patients (12.9%) and nine controls (4.2%), was subclinical in 29 patients and of nonautoimmune origin in 21. There was no difference regarding hyperthyroidism, whereas autoimmune thyroid disease with euthyroidism was present in 39 patients (16.2%) and eight controls (3.8%). In most patients who strictly followed a 1-yr gluten withdrawal (as confirmed by intestinal mucosa recovery), there was a normalization of subclinical hypothyroidism. Twenty-five percent of patients with euthyroid autoimmune disease shifted toward either a subclinical hyperthyroidism or subclinical hypothyroidism; in these subjects, dietary compliance was poor. In addition, 5.5% of patients whose thyroid function was normal while untreated developed some degree of thyroid dysfunction 1 yr later.

CONCLUSIONS: The greater frequency of thyroid disease among celiac disease patients justifies a thyroid functional assessment. In distinct cases, gluten withdrawal may singlehandedly reverse the abnormality. (Am J Gastroenterol 2001; 96:751–757. © 2001 by Am. Coll. of Gastroenterology)

INTRODUCTION

Many afflictions have been associated with celiac disease (CD) (1); however, because the high prevalence of this disease (2), chance associations may exist. Recent studies have shown an increased incidence of thyroid diseases (TD) among patients with CD (3, 4) but, thus far, data on the prevalence and clinical significance of this association are lacking.

This article describes a multicenter study, carried out under the auspices of the Italian "Club del Tenue," that aimed to establish the prevalence of thyroid involvement among adult patients newly diagnosed with CD and to evaluate the effect of a 1-yr gluten withdrawal on thyroid function.

MATERIALS AND METHODS

Five adult study centers from various regions of Italy (Fig. 1) took part in this prospective study.

Patients

Between January 1996 and July 1998, 241 consecutive adult patients who were newly diagnosed with CD were enrolled. The study population included 64 men (median age 29 yr, range 18–82 yr) and 177 women (median age 31 yr, range 19–85 yr).

The diagnosis of CD was made according to the accepted criteria (5), *i.e.*, clinical history and typical histological appearance of the small intestinal mucosa. In 224 of 241 subjects (93%), CD-related serology, *i.e.*, antiendomysium antibodies (IgA-EmA), was also positive. Persistence of symptoms before diagnosis ranged from 6 to 120 months in 161 patients (66.8%), whereas symptoms had been present in 41 patients (17%) since childhood. The clinical pattern was typical in 40%, atypical in 44%, and silent in 16% of patients, respectively (6); in the silent disease group, diagnosis was reached because of a screening program in a family study.

Control Subjects

Because an Italian survey to appraise the prevalence of TD (both subclinical or overt) in the general population had not yet, to our knowledge, been performed, sera from 212 control subjects matched for sex, ethnic origin, and age (±3 yr)

Figure 1. Centers participating in the study.

were screened for TD as well. Controls (64 men and 148 women) were healthy volunteers recruited among medical and nursing staff, blood donors, or patients affected by chronic obstructive pulmonary disease (COPD), peptic ulcer, or nonulcer dyspepsia (NUD) attending for upper endoscopy; none had a past or present history of thyroid function impairment. Exclusion criteria included age <19 yr and the presence of disease that may affect thyroid function (*i.e.*, chronic liver or renal disease, malignancy, malnutrition) or the use of medication known to influence serum TSH or fT4 (*i.e.*, dopamine, glucocorticoids, heparin, furosemide). In all participants, CD was excluded by means of clinical findings and an IgA-EmA test or by duodenal biopsy performed during endoscopy.

Study Design

At the time of entry into the study, all patients were untreated. Initial data collection included clinical history (6) and findings, associated diseases, clinical and biochemical nutritional assessment, intestinal biopsy, and thyroid function appraisal: thereafter, patients were instructed to follow a gluten-free-diet (GFD) and were considered as treated. Patients with overt hypo- or hyperthyroidism were started on an appropriate medical treatment. A thorough assessment, including intestinal biopsy, was repeated within 12 ± 1 months.

The study was performed according to the principles of the Declaration of Helsinki, and informed consent was obtained from each patient. The research was approved by the Scientific Committee of the "Club del Tenue."

Nutritional Assessment

Nutritional status was evaluated by calculating the body mass index (BMI; kg/m^2, reference range: men >20, women >19). Biochemical assessment, performed by standard methods, included the following: Hb (reference range 14–18 g/dl (for men) and 12–16 g/dl for women); serum albumin (Alb, reference range 3.6–5.0 g/dl); serum iron (Fe, reference range 59–158 μg/dl for men and 37–145 μg/dl for women).

Thyroid Function Assessment

Serum fT3 and fT4 were estimated by radioimmunoassay (Ortho-Clinical Diagnostic, Amersham, UK). The sensitivities of the assays were 0.768 pmol/L for fT3 and 0.769 pmol/L for fT4, respectively, with intra-assay percentage coefficients of variation (CV) of 4% and 3.8%, and interassay CV of 6.4% and 6.2%.

Serum TSH levels were evaluated by immunoradiometric assay (Biocode, Liège, Belgium) on solid phase. The minimum measurable concentration was at 0.05 μ IU/ml. The interassay CVs were 5% and 5.5%, respectively.

Serum thyroid microsome antibodies (TM-Ab) were appraised by immunoradiometric assay (Biocode). The detection limit has been evaluated at 2.5 IU/ml. The intra-assay and interassay CVs were 8.1% and 7.9%, respectively. Serum levels of thyroperoxidase antibodies (TPO-Ab) were detected by radioimmunoassay (Biocode). The sensitivity has been evaluated at 7 IU/ml. The intra and interassay CVs were 8.9% and 9.4%, respectively.

We considered as normal the following serum levels: TSH 0.3–3.0 μIU/ml, fT3 2.2–4.7 ng/L, fT4 8–20 ng/L, TM-Ab ≤ 50IU/ml, and TPO-Ab ≤ 50 IU/ml.

Thyroid disease was classified, according to the American Thyroid Association guidelines, as follows (7): overt hyperthyroidism: TSH <0.3 μIU/ml and fT4 >20 ng/ml; subclinical hyperthyroidism: TSH <0.3 μIU/ml and fT4 in the normal range; overt hypothyroidism: TSH >3 μIU/ml and fT4 <8 ng/ml; subclinical hypothyroidism: TSH >3 μIU/ml and a normal fT4; subclinical autoimmune (AI) hypothyroidism: TSH >3 μIU/ml and a normal fT4 and >100 IU/ml serum levels of TPO-Ab or TM-Ab or both; subclinical nonautoimmune hypothyroidism (NAI): TSH >3 μIU/ml and a normal fT4, without autoantibody serum level increase; and autoimmune thyroid disease with euthyroidism (ATDE): TSH and fT4 in the normal ranges and >100 IU/ml serum levels of TPO-Ab or TM-Ab or both. All reference limits were provided by the manufacturers, and all biochemical values were compared with those for the individual analyte reference range established in the laboratory.

Intestinal Morphology

All patients underwent intestinal biopsy from the second part of the duodenum during upper endoscopy. Mucosal tissue was graded according to the Marsh criteria (8).

Table 1. Prevalence of Thyroid Function Impairment Among Newly Diagnosed Celiac Disease Patients and Controls

Thyroid Function	Untreated Celiac Disease Patients	Controls	
Hypothyroidism			
Number (%)	31/241 (12.9%)	9/212 (4.2%)	$\chi^2 = 9.362$, $p < 0.003$
Sex	26 F, 5 M	7 F, 2 M	
Hyperthyroidism			
Number (%)	3/241 (1.2%)	7/212 (3.3%)	NS
Sex	2 F, 1 M	7 F, 0 M	
Autoimmune thyroid disease with euthyroidism			
Number (%)	39/241 (16.2%)	8/212 (3.8%)	$\chi^2 = 17.366$, $p < 0.0005$
Sex	33 F, 6 M	5 F, 3 M	
Total			
Number (%)	73/241 (30.3%)	24/212 (11.3%)	$\chi^2 = 23.004$, $p < 0.0005$
Sex	61 F, 12 M	19 F, 5 M	

Statistical Analysis

Statistical data were generated using the MedCalc software for Windows (Mariakerke, Belgium). To ascertain whether possible differences in TD between patients and controls may be clinically meaningful and worthwhile to detecting, we previously estimated the required sample size by calculating the probabilities α and β of a type I and type II error, respectively.We calculated that 184 patients and 184 controls should be enrolled by assuming that the expected prevalence of TD among the general population (4) (and therefore among our controls) is 5%, that the relative risk for TD in CD is 3-fold higher and by accepting an α error (type I error) of 5% and a power (1-β) = 90%.

Data were analyzed using the χ^2 test (or Fisher's exact test, where indicated) for differences in frequencies, the *t* test (paired or unpaired, as appropriate) for comparison of means, and the r correlation coefficient. For all statistical analysis, a two-tailed *p* value < 0.05 was considered significant.

RESULTS

Thyroid Function and Clinical Findings at Diagnosis (Untreated Subjects)

As shown in Table 1, overall TD was found in 73 (61 women and 12 men) of 241 (30.3%) patients with CD, and in 24 (19 women and five men) of 212 controls (11.3%) ($\chi^2 = 23.004$, $p < 0.0005$). However, the differences were statistically significant only for women ($\chi^2 = 19.165$, $p < 0.0005$).

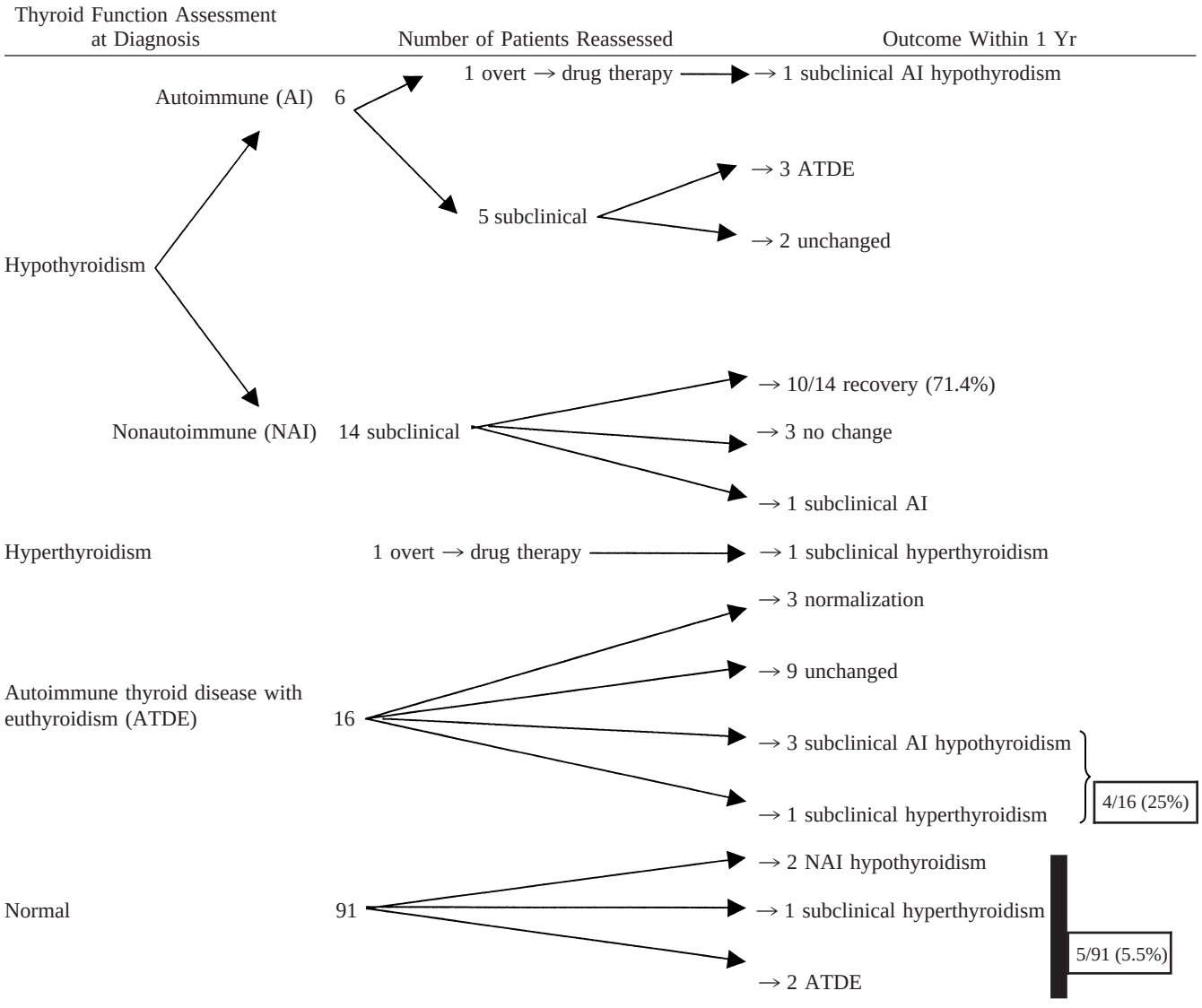
Overall hypothyroidism, which had been diagnosed in 31 patients and nine controls ($p < 0.003$), was subclinical in 29 patients and eight controls and was overt in the remainder; however, the differences were statistically significant only for women ($\chi^2 = 8.284$, $p = 0.0045$). In 21 patients and four controls, a NAI hypothyroidism was found, whereas in 10 patients and five controls an AI hypothyroidism was present. NAI hypothyroidism was significantly higher ($\chi^2 = 11.821$, $p = 0.0006$) than AI.

Table 2. Nutritional Assessment in Untreated Patients With Celiac Disease With and Without Associated Thyroid Function Impairment

Characteristic	Celiac Disease Without Thyroid Disease	Celiac Disease and Thyroid Disease	*p* Value*
BMI kg/m^2	M 20.6, F 20.4	M 22.3, F 19.7	
M $<$ 20 kg/m^2	21/52 (40.4%)	1/12 (8.33%)	0.0448 (Fischer's),
F $<$ 19 kg/m^2	37/116 (31.9%)	22/61 (36%)	NS
Hb g/dl	M 12.8, F 11.4	M 12.1, F 11.6	
M $<$ 14 g/dl	19/52 (36.5%)	8/12 (66.7%)	NS
F $<$ 12 g/dl	58/119 (50%)	26/61 (42.6%)	NS
Serum albumin g/dl	4.7	4.4	
$<$ 3.5 g/dl	18/168 (10.7%)	5/73 (6.8%)	NS
Serum iron μg/dl	M 80, F 48	M 63, F 51	
M $<$ 59 μg/dl	11/52 (21.1%)	6/12 (50%)	NS
F $<$ 37 μg/dl	45/116 (38.8%)	16/61 (26.2%)	NS

Data are median values and number of patients with values below the lower limit. BMI = body mass index; F = female; M = male.
* *p* Values determined by χ^2 test unless stated otherwise.

Table 3. Thyroid Function Outcome in 128 Celiac Disease Patients Within 1 Yr of Gluten Withdrawal



Subclinical hypothyroidism normalized in 10 of 14 patients with NAI, seven of whom had adhered strictly to the diet. In subjects without thyroid function improvement, compliance with diet was generally poor. In five patients with a normal thyroid function at diagnosis, there was a shift toward some impairment; only one of these did not strictly comply with the diet.

AI/NAI = autoimmune/nonautoimmune thyroid disease; ATDE = autoimmune thyroid disease with euthyroidism.

Hyperthyroidism was diagnosed in three patients and seven controls, and was subclinical in two patients and in five controls.

ATDE was present in 39 patients and eight controls; but, again, the difference was statistically significant only in women ($\chi^2 = 16.744$, $p < 0.0005$).

The presence of TD was not influenced by geographic factors. The age of patients and controls with associated TD did not differ from that of patients and controls with a normal thyroid function (median age 33 and 32.5 yr, and 29 and 30.5 yr, respectively). There was no variation in TD prevalence in age groups. The clinical pattern of CD (classic, atypical, silent) (6), presenting symptoms (diarrhea, anaemia, weight loss, dyspepsia, bloating, fatigue, weakness, osteoporosis), associated diseases (dermatitis herpetiformis, insulin-dependent diabetes mellitus, arthritis, vitiligo, aphthous stomatitis), and histological scores (8) were comparable in patients with and without TD. In three of 73 patients (0.96%) with thyroid function impairment, TD diagnosis preceded CD recognition.

Nutritional Assessment

At diagnosis, median BMI values and Hb, serum iron, and albumin levels were similar in patients with and without TD. In each group, a number of subjects showed abnormal values that did not reach a statistical significance, with the exception of BMI among men (Table 2). No significant correlation was found among nutritional indices and TSH or fT3 values.

Table 4. Nutritional Outcome in Celiac Disease Patients

Characteristic	Untreated	Treated	*p* Value
BMI kg/m^2	M 21.15 ± 3.2, F 22.6 ± 3.3	M 20.8 ± 3.68, F 23 ± 3.44	0.043 (M)*, NS (F)*
M < 20 kg/m^2	22/64 (34.4%)	7/31 (22.6%)	NS
F < 19 kg/m^2	59/177 (33.33%)	13/97 (13.4%)	0.0006
Hb g/dl	12.74 ± 6.39	13.6 ± 1.64	NS*
M < 14 g/dl	27/64 (42.2%)	4/31 (12.9%)	0.0091
F < 12 g/dl	84/177 (47.5%)	10/97 (10.3%)	>0.0005
Serum albumin g/dl	4.9 ± 0.503	5.13 ± 0.57	<0.0001*
<3.5 g/dl	23/241 (9.54%)	5/128 (3.9%)	NS
Serum iron μg/dl	63 ± 38.13	92 ± 33.7	<0.0001*
M < 59 μg/dl	17/64 (26.6%)	0.31 (0%)	0.0044
F < 36 μg/dl	61/177 (34.4%)	2/97 (2.04%)	<0.0005

Data given as mean ± SD and number of patients with values below the lower limit in each group. BMI = body mass index; F = female; M = male.
* Statistical analysis by paired Student *t* test; other statistical analysis by unpaired student *t* and χ^2 test.

Effect of a 1-Yr Gluten-Free Diet: Thyroid Function and Clinical Findings

A total of 128 patients (53.1%) underwent a complete reassessment within 12 ± 1 months after the beginning of gluten withdrawal, 91 with a normal thyroid function and 37 with an impaired function at diagnosis. An exhaustive review of diet to assess compliance did not show a significant difference between the two groups. Intestinal biopsy repeated in 75 of 128 (58.6%) subjects showed a mucosal recovery in 43 (57.3%) and persisting partial or total atrophy in the remaining 32 (42.7%).

The outcome of the 128 patients' thyroid function is shown in Table 3. Three points must be stressed. First, subclinical hypothyroidism normalized in 10 of 14 (71.4%) patients with NAI disease, seven of whom had presumably adhered strictly to the GFD; in three of five (60%) patients with AI disease (two of whom were compliant with the diet), there was a shift to ATDE. In four of five subjects with no improvement in thyroid function, compliance with the diet was poor, as demonstrated by the incomplete recovery of the intestinal mucosa at duodenal biopsy. Second, out of four of 16 (25%) patients with ATDE, one patient developed a subclinical hyperthyroidism, whereas three had AI subclinical hypothyroidism; three of these subjects did not strictly comply with the diet. Third, 1 yr later, out of five of 91 (5.5%) patients with a normal thyroid function at diagnosis, one patient had developed subclinical hyperthyroidism, two ATDE, and two NAI subclinical hypothyroidism; only one of these patients did not strictly comply with the diet.

Nutritional Assessment

A 1-yr gluten withdrawal led to a significant improvement of nutritional indices (Table 4), which was comparable in patients with and without TD, as shown in Figure 2. In most patients with persistent mucosal impairment, nutritional indices continued to be abnormal.

DISCUSSION

Our study confirms that patients with celiac disease are at risk for developing thyroid disease, with an overall 3-fold higher frequency than in controls. In both populations, women were significantly more affected than men; prevalence of TD did not differ between age groups. These data should be representative of the Italian population overall, as a large number of subjects, evenly distributed across the country, were examined.

In seven patients, diagnosis of TD preceded recognition of CD (*i.e.*, the disorder developed in a condition of unrecognized and untreated CD).

Clinical presentation, age at diagnosis and incidence of associated diseases were comparable in patients with and without TD: our data do not seem to support, at least as far as thyroid function involvement is concerned, the theory of Ventura *et al.* (9) that age at diagnosis, which indirectly mirrors the duration of gluten exposure, may increase the risk of developing autoimmune disorders. The discrepancy could be due to a bias caused by the age of our patients, *i.e.*, adults, *versus* adolescents in the study by Ventura *et al.*

Our findings confirm the infrequent impairment of nutritional status in untreated CD both with and without TD, although approximately one-half had anemia and one-third had iron deficiency. Notwithstanding a sufficient nutritional status, it is probable that in 21 of 31 patients hypothyroidism was not of autoimmune origin but rather was attributable to a decreased thyroid hormone synthesis, induced either by an iodine organification defect or by a functional hypothalamic–pituitary disturbance consequent to isolated malnutrition (10, 11). This hypothesis may be supported both by the relationship between normalization of thyroid function, by means of gluten withdrawal alone, and by the histological recovery of duodenal mucosa, or, conversely, by the absence of thyroid function improvement in subjects with persistent villous atrophy. This strengthens the view that gluten withdrawal by itself is able to eliminate the main etiological factor of NAI hypothyroidism.

The prevalence of thyroid antibody positivity in euthyroid subjects was 4-fold higher in CD than in controls. It has been postulated that thyroid autoimmunity is enhanced in iodine-depleted geographical areas, where an increased prevalence of goiter and hyperthyroidism of nonautoim-

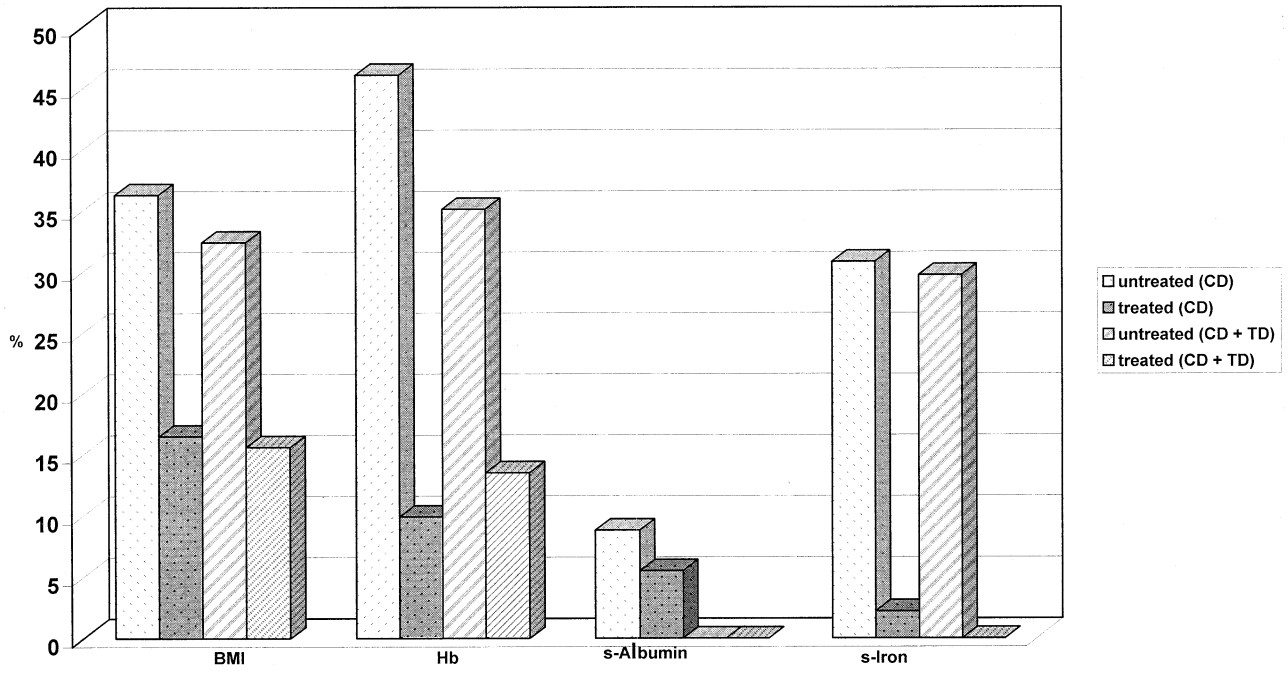


Figure 2. Percentage of abnormal results, as compared to initial values (untreated) most of nutritional indices showed a significant improvement (χ^2 test, on actual numbers) after a 1-yr gluten withdrawal (treated). No statistical difference was found between patients with and without associated thyroid disease. BMI = body mass index; s-albumin = serum albumin; s-iron = serum iron.

mune origin are more frequent (12). Although thyroid ultrasonography was not performed because of a possible operator-dependent bias (as this was a multicenter study), this statement does not apply to our patients; the rate of antibody positivity was similar in regions with variable iodine supplies (Napoli and Cagliari are located by the sea), and both patients and controls had a low overall hyperthyroidism rate. Although the clinical significance of these antibodies in CD is still unclear, there is probably a higher propensity for thyroid autoimmunity; proposed mechanisms of autoimmune endocrine disease involve a sequence of immune, inflammatory events in a genetically susceptible individual. In most cases, the immune response to the target cell progressively destroys the endocrine gland, and hypofunction is the main clinical manifestation (13). This mechanism seems to be sustained by the fact that, 1 yr later, three out of 16 (19%) patients with ATDE developed AI subclinical hypothyroidism and one (6%) a subclinical hyperthyroidism. Thus, a longitudinal follow-up would seem necessary in patients who have a positive AI thyroid serology but who are currently euthyroid; this course would help to evaluate whether these findings should be considered only as an epiphenomenon or should be of prognostic help. This circumstance could change the attitude toward the cost-effectiveness of screening, as it could be very useful to have some advance knowledge about subjects who may become clinically hypothyroid (or, less likely, hyperthyroid).

The importance of gluten withdrawal was further underlined, 1 yr later, by the normalization of antithyroid antibodies in three of these 16 ATDE patients (19%), who were strictly diet compliant, although there exists the possibility of a spontaneous fluctuation of antibodies.

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