

Screening for celiac disease in patients with autoimmune thyroid disease: from research studies to daily clinical practice

Giuseppe Fanciulli, Paolo A. Tomasi, Fabrizia Caucci, Elisabetta Lai, Franca Sanciu, Giuseppe Delitala

Screening procedures performed in research-setting studies have shown that the prevalence of celiac disease in patients with autoimmune thyroid disease is approximately 4-15 times higher than the general population, thus suggesting that patients with autoimmune thyroid disease should be routinely screened for celiac disease. However, the performance of these screening programs has never been evaluated in everyday, clinical-practice setting. We invited newly diagnosed patients with autoimmune thyroid disease, seen at our Hospital, to participate in a serological screening for celiac disease. Two-hundred and thirty-one patients, female to male ratio 8.89:1, mean age 41.3 ± 18.1 years, range 7.1-80.5 years were included. The number of diagnosed celiac disease was 0. Our results do not support the usefulness of a screening for celiac disease in patients with autoimmune thyroid disease in daily practice, despite the favorable results obtained in research-setting studies. Since screening is a resource-consuming activity, for both patients and clinicians, we suggest that a careful evaluation of the yield of a screening is always warranted before its adoption in the clinical practice.

(Ann Ital Med Int 2005; 20: 39-44)

Key words: Autoimmune thyroid disease; Celiac disease; Diagnosis; Screening.

Introduction

Celiac disease (CD) is an intolerance to gliadin responsible for an immunologically mediated enteropathy in genetically susceptible subjects¹. It is frequently associated with other autoimmune disorders²⁻⁶; in particular, the prevalence of autoimmune thyroid disease (ATD) in patients with CD is 14 to 20%^{7,8}. Conversely, the prevalence of CD in patients with ATD has been reported to be 2.9-7.8%, much higher than the 0.25-1% of CD found in control populations⁹⁻¹⁴.

Since early administration of a gluten-free diet is believed to prevent many complications of the disease¹⁵⁻¹⁷, a serological screening for CD in high-risk populations (such as ATD patients) appears justified.

It should be considered, however, that research studies of screening procedures are usually conducted under conditions which may be difficult to replicate in everyday practice.

As a rule, in research screening studies the following policies are applied: a) patients are invited to participate in the study by highly motivated staff; b) patients are usually tested (by blood sampling or other procedures) in the same clinical setting, and do not incur expenses for the

diagnostic procedures that are performed as part of the screening; c) laboratory determinations are done using the best possible methods available, often regardless of cost issues; d) data collection and the following work-up (patient contacts and decision whether executing further diagnostic procedures) are performed directly by the staff involved in the research protocol.

In summary, research-setting studies are geared to evaluate whether the program performs well under controlled experimental conditions (*efficacy*)¹⁸. This is certainly necessary, since "if the intervention doesn't work under such ideal conditions it surely doesn't work under usual conditions"¹⁹, but offers no guarantee of being useful in everyday clinical practice (*effectiveness*)¹⁸.

Previous literature data have confirmed the *efficacy* of screening for CD in patients with ATD⁹⁻¹⁴; thus, we set out to investigate the real *effectiveness* of this procedure, by performing routine clinical diagnostics for CD in patients seen for ATD in our Thyroid Clinic.

Methods

Study population

The inclusion criterion was as follows: all patients who were first diagnosed in our Thyroid Clinic as having ATD from April 1, 2001 through March 31, 2002 were included in the initial evaluation; we then proceeded to exclude all patients who had had a previous diagnosis of CD.

Istituto di Clinica Medica (Direttore: Prof. Giuseppe Delitala), Università degli Studi di Sassari

This study was partly supported by grant n. 34/39-2000 (Epidemiology, clinical relevance and prevention of silent celiac disease and iodine-deficiency diseases) to G.D. from Regione Autonoma della Sardegna.
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All subjects underwent a complete thyroid evaluation, including physical examination, thyroid ultrasound examination, and measurement of serum free-T₄, free-T₃, thyroid-stimulating hormone, anti-thyroperoxidase and anti-thyreoglobulin antibodies. The diagnosis of ATD was made on clinical and biochemical grounds on the basis of positive titres of anti-thyroperoxidase and/or anti-thyreoglobulin antibodies, and a positive ultrasound scan (defined by either a diffusely hypoechoic gland, or a non-homogeneous pattern with hypoechoic areas¹²).

Screening methodology

Patients were given basic knowledge about the screening rationale and background, according to criteria developed among the medical staff involved in the study. The information included: 1) notions about possible clinical manifestations and complications of CD; 2) prevalence of CD in the general population and in ATD patients; 3) possibility of prevention of some complications with an early diagnosis of CD. In order to detect also asymptomatic subjects, the screening was proposed irrespectively of the presence or absence of signs or symptoms suggestive of CD.

We obtained informed consent from our patients, with the authorization to publish statistical data and anonymous clinical data.

All patients were given a lab requisition form for the serological assay of IgA class antiendomysium antibodies (EMA), total IgA class antibodies (t-IgA), and anti-gliadin antibodies (AGA), both IgG and IgA.

EMA were selected for their high positive predictive value in detecting CD (94%)²⁰. The determination of the t-IgA level was included to rule out a selective deficiency of IgA, which is associated both with CD and a confounding factor in the diagnosis, as it causes false negative results of the EMA and AGA IgA tests²¹. AGA have lower positive predictive value than EMA for the detection of CD²⁰. However we included them as they are a quantitative assay and allow to reduce the number of possible false negatives of the EMA test, which is an immunofluorescence positive/negative test and thus is rather operator-dependent.

Duodenal biopsy to confirm the diagnosis of CD was planned for EMA-positive subjects, or for those with IgA deficiency. We addressed patients with a positive AGA test (IgG or IgA), but who were EMA-negative, to a specialist center for re-assay of EMA and determination of anti-tissue transglutaminase antibodies (tTG), and planned to offer biopsy in case at least one test resulted positive.

Patients were free to perform the screening panel tests in a laboratory of their choice. The follow-up appointment

was booked in accordance with clinical needs relative to the diagnosis of ATD, and not simply to check the results of the screening panel for CD; thus, most follow-up appointments were set within 6-12 months from the initial visit.

The study was closed on September 30, 2003, 18 months after the last day of enrolment (March 31, 2002).

Endpoint and statistical analysis

The aim of the study was to detect the percentage of histologically confirmed CD in patients with ATD, to whom a screening was offered according to everyday clinical practice procedures.

Since we planned to evaluate the effectiveness of a screening program, an intention-to-treat approach to data analysis was used. With this approach, all participants were included in the analysis, whether or not they completed the given intervention.

Results

From April 1, 2001 to March 31, 2002, a first diagnosis of ATD was made in 238 patients followed by our clinic. Of these, 7 were known CD patients and had actually been referred from other specialists because of the association between ATD and CD; thus, we excluded them from the study. In these 7 subject, the diagnosis of CD had been prompted by the presence of iron deficiency anemia (3 cases), recurrent abdominal pain (2 cases), short stature (1 case), family history of CD (1 case).

The demographic data of the remaining 231 patients were as follows: female to male ratio 8.89:1, mean age 41.3 ± 18.1 years, range 7.1-80.5 years. Thyroid function was classified according to the generally accepted criteria²²: there were 47 patients with overt hypothyroidism, 67 with subclinical hypothyroidism, 2 with subclinical hyperthyroidism, and 32 with overt hyperthyroidism; 83 subjects were euthyroid.

No patient reported previous testing for CD.

The results of the screening program are summarized in figure 1.

Of 231 initial study patients, 2 (0.87%) were not interested in performing the screening; 19/231 patients (8.23%) did not present at the follow-up appointment; 15/231 (6.49%) came to follow-up visit but had not performed the screening tests, even if they had expressed their willingness to participate in the study. Overall, 195/231 (84.42%) subjects had screening test results, and no patients were positive for EMA or AGA-A. There were 2 positive tests for AGA IgG, with subsequent negative results for EMA and tTG (performed in a specialized center). Finally, 1 sub-

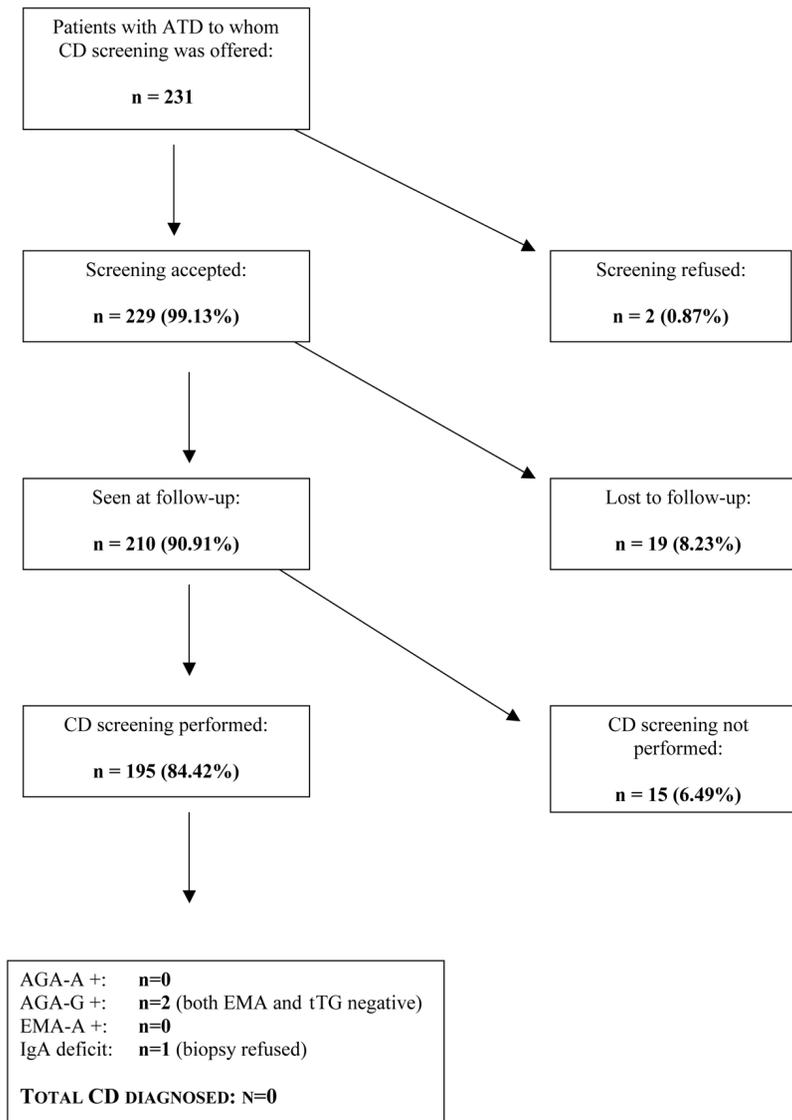


FIGURE 1. Results of the screening program for celiac disease (CD) in patients with autoimmune thyroid disease (ATD).

AGA-A+ = IgA class antigliadin antibodies positive subjects; AGA-G+ = IgG class antigliadin antibodies positive subjects; EMA-A+ = IgA class antiendomysium antibodies positive subjects; IgA = total IgA class antibodies; tTG = anti-tissue-transglutaminase antibodies.

ject had a selective IgA deficiency (and negative AGA IgG). Duodenal biopsy was offered; however the patient did not consent to the procedure.

In conclusion, the number of newly diagnosed CD in our patients with ATD, who had been offered a non-research setting screening program, was 0.

Between 1999 and 2001, six research studies were performed on the prevalence of CD in patients with ATD (Table I), including one performed in our Center by three of the authors of the present paper¹². Globally, in these six studies 41/1021 patients with ATD also had CD (4.02%;

95% confidence interval 2.90-5.41). The difference between our results (0/231) and the sum of these studies is extremely significant ($p < 0.0003$, Fisher's exact test).

Discussion

Discrepancies between the results of clinical research screening studies and those observed in everyday clinical practice have already been reported in the literature^{23,24}. These discrepancies have obvious clinical and economic implications: interventions characterized by high *effica-*

TABLE I. Prevalence of celiac disease (CD) in patients with autoimmune thyroid disease (ATD) (literature data).

References	No. patients with ATD	No. patients with CD	% of CD (95% CI)
Cuoco et al. ⁹ , 1999	92	4	4.35 (1.20-10.76)
Valentino et al. ¹⁰ , 1999	150	5	3.33 (1.09-7.61)
Berti et al. ¹¹ , 2000	172	5	2.91 (0.95-6.65)
Meloni et al. ¹² , 2001	297	13	4.38 (2.35-7.37)
Larizza et al. ¹³ , 2001	90	7	7.78 (3.18-15.37)
Volta et al. ¹⁴ , 2001	220	7	3.18 (1.29-6.45)
Total	1021	41	4.02 (2.90-5.41)

CI = confidence interval.

cy, but low *effectiveness*, have a questionable *efficiency* (defined as “the effect of an intervention in relation to the resources it consumes”¹⁹); in other words, the cost/benefit ratio may not be justifiable.

Our study suggests that a serological screening for CD in ATD patients in a practical clinical setting has no effectiveness, and thus the intervention does not have a valid efficiency.

The discrepancy between research-setting screening studies and our results is probably due to more than one cause.

First of all, research-setting screenings tend to minimize the number of patients who are lost to follow-up, or refuse the screening tests, through a strict control of the testing procedure: for example, patients are usually tested in the same clinical setting, and do not incur expenses (such as co-payments) for the diagnostic procedures that are performed as a part of the screening.

In the present study, 17 patients (7.36%) did not comply with the procedure, either by stating it outright (2 patients), or by not performing the test even if they still showed at the follow-up visit (15 patients). The reason stated by the first 2 patients, and by 4 of the 15 who had initially accepted the screening, was the desire to “avoid awareness of a second disease”. The remaining 11 patients gave more varied explanations: “forgetting the information received” was reported by 4, “losing the request form for the test” by 2, “no time to take the test” by 2, “co-payment too expensive” by 1, and finally no specific reason for not performing the test was reported by 2 patients. The availability of the tests in the laboratories chosen by the patients was not an issue, in that all laboratories were able to perform the requested procedures. Also, 19 patients (8.23%) of our initial cohort were lost to follow-up, so that a total of 36 patients (15.58%) had no available test results.

Since the lack of detection of patients with CD in our population was to us somewhat unexpected, we tried to contact the 19 patients lost to follow-up, in order to exclude a possible bias (e.g. that patients with CD were

not showing at follow-up, since they were being seen at another facility). We were able to contact 12/19 patients. Among the 12 patients, 3 subjects had not performed the screening; 8 had negative serology for CD; 1 patient forgot the information received. Since contacting patients was not planned in the initial protocol (see above), these data have not been included in the section “results”.

Another difference may be due to the laboratory determinations. In research-setting studies they are usually done using the best possible method available; in our study, patients were free to perform the screening panel tests in a laboratory of their choice, be it a hospital or a private laboratory. Consequently, another important issue can be the quality of assays performed in centers with no specific training e.g. in immunofluorescence, with possible false-negative EMA tests. However, these laboratories are those usually employed in our daily clinical practice.

There may be another factor that could explain our findings. For example, CD has been the subject of considerable interest recently, both in the specialist and the lay press, and clinicians worldwide are more prone to suspect it and request the appropriate tests even in the absence of the classical symptoms of advanced disease. In our region, in particular, large epidemiological studies have been conducted in this field, aiming at identifying sub-clinical cases of CD²⁵. Thus, it is possible that our ATD patients had been somewhat selected, i.e. patients with CD had already been “skimmed” from the cohort by testing done for other reasons (growth delay, anemia, unspecific abdominal complaints, etc.). Our observation that during the same time frame 7 patients who had already been diagnosed as having CD were referred to our Center and subsequently diagnosed as having ATD, can lend support to this speculation.

We think that these factors (different organization of the study and different time frame), can at least in part explain the significant difference observed between this study (0/231) and the previous results of our research-setting study¹² done in the same population (13/297, $p < 0.001$ by Fisher’s exact test).

In order to exclude that our cohort was too small for the observed difference to be of real clinical significance, we set to evaluate the power of our study in comparison with previously published data. Previous studies done outside our region had shown a prevalence of CD that was 8 to 15 times higher in patients with ATD compared to controls^{9-11,13,14}; our previous study reported that the prevalence of CD in patients with ATD is 4.38% (Table I), 4.13 times higher than the prevalence of CD in the general population¹². We thus calculated that our number of patients (231) has a 99.8% power (Fisher's exact test) to discriminate an expected prevalence of CD of 4.38% from that observed (0%), at the 0.05 significance level. Power calculations were done as previously described²⁶.

Finally, one could argue that quantitative assay of tTG, with its high sensitivity and specificity in the diagnosis of CD²⁷ (test not included in our screening since at the start of the study was not available in all the regional laboratories), could have allowed the detection of subjects with CD in our population. This hypothesis seems not to be supported by the results of a research-setting screening for CD performed in patients with ATD by using a combined EMA, AGA and tTG approach²⁸; in this study, of 514 patients aged < 65 years (as were 209/231 of the patients in our study), just one celiac subject with EMA negativity and tTG positivity was detected. This subject, however, had high AGA-G levels; consequently, our methodology of screening (addressing patients with a positive AGA test, but EMA-negative, to a specialist center for re-assay of EMA and determination of tTG) would have allowed the detection of CD.

In conclusion, our study suggests that serological screening for CD in ATD patients seen and followed in everyday clinical practice is not *effective*. We suggest that the opportunity of screening these patients should be reconsidered, at least outside of a research setting and in the absence of at least some clinical suspicion of the presence of CD. However, the *effectiveness* of such a screening in populations where CD is underestimated remains to be determined.

Since screening is a resource-consuming activity, for both patients and clinicians, we suggest that a careful evaluation of the *effectiveness* of a screening procedure is always warranted before adopting even strategies with proven *efficacy* in a research-setting screening protocol.

Riassunto

Le procedure di screening realizzate nell'ambito di studi di ricerca hanno dimostrato che la prevalenza di malattia celiaca in pazienti con tireopatia autoimmune è da 4 a 15 volte superiore rispetto a quella della popolazione generale. Tali studi pertanto suggeriscono che i pazienti con ti-

reopatia autoimmune debbano essere sottoposti routinariamente a screening per malattia celiaca. Tuttavia, la validità nella pratica clinica quotidiana di questi programmi di screening non è mai stata valutata.

Abbiamo invitato pazienti con prima diagnosi di tireopatia autoimmune, giunti all'osservazione presso il nostro Ospedale, a partecipare ad uno screening sierologico per malattia celiaca. Sono stati inclusi nello studio 231 pazienti, rapporto femmine/maschi 8.89:1, età media 41.3 ± 18.1 anni, range 7.1-80.5 anni.

Il numero di soggetti in cui lo screening ha portato alla diagnosi di malattia celiaca è risultato 0.

Nonostante i risultati favorevoli ottenuti all'interno di studi di ricerca, l'introduzione dello screening sierologico per malattia celiaca nei pazienti con tireopatia autoimmune non sembra avere alcuna utilità nella pratica clinica quotidiana. Poiché lo svolgimento di un'attività di screening comporta un notevole consumo di risorse (sia per i pazienti che per il personale che vi partecipa) suggeriamo che un'attenta valutazione dell'utilità di uno screening nella pratica clinica quotidiana debba sempre essere effettuata prima della sua adozione.

Parole chiave: Diagnosi; Malattia celiaca; Screening; Tireopatia autoimmune.

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Manuscript received on 1.9.2004, accepted on 12.1.2005.

Address for correspondence:

Dr. Giuseppe Fanciulli, Istituto di Clinica Medica, Università degli Studi, Viale San Pietro 8, 07100 Sassari. E-mail: gfanciu@uniss.it