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Is it Necessary to Screen for Celiac Disease in Postmenopausal Osteoporotic Women?

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Abstract. Decreased bone mass is a frequent finding in celiac patients, and subclinical celiac disease (CD) appears to be unusually overrepresented among patients with idiopathic osteoporosis. Since silent CD may be more common than previously believed, it has been suggested that all osteoporotic patients should be checked for occult CD. The aim of this study was to explore the prevalence of CD in a well-defined population of postmenopausal osteoporotic women. We evaluated 127 consecutive postmenopausal patients (mean age: 68 years; range: 50–82 years) with verified osteoporosis. The observed prevalence of CD in this group was compared to that observed in a group of 747 women recruited for a population-based study. The screening algorithm used to diagnose CD was based on a 3-level screening using type IgA and IgG antigliadin antibodies (AGA) in all the patients (1st level) followed by antiendomysial antibodies (EmA) and total IgA (2nd level) of samples testing positive, and intestinal biopsy of positive cases (3rd level). At the end of the serological screening, only 1 of 127 osteoporotic women was eligible for jejunal biopsy showing a characteristic celiac flat mucosa (prevalence $7.9 \times 1{,}000$; 95% CI 0.2–43.1). In addition, CD was diagnosed in 6 of 747 women of the population-based study (prevalence: $8.0 \times 1{,}000$; 95% CI 3.3–18.3). There was no significant difference between the two groups. Therefore, our study showed that the prevalence of CD in postmenopausal osteoporotic women was lower than that reported in previous studies and similar to that of the general population. In conclusion, although the relatively small size of the group tested does not allow us to be conclusive, the results suggest that a case finding policy in postmenopausal osteoporosis would have a high cost/benefit ratio except for patients not responding to conventional therapies, or presenting borderline laboratory results.

Key words: Osteoporosis — Celiac disease — Antigliadin antibodies — Antiendomysial antibodies

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Celiac disease (CD) is an inflammatory condition of the gastrointestinal tract affecting the small intestine caused by exposure to dietary gluten in genetically predisposed individuals. The disorder was previously thought to be rare, but is now being increasingly recognized, with prevalence values of 7×1000 in the overall Argentine population [1]. Osteoporosis and osteopenia are well recognized complications of CD. However, whether or not it causes an increment in fractures seems to be controversial [2, 3]. Decreased bone mass can be found not only in symptomatic untreated celiac patients but also in symptom-free adults treated with gluten-free diet [4–6] or in symptom-free adults identified by screening programs [7, 8]. The rationale for a screening process in case-finding is based on both the possibility to proceed to treatment thus avoiding later complications and the existence of very effective tools to screen for CD [9–11].

The prevalence of CD in the population with osteoporosis reported in a previous study was higher than the estimates for the general population [12]. According to this finding and the fact that silent CD may be more common than previously believed, it has been suggested that serological screening for CD may be a valuable addition in the routine study of osteoporotic patients, since detection of silent CD will allow implementing a specific treatment leading to a significant increase in bone mineral density [8, 13–15]. The objective of our study was to gain further insight into this issue exploring the prevalence of CD in a well-defined population of postmenopausal osteoporotic women.

Patients and Methods

Patients

We examined serum samples of 127 consecutive osteoporotic patients attending the outpatients unit of the University Hospital. Their mean age was 68 years (range 50–82). Diagnosis of osteoporosis was based on the presence of at least one

Table 1. Bone mineral density in osteoporotic patients with at least one fragility fracture and lumbar spine and/or femoral neck T-score below −2.5

	Lumbar spine	Femoral neck
g/cm^2	0.809 ± 0.159	0.684 ± 0.102
T-score	−3.2 ± 1.0	−3.0 ± 1.0
Z-score	−1.9 ± 0.8	−1.7 ± 0.7

Values are reported as mean ± 1SD

nontraumatic fracture and lumbar spine (L2–L4) and/or femoral neck bone mineral density (BMD) below T-score −2.5.

Vertebral fractures were diagnosed in 118 patients, wrist fractures in 19, hip fractures in 6, humerus in 5, rib fractures in 3, tibia in 2, and pelvis in 1 patient. BMD was measured using DXA (Lunar N DPX, Madison, WI). Results are reported as absolute values (g/cm^2) T-scores and Z-scores. The T-score and Z-score were calculated using the reference values for the normal population in Buenos Aires [16]. The values for mineral density in our population are similar to those of the white population in the United States [17]. Mean BMD values for lumbar spine and femoral neck were: 0.809 ± 0.159 g/cm^2 (T-score = −3.2 ± 1.0; Z-score = −1.9 ± 0.8) and 0.684 ± 0.102 g/cm^2 (T-score = −3.0 ± 1.0; Z-score = −1.7 ± 0.7), respectively (Table 1).

Prevalence of CD in the studied population was compared with that estimated in 747 women (mean age 29 years; range 16–79) from a population-based study aiming to determine the prevalence of CD in Argentina [1]. This study was performed by screening 1500 subjects recruited at a centralized laboratory in La Plata city (Buenos Aires Province), attending couples going in for a mandatory prenuptial examination. All the subjects were asked to participate in a screening program for CD.

Study Design

Both osteoporotic patients and the general population were screened using a similar algorithm. All patients gave consent and clinical interviews were performed prior to collecting serum samples. The protocol was based on a three-level evaluation. The first level consisted of determining serum levels of IgA and IgG antigliadin antibodies (AGA). Samples testing positive for either or both antibodies accessed the second level of the screening, which consisted of determining IgA antiendomysial antibody (EmA) and total serum IgA in samples that were only IgG AGA positive, to exclude IgA deficiency.

Samples with low total IgA serum levels were tested for IgG EmA. Finally, subjects testing positive for either or both EmA antibodies were eligible for small intestinal biopsy.

Celiac Disease-Related Serology

Serological determinations were performed on frozen samples collected at the time of the clinical interview. AGA types IgA and IgG were evaluated by the enzyme-linked immunoabsorbent microassay (micro ELISA) (18) using commercial kits (INOVA Diagnostics Inc., CA; USA). Cut-off values for both tests were 15 AU/ml and 20 AU/ml for AGA IgA and IgG, respectively.

Antiendomysial antibody was determined by the immunofluorescence method using a commercial kit (INOVA Diagnostics Inc., CA, USA) which employs a 5 μm thin, cryostat section of monkey esophagus as a substrate. Duplicate serum samples were tested at a 1:5 dilution.

Small Bowel Histology

All small intestinal mucosa samples from the distal duodenum were obtained by duodenoscopy. They were carefully oriented on Millipore paper (Millipore, USA) and processed conventionally. Histological and morphometric evaluations were performed by an experimented independent observer who was unaware of the clinical and laboratory findings, and diagnosis of other pathologists. The histological characteristics of the intestinal mucosa were assessed by conventional microscopy.

Diagnosis of Celiac Disease

CD diagnosis was based on the histological characteristics of the intestinal mucosa (villous atrophy, crypt hyperplasia, increased intraepithelial lymphocyte infiltration [>30%], and the presence of celiac disease-related serology.

Statistical Analyses

Prevalence of CD was estimated using conventional formulae and expressed as number of cases ×1000 individuals and 95% confidence intervals (95% CI). Fisher's exact test was used to detect differences between both groups.

Results

Figure 1 shows the results of the case-finding investigation in the studied population of postmenopausal women. At the end of the first-level examination, only 8 patients (6%) had increased serum levels of AGAs (either or both IgA and IgG types). All these patients underwent the second-level analysis. According to this serological selection, only one patient was positive for EmA, and therefore eligible for small intestine biopsy. In this context, histology evidenced a complete villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes infiltration. The figure represents a prevalence of CD for this population of postmenopausal osteoporotic women of 7.9 × 1000 patients (95% CI 0.2–43.1).

Figure 2 shows the outcome of the screening algorithm in women from the overall population. At the end of the first-level screening, 96 individuals (12.8%) showed increased concentrations of one or both AGAs, and underwent the next step. Of those accessing the second-level screening, only four were EmA positive and the remaining two had very low total serum IgA. Thus, only six subjects were candidates for intestinal biopsy. All of them presented histological features of CD. Therefore, the estimated prevalence of CD in the overall female population was 8.0 × 1000 individuals (95% CI 3.3–18.3).

Discussion

The clinical diversity of CD and its potential complications are leading to noninvasive screening in order to identify and treat new patients hitherto unrecognized. In this context, osteopenia, osteoporosis, and bone frac-

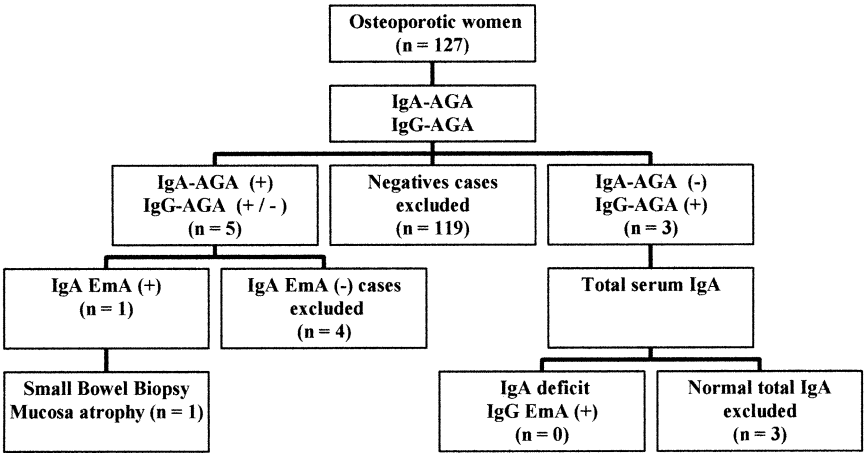

Fig. 1. Results of the screening algorithm in the osteoporotic population.

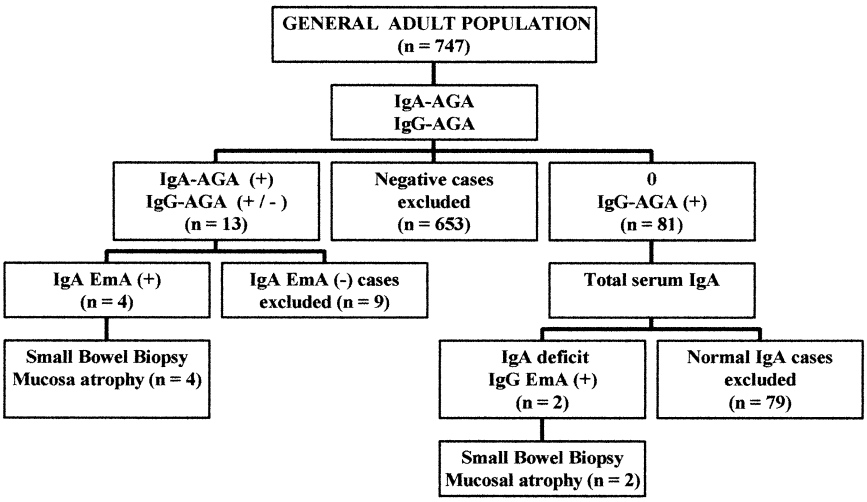

Fig. 2. Results of the screening algorithm in women of the overall female population.

tures are the most frequent complications of adults with untreated CD. These observations suggest that assessment of the bone characteristics of untreated celiac patients is mandatory. Conversely, whether screening for CD is required for osteoporotic patients has not been explored. In this study, we aimed to determine the prevalence of CD in a well-defined population of postmenopausal osteoporotic women. The case-finding process was based on a well-explored methodology, to date, considered the gold standard in screening for CD [9–11, 19]. Our study revealed CD in only one of 127 osteoporotic women. This figure represents a similar prevalence to that established for adult women in a population-based study in Argentina (7.9×1000 vs. 8.0×1000).

In our opinion, at least three aspects of our study deserve further comments. Firstly, our results are clearly different from those previously published by Lindh et al. [12] who observed that prevalence of positive CD serology (AGAs) is tenfold higher in osteoporotic patients compared with the general Swedish population. Conversely, our results are in agreement with those recently published by Mather et al. [20]. It is not simple to understand the differences between Mather's and Lindh's study. Interestingly, two aspects of these studies are conflictive. On the one hand, while the age distribution of patients in both studies is lacking, the mean age data and standard deviations reported suggest that an important proportion of studied osteoporotic cases are premenopausal women. On the other hand, Lindh et al. [12] screened patients referred for evaluation of bone disease. However, although BMD was measured by single photon absorptiometry in the radius, the basis on which diagnosis of osteopenia or osteoporosis was made is not mentioned. Furthermore, there is no reference to the densitometric criteria used, to the reference normal values (which could suggested the magnitude of osteopenia), or to the occurrence of fractures. Since the prevalence study of CD in the Swedish population considered by Lindh et al. was performed in blood

donors, only subjects with normal hemoglobin were included [21]. A higher prevalence of CD has been reported more recently in a randomly selected sample of the general adult population [22]. Certainly, prevalence of undiagnosed CD is significantly greater than was previously estimated, and may vary considerably from country to country [10].

A second aspect to discuss regards the screening algorithm used in this study. As mentioned above, the protocol was widely and successfully used in case-finding interventions, and to determine prevalence of CD in the overall population. The algorithm based on the sequential use of a set of serological tests and the confirmatory intestinal biopsy have proven valuable. Thus, while the combination of both AGA tests showed a 92% to 96% sensitivity, association with EmA gives the protocol an almost 100% specificity [11, 21].

Finally, the comparison of the prevalence of CD in the studied population with that estimated in the overall female population requires further comments. We believe that this comparison adds valuable information to this study, since both adult populations are from the same geographic area and share a common ethnic origin, and despite clear differences between populations regarding distribution according to age. In our opinion, this kind of difference is not relevant to the comparison of our results. Celiac disease is a very interesting lifelong disorder. Its prevalence is more than twofold higher in women than in men and the greatest proportion of cases occur mostly before menopause. It is therefore likely that CD prevalence corresponding to the age range of the control population will remain almost unchanged for the osteoporotic population.

In conclusion, although the relatively small size of our population does not allow us to be conclusive, the results suggest that the screening for CD in postmenopausal osteoporotic women would have a high cost/benefit ratio. Therefore, the search for CD should be reserved for osteoporotic patients that do not respond to conventional therapies, or with borderline laboratory results.

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