Positive IgA against transglutaminase 2 in patients with distal radius and ankle fractures compared to community-based controls.

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Abstract

Backgroud: Patients with celiac disease (CD), including adults with subclinical disease, have low bone mineral density (BMD), deteriorated bone microarchitecture; metanalysis show an increased risk of fracture. Immunoglobulin A (IgA) against transglutaminase 2 (IgA TG2) is a highly reliable marker to detect CD.

Main objective: To explore the prevalence of positive IgA TG2 and CD in patients with distal radius and ankle fracture compared to community-based controls.

Methods: 400 patients age 40 years or above with distal fractures were included in a case-control study. 197 controls were identified from the National Population Registry, those included had never suffered a fracture. BMD was measured, and comorbidities, medications, physical activity, smoking habits, body mass index (BMI) and nutritional factors were registered. Blood analysis to detect common causes of secondary osteoporosis was performed.

Results: 2.5% of the fracture patients had positive IgA TG2, compared to 1% in the control group. The odds ratio, adjusted for sex and age, of having positive IgA TG2 was 2.50 (95% CI 0.54 – 11.56).

Conclusions: There were no significantly increased odds of CD in adult patients with fractures compared to controls, however results imply that positive IgA TG2 is more prevalent in fracture patients than in controls. This study indicates that universal screening for CD in fracture patients is not warranted, but supports current clinical practice in Norway to suspect and investigate for CD in patients with fracture, osteoporosis and other risk factors for CD.

Keywords celiac disease • fracture • osteoporosis • bone mineral density • IgA against transglutaminase 2

Introduction

Patients with celiac disease (CD) have lower bone mineral density (BMD) than their healthy peers [1, 2]. Lower BMD than expected also affects about half of patients with subclinical CD, who have mild symptoms and often remain undiagnosed [3]. In addition to low BMD, the bone microarchitecture may be deteriorated [4, 5] making CD patients more susceptible to low energy fractures. Evidence of increased fracture risk in CD patients is however not consistent [6] and the need for BMD screening is debated. Additionally, the studies performed on the topic are mainly cross-sectional [7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17], typically small, use different designs and inclusion criteria and are thus difficult to compare [18].

CD is an autoimmune enteropathy triggered by exposure to wheat gluten and similar proteins in rye and barley, affecting genetically susceptible persons. The estimated population prevalence of CD in Northern Europe is (1.0- 1.5 %) [19]. While more cases are being diagnosed as a consequence of increased awareness, studies indicate that most patients with CD still remain undiagnosed [3, 20]. An enzyme-linked immunosorbent assay (ELISA) for IgA TG2 has a sensitivity of 88- 98 % and specificity of 82-97% in the diagnosis of CD [21, 22], however, duodenal biopsy is warranted to confirm.

Low BMD as measured by dual-energy X-ray absorptiometry (DXA) represents a strong risk factor for fractures [23]. The BMD in newly diagnosed adult CD patients improves with a gluten-free diet (GFD), but will in most cases not be restored to normal [24, 25, 26]. Asymptomatic CD patients also have lower BMD than expected [27, 28] indicating that malabsorption due to villous atrophy is not the main cause. 25OH- vitamin D deficiency which is a risk factor for osteoporosis and falls [29] is common among CD patients (65- 70% [30]) and is not related to intestinal injury [31]. CD patients may also have impaired zink

absorption and increased serum pro-inflammatory cytokines [1]. Untreated CD affects osteoclastogenesis and osteoblast activity via the RANKL/RANK/osteoprotegerin pathway, leading to increased bone resorption [32, 33].

Early detection and treatment of CD is important to avoid excess fractures. Once treatment with a GFD is initiated, the risk of fracture diminishes [16], and the younger the patients are when starting a GFD, the better the response will be.

Positive IgA TG2 is used as a diagnostic criterion for celiac disease autoimmunity, at least in epidemiological settings [34, 35]. TG2 may also play a role in modulating maturation of bone/cartilage matrix, facilitating the final mineralization [36]. Findings from cross-sectional studies suggest that osteoporosis is more common in patients with elevated antibodies against TG2 [34, 37, 38, 39, 40].

The aim of this study was to explore the prevalence of positive IgA TG2 and CD in patients with distal radius and ankle fractures compared to community-based controls.

Materials and methods

Subjects

From March 1, 2012 until January 13, 2017, patients over the age of 40 living in Sogn og Fjordane County with acute distal radius or ankle fractures were included in a case-control study. Physicians at the local orthopedic department referred those agreeing to participate to our osteoporosis clinic. Those not able to give an informed consent were excluded. All patients were recommended a BMD measurement if clinically indicated, regardless of participation in the study or not.

The controls were identified by the Norwegian Population Registry and were included from June 7, 2012 until January 13, 2017. They received postal written information and a request to participate. Exclusion criteria for the controls were previous fractures and not being able to give an informed consent.

Each participant signed a written informed consent form, and the study protocol was approved by the Regional committee for medical and health research ethics (REK no 2011/1624).

Procedures and Measurements

BMD was measured by DXA technology (Lunar Prodigy Rtg 5603, manufacture year 2000, GE Healthcare) with a daily quality assurance of +/- 2 %. BMD was reported as g/cm^2 and T-scores by standard definition [41]. History of previous fractures, comorbidities, medications and lifestyle factors were registered. Height and weight were measured. Serum analyses included white blood cell count, hemoglobin, sedimentation rate, serum electrophoresis, ionized calcium, albumin, thyroid-stimulating hormone, parathyroid hormone, 25-OH vitamin D, phosphate, C-reactive protein, liver enzymes, alkaline phosphatase, ferritin, folic acid, total IgA and IgA TG2. Patients and controls were informed about the results of the DXA scan on the day of examination, and appropriate treatment was either initiated or recommended to the general practitioner. Patients with positive IgA TG2 were referred to the local gastroenterology department.

TG2 IgA was in 52.1% analyzed with an ELISA-test, 5.7% by an EliA method (Unicap 100 by Phadia®) and in the remaining 42.2% by a multiplex flow immunoassay (BioPlex® 2200 Celiac IgA). This change of methods was due to the unexpected closing of the original laboratory used. Total IgA was also quantified to rule out false-negative IgA TG2.

Statistical analysis

Data are described as means and percentages. Associations between categorical variables were calculated using Pearson's χ^2. Associations between CD and fracture are presented in terms of odds ratios (ORs) with 95% confidence intervals, estimated from logistic regression models. All analyses were performed using IBM® SPSS Statistics Version 24, 2016 and R (version 3.4.1 for Mac OS). All *p* values are 2-sided, and values <0.05 are considered statistically significant.

Results

The participation rate was 51.3% among patients and 42.8% in the control group. There were 82.7 % female controls compared to 77.3 % female fracture patients (*Table 1*). In the ankle fracture group, the patients were younger than both the controls and the radius fracture patients, and a higher proportion were overweight or obese as classified by the WHO BMI classification criteria [42].

Overall vitamin D levels were sufficient, and there were no statistically significant differences between cases and controls. The prevalence of osteoporosis was significantly higher in the radius fracture group than in the healthy controls and ankle fracture patients (p<0.001).

In the control group, there were three individuals with known CD treated with a GFD, and they consequently had negative IgA TG2. Two had positive IgA TG2, one had a positive duodenal biopsy (Marsh 2), the other was after clinical consideration by the local gastroenterologist not recommended to have a biopsy performed. In the radius fracture group, three patients had known CD and were on a GFD. None in the ankle fracture group had known CD. Among all fracture cases, there were 10 with positive IgA TG2. Of the nine who

went through a duodenal biopsy, six had the CD diagnosis confirmed, all graded as Marsh 3a or 3b. One patient with positive Ig A TG2 was diagnosed with MALT lymphoma. Two patients had subtle histologic changes, but the findings were not indicative for CD.

In the control group, one of the three with known CD was osteoporotic, while one out of two with positive IgA TG2 had osteoporosis. Amongst the fracture patients, all three with previously diagnosed CD had osteoporosis, while six out of 10 with positive IgA TG2 were osteoporotic.

Examining fractures as a risk factor for having positive IgA TG2, the odds ratio (OR) was 2.50 (95% CI 0.65 – 16.4) (*Table 2*). The crude ORs did not differ from the ORs adjusted for sex and age. Additional adjustment for potential confounding factors including BMI, smoking, vitamin D level and PTH did not materially affect the OR.

In the radius fracture group, the OR of fracture when positive IgA TG2 was 2.39 (95% CI 0.56-16.1), and for the ankle fracture group 2.77 (95% CI 0.45 – 21.3).

In summary, seven previously unknown CD patients were diagnosed. Twelve participants (ten fracture patients and two controls) had positive IgA TG2, among whom seven were osteoporotic and the remaining had osteopenia. The occurrence of positive IgA TG2 was 2.5% in the combined fracture group, compared to 1.0% in the control group, yielding an odds of positive IgA TG2 when suffering a fracture 2.5 (95% CI 0.65 – 16.4).

Discussion

In this study we did not find any significant difference in the prevalence of CD (diagnosed and undiagnosed) in patients with fractures compared to healthy controls. There was neither

any significant difference in prevalence of positive IgA TG2 and CD in fracture patients vs controls.

To our knowledge, no case-control study has previously investigated the proportions with CD and positive IgA TG2 among fracture patients vs. controls without fracture. Although not statistically significant, our results indicate that positive IgA TG2 is more commonly found in fracture patients than in controls. It may be hypothesized that elevated IgA TG2 is an independent risk factor for fracture mediated by systemic inflammatory effects, even in those who do not fulfill the criteria for clinically active CD. Our study highlights the need for large, population-based prospective studies to examine the associations of not only biopsy confirmed CD, but also subclinical and latent CD, with bone fracture.

In a study by Zanchetta et al [43] improvement of trabecular density, trabecular/bone volume fraction and trabecular thickness after one year on GFD in premenopausal women was demonstrated, and change in TG2 antibody was the only variable that was significantly and independently related to the positive changes found in bone microarchitecture. In a large retrospective Danish study [44], low BMD only occurred in the CD patients with increased TG2 antibody levels. A prospective cohort study from Finland [20] found that those with positive TG2 antibodies had an 1.6 to 2.2-fold risk (HR) of hip fracture compared to seronegative individuals during 30 years follow-up.

Starting GFD in CD patients increases BMD values [24, 25, 26]. Concerning the medical treatment of osteoporosis we know of no longditudinal studies on BMD improvement or fracture prevention among CD patients, thus the current approch is based on standard treatment for post-menopausal osteoporosis. The need for bone density scanning and evaluation of fracture risk in newly diagnosed adult CD patients is debated [45], and there are only a few studies available to inform guidelines [46]. The British Society of

Gastroenterology guidelines [47] suggest referral for DXA measurement only for CD patients at high risk of developing osteoporosis, while the American Gastroenterological Association (AGA) recommends BMD measurement of all adult CD patients at the time of diagnosis [48]. A recent study suggests the use of The Fracture Risk Assessment (FRAX) tool to avoid the use of DXA scans in CD patients with a perceived low risk of osteoporosis [49].

*Strengths of the study***.** The county of Sogn og Fjordane has a stable population with little migration. The controls were from the same geographic area as the patients, considered important since previous studies from Norway have shown significant regional differences in hip BMD [50]. The use of population-based instead of hospital-based controls reduces selection bias (sampling bias and susceptibility bias). All DXA measurements were performed on the same machine by the same technician and in the same time period. The information on known and potential confounding factors was extensive and reliable.

Limitations of the study A case control design is appropriate for investigating a suspected risk factor, and here we examined positive IgA TG2 as a potential risk factor for distal radius and ankle fractures. The study is, however, too small and statistically underpowered to be able to demonstrate statistically significant results. The different techniques for IgA TG2 analyses may be regarded a limitation because of small differences in sensitivity and cut off levels, but it reflects the tests available and used in clinical practice during the the study period. The etiology of ankle fractures and radius fracture differ. In our study radius fracture was strongly correlated with osteoporosis, while this was not the case in the ankle fracture group. Combining these two different fracture types may potentially dilute some of the results regarding the association between increased fracture risk in CD.

Conclusion

We did not find any statistically significantly increased risk of having CD in adult patients with fractures compared to controls, thereby indicating that universal screening for CD in fracture patients may not be warranted. There was however a tendency, although not significant, towards higher odds ratio of positive IgA against TG2 among those with fracture than controls. This may support that in clinical practice, the threshold for investigating CD should be low in adult fracture patients with osteoporosis and additional symptoms on malabsorption suspicious of CD.

Declaration of interest statements The authors report no conflicts of interest

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Table 1. Sample characteristics

	Cases			Controls
	Radius fracture n=293	Ankle fracture n=107	All fractures n=400	n=197
Age (years)				
Mean	62.9 (SD[1] 10.3)	57.1 (SD 9.9)	61.4 (SD 10.5)	60.3 (SD 10.6)
Range	40 - 92	41 - 81	40 - 92	40 - 87
40-49	11.3 %	24.3 %	14.8 %	18.3 %
50-59	25.9 %	37.4 %	29.0 %	27.9 %
60-69	35.8 %	21.5 %	32.0 %	33.0 %
≥ 70	27.0 %	16.8 %	24.3 %	20.8 %
Gender				
Female[2]	80.2 %	69.2 %	77.3 %	82.7 %
Male	19.8 %	30.8 %	22.8 %	17.3 %
BMI[3] (kg/m^2)				
mean	26.4 (SD 4.8)	28.6 (SD 4.9)	27.0 (SD 5.0)	27.3 (SD 5.2)
≤ 18.5	1.4 %	0	1.0 %	1.5 %
18.5-24.99	43.0 %	27,1 %	38.8 %	36.5 %
25-29.55	33.1 %	39.3 %	34.5 %	36.0 %
≥30.0	22.5 %	33.6 %	25.8 %	25.9 %
BMD[4] (DXA[5])				
Osteoporosis[6]	44.7 %	22.4 %	39.0 %	22.3 %
Osteopenia[7]	43.7 %	47.7 %	44.5 %	51.8 %
Normal BMD[8]	11.6 %	29.9 %	16.5 %	25.9 %
Celiac disease				
Known	1.0 %	0	0.3 %	1,5 %
Positive IgA TG2[9]	2.4 %	2.8 %	2.5 %	1.0 %
Smoking status				
Current	15.4 %	18.7 %	16.3 %	11.2 %
Previously	42.0 %	36.4 %	40.5 %	40.6 %
Never	41.3 %	44.9 %	42.3 %	48.2 %
Vitamin D (nmol/L)				
Mean	72.2 (SD 21.6)	69.3 (SD 22.7)	71.5 (SD 21.9)	67.7 (SD 21.4)
Deficiency[10]	2.7 %	6.5 %	3.0 %	5.6 %

[1]Standard deviation [2]One female had both ankle and radius fracture co-occuring, and is included in both fracture groups [3]Body mass index [4]Bone mineral density [5]Dual-energy X-ray absorptiometry [6]T-score ≤ -2,5 [7]T-score -1.0 to -2.5 [8]T-score ≥ -1.0 [9]IgA against transglutaminase 2 [10]here defined as ≤ 37 nmol/l

Table 2: Odds ratio of having celiac disease in fracture patients compared to controls

	Crude OR (95% CI)	Adjusted[1] OR (95 % CI)
Total fracture		
Known CD[2]	0.49 (0.09-2.66)	0.43 (0.08-2.39)
Positive IgA TG2[3]	2.50 (0.65-16.4)	2.50 (0.65-16.4)
Radius fracture		
Known CD[2]	0.67 (0.12-3.65)	0.65 (0.12-3.56)
Positive IgA TG2[3]	2.39 (0.56-16.1)	2.33 (0.55-15.8)
Ankle fracture		
Known CD[2]	None[4]	None[4]
Positive IgA TG2[3]	2.77 (0.45-21.3)	3.63 (0.58-28.6)

[1]Adjusted for age and sex. Further adjustment for known confounders did not significantly affect the OR (BMI, Vit D, smoking). [2]Referent group defined as all not-known CD [3]Referent group defined as negative TG2 + known CD (since the treated CD patients have negative TG2) [4]There were no patients with previously diagnosed celiac disease in the ankle fracture group