Celiac disease-related osteopathy among Saudi celiac patients: Are we adherent to recommendations?

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INTRODUCTION

Celiac disease (CD) is a permanent immune-mediated intolerance to gluten leading to small bowel mucosal inflammation, villous atrophy, and crypt hyperplasia in the presence of a genetic susceptibility (HLA-DQ2 or HLA-DQ8) leading to autoantibody activation upon exposure to the offending antigens.[1,2] The disease is heterogeneous with different forms of presentation from the classic features of malabsorption, weight loss, and steatorrhea to the extra intestinal forms such as osteoporosis or anemia. Many cases remain undetected or clinically silent.[3,4]

There has been a rise in the reported prevalence of the disease over the last two decades. Western studies reported a prevalence of 0.2:100 rising to 1:100 in more recent studies.[5-7] The higher prevalence could have resulted from

Background/Aims: There are no reports from Saudi Arabia documenting the picture of osteopathy in celiac disease (CD) and the adherence of physicians to the guidelines and recommendations to screen for bone disease. We conducted this study to document the prevalence of CD-related osteopathy and the Saudi physicians’ adherence to the screening recommendations.

Patients and Methods: We identified the biopsy proven CD cases diagnosed between 2003 and 2012. In addition to demographic data, we collected laboratory (serum calcium, phosphate, alkaline phosphatase, 25-dihydroxy vitamin D, and parathyroid hormone levels) and imaging [Dual-energy X-ray absorptiometry (DEXA)] data. Vitamin D levels of <50 nmol/L and 50−<75 nmol/L defined deficiency and insufficiency, respectively. T score (of lumbar spine and femoral neck) of ≤−2.5 defined osteoporosis and a score of ≤−1 and >−2.5 defined osteopenia.

Results: We identified 80 children and 128 adults with CD. Only 42% of children and 67% of adults had their serum vitamin D level measured. DEXA was ordered in 7% of children and 36% of adults. Vitamin D deficiency was widely prevalent and significantly higher in adults (95.3%) than children (76.3%). Low bone mass density (BMD) in adults was 86.9% (45.6% with osteopenia and 41.3% with osteoporosis).

Conclusions: We document low adherence of physicians to recommended guidelines to recommendations to screen for osteopathy in CD. Vitamin D deficiency and low BMD are highly prevalent among Saudi CD patients. This may be a reflection of the low vitamin D stores in the Saudi general population.

Keywords: Bone disease, celiac disease, metabolic osteopathy, osteopenia, osteoporosis, vitamin D deficiency

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the wider use of highly sensitive and specific serological markers for diagnosis or a true rise in the incidence of the disease.[3-7] Serological surveys in three regions of Saudi Arabia reported a prevalence of 2.2% of CD in the general adolescent population.[8] A recent mass screening study revealed a prevalence rate of biopsy proven CD of 1.5% among school-aged children (6–15 years) in Riyadh city, the capital of Saudi Arabia.[9]

Metabolic osteopathy (MO) is a common manifestation of CD with prevalence of low bone mass density (BMD) (osteopenia or osteoporosis) varying between 9 and 72%.[10,11] The wide range reflects the fact that various studies recruited different populations with variable degrees of gluten abstinence.[10] Secondary hyperparathyroidism and osteomalacia due to vitamin D and calcium malabsorption are the main culprits for low BMD in CD.[12] The rise of proinflammatory cytokines also plays a role.[12]

The guidelines of the British Society of Gastroenterology recommended screening with dual-energy X-ray absorptiometry (DEXA) only in those at high risk of developing osteoporosis.[13] In contrast, the American college of Gastroenterology recommends BMD and serum vitamin level measurement at the time of diagnosis.[14] The more recent reviews support this approach.[13] We are not aware of any reports in Saudi Arabia documenting the prevalence or manifestations of MO in CD. In addition there are no published indicators of the physicians’ adherence to the guidelines recommendation to screen CD patients with serum vitamin D level and DEXA.[14,15]

Therefore, we conducted a retrospective study of cases of CD during 2003–2012 at King Khalid University Hospital, King Saud University, Saudi Arabia to document the following:

- The physicians’ adherence to the recommendations to screen for osteoporosis and Vitamin D deficiency
- The prevalence of Vitamin D deficiency and low BMD in the Saudi CD population in comparison with international reports
- The difference in biochemical markers of MO between children and adults with CD.

**PATIENTS AND METHODS**

This is a retrospective study conducted at King Khalid University Hospital, Riyadh. Cases of CD were identified through the histopathology registry of celiac disease. The data were collected from 2003 to 2012.

The criteria for the diagnosis of CD were positive IgA-Endomyseal antibody (IgA-EMA) and/or positive tissue transglutaminase antibody titer (IgA-tTG) and intestinal changes on duodenal biopsies consistent with CD, according to Marsh–Oberhuber classification.[16-18] Before 2006, we used IgA-EMA test to screen for CD. The IgA-EMA was performed at our hospital by indirect immunofluorescence method using endomyseal lining of smooth muscle bundles (IMMCO Diagnostic, The Hague, Netherlands); a titer of ≥1:20 was considered positive. The IgA-tTG was performed using enzyme-linked immunosorbent assay (ELISA) (Inova Diagnostics, San Diego, USA); a value of >20.0 U/ml was considered positive. As IgA-tTG was available in our hospital only after 2006, both serological tests were performed together after that date.

The files of all patients were reviewed jointly by the author and a research assistant. In addition to personal data, CD presentation, and complications, the following results were recorded – serum calcium, phosphate, alkaline phosphatase, 25-dihydroxy vitamin D, and parathyroid hormone levels. Vitamin D levels of <50 nmol/L and 50−<75 nmol/L were diagnosed as deficiency and insufficiency, respectively, in accordance with the US Endocrine Society guideline.[19,20] Also recorded were the results of DEXA and technetium bone scan, when performed. The DEXA was performed by using a scanning arm which emits two X-rays aimed at the soft tissues and the bones. The density of the bones is obtained by subtracting that of the soft tissues. Bone scans were performed by injecting technetium-99 m intravenously following by scanning with a gamma camera, which acquires single photon emission computed tomography. Osteomalacia and rickets manifest as areas of high technetium uptake caused by increased osteoblasts activity. The technique is highly sensitive for the detection of osteomalacia even when the biochemical tests are equivocal.[21,22] All the above data were recorded before gluten abstinence.

As defined by the World Health Organization, osteoporosis corresponded to a T score of ≤−2.5 and osteopenia to a score of ≤−1 and >−2.5.[23] T score is the standard deviation of BMD from the reference value for healthy young adults. In accordance with the same guidelines, the lowest T score of lumbar spine and femoral neck was recorded.[23] Z Scores, defined as the SD score based on age and gender-specific norms, are used in children.[24,25] A Z score of −2.0 or less is defined as “below the expected range for age” or low BMD.[24,25]

The machine used for DEXA was Lunar Prodigy in the early tests followed by Lunar iDXA (General Electric,
Madison, Wisconsin, USA). The machine used for bone scans was JETStream Workspace R1.0 in the early tests followed by JETStream Brightview XCT SPECT (Philips, Eindhoven, Netherlands).

**RESULTS**

We identified 90 children and 128 adults with CD [Table 1]. Vitamin D deficiency was widely prevalent and significantly higher (P = 0.005) in adults (95.3%) than in children (76.3%). Only 2.6% of the children and none of the adults had a normal serum vitamin D level. The mean (±SD) serum level of Vitamin D was 38.69 (±19) nmol/L in children and 22.45 (±15.2) nmol/L in adults, respectively (P < 0.001). The percentage of adults with low BMD was 86.9% (45.6% with osteopenia and 41.3% with osteoporosis). The mean T score for adults was −2.37. The T score is not used among children. Apart from vitamin D deficiency, there was no significant difference in biochemical indices between children and adults. The physicians’ adherence to the screening recommendations was low. Only 38/90 (42%) children and 86/128 (67%) adults had a serum vitamin D level estimation. DEXA was ordered in 6/90 (7%) children and 46/128 (36%) adults for screening purposes. None of the patients had any history of bone disease.

**DISCUSSION**

The main findings of the study are that the physicians’ adherence to the guidelines recommendations was poor with regards to performing serum vitamin D level (42% in children and 67% in adults) and DEXA (7% in children and 67% in adults). The biochemical markers were not significantly different except for Vitamin D deficiency, which was higher in adults (95.3%) than that in children (76.3%). Both age groups had high rates of reduced BMD.

The presence of low BMD (osteopenia or osteoporosis) among CD patients varied widely between 9–72% in all series and 38–72% before gluten restriction.10,11 This puts Saudi Arabia with 86.9% (45.6% osteopenia and 41.3% osteoporosis) at the high end of the scale. The wide variation between countries may reflect differences in ethnicity, economic status, and sun exposure. Low BMD is more common in adults and may be present even in asymptomatic patients at the time of diagnosis.11,26 Therefore, it is surprising that the screening in our hospital for BMD and vitamin D deficiency is so low despite the increasing awareness of bone disease and clear recommendations in the guidelines.14,15 However, this lack of adherence to guidelines has been documented in other university hospitals. In 2016, Singh and Garber reported from Harvard Medical School, USA, that among 222 adults with CD, only 80 (36%) underwent DEXA, and of these 80 patients, only 43 had DEXA screening specifically in relation to their celiac diagnosis.27 The DEXA screening was only 15.8% in children.27 A therapeutic intervention was made in the majority of these patients as a result of DEXA.27 There is no conclusive explanation for the low adherence in teaching hospitals in USA and Saudi Arabia. However, we speculate that the prevailing impression that CD is a “gastrointestinal disease” rather than a bone disease may have contributed to this nonadherence to guidelines. We recommend universal testing of biochemical markings of osteopathy as well as DEXA in Saudi CD patients given the high prevalence of bone disease.

Our study found rates of vitamin D deficiency (in both children and adults) and reduced BMD that are higher than previously reported worldwide. Vitamin D deficiency or insufficiency was reported in only 1/4 to 1/3 of children with CD in most Western series.28,29 In a recent American retrospective study among 530 adults with CD, 59% had deficiency or insufficiency of vitamin D (compared with

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**Table 1: Comparison between children and adults with celiac disease**

|                  | Children (n=90) | Adults (n=128) | P     |
|------------------|----------------|---------------|-------|
|                  | ≤15 years      | >15 years     |       |
| Age (years) mean±SD | 10.19±3.696   | 30.27±12.306  |       |
| (Range)           | (1–15 y)       | (16–75 y)     |       |
| Gender            |                |               |       |
| Male              | 31 (34.4%)     | 38 (29.7%)    | 0.457 |
| Female            | 59 (65.6%)     | 90 (70.3%)    |       |
| Serum calcium     |                |               |       |
| Low (Normal lab. range 2.1–2.6 mmol/L) | 6/76 (7.9%) | 21/118 (17.8%) | 0.144 |
| Serum phosphate   |                |               |       |
| Low (Normal lab. range 0.8–1.45 mmol/L) | 16/76 (21.1%) | 18/114 (15.8%) | 0.185 |
| Serum alkaline phosphate | High (Normal lab. range 41–133 units/L) | 23/76 (30.3%) | 45/113 (39.8%) | 0.125 |
| Serum Vitamin D   |                |               |       |
| Deficiency        | 29/38 (76.3%)  | 82/86 (95.35%)| 0.005†|
| Insufficiency     | 8/38 (21.1%)   | 4/86 (4.65%)  |       |
| Serum parathormone|                |               |       |
| High (Normal lab. range 1.2–5.7 pmol/L) | 4/8 (50%) | 25/38 (65.79%) | 0.325 |
| DEXA*             |                |               |       |
| Low BMD (children)| 6/6 (100%)     |               |       |
| Osteopenia (adults)| 21/46 (45.6%) |               | 0.209 |
| Osteoporosis (adults) | 19/46 (41.3%) |               |       |
| Technetium Bone Scan | Rickets (children) | 2/2 (100%) | 14/19 (73.7%) | 0.437 |
| Osteomalacia (adults) |                |               |       |

*Dual-energy X-ray absorptiometry. †Statistically significant
100% in our study).[29] Their cut-off levels for diagnosing deficiency and insufficiency of vitamin D were similar to ours.[30] Saudi Arabia is documented to have high levels of deficiency in the general population, attributed to inadequate exposure to sunlight and manifesting particularly in young adults and adolescents.[31‑33] This may explain why our adult CD group (mostly young) displayed greater vitamin D deficiency than children. Some Western series demonstrated greater deficiency in adults with CD than children (like ours) whereas others reported no age-related difference.[34,35]

The main complication of osteopathy is bone fracture and its sequelae.[35] Other workers have stressed the importance of dental screening in CD in view of the high prevalence of recurrent oral ulcerations and enamel hypoplasia.[36] We recommend universal testing of biochemical markings of osteopathy as well as DEXA in Saudi CD patients given the high prevalence of bone disease. Gluten abstinence, correction of deficiencies, and medical management of osteoporosis are documented to improve the fracture risk and low BMD.[2,12,34,37,38]

The study has several limitations. The retrospective nature has resulted in some information gaps such as supplements received. Similarly, we cannot comment on any confounding factors that could have contributed to low T score such as hormonal therapy or low body mass index. Finally, we have no data on what action was taken for these patients and the response to treatment.

CONCLUSION

We report low adherence of physicians to the guidelines’ recommendations to screen with serum vitamin D level and DEXA. The rates of vitamin D deficiency and reduced BMD approach 100% and are higher than reported worldwide. This may be a reflection of the low vitamin D levels in the general population in Saudi Arabia. Applying these points to clinical practice may improve the care of CD patients in Saudi Arabia.

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Conflicts of interest

There are no conflicts of interest.

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