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ORIGINAL ARTICLE

Celiac disease and severe vitamin D deficiency: the case for anti-tissue transglutaminase antibody screening

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Abstract

Summary Vitamin D-deficient Saudi adolescent girls were screened for anti-tissue transglutaminase (IgA-tTG) antibodies to determine whether the presence of severe vitamin D deficiency was associated with celiac disease. All 9 participants who were positive for IgA-tTG antibodies had severe vitamin D deficiency (25(OH)D < 12.5 nmol/l), suggesting that this population should be screened for celiac disease.

Purpose The current cross-sectional study aimed to see if severe vitamin D deficiency is associated with celiac disease (CD) among Saudi adolescent girls.

Methods A total 200 adolescent females aged 13–19 years old with vitamin D deficiency (serum 25(OH)D < 50 nmol/l) were screened for IgA tTG (anti-tissue transglutaminase antibodies).

Results Of the 200 girls, 9 (4.5%) were positive for IgA tTG antibodies; all of whom had serum 25(OH)D < 12.5 nmol/l. A strong significant inverse association was observed between tTG antibody levels and serum 25(OH)D ($R = -0.53$; $p < 0.001$) among antibody negative participants. Finally, participants with positive IgA tTG antibodies was 37.2 times higher for participants with 25(OH)D < 12.5 nmol/l than those whose vitamin D status was higher [OR = 37.2 (95% CI 4.6–299.7) ($p = 0.0002$)].

Conclusion The data suggests that CD maybe a risk factor for severe vitamin D deficiency and that patients presenting with very low levels of 25(OH)D of less than 12.5 nmol/l—in the absence of an obvious cause—may need to be screened for CD.

Keywords Celiac disease · Vitamin D deficiency · Adolescents

Abbreviations

25(OH)D	25 hydroxyvitamin D3
IgA-tTG	anti-tissue transglutaminase antibodies

Introduction

Vitamin D deficiency has emerged as a major health problem in Saudi Arabia and worldwide [1–4]. We and others have documented that the major causes of vitamin D deficiency are related to limited sun exposure, life style, and nutritional deficiency [5–10]. In recent years, celiac disease (CD) has been recognized as an important risk factor for extraintestinal abnormalities such as short stature and delayed puberty in the absence of the classical well-recognized presentation of steatorrhea. In addition, nutritional deficiencies have been recognized as an important consequence of this disease. Vitamin D deficiency in newly diagnosed CD patients has ranged from 20.3 to 54.5% [11–13]. However, estimation of the prevalence of CD among patients with severe vitamin D deficiency has not been done before. This study was conducted to determine if CD is associated with severe vitamin D deficiency among Saudi adolescent girls and to draw guidelines if routine screening for CD is necessary in severely vitamin D-deficient individuals.

Methodology

In this cross-sectional study, a total of 200 Saudi adolescent females aged 13–19 years old with vitamin D deficiency (serum 25(OH)D < 50 nmol/l) and who were not on vitamin D supplements were randomly selected from a large cohort of 2000

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female students in intermediate and secondary schools who previously participated in the study on the prevalence of vitamin D deficiency in Riyadh region, Saudi Arabia (latitude, 24.6 N). Vitamin D deficiency was defined based on the cutoff recommendations by Institute of Medicine (IOM) that has been supported by the national consensus for the correction of vitamin D deficiency in Saudi Arabia [14, 15]. Ethical approval was granted by King Abdulaziz City for Science and Technology (KACST), Riyadh, Saudi Arabia, in accordance with the principles of Helsinki Declaration. Permission to conduct the study was also obtained from the Ministry of Education (directorate of school girl's health). Informed consent and assent (for those less than 18 years old) were collected. All consenting participants completed a questionnaire which included basic demographic data, medical history related to bone health and life style data. All girls completed a questionnaire of 34 items, which included basic demographic data, medical history related to bone health and lifestyle data. Direct sun exposure to the face and arms in minutes per day during weekdays and weekend in the last week was recorded. Dietary intake including vitamin D and calcium using the 7-day semi-quantitative food frequency questionnaires were adapted for use from previous local studies [16, 17]. The questionnaire consisted of Saudi food list, definition of portion sizes, and frequency of consumption with emphasis on dietary calcium—in dairy or nondairy products, supplements, or foods fortified with vitamin D. A general practitioner obtained anthropometric data. Height (cm) was obtained using a standard stadiometer and weight (kg)—without shoes—were measured.

Blood collection and analysis

Fasting serum samples were obtained by two experienced nurses. The serum levels of calcium, phosphorous, and alkaline phosphate were determined using dimension Xpand plus autoanalyzer (Siemens Healthcare Diagnostic, Erlangen, Germany). Serum 25(OH)D was measured using electrochemiluminescence binding assay (limit of detection 7.5 nmol/l) (Roche Cobas e 411 analyzer, IN, USA). These were performed in A RIQAS-Randox International Quality Assessment Scheme certified laboratory at King Khalid University Hospital, Riyadh, Saudi Arabia. The intra-assay coefficient variation was 2.2–6.8, while the inter-assay variability was 3.4–13%. Serum parathyroid hormone (PTH) was measured using electrochemiluminescence assay (Roche-molecular E-170). Carboxy-terminal collagen crosslinks (CTX) and osteocalcin were also determined using the Roche automated system. Immunoglobulin A (anti-tissue transglutaminase) antibodies were screened using ELISA (ETI MAX 3000, Diasorin, Italy). According to the manufacturer, the cutoff volume for a positive test was set at 20 relative units (RU)/ml and above. Results below 20 RU/ml are considered negative. Samples were also tested for total IgA levels (normal 0.7–3.12 g/l) by nephelometry technique using BNProspec (Siemens, Germany). Those with low total IgA and negative IgA-tTG antibodies were tested for IgG-tTG antibodies to exclude a false negative result [18].

Data analysis

The Statistical Package for Social Sciences version 21 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Descriptive statistics (mean, standard deviation, and percentages) were used to describe the quantitative and categorical variables. All continuous variables were checked for normality and transformed prior to parametric tests. Student's *t* test for independent samples was used to compare the mean values of participants with positive IgA-tTG antibodies and those whose test was negative. Linear regression was done to determine the association between 25(OH)D and IgA-tTG antibodies. Odds ratio was used to determine the association of CD to vitamin D status using positive TtG test as the dependent variable and severe vitamin D deficiency (25(OH)D < 12.5 nmol/l) as independent variable. Lastly, receiver operating characteristic (ROC) analysis was done to determine sensitivity and specificity for celiac immunity. A p value of < 0.05 was considered significant.

Results

Table 1 shows the anthropometric and biochemical data of all participants according to IgA-tTG antibody status. With the exception of serum 25(OH)D in which those who were screened positive had significantly lower levels than those who screened negative ($p = 0.0001$), all clinical and biochemical indices were not significantly different from one another. Furthermore, all girls had minimal exposure to sunlight. Nevertheless, this did not affect the vitamin D status ($p = 0.49$). Vitamin D intake was minimal with 55% of the girls consuming < 1 cup of milk/day, 35% consuming 1–3 cups/day, and 10% consuming 4 or more cups of milk/day (one cup has 100 IU of vitamin D_3 fortification). Mean calcium intake was 243.4 ± 73.0 mg in the whole group and 245.6 ± 62.3 mg in the affected group ($p = 0.75$). Out of the 200 participants, 9 (4.5%) were positive for IgA-tTG antibodies. Only one tested negative for IgA-tTG antibodies who had a low total IgA level (0.45 g/l) was found to have negative IgG-tTG antibodies. Furthermore, 50 participants (25%) had severe vitamin D deficiency (25(OH)D < 12.5 nmol/l) and within this group, 9 (18%) or almost 1 out of every 5 severely deficient adolescent female participant was positive for IgA-tTG antibodies (not found in table). The odds of having positive antibodies is 37.2 times higher for participants with 25(OH)D < 12.5 nmol/l than those whose vitamin D status was higher but still within the deficient range [OR = 37.2

Table 1 General characteristics according to CD screening outcome

Parameter	Positive tTG Ab	Negative tTG Ab	*p* value
N	9	191	
Age (years)	16.9 ± 1.29	16.6 ± 1.3	0.34
Height (cm)	153.4 ± 19.60	152.3 ± 5.6	0.10
Weight (kg)	55.8 ± 13.6	55.8 ± 8.4	0.79
Calcium (2.1–2.5 nmol/l)	2.3 ± 0.1	2.3 ± 0.2	0.54
Alkaline phosphate (35–100 u/l)	140.9 ± 112.8	126.9 ± 38.2	0.13
PTH (1.3–6.8 pmol/l)	5.0 ± 1.5	9.2 ± 0.7	0.16
Osteocalcin (11–43 ng/ml)	41.1 ± 20.7	37.08 ± 14.07	0.61
ß-CTX (0.10–5.94 μg/l)	0.5 ± 0.3	0.5 ± 0.2	0.52
25(OH)D (50–125 nmol/l)	9.44 ± 1.7	17.5 ± 6.4	0.0001
Exposure to sun in minutes/day	2.2 ± 0.7	2.1 ± 0.7	0.49

Data presented as mean ± SD. Significant at $p < 0.05$

(95% CI 4.6–299.7) ($p = 0.00002$)]. Figure 1 shows the strong significant inverse association between levels IgA-tTG antibodies and 25(OH)D ($R = -0.53$; $p < 0.001$) among antibody-negative participants. None of the girls with positive anti-tTG antibodies had history of diarrhea. Lastly, area under the ROC curve using 25(OH)D cutoff ≤ 12.5 nmol/l revealed a sensitivity of 100% (CI 66.4–100) and a specificity of 79.1% (CI 72.6–84.6) ($p < 0.001$) (Fig. 2).

Discussion

The two main sources of vitamin D are its synthesis in the skin under exposure to ultraviolet radiation and dietary intake of natural vitamin D sources [19, 20]. Although the contribution from dietary sources is much less than skin production of cholecalciferol, adequate dietary intake and absorption may become important when adequate sun exposure is not sufficient [21].

The present study adds one more confounding factor to the vitamin D deficiency complicated by the coexistence of CD in patients already deficient through poor sun exposure. Interestingly, all girls with positive IgA-tTG antibodies had vitamin D levels below 12.5 nmol/l in the absence of the well-known traditional symptoms of CD such as diarrhea, abdominal bloating, or abdominal pain. Furthermore, the strong inverse association between vitamin D status and tTG titer among participants with negative IgA-tTG antibodies implicate that vitamin D levels on the extreme low is suggestive of elevated IgA-tTG antibodies and, therefore, a risk for CD. The impact of CD on the bone has been suggested by Armagan et al. who showed that in premenopausal women with idiopathic osteoporosis, serologic tests were positive in 19% and 10.1% for IgA anti-gliadin antibodies and IgA endomysial antibodies, respectively [22]. Karakan et al. found positive IgA anti-endomysial antibody in 9.6% of 135 Turkish patients with idiopathic osteopenia [23]. In these studies, the impact of CD on bone metabolism was attributed to reduced calcium absorption and hypovitaminosis D [24, 25].

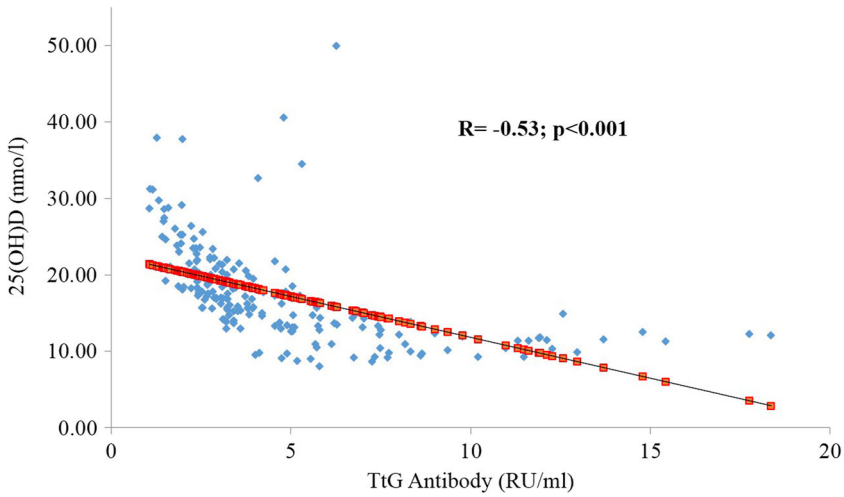

Fig. 1 Significant inverse association between tTG antibody and 25(OH)D levels among participants with negative tTG antibody

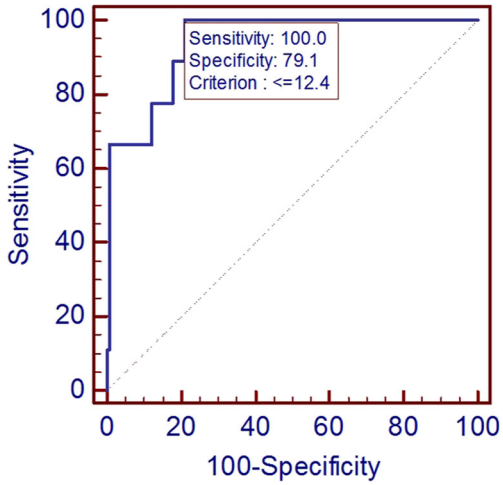

Fig. 2 Sensitivity and specificity AUC for detecting positive IgA tTG at 25(OH)D level < 12.5 nmol/l

Interestingly, Kavuncu et al. found no such association in Turkish postmenopausal women [26]. In our population, the effects of CD on 25(OH)D levels were not accompanied with a rise in PTH levels and this could be related to magnesium deficiency [27]. Intracellular reductions in magnesium can result in a paradoxical block of PTH secretion possibly due to the effects of intracellular magnesium on the alpha subunits of the G proteins associated with the calcium-sensing receptor [28, 29].

The question that needs to be addressed is whether universal screening for CD is justified for patients with severe vitamin D deficiency. This issue may be difficult. The American College of Gastroenterology (ACG) stated that metabolic bone disease and osteoporosis were among the conditions in which CD occurs more frequently than in the general population [30] Although vitamin D deficiency was not particularly included among conditions which require screening for CD, ACG recommended screening for "patients with symptoms, signs, or laboratory evidence for which CD is a treatable cause" [30]. The US Preventive Services Task Force recommendation regarding screening for CD was that "the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic persons." [31]. The NICE guidelines for the recognition, assessment, and management of CD did not include hypovitaminosis D among their list of cases which deserve screening for the disease [32]. Different societies have agreed that screening for CD is needed in high-risk patients with autoimmune disease history such as type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune liver disease, Turner syndrome, Down syndrome, and those with positive family history of CD [30–32]. Exclusion of CD has been suggested when there is lack of response to vitamin D supplementation. Previous studies suggested that severe vitamin D deficiency with clinical presentation of rickets may be an indication to exclude CD. Assiri et al. diagnosed CD in 38.4% of 26 Saudi children with unexplained rickets [33]. CD was previously reported to be responsible for initial presentation of osteomalacia [34]. Many of these evidences were reported as case reports [35–40]. In the series of Gifre involving 28 cases of osteomalacia, CD was responsible for 10% of the cases [41]. The present data suggests that in addition to the indications for CD screening, exclusion of CD may be recommended in individuals with 25(OH)D levels below 12.5 nmol/l even if there is evidence of lack of direct sun exposure. Despite that mass screening of CD meets WHO criteria for general screening, there is still a debate whether mass screening for CD in the general population or low-risk groups is justified [42–44]. However, in a targeted population such as those with severe vitamin D deficiency, a case can be made for screening for CD [45]. This is important as CD was found to be associated with reduced bone mineral density and increased FRAX scores in the US National Health and Nutrition Examination Survey [46]. Exceptions to such screening would be if there is another obvious cause such as previous bariatric surgery for example.

The study has some limitations. The small sample size has limited the analysis in performing further stratifications on vitamin D status. Intestinal biopsies were not performed, and such CD is presumptive, not definite. This is relevant as we only used serology for diagnosing CD. The association in our study was found in patients with tTG antibodies of ≥ 20 RU/ml. Titers higher than 100 RU/ml or as much as 10 times the upper limit of normal are currently considered highly predictive of the disease [47, 48]. Accordingly, it has been suggested that as tTG antibody levels increase, there is a corresponding increased risk for having CD. This same pattern could display a spectrum where levels below 20 RU/ml might be associated with severe 25(OH)D deficiency as shown in Fig. 1. The association however needs further investigation with respect to the limitations of the present study. Causality cannot be inferred because of the cross-sectional design. In addition, response of gluten-free diet on their 25(OH)D levels was not taken into account. Nevertheless, it is the first study to examine the clinical and biochemical variables of CD in vitamin D-deficient adolescent population. Further studies are needed to examine this association in other parts of the world, in both sexes and all age groups.

In summary, vitamin D status is inversely associated with IgA-tTG antibodies, and the chances of presumptive CD among Saudi Arab female adolescents with severe-to-extreme vitamin D deficiency is very high. The present findings call for further investigation on a larger population to determine threshold effects. Studies on other ethnicities and age groups are also recommended to confirm or refute the present study's observations. Until then, screening for CD in asymptomatic patients with severe-to-extreme vitamin D deficiency should be considered on an individual basis taking into account the clinical presentation of the patient.

Compliance with ethical standards

Conflicts of interest None.

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