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Original Article

Coeliac autoimmunity in type I diabetes mellitus

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ABSTRACT

Background and study aims: Coeliac autoimmunity (CA) has a known association with type 1 diabetes mellitus (T1DM) for which screening is routinely recommended but less frequently followed. The impact of CA in T1DM has been variably reported. The aims of this study are as follows: (1) to study the prevalence of CA in patients with T1DM and (2) to study the impact of CA not only on nutritional parameters but also on glycaemic control, endocrine axes and bone health.

Patients and methods: Eighty-six consecutive patients with T1DM were screened for CA using immunoglobulin A (IgA) tissue transglutaminase as a marker (TTG; IgG anti-gliadin in IgA-deficient case). CA positive (CA+) cases were compared with age-matched and sex-matched CA negative (CA−) T1DM cases for anthropometry, glycaemic control (assessed by glycated haemoglobin (HbA1c) and hypoglycaemic/hyperglycaemic episodes), endocrine (thyroid function, cortisol, growth hormone (GH) axis, gonadal axes), haematological (haemoglobin, iron profile and vitamin B_{12} status) and calcium metabolism parameters and bone densitometry (by dual-energy X-ray absorptiometry (DXA)). Consenting patients with CA also underwent upper gastrointestinal (GI) endoscopy with duodenal biopsy.

Results: Out of 86 patients, 11 (12.75%) screened positive for CA (seven patients underwent duodenal biopsies which were suggestive of Marsh grade III(2), II(3) and I(2) disease). The CA+ T1DM patients were comparable with CA− T1DM in terms of anthropometry. CA+ patients had higher HbA1c (10.7 ± 1.8 vs. 8.4 ± 1.0 (93 ± 19 vs. 68 ± 11 mmol/mol); $p < 0.01$), more hypoglycaemic episodes (five vs. two; $p < 0.05$), higher prevalence of iron and vitamin B_{12} deficiency, lower insulin-like growth factor-1 (IGF-1) levels and lower bone mineral density (BMD) *z*-score at total body (−1.91 ± 1.05 vs. −0.63 ± 0.73; $p < 0.05$) and lumbar spine (−1.69 ± 0.92 vs. −0.36 ± 0.93; $p < 0.05$). The incidence of fractures in the past 3 years was also more in CA+ patients than in CA− patients (four vs. one; $p < 0.05$).

Conclusion: CA has an important autoimmune association with T1DM. The concomitant presence of CA adversely affects stature, bone health, glycaemic control and iron and B_{12} levels in T1DM. IgA sufficiency should be ensured before using an IgA-based screening test for CA.

Introduction

Coeliac disease (CD) is an autoimmune disorder of the small intestine occurring in people genetically predisposed to CD. It has a known association with T1DM. The concomitant occurrence of coeliac autoimmunity (CA) with T1DM results in poor glycaemic control, fluctuating insulin requirement, more hypoglycaemic episodes, nutritional deficiencies, poor bone health, short stature and delayed puberty [1,2]. CA in T1DM can be asymptomatic and there might be a complete absence of gastrointestinal (GI) symptoms [3]. Hence, various authorities have now come up with guidelines advocating routine screening of all T1DM patients for CA [4–7]. Even after this, the screening rate for CA in T1DM population, even in most developing countries, is not more than 40% [8]. T1DM itself may be associated with short stature, poor bone health and delayed puberty apart from increased incidence of other autoimmune endocrinopathies [9]. The concomitant presence of CA worsens all of these apart from worsening glycaemic control. CD, thus, represents an important, easily treatable, but often missed/undiagnosed, association with T1DM [1]. The primary

Abbreviations: CD, coeliac disease; T1DM, type 1 diabetes mellitus; CA, coeliac autoimmunity; TTG, tissue transglutaminase; BMC, bone mineral content; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; ELISA, enzyme-linked immunosorbent assay; CLIA, chemiluminometry; IRMA, immunoradiometric assay; RIA, radioimmunoassay; IGF, insulin-like growth factor; GI, gastrointestinal; GFD, gluten-free diet.

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aim of this study was to determine the impact of screening-identified CA on growth, bone mineralisation, haematological parameters, endocrine axes and diabetes control.

Patients and methods

The study was conducted in accordance with the code of ethics of World Medical Association (Declaration of Helsinki). After acquiring permission from the ethics committee (Ethics Committee of Topiwala National Medical College and BYL Nair Charitable Hospital), consecutive consenting (assent in age group 6–18 years) patients with T1DM attending the Diabetes Clinic at T.N. Medical College and BYL Nair Charitable Hospital, which is a large tertiary care municipal corporation hospital in Mumbai (latitude 18° 55′ N longitude72° 54′ E), were included in the study except those who met the exclusion criteria (proven secondary diabetes, type 2 diabetes mellitus and pancreatic diabetes). Patients/relatives were given a detailed explanation of the protocol before taking consent.

Patients were screened for CA by estimating immunoglobulin A (IgA) levels by immunoturbidimetry followed by IgA tissue transglutaminase (TTG) levels in IgA-sufficient cases (by enzyme-linked immunosorbent assay (ELISA) from genesis diagnostics) and IgG anti-gliadin levels in IgA-deficient cases (also by ELISA). Tests were done in duplicate and only the doubly confirmed patients were labelled CA+. Consenting patients underwent upper GI endoscopy ($n = 7$) with duodenal biopsy. CA+ ($n = 11$) T1DM patients were compared with age-matched and sex-matched T1DM controls who were CA− ($n = 22$). One patient who had IgA deficiency had trismus due to oromucosal infection and thereby did not undergo endoscopy. Three patients did not undergo endoscopy and knowingly refused for the same.

Glycaemic control was assessed by estimating levels of glycated haemoglobin (HbA1c; at least two values in last 1 year were averaged) using ion exchange resin chromatography. In addition, the number of hypoglycaemic episodes as well as ketoacidotic episodes were obtained by recall history and hospital records. Haematological parameters assessed included haemogram, serum iron profile (serum iron, total iron-binding capacity, saturation index and ferritin level) and vitamin B_{12} levels (chemiluminometry (CLIA)). Iron deficiency was defined by low serum iron level and percentage saturation. Endocrine axes' assessment included a thyroid function (free T4 estimated by radioimmunoassay (RIA) by Immunotech by Beckman Coulter, Czech republic, Murmanska; analytical sensitivity (AS) < 0.1 ng/ml) and TSH (by immunoradiometric assay (IRMA) Immunotech; AS < 0.1 μIU/ml), antithyroid antibodies (by microtitre particle agglutination), cortisol (by RIA Immunotech; AS < 0.2 mcg/dL), insulin-like growth factor-1 (IGF-1; IRMA Immunotech; AS < 2 ng/ml), IGF-BP3 (IRMA Beckman; AS < 0.5 ng/ml), testosterone (RIA Immunotech; AS < 0.1 ng/ml) and follicle-stimulating hormone (FSH; IRMA Immunotech; AS < 0.3 μIU/ml). Patients having documented thyroid-stimulating hormone (TSH) > 10 at least once were labelled to have overt hypothyroidism. Calcium metabolism parameters assayed were serum calcium, phosphorus, albumin, alkaline phosphatase, serum creatinine, 25(OH) vitamin D_3 (RIA by Biosource at San Diego, USA; AS – 0.5 ng/ml) and intact parathormone (PTH; IRMA by Immunotech; AS < 0.2 pg/ml). Vitamin D deficiency/insufficiency was defined as vitamin D level <30 ng/ml. Bone mineral content (BMC) and bone mineral density (BMD; BMC divided by bone area) measurements of lumbar spine (LS) (L2–L4), total body (TB) and left femur were obtained by dual-energy X-ray absorptiometry (DXA) scan, which was done on a Single Lunar Prodigy machine by GE medical systems at Chalfort, UK (model number DF+14230) with daily quality control by the manufacturer. Precision of individual technologist for TB, lumbar spine and femoral neck was 1%, 0.9% and 1.1%, respectively. The BMC was adjusted for age, sex and pubertal status as per the model suggested by Warner et al. [10].

Statistical analysis was done using SPSS version 19. Subjects were divided into those with CA+ ($n = 11$) and CA− ($n = 22$) age-matched and sex-matched T1DM cases as controls. Mean ± standard deviation (SD) was given as descriptive statistics. Log transformations were applied to highly skewed variables. Chi-square test of independence or Fisher's exact test was used to test the distribution of discrete variables. The Wilcoxon rank sum test was used to test the difference amongst groups in continuous variables at baseline. A p value <0.05 was considered significant.

Results

Eighty-six consecutive T1DM patients were screened for the study, of whom 85 were IgA sufficient and one was IgA deficient. Of the 85 IgA sufficient patients, 10 had increased IgA TTG levels confirming CA positivity. Seven out of these 10 underwent upper GI endoscopy. Two had Marsh grade 3 disease, three had Marsh grade 2 and two had Marsh grade 1. One patient who was IgA deficient had increased IgG anti-gliadin levels which was the only IgG-based test available. In addition, he had oral abscesses and trismus and so upper GI endoscopy was not possible. Hence, we had a seroprevalence of CA of 12.75% (11 out 86), 10.1% (6/59 males) and 18.51% (5/27 females). The age range was 12–44 years. On retrospective enquiry, seven patients had GI symptoms, six had neuropsychiatric disturbances, five had anaemia, four had fracture/fractures in past 3 years, four females had menstrual irregularity and one was being worked up for infertility. Two children aged 12 and 15 years had concerns about short stature.

There was no difference in age, sex and duration of diabetes mellitus (DM) in the two groups. The groups were comparable in terms of height, weight, body mass index (BMI) and body fat content. All three patients who were below the age of 18 years lagged behind in their height by −3.0, −1.9 and −3.6 SD and in their weight by −2.9, −2.7 and −1.5 SD. The height, weight and BMI standard deviation score (SDS) of these children are shown in Table 1. T1DM patients who were CA+ had poor glycaemic control compared with CA− patients (HbA1c 10.7 ± 1.8 vs. 8.4 ± 1.0 (93 ± 19 vs. 68 ± 11); $p < 0.05$). The number of severe hypoglycaemic episodes (hypoglycaemic episodes requiring other persons' assistance for recovery or requiring hospitalisation) was more in CA+ compared with CA− (five vs. two; $p < 0.05$). The number of subjects having ketoacidotic episodes was also more in the CA+ group compared with CA− but the result was not statistically significant (four vs. two; $p = 0.06$). Out of the four CA+ patients who had ketoacidotic episodes, three required admission more than once in past 3 years for diabetic ketoacidosis. The insulin requirement per kilogram body weight in the two groups was not significantly different (1.08 + 0.43 U/kg vs. 0.97 + 0.26 U/kg; $p = 0.40$). Moreover, CA+ patients had more number of both hypoglycaemic and ketoacidotic episodes reflecting that CA is responsible for glycaemic variation on either side (Table 2).

There was no difference in the haemoglobin levels in the two groups; however, both iron and vitamin B_{12} deficiency were more common in CA+ T1DM cases compared with CA− T1DM cases. All CA+ patients and nine of 22 CA− patients were iron deficient (low

Table 1
Anthropometry standard deviation score of CA positive cases <18 years old.

Sex/age	Height	Weight	BMI
12/M	−3	−2.9	−1.1
13/M	−1.9	−2.7	−2.5
15/F	−3.6	−1.5	−0.9