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INCREASED PREVALENCE OF FRACTURE AND HYPOGLYCAEMIA IN YOUNG ADULTS WITH CONCOMITANT TYPE 1 DIABETES MELLITUS AND COELIAC DISEASE

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Conflicts of Interest

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ABSTRACT

Background: Both Type 1 diabetes mellitus (T1DM) and coeliac disease (CD) are independently associated with reduced bone mineral density (BMD) and increased fracture risk. Whilst poorer glycaemic control and increased microvascular complications have been described, the literature examining bone health and fractures in adults with concomitant T1DM and CD (T1DM+CD) is limited.

Objective: To evaluate fracture prevalence and explore associations with glycaemic control, hypoglycaemia and microvascular disease in T1DM+CD compared with T1DM alone.

Methods: We conducted a retrospective cross-sectional study of young adults with T1DM, who attended diabetes clinics at a large tertiary referral centre between August 2016 and February 2017. Clinical information, radiological and biochemistry results were extracted from medical records. Patients with comorbid chronic kidney disease, glucocorticoid use, hypogonadism and untreated hyperthyroidism were excluded.

Results: 346 patients with T1DM alone (median age 23 years) and 49 patients with T1DM+CD (median age 24 years) were included. Median age, gender distribution, BMI, haemoglobin A1c, daily insulin dose and serum 25-hydroxyvitamin D levels were similar between groups. Higher adjusted fracture risk was observed in T1DM+CD compared with T1DM (12.2% vs. 3.5%; OR 3.50, 95% CI 1.01–12.12, $p=0.01$), yet bone mineral density was only measured in 6% of patients. The adjusted risk of hypoglycaemia ≥ 2 /week was greater for T1DM+CD (55% vs. 38%, OR 3.28, 95% CI 1.61–6.69, $p=0.001$), however this was not independently associated with fractures. Replete vitamin D (≥ 50 nmol/L) was

associated with less hypoglycaemia (OR 0.48, 95% CI 0.29-0.80; $p=0.005$), but not with fractures.

Conclusions: CD status was independently associated with increased fracture prevalence in young adults with T1DM. Recurrent hypoglycaemia was also increased in T1DM+CD, although hypoglycaemia was not independently associated with fractures. Prospective studies are required to determine the long-term impacts of CD on bone health and on glycemic control in T1DM.

Introduction

The association between Type 1 diabetes mellitus (T1DM) and coeliac disease is well described. Coeliac disease (CD) is an autoimmune condition characterized by gluten-induced enteropathy, with a global prevalence of 3-16% in individuals with T1DM (1, 2). Both these autoimmune conditions share similar genetic and environmental risk factors (3), which may explain the 4-6 fold increased prevalence of CD in T1DM, compared with the general population (4). The diagnosis of CD is made by serological tests and confirmed on duodenal biopsy (5). The hallmark of this condition is duodenal villous atrophy and intraepithelial lymphocytosis, which may give rise to nutrient deficiencies and gastrointestinal symptoms. However, not all cases present with overt symptoms, and children with T1DM are more likely to have subclinical disease (6), potentially manifesting as increased glycaemic variability and hypoglycaemia, growth failure and decreased bone mass (6-8).

An increased risk of microvascular complications (9, 10) has been reported in patients with concomitant T1DM and coeliac disease (T1DM+CD). The mechanism by which CD may impact on microvascular disease in T1DM is unclear. The causes are likely to be multifactorial and include chronic inflammation, nutritional deficiencies and endothelial dysfunction. (9). CD is also a recognized risk factor for secondary osteoporosis and fracture (11, 12). The main driver of bone loss is thought to be calcium malabsorption and vitamin D deficiency, leading to secondary hyperparathyroidism. Hypogonadotropic hypogonadism is also associated with CD, and this may contribute to further bone loss (11).

T1DM is associated with impaired bone quality and increased fracture rates. Recent large observational studies and meta-analyses have reported a 2-7 fold greater risk of hip fracture in patients with T1DM compared with non-diabetic controls (13-15). Osteoblast dysfunction,

disruption of collagen cross-linking, altered bone material properties, and calcium and vitamin D deficiency have been postulated as mechanisms for skeletal fragility in T1DM (16). The risk of impaired bone microarchitecture and fracture appear to be greater in those with poor glycaemic control and microvascular complications (17, 18).

As T1DM and CD are both associated with bone fragility and fracture risk, this may be additive in T1DM+CD. Few studies have evaluated bone health in those with T1DM+CD, with some studies suggesting a negative impact on bone mineral density (BMD) (7, 19, 20), whereas a large cohort study did not demonstrate increased fracture risk (21). These studies were primarily conducted in children and extrapolation of results to an adult population, is potentially inappropriate. We therefore aimed to investigate the relationship between CD status on fracture rates in young adults with T1DM, and explore potential interactions between hypoglycaemia, glycaemic control and microvascular complications with fracture risk.

Methods

Patients

We retrospectively reviewed medical records of patients attending specialist diabetes outpatient clinics between August 2016 to February 2017 at Monash Health, a large tertiary centre and accredited Australian centre of excellence in diabetes. All patients attending with T1DM aged between 18 to 45 years of age were included in the study, except those with comorbid end-stage kidney disease, previous transplantation, glucocorticoid use, malignancy, hypogonadism and untreated hyperthyroidism, who were excluded. A history of hypogonadism was established from the medical record, defined in males as the use of androgen-replacement therapy or low testosterone levels (<8 nmol/L), documented on two separate occasions. In females, hypogonadism was defined as the use of hormone-replacement therapy (HRT) for induction of pubertal development, menopause before the age of 40 years, or documentation of low estradiol levels (<73 pmol/L), on two separate occasions at least 6 months apart. In addition, females with documented amenorrhea (of greater than 3 months duration) or individuals with eating disorders were excluded from the study.

Clinical information pertaining to previous fracture, duration of T1DM, glycaemic control, height and weight, hypoglycaemia, daily dose of insulin, microvascular complications and

coeliac disease status were obtained from medical records, radiological and laboratory reports. This study was approved by the Monash Health Human Research Ethics Committee.

Type 1 diabetes mellitus and coeliac disease

The diagnosis of T1DM was confirmed on medical records or biochemically on antibody positivity to glutamic acid decarboxylase (GAD) and/or islet antigen-2 (IA-2). All patients with T1DM were screened for coeliac disease with deamidated gliadin and tissue transglutaminase (tTG) antibody testing, as part of an annual complication and autoimmune disease screening policy. Patients were classified as having CD based on sero-positivity to coeliac antibodies and/or histological evidence of villous atrophy on small bowel biopsy. Information regarding documented gastrointestinal symptoms and adherence to a gluten-free diet (GFD) in individuals with coeliac disease were also obtained.

Other auto-immune diseases

One individual in the T1DM+CD group and three individuals in the T1DM group had Graves' disease, all of whom were biochemically euthyroid for at least 3 months prior to inclusion into the study. Fifteen individuals had established hypothyroidism (T1DM+CD, n=3; T1DM only, n=12) and all were biochemically euthyroid. No individual in the study had Addison's disease. Two individuals from the T1DM group had rheumatoid arthritis, and neither reported glucocorticoid therapy.

Laboratory analyses

Biochemical tests were performed in 3 different laboratories, with the exception of whole blood haemoglobin A1c (HbA1c) which was measured by ion-exchange high performance liquid chromatography via Arkray Adams-A1c HA-8160 (Arkray Inc., Kyoto, Japan) at a single laboratory. HbA1c was reported as percentage of glycated haemoglobin (National Glycohaemoglobin Standardisation Program) and in mmol/mol (International Federation of Clinical Chemistry). Serum creatinine and urinary albumin-to-creatinine ratio were measured on the Beckman Coulter AU 5800 (Beckman Coulter, Brea, CA, USA), Roche Cobas Integra (Roche Diagnostics Ltd., Switzerland) and Siemens Advia (Siemens Corp., Tarrytown, NY, USA) platforms, respectively, at each laboratory. Serum 25-hydroxyvitamin D levels were measured using the same Diasorin Liason XL assay (DiaSorin Inc, Stillwater, MN, USA) at all 3 laboratories. A serum 25-hydroxyvitamin D level of ≥ 50 nmol/L was used as a cut-off for vitamin D sufficiency. Calculation of estimated glomerular filtration rate (eGFR) was

based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (22). Urinary albumin and antibodies to GAD and IA-2 were detected by an enzyme-linked immunofluorescence assay ELISA. Antibodies to deamidated gliadin and tTG were detected using a Luminex-based assay.

Fractures

All prevalent fractures, occurring after the diagnosis of T1DM and/or coeliac disease, were verified by radiological reports and medical records. Information on fracture mechanisms, age and site at which the fracture(s) occurred in each patient, were also collected.

Hypoglycaemia

Patients' glucose monitoring devices or logbooks were reviewed in clinic by experienced clinicians to evaluate the presence and frequency of hypoglycaemia, defined by a recorded capillary blood glucose concentration of ≤ 3.9 mmol/L. Recorded hypoglycaemia was noted and we were able to directly verify the frequency of hypoglycaemia in all patients on continuous subcutaneous insulin infusion (CSII) therapy, from blood glucose log printouts in individual medical records. Hypoglycaemic events were considered a frequent occurrence if two or more events per week, on average, were documented or captured. Frequency of hypoglycaemia was further stratified into: infrequent, 2-4 episodes per week, 5-9 episodes per week and >9 episodes per week. Severe hypoglycaemia was deemed as an episode associated with impaired consciousness or requiring third-party assistance (23).

Microvascular complications

Microvascular diabetic complications were evaluated at least annually. Documented diagnosis of diabetic retinopathy was confirmed on ophthalmology or optometry reports. The presence of microalbuminuria was determined by an albumin-to-creatinine ratio of greater than 3.5mg/mmol (30mg/g) (24), confirmed on at least two occasions. Neuropathy was assessed in the clinic by vibration, pressure sensation (10g monofilament test applied at the distal hallux) or pinprick testing. Examination findings were documented in medical records.

Statistical analyses

Results were expressed as median and interquartile ranges for continuous data and as percentages for categorical data. Continuous and categorical variables were compared using

the Mann-Whitney U test, and χ^2 and Fisher's exact test, respectively. Univariable analyses were performed, followed by multivariable regression analyses adjusting for significant and clinically relevant covariates for bone loss. Data were analysed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA).

Results

A total of 395 patients with T1DM were captured in the study, of which 346 (median age 23 years, range 20-27) had T1DM only and 49 patients (median age 24.0 years, range 23-28) had T1DM+CD. There were no differences in median age, sex, glycaemic control, serum 25-hydroxy vitamin D levels, body mass index (BMI), total daily dose of insulin between the two groups (Table 1). The use of CSII devices was also similar across the two groups (18.4% vs 24.0%, $p=0.47$). Patients with T1DM+CD had a longer median duration of T1DM (14.0 years vs. 11.0 years, $p=0.01$). Median duration of coeliac disease was 8.0 years (range 3-14). The diagnosis of coeliac disease preceded T1DM in six patients. Median serum HbA1c values (National Glycohemoglobin Standardisation Program) were similar in both groups (8.3% vs. 8.3%, $p=0.57$), as was the prevalence of microvascular complications (14.3% vs. 12.4%, $p=0.65$).

Fractures

A total of 21 fractures were documented in 18 patients. Fracture mechanisms were cross-referenced with emergency department records. In the T1DM+CD group, two of six patients (33.3%) sustained minimal trauma fractures (MTF), defined as a fracture sustained due to low impact or a fall from standing height or less. Two fractures in this group (33.3%) occurred during sport or motor vehicle accidents. Three out of 12 patients (25%) patients in the T1DM only group had MTF. Seven fractures in this group (58.3%) were sport- or motor vehicle accident-related. The mechanism of fracture for four patients (2 in each group) was unable to be determined. Median age at fracture was 18 and 21 years in the T1+CD and T1DM alone groups, respectively, with the highest proportion of fractures occurring at the radius and tibia/fibula (Table 2).

Overall, a higher proportion of patients had documented fractures in the T1DM+CD group, compared to the T1DM only group (12.2% vs. 3.5%, $p=0.02$). However, there was no difference in MTF prevalence between the two groups (33.3% vs 25.0%, $p=1.00$). Despite the increased risk of malabsorption and fracture in the T1DM+CD group, only 3 patients (6.1%)

had documented evaluation of their bone mineral density (BMD) within the last 5 years. Information regarding dietary calcium intake was not consistently assessed in patients with T1DM+CD and T1DM alone. No patients had documented calcium supplementation. There were no significant differences between the proportion of patients who were vitamin D sufficient (36.6% vs. 42.1%, $p=0.61$), and who received supplementation with vitamin D (14.3% vs. 18.2%, $p=0.69$) between the T1DM+CD and T1DM only groups. In the univariate analysis, CD status was independently associated with fracture (OR 3.88, 95% CI: 1.39-10.88, $p=0.01$); no associations were observed for duration of T1DM, HbA1c, presence of microvascular complications or vitamin D status with fracture. The relationship between CD and fractures remained significant after adjustment for age, sex, BMI, vitamin D status, hypoglycaemia, microvascular complications and HbA1c (OR 3.50, 95% CI 1.01-12.12; $p<0.05$).

Hypoglycaemia

T1DM+CD patients had a higher prevalence of frequent hypoglycaemia (≥ 2 episodes per week) compared with T1DM alone (55.1% vs. 37.7%, $p<0.001$). When hypoglycaemia frequency was stratified by episodes per week, there was a higher proportion of patients with T1DM+CD with 2-4 episodes per week (36.7% vs. 22.3%, $p=0.03$) and 5-9 episodes per week (14.3% vs. 4.3%, $p=0.01$) compared with T1DM alone. The proportion of patients with >9 hypoglycaemic episodes per week (4.1% vs. 1.2%, $p=0.16$), and severe hypoglycaemia (10.2% vs. 5.5%, $p=0.20$) were similar in both groups (Table 3). In the univariate analysis, duration of T1DM, HbA1c, vitamin D sufficiency and CD status were significantly associated with hypoglycaemia. After adjustment for age, sex, duration of diabetes, HbA1c, BMI and total daily dose of insulin, the relationship between CD status and hypoglycaemia remained significant (OR 3.28, 95% CI 1.61–6.69, $p=0.001$). Although age was not associated with hypoglycaemia in the univariate analysis, this relationship became significant after adjustment for clinically relevant risk factors (OR 0.94, 95% CI 0.89-0.99, $p = 0.03$) [Table 4].

Higher HbA1c value (OR 0.71, 95% CI 0.60-0.85, $p<0.001$) and serum vitamin D level ≥ 50 nmol/L (OR 0.48, 95% CI: 0.29-0.80, $p=0.005$) were associated with a reduced risk of hypoglycaemia; the relationships of both covariates with hypoglycaemia were strengthened in the multivariable logistic regression. Conversely, a longer duration of T1DM, was observed to increase the risk of hypoglycaemia (OR 1.05, 95% CI: 1.01-1.10, $p = 0.01$) [Table 4]. The duration of CD had no effect on hypoglycaemia ($p=0.56$).

Coeliac disease

Thirty-six out of 49 patients (73.5%) in the T1DM+CD group had documented compliance with a GFD. The majority of those who were non-compliant (12 out of 13 patients with CD) reported an absence of classical gastrointestinal symptoms due to coeliac disease, and this may partly explain the non-compliance to a gluten-free diet. Adherence to a GFD was not associated with hypoglycaemia or fracture risk. Only 11 patients (22.4%) had ongoing gastroenterology follow-up.

Discussion

In this cross-sectional study of young adults with T1DM attending diabetes outpatient clinics at a large tertiary hospital, reported prevalence of fractures was increased in patients with T1DM+CD compared to T1DM alone, with few documented bone mineral density measurements. Reported hypoglycaemia was also increased and independently associated with CD status in T1DM, although glycaemic control and prevalence of microvascular complications were similar between groups. Associations between coeliac disease and fracture were significant after adjustment for various risk factors, including age, sex, BMI, vitamin D status, glycaemic control and microvascular complications; however hypoglycaemia was not independently associated with fracture. Replete vitamin D (≥ 50 nmol/L) was associated with less hypoglycaemia (OR 0.48, 95%CI 0.29-0.80; $p=0.005$), but not with fractures.

Up to 70% of patients with coeliac disease have low BMD, with appendicular sites rich in cortical bone being more affected than the axial skeleton (11). While Australian and British Gastroenterology guidelines have recommended assessment of BMD at baseline (5, 25), an overall consensus has not yet been reached on either the necessity or timing of BMD assessment (8). Strict adherence to a GFD is the mainstay of treatment in coeliac disease and, together with adequate calcium intake and optimal vitamin D, has been shown to restore BMD to normal levels in children, although this may not always be the case in adults (11). The propensity to fracture is increased in individuals with CD. A recent meta-analysis demonstrated that compared to controls, patients diagnosed with CD had a 69% and 30% increased risk of hip and any fractures, respectively (12). Studies examining fracture outcomes in adults with T1DM+CD are scarce. A prospective cohort study of over 5,000 Swedish patients with T1DM did not demonstrate an increased risk of fracture in those with

concomitant CD, compared to T1DM alone (21). However, there were several limitations of the study, including the large patient age range (4-71 years), incomplete reporting of fractures, and lack of information on glycaemic control and adherence to a GFD. In contrast, Weber et al. observed a significantly increased fracture risk in females with T1DM+CD compared to non-diabetic individuals (hazard ratio 1.8), in a large population-based cohort study in the United Kingdom (13). Whilst the absolute risk of fracture in young adults with chronic disease can be difficult to assess, the increased prevalence of fracture in those with T1DM+CD in our study highlights a gap in current literature of bone health and fracture outcomes in this population.

Hypoglycaemia is a complication of insulin therapy in T1DM and leads to considerable morbidity and psychological distress (23). The phenomenon of increased hypoglycaemia in adults with T1DM+CD was first described in 1978 by Walsh et al. (26), who noted “troublesome hypoglycaemia” and unstable glycaemic control in 14 cases, since confirmed in other reports (27, 28). Intestinal mucosal changes associated with coeliac disease are thought to interfere with carbohydrate absorption, leading to increased glycaemic variability and hypoglycaemia (27). In 124 adults with T1DM with severe and recurrent hypoglycaemia who met the criteria for islet cell transplantation, the prevalence of coeliac disease was 8%; 7 out of 10 patients were newly diagnosed with coeliac disease (29). A nationwide Swedish study reported that the risk of diabetic ketoacidosis and hypoglycaemia was not increased in T1DM+CD; however, only subjects who required admission to hospital for hypoglycaemia were examined, with the true incidence of hypoglycaemia likely to be underestimated (30). Our results showing that CD is independently associated with reported hypoglycaemia, is consistent with much of the published literature, showing the need for greater vigilance in T1DM+CD. Here with relatively small numbers reporting non-compliance to a GFD, we did not show a relationship with compliance and hypoglycaemia, yet others have shown that adherence to a strict GFD may benefit patients who suffer from recurrent hypoglycaemia (27).

Recurrent hypoglycaemic events can lower the hypoglycaemic threshold at which symptoms occur in an individual, due to attenuation of the sympatho-adrenal response (23). Impaired hypoglycaemic awareness increases the severity of hypoglycaemia and is a significant risk factor for falls and serious injury. Musculoskeletal injuries and vertebral fractures have been reported in patients with T1DM in the setting of hypoglycaemic convulsions (31). Although we did not observe an independent association between hypoglycaemia and fracture in our

study, this can be attributed to reduced statistical power, given the relatively small number of reported fractures.

Vitamin D deficiency is prevalent in individuals with T1DM (32), and this may be exacerbated by concomitant CD. The proportion of patients with vitamin D insufficiency in our study was 36.6% and 42.2% in the T1DM+CD and T1DM group, respectively. This is comparable to the general Australian population, where up to 50% of Australians are vitamin D deficient, depending on the season (33). We found that a serum 25-hydroxyvitamin D level of ≥ 50 nmol/L was inversely associated with hypoglycaemia. Only one other study has reported an increased frequency of hypoglycaemia associated with vitamin D deficiency in T1DM, albeit in a paediatric cohort (34). Although the mechanism by which vitamin D is related to hypoglycaemia is unclear, it has also been linked to adverse cardio-metabolic outcomes in patients with T1DM (35). Overall as proposed in other conditions, vitamin D levels may be a surrogate marker of general nutrition and health in this population.

In comparison to a large German-Austrian cohort study by Rohrer et al., (10), where coeliac disease was found to be an independent risk factor for the development of retinopathy and nephropathy, we did not find an increased risk of microvascular complications in our study. However, the development of retinopathy and nephropathy in patients with T1DM and coeliac disease in that study occurred at median diabetes durations of 18.6 and 24.1 years, respectively. In our study, the median duration of diabetes was 14 and 11 years in the T1DM+CD and T1DM groups, respectively, and this may not have allowed sufficient time for microvascular complications to develop.

Strengths & limitations

There are several limitations of this study. Firstly, given the observational and retrospective study design, only documented fractures and hypoglycaemic episodes could be captured and data may be incomplete. The correlation of fracture risk to BMD was not possible, as few had bone densitometry. Calcium and PTH levels were not routinely measured. In a cohort at risk of vitamin D deficiency and malabsorption, calcium, PTH levels and other bone turnover markers may provide additional information on bone metabolism. Information on smoking, alcohol consumption and a family history of osteoporosis was not available for all patients. Lastly, the selection of patients attending specialist clinics at a tertiary centre may also reflect a cohort of patient with more severe or complex disease, intrinsically at greater risk of glycaemic instability and bone fragility. Strengths include that to our knowledge, this is the

first study examining fracture prevalence and exploring associations with glycaemic control and microvascular complications in young adults comparing T1DM+CD with T1DM alone. We were able to obtain detailed information from individually reviewed medical records with proformas requiring structured recording of hypoglycaemic frequency and of CD status.

Conclusion

In a large tertiary outpatient setting, adults with T1DM+CD had increased documented fractures compared to those with T1DM alone, with CD status independently associated with fractures. Despite these risks, few patients had documented bone density measurements. Hypoglycaemia was also increased and independently associated with CD, but not with fractures. Vitamin D ≥ 50 nmol/L was inversely associated with hypoglycaemia, but was not related to fractures. Awareness of bone health in patients with T1DM+CD is important. Whilst this study provides unique data on fracture outcomes and hypoglycaemia in a young adult population, additional longitudinal data including an older cohort with T1DM and CD, with a higher absolute risk of fracture, is warranted. Future prospective cohort studies examining the impact of T1DM and CD on bone density, fracture risk and glycaemic control, may help guide management and fracture risk assessment of these patients.

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Table 1. Baseline characteristics of patients

	T1+CD (n=49)	T1DM only (n=346)	p-value
Age, years	24 (23 – 28)	23 (20 – 27)	0.054
Female sex (%)	25 (51.0%)	160 (46.2%)	0.54
Duration of T1DM, years	14 (7.5 – 20.5)	10 (6 – 15)	0.01
CSII (%)	9 (18.4%)	83 (24.0%)	0.47
NGSP HbA1c, %	8.3 (7.5 – 9.2)	8.3 (7.6 – 9.7)	0.57
IFCC HbA1c, mmol/mol	67 (58 – 77)	67 (59 – 81)	0.61
eGFR	90 (0)	90 (0)	0.35
Urine ACR	0.90 (1.3)	0.90 (1.5)	0.67
25(OH) vitamin D, nmol/L	61 (42 – 74)	54 (39 – 67)	0.13
BMI, kg/m ²	24.9 (21.3 – 28.2)	25.5 (22.8 – 28.5)	0.21
Total daily insulin dose, IU	58 (34 – 60)	60 (47 – 80)	0.10
Duration of CD, years	8 (3 – 14)		
Compliance to GFD (%)	36 (73.5%)		

Interquartile ranges are expressed in brackets. CSII: continuous subcutaneous insulin infusion; NGSP: National Glycohemoglobin Standardisation Program; IFCC: International Federation of Clinical Chemistry; HbA1c: haemoglobin A1c; eGFR: estimated glomerular filtration rate; ACR: albumin-to-creatinine ratio; BMI: body mass index; CD: coeliac disease; GFD: gluten-free diet

Table 2. Fracture distribution and mechanisms

	T1+CD (n=49)	T1DM only (n=346)	p-value
Number of patients with fracture (%)	6 (12.2%)	12 (3.5%)	0.02
Female sex	2 (33.3%)	4 (33.3%)	1.00
Median age at fracture, years	18 (12 - 25)	21 (17 – 22)	0.62
Fracture mechanism			
MTF	2(33.3%)	3 (25%)	
Sport or trauma-related	2 (33.3%)	7 (58.3%)	
Indeterminate	2 (33.3%)	2 (16.7%)	
Fracture site			
Radius	3 (50%)	4 (33.3%)	
Tibia/fibula	1 (16.7%)	4 (33.3%)	
Vertebra	0	2 (16.7%)	
Rib	0	1 (8.3%)	
Foot	1 (16.7%)	1 (8.3%)	
Other	1 (16.7%)	1 (8.3%)	

MTF: minimal trauma fracture

Table 3. Glycaemic control, microvascular complications and hypoglycaemia frequency

	T1+CD (n=49)	T1DM only (n=346)	p-value
Any microvascular complication (%)	7 (14.3%)	43 (12.4%)	0.65
Retinopathy (%)	7 (14.3%)	42 (12.1%)	0.65
Nephropathy (%)	7 (14.3%)	32 (9.2%)	0.30
Neuropathy (%)	0 (0%)	9 (2.6%)	0.61
Hypoglycaemia (≥ 2 /week) [%]	27 (55.1%)	96 (27.7%)	<0.001
2 – 4 episodes/week	18 (36.7%)	77 (22.3%)	0.03
5 – 9 episodes/week	7 (14.3%)	4 (4.3%)	0.01
> 9 episodes/week	2 (4.1%)	4 (1.2%)	0.16
Severe hypoglycaemia (%)	5 (10.2%)	19 (5.5%)	0.20

Table 4. Univariable analysis and multivariable logistic regression model displaying risk factors for hypoglycaemia

	Univariable analysis				Multivariable logistic regression			
	B	OR	95% CI	p-value	B	OR	95% CI	p-value
Age	-0.13	0.99	0.95 – 1.03	0.51	-0.06	0.94 [#]	0.89 – 0.99	0.03
Duration of T1DM	0.05	1.05	1.02 – 1.08	0.002	0.05	1.05 [#]	1.01 – 1.10	0.01
HbA1c	-0.26	0.78	0.67 – 0.89	<0.001	-0.34	0.71 [#]	0.60 – 0.85	<0.001
Vitamin D sufficiency	-0.50	0.61	0.38 – 0.96	0.03	-0.74	0.48 [#]	0.29 – 0.80	0.005
Coeliac disease	1.16	3.20	1.74 – 5.88	<0.001	1.19	3.28 [#]	1.61 – 6.69	0.001

[#]Adjusted for gender, body mass index (per kg/m² increase), microvascular complications (absence/presence) and total daily dose of insulin (per international unit increase); B: beta coefficient; OR: odds ratio; CI: confidence interval.

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