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Risk factors for fragility fractures in type 1 diabetes

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ABSTRACT

Objective: To determine clinical diabetes-related risk factors for fragility fractures in type 1 diabetes (T1D).
Research design and methods: History of bone fragility fractures occurring after T1D diagnosis was assessed by questionnaire in this cross-sectional study in 600 T1D subjects. Glycated hemoglobin A1c (HbA1c) over the previous 5 years was used as an index of long-term glycemic control; complications were adjudicated by physician assessment. Multinomial logistic regression models were used to assess the associations between diabetes-related risk factors and fracture history.
Results: One-hundred-eleven patients (18.5%) reported at least one fracture; of these 73.8% had only one and 26.2% had more than one fracture. Average age was 41.9 ± 12.8 years, with even gender distribution; disease duration was 19.9 ± 12.0 years; and BMI was 24.4 ± 3.7 kg/m^2. The 5-year average HbA1c was 7.6 ± 1.0% (60 mmol/mol). In adjusted models, reduced risk for 1 fracture was found in those with higher creatinine clearance rate (CCr) (RRR 0.22 [95% CI: 0.06–0.83] for 1 unit increase in lnCCr, p = 0.03) and increased risk in those with neuropathy (RRR 2.57 [1.21–5.46], p = 0.01). Increased risk for ≥2 fractures was found in subjects in the highest tertile of HbA1c (≥7.9%) compared with the lowest tertile (≤7.17%) (RRR 3.50 [1.04–11.7], p = 0.04) and of disease duration (≥26 years versus < 14 years) (RRR 7.59 [1.60–35.98], p = 0.01).
Conclusions: Poor glycemic control and long exposure to the disease are independent diabetes-related risk factors for multiple bone fractures in T1D.

1. Introduction

Type 1 diabetes (T1D) is an autoimmune disease characterized by absolute insulin deficiency due to pancreatic beta-cell destruction and consequent hyperglycemia. Diabetes-related complications are the main cause of morbidity and mortality in subjects with T1D and bone fragility is being recognized as a new complication of both type 1 and type 2 diabetes (T2D) [1,2]. The association between diabetes and hip fracture is however stronger for T1D than (T2D) (hazard ratio [HR] 6.3 vs. 1.4) [3] and Weber et al. showed that the increased risk of hip fractures in subjects with T1D starts already in young adulthood [4]. While risk factors for fractures in T2D have been characterized [5,6], risk factors for fractures in T1D have not yet been fully elucidated. Hypoinsulinemia, low levels of IGF-1 and vitamin D, poor metabolic control, vascular complications and lipid profile [7–9] have all been studied as possible contributors to poor bone health in T1D, with controversial results [10,11]. The majority of available clinical studies in this regard are limited in the number of subjects or by the lack of information about crucial data such as metabolic control, insulin exposure or hypoglycemic events [12–14]. The incidence of T1D is

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increasing worldwide [15]. Together with an increased life expectancy as a consequence of the improving quality of care, this is causing an exponential increase in the overall number of subjects with T1D in the age range at increased risk of fragility fractures. As bone fractures are associated with increased morbidity and mortality, a better understanding of factors related to bone fragility in T1D is crucial to identify risk factors to be tackled to decrease the incidence of fractures in this population. The goal of the present study was to investigate diabetes-related clinical factors associated with non-vertebral fragility fractures in T1D.

2. Material and methods

Patients with T1D attending an outpatient clinic at one of three participating Institutions (Campus Bio-Medico University of Rome, Cattolica University of Rome and Sandro Pertini Hospital Rome, Italy) who had been followed for up to 5 years were deemed eligible for this cross-sectional study. Diabetes diagnosis was based on the American Diabetes Association criteria [16]. Every diagnosis was confirmed by Glutamic Acid Decarboxylase Autoantibodies (GADA or Anti-GAD) and Insulin Autoantibodies (IAA) or Insulinoma-Associated-2 Autoantibodies (IA-2A) tests. Moreover, patients also had c-peptide measurement. Inclusion criteria for this analysis were: age ≥18 years, and eugonadal status. The exclusion criteria were: 1) history of secondary causes of osteoporosis (i.e., non-compensated hypothyroidism, hyperthyroidism, hyperparathyroidism, inflammatory bowel disease, malignancy, anorexia nervosa, rheumatoid arthritis, severe liver impairment or chronic obstructive pulmonary disease), 2) use of drugs that can affect bone metabolism (e.g. bisphosphonates, glucocorticoids, anticonvulsants, hormone replacement therapy, denosumab, teriparatide). A total of 701 T1D patients were initially screened. After exclusion of 101 subjects according to the above mentioned criteria, 600 subjects (300 males and 300 females) were enrolled. All recruited participants gave their witnessed, informed consent before entering the study, which was approved by local ethical committees and conducted in accordance with Helsinki Declaration II.

Enrolled participants attended a study visit that included measurement of height and weight for body mass index (BMI) calculation and an interview during which the number of monthly hypoglycemic episodes and family history of fragility fractures in a blood relative (first or second degree, e.g., aunts and grandmothers) were recorded. Fractures were evaluated by a previously used questionnaire [17]. Participants were asked to report the occurrence and circumstances of any fractures after the diagnosis of T1D, including their age at the time of each reported fracture. Only non-vertebral fractures, including hip, wrist, and other non-vertebral sites (clavicle, upper arm, rib, pelvis, ankle, upper leg, lower leg, foot, hand, shoulder, knee, and elbow), and occurrence of single or multiple fractures were included in this analysis [18]. Also, the interview explored the circumstances of the fracture, in order to exclude fractures resulting from major trauma. Only low-trauma fractures caused by a fall from a standing height or less were included in this analysis [19]. We verified the occurrence of these self-reported low-trauma non vertebral fractures through medical records (e.g., hospital discharge summary, operative note, clinic visit note, or operative note) or by radiology reports (e.g., magnetic resonance imaging, computed tomography scan, or x-ray). We excluded from the analysis strains, sprains and all other types of injuries that were not bone fractures, including knee lesions or injuries.

Furthermore, medical history of the enrolled participants was obtained from clinical electronic records. To assess long-term glucose control, we considered the average of HbA1c measurements obtained by study subjects for up to 5 years before enrollment. All clinical records included the physician's evaluation of macrovascular complications, neuropathy, and retinopathy, for which we included in the analysis the status at the most recent available visit. Specifically, the presence of cardiovascular disease (CVD) was assessed as recent history or evidence of coronary heart disease, cerebrovascular disease, or peripheral arterial disease. Diabetic neuropathy evaluation was based on symptoms, quantitative sensory testing (temperature, vibration, and pressure perception) and quantitative motor testing (patellar and ankle reflexes) as assessed by the physician in the medical history. Additionally, all patients underwent funduscopic examination to assess retinopathy as part of standard clinical care. In order to assess the presence of reduced kidney function in our cohort, we considered the latest available serum creatinine and urine analyses. In particular, microalbuminuria and macroalbuminuria were diagnosed on the basis of albumin excretion rate between 30 and 299 mg/day or ≥300 mg/day, respectively, using the last available measurement available in the medical record. Creatinine clearance (CCr) was calculated with the EPI-CKD formula. Nephropathy was defined as the presence of both albumin-to-creatinine ratio (ACR) ≥30 mg/g and CCr < 60 mL/min. The last available cholesterol (total cholesterol, HDL, LDL) and triglycerides serum values were used to evaluate the lipid profile.

2.1. Statistical analysis

Statistical analysis was performed using STATA Stata/IC 12.1 software (StataCorp, College Station, TX, USA). The distribution of variables was tested with the Kolmogorov-Smirnov test. The results are expressed as mean ± SD or median [interquartile ranges (IQRs)] as appropriate. Comparisons were done using Student's *t*-test, Kruskal–Wallis and Chi-square depending on distribution; Analysis of variance (ANOVA) was used for comparisons of continuous variables between more than two groups. Pearson correlation test was used to assess the correlations of HbA1c values of each subject at a given time point with a different time point (1st measurement vs 2nd, 1st vs 3rd, 2nd vs 3rd, etc.) and with the 5-year mean HbA1c. Multinomial logistic regression was used to determine the contribution of the explanatory variables to the occurrence of a single and multiple (≥2) fractures. Results are reported as relative risk ratios (RRR) and 95% confidence intervals. Each variable of interest was first assessed with minimal adjustment for age, sex and BMI. Variables listed in Table 1 were then tested to develop a final model using forward stepwise entry (p for retention < 0.1). Age, sex and BMI were forced into the model. The effects of independent variables on the different categories of the dependent variable were tested for equality. Non-normally distributed continuous variables were ln-transformed before they were tested in the ANOVA and in the multinomial logistic regression model. Two-tailed p-value < 0.05 was considered statistically significant.

3. Results

The average age of patients was 41.9 ± 12.8 years (range 18–79). Average BMI and disease duration were 24.4 ± 3.7 kg/m^2 (15.6–44.8) and 19.9 ± 12.0 years (1–63). Mean HbA1c over the previous 5 years was 7.6 ± 1.0% (5.3–13.0). On average, patients had 10 HbA1c measurements over the 5 years. We had a total of 577 patients with at least 1 HbA1c measurement over 5 years and 501 subjects that had 3 or more HbA1c measurements over 5 years. Moreover, a total of 442 patients (76.6%) had at least one A1c measurement a year and a total of 181 patients (31.3%) had 3 or more HbA1c measurement per year over the last 5 years. We evaluated the variability of HbA1c over time and found strong within subject correlations between HbA1c measurements at different time points ($r > 0.50$, $p < 0.001$ for all correlations) and between each HbA1c measurements and the 5-year mean HbA1c ($r > 0.80$, $p < 0.001$ for all correlations). Mean insulin requirement was 0.56 ± 0.19 IU/kg/day. A total of 111 subjects (18.5%) reported at least one fragility fracture after diabetes diagnosis, and 29 of the fractured subjects reported ≥2 fractures. Median ages [25th–75th percentiles] of first fracture and second fracture were 37 [25–47] years and 41 [26–54] years, respectively. We did not find significant correlations between mean HbA1c and age at fracture onset ($r = -0.12$,

Table 1
Clinical features.

	0 fractures (n = 489)	1 fracture (n = 82)	≥2 fractures (n = 29)	p-Value
Age (years)	40 (32–49)	43 (34–54)	47 (37–54)	0.018
BMI (Kg/m^2)	23.7 (21.6–26.5)	24.4 (21.6–27.1)	25.6 (23.1–28.1)	0.052
Sex (men)	240	46	14	0.492
Family history of fracture (Y)	162	41	15	0.003
Age at onset	21 (11 – 31)	19 (13 – 31)	15(11–18)	0.061
Disease duration (years)	18 (10–27)	20 (12 – 31)	31 (23–39)	< 0.001
Insulin unit (IU/kg)	0.54 (0.44–0.66)	0.55 (0.45–0.67)	0.53 (0.46–0.68)	0.774
Monthly hypoglycemic episodes (n)	6 (4–10)	8 (4–12)	8 (4–15)	0.707
eGFR (ml/min)	105.8 (92.2–116.7)	101.6 (81.2–113.5)	96.9 (84.1–107.6)	0.002
Total cholesterol (mg/dl)	178 (155–197)	176 (156–193)	173 (160–195)	0.840
HDL (mg/dl)	61 (51–75)	64 (50–74)	60.5 (52–73)	0.793
LDL (mg/dl)	97 (80–115)	95 (74–115)	95 (86–104)	0.279
Triglycerides (mg/dl)	66 (52–89)	72 (58–83)	72.5 (55–125)	0.252
A1C				0.181
- Tertile 1 (n)	164	25	4	
- Tertile 2 (n)	152	29	11	
- Tertile 3 (n)	155	24	13	
CVD (n)	31	8	6	0.012
Retinopathy (n)	97	20	14	0.001
Neuropathy (n)	47	15	8	0.002
Nephropathy (n)	3	0	1	0.263
Celiac disease (n)	19	1	0	0.440

Values are median (interquartile range).

p = 0.25 for first fracture and r = −0.31, p = 0.21 for second fracture). The most common fracture sites were: hand (18.6%), foot (17.1%), tibia/fibula (10.5%), wrist (9.3%) and ribs (8%).

3.1. Clinical factors associated with single and multiple fractures

Clinical features of T1D patients by fracture status (none, 1, 2+) are reported in Table 1. Variables that differed by fracture status included age (p = 0.02), BMI (p = 0.05), family history of fracture (p < 0.01), disease duration (p < 0.01) and CCr (p < 0.01). Diabetic retinopathy (p < 0.01), neuropathy (p < 0.01) and CVD (p = 0.01) were more prevalent in subjects with higher number of fractures. In particular, subjects who experienced 2+ fractures showed higher prevalence of CVD (p = 0.004), retinopathy (p < 0.001) and neuropathy (p = 0.007) than subjects with no history of fractures. On the contrary, CVD and retinopathy did not differ between subjects with 1 fracture vs no fracture [Fig. 1]. Only 4 (0.7%) patients had nephropathy, and only 20 (3.3%) had celiac disease. Because of this low prevalence, mainly in the non-fractured group, these two variables were not considered in adjusted analysis.

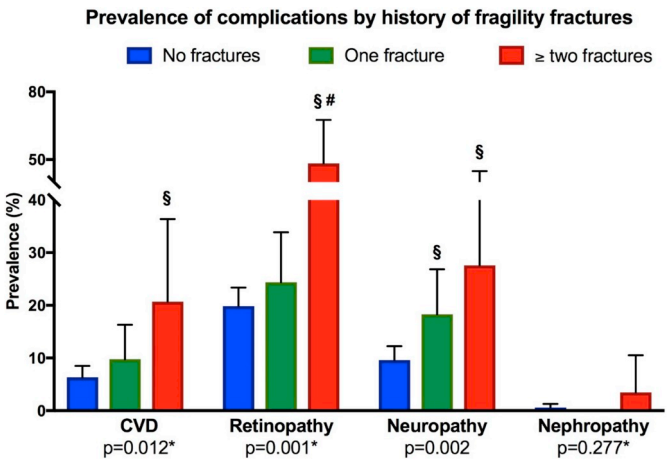

Fig. 1. Complications by groups of number of fractures. Positive history of cardiovascular disease, nephropathy and neuropathy were more frequent with the increasing number of fractures. *p-Value at univariate ANOVA; §p < 0.05 vs no fracture; #p < 0.05 vs 1 fracture.

In models minimally adjusted for age, sex, BMI and family history of fracture, none of the variables were associated with history of a single fracture (Table 2). Neuropathy, retinopathy, disease duration and earlier age at onset were each associated with history of multiple fractures. After full adjustment, HbA1c, disease duration, CCr and neuropathy were the independent variables retained in the final multivariate multinomial regression model (Table 2 and Fig. 2). Subjects in the highest tertile of HbA1c (HbA1c ≥7.9%) had an increased risk of having ≥2 fractures (adjusted RRR: 3.50 [95% CI 1.04–11.73] compared to subjects in the lowest tertile (HbA1c < 7.2%). However, HbA1c did not appear to influence the risk of a single fracture, even in the highest tertile of HbA1c (adjusted RRR 0.98 [95% CI 0.51–1.89]). Similarly, subjects in the highest tertile of disease duration (disease duration ≥26 years) had an adjusted RRR for multiple fractures of 7.59 [95% CI 1.60–35.98] when compared to subjects in the lowest tertile (disease duration < 14 years), but no significant association was found with single fracture (adjusted RRR: 1.06 [95% CI: 0.52–2.18]). Testing for equality confirmed the differential association of HbA1c and disease duration with one and ≥2 bone fractures (p-values for the differences of the effects on outcome: p = 0.044 for HbA1c; p = 0.020 for disease duration).

Greater CCr was protective for a single fracture (adjusted RRR: 0.22 [95% CI 0.06–0.83]), with a similar association for multiple fractures (adjusted RRR: 0.23 [95% CI 0.04–1.48]) (p-value for the difference of the effect on outcomes p = 0.95) The presence of neuropathy increased the risk of single fracture (adjusted RRR: 2.57 [95% CI: 1.21–5.46]), and this association was similar (p-value for the difference of the effect on outcomes: 0.99) for multiple fractures (adjusted RRR 2.57 [95% CI: 0.92–7.15]).

4. Discussion

In this population of well-characterized young adults with T1D and a high prevalence (18.5%) of non-vertebral fragility fractures, poor glycemic control and long disease duration were independent risk factors for multiple fractures. Family history of fragility fractures, and diabetic neuropathy were also associated with an increased risk of fracture. To our knowledge, this is the first study assessing fracture risk factors in a sub-population of multi-fractured T1D patients. This

Table 2
Adjusted multinomial logistic regression models for history of 1 or 2+ fractures.

Variable	Units	Model 1		Model 2	
		1 FX	≥2 FX	1 FX	≥2 FX
Ln CCr	1 unit	0.31 (0.09–1.08)	0.27 (0.05–1.50)	0.22 (0.06–0.83)	0.23 (0.04–1.48)
Neuropathy	Yes/no	1.86 (0.96–3.62)	2.60 (1.03–6.60)	2.57 (1.21–5.46)	2.57 (0.92–7.15)
A1C					
Tertile 1	≤7.17	Ref	Ref	Ref	Ref
Tertile 2	7.18–7.9	1.19 (0.66–2.15)	2.54 (0.78–8.27)	1.44 (0.76–2.72)	3.42 (0.97–12.05)
Tertile 3	> 7.9	1.02 (0.55–1.88)	3.00 (0.94–9.58)	0.98 (0.51–1.89)	3.50 (1.04–11.73)
Disease duration					
Tertile 1	< 14 yrs	Ref	Ref	Ref	Ref
Tertile 2	14–25 yrs	1.66 (0.92–3.01)	4.28 (0.89–20.59)	1.68 (0.89–3.19)	3.43 (0.68–17.24)
Tertile 3	≥26 yrs	1.23 (0.63–2.39)	10.10 (2.20–46.4)	1.06 (0.52–2.18)	7.59 (1.60–35.98)
Family history of fragility fractures	Yes/no			2.08 (1.23–3.50)	2.83 (1.21–6.59)
Lipid profile					
Ln (total chol)		0.69 (0.18–2.69)	1.25 (0.15–10.44)	–	–
Ln (HDL)		1.83 (0.65–5.13)	1.18 (0.24–5.87)	–	–
Ln (LDL)		0.49 (0.21–1.16)	0.97 (0.24–3.87)	–	–
Ln (triglycerides)		1.13 (0.62–2.05)	1.46 (0.58–3.67)	–	–
Ln (age at onset)		0.86 (0.60–1.23)	0.42 (0.26–0.68)	–	–
Ln (hypo/month)		1.08 (0.82–1.43)	1.20 (0.78–1.85)	–	–
Ln (insulin dose)		1.27 (0.66–2.47)	1.47 (0.51–4.24)	–	–
CVD	Yes/no	1.22 (0.50–2.95)	2.46 (0.81–7.49)	–	–
Nephropathy	Yes/no	0.00	4.76 (0.44–51.42)	–	–
Celiac disease	Yes/no	0.29 (0.04–2.19)	–	–	–
Retinopathy	Yes/no	1.13 (0.64–2.01)	2.94 (1.32–6.57)	–	–

Model 1 adjusted for age, sex, BMI. Model 2 adjusted for age, sex, BMI and other variables in table that were retained in the model. CVD = stroke, CHD, PAD, bypass or stent.

allowed us to show that poor glycemic control over the previous 5 years and long disease duration are associated with increased risk of multiple fractures. Although an association between poor glycemic control and increased fracture risk has been reported for individuals with T2D [20–22], the evidence on glycemic control and fracture risk in T1D is less consistent [4,23,24]. Weber and colleagues found that each 1% (11 mmol/mol) greater average HbA1c level was associated with a 5% greater risk of incident fracture in males and an 11% greater risk of fracture in females participating in a large population-based cohort study [4]. Diabetes duration in this cohort was not reported. Conversely, Zhukouskaya and colleagues found no difference in either HbA1c levels or diabetes duration between T1D patients with and without vertebral fractures [24]. This may be due to lack of multiple HbA1c measurements, as reported in recent studies [25], or different associations between glycemic control and fracture site. Also, these studies did not consider those with multiple fractures as a separate group. Our findings suggest that poor glycemic control and long disease duration associate with the presence of multiple fractures, identifying a "severe bone fragility" phenotype in T1D.

Here we show that subjects with longer disease duration and worse glycemic control have an increased prevalence of fragility fractures, independent of mean insulin dose [26]. This provides important new information as only one previous study has, to our knowledge, considered all of these factors in relation to fracture risk. Some [4,23], but not all [24], previous studies have reported an association between glycemic control and increased fracture risk in T1D. Of these previous studies, only Zhukouskaya et al. considered insulin dose or disease duration, and these factors were not associated with risk of prevalent vertebral fracture [24]. It is not surprising that both factors contribute independently to fracture risk as duration of disease provides a measure of how long the skeleton has been exposed to hyperglycemia, while mean HbA1c reflects the degree of hyperglycemia. This is in accordance with pre-clinical and clinical data showing that chronic hyperglycemia may impact osteoblast function [7,27] and bone quality [28] specifically in subjects with T1D.

Vascular complications have been suggested as possible contributors to the increased bone fragility by impacting bone mineral density [9], bone quality [29], final risk of fractures [12] and potentially as markers of reduced vascular function in bone. In this study we found a higher prevalence of retinopathy, and diabetic neuropathy, as well as significantly lower CCr among T1D patients with positive history of fractures. With adjustment for glycemic control, disease duration and each other, neuropathy, but not retinopathy, was retained as an independent risk factor for fracture. This is consistent with the findings of Weber and colleagues, who reported that diabetic neuropathy was a significant risk factor for incident fracture in males (HR 1.33; 95% CI 1.03–1.72) and females (HR 1.52; 95% CI 1.19–1.92) with T1D [4], and with those of Miao and colleagues, who found that presence of diabetic complications (including neuropathy, nephropathy, retinopathy and CVD) increased hip fracture risk among individuals hospitalized for T1D [12]. Conversely, Vestergaard and colleagues found that, after adjustment for other complications and multiple confounders (e.g. drugs, CVD, working status etc.) presence of diabetic neuropathy or other complications – except for diabetic kidney disease - did not increase fracture risk in T1D [30]. Several studies have documented an increased risk of cardiac events in the presence of decreased skeletal health [31] but few studies have assessed the relationship between bone health and CVD in individuals with T1D. In our study, CVD was more prevalent in subjects with higher number of fractures, but the association was not significant after adjustment for confounders (age and disease duration in particular). In contrast, we have recently shown an association between BMD at the femoral neck and history of cardiovascular disease in older people with long-standing T1D who were homogeneous in terms of age, metabolic control and disease duration [9].

We did not find evidence of an association between fracture risk and hypoglycemic episodes, possibly because there were relatively few hypoglycemic episodes. Finally, although an association between atherogenic lipid profile and low BMD has been reported in subjects with long-standing T1D [9], we did not find evidence of an association between lipids and fracture risk.

Our study has several strengths. We were able to consider a full set of clinical risk factors, including glycemic control, insulin dose, disease duration, hypoglycemic episodes, lipid profile and complications.

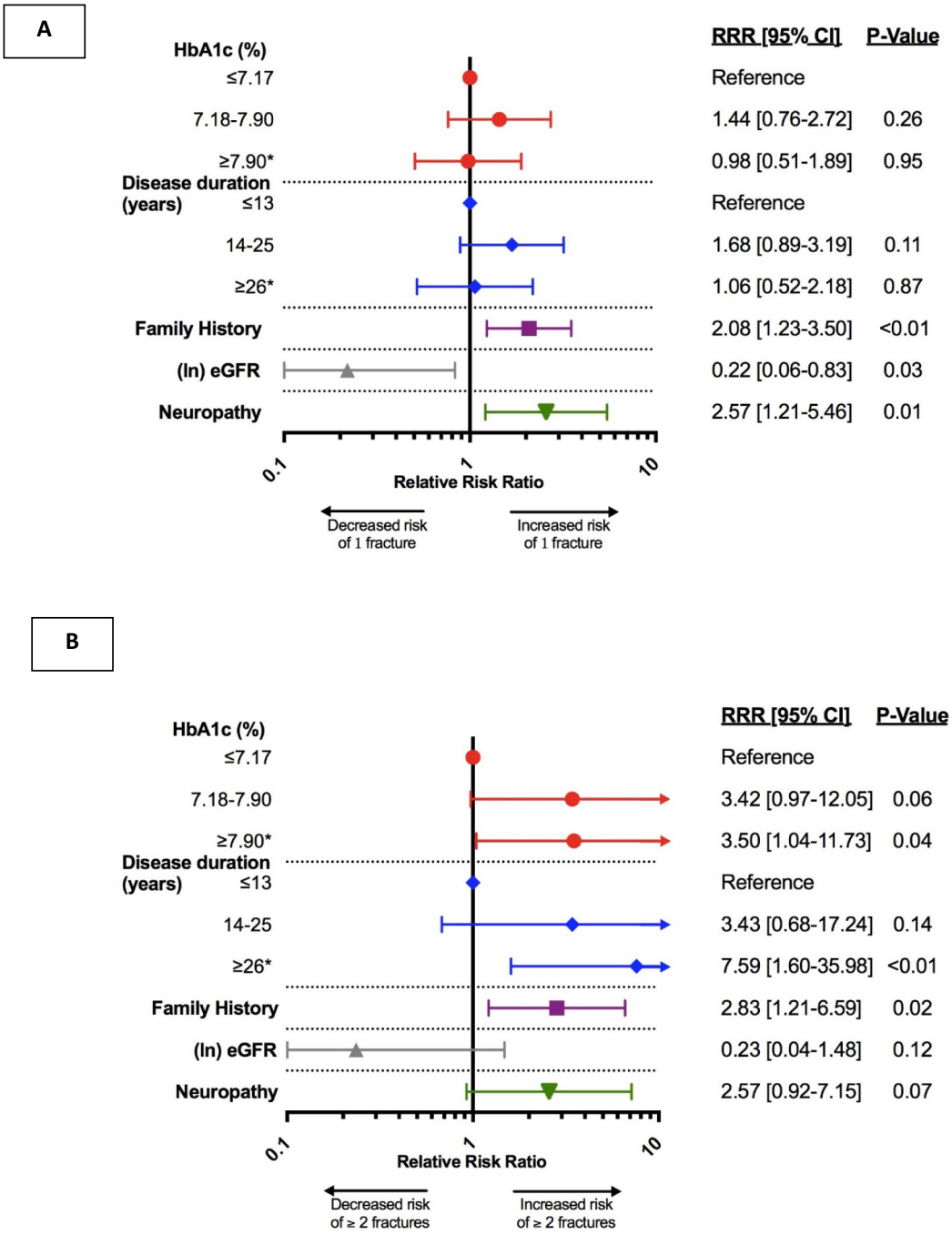

Fig. 2. Graphical representation of the multinomial regression model with fractures [single (A) and ≥2 (B)] as dependent variable. Only variables significantly associated with the outcome in the fully adjusted model are represented. Values of HbA1c and disease duration are the respective tertiles' cut-offs. *p-Value for the difference in the effects of the independent variable on single vs ≥2 fractures < 0.05.

Differently from previous studies conducted on population-based registries, we analyzed glycemic control through frequent HbA1c measurements over 5 years, which better describes the long-term glucose control as compared with a single measurement. We also acknowledge that this study has limitations. We cannot determine the temporal relationship between glycemic control and fractures, although it has been previously shown that HbA1c in adults with T1D is quite stable over time [32]. To confirm this observation in our population, we evaluated the variability of HbA1c over time and found strong correlations between HbA1c of each subject at different time points ($r = 0.65$, $p < 0.001$), suggesting a minimum variability of glycemic control in our population over the time. Although participant fracture reports were confirmed by medical record review, some fracture events may not have been reported. Any resulting misclassification of fractures is unlikely to differ with respect to the risk factors considered and any bias of associations would tend towards the null.

5. Conclusion

In conclusion, our study identified diabetes-specific factors that can be used to evaluate fracture risk in T1D patients, namely disease duration, presence of neuropathy, HbA1c and CCr values. Importantly, glycemic control and kidney function are modifiable risk factors that could be targeted for prevention of fractures in diabetes. Prospective

longitudinal studies of fracture risk in T1D that include diabetes-specific risk factors are needed to confirm our findings.

Declaration of interest

None.

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G.L. and E.M. collected, analyzed and interpreted the data and prepared the manuscript. D.P. collected and interpreted the data. C.C. analyzed and interpreted the data and prepared the manuscript. A.R.M., A.L.P, C.S. and M.A. collected the data. R.S. analyzed and interpreted the data. P.P. analyzed and interpreted the data and reviewed the manuscript. A.V.S. performed the statistical analysis with E.M. and analyzed and interpreted the data. N.N. analyzed and interpreted the data and reviewed the manuscript.

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