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Glycemic control and 10-year odds of all-cause fractures in elderly veterans with type 2 diabetes

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ABSTRACT

Aims: To investigate the relationship of average level of glycemic control and fractures in elderly Veterans.

Methods: Retrospective cohort of Veterans (age ≥65) grouped as follows: no diabetes, HbA1c ≤7.0% [≤53 mmol/mol], HbA1c 7.1–8.0% [54–64 mmol/mol], HbA1c 8.1–9.0% [65–75 mmol/mol], and HbA1c >9% [>75 mmol/mol]. Data from January 1, 2010 – January 1, 2017 from the Veteran's Affairs Corporate Data Warehouse was analyzed using Chi-square and Cox regression analysis.

Results: 3434 fractures occurred from the 36,744 Veterans included. The fracture incidences were 14.4, 11.7, 7.9, 8.2, and 10.8 events per 1000 patient years and the hazard ratios were 1.233 (1.130–1.345); $p < 0.0001$, 0.718 (0.626–0.825); $p < 0.0001$, 0.682 (0.545–0.854); $p = 0.0009$, and 0.887 (0.633–1.245); $p = 0.4915$ in the no diabetes, HA1c ≤7% [≤53 mmol/mol], 7.1–8% [54–64 mmol/mol], 8.1–9% [65–75 mmol/mol], and >9% [>75 mmol/mol] groups after accounting for covariates in the final model.

Conclusion: In elderly Veterans with type 2 diabetes the average HbA1c 7.1–8.0% [54–64 mmol/mol], and 8.1–9% [65–75 mmol/mol] have the lowest fracture incidence and those without diabetes showing the highest incidence rate; however, due to the overall low rate of fracture, the absolute difference in incidence of fracture was very small at 2–5 per 1000 patient years. Beyond limiting the risk factors identified these results don't support altering diabetes treatment goals to reduce fracture risk.

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1. Introduction

There are a growing number of studies correlating type 1 and type 2 diabetes with an increased risk of fractures [1–7]. This risk further increases for elderly patients with diabetes as they are at a two-to-eight fold increased risk of fragility fractures when compared to similarly aged individuals without diabetes [1]. Along with these risks comes a larger financial burden, higher morbidity, and higher mortality associated with fractures [8].

There are several hypotheses behind this association including hypoglycemia related falls, certain anti-diabetic medications, polypharmacy, several comorbidities, impaired bone remodeling, differing bone geometry, and duration of diabetes [1–9]. Additionally, a cross-sectional study by Shanbhogue et al. on adult patients with Type 1 Diabetes found a

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significant relationship between microvascular complications on excess skeletal fragility [10].

The American Diabetes Association (ADA) and The Department of Veterans Affairs (VA) and Department of Defense (DoD) have each published clinical practice guidelines for the management of type 2 diabetes mellitus [11,12]. The VA/DoD recommendations were updated in April 2017 with the purpose of moving toward individualized treatment goals for each patient instead of a single standardized goal [12]. Each of these guidelines have recommendations on HbA1c goal ranges based on the presence of major comorbidities and life expectancy [12–14]. However, neither of these guidelines include an assessment on the risk of fractures when determining a patient's HbA1c goal range [12–14].

Some of the proposed mechanisms by which diabetes and medications affect bone act in opposite directions and there is still debate over how diabetes affects the bones [15]. Current literature illustrates conflicting evidence on whether the level of glycemic control over time affects the risk of fractures [1–7]. This study specifically was aimed at looking at the impact of glycemic control over time on fractures and consequently if fracture risk should be incorporated in decision making regarding diabetes treatment in elderly patients.

2. Subjects

This trial was a retrospective cohort study, of elderly Veterans from January 1, 2007 through January 1, 2017. The study included data from Veterans Integrated Services Network (VISN) 15 which consists of eight VA hospitals across three Midwestern states including Kansas, Missouri, and Illinois and was approved by the Kansas City VA institutional review board and VA Eastern Kansas Research and Development Committee.

The study population was identified using the national Corporate Data Warehouse (CDW) database (VA. 79 FR 4377) using resources and facilities at the VA Informatics and Computing Infrastructure (VINCI), (VA HSR RES 13-457) [16]. Patients were included if they were at least 65 years of age as of January 1, 2007. Patients were excluded if they were recorded as being deceased prior to January 1, 2008, had a diagnosis of gestational or type 1 diabetes, missing baseline data including HbA1c, serum creatinine (SCr), height, or weight. Baseline data was considered missing if there was no height, no weight and no SCr recorded within 1 year after the start of the study, and no blood pressure and HbA1c recorded within 3 months after the start of the study. Patients were also excluded if they didn't have a recorded HbA1c from at least 30% of qualifying study years during the study, did not have a diagnosis of diabetes at baseline but had an HbA1c of ≥6.5% [> 42 mmol/mol] prior to January 1, 2007, developed type 2 diabetes during the study period, or deceased prior to January 1, 2008. Qualifying study years are defined as the number of calendar years between January 1, 2007 and when the patient either died, experienced the primary outcome, or January 1, 2017 whichever occurred first. Patients were considered to have diabetes if they had a diagnosis of diabetes recorded in coding data from any outpatient visit, inpatient admission, if diabetes existed on their VA problem list, had a recorded HbA1c of ≥6.5% [48 mmol/mol] at any time, or been dispensed more than a total of 6 months of any hypoglycemic medication.

3. Materials and methods

Patient glycemic control was defined by average HbA1c, calculated as the average of the first recorded HbA1c from each qualifying study year until the patient died, experienced the primary outcome, or January 1, 2017 whichever occurred first. Patients were grouped based on level of glycemic control into one of five study arms based on average HbA1c: Group 1: no diabetes, Group 2: average HbA1c ≤7.0% [≤53 mmol/mol], Group 3: average HbA1c 7.1–8.0% [54–64 mmol/mol], Group 4: average HbA1c 8.1–9.0% [65–75 mmol/mol], and Group 5: average HbA1c >9% [>75 mmol/mol]. The primary and secondary outcomes were the 10-year all-cause fracture rates (excluding fractures of the skull, hand, or foot) and hip-fracture rates respectively.

Demographic and clinical data gathered from electronic health records through use of Microsoft SQL Server query included sex, age, race, average weight, average SCr, average calculated body mass index (BMI), average systolic and diastolic blood pressure, average HbA1c, presence of Vitamin D level <30 ng/mL, baseline comorbidities, microvascular complications, use of medications known to affect risk of fractures where at least a one year total days supply of medication was dispensed throughout the study period, and fracture diagnoses prior to and during the study period. ICD9 and ICD10 codes documented from any VA hospital admission, outpatient clinic visit were used to identify patient comorbidities and occurrence of fracture. Fracture cases were identified based on ICD 9 codes 805–814, 818, 820–824, 827, 829 and 733, and ICD 10 codes S12, S22, S32, S42, S52, S62.0, S62.1, S62.9, S72, S82, S92.0, S92.1, S92.2, S92.9, M80, M84.3, M84.4, M84.6, M84.7.

Data were collected until the patient deceased, coding of a fracture, or until the end of the study on January 1, 2017.

All analyses were performed using SAS Enterprise Guide Version X (SAS, Cary, NC, USA). Baseline characteristics were analyzed by chi-squared for categorical and ANOVA for continuous variables respectively. The primary outcome was analyzed using a Cox Proportional Hazards Model Regression analysis. The included covariates were determined through consensus of both forward and backward stepwise selection with a p-value to enter and exit the model of 0.1. Subsequently, biologically plausible interactions were assessed by the same criterion. Finally, additional covariates were added to the model if they improved overall model fit as measured by the overall c-statistic [17]. Additionally, insulin use was included due to its potential anabolic effects on bone [15]. The covariates included in the final regression model included: age, sex, race, BMI, natural log of the average SCr, prior fracture, corticosteroid use, proton pump inhibitors, selective serotonin reuptake inhibitors, enzyme-inducing antiepileptic drugs, aromatase inhibitors/gonadotropin-releasing hormone agonists, insulin use, Charlson Comorbidity Index (CCI) [18], other comorbidities (osteoporosis, nicotine use disorder, alcohol use disorder, microvascular complications),

history of fall, history of hypoglycemia, history of hypotension, history of low vitamin D (<30 ng/dL), and interaction effects between falls and hypoglycemia/hypotension. The definition of fall, hypoglycemia, and hypotension were limited to ICD9 and ICD10 codes documented from coding data associated with any VA hospital admission or outpatient clinic visits or blood pressure vitals <90/60 mmHg for hypotension. A log transformation was applied to SCr to improve linearity due to skewed data and was included in the model despite not meeting entry requirements due to the plausibility of CKD affecting bone health. Ten-year incidence of hip fracture was analyzed using Chi-Square analysis.

4. Results

Fig. 1 shows the derivation of the cohort. A total of 266,592 Veterans were identified that met the inclusion criteria. After applying the exclusion criteria, 36,744 Veterans were included in the analysis with 17,314 Veterans in Group 1 (no diabetes), 12,052 Veterans in Group 2 (average HbA1c ≤7.0% [≤53 mmol/mol]), 5,135 Veterans in Group 3 (average HbA1c 7.1–8.0% [54–64 mmol/mol]), 1665 Veterans in Group 4 (average HbA1c 8.1–9.0% [65–75 mmol/mol]), and 578 in Group 5 (average HbA1c >9% [>75 mmol/mol]). The baseline characteristics are presented in Table 1. The majority of Veterans were Caucasian males with an average age of 75 years. Most differences were statistically significant due to the sample size, though largely not clinically significant between levels of diabetes control.

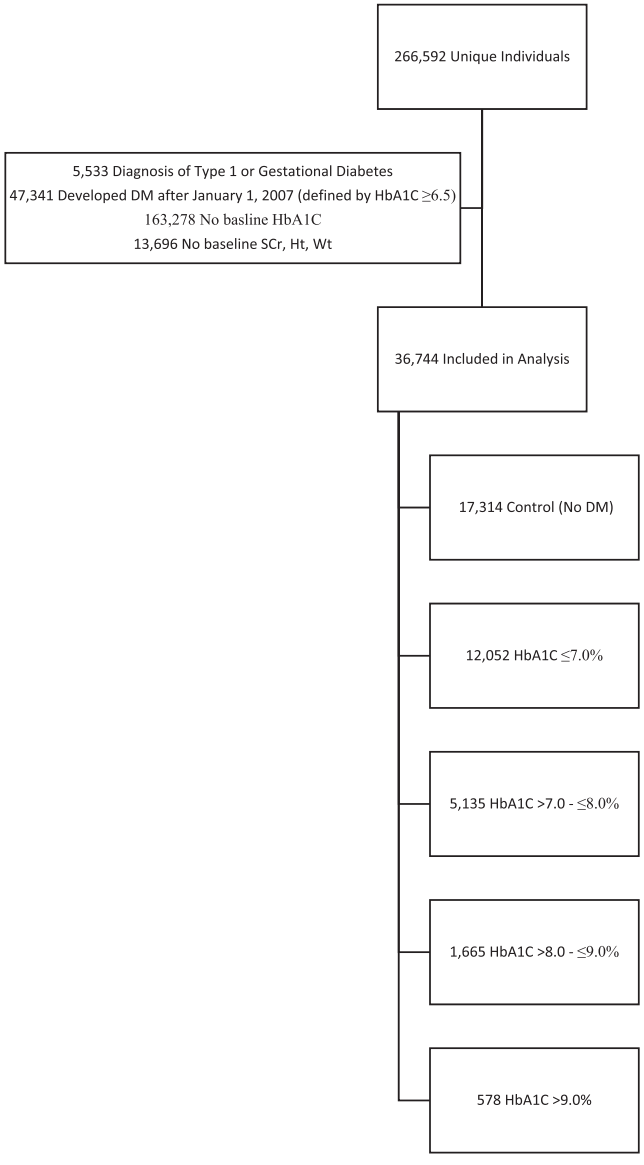

Fig. 1 – Derivation of the cohort.

There were 3434 fracture events from the 36,744 Veterans included in the analyses. Patients in the no diabetes group had the highest fracture incidence of 14.4 events per 1000 patient years as compared to the fracture incidences of 11.7, 7.9, 8.2, and 10.8 events per 1000 patient years in the HA1c ≤7% [≤53 mmol/mol], 7.1–8% [54–64 mmol/mol], 8.1–9% [65–75 mmol/mol], and >9% [>75 mmol/mol] groups respectively (Table 2). When compared with the HbA1c ≤7% group (well-controlled diabetes) the hazard ratios (95% CI) for the no diabetes, 7.1–8% [54–64 mmol/mol], 8.1–9% [65–75 mmol/mol], and >9% [>75 mmol/mol] groups were 1.247 (1.155–1.345); $p < 0.0001$, 0.678 (0.596–0.771); $p < 0.0001$, 0.702 (0.570–0.866); $p < 0.0009$, 0.916 (0.662–1.266); $p = 0.4915$ respectively after accounting for covariates included in the final model. As seen in Table 2, while the model and covariates were significant, these HRs were not practically different from the unadjusted model taking into account only level of glycemic control. This could be related to baseline characteristics being clinically similar between groups. Similarly, a model was conducted by pooling those with type 2 diabetes together as compared to those without identified diabetes (controlling for the same covariates), which illustrated similar results, HR (95% CI): 0.708 (0.662–0.758). Additionally, as other concomitant comorbidities can affect bone health, a separate model was evaluated on a subgroup of the sample where subjects were excluded if they had diagnoses of gastrointestinal disease that could affect absorption, diagnosis of autoimmune disorders (e.g. rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis), end-stage renal disease, malignancy, alcohol use disorder, record of low vitamin-D levels, or use of corticosteroids. As seen in Table 3, the results of this model were not markedly different from those of the adjusted model in Table 2. A Kaplan-Meier Survival Curve depicting the time to first fracture for each group can bee seen in Fig 2.

As would be expected, prior fracture was the strongest predictor of future fracture with a HR (95% CI), 3.816 (3.485–4.178); $p < 0.0001$ and female sex showed an increased risk of fracture when compared to male sex with a HR, 1.76 (1.477–2.101); $p < 0.0001$. The following medications were associated with an increased risk of fracture: gonadotropin-releasing hormone (GNRH) agonists or aromatase inhibitors, selective serotonin reuptake inhibitors (SSRI), enzyme-inducing antiepileptic drugs (EIAED), proton pump inhibitors (PPI), and corticosteroids. Hypotension, hypoglycemia, history of falls, and the interaction between hypotension and history of falls all were significant contributors to the regression model and were associated with an increased risk of fracture. The hazard ratio of these predictors differs based on the level

Table 1 – Demographics at baseline.

Characteristic	Glycemic Control Group					
	No Diabetes (N = 17314)	HbA1C ≤7% (N = 12052)	HbA1C 7.1–8.0% (N = 5135)	HbA1C 8.1–9.0% (N = 1665)	HbA1C ≥ 9.0% (N = 578)	All Patients (N = 36744)
Mean Age ± S.D. (yr)*	74.7 ± 6.2	76.4 ± 6.2	75.7 ± 6.1	75.2 ± 6.1	74.4 ± 6.1	75.3 ± 6.2
Female, no. (%)*	385 (2.2)	169 (1.4)	57 (1.1)	16 (1.0)	10 (1.8)	637 (1.7)
Mean Body Mass Index ± S.D. (kg/m^2)[b,*]	28.3 ± 4.9	29.9 ± 5.4	30.6 ± 5.5	30.8 ± 5.5	30.9 ± 5.8	28.7 ± 5.3
Caucasian, no. (%)*	14,744 (85.16)	10,197 (84.61)	4459 (86.84)	1435 (86.19)	469 (81.14)	31,304 (85.19)
Mean SBP/DBP ± S.D. (mmHg)[a,*]	134/73 ± 18/11	135/71 ± 19/11	136/71 ± 19/11	136/71 ± 20/11	137/72 ± 19/11	135/72 ± 18/11
Median CCI (IQR)[a,*]	5 (4–6)	6 (5–8)	6 (5–8)	6 (5–8)	7 (5–8)	6 (5–7)
Comorbidities, no (%)[a]	No Diabetes	HbA1c ≤7%	HbA1C 7.1–8.0%	HbA1C 8.1–9.0%	HbA1C ≥ 9.0%	All Patients
Rheumatoid Arthritis*	532 (3.07)	252 (2.09)	100 (1.95)	32 (1.92)	7 (1.21)	923 (2.51)
Any Autoimmune Disorder*	644 (3.72)	336 (2.79)	110 (2.14)	39 (2.34)	16 (2.77)	1145 (3.12)
Alcohol Use Disorder*	1702 (9.83)	621 (5.15)	136 (2.65)	49 (2.94)	26 (4.5)	2534 (6.90)
Microvascular Complications*	296 (1.71)	3372 (27.98)	1979 (38.54)	762 (45.77)	286 (49.48)	6695 (18.22)
Nicotine Use*	4394 (25.38)	2634 (21.86)	1023 (19.92)	346 (20.78)	130 (22.49)	8527 (23.21)
Osteoporosis*	1916 (11.07)	880 (7.3)	259 (5.04)	79 (4.74)	25 (4.33)	3159 (8.60)
Renal disease*	1478 (8.54)	1623 (13.47)	652 (12.7)	246 (14.77)	72 (12.46)	4071 (11.08)
End Stage Renal Disease*	716 (4.14)	952 (7.9)	366 (7.13)	141 (8.47)	37 (6.4)	2212 (6.02)
Severe Liver Disease	56 (0.32)	44 (0.37)	7 (0.14)	3 (0.18)	1 (0.17)	111 (0.30)
Gastrointestinal Condition associated with Malabsorption*	559 (3.23)	325 (2.7)	87 (1.69)	35 (2.1)	11 (1.9)	1017 (2.77)
Any Vitamin D < 30 ng/dL*	5655 (32.66)	2815 (23.36)	1296 (25.24)	473 (28.41)	129 (22.32)	10,368 (28.22)
Prior Fall via ICD coding, no. (%)*	1842 (10.64)	1160 (9.62)	476 (9.27)	166 (9.97)	44 (7.61)	3688 (10.04)
Prior hypoglycemia, no. (%)*	149 (0.86)	400 (3.32)	310 (6.04)	133 (7.99)	45 (7.79)	1037 (2.82)
Prior hypotension, no. (%)*	3711 (21.43)	2333 (19.36)	885 (17.23)	346 (20.78)	141 (24.39)	7416 (20.18)
Medication, no (%)[c]						
Corticosteroids*	994 (5.74)_	551 (4.57)	187 (3.64)	71 (4.26)	13 (2.25)	1816 (4.94)
Enzyme-inducing antiepileptic drugs*	509 (2.94)	321 (2.66)	87 (1.69)	28 (1.68)	8 (1.38)	953 (2.59)
Gonadotropin-releasing hormones*	628 (3.63)	362 (3.0)	115 (2.24)	51 (3.06)	15 (2.6)	1171 (3.19)
Aromatase Inhibitors*	23 (0.13)	2 (0.02)	2 (0.04)	2 (0.12)	1 (0.17)	30 (0.08)
Immunosuppressant	176 (1.02)	117 (0.97)	37 (0.72)	16 (0.96)	3 (0.52)	349 (0.95)
Insulin*	0 (0)	1272 (10.55)	2098 (40.86)	1049 (63)	384 (66.44)	4803 (13.07)
Lithium*	60 (0.35)	20 (0.17)	2 (0.04)	0 (0)	0 (0)	82 (0.22)
Loop diuretics*	2801 (16.18)	3075 (25.51)	1544 (30.07)	579 (34.77)	185 (32.01)	8184 (22.27)
Proton Pump Inhibitors*	7045 (40.69)	4333 (35.95)	1767 (34.41)	569 (34.17)	154 (26.64)	13,868 (37.47)
Serotonin Selective Reuptake Inhibitors	2649 (15.3)	1831 (15.19)	734 (14.29)	249 (14.95)	82 (14.19)	5545 (15.09)
Metformin*	0 (0)	4348 (36.08)	2549 (49.64)	776 (46.61)	239 (41.35)	7912 (21.53)
Thiazolidinediones*	0 (0)	796 (6.6)	841 (16.38)	298 (17.9)	79 (13.67)	2014 (5.48)
Dipeptidyl peptidase-4 (DPP-4) inhibitor*	0 (0)	86 (0.71)	191 (3.72)	50 (3.0)	16 (2.77)	343 (0.93)
Glucagon-like peptide-1 (GLP-1) receptor agonist*	0 (0)	5 (0.04)	12 (0.23)	1 (0.06)	2 (0.35)	20 (0)
Sodium-glucose co-transporter 2 (SGLT2) inhibitor	0 (0)	0 (0)	1 (0.02)	1 (0.06)	0 (0)	2 (0)
Medications that can prevent BMD reduction, no (%)						
Bisphosphonate (any time prior to censoring)*	1234 (7.13)	590 (4.90)	166 (3.23)	47 (2.82)	15 (2.60)	2052 (5.58)
Any anti-osteoporosis medications*	1999 (11.55)	953 (7.91)	294 (5.73)	98 (5.89)	27 (4.67)	3371 (9.17)

* $p < 0.01$.

[a] Characteristic at baseline documented closest to January 1, 2007 prior to March 1, 2007.

[b] Characteristic at baseline documented closest to January 1, 2017 prior to January 1, 2018.

[c] Medications where at least a one-year total day supply of medication was dispensed.

Table 2 – Cox proportional hazards regression analysis of fractures.

Parameter	Fracture events, N (Incidence rate/1000 patient years)	Unadjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
Glycemic Control Group					
Group 1 (No DM)	2009 (14.4)	1.247 (1.155–1.345)	<0.0001	1.233 (1.130–1.345)	<0.0001
Group 2 (HbA1c ≤7%)	987 (11.7)	–	–	–	–
Group 3 (HbA1c 7.1–8.0%)	304 (7.9)	0.678 (0.596–0.771)	<0.0001	0.718 (0.626–0.825)	<0.0001
Group 4 (HbA1c 8.1–9.0%)	96 (8.2)	0.702 (0.570–0.866)	0.001	0.682 (0.545–0.854)	0.0009
Group 5 (HbA1c > 9.0%)	38 (10.8)	0.916 (0.662–1.266)	0.5397	0.887 (0.633–1.242)	0.4915
No DM versus DM					
Group 1 (No DM)		–	–	–	–
Groups 2–5 (T2DM)		0.708 (0.662–0.758)	<0.0001	0.760 (0.699–0.827)	<0.0001

Covariates (Adjusted model by glycemic control group)	Hazard Ratio (95% CI)	P Value
Age	1.015 (1.009–1.021)	<0.0001
Female Gender	1.76 (1.477–2.101)	<0.0001
Non-Caucasian or Unknown race	0.963 (0.874–1.060)	0.4357
BMI	0.986 (0.979–0.993)	<0.0001
Ln (mean SCr)	0.895 (0.773–1.036)	0.1377
Nicotine Use Disorder Dx	1.136 (1.051–1.229)	0.0014
Alcohol Use Disorder Dx	1.285 (1.152–1.435)	<0.0001
History of Vitamin D <30 ng/dL	1.098 (1.023–1.178)	0.0094
Osteoporosis diagnosis	1.184 (1.071–1.308)	0.001
Prior fracture	3.816 (3.485–4.178)	<0.0001
Charlson Comorbidity Index	1.05 (1.031–1.070)	<0.0001
Microvascular complication	1.118 (1.011–1.247)	0.0305
Insulin Use	1.043 (0.906–1.201)	0.5546
Enzyme-inducing antiepileptic drugs	1.315 (1.121–1.542)	0.0008
Gonadotropin-releasing hormones and/or Aromatase inhibitors	1.436 (1.241–1.661)	<0.0001
Proton Pump Inhibitors	1.148 (1.070–1.231)	<0.001
Corticosteroids	1.26 (1.116–1.423)	0.0002
Serotonin Selective Reuptake Inhibitors	1.363 (1.257–1.477)	<0.0001
History of hypoglycemia (HR at history of fall = No)	1.608 (1.333–1.942)	<0.0001
History of hypotension (HR at history of fall = No)	2.475 (2.278–2.688)	<0.0001
Fall (HR at history of hypotension and hypoglycemia = No)	2.545 (2.283–2.841)	<0.0001
Hypoglycemia/Fall history interaction		0.0659
Hypotension/Fall history interaction		<0.0001

Table 3 – Cox Proportional Hazards Regression Analysis: Subgroup excluding subjects with a baseline history of gastrointestinal diseases associated with malabsorption, autoimmune disease, end-stage renal disease, malignancy, alcohol use disorder, low vitamin-D, or corticosteroid use.

Parameter	Unadjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
Glycemic Control Group				
Group 1 (No DM) (n = 7206)	1.247 (1.155–1.345)	<0.0001	1.299 (1.118–1.510)	0.0006
Group 2 (HbA1c ≤7%) (n = 5927)	–	–	–	–
Group 3 (HbA1c 7.1–8.0%) (n = 2708)	0.678 (0.596–0.771)	<0.0001	0.706 (0.565–0.881)	0.0021
Group 4 (HbA1c 8.1–9.0%) (n = 825)	0.702 (0.570–0.866)	0.001	0.826 (0.585–1.167)	0.2782
Group 5 (HbA1c >9.0%) (n = 308)	0.916 (0.662–1.266)	0.5397	0.861 (0.485–1.529)	0.2603

Covariates (Adjusted model by glycemic control group)	Hazard Ratio (95% CI)	P Value
Age	1.011 (1.001–1.022)	0.0401
Female Gender	1.901 (1.383–2.614)	<0.0001
Non-Caucasian or Unknown race	0.963 (0.874–1.060)	0.4357
BMI	0.989 (0.977–1.002)	0.0878
Ln (mean SCr)	0.677 (0.485–0.945)	0.0218
Nicotine Use Disorder Dx	1.288 (1.123–1.478)	0.0003
Osteoporosis diagnosis	1.258 (1.035–1.530)	0.0213
Prior fracture	5.216 (4.446–6.119)	<0.0001
Charlson Comorbidity Index	1.081 (1.029–1.136)	0.002
Microvascular complication	1.093 (0.905–1.321)	0.3555
Insulin Use	0.964 (0.760–1.223)	0.7657
Enzyme-inducing antiepileptic drugs	1.171 (0.872–1.572)	0.2948
Gonadotropin-releasing hormones and/or Aromatase inhibitors	0.699 (0.313–1.563)	0.3835
Proton Pump Inhibitors	1.087 (0.963–1.227)	0.1769
Serotonin Selective Reuptake Inhibitors	1.295 (1.116–1.502)	0.0006
History of hypoglycemia		0.0003
History of hypotension		<0.0001
Fall		<0.0001
Hypoglycemia/Fall history interaction		0.2229
Hypotension/Fall history interaction		0.0104

of the interacting variable. The hazard ratio (HR) reported in Table 2 represents the HR of fracture based on history of hypoglycemia or hypotension in the absence of a history of falls. The overall C-statistic as a measure of overall fit for the final model was 0.64342 (95% CI: 0.61105–0.67514) [17]. The c-statistic being >0.5 indicates a decent fit of the model to the data. However, with only modest fit, there are likely missing significant co-variates.

The Chi-Square analysis showing the secondary outcome is presented in Table 4. Similar to the primary outcome, there was a statistically significant difference in hip-fractures when comparing the glycemic control groups. However, although the results were statistically significant there was only an absolute difference in fracture rates of <1% between glycemic control groups.

5. Discussion

Historically, patients with diabetes have been associated with an increased risk of fractures, especially hip fractures [1–7]. In contrast, our results showed patients in the no diabetes group had the highest fracture incidence of 14.4 events per 1000 patient years as compared to the fracture incidences of 11.7, 7.9, 8.2, and 10.8 events per 1000 patient years in the HA1c ≤7% [≤53 mmol/mol], 7.1–8% [54–64 mmol/mol], 8.1–9% [65–75 mmol/mol], and >9% [>75 mmol/mol] groups respectively (Table 2). Although, there was a statistically significant difference in fracture risk between several of the study arms the absolute difference in the incidence of fracture was very small at 2–5 per 1000 patient years. There was only less than 1% absolute risk difference for hip-fractures among all groups over 10 years. The small absolute risk differences among these groups over 10-years are likely not clinically significant when compared to other known strong risk factors for fracture. Average achieved HbA1c between 7.1 and 9% [53–75 mmol/mol] seemed to be associated with a slightly lower incidence of fracture as compared to well-controlled diabetes. The reason for this is unclear.

Our findings may be explained by a few differences that were found in the no diabetes group. The no diabetes group did have a greater rate of documented osteoporosis and a higher usage of bisphosphonates; thus, you would expect those with osteoporosis to be at higher risk of fracture. It is quite possible that this difference in co-morbid osteoporosis was not fully controlled for in this retrospective model. In the future, an analysis in those with diagnosed osteoporosis could help reduce this confounding. Similarly, the control group also contained a larger percentage of patients with a history of diagnosed alcohol use disorder, which may also have been imperfectly controlled for. This is a notable finding as previous studies have concluded that heavy alcohol intake may be associated with lower bone mineral density in men

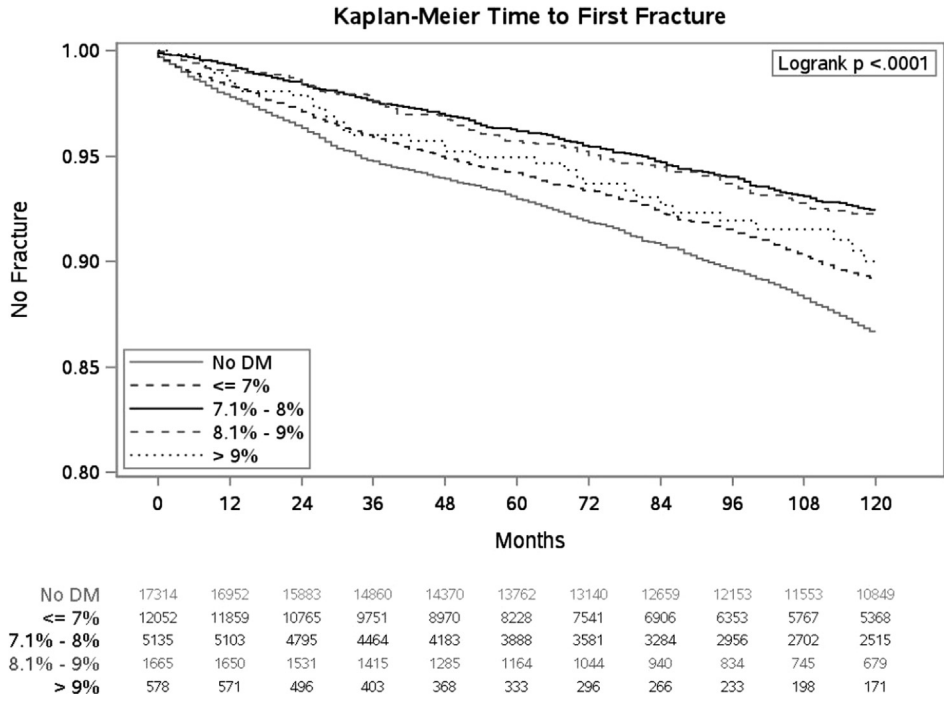

Fig. 2 – KM survival curve.

[19]. Additionally, there was a substantial proportion of patients in this population who were prescribed insulin, which could also contribute to this lower fracture incidence due to the potential anabolic effect of insulin on bone [15]. Overall, this study had a low incidence of fractures compared to the international osteoporosis foundation reported incidence of 15% for men and women over the age of 50 years in the year 2000 [20]. This lower incidence was likely due to the primarily male population which is known to be at a lower risk of fractures [20]. It could not be ruled out that these patients may have been wheel-chair or bed bound, had limited mobility, or deceased before a fracture could occur which reduced their fracture risk.

There are previous studies who have found an association between glycemic control and risk of fracture [1–5]. Additionally, we and others also failed to confirm a clinically meaningful association between glycemic control and risk of fracture in type 2 diabetes patients [3,21,22]. The ACCORD BONE study by Schwartz et al. [3], an ancillary study to the ACCORD Randomized Trial [23], is the only randomized controlled trial that has studied the effect of glycemic control on fractures and falls as outcomes. This study did not include a no diabetes group but the authors concluded that compared with standard glycemic control (average HbA1c of 7.5% [58 mmol/mol]) intensive glycemic control (average HbA1c of 6.4% [64 mmol/-mol]) did not increase or decrease fracture or fall risk [3]. Maddaloni et al. also found lower than expected fragility fractures in patients with diabetes when compared to peers without diabetes [21]. Maddaloni et al. found a significant association between cardiovascular disease and lower bone mineral density independent of HbA1c suggesting that there are other risk factors contributing to poor bone health in these patients. Maddaloni et al. is not directly comparable to our study because it was conducted in patients from the Joslin Medalist Study which studied the effects of diabetes complications in patients with Type 1 diabetes for more than 50 years. The retrospective design of our study limited the ability to determine duration of diabetes accurately so this covariate could not be included in our analysis. However, both studies explicitly included elderly patients which could in part help explain the similar results [21]. Vavanikunnel et al. recently published a case-control study where they similarly concluded there was no effect of HbA1c in patients with type 2 diabetes [22]. They additionally found the risk of fracture was elevated with use of a thiazolidinedione, independently of glycemic control. This study was similar in that it also had a large cohort, used a mean of HbA1c measurements per person, and had access to additional information to adjust for risk factors. This study included one possible explanation for the lack of association between glycemic control and fractures could be the beneficial effect of insulin resistance in type 2 diabetes. They went on to explain that patient with type 2 diabetes have obesity-related insulin resistance and hyperinsulinism compared to healthy controls. Insulin is known to have anabolic effects on bone thus, patients with type 2 diabetes usually present with higher bone mass compared to those without diabetes [22].

Table 4 – Chi-square analysis of the hip fractures.*

Glycemic Control Group	Hip Fracture N (%)
Group 1 (Control)	405 (2.34)
Group 2 (HbA1c ≤7%)	211 (1.75)
Group 3 (HbA1C 7.1–8.0%)	74 (1.44)
Group 4 (HbA1C 8.1–9.0%)	27 (1.62)
Group 5 (HbA1C ≥9.0%)	9 (1.56)

* Overall $p < 0.0001$.

Other explanations to the difference in our studies results may be because there have been several changes to the treatment of diabetes over time. These include a reduction in the use of thiazolidinediones [24], and higher use of medications with lower hypoglycemia risks including longer acting insulins [25], GLP-1 agonists [26], DPP-4 inhibitors, and SGLT2 inhibitors [27]. There is a possibility that these treatment changes could be reducing the risk of fractures in patients with type 2 diabetes since thiazolidinediones have been associated with fractures [28] and hypoglycemia has been associated with falls causing fractures [6]. Of note the use of thiazolidinediones in this study was not associated with a statistically significant increase in fractures. This result is consistent with previously published studies that found only an increase in fractures when thiazolidinediones were used in women and not men [28].

We did identify some possible modifiable risk factors which can be seen in Table 2 such as medication, Vitamin D supplementation, reduction in alcohol consumption and nicotine use, along with fall preventative measures. Vitamin D deficiency and heavy alcohol use are risk factors known to be associated with low bone mineral density [19,29]. Our results suggest that vitamin D deficiency (<30 ng/dL), alcohol use disorder, and lower BMI were significantly associated with higher incidence rates of fractures suggesting that treating these risk factors may play an important role in preventing fractures.

There were some advantages of this study compared to previous studies, which include the availability of data beyond simply ICD 9 and 10 codes. The VA being an integrated healthcare system uses the VINCI database, which provides access to laboratory test results, and medication dispensing records. This study was longer than many of the previous studies, and provided a more accurate estimate of the effect of glycemic control over time by calculating an average HbA1c as reported above instead of only a baseline HbA1c which was done in the studies by Li et al. [1], Puar et al. [4], and Oei et al. [5]. The specific calculation for average HbA1c was chosen in order to reduce skewed results for patients who may have had more frequent laboratory monitoring when their HbA1c was not well controlled, however; this technique was also limited by utilizing only the first data entry for each qualifying study year. The study included a large sample size from eight different hospitals within the VA healthcare system from real-world subjects. Lastly, this study collected data on confounding factors including risk and protective factors for osteoporosis or fractures unlike some of the previous studies.

However, several limitations should be considered. While attempts were made to adjust for other confounders, unmeasured confounders or potential lack of consistent coding by providers for significant confounders such as falls, hypoglycemia, and hypotension could also affect this difference. The hazard ratios for these confounders should be interpreted cautiously knowing that episodes of hypoglycemia and hypotension may be underreported in retrospective data based on ICD coding. Additionally, coding for these events as visit or admission diagnoses may be more likely to occur in more severe cases where hospitalization or immediate clinical attention is needed. Regardless, the hazard ratios do show an increased risk for fractures among patients with encounters that coded for hypoglycemia, hypotension, or fall. It is difficult to determine the overlapping effect of these variables due to the low numbers of patients with coding for multiple of the three variables. Additionally, in those, for instance, both with history of hypoglycemia and fall, it is uncertain which predates the other. From these retrospective data, it is not possible to determine any causal relationship between hypoglycemia/hypotension and falls. Additionally, there is potential for undocumented, miss-coded events and comorbidities as this study relied on provider's ICD9/ICD10 coding on patient encounters to be accurate and does not include events that may have been treated at non-VA hospitals and not documented into a patient's electronic medical chart, which may be more likely in more rural areas. Attempts were made to limit the possibility of a misclassification bias by classifying subjects who received antihypoglycemic medication for diabetes as having diabetes even if there was no clinical encounter coded with a diabetes ICD9/ICD10 code. Though, it is also possible that some patients may have had diabetes diagnosed and treated outside of the VA system, which this analysis would not be able to detect. As with any retrospective study there is a major limitation caused by the possibility for unmeasured confounding factors including the inability to extract bone mineral density results electronically from the medical record and unreported falls, hypoglycemia, or hypotensive events. The larger sample size in the no diabetes group may have increased the power for comparisons with this group leading to the ability to statistically detect smaller effect sizes. Finally, while attempts were made to control for pre-existing diagnoses, such as renal disease and alcohol use disorders, that could affect bone mineral density through regression analysis, subjects with these conditions could have been excluded from the study to prevent controlling incompletely for confounding based on these surrogate measures.

The effects of hypoglycemia on fractures is difficult to capture in studies due to the complexity of gathering accurate data on hypoglycemia. The ACCORD BONE study excluded patients with severe frequent hypoglycemia which may have significantly influenced the study results [3]. The retrospective studies by Conway et al. and Puar et al. were unable to gather any information about hypoglycemia [2,4]. Similar to our study, the retrospective study by Li et al. used ICD codes from inpatient admissions and outpatient clinic visits to control for hypoglycemia, however they did not find hypoglycemia to be a statistically significant risk factor for hip fractures [1]. Unlike, Li et al. [1] our study did not find a higher risk of fractures with higher HbA1c averages, which may have been due to the smaller sample size in Group 5 (average HbA1c >9% [>75 mmol/mol]). This smaller sample size may have decreased the power in this group. Metformin may be associated with less risk of fracture and there is growing evidence that SGLT2 inhibitors pose an increased risk of fracture. The effect of DPP-4 inhibitors and GLP-1 agonist seem to still be uncertain [30]. In this study, the exposure to SGLT2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors were limited based on the timeframe studied. Metformin, SGLT2 inhibitors, DPP-4 inhibitors, and GLP-1 agonist were evaluated for the final regression model though none met the criterion to stay in the model or improved model fit.

Further studies should evaluate fracture risk based on glycemic control for the populations not well represented in this study including women and minorities races. Prospective cohort studies would be needed to accurately measure confounding factors such as hypoglycemia, hypotension, falls, duration of diabetes, and bone mineral density.

6. Conclusion

In elderly Veterans with type 2 diabetes the average HbA1c 7.1–8.0% [54–64 mmol/mol] and 8.1–9% [65–75 mmol/mol] have the lowest incidence rate of fracture events compared with those without diabetes showing the highest incidence rate; however, due to the overall low rate of fracture, the absolute differences in fracture incidences were small. The no diabetes group is associated with the highest fracture risk which may be due to the larger sample size, increased prevalence of osteoporosis diagnosis, alcohol use disorder and vitamin D deficiency. Additionally, this might be attributed to the anabolic effects of insulin due to obesity-related insulin resistance in type 2 diabetes. Beyond limiting modifiable risk factors such as vitamin D supplementation these results do not support altering diabetes treatment strategies to reduce fracture risk. Additional prospective studies are needed to understand the risk and time course of hypoglycemia, hypotension, and falls on fracture risk.

Conflict of interest

The authors declared that there is no conflict of interest.

Acknowledgments

SLB designed the study, wrote the manuscript and analyzed the data. TG designed the study and analyzed the data, and reviewed and edited the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.027.

REFERENCES

[1] Li C, Liu C, Lin W, et al. Glycated hemoglobin level and risk of hip fracture in older people with type 2 diabetes: a competing risk analysis of Taiwan diabetes cohort study. J Bone Mineral Res 2015;30(7):1338–46. https://doi.org/10.1002/jbmr.2462.
[2] Conway B, Long D, Figaro M, May M. Glycemic control and fracture risk in elderly patients with diabetes. Diabetes Res Clin Pract 2016;115:47–53. https://doi.org/10.1016/j.diabres.2016.03.009.
[3] Schwartz A, Margolis K, Sellmeyer D, et al. Intensive glycemic control is not associated with fractures or falls in the ACCORD randomized trial. Diabetes Care 2012;35(7):1525–31. https://doi.org/10.2337/dc11-2184.
[4] Puar T, Khoo J, Cho L, et al. Association between glycemic control and hip fracture. J Am Geriatr Soc 2012;60(8):1493–7. https://doi.org/10.1111/j.1532-5415.2012.04052.x.
[5] Oei L, Zillikens M, Dehghan A, et al. High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: the Rotterdam study. Diabetes Care 2013;36(6):1619–28. https://doi.org/10.2337/dc12-1188.
[6] Johnston SS et al. Association between hypoglycemic events and fall-related fractures in medicare-covered patients with type 2 diabetes. Diabetes Obesity Metabol 2012;14(7):634–43.
[7] Miao J, Brismar K, Nyren O, Ugarph-Morawski A, Ye W. Elevated hip fracture risk in type 1 diabetic patients: a population-based cohort study in Sweden. Diabetes Care 2005;28(12):2850–5.
[8] Brauer Carmen A. Incidence and mortality of hip fractures in the United States. JAMA302.14 2009:1573 [Web. 16 July 2017].
[9] Keenan H, Maddaloni E. Bone microarchitecture in type 1 diabetes: it is complicated. Curr Osteoporos Rep 2016;14(6):351–8. https://doi.org/10.1007/s11914-016-0338-8.
[10] Shanbhogue V, Hansen S, Frost M, et al. Bone geometry, volumetric density, microarchitecture, and estimated bone strength assessed by HR-pQCT in adult patients with type 1 diabetes mellitus. J Bone Mineral Res 2015;30(12):2188–99. https://doi.org/10.1002/jbmr.2573.
[11] Standards of medical care in diabetes – 2012. Diabetes Care.
[12] Departments of Veterans Affairs and Defense. VA/Dod clinical practice guideline for the management of type 2 diabetes mellitus in primary care version 5.0. The Management of Type 2 Diabetes Mellitus in Primary Care Work Group; 2017. p. 28–35.
[13] Glycemic Targets. Diabetes Care 2016;40(Supplement 1):S48–56. https://doi.org/10.2337/dc17-s009.
[14] Older Adults. Diabetes Care 2016;40(Supplement 1):S99–S104. https://doi.org/10.2337/dc17-s014.2011;35(Supplement_1):S11-S63 [doi:10.2337/dc12-s011].
[15] Ghodsi M, Larijani B, Keshtkar A, Nasli-Esfahani E, Alatab S, Mohajeri-Tehrani M. Mechanisms involved in altered bone metabolism in diabetes: a narrative review. J Diabetes Metabol Disord 2016;15(1). https://doi.org/10.1186/s40200-016-0275-1.
[16] US Department of Veterans Affairs. 172VA10P2: VHA Corporate Data Warehouse-VA [79 FR 4377. Updated January 1, 2018. Accessed April 30, 2018].
[17] Pencina MJ, D'agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004;23(13):2109–23.
[18] Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43(11):1130–9. https://doi.org/10.1097/01.mlr.0000182534.19832.83.
[19] Cho Y, Choi S, Kim K, Lee G, Park S. Association between alcohol consumption and bone mineral density in elderly Korean men and women. Arch Osteoporos 2018;13(1). https://doi.org/10.1007/s11657-018-0462-4.
[20] Osteoporosis Facts and Statistics | International Osteoporosis Foundation. Iofbonehealth; 2018. Available at: https://www.iofbonehealth.org/facts-and-statistics/hipfracture-incidence-map [accessed May 28, 2018].
[21] Maddaloni E, D'Eon S, Hastings S, et al. Bone health in subjects with type 1 diabetes for more than 50 years. Acta Diabetol 2017;54(5):479–88. https://doi.org/10.1007/s00592-017-0973-2.
[22] Vavanikunnel J, Charlier S, Becker C, et al. Association between glycemic control and risk of fracture in diabetic patients: a nested case-control study. J Clin Endocrinol Metabol 2019. https://doi.org/10.1210/jc.2018-01879.
[23] Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358(24):2545–59. https://doi.org/10.1056/nejmoa0802743.

[24] Starner C, Schafer J, Heaton A, Gleason P. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J Manag Care Pharm 2008;14(6):523–31. https://doi.org/10.18553/jmcp.2008.14.6.523.

[25] Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005;28(4):950–5. https://doi.org/10.2337/diacare.28.4.950.

[26] Bajaj H, Venn K, Ye C, et al. Lowest glucose variability and hypoglycemia are observed with the combination of a GLP-1 receptor agonist and basal insulin (VARIATION study). Diabetes Care 2016;40(2):194–200. https://doi.org/10.2337/dc16-1582.

[27] SGLT2 inhibitors: a new treatment option for type 2 diabetes. Pharmacytimes; 2018. Available at: https://www.pharmacytimes.com/publications/health-system-edition/2014/september2014/sglt2-inhibitors-a-new-treatment-option-for-type-2-diabetes [accessed May 28, 2018].

[28] Zhu Z, Jiang Y, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone 2014;68:115–23. https://doi.org/10.1016/j.bone.2014.08.010.

[29] Napoli N, Strollo R, Sprini D, Maddaloni E, Rini G, Carmina E. Serum 25-OH Vitamin D in relation to bone mineral density and bone turnover. Int J Endocrinol. 2014;2014:1–5. https://doi.org/10.1155/2014/487463.

[30] Palermo A, D'Onofrio L, Eastell R, et al. Oral anti-diabetic drugs and fracture risk, cut to the bone: safe or dangerous? A narrative review. Osteoporos Int 2015;26:2073–89.