Published in final edited form as:

Diabetes Res Clin Pract. 2016 May ; 115: 47–53. doi:10.1016/j.diabres.2016.03.009.

Glycemic Control and Fracture Risk in Elderly Patients with Diabetes

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Abstract

Aims—Elderly patients with diabetes are at increased fracture risk. Although long exposure to hyperglycemia may increase fracture risk via adverse effects on bone metabolism, tight glycemic control may increase risk via trauma subsequent to hypoglycemia. We tested the prospective relationship between glycemic control and fracture risk in 10,572 elderly patients (age ≥ 65) with diabetes.

Methods—Geriatric patients with diabetes were drawn from Vanderbilt University Medical Center's Electronic Health Record. Baseline was defined as age at first HbA1c after the latter of age 65 or ICD 9 code for diabetes. Cox analysis was used to test the relationship of updated mean HbA1c (average HbA1c over follow-up) with time to first fracture since baseline. HbA1c was categorized as follows: <6.5% [<48 mmol/mol]; 6.5–6.9% [48–52 mmol/mol]; 7–7.9% [53–63 mmol/mol]; 8–8.9% [64–74 mmol/mol]; ≥ 9% [≥ 75 mmol/mol]. The number of BMI measurements was used as a surrogate for relative frequency of outpatient visits, i.e. patient-provider contacts.

Results—During follow-up, there were 949 fracture events. HbA1c demonstrated a cubic relationship with fracture risk ($p < 0.05$). In analyses accounting for age, sex, race, and number of BMI measures (a surrogate for patient-provider interaction), compared to an HbA1c of 7–7.9%, HR (95% CIs) were: HbA1c < 6.5% HR = 0.97 (0.82–1.14), 6.5–6.9% HR = 0.80 (0.66–0.97), 8–8.9% HR = 1.13 (0.92–1.40), ≥ 9% HR = 1.19 (0.93–1.54).

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This paper was presented in abstract form at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, June, 2014.

Conclusions—An HbA1c of 6.5-6.9% is associated with the lowest risk of fracture in elderly patients with diabetes. Risk associated with an HbA1c $\geq 9\%$ may be a marker of infrequent patient-provider interaction.

Keywords

glycemic control; hypoglycemia; HbA1c; fracture; diabetes; geriatric

Introduction

Each year Americans experience over 2 million fragility fractures,⁽¹⁾ costing over \$16 billion.⁽²⁾ Consequences of fragility fractures include temporary or permanent disability, loss of independence, increased in-patient hospital stay days,⁽³⁾ and increased nursing home facilities use. More importantly, fragility fractures increase rates of mortality, with reported mortality rates up to 20–24% in the first year.⁽⁴⁻⁶⁾

Fragility fractures are more common among patients with diabetes. In the geriatric population already at an increased risk of fractures, diabetes increases this risk several fold.^(7, 8) Those with diabetes and fractures also are at an increased risk of infections,^(9, 10) have longer hospital stays,⁽¹¹⁾ and require a longer time to heal following fractures.^(12, 13)

Lowering HbA1c to the American Diabetes Association (ADA) recommended HbA1c target of $<7\%$ offers protection against microvascular complications, particularly in young and middle-aged patients.⁽¹⁴⁾ ADA recommendations for 2012-2014 included two additional groups: 1) HbA1c $<6.5\%$ for selected individual with short duration of diabetes, expected long lifespan, and the absence of severe cardiovascular disease; 2) less-stringent HbA1c goals, such as $<8\%$, for those with limited life expectancy, severe microvascular and macrovascular complications, and comorbidities. However, there is some evidence that tight glycemic control in older patients with longer history of diabetes may increase the risk of fractures. Tight glycemic control was associated with increased fracture risk in a Taiwanese population with diabetes.⁽¹⁵⁾ The proposed reasons for this association include confusion, gait abnormality, and instability during the hypoglycemic episodes, medication effects from some classes of diabetes drugs, as well as contribution from traditional osteoporosis risk factors and secondary osteoporosis.⁽¹⁶⁾ Nevertheless, long term exposure to poor glycemic control may also increase fracture risk via effects on bone metabolism and structural architecture^(17, 18) and diabetes complications, such as neuropathy and retinopathy, affecting falls risk.

As both tight and poor glycemic control may affect fracture risk in elderly individuals with diabetes, we investigated the relationship of glycemic control with risk of fracture in a large geriatric patient population with diabetes. To do this, we examined the relationship of HbA1c, stratified into five different categories, with risk of fracture in approximately 10,000 elderly patients with diabetes receiving care at Vanderbilt University Medical Center.

Materials and Methods

This study prospectively followed a cohort of 10,572 patients over the age of 65 years with diabetes. Data were retrieved from the Synthetic Derivative (SD), which is a de-identified, non-relinkable copy of the electronic medical records database at Vanderbilt University Medical Center (VUMC). The SD was developed as a research tool to enable epidemiological investigation using routine clinical data. The data have been collected daily since the early 1990s and include over 1.7 million in- and out-patient medical records. Inclusion of patients was on an opt-out basis, which means that the patients have to specifically opt-out of the SD when they were consenting to treatment at VUMC. The SD includes approximately 95% of the VUMC patient population. The database included information such as diagnostic (ICD9) and procedure (CPT) codes, basic demographics, and clinical care text.

All HIPAA identifiers were removed from medical records, in accordance with human subjects research (45 CFR 46), through a process of scrubbing which utilized a de-identification algorithm.⁽¹⁹⁾ All dates within the medical records were shifted 1 to 364 days in the past so that chronological order and date intervals were retained for each record, but the date could no longer be used to identify the individual.⁽²⁰⁾ Because the date shift is consistent within each record and new data are appended to existing patient records, longitudinal analysis of the records is possible. The earliest start date was within one year prior to March 27, 1991. A full description of the Standard Derivative and de-identification process has been previously published.⁽¹⁹⁾ This study met criteria for non-human subjects research and received approval as a non-human subjects designation from both the Vanderbilt University IRB and the federal Office for Human Research Protections (OHRP).

Figure 1 shows the derivation of our cohort of geriatric patients with diabetes. Patients with diabetes were identified by ICD 9 codes 250-250.9. Fracture cases were identified based on ICD 9 codes 820-829 or 733 (Online Supplementary Table 1). Inclusion criteria for the current study included an ICD 9 code for diabetes (ICD 9 code 250-250.9), age 65 years or older, and a minimum of two HbA1c values at or after the latter of six months prior to age 65 years or ICD9 code for diabetes. Study baseline was defined based on the following hierarchy: 1) age at first HbA1c measurement at or after the latter of age 65 or ICD 9 code for diabetes at or prior to first fracture; 2) for those with no HbA1c data at or after the latter of age 65 or ICD 9 code for diabetes, within six months prior to the latter of age 65 or ICD 9 code for diabetes. Thus, of the 99,241 patients identified in the EMR with ICD 9 codes for diabetes, 557 were excluded due to missing age at time of recording of ICD 9 code for diabetes and another 87,022 patients were excluded due to missing data on HbA1c at study baseline. An additional 2,202 patients had only one HbA1c value recorded during the study time period. The remaining 10,572 patients, with at least two HbA1c values during the study time period formed our study population.

Cox proportional hazards modeling, using age as the time scale, was used to determine hazard ratios (HRs) and their 95% confidence intervals (CIs) for first fracture at the latter of age 65 or ICD 9 code for diabetes. For clinical meaningfulness in the relationship of glycemic control with fracture risk, HbA1c was modeled in groups defined by HbA1c

levels: <6.5% [<48 mmol/mol]; 6.5-6.9% [48-52 mmol/mol]; 7-7.9% [53-63 mmol/mol]; 8-8.9% [64-74 mmol/mol]; 9% [≥ 75 mmol/mol]. We tested the association of baseline and updated mean HbA1c with fracture risk. Baseline was defined as in Figure 1, that is age at the first HbA1c after the latter of age 65 years or ICD 9 code of diabetes and before or within six months of the first fracture. Updated mean HbA1c was defined as the average of all HbA1c values from baseline until the first fracture or censoring.

In addition to HbA1c, multivariable models included race (White, African American, Other race, Unknown race), sex, and number of BMI measurements. Number of BMI measurements was used as a surrogate for relative frequency of outpatient visits with a provider. The criterion for statistical significance was a p-value <0.05 otherwise. Statistical analyses were conducted using SAS version 9.3 (Cary, North Carolina).

Results

Table 1 shows the baseline characteristics of the 10,572 Vanderbilt University Medical Center geriatric patients with diabetes. Patients were on average 72 years of age at study baseline and 51% were female. Seventy-three percent of patients were White, 15% were African American, 2% were identified to be of other racial background, and 10% of the patients had no documented race (Unknown race). The study population was in good glycemic control, with a mean baseline HbA1c of 7.3% (56 mmol/mol) and an updated mean HbA1c of 7.2% (55 mmol/mol).

The median number of BMI measurements was 8. Twenty-four percent of the population had zero BMI measurements. The percentage of patients with zero BMI measurements increased with increasing HbA1c category; 19.1% and 19.3% of those with an HbA1c $<6.5\%$ and between 6.5-6.9% had zero BMI measurements, 24.5% of those with an HbA1c between 7-7.9% had zero BMI measurements, while 36.3% and 38% of those with an HbA1c between 8-8.9% and 9%, respectively, had zero BMI measurements.

During an average of 3.3 (SD=3.1) years of follow-up, there were 949 first fracture events. Compared to those with a baseline HbA1c between 7 and 7.9%, those with a higher HbA1c were at an increased fracture risk (HbA1c 8-8.9% HR=1.35, 95% CI=1.09-1.66; HbA1c 9% HR=1.21, 95% CI=0.97-1.52). No increase in risk was observed in those with an HbA1c $<7\%$ compared to those with an HbA1c between 7 and 7.9% (HbA1c <6.5 HR=0.89, 95% CI=0.75-1.06 HbA1c 6.5-6.9=0.92, 95% CI=0.76-1.12).

Kaplan-Meier curves depicting risk of fracture by updated mean HbA1c category and using a) age and b) follow-up-time as the time scale are depicted in Figure 2. Panel A shows that the lowest fracture hazard was for patients with an HbA1c between 6.5 and 6.9%. Those with an HbA1c between 8 and 8.9% and 9% were at a similarly high risk of fracture up until their late 70s, after which an HbA1c 9% posed the greatest risk of fracture. After approximately age 90, all patients were at a similar risk of fracture regardless of updated mean HbA1c category. Panel B suggests that the excess fracture risk associated with an HbA1c $>9\%$ increased over time. Comparison of panels A and B also suggests that age had

a greater impact on fracture risk than the number of years after the age of 65 that the patient had lived with diabetes.

Table 2 shows the multivariable adjusted association between updated mean HbA1c and fracture risk. Model 1 shows analyses accounting for age, sex, and race. Compared to those with an average HbA1c between 7 and 7.9% during follow-up, those having an average HbA1c <6.5% were at similar risk, while those having an HbA1c between 6.5 and 6.9% were at lower risk of fracture. Having an HbA1c ≥8% increased risk of fracture, with the greatest risk observed for those with an HbA1c ≥9%. Additionally accounting for the number of BMI measurements during follow-up, our marker of relative frequency of visiting a provider, removed the excess risk associated with having an HbA1c ≥8% but had no effect on the protection against fracture associated with having an HbA1c between 6.5 and 6.9% (model 2). If an HbA1c of 6.5-6.9% was used as the reference, an HbA1c <6.5% was associated with significantly increased fracture risk, HR=1.24 (95% CI=1.02-1.51). Formal tests for linearity revealed that HbA1c demonstrated a cubic relationship with fracture (p-value=0.005, p-value =0.049 after further adjustment for number of BMI measurements). This further supports an HbA1c between 6.5-6.9% as the nadir for fracture risk in this population, with increased risk both above and below this range.

The 10 most common fracture types were fractures of the femoral neck (n=140), vertebral column without spinal injury (n=132), ribs (n=86), ankle (n=77), radius (n=75), humerus (n=71), tarsals (n=68), hip (n=49), tibia (n=37), and foot (n=35). When grouped broadly into upper body, lower body, and hip, the nadir for fracture remained in the 6.5-6.9% HbA1c range, though a protective relationship against lower body fracture was also observed for the <6.5% HbA1c range (Online Supplementary Table 2). As with all-cause fracture risk, accounting for the number of BMI measurements greatly attenuated excess risk associated with an HbA1c ≥9% for each of the broad categories of fracture.

Discussion

We examined the prospective associations of HbA1c with fracture risk in 10,572 geriatric patients with diabetes. We found that an HbA1c at baseline and an average HbA1c over time in the 6.5-6.9% range was associated with the lowest fracture risk, with fracture risk increasing both above and below that range. When stratified by fracture type, the nadir for fracture risk remained in the 6.5-6.9% range. Risk associated with an HbA1c ≥9% appeared to be a marker of infrequent patient-provider interaction.

Elderly individuals with diabetes are at a 2-to-8-fold increased risk of fragility fractures compared to similarly aged individuals without diabetes.(7, 8, 21, 22) This is true even in persons with type 2 diabetes despite similar or increased bone mineral density compared to those without diabetes.(8, 23) Possible mechanisms for increased fracture risk in diabetes include organic factors affecting bone density and strength,(17, 18, 24, 25) diabetes complication-related factors increasing the risk of falls, and medications affecting both bone strength and fall risk.(26-28) Poor glycemic control may also affect fracture risk indirectly by increasing the incidence and progression of microvascular complications such as retinopathy, nephropathy and neuropathy which may in turn affect fall risk. Any of these

mechanisms may be mediators of the relationship between glycemic control and fracture risk. The current ADA Clinical Practice Recommendations are that glycemic control targets in elderly patients should be individualized based on the complexity of the patient's health status, with falls risk being listed as one of the patient characteristic placing the patient in the complex/intermediate health status.(29) In this study we have focused on the risk associated with degree of glycemic control, since falls risk, as a proxy for fracture risk, is a complex/intermediate health status that would suggest glycemic control target of <8%.

We found that an HbA1c between 6.5 and 6.9% was the optimal glycemic control range with respect to fracture. Risk of fracture increased when HbA1c was either below or above this range, suggesting that both hypoglycemia and moderate to high hyperglycemia increase fracture risk, albeit perhaps via different mechanisms. An HbA1c >8% was associated with increased hospitalization due to fracture in the Atherosclerosis Risk in Communities study. (30) In the Rotterdam Study, an HbA1c greater than 7.5% was associated with increased fracture risk relative to those with a lower HbA1c or to those without diabetes.(31) In a large geriatric population with diabetes, Li et al. observed an increased risk of fracture associated with an HbA1c of 9% or greater compared to an HbA1c of 6-7%, findings consistent with ours when frequency of patient provider interaction was not taken into account.(32) Other studies, however, have failed to show an association of poorer glycemic control with increased fracture risk.(15, 33, 34) The lack of an association with fracture risk may be due to the varied age ranges of the populations studied, differences in the time window in which the association was assessed, that is whether the relationship was investigated cross-sectionally or prospectively, and whether glycemic control was forced to have a linear relationship with fracture risk in the statistical analysis. By allowing HbA1c to have a non-linear relationship with fracture risk in our statistical analysis, we have shown that glycemic control has a curvilinear relationship with fracture risk in geriatric patients with diabetes. However, our data also suggests that the increased risk associated with higher HbA1c in our population may reflect factors associated with frequency of patient provider interaction. After controlling for number of BMI measurements, our surrogate for relative frequency of outpatient visits with the provider, the excess risk associated with an HbA1c > 7-7.9% disappeared. This might be related to the salutary effect of medical management on risk factors for falls and fractures (appropriate A1c control for level of risk, use of Vitamin D and bisphosphonates).

In contrast to the weak evidence of a relationship between poor glycemic control and fracture risk, studies have shown an increased risk of fractures associated with hypoglycemia (35) or tighter glycemic control.(15, 23) A case-control study in Taiwanese geriatric patients with Type 2 diabetes showed that tighter glycemic control (HbA1c <7%) was associated with increased risk of fractures.(15) In the Health, Aging and Body Composition study, an HbA1c <6% compared to an HbA1c>8% was associated with an increased risk of falls in elderly patients with diabetes.(36) However, this association was observed in insulin users only, suggesting that hypoglycemia was a mediator of the relationship between very tight glycemic control and falls risk.(36) It is possible that trauma resulting from hypoglycemic events may result in fractures in the elderly. In our population, a cumulative average HbA1c <6.5% up to time of fracture or end of follow-up was associated with increased fracture risk. By contrast, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,

intensive glucose control was not associated with fracture risk in persons with diabetes. The failure to show any relationship of lower HbA1c with fracture risk may have been due to exclusion criteria that included frequent serious hypoglycemia, BMI ≥ 45 kg/m², serum creatinine >1.5 mg/dL, or other serious illness at the time of the study. No such exclusion criteria were in our study and may explain the discrepancy between our results and that of the ACCORD trial.

Strengths of our study include the large size of the cohort studied, racial diversity, and prospective design. However our study is not without the limitations common to studies that repurpose EHR data for epidemiology research, such as the use of ICD codes for the selection of disease phenotypes, missing data on HbA1c and BMI, and the inability to determine those for whom VUMC was the true medical home. ICD 9 codes are reimbursement codes and the use of ICD 9 codes for the selection of our diabetes cohort may have resulted in the exclusion of some patients with diabetes for whom no ICD 9 code for diabetes was recorded. The use of ICD 9 codes may also have resulted in false positive diabetes cases; however as two HbA1c measurements were available on each patient in our cohort, we believe this limits the number of false positive diabetes cases. Additionally, if HbA1c was being obtained in people without diabetes, low HbA1c ($<6.5\%$) as a marker of normal glucose tolerance would not be associated with increased fracture risk. A potential limitation of this study is that no distinction was made between Type 1 and Type 2 diabetes. Although algorithms have been developed for distinguishing between Type 1 and Type 2 diabetes in EHR systems, these have not been validated in geriatric populations. While it is possible that the risk of fracture associated with glycemic control may vary between type 1 and type 2 diabetes, ours was a geriatric diabetic population and therefore the percentage of this diabetic population with Type 1 diabetes would likely have been minuscule and thus with minimal effect on our results. Another potential limitation was that ICD 9 codes were used to select for fracture cases which may have resulted in misclassification of outcome status if the patient was not treated for fracture at Vanderbilt; however, all patients in our cohort having at least two HbA1c measurements increases the likelihood of VUMC being the patient's medical home and our ability to capture a fracture event.

The concept of missing data in the EHR, such as for HbA1c or BMI is an arguable limitation as it is not clear that the data are truly missing if they were never intended to be collected. Nevertheless data such as BMI may potentially serve as a proxy for the relative frequency for which the patient is being seen on an out-patient basis or the intensity of care the patient is receiving. In our patient cohort, the number of BMI measurements was a strong inverse marker of fracture risk. Further evaluation of this marker is warranted.

Fracture risk is increased with both poor and very tight glycemic control in elderly patients with diabetes. Our data suggests that sparse patient-provider interaction is a major modulator of this risk in those with elevated HbA1c, particularly in non-Whites. HbA1c goals for elderly patients with diabetes may benefit from being neither too low $<6.5\%$ nor too high $>9\%$ to prevent excess risk for fractures, although risk associated with an A1c $\geq 9\%$ may be an indicator of less frequent patient-provider interaction. Using the number of BMI measurements in an EHR may be a simple mechanism to assess the relative frequency of

outpatient patient-provider interaction in studies utilizing routine clinical data for epidemiology purposes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

BNC conceived and designed the study, wrote the manuscript and analyzed the data. DML designed the study and analyzed the data. KF reviewed the manuscript, contributed to the discussion, and reviewed and edited the manuscript for scientific content. MEM conceived the study and reviewed and edited the manuscript for scientific content. BNC serves as guarantor and takes full responsibility for integrity of all of the content of this manuscript, from inception to published article. The authors would like to thank Dr. William Herman for critical review of this manuscript. The authors have no conflicts of interests to declare.

This study was supported in part by the West Virginia University grant CTSI grant U54GM1049 from the National Institutes of Health (NIH) and the Vanderbilt University CTSA grant UL1 TR00445 from NCATS/NIH.

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- The relationship of glycemic control and fracture in elderly patients with diabetes was assessed
- An HbA1c between 6.5 to 6.9% range was optimal for minimizing fracture risk
- Risk associated with n HbA1c 9% may be an indicator of less frequent patient-provider interaction

Figure 1.
Derivation of the cohort. *SD=Synthetic Derivative

Figure 2.

Kaplan-Meier curves of fracture risk by updated mean HbA1c category, with age as the time scale. Pane a: age is used as the time scale; panel b: follow-up time is used as the time scale. HbA1c <6.5% [<48 mmol/mol] $n=3,417$; HbA1c 6.5-6.9% [$48-52$ mmol/mol] $n=2,044$; HbA1c 7-7.9% [$53-63$ mmol/mol] $n=2,927$; HbA1c 8-8.9% [$64-74$ mmol/mol] $n=1,234$; HbA1c $\geq 9\%$ [≥ 75 mmol/mol] $n=837$.

Table 1

Characteristics of the Vanderbilt University Geriatric Population with Diabetes, mean (std), median (IQR), or n (%)

Characteristic	
Age, years	71.6(6.6)
Sex, female	5,370 (50.8)
Race	
White	7764 (73.4)
Black	1559 (14.7)
Other race	241 (2.3)
Unknown race	1008 (9.5)
Baseline HbA1c, %; [mmol/mol]	7.3 (3.5); [56 (15) mmol/mol]
Updated mean HbA1c, %; [mmol/mol]	7.2 (2.6); [55 (4.9) mmol/mol]
Last HbA1c, %; [mmol/mol]	7.1 (2.4); [54 (2.7) mmol/mol]
BMI, kg/m ²	30.7 (8.1) *
Number of BMI measurements	8 (1-21)

* 24% of the population had zero BMI measurements.

Table 2

Multivariable adjusted association of updated mean HbA1c with time to first geriatric fracture after known history of diabetes

	Model 1	Model 2
	HR (95% CI)	HR (95% CI)
Updated mean HbA1c category		
<6.5% [<48 mmol/mol]	0.96 (0.81-1.13)	0.97 (0.82-1.14)
6.5-<7.0% [48-52 mmol/mol]	0.77 (0.64-0.93)	0.80 (0.66-0.97)
7.0-<8.0% [53-63 mmol/mol]	Ref	Ref
8.0-<9.0% [64-74 mmol/mol]	1.22 (0.99-1.50)	1.13 (0.92-1.40)
9% [75 mmol/mol]	1.55 (1.21-2.00)	1.19 (0.93-1.54)
Sex, female	1.72 (1.50-1.97)	1.69 (1.48-1.94)
Race category		
White	Ref	Ref
Black	0.73 (0.61-0.88)	0.79 (0.66-0.94)
Other	0.95 (0.64-1.43)	1.01 (0.67-1.51)
Unknown	0.40 (0.26-0.61)	0.28 (0.19-0.43)
Number of BMI measurements	-----	0.97 (0.96-0.97)

HbA1c <6.5% [<48 mmol/mol] n=3,417; HbA1c 6.5-6.9% [48-52 mmol/mol] n=20,4%; HbA1c 7-7.9% [53-63 mmol/mol] n=2,927; HbA1c 8-8.9% [64-74 mmol/mol] n=1,234; HbA1c 9% [75 mmol/mol] n=837.

Formal tests for linearity revealed that HbA1c demonstrated a cubic relationship with fracture (p-value=0.005, p-value =0.049 after further adjustment for number of BMI measurements).