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노인과 중년 당뇨병 환자의 골절의 발생 빈도 위험과 혈당조절의 관계

신혜연*
덕성여자대학교 약학대학
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Risk of Fracture Prevalence and Glycemic Control in Korean Older and Middle-aged Patients with Diabetes: A Retrospective Analysis of a Cohort Derived from the Korean National Health Insurance Sharing Service Database, 2009-2013

Hye Yeon Sin*
College of Pharmacy, Duksung Women's University, Seoul 01369, Republic of Korea
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ABSTRACT

Background: Bone fractures are high in elderly patients with type 2 diabetes mellitus (T2DM). Hyperglycemia and chronic kidney disease may increase the risk of fracture prevalence via altered bone metabolism, but whether glycemic control and kidney function are associated with the risk of fracture prevalence remains unclear. This study evaluated the relationship between glycemic control and baseline estimated glomerular filtration rate (eGFR) and risk of fracture prevalence in older and middle-aged patients with T2DM. **Methods:** Patients who underwent a general medical check-up between 2009 and 2013 were selected from the Korean National Health Insurance Sharing Service records. Chi-square test and multiple logistic regression analysis were used to assess the relationship between glycemic control and eGFR and risk of fracture prevalence. **Results:** Cumulative fracture prevalence were higher in patients with T2DM, irrespective of whether they had tight or less stringent glycemic control (fasting blood glucose [FBG] ≥ 110 mg/dL). After adjustment for baseline age and FBG, tight and less stringent glycemic control was significantly associated with increased adjusted risk of fracture prevalence in middle-aged patients with T2DM (OR=1.13, 95% CI, 1.05-1.21, p=0.0005 vs OR=1.13, 95% CI, 1.06-1.20, p=0.0001), but not in older patients. Baseline eGFR was not significantly related to fracture prevalence in either older or middle-aged patients. **Conclusion:** Less stringent glycemic control significantly increased the adjusted risk of fracture prevalence in middle-aged patients with T2DM. Further studies are needed to confirm the effect of tight glycemic control on fracture prevalence.

KEY WORDS: Fracture prevalence, type 2 diabetes mellitus, glycemic control, glomerular filtration rate

The risk of bone fracture in both men and women with type 2 diabetes mellitus (T2DM) is known to be high.[1-6] Patients with diabetes and fractures are at high risk of post-fracture infections.[7] Fracture risks in diabetes have been linked to multiple factors including aging, body mass index (BMI), estimated glomerular filtration rate (eGFR), glycated hemoglobin, low bone turnover, bone mineral density (BMD), and medication use.[8-12] Lowering blood glucose levels to the target level has been shown to reduce microvascular complications,[13-14] whereas it has been shown to increase the risk of cardiovascular disease and mortality in middle-aged patients with diabetes.[15] Less stringent glycemic control (HbA1C < 8%) in patients with limited life expectancy or severe hypoglycemia is associated with increased risk of fracture and macro- and microvascular complications.[16-17] However, a recent study showed that fracture risk did not depend on the level of glycated hemoglobin and/or

*Correspondence to: Hye Yeon Sin, College of Pharmacy, Duksung Women's University, Samyang-ro 144 gil 33, Dobong-gu, Seoul 03169, Republic of Korea
Tel: +82-2-901-8739; Fax: +82-2-901-8386
E-mail: hyshin@duksung.ac.kr

fasting blood glucose (FBG) in patients with T2DM.[18-19] Tight glycemic control was shown to be related to increased hypoglycemic risk and fracture prevalence in patients with diabetes in Singapore.[20]

Vertebral fracture risk was higher in patients with T2DM and lower eGFR[21-22] than in those with normal eGFR in a study by Mishima *et al*.[10] However, in the randomized observational Action to Control Cardiovascular Risk in Diabetes Trial (ACCORD),[23] there was no difference in fracture prevalence between older patients with T2DM and normal baseline eGFR (> 60 ml/min/1.73 m^2) and those with T2DM and low baseline eGFR (< 60 ml/min/1.73 m^2).

Tight as well as less stringent glycemic control may influence the risk of fracture by influencing bone metabolism and structure in diabetic patients.[24] Chronic kidney disease in patients with diabetes may affect mineral metabolism and effectively reduce bone strength,[25] but baseline eGFR in patients with diabetes is not related to fracture prevalence in diabetes. As limited data are available regarding the association of glycemic control and kidney function with fracture prevalence, this study evaluated the association of glycemic control and baseline eGFR with fracture prevalence in a large cohort of older and middle-aged patients with T2DM.

Methods

Data sources

This study retrospectively evaluated a cohort of 71,025 adults aged 45 to 79 years. Community-dwelling adults who met the research criteria and had visited health care institutions including tertiary and secondary hospitals, long-term care facilities, clinics, and public health clinics, for a general medical check-up at least bi-annually in the regional areas of South Korea from January 01, 2009, to December 31, 2013, were included. The data were collected as follows: the Cohort database provided by the Korean National Health Insurance Sharing Service (KNISS) included diagnostic, procedure, and health examination codes and basic characteristics. The cohort had been randomly selected from the electronic medical records of insurance enrollees, aged 45 to 79 years, between 2009 and 2013. Through a centralized database extracted from the KNISS, with non-personally identifiable information only used for research, subjects were selected based on a table that was created using the database link, with person identification as a joint key according to KNISS algorithm. The Institutional Review Board (IRB) of Duksung Women's University approved the research protocol with non-human designation. Additionally, the study was approved by the KNISS and was conducted in accordance with the Declaration of Helsinki.

Study Design

Using the longitudinal cohort database of 510,000 individuals from KNISS, 71,025 subjects, aged 45 to 79 years, who met the inclusion criteria based on the study protocol, were selected. There were 11,235 subjects with the diagnosis of T2DM and 59,790 age-matched subjects without any diagnosis of diabetes mellitus. To identify subjects with or without diabetes, this study required at least two FBG and two eGFR measurements during the study period. Subjects with any fracture diagnosis between January 1, 2009, and December 31, 2013, were included because it was difficult to distinguish the record of fracture occurring in a particular year from the duplicated fracture record that would appear next year in the KNISS database. Subjects were excluded if they were less than 45 years old, had type-1 diabetes mellitus, had received a kidney transplant, had a history of pancreatic cancer, or had osteoporosis; a total of 276,580 individuals were excluded. Osteoporosis was excluded to minimize negative osteoporotic effects on fracture events. Individuals were excluded if baseline FBG and eGFR measurements were missing, or only 1 FBG and eGFR measurement was obtained during the bi-annual visits over the 5-year follow-up period. Figure 1 illustrates the derivation of cohorts with and without diabetes. To identify coexisting medical status with respect to diabetes and fracture, subjects with T2DM were identified by KCD codes E11-E11.9 corresponding to physician-diagnosed diabetes mellitus or FBG > 126 mg/dL. Subjects without a diabetes diagnosis and fasting blood glucose less than 125 mg/dL between January 1, 2009, and December 31, 2013, were the reference cohort. Adults aged 45 to 64 years were classified as middle-aged patients, and adults aged 65 to 79 years were classified as older patients.

To evaluate risk of fracture prevalence according to glycemic control, FBG status was classified as tight glycemic control (FBG < 110 mg/dL) and less stringent glycemic control (FBG > 110 mg/dL) using the American Association of Clinical Endocrinologists (AACE) clinical guidelines (2015). To evaluate risk of fracture prevalene according to kidney disease, eGFR was

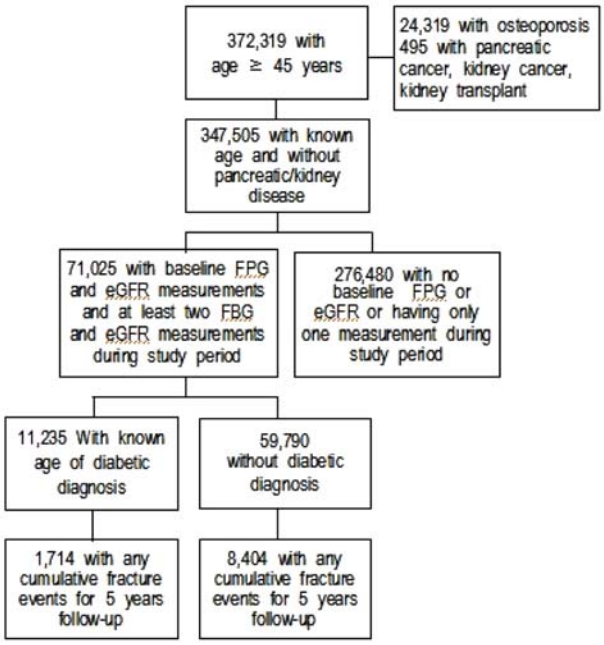

Fig. 1. The derivation of cohort with type 2 diabetes or without diabetes

classified using the KNISS definition of kidney disease status as normal eGFR (≥ 60 ml/min/1.73 m^2) and low eGFR (< 60 ml/min/1.73 m^2).

Definitions

This study used KCD CODE to define medical conditions. Subjects with T2DM were identified by KCD codes E11-E11.9. Fracture cases were identified by KCD codes as follows: skull and facial bones (S02.0-S92.291), neck (S12.0–S12.9), rib, sternum and thoracic spine (S22.0–S22.9, 807 809, 810), lumbar spine (S32.0–S32.8, 808–808.09,808.11–808.19, 808.91–808.99, 809, 805–806), pelvic (S32.0–S32.8, T02.1-T02.71, M48.40-M48.49, M84.0-M84.49), shoulder and upper arm (S42.0–S42.9, 811–812, 818–819), forearm (S52.0–S52.9, 813, 818–819), wrist and hand (S62.0-S62.9, 814–816.09, 816.19, 816.99–817, 818–819), femur (S72.0-S72.9, 820-820.12, 820.18-820.92, 820.98-821.22, 821.28-821.32, 821.38-821.92, 821.98-821.99, 827-829), lower leg and ankle (S82.0-S82.9, 822-824.03, 824.08-824.13, 824.18-824.93, 824.98-824.99, 827-829), and foot (S92.0-S92.9, 825 826.01-826.19, 826.99-829.99). To determine the baseline for medication use, insulin and other antidiabetic drugs were identified using the Health Insurance Review and Evaluation Center Pharmaceutical Standards Information (HIREC-PSI) codes: insulin (461801BIJ - 488701BIJ), alpha-glucosidase inhibitors (100601ATB, 348002ATB - 249002ATD), biguanides (498100ATB, 502300ATB - 507100ATB, 513700ATB - 519600ATB), sulfonylureas (474200ATB-TR, 165801ATB - 165901ATB, 471900ATB, 497200ATB), glinides (486101ATB, 430201ATB - 430203ATB), glitazones (431901 ATB - 431902ATB 525901ATB, 348002ATB), GLP-1 receptor agonists (512101BIJ - 512102BIJ, 626601BIJ - 626602BIJ), DPP-4 inhibitor (500801ATB - 501103ATB, 520500ATB - 520700ATB, 520500ATB - 520700ATB), and SGL2 inhibitors (527301ATB - 527302ATB). Other drugs that can increase blood glucose or affect bone formation were identified by their HIREC-PSI codes: bisphosphonates (358001ATB, 442330ATB, 480304ATB, 500200ATB), vitamin D/calcium (473800ATB, 498200ATB - 498300ATB, 503100ATB), thyroxine (183601ATB), corticosteroids (116530BIJ, 142232BIJ, 243335BIJ, 170901ATB, 193302ATB, 622901ATR), and estrogen therapy (239001ATB, 297600ATB, 490400ATB, A14500ATB-A15500ATB, A43900ATB, 557100ATB, 183403ATB). Past medical history and family history of heart disease included myocardial infarction and angina. Past medical history was identified by KNISS code as follows: T2DM (HCHK_DIABML_PMH_YN), hypertension (HCHK_HPRTS _PMH_ YN), heart disease (HCHK_HDISE_PMH_YN), and hyperlipidemia (HCHK_ HPLPDM_PMH_YN). Family history was identified as T2DM (FMLY_DIABML_PATIEN _YN), hypertension (FMLY_HPRTS_PATIEN_YN), and heart disease (FMLY_HDISE_PATIEN_YN).

Statistical Analysis

Descriptive statistics and univariate analyses were used to assess baseline patient characteristics. Chi-square test and Kaplan-Meier methods, using FBG as the time scale and eGFR, were used to determine cumulative risk of fracture over time for patients with T2DM or without diabetes. Adjusted fracture prevalence by age, FBG, eGFR, body mass index (BMI), sex, medication use, and past medical history of diabetes were used to estimate potential confounding factors using a multiple logistic regression model and the Wald Chi-square test. Risk of fracture was evaluated using a Chi-square test and was stratified by FBG and eGFR level. Odds ratio of risk of fracture prevalence by the location (femur bone, pelvic bone, spinal bones) was evaluated using the Chi-square test. For statistical significance, p-value was set at < 0.05. Data

Table 1. Baseline characteristics

Variables	Type 2 diabetes	Reference cohort	*p*-value
Number of patients, N	11,235	59,790	
Gender n(%)[a]			
Male	6,512(58.0)	31,806(53.2%)	<.001
Female	4,723(42.0)	27,984(46.8%)	<.001
Follow up, years	5.0	5.0	
Age years[b], n(mean, S.D)[b]			
45-54	3,089(50.7±2.4)	29,232(50.1±2.5)	<.0001
55-64	4,019(60.3±2.5)	17,340(59.9±2.5)	<.0001
65-74	3,273(69.8±2.5)	10,308(69.8±2.5)	0.69
>75	854(79.7±3.1)	2,910(79.9±3.3)	0.12
Family history n(%)[a]			
Diabetes	1,976(17.6)	3,503(5.9)	<.0001
Hypertension	1,296(11.5)	7,134(11.9)	<.0001
Heart disease	304(2.7)	1891(3.2)	0.04
Past medical history n(%)[a]			
Diabetes	6,847(60.6)	0	<.0001
Hypertension	4,883(43.5)	18,109(30.3)	<.0001
Heart disease	653(5.8)	2,246(3.8)	<.0001
Hyperlipidemia	1,024(10.5)	3,465(5.8)	<.0001
Fracture	1,636(14.6)	7,705(12.9)	<.0001
Laboratory data, mean(S.D)[c]			
Height (cm)	161.1(±8.9)	161.3(±8..7)	0.18
Weight (kg)	64.7(±10.7)	62.7(±10.2)	<.0001
BMI (Kg/m^2)	24.8(±3.2)	24.1(±3.0)	<.0001
45-64 years	25.00(±3.2)	24.1(±2.9)	<.0001
65-84 years	24.7(±3.3)	23.9(±3.1)	<.0001
SBP (mmHg)	128.6(±15.6)	125.8(±15.6)	<.0001
DBP (mmHg)	78.2(±9.9)	78.0(±10.1)	0.02
eGFR (ml/min/1.73m^2)	81.2(±28.2)	82.3(±38.9)	0.0006
Scr (mg/dL)	1.1(±1.2)	1.2(±1.5)	<.0001
FBG (mg/dL)	136.2(±49.7)	97.0(±17.3)	<.0001
Urine albumin (mg/dL)	1.23(±0.7)	1.09(±0.4)	<.0001
Triglyceride (mg/dL)	165.8(±113.4)	140.1(±92.5)	<.0001
LDL-Cholesterol (mg/dL)	109.4(±44.5)	119.2(±41.4)	<.0001
Medication n(%)[a]			
Insulin	294(2.6)	0	<.0001
Antidiabetic agents	8,470(75.4)	0	<.0001
Bisphophanates	12(0.1)	28(0.05)	0.01
Vitamin D/calcium	48(0.4)	104(0.2)	<.0001
Thyroxine	198(1.7)	961(1.6)	0.23
Corticosteroids	1,544(13.7)	9,042(15.1)	0.0002
Estrogen therapy	140(1.3)	996(1.7)	0.001

[a] Data for gender, family history, past medical history, medications are reported as number of people (%). [b]Data for age reported as number of people (mean, standard deviation). [c]Data for laboratory data are reported as mean(standard deviation). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; FBG, fasting blood glucose; LDL, low density lipoprotein cholesterol

were analyzed using SAS, version 9.2 (SAS Institute, Cary, NC, USA). Patient medical records were selected and assessed by professional statisticians.

Results

Baseline characteristics

Baseline characteristics of patients with and without diabetes during follow-up were compared, and the data are shown in Table 1. Of a total of 372,319 individuals, 71,025 were included and evaluated retrospectively. A total of 11,235 individuals were diagnosed with T2DM, and 59,790 individuals without diabetes were used as the reference cohort. The following subjects were excluded: 276,480 with data missing for FBG and eGFR recorded at baseline and at bi-annual (minimum) visits over the 5-years of follow-up, 495 with pancreatic cancer, kidney cancer, or kidney transplant, and 24,319 with osteoporosis. During 5 years of follow-up, there were 1,714 cumulative fracture events in patients with T2DM. The mean age was 61.9 years at baseline. A family history of diabetes and hypertension was significantly higher in patients with diabetes ($p < 0.001$). Overall, past medical history of bone fracture was significantly higher in patients with diabetes than in the reference cohort ($p < 0.0001$). Compared with the reference cohort, mean FBG level ($p < 0.0001$), mean eGFR ($p = 0.0006$), mean BMI ($p < 0.0001$), and medication use, including bisphosphonates, vitamin D/calcium, and thyroxine, was higher in patients with T2DM, whereas the reference cohort used more corticosteroids and estrogen therapy at baseline.

Effects of glycemic control on fracture prevalence

Cumulative fracture prevalence was higher in patients with T2DM than in the reference cohort during follow-up. A significantly higher risk of fracture prevalence was observed in middle-aged T2DM patients with less stringent glycemic control (FBG ≥ 110 mg/dL, OR = 1.29, 95% CI: 1.16-1.43, $p = 0.0001$). Older patients with diabetes and older reference cohorts with FBG of < 110 mg/dL and ≥ 110 mg/dL both showed similar high fracture prevalence than middle-aged patients, as shown in Table 2. Cumulative fracture prevalence increased for all age groups over time, as shown in Figure 2. Comparison of fracture prevalence suggests that age had a negative effect on fracture prevalence, while mean FBG < 110 mg/dL did not significantly increase fracture prevalence in patients with diabetes. However, with a multivariable adjustment for baseline

Table 2. Relationship between glycemic control and cumulative risk of fracture prevalence in older and middle aged patients type2 diabetes for 5 years of follow-up

Age	Middle aged patients (45-64 years)			older patients (65-79 years)		
Fasting blood Glucose (mg/dL)	Diabetes %[a] (n/total)	Reference cohort %[a] (n/total)	*p*-value OR 95% CI	Diabetes %[a] (n/total)	Reference cohort %[a] (n/total)	*p*-value OR 95% CI
<110	15.0 (308/2,049)	14.0 (5,550/39,529)	0.23 1.08 (0.95-1.22)	18.2 (240/1,318)	16.8 (1,715/10,203)	0.20 1.10 (0.95-1.28)
≥110	15.6 (766/4,896)	12.6 (821/6,529)	0.0001 1.29 (1.16-1.43)	16.8 (400/2,379)	15.8 (318/2,008)	0.38 1.07 (0.91-1.26)

[a]Data for fracture incidence are reported as number of people per total patients (%). Abbreviations: CI, confidence interval; OR, odds ratio. Cumulative fracture prevalence was higher in both oldr and middle aged patients with T2DM compared to reference cohort during follow-up. Less stringent glycemic control (FBG≥110 mg/Dl) in middle aged patients with T2D was associated with significantly increased risk of fracture prevalence.

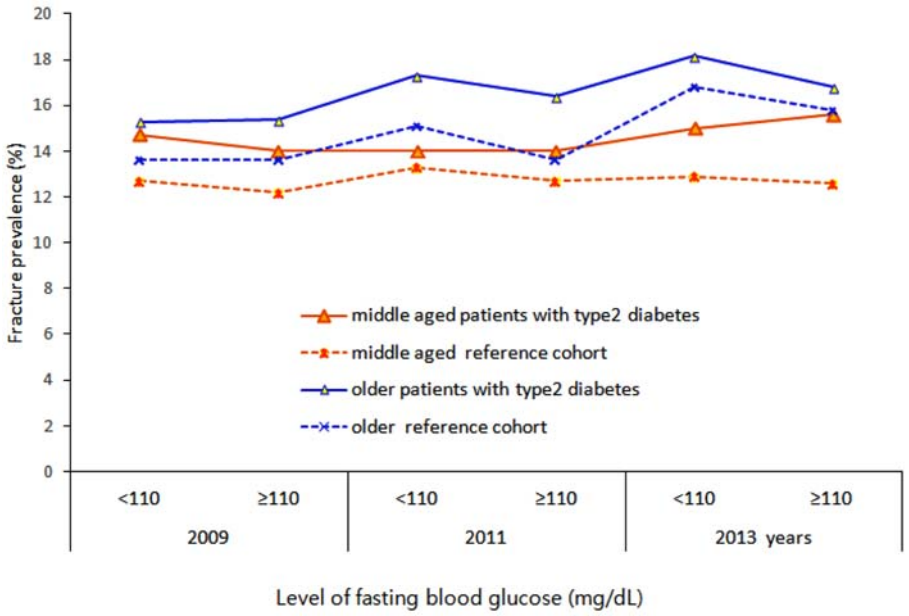

Fig. 2. Comparison of cumulative fracture prevalence in older and middle-aged patients in relation to glycemic control for five years of follow-up
Cumulative fracture prevalence gradually increased with age in patients with T2DM. Odds ratio of fracture risk was significantly higher in middle-aged patients with diabetes with less stringent glycemic control than the age-matched reference cohort (p < 0.0001, OR = 1.29, 95% CI = 1.16-1.43). Abbreviations: CI: confidence interval, FBG: fasting blood glucose, Reference cohort: without diabetes mellitus, OR: odds ratio, p: p-value, DM: type2 diabetes mellitus

age and FBG, the adjusted risk of fracture prevalence was significantly higher in middle-aged patients with T2DM (OR = 1.13, p=0.0001 vs OR=1.13, p=0.0005). The adjusted association between age, FBG, FBG, eGFR, BMI, sex, medication use, history of diabetes, and risk of fracture is shown in Table 3. After adjusting for sex, BMI, and medication use, both males and females and obesity was significantly associated with increased risk of fracture prevalence, but medication use was significantly associated with decreased risk of fracture prevalence in patients with diabetes compared to the reference cohort.

Effect of eGFR on fracture prevalence

Cumulative fracture prevalence was not significantly different in older and middle-aged patients with type 2 diabetes compared to those in the reference cohort, irrespective of whether baseline eGFR was normal (≥ 60 ml/min/1.73 m^2) or low (< 60 ml/min/1.73 m^2). The greatest risk of hip fracture prevalence was seen in middle-aged patients with diabetes and normal eGFR (OR = 1.44, 95% CI: 1.00-2.06, p=0.04), as shown in Figures 3-1 and 3-2. Subjects with normal eGFR ≥ 60 ml/min/1.73 m^2 and low eGFR < 60 ml/min/1.73 m^2 had the same degree of risk for spinal fracture prevalence in

Table 3. Association of adjusted multivariable factors with risk of fracture prevalence

Parameters	Odds ratio, 95% CI	p-value
Age, years		
45~64	1.09 (1.04-1.15)	0.0007
65~79	1.06 (0.99-1.14)	0.09
Sex		
Male	1.07 (1.02-1.13)	0.01
Female	1.13 (1.06-1.20)	0.0002
FBG, mg/dL		
<110	1.13 (1.05-1.21)	0.0005
≥110	1.13 (1.06-1.20)	0.0001
eGFR, ml/min/1.73m^2		
<60	1.02 (0.91-1.14)	0.78
≥60	1.10 (1.05-1.15)	<.0001
BMI, kg/m^2		
<25	1.07 (1.01-1.13)	0.02
≥25	1.11 (1.04-1.18)	0.0008
Medication use		
Yes	0.82 (0.77-0.86)	<0.0001
No	0	
History of T2DM		
Yes		0
No	1.14 (1.06-1.23)	0.0003

Multiple logistic regression tests showed that age, sex, FBG, eGFR, BMI, history of T2DM were significantly associated with risk of fracture prevalence. Old age and low eGFR was associated with increased risk of fracture prevalence in diabetes, but it was not significant. Medication use was also related to low risk of fracture prevalence. Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; OR, odds ratio

patients with diabetes. This suggests that normal eGFR ≥ 60 ml/min/1.73 m^2 had no protective effect against fracture. The risk of fracture prevalence at the femoral, hip, and lumbar spinal sites by eGFR level is shown in Table 4. Table 3 shows multivariable adjusted association between eGFR and fracture. Compared to eGFR matched patients without diabetes, the adjusted risk of fracture prevalence was significantly higher in both older and middle-aged patients with diabetes and normal eGFR.

Discussion

Using a nationwide cohort of patients with diabetes, this retrospective cohort study assessed the risk of fracture prevalence in older and middle-aged patients with T2DM by FBG and eGFR to determine whether risk of fracture prevalence was associated with glycemic control and kidney disease during the follow-up period. This study found that overall cumulative fracture prevalence was higher in both older and middle-aged T2DM patients than in the reference cohort. Both tight and less stringent glycemic control were associated with increased adjusted risk of fracture prevalence in diabetes over time. A case-control study from Singapore reported that tight glycemic control (HbA1C < 7%) was related to increased hypoglycemia and increased age-adjusted fracture

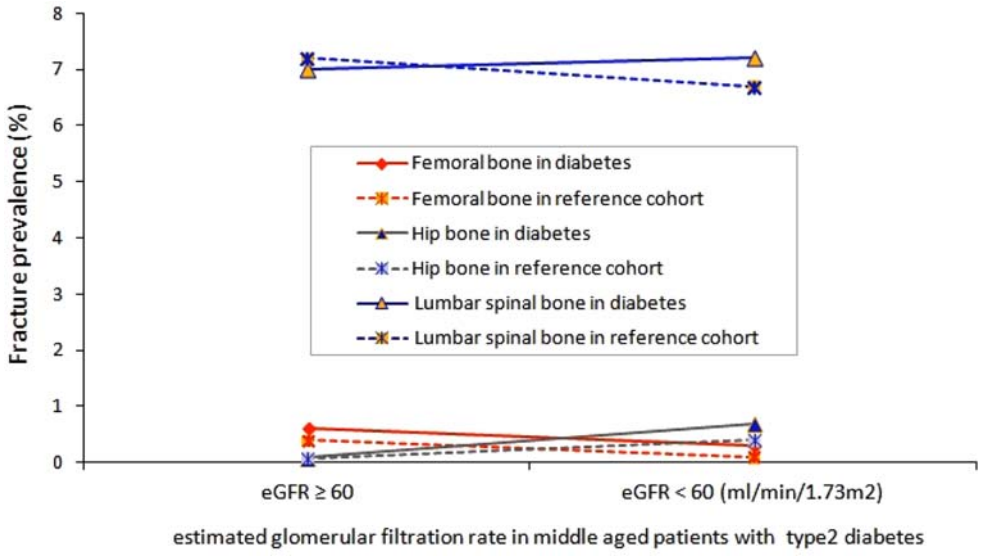

Fig. 3-1. Comparison of cumulative fracture prevalence in middle-aged patients with and without diabetes, when stratified by eGFR, over five years of follow-up
Cumulative fracture prevalence at the hip site was significantly higher in middle-aged patients with type 2 diabetes (OR = 1.44, 95% CI: 1.00-2.06, p = 0.04) than in the reference cohort irrespective of whether baseline eGFR was normal (≥ 60 ml/min/1.73m^2) or low (< 60 ml/min/1.73 m^2). Abbreviations: CI: confidence interval, eGFR: glomerular filtration rate, OR: odds ratio, p: p-value, reference cohort: without diabetes mellitus

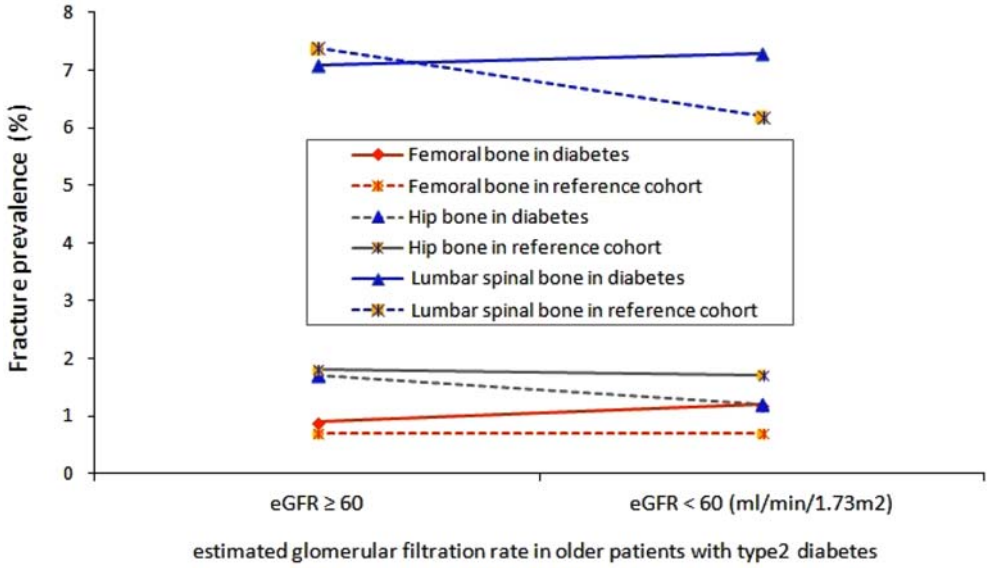

Fig. 3-2. Comparison of cumulative fracture prevalence in older patients with and without diabetes, as stratified by eGFR, over five years of follow-up
Fracture prevalence at the hip site was not significantly altered in older patients with diabetes compared to those in the reference cohort (OR = 0.94, 95% CI: 0.68-1.30, p = 0.69) with normal eGFR.Abbreviation: eGFR: glomerular filtration rate, OR: odds ratio, CI: confidence interval, p: p-value, reference cohort: cohort of individuals without diabetes mellitus

prevalence in older patients with T2DM,[20] this suggested that age had a negative effect on fracture prevalence, but tight glycemic control had no protective effect against fracture, perhaps via different mechanisms influencing bone fragility. However, in a geriatric study, Conway[5] described that tight glycemic control (HbA1C < 7%) was associated with a lower risk of

Table 4. Cumulative risk of fracture prevalence at femoral, hip, lumbar spinal sites by category of eGFR between type2 diabetes and reference cohort

Category of eGFR (ml/min/1.73 m^2)	eGFR ≥ 60		eGFR < 60	
Fracture prevalence	Middle aged diabetes/ reference cohort (n=6,453/43,034)	older diabetes/ reference cohort (n=3,149/10,974)	Middle aged diabetes/ reference cohort (n=655/3,532)	older diabetes/ reference cohort (n=978/2,244)
Femoral fracture, n (%)[a]				
Type2 diabetes	7(0.11)	25(0.9)	2(0.3)	10(1.2)
Reference cohort	32(0.08)	65(0.7)	4(0.1)	13(0.7)
p-value	0.40	0.18	0.23	0.14
OR, 95% CI	1.42 (0.63-3.22)	1.37 (0.86-2.18)	2.71 (0.49-14.82)	1.84 (0.80-4.21)
Hip fracture, n (%)[a]				
Type2 diabetes	36(0.6)	47(1.7)	4(0.7)	10(1.2)
Reference cohort	163(0.4)	178(1.8)	13(0.4)	33(1.7)
p-value	0.04	0.69	0.37	0.36
OR, 95% CI	1.44 (1.00-2.06)	0.94 (0.68-1.30)	1.67 (0.54-5.13)	0.72 (0.35-1.46)
Lumbar Spinal fracture, n (%)[a]				
Type2 diabetes	427(7.0)	198(7.14)	44(7.2)	60(7.3)
Reference cohort	2847(7.2)	731(7.42)	221(6.7)	121(6.2)
p-value	0.60	0.61	0.65	0.28
OR, 95% CI	0.97 (0.87-1.08)	0.96 (0.81-1.13)	1.08 (0.77-1.51)	1.19 (0.86- 1.64)

[a]Data for frequency of bone fractures are reported as number of people (%). [b] Data for age, FPG, eGFR are reported as mean(standard deviation). Abbreviations: eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; OR, odds ratio; reference cohort, patients without type2 diabetes mellitus

fracture in elderly patients with T2DM than in patients with a baseline glycated hemoglobin level of 7-7.9%. In contrast, Schwartz[26] failed to show an association between tight glycemic control (A1C of 6.4-7.5%) and decreased fracture risk in older patients with T2DM.

Some aspect of a subject, Potential confounding variables may affect risk of fracture or fracture prevalence in diabetes. This study investigated the known confounders and risk factors such as advanced age[1-4], poor glycemic control,[5, 13-16] low GFR level,[21-22] high BMI,[27] medication use,[28-30] and female sex,[28, 30] to identify the relationship between these variables and risk of fracture prevalence using a multiple logistic regression model. Evaluating adjusted outcomes, the association between fracture prevalence and age differed between the middle-aged patients with T2DM and the age-matched reference cohort. Adjusted risk of fracture prevalence was significantly higher in only middle-aged patients with diabetes in this study. It can be inferred that middle-age may be negatively correlated with fracture prevalence because this group had low cortical volumetric BMD and high cortical porosity at the radius site, despite having low resorption than the control group.[30] However, in geriatric patients with CKD, Bacchetta et al. reported that older men and women with CKD had lower total volumetric BMD, trabecular volumetric BMD, and cortical thickness, and higher cortical porosity,[22] suggesting that cortical thickness and volumetric trabecular BDM was negatively associated with older patients with CKD. In contrast, Napoli failed to show an association between older diabetes and increased risk of fracture at the vertebral site.[31] In a study conducted by Shanbhogue, both older and middle-aged diabetes patients with macrovascular disease had lower cortical volumetric BMD, cortical thickness, and higher cortical porosity at the radius site.[30] The inconsistent association with risk of fracture prevalence might be due to the varied population parameters, such as age, FBG, chronic kidney disease, diabetic complications, and bone microarchitecture, evaluated in several previous studies.

This study found that cumulative fracture prevalence was not different in older and middle-aged patients with diabetes than in the reference cohort, irrespective of whether baseline eGFR was normal ($\geq$ 60 ml/min/1.73 m^2) or low ($<$ 60 ml/min/1.73 m^2). Bacchett reported that trabecular volumetric BMD and cortical thickness was significantly lower in CKD patients than in those with normal GFR, which was related to higher risk of fracture.[22] In contrast, the unadjusted fracture incidence was not increased or decreased in those with low GFR than in those with normal GFR in an Isavoka study,[23] suggesting that a normal eGFR $\geq$ 60 ml/min/1.73 m^2 had no protective effect against fracture. Factors that contribute to risk of fracture prevalence remain controversial.[30,31] The inconsistent evidence underlying fracture risk estimates may be due to the varied population parameters selected for previous studies or the small number of patients with recorded eGFR used for validation in this study.

Another study suggested that antidiabetic agents and other drugs had a positive effect on adjusted risk of fracture prevalence in patients with diabetes, but a few previous studies regarding interaction between antidiabetics or other drugs and bone fracture have shown variable results depending on the population parameters.[30, 31, 32-34] This could be explained by glucose metabolism and bone microarchitecture: osteocalcin is a protein that affects the pancreatic β-cell and adipose tissue,[35] and low osteoblast activity,[36] osteocalcin, and pro-collagen type 1 amino-terminate peptide[37] were associated with decreased bone formation or increased osteoblast proliferation, and collagen synthesis,[38] insulin use,[33-34, 39] and high fasting glucose levels were associated with increased fracture risk.[5, 39] A systematic meta-analysis[40] suggested that antidiabetic drugs such as insulin may affect bone metabolism and fracture, leading to increased fracture prevalence.[30, 33] Tight glycemic control with antidiabetic agents, including insulin, did not decrease or increase fracture prevalence in older patients with diabetes compared to those with standard glycemic control.[26] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) randomized trial failed to show the relationship between intensive glycemic control and decreased fracture risk in diabetes. Although diabetes is pathophysiologically involved in the negative regulation of bone formation and bone remodeling, this discrepancy may have been due to different population parameters and the disease status of patients included in the cohorts.

Strengths of this study included the use of a cohort design and a large sample size. Thus, the cohort is representative of the characteristics of the entire Korean population. Therefore, it may provide clinical information regarding fracture prevalence with respect to FBG and eGFR in Korean adults with T2DM. This study also has a few limitations. First, the data were obtained from a predominantly Korean population. Therefore, these results may not be extrapolated to the general population. Also, it is difficult to identify between new fracture incidences

and old fracture events using KCD code recorded in the KNISS database system, although cumulative fracture event estimates may counter this limitation. Second, potential limitation of this study is that antidiabetic agents and drugs that affect bone formation were not evaluated separately. This may obscure the individual effects of each antidiabetic agent and other drugs associated with risk of fracture prevalence. Third, the accuracy of diagnosis information in claim Health Insurance Review and Assessment Service (HIRA) data is limited. Though, there seems to be possible bias between diagnoses in HIRA data and actual medical conditions that a patient has, Park BJ study showed that an average of 70% of diagnoses in HIRA data is consistent with diagnoses at actual medical records.[41-42] Based on International Classification of Diseases 10th Revision (ICD-10) in Korea, accordance rate was 87.2% for diabetes (E10-14), 75.9% for inpatients setting and 72.3% for outpatients setting.[43] The variable results observed regarding fracture prevalence depend on various population parameters. For these reasons, it is crucial to consider a homogeneous population-based study to evaluate fracture risk and its effect on fracture prevalence as a protective factor in diabetes.

Conclusion

Tight glycemic control and less stringent glycemic control increased the adjusted risk of fracture prevalence in Korean middle-aged patients with diabetes. This study suggests that greater caution for middle-aged patients with diabetes, who exhibit less stringent glycemic control, may benefit to prevent fractures prevalence. Further longitudinal studies are needed to confirm the association between fracture prevalence and glycemic control.

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Conflict of Interest Statement

The author has no institutional interest or conflicts.

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