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Association of hip fractures with cardiometabolic-renal risk factors in Southern Chinese patients with type 2 diabetes – the Hong Kong Diabetes Register

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ABSTRACT

Introduction: Diabetes and bone health are closely related. We examined the incidence and risk factors of hip fractures in Chinese patients with type 2 diabetes (T2D).

Materials and Methods: In this prospective cohort, we consecutively enrolled 22,325 adults with T2D above the age of 40 years in the Hong Kong Diabetes Register between 1994 and 2015 with crude hip fracture incidence rate censored in 2017.

Results: At baseline, the mean age of this cohort was 60.9 ± 10.5 years (mean duration of diabetes 6 years, 52.4% male). During a mean ± standard deviation (SD) follow-up period of 8.7 ± 5.2 years with 193,553 person-years, 603 patients were hospitalized due to hip fractures with an incidence (95% confidence interval, CI) of 315.1 (290.4–341.3) per 100,000 person-years. On multivariable analysis with competing death risk adjusted, the independent hazard ratios (95% CI) for hip fractures in T2D were 2.01 (1.61–2.51) for female sex, 1.08 (1.07–1.09) for age, 0.93 (0.90–0.95) for body mass index, 1.52 (1.25–1.85) for albuminuria and 1.12 (1.02–1.23) for low density lipoprotein-cholesterol. In men, the 30-day, 1-year and 5-year post-hip fracture mortality rate (95% CI) were 5.8 (2.4–9.1) %, 29.2 (22.3–35.5) % and 65.9 (57.3–72.8) % respectively. The corresponding rates in women were 3.4 (1.6–5.1) %, 18.6 (14.7–22.4) %, and 46.8 (40.9–52.1) %.

Conclusions: Southern Chinese patients with T2D have a high risk of hip fracture associated with suboptimal cardiometabolic-renal risk factors and a high post-fracture mortality rate. The effects of improving modifiable risk factors on bone health warrants further evaluation.

INTRODUCTION

Globally and locally, the prevalence of type 2 diabetes (T2D) and osteoporosis are increasing. Osteoporosis and T2D are common age-related diseases, incurring a heavy burden on health care systems. People with type 1 diabetes (T1D) and T2D have increased risk of osteoporotic fractures[1-4]. Evaluation of fracture risk is now recommended as part of diabetes management with diabetic osteodystrophy viewed as one of the diabetes complications[2]. While patients with T1D are reported to have low bone mass contributing to increased risk of fractures[3], the association between T2D and bone mineral density (BMD) is more controversial with most studies reporting increased BMD in Caucasian patients with T2D[1], even after adjustment for body size[4].

Meta-analyses have confirmed the high incidence of fragility fracture due to minimal (e.g. fall from a standing height or

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lower) or no identifiable trauma in patients with T2D[5]. However, epidemiological data regarding fragility fractures among patients with T2D in Asia are scarce. In Asia, the number of hip fractures has been projected to increase by 2.28-fold from 1,124,060 in 2018 to 2,563,488 in 2050[6]. The number of hip fractures in Hong Kong, a cosmopolitan city in Southern China with 7.5 million people, has been projected to increase by 3-fold from 9,590 to 27,468 during the same period of time[6]. Caucasian patients with T2D usually have high BMD which might protect them from osteoporotic fractures. It is unknown whether the low body mass index (BMI) in Asian patients with T2D might be associated with increased risk of fracture. Given the potential impacts of abnormal metabolic milieu on cell metabolism, we hypothesize that the increased hip fracture risk in Chinese patients with T2D may be associated with modifiable cardiometabolic-renal risk factors.

In this study, we aimed to examine the incidence and risk factors for hip fracture among Hong Kong Chinese patients with T2D enrolled in a hospital-based diabetes register. Hip fracture was chosen because this is the most serious consequence of osteoporosis associated with substantial health, financial and societal burden. Moreover, since all patients with hip fractures required hospital admission for either operation or conservative treatment, the capture of hip fracture incidence using hospitalization admission data is reliable.

MATERIAL AND METHODS

The healthcare system in Hong Kong is heavily subsidized and the majority of patients with hip fractures, as well as chronic diseases including T2D, received care from public-funded healthcare facilities governed by the Hospital Authority (HA). HA provides > 90% of outpatient and inpatient care in Hong Kong. Since 2000, HA has established a territory-wide Clinical Management System (CMS) to record all health data including diagnoses and hospitalizations.

The Hong Kong Diabetes Register (HKDR) has been established since 1994 as a research-driven quality improvement program at the Prince of Wales Hospital (PWH) which serves a population of > 1.3 million. The details of HKDR have been published[7]. In brief, since 1994, all patients attending the PWH medical clinics were referred to the Diabetes and Endocrine Centre to undergo structured evaluation by trained nurses using case report forms to document sociodemographic data, lifestyle and self-management, history of comorbidities, current medications as well as anthropometric measurements, eye and feet examination[8]. Blood and urine samples were collected after at least 8 hours of fasting. All patients had unique identifiers which were linked to the HA Clinical Data Analysis and Reporting System (HA-CDARS) as part of the HA data system to capture hospitalization data for evaluation of outcomes including death.

Macrovascular disease was defined by a history of ischemic heart disease, cerebrovascular disease or peripheral vascular disease (lower extremity amputation, revascularization or ankle-brachial index ≤ 0.9). Diabetic retinopathy was detected by fundus photos which were read by endocrinologists or trained internists. Severe diabetic retinopathy was defined as pre-proliferative or proliferative retinopathy, or prior use of laser therapy. Sensory neuropathy was defined by the presence of two of three criteria: (i) abnormal sensation in the lower extremities, (ii) reduced sensation to monofilament, or (iii) reduced vibration sense to graduated tuning fork testing. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 derived from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[7]. End stage kidney disease was defined as eGFR < 15 ml/min/1.73m^2[7]. Microalbuminuria was defined as urinary albumin-creatinine ratio (ACR) of 2.5–30 mg/mmol in men or 3.0–30 mg/mmol in women, and macroalbuminuria as urinary ACR > 30 mg/mmol[7]. Severe hypoglycemia was defined as hypoglycemia events requiring hospitalizations or assistance by a third person, based both on self-report and hospital record. All participants gave written informed consent for analysis and reporting of the anonymized data. The study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee. The Institutional Review Board number of this study was CREC Ref. No. 2017.460.

Fracture ascertainment

Admission data for fractures were ascertained from the HA-CDARS using International Coding of Diseases (ICD) 9 codes: 820 for hip fracture, 813 for wrist fracture, 805 for spinal fracture and 812 for proximal humerus fracture. Fractures at hip, wrist, spine and proximal humerus are termed collectively as major osteoporotic fractures (MOF). Repeated admissions of the same patient were excluded from the analysis. Time to first hip fracture after study entry was calculated according to the first date of the X-ray during the admission. All hip fractures were fragility fractures (i.e. fractures resulting from minor injuries like fall from standing height or less) ascertained by X-ray.

For comparison, we used a territory-wide report on the incidence of hip fracture in Hong Kong[9]. These data were obtained through HA-CDARS. Patients aged 50 years and above with a principal diagnosis coded as ICD10 S72.0–72.2 from all hospital admissions in 2000–2004 in Hong Kong were reported. We also compared the mortality rate in our cohort with another territory-wide report on mortality rate of Hong Kong adults aged ≥ 65 years who underwent surgery for hip fracture between January 2000 to December 2011[10]. These data were also retrieved from HA-CDARS[10].

Statistical analysis

The first hip fracture to occur after recruitment was considered the end point for analysis.

Person-years were calculated from the date of enrolment to the HKDR until the date of hip fracture, death or end of study; whichever was earlier. Age- (grouped into 5-year age groups)

and sex-specific incidence rates for hip fractures were calculated. Data were presented as mean ± standard deviation (SD) or percentages, medians (IQR, interquartile range) and incidence (95% confidence interval, CI). Differences in the mean values or proportions between the hip fracture group and the no-hip fracture group (no-MOF group plus those with fractures at spine, humerus or distal radius) for the whole cohort, were tested using Student t test or χ^2 test or Fisher's exact test, as appropriate.

After excluding patients with prior history of MOF (n = 308), we performed Cox proportional hazards regression on those without prior history of MOF (n = 22,107) to identify risk factors for hip fracture outcome (Group B in Figure 1). Since the competing risk of death would influence the occurrence of hip fracture, we applied the competing-risk regression model. We entered covariates based on prior knowledge[1,2,4,6] and those with significantly different values in the univariate analysis. We performed sequential adjustment with Cox regression using 6 models (model 1: age, sex, duration of diabetes and HbA_{1c}; model 2: model 1 + BMI; model 3: model 2 + history of severe hypoglycemia; model 4: model 3 + systolic blood pressure (BP), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), smoking (ex- or current); model 5: model 4 + presence of CKD, microvascular complications including sensory neuropathy, severe retinopathy, albuminuria; model 6: model 5 + presence of macrovascular complications and insulin usage. HbA_{1c} was modelled as a continuous valuable. We performed these sequential models using 2 methods: (i) incident hip fracture group (group B in Figure 1) versus no-hip group (group E + F in Figure 1) and (ii) incident hip fracture group (group B) versus no-MOF group (group F). Estimates of risk association were expressed as hazard ratio (HR) and 95% CI.

So, this is a case control study in a well-defined cohort. This cohort consisted of patients enrolled in the HKDR between 14th July 1994 and 31st May 2015. We performed two separate Cox regression analyses. The cases were those patients who developed incident hip fractures on follow up. In the first analysis, the controls were those without incident hip fracture (no-hip fracture group, group E + F in Figure 1). In the second analysis, the controls were those without incident MOF (no-MOF group, group F in figure 1).

RESULTS

Figure 1 summarizes the cohort included for different analyses. We included consecutive patients enrolled in the HKDR between 14th July 1994 and 31st May 2015 with censor date on 30th June 2017 after excluding participants with non-Chinese ethnicity, type 1 diabetes and age less than 40 years old (n = 22,325, 52.4% men, mean age 60.9 ± 10.5 years). At baseline, the mean age of this cohort was 60.9 ± 10.5 years. During a mean follow-up of 8.7 ± 5.2 years, 189 men and 414 women (total 603) had an admission diagnosis of hip fracture. The crude hip fracture incidence rate was 315.1 (290.4–341.3) per 100,000 person years. The majority of hip fractures occurred in older adults aged ≥ 65 years (n = 545, 90.4%) with a crude incidence of 766.1 (696.1–841.2) per 100,000 person years. The corresponding figure in patients aged < 65-years was 121.9 (103.9–142.1) per 100,000 person years. Table 1 summarized the difference between the patients with incident hip fractures and those without (including those had wrist, spine or humeral fractures).

At baseline, in the entire cohort (n = 22,325), patients who sustained incident hip fractures (n = 603, group A + B) were more likely to be women, older, non-smoker, with longer duration of diabetes, lower BMI and waist circumference (in men) than the no-hip fracture group (n = 21,722, group C + D+E + F) (Table 1). They were more likely to have suboptimal control of cardiometabolic risk factors (HbA_{1c}, fasting plasma glucose, total cholesterol, LDL-C, systolic BP),

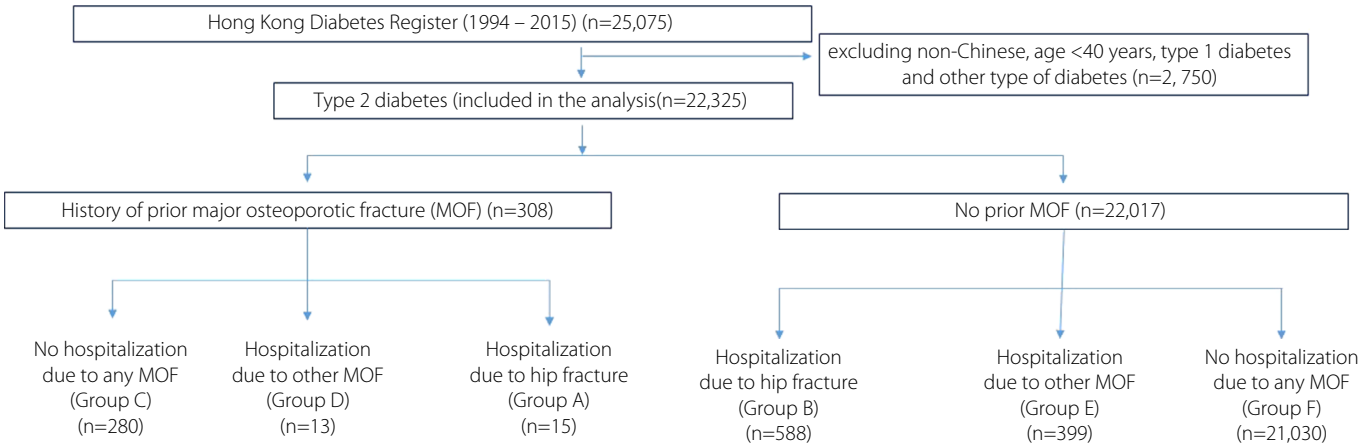

Figure 1 | Study flow including definitions of study cohorts and outcomes

Table 1 | Comparison of baseline characteristics and outcome (all-cause mortality) between people with type 2 diabetes (T2D) who had hospitalization due to incident hip fractures (group A + group B in Figure 1) and those without incident hip fractures (group C + D + E + F in Figure 1)

	hip fracture group (n = 603)	No-hip fracture group* (n = 21,722)	P value
Age (years)	70.0 ± 9.1	60.6 ± 10.5	<0.001
Female (%)	68.7% (414)	47% (10,204)	<0.001
Duration of diabetes (years)	9 (4–14)	6 (2–11)	<0.001
Smoking status			0.002
Current Smoker	8.0% (48)	11.8% (2,565)	
Ex-smoker	17.8% (107)	20.2% (4,387)	
Non-smoker	74.2% (446)	67.9% (14,732)	
Clinical measurements			
Body mass index (kg/m^2)	24.1 ± 3.7	25.6 ± 4.1	<0.001
Waist circumference (cm)			
Male	86.6 ± 9.6	90.5 ± 10.1	<0.001
Female	84.6 ± 9.7	85.4 ± 10.4	0.074
Systolic blood pressure (mmHg)	143.0 ± 21.1	136.0 ± 19.4	<0.001
Diastolic blood pressure (mmHg)	74.5 ± 11.3	77.1 ± 10.8	<0.001
Macro-vascular complications	24.0% (145)	19.7% (4,285)	0.01
Stroke	8.8% (53)	6.3% (1,369)	0.017
Ischemic heart disease	8.8% (53)	11.4% (2,481)	0.052
Peripheral arterial disease	10.8% (65)	4.7% (1,013)	<0.001
Micro-vascular complications			
Sensory Neuropathy	26% (157)	12% (2,598)	<0.001
Severe Retinopathy	34.8% (210)	26.6% (5,773)	<0.001
Albuminuria	61.2% (353)	40.7% (8,570)	<0.001
Microalbuminuria	37.1% (214)	27.3% (5,748)	<0.001
Macroalbuminuria	24.1% (139)	13.4% (2,822)	<0.001
Chronic kidney disease (CKD)	39.6% (239)	19.7% (4,283)	<0.001
End stage kidney disease	2.2% (13)	1.5% (333)	0.292
Medications			
Oral anti-diabetic agents	72.4% (436)	78.4% (17,013)	0.001
Insulin	22.2% (134)	17.7% (3,838)	0.005
On any anti-hypertensives	63.8% (385)	59% (12,798)	0.018
On any lipid-regulating drugs	23.4% (141)	39% (8,457)	<0.001
Severe hypoglycemia	6.0% (36)	3.8% (828)	0.009
Laboratory results			
HbA_{1c} (%)	7.8 ± 1.8	7.5 ± 1.6	0.002
Fasting plasma glucose (mmol/l)	8.5 ± 3.4	8.1 ± 2.8	0.001
Total cholesterol (mmol/l)	5.2 ± 1.2	4.9 ± 1.1	<0.001
HDL cholesterol (mmol/l)	1.4 ± 0.4	1.3 ± 0.4	0.001
LDL cholesterol (mmol/l)	3.1 ± 1.2	2.8 ± 1.0	<0.001
Triglyceride (mmol/l)	1.4 (1.0–2.1)	1.4 (1.0–2.0)	0.215
Estimated glomerular filtration rate (ml/min/1.73m^2)	65.6 ± 22.3	79.1 ± 22.9	<0.001
Urinary albumin: creatinine ratio (mg/mmol)	5.77 (1.39–28.50)	1.82 (0.70–8.40)	<0.001
Outcome (after a mean follow-up of 8.7 ± 5.2 years)			
All-cause death	55.0% (331)	18.3% (3,979)	<0.001

Data were expressed as mean ± standard deviation, median (interquartile range) or percentage (number), as appropriate. Chronic kidney disease was defined as estimated glomerular filtration rate < 60ml/min/1.73m^2; End stage kidney disease was defined as estimated glomerular filtration rate < 15 ml/min/1.73m^2; HbA_{1c}, Glycated haemoglobin; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; Macroalbuminuria was defined as urine albumin-creatinine ratio ≥ 25mg/mmol; Microalbuminuria was defined as urine albumin-creatinine ratio ≥ 2.5mg/mmol in men and ≥ 3.5mg/mmol in women; Severe hypoglycemia was defined as hospitalization due to hypoglycemia or requirement of assistance from third person; TG, triglyceride. *Patients with prior history of major osteoporotic fractures (MOF) were included in this analysis.

macrovascular complications (stroke and peripheral arterial disease) and microvascular complications (CKD, albuminuria, sensory neuropathy and severe retinopathy) (Table 1). The hip fracture group was less likely to be treated with oral anti-diabetic agents and lipid-regulating drugs than the no-hip fracture group. In contrast, they were more likely to be treated with insulin and had history of severe hypoglycemia than the no-hip fracture group. They were also more likely to be on anti-hypertensive drugs. In the hip fracture group, 55% of patients died during the follow up period, compared with only 18.3% in the no-hip fracture group (Table 1).

In these 22,325 subjects, 308 patients had a prior history of MOF (Figure 1) and were excluded from the Cox regression analysis. For the remaining 22,017 patients, 588 patients developed incident hip fractures (group B in Figure 1). Another 399 patients developed other MOF (group E in Figure 1) while 21,030 patients did not sustain any MOF (group F). We performed two separate Cox regression analyses. In both analysis, cases were patients who developed hip fractures (n = 588). In the first analysis, patients without incident hip fracture (Group E + F, no-hip fracture group, n = 21,429) were used as control while in the second analysis, patients without incident MOF (Group F, no-MOF group, n = 21,030) were used as control subjects (Figure 1).

Table 2 shows the sequentially adjusted hazard ratios (HRs) of risk factors with hip fracture after excluding patients with prior MOF (n = 22,017) and using the no-MOF group (group F) as controls. Apart from age and female sex, HbA_{1c} and BMI were shown up as independent risk factors for hip fracture in model 2. After including other cardiometabolic risk factors, notably LDL-C and albuminuria, the HR of HbA_{1c} was rendered not significant although that of BMI remained. In the fully adjusted model, female sex (HR 2.01, 95% CI 1.61–2.51), age (HR 1.08, 95% CI 1.07–1.09), BMI (HR 0.93, 95% CI 0.90–0.95), albuminuria (HR 1.52, 95% CI 1.25–1.85), and LDL-C (HR 1.12, 95% CI 1.02–1.23) were identified as independent risk factors for hip fracture (Table 2). The analysis using no-hip fracture group (Group E + F) as control showed similar results (Table 3).

We compared the incidence of hip fracture in our T2D cohort versus the territory-wide age-specific hip fracture incidence between 2000 and 2004 including adults with and without diabetes[9]. In the latter report, there were 25,794 hip fractures in Hong Kong Chinese subjects aged ≥ 50 years between 2000 and 2004[9]. Since follow up duration and 95% CI of the hip fracture incidence were not available in the territory-wide report[9], direct comparison with our results was not performed. Visually, the incidence of hip fracture in our T2D cohort tended to be higher in the 50–79 years age group but lower in the over 85-year age group than the general population (Figure S1a,b).

In our T2D cohort, the 30-day, 1-year and 5-year mortality rates after hip fracture among men were 5.8 (2.4–9.1)%, 29.2 (22.3–35.5)% and 65.9 (57.3–72.8)% respectively. The corresponding rates in women were 3.4 (1.6–5.1)%, 18.6 (14.7–22.4)% and 46.8 (40.9–52.1)% (Figure S2). Compared with local data on post-operative mortality in patients with hip fracture[10], the overall 30-day, 1-year and 5-year post-hip fracture mortality rates in our T2D cohort appeared to be higher (Figure S2a–f). However, these figures were not age standardized and direct comparison between these two populations would not be appropriate due to the lack of information of the characteristics of the historical cohort of the general population[10].

DISCUSSION

In this prospective cohort of 22,325 Chinese patients with T2D, 1.4% had prior MOF at enrolment. During a mean follow up of nearly 9 years, 2.7% had incident hip fracture. After excluding the patients with prior history of MOF (n = 22,017), old age, female sex, low BMI, LDL-C and albuminuria were independent risk factors for hip fracture. Compared with historical cohorts including general population, the incidence of hip fracture and post hip fracture mortality appeared to higher in patients with T2D.

By 2050, more than half (51.1%) of the world's hip fracture occurring in women aged 65 years and above was projected to take place in Asia[11]. The number of people with T2D is also increasing in Asia. In Caucasians, the higher in-patient complications and mortality rates among patients with T2D who sustained hip fracture, compared to those without diabetes is well known. In a study conducted in Turkey, after an index hip fracture, the one-year mortality rate for patients without diabetes was 13% compared with 32% in patients with T2D[12]. In our T2D cohort, around 30% of men and 20% of women have died at 1 year after the fracture event. By year 5, nearly 50% of these women and two-thirds of men have died. Other studies have reported more frequent adverse events including pain, post-operative complications (e.g. urinary tract infection, pressure sore) and cardiovascular-renal complications in patients with T2D than those without T2D after hip fracture[13] although these events were not captured in our analysis.

In four meta-analyses, diabetes increased the relative risk (RR) for hip fracture by 1.08-2.00 compared to those without diabetes[14-17]. Among these meta-analyses, only three studies examined the epidemiology of hip fractures in Asian populations. Two of these studies did not differentiate between the types of diabetes although it is likely that the majority of subjects had T2D. In one meta-analysis of 21 studies involving 6,995,272 patients including T1D and T2D and 82,293 hip fracture events, the RR of hip fracture for T2D versus non-DM was 1.34[15]. In this meta-analysis, there were two studies from Asia (Taiwan and Singapore). The Taiwanese study consisted of 500,868 patients with diabetes (without differentiating between T1D and T2D), with 6 years of follow-up. They reported increased risk of hip fracture in patients with diabetes for both sexes and all age-groups (≥35 years) except in men aged > 74 years and women aged > 84 years. In the nationwide Singapore study, after multiple adjustments, patients with diabetes had 2-fold higher fracture risks than those without diabetes. Although the types of diabetes were not

Table 2 | Sequential regression models with competing death risk adjustment (hip fracture vs no-MOF)

Risk factors	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.09 (1.08–1.09)	<0.001	1.09 (1.08–1.09)	<0.001	1.08 (1.08–1.09)	<0.001	1.08 (1.07–1.09)	<0.001	1.08 (1.07–1.09)	<0.001	1.08 (1.07–1.09)	<0.001
Disease duration of diabetes	1.01 (1.00–1.02)	0.177	1.01 (1.00–1.02)	0.279	1.01 (1.00–1.02)	0.315	1.01 (1.00–1.02)	0.233	1.00 (0.99–1.01)	0.86	1.00 (0.99–1.01)	0.963
Female	2.01 (1.68–2.40)	<0.001	2.04 (1.71–2.44)	<0.001	2.04 (1.71–2.44)	<0.001	1.96 (1.58–2.42)	<0.001	2.01 (1.62–2.51)	<0.001	2.01 (1.61–2.51)	<0.001
HbA1c (%)	1.08 (0.88–1.33)	0.005	1.06 (1.01–1.12)	0.011	1.06 (1.01–1.12)	0.011	1.05 (1.00–0.96)	0.061	1.04 (0.98–1.09)	0.178	1.03 (0.98–1.09)	0.219
BMI (kg/m^2)			0.93 (0.91–0.96)	<0.001	0.93 (0.91–0.96)	<0.001	0.93 (0.91–0.96)	<0.001	0.93 (0.90–0.95)	<0.001	0.93 (0.90–0.95)	<0.001
Severe hypoglycaemia					1.11 (0.74–1.66)	0.626	1.17 (0.78–1.77)	0.446	1.21 (0.80–1.82)	0.373	1.19 (0.79–1.81)	0.408
SBP (mmHg)							1.00 (1.00–1.01)	0.042	1.00 (1.00–1.01)	0.298	1.00 (1.00–1.01)	0.283
LDL cholesterol (mmol/l)							1.13 (1.03–1.24)	0.008	1.12 (1.02–1.22)	0.021	1.12 (1.02–1.23)	0.022
HDL cholesterol (mmol/l)							1.05 (0.83–1.33)	0.673	1.08 (0.86–1.37)	0.503	1.07 (0.85–1.36)	0.557
Ex–smoker							1.00 (0.77–1.29)	0.988	1.02 (0.79–1.32)	0.878	1.02 (0.79–1.32)	0.884
Current smoker							1.15 (0.82–1.61)	0.415	1.19 (0.84–1.68)	0.322	1.19 (0.84–1.67)	0.326
Chronic kidney disease									0.96 (0.77–1.20)	0.703	0.96 (0.77–1.19)	0.691
Albuminuria									1.52 (1.25–1.86)	<0.001	1.52 (1.25–1.85)	<0.001
Severe diabetic retinopathy									1.31 (1.00–1.73)	0.052	1.31 (1.00–1.72)	0.057
Diabetic neuropathy									1.13 (0.91–1.39)	0.278	1.13 (0.91–1.39)	0.275
Macrovascular complications											0.94 (0.75–1.16)	0.547
On insulin treatment											1.07 (0.84–1.37)	0.565

MOF represents major osteoporotic fracture. No-MOF group referred to patients with no MOF on follow up. Data were expressed as mean ± standard deviation, median (interquartile range) or percentage (number), as appropriate; Chronic kidney disease was defined as estimated glomerular filtration rate < 60ml/min/1.73m^2; Confidence interval, CI; Glycated haemoglobin, HbA_{1c}; Hazard ratio, HR; Systolic blood pressure, SBP; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; BMI, body mass index; Severe hypoglycemia was defined as hospitalization due to hypoglycemia.

Table 3 | Sequential regression models with competing death risk adjustment (hip fracture vs no-hip fracture)

Risk factors	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.09 (1.08–1.09)	<0.001	1.08 (1.08–1.09)	<0.001	1.08 (1.08–1.09)	<0.001	1.08 (1.07–1.09)	<0.001	1.08 (1.07–1.09)	<0.001	1.08 (1.07–1.09)	<0.001
Disease duration of diabetes	1.01 (1.00–1.02)	0.185	1.01 (1.00–1.02)	0.292	1.01 (1.00–1.02)	0.333	1.01 (1.00–1.02)	0.241	1.00 (0.99–1.01)	0.885	1.00 (0.99–1.01)	0.971
Female	1.94 (1.62–2.31)	<0.001	1.97 (1.65–2.36)	<0.001	1.97 (1.65–2.36)	<0.001	1.89 (1.53–2.33)	<0.001	1.94 (1.56–2.41)	<0.001	1.94 (1.56–2.41)	<0.001
HbA1c (%)	1.08 (1.02–1.13)	0.004	1.07 (1.02–1.12)	0.01	1.06 (1.01–1.12)	0.01	1.05 (1.00–1.11)	0.053	1.04 (0.99–1.1)	0.156	1.04 (0.98–1.10)	0.19
BMI (kg/m^2)			0.933 (0.91–0.96)	<0.001	0.93 (0.91–0.96)	<0.001	0.93 (0.91–0.96)	<0.001	0.92 (0.90–0.95)	<0.001	0.92 (0.90–0.95)	<0.001
Severe hypoglycaemia					1.12 (0.75–1.69)	0.573	1.19 (0.79–1.79)	0.404	1.23 (0.81–1.85)	0.331	1.22 (0.80–1.85)	0.361
SBP (mmHg)							1.00 (1.00–1.01)	0.049	1.00 (1.00–1.01)	0.33	1.00 (1.00–1.01)	0.309
LDL cholesterol (mmol/l)							1.13 (1.03–1.24)	0.008	1.12 (1.02–1.23)	0.021	1.12 (1.02–1.23)	0.023
HDL cholesterol (mmol/l)							1.04 (0.82–1.31)	0.75	1.07 (0.85–1.36)	0.57	1.06 (0.84–1.34)	0.63
Ex–smoker							0.99 (0.77–1.28)	0.953	1.01 (0.78–1.31)	0.929	1.01 (0.78–1.31)	0.931
Current smoker							1.14 (0.82–1.60)	0.435	1.18 (0.84–1.66)	0.344	1.18 (0.84–1.66)	0.346
Chronic kidney disease (CKD)									0.96 (0.77–1.19)	0.699	0.96 (0.77–1.20)	0.696
Albuminuria									1.51 (1.24–1.84)	<0.001	1.51 (1.24–1.84)	<0.001
Severe diabetic retinopathy									1.31 (1.00–1.73)	0.052	1.31 (0.99–1.72)	0.057
Diabetic neuropathy									1.12 (0.91–1.39)	0.293	1.12 (0.91–1.39)	0.287
Macrovascular complications											0.93 (0.74–1.15)	0.496
On insulin treatment											1.06 (0.84–1.36)	0.614

MOF represents major osteoporotic fracture. No-hip fracture group referred to patients with no hip fracture on follow up. Data were expressed as mean ± standard deviation, median (interquartile range) or percentage (number), as appropriate; Chronic kidney disease was defined as estimated glomerular filtration rate < 60ml/min/1.73m^2; Confidence interval, CI; Glycated haemoglobin, HbA_{1c}; Hazard ratio, HR; Systolic blood pressure, SBP; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; BMI, body mass index; Severe hypoglycemia was defined as hospitalization due to hypoglycemia.

specified, most of the patients were likely to have T2D. Similar to the Taiwanese study, in our analysis, there was also a tendency for the incidence of hip fracture to be lower in our patients with advanced age compared to the general population which might be due to the higher death rate in elderly patients with diabetes[18].

The mechanisms underlying increased risk of fracture in T2D remain unclear although there are some evidence suggesting perturbation of bone turnover in T2D. These included reduced circulating levels of CTx[19] and osteocalcin[20] which are markers of bone remodeling, and increased levels of sclerostin which inhibits osteoblastogenesis and bone formation[21]. Bone histomorphometry study on bone biopsies from patients with T2D showed reduced bone formation and osteoblasts number[22]. These changes can lead to increased cortical porosity[23] and reduced bone strength as shown by finite element analysis and micro-indentation[24,25], resulting in increased fracture risk.

Risk factors for hip fracture in general population such as ageing, low BMI, female sex and prior fragility fractures also apply to patients with T2D. Other T2D-specific factors include long disease duration [26], poor glycemic control[27-29] and presence of complications[30] while insulin is known to have anabolic effect on bone, possibly via its cognate effect on IGF-1 pathway[31].

In our multivariable analysis, HbA_{1c} was associated with increased risk of hip fracture in model 2 but this was rendered non-significant once other metabolic risk factors were adjusted. This is likely that there exists a HbA_{1c} threshold above which hip fracture increases significantly. In Taiwan, researchers reported a linear trend of HbA_{1c} with fracture in 20,025 patients with T2D aged ≥ 65 years followed up for 7.4 years with a threshold of 9%, above which hip fracture risk increased[27]. Other researchers had reported increased fracture-related hospitalizations in patients with $HbA_{1c} \geq 8\%$[29]. In a recent report involving patients with T2D in Hong Kong, those with $HbA_{1c} > 8\%$ had 25% higher risk of incident hip fractures than those with mean $HbA_{1c} < 7\%$[32]. In this report, those with HbA_{1c} 7-7.9% were not at increased risk of hip fracture. The mean HbA_{1c} in the present cohort did lie within this range. In the prospective Rotterdam study, patients with T2D and $HbA_{1c} \geq 7.5\%$ had 47% and 62% higher risk of fracture than those without diabetes and patients with $HbA_{1c} < 7.5\%$, respectively[28]. The authors suggested that poor control of T2D might thicken femoral cortices in a narrow bone, leading to accumulation of microcracks with increased cortical porosity and impaired bone repair[28]. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, patients who received intensive glycemic control (median HbA_{1c}, 6.4%), had similar fracture rate as those with standard control (median HbA_{1c}, 7.5%)[33].

On the other hand, LDL-C remained an independent risk factor after multiple adjustments. The relationship between lipids and fracture risk was less well studied although lipid particles can be proinflammatory and may affect microcirculation[2]. In a twin-study involving postmenopausal Australian women, the authors reported an inverse relationship between LDL-C and BMD[34]. Similarly, in Japan, researchers reported association between high LDL-C and non-vertebral fragility fracture after multiple adjustments among postmenopausal women[35].

Albuminuria was an independent risk factor for hip fracture in our study. Of note, albuminuria is a strong predictor for vascular health and renal disease, closely related to disease duration[30]. Other workers have reported increased risk of hip fractures and MOF in patients with more than 7 years[36] or 10 years of disease duration, respectively[26] while others have reported increased cortical porosity in patients with diabetic microvascular complications[37].

Medications such as thiazolidinediones, sodium-glucose co-transporter-2 (SGLT2) inhibitors and insulin have been shown to be associated with increased fracture risk. In this cohort, only 2.9% of patients were prescribed thiazolidinediones ($n = 383$). The small sample size would not be expected to have significant impact on the overall fracture risk. None of our patients were put on SGLT2 inhibitors because this relatively new class of medication was introduced to the study site at PWH after 2015. The association between insulin use and fracture risk was examined and there was no significant association of insulin treatment with hip fracture risk (Tables 2 and 3). Indeed, data are conflicting regarding insulin use and fracture risk. Some studies reported 87%[29] and 2.7 fold[38] increased risk of hip fracture amongst insulin users compared with non-insulin users. In the Study of Osteoporotic Fractures cohort, the use of insulin analog was associated with an increased risk of foot fracture among postmenopausal women (RR = 2.54), but not with fractures at other sites[4]. In men with T2D, for a given T-score, insulin treatment was associated with increased risk of non-vertebral fractures in a pool analysis of three observation studies[39]. For hip fracture, the increased risk was independent of insulin treatment. Similarly, women with T2D, whether treated with insulin or not, had higher risk of non-vertebral fractures and hip fractures than those without diabetes. In our cohort, although patients with fracture were more likely to be treated with insulin and had history of severe hypoglycaemia at baseline, these associations were not significant after adjusting for confounders on multivariable analysis. Unfortunately, we did not have information regarding insulin treatment and hypoglycaemia at the time of hip fracture.

Given the growing burden of diabetes and increased risk of hip fracture and high post hip fracture mortality among patients with T2D, our data suggest that poor metabolic control as evidenced by high LDL-C and albuminuria might accentuate these risks. The low BMI which might reflect poor health status or low insulin reserve which can also contribute to the high risk of fractures in T2D[40]. These risk factors can potentially help to identify high-risk individuals for counselling on fall precaution and balance training with BMD measurement and drug treatment as appropriate.

Our study has several limitations. We did not have a comparison group without diabetes. We only used hospitalization data to define fracture outcomes which might not capture some

wrist, spinal and humeral fractures not requiring admissions. We also did not have data on morphometric vertebral fractures. Potential confounders such as fall risk, physical performance, menopausal status, vitamin D level, exercise and dietary habits were not collected. Physical performance and fall risk can both affect hip fracture incidence. However, this study was carried out in an ambulatory care setting with a mean age at baseline of 60.9 years with exclusion of those patients with prior major osteoporotic fracture in the final analysis, it would be reasonable to believe that all patients included in the analysis should be of low fall risk and with good physical performance. Moreover, because the average age of menopause in Hong Kong is 51 years, most of women in this study were post-menopausal. We did not have data on metabolic bone diseases or drugs which may affect bone metabolism such as steroid use. The cardiometabolic risk factors were collected only at enrolment but not when patients sustained hip fractures. Lack of data regarding weight change of the study cohort is another limitation needed to be addressed. Although rapid and significant magnitude of weight loss is often associated with loss of bone density, this was not commonly encountered in most of the patients. There may also be referral bias because data was only collected from a single major hospital. Nonetheless, the large sample size, long duration of follow-up and comprehensive evaluation of risk factors and complications have generated data that filled our knowledge gaps. The independent risk associations of hip fracture with cardiometabolic-renal risk factors raised the possibility whether optimizing care and reducing risk of hypoglycaemia might reduce fracture risk although randomized clinical trials are needed to confirm these hypotheses.

In conclusion, Hong Kong Chinese patients with T2D had high risk of hip fracture and post-fracture mortality rate. The associations of both modifiable and non-modifiable risk factors with hip fracture call for regular surveillance and optimal management to reduce the double burden of diabetes and bone fracture.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Hip fracture incidence in women (1a) and men (1b) with type 2 diabetes compared to general population. Reference general population only involved people aged 50 years and above (reference 9).
Figure S2 | Mortality rates after hip fractures in people with type 2 diabetes and general population after hip fractures.