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Original article

Hip fracture is associated with a reduced risk of type 2 diabetes: A retrospective cohort study

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ABSTRACT

Objectives: Type 2 diabetes mellitus (T2DM) shares a complex relationship with bone metabolism and few studies investigated the effect of impaired bone health on the risk of T2DM. This study was conducted to investigate the association between hip fractures and the risk of incident T2DM.

Methods: This is a retrospective cohort study using data from the real-world hip fracture cohort. Hong Kong Chinese patients aged ≥ 65 years without T2DM who were admitted to public hospitals due to a fall between 2008 and 2015 were included in the study. Patients who sustained falls with and without hip fractures were matched by propensity score (PS) at a 1:1 ratio. Competing risk regression was used to evaluate the association between hip fracture and incident T2DM, with death being the competing event.

Results: A total of 23,314 hip fracture cases were matched to 23,314 controls. The median follow-up time was 5.09 years. The incidence rate of T2DM was 11.947 and 14.505 per 1000 person-years for the hip fracture and control group respectively. After accounting for the competing risk of death, the hip fracture group had a significantly lower risk of developing T2DM (HR: 0.771, 95% CI: 0.719–0.827). Similar results were observed in all subgroups after stratification by age and sex.

Conclusions: Hip fracture was found to be associated with a reduced risk of T2DM. These findings provide insight into the topic of bone and glucose metabolism and prompt further research in evaluating the role of bone health in the management of T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder that has been shown to impact bone metabolism [1], although the relationship between the two is paradoxical. Despite T2DM patients often present with higher bone mineral density (BMD) [2], they are associated with an increased risk of fragility fracture [3].

There is a substantial body of evidence investigating the impact of diabetes on fractures. Many studies have shown that the risk of hip fracture is increased in those diagnosed with T2DM, and even pre-diabetes [4–7]. The increased risk of fractures in T2DM patients may be due to several mechanisms, including the effects of medications such as thiazolidinediones, hormonal changes (decreased IGF-1, vitamin D, and hypogonadism), neuropathy, reductions in stability leading to more falls, altered body compositions and even inflammation and oxidative stress [6–8]. These factors together may alter the process of bone turnover while affecting the composition of the bone and therefore bone microarchitecture. This may explain why increased fracture risk is seen

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despite higher BMD.

Previous studies have provided compelling evidence suggesting that bone, traditionally viewed as a static and inert tissue, is an important endocrine organ involved in the regulation of whole-body energy metabolism [9]. Thus, the crosstalk between bone and glucose metabolism is complex and unlikely to be unidirectional. Recently, we showed that high BMD is associated with an increased risk of developing T2DM using both conventional association study and Mendelian Randomization analysis [10]. In this study, we aimed to further understand the impact of bone health on T2DM by examining the relationship of hip fracture with the risk of incident diabetes using a retrospective cohort design in the real-world hip fracture cohort.

2. Methods

2.1. Data source and cohort definition in the real-world hip fracture cohort analysis

The retrospective cohort study evaluating the association between hip fracture and the risk of diabetes was conducted using data from the real-world hip fracture cohort. The real-world hip fracture cohort is a large, population-based cohort study that utilizes data from the Clinical Data Analysis and Reporting System (CDARS), a database that has been widely used in high-quality epidemiology studies [11,12]. The validity of CDARS has been previously confirmed, with a positive predictive value of 100% for hip fractures, making it a reliable data source for use in analyses [13]. Records of the history of diagnosis and prescription for all participants were also available from CDARS and were obtained via International Classification of Diseases 9th revision (ICD-9) codes or British National Formulary (BNF) codes respectively.

Given that the majority of hip fractures are due to falls, the risk of T2DM was compared among patients who had experienced falls with and without hip fractures in the real-world hip fracture cohort. This was done to minimize potential confounding [14]. The cohort study included all patients aged $\geq$ 65 who were admitted to the hospital between 1 January 2008 to 31 December 2015 for in-patient care with a diagnosis of accidental fall (ICD-9 E880-E888) [14,15] in the corresponding in-patient record on the same day of admission. Patients were separated into two groups based on their hip fracture status upon admission to the hospital: a hip fracture group and a control group. The hip fracture group was defined as those who had a diagnosis of hip fracture (ICD-9 820.XX) during the admission period. Only the first admission of fall was considered. Patients with a history of hip fracture before the admission date and missing demographic information were excluded. The index date for the study was set as the discharge date from the hospital and any patient with a history of diabetes, prescription of anti-diabetic drugs, or prescription of $>$ 21 consecutive days of insulin prior to the discharge date were also excluded.

The outcome of interest was the incidence of T2DM. The first diagnosis of T2DM [16,17] was defined as the first date of T2DM (ICD-9 250.xx), the first prescription date of diabetic drugs (Supplementary Table S1), or the first prescription date of $>$ 21 consecutive days of insulin prescription. Even though the diagnostic criteria for T2DM may encompass individuals with type 1 diabetes, given the advanced age ($>$ 80 years) of the study participants and the outcome being incident diabetes, it was anticipated that the vast majority of cases, if not all of them, would pertain to T2DM. Patients were followed from the date of discharge of their first fall to the first diagnosis of T2DM, date of death, or study end (31 December 2020), whichever came first.

To address potential selection bias between the hip fracture group and control group, propensity score (PS) matching was used to balance the baseline characteristics between the two groups. The PS model included 4 demographic variables (including age, sex, institution cluster, and year of fall admission date), 17 baseline diagnoses defined using ICD-9 codes (covering disease groups such as cardiovascular diseases and endocrine and metabolic disorders), and 9 medication uses at baseline. The list of variables can be found in Table 1, while their corresponding ICD or BNF codes and the observational periods used for PS matching can be found in Supplementary Table S1. Logistic regression was applied to compute the PS of each patient. Matching between the two groups was conducted using a caliper of 0.2 standard deviation (SD) without replacement. Standardized mean differences (SMD) were calculated for each covariate and those with SMD $>$ 0.1 were adjusted in subsequent regression analysis.

2.2. Statistical analysis

Baseline characteristics were summarized as mean (SD) and frequency (%) for continuous and categorical variables, respectively. For categorical variables, χ^2 test was used to detect differences, while independent *t*-tests were used for continuous variables.

After PS-matching, a competing risk regression model was used in this retrospective study to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of the hip fracture group with reference to the control group (patients with falls but without hip fracture). Death was modelled as a competing event for diabetes due to the previously reported higher mortality in the hip fracture population [18]. A two-sided P-value $<$ 0.05 was considered statistically significant. Subgroup analyses were conducted by age and sex. As a sensitivity, all analyses were conducted without excluding participants who had a hip fracture diagnosis prior to the index date.

The study protocol was approved by the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster Hospitals (IRB number: UW 17-364).

3. Results

Baseline characteristics are presented in Table 1 for the unmatched and matched cohorts.

After PS matching, a total of 46,628 participants remained out of the initial 76,402 participants in the real-world hip fracture cohort who were admitted due to falls and had no history of diabetes, with 23,314 participants in both the hip fracture group (fall patients with hip fracture) and the control group (fall patients without hip fracture). Before matching, the only covariate with SMD $>$ 0.1 was age, with participants in the hip fracture group having a higher mean age. After matching, all parameters included in the PS model were well balanced between the groups, with SMD $<$ 0.1 for all variables, indicating a good balance between the groups. Therefore, no further adjustment was required in the competing risk regression analysis.

The mean age of the hip fracture group was 83.80 (7.41 SD) while that of the control group was 83.87 (7.72 SD). Both groups were predominantly comprised of females, with a male percentage of 33.4% each. The matched cohort had a median follow-up time of 5.09 years (total follow-up time of 236,596 person-years) and a total of 3138 individuals developed T2DM during the follow-up period. Among these, 1372 and 1766 of them were from the hip fracture group (incidence rate 11.947 per 1000 person-year) and the control group (incidence rate 14.505 per 1000 person-year), respectively. After accounting for the competing risk of death, the hip fracture group had a significantly lower risk of developing T2DM (Table 2; HR: 0.771, 95% CI: 0.719 to 0.827, P $<$ 0.001). Fig. 1 shows the cumulative incidence of T2DM in the hip fracture group vs the control group.

In the sub-group analysis by age, a significant reduction in risk of T2DM was observed in both cases, ie, hip fracture patients with ages lower and higher than the median age. For hip fracture patients with ages lower than the median, HR of 0.752 (95% CI: 0.687 to 0.823, P $<$ 0.001; Table 2; Fig. 2A) was observed, while for hip fracture patients with ages higher than the median age, HR of 0.802 (95% CI: 0.716 to 0.897, P $<$ 0.001; Table 2; Fig. 2B) was observed. Furthermore, the subgroup analysis by sex found that hip fracture was associated with a significantly lower risk of T2DM regardless of sex, with HR of 0.763

Table 1
Baseline characteristics of the real-world hip fracture cohort after matching.

	Before PS-matching			After PS-matching		
	Without hip fracture	With hip facture	SMD	Without hip fracture	With hip facture	SMD
N	53,052	23,350		23,314	23,314	
Age [mean (SD)], yrs	80.31 (8.20)	83.82 (7.42)	0.449	83.87 (7.72)	83.80 (7.41)	0.01
Male [N (%)]	18,760 (35.4)	7795 (33.4)	0.042	7787 (33.4)	7782 (33.4)	<0.001
Institution cluster [N (%)]			0.156			0.016
HKE	7685 (14.5)	2645 (11.3)		2594 (11.1)	2645 (11.3)	
HKW	5029 (9.5)	1895 (8.1)		1937 (8.3)	1895 (8.1)	
KC	9936 (18.7)	4532 (19.4)		4557 (19.5)	4532 (19.4)	
KE	6722 (12.7)	3364 (14.4)		3336 (14.3)	3346 (14.4)	
KW	11,308 (21.3)	4400 (18.8)		4426 (19.0)	4382 (18.8)	
NTE	7180 (13.5)	3956 (16.9)		3860 (16.6)	3956 (17.0)	
NTW	5192 (9.8)	2558 (11.0)		2604 (11.2)	2558 (11.0)	
Index year of fall [N (%)]			0.129			0.013
2008	5954 (11.2)	3385 (14.5)		3288 (14.1)	3367 (14.4)	
2009	6443 (12.1)	3082 (13.2)		3088 (13.2)	3078 (13.2)	
2010	6992 (13.2)	3052 (13.1)		3120 (13.4)	3047 (13.1)	
2011	6611 (12.5)	3127 (13.4)		3122 (13.4)	3123 (13.4)	
2012	7020 (13.2)	2955 (12.7)		2934 (12.6)	2954 (12.7)	
2013	7325 (13.8)	2902 (12.4)		2915 (12.5)	2900 (12.4)	
2014	7556 (14.2)	2996 (12.8)		3007 (12.9)	2994 (12.8)	
2015	5151 (9.7)	1851 (7.9)		1840 (7.9)	1851 (7.9)	
Comorbidities [N (%)]						
Coronary heart disease	6508 (12.3)	2811 (12.0)	0.007	2834 (12.2)	2808 (12.0)	0.003
Congestive heart failure	4940 (9.3)	2335 (10.0)	0.023	2377 (10.2)	2328 (10.0)	0.007
Cerebrovascular disease	8071 (15.2)	3629 (15.5)	0.009	3742 (16.1)	3627 (15.6)	0.014
Hypertensive disease	18,869 (35.6)	8881 (38.0)	0.051	8997 (38.6)	8864 (38.0)	0.012
Arrhythmia and conduction disorder	7334 (13.8)	3091 (13.2)	0.017	3198 (13.7)	3086 (13.2)	0.014
Arterial disease	1993 (3.8)	1039 (4.4)	0.035	1099 (4.7)	1036 (4.4)	0.013
Chronic obstructive pulmonary disease, asthma, bronchiectasis	5353 (10.1)	2794 (12.0)	0.06	2816 (12.1)	2784 (11.9)	0.004
Obesity	134 (0.3)	32 (0.1)	0.026	32 (0.1)	32 (0.1)	<0.001
Hyperlipidaemia	4694 (8.8)	1722 (7.4)	0.054	1760 (7.5)	1722 (7.4)	0.006
Thyroid disease	1553 (2.9)	661 (2.8)	0.006	650 (2.8)	661 (2.8)	0.003
Chronic kidney disease	1932 (3.6)	954 (4.1)	0.023	979 (4.2)	953 (4.1)	0.006
Esophageal varices, chronic liver disease, hepatic failure, cirrhosis	384 (0.7)	153 (0.7)	0.008	156 (0.7)	153 (0.7)	0.002
Osteoporosis	2208 (4.2)	1138 (4.9)	0.034	1184 (5.1)	1132 (4.9)	0.01
Paget's disease	14 (0.0)	4 (0.0)	0.006	7 (0.0)	4 (0.0)	0.008
Connective tissue diseases	513 (1.0)	219 (0.9)	0.003	239 (1.0)	219 (0.9)	0.009
Dementia	2850 (5.4)	1830 (7.8)	0.099	1765 (7.6)	1819 (7.8)	0.009
Accidental fall	11,583 (21.8)	4292 (18.4)	0.086	4392 (18.8)	4289 (18.4)	0.011
Medication [N (%)]						
Thiazide and related diuretics	2233 (4.2)	939 (4.0)	0.009	987 (4.2)	939 (4.0)	0.01
Beta-adrenoceptor blocking drugs	12,395 (23.4)	5379 (23.0)	0.008	5418 (23.2)	5370 (23.0)	0.005
Nitrates	5785 (10.9)	2573 (11.0)	0.004	2572 (11.0)	2568 (11.0)	0.001
Lipid-regulating drugs	9476 (17.9)	3458 (14.8)	0.083	3535 (15.2)	3457 (14.8)	0.009
Antidepressant drugs	4968 (9.4)	2552 (10.9)	0.052	2506 (10.7)	2539 (10.9)	0.005
Hypnotics and anxiolytics	0 (0.0)	0 (0.0)	0.000	0 (0.0)	0 (0.0)	0.000
Inhaled corticosteroid	2964 (5.6)	1626 (7.0)	0.057	1639 (7.0)	1619 (6.9)	0.003
Osteoporotic drug	2173 (4.1)	804 (3.4)	0.034	857 (3.7)	803 (3.4)	0.013
Angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists	11,218 (21.1)	5048 (21.6)	0.012	5059 (21.7)	5041 (21.6)	0.002

HKE, Hong Kong East; HKW, Hong Kong West; KC, Kowloon Central; KE, Kowloon East; KW, Kowloon West; NTE, New Territories East; NTW, New Territories West; SMD, Standardized mean difference.

Table 2
Results of the competing risk regression analysis, including subgroup analyses by age and sex.

Outcome	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
Type 2 diabetes mellitus	0.771	0.719	0.827	< 0.001
Male	0.791	0.693	0.903	< 0.001
Female	0.763	0.702	0.83	< 0.001
> Median age	0.802	0.716	0.897	< 0.001
≤ Median age	0.752	0.687	0.823	< 0.001

CI, confidence interval.

(95% CI: 0.702 to 0.83, P < 0.001) and 0.791 (95% CI: 0.693 to 0.903, P = 0.001) for females and males respectively (Table 2, Fig. 2C and D).

The sensitivity analysis including participants with a hip fracture prior to the index date showed similar results. Due to including more individuals, the size of the matched cohort increased to 49,582 individuals with a median follow-up time of 4.91 years (total follow-up time of 248,162 person-years) and 3230 cases of incident diabetes. Among these, 1448 and 1782 were from the hip fracture group and control group respectively. After accounting for the competing risk of death, the hip fracture group had a significant reduction in the risk of T2DM (Table 3; HR: 0.807, 95% CI: 0.753 to 0.865, P < 0.001). Similarly, the subgroup analyses also showed a significant reduction in the

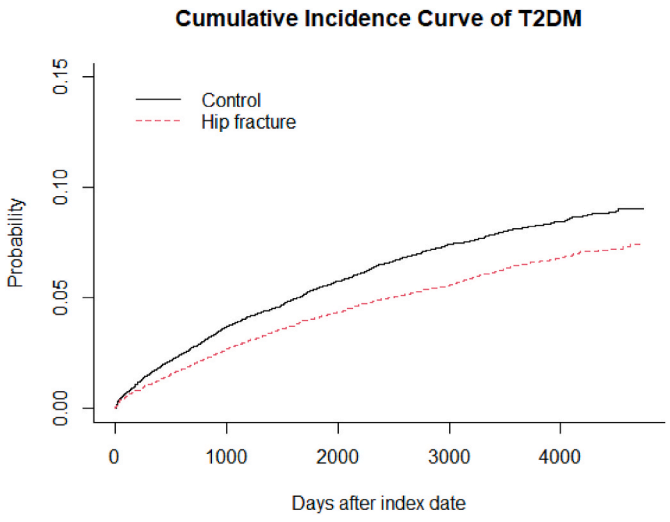

Fig. 1. Cumulative incidence rate of diabetes mellitus among fall patients who suffered from hip fracture compared to those who did not.

risk of developing T2DM for those in the hip fracture group compared to the control group.

4. Discussion

In the current study, we showed that the presence of hip fracture is associated with a reduced risk of T2DM after accounting for the competing risk of death. Similar associations were observed in both women and men, as well as patients who were younger and older than the median age. These findings support the hypothesis that bone metabolism plays a role in glucose metabolism in humans.

To the best of our knowledge, no study has investigated whether fracture predicts the risk of diabetes. The relationship of fracture with the risk of diabetes is complex. Previous studies showed that both prediabetes and diabetes were associated with a higher risk of fracture, thus one would expect that fracture could be associated with a higher risk of T2DM since prediabetes is often undiagnosed and asymptomatic. However, we demonstrated that in fall patients, hip fracture was strongly associated with a lower risk of diabetes when compared to those without hip fracture. As undiagnosed prediabetes or diabetes could not be accounted for, it is likely that their presence underestimated the association observed in this study. Therefore, future studies incorporating glycaemic markers in the study design may find that the observed association could be further from the null. Notably, a possible bias of the competing risk of death in hip fracture patients could lead to a reduced risk of T2DM but competing risk regression was used to account for this, thus the effect of such bias is minimal. Furthermore, as those who have experienced a previous hip fracture are at a higher risk of subsequent fractures, excluding these higher-risk individuals could lead to biased observations. To address this, we performed a sensitivity analysis which included those with previous hip fractures. Similar results were observed, suggesting that our main findings are robust.

It is important to note that those with hip fractures may be immobilized and suffer from pain as well as fatigue. In the short-term, this

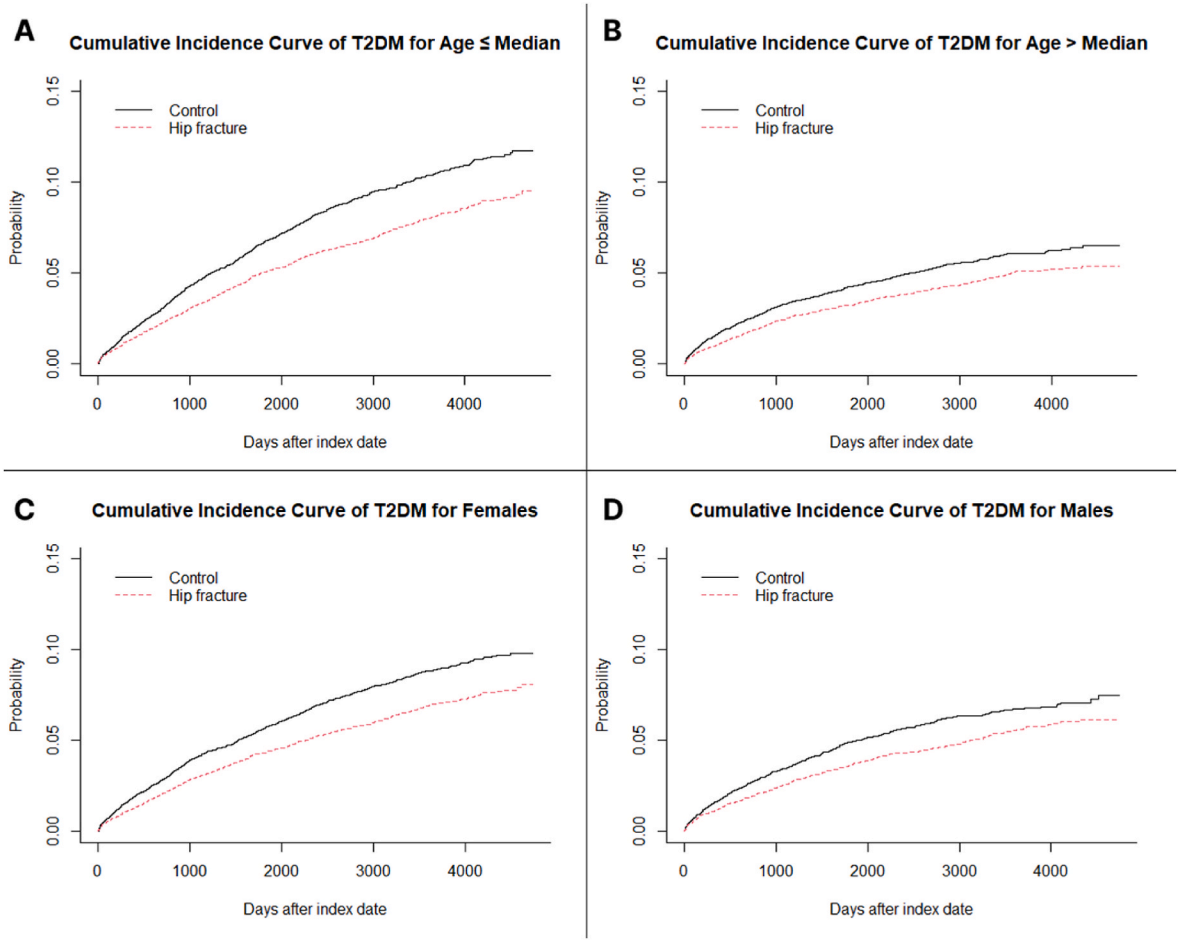

Fig. 2. Cumulative incidence rate of diabetes mellitus comparing fall patients who suffered from hip fracture compared to those who did not for: A) Patients with age $\leq$ the median age, B) Patients with age $>$ the median age, C) Female patients, and D) Male patients.

Table 3
Results of the sensitivity analysis, including subgroup analyses by age and sex.

Outcome	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
Type 2 diabetes mellitus	0.807	0.753	0.865	< 0.001
Male	0.720	0.634	0.818	< 0.001
Female	0.847	0.780	0.920	< 0.001
> Median age	0.886	0.793	0.990	0.033
≤ Median age	0.757	0.693	0.827	< 0.001

CI, confidence interval.

may lead to a loss of appetite and consequent reduction in BMI and adiposity, however, whether these remain in the long-term is still unclear. Considering the > 5 years median follow-up period in this study, we believe that the reduced risk of diabetes in hip fracture patients observed in this study was likely contributed to by a difference in BMD when compared with the control group, which were fall patients without hip fractures. Previous cross-sectional studies showed inverse associations of bone turnover markers (BTMs) with fasting glucose [10,19], HbA1c [10,20], and HOMA-IR [21]. Increased bone turnover is responsible for rapid bone loss in age-related and post-menopausal osteoporosis. Furthermore, we recently showed that higher BMD is significantly associated with an increased risk of developing T2DM using both conventional association study and Mendelian Randomization analysis [10]. Thus, these studies, together with the real-world hip fracture cohort analysis in the current study, suggest that higher bone turnover and lower BMD may lead to improved glycaemic control.

Our study has important clinical implications. Diabetic bone disease is now suggested as one of the diabetic complications, which is characterized by lower bone turnover [1]. Lower bone turnover is associated with higher fasting glucose and HbA1c, even in the absence of impaired fasting glucose and diabetes. Thus, our study opens a new area for future investigation. For example, it would be intriguing to investigate whether glucose control in diabetic patients is improved after hip fracture due to high bone turnover. On the other hand, future studies evaluating whether bone parameters, such as BMD and bone turnover markers, could be used to improve the management of diabetes, such as predicting glycemic control and diabetic complications, are warranted. Similarly, whether pharmacological agents altering bone metabolism would affect glycemic control and risk of diabetes warrants further investigation. Furthermore, together with previous studies, these results indicate that high BMD and low bone turnover may be a cause instead of a consequence of T2DM. However, further research is warranted to understand the mechanism underlying the increased risk of hip fracture after the diagnosis of T2DM.

This study has several strengths. First, a large and well-characterized cohort was used, which provided a sufficient sample size for a well-powered study. Second, PS matching was utilized to balance covariates between the exposed (hip fracture) and unexposed (without hip fracture) groups. This method has been well-established and can approximate comparisons in observational studies similar to randomized control trials [22,23]. Finally, this is the first study to evaluate the association of hip fractures with the risk of diabetes. However, our study also has limitations. First, measurements of BTMs and BMD were not available in the real-world hip fracture cohort, thus we were not able to evaluate if BTMs and/or BMD were mediators or confounders in the association. Second, the study population in the observational study was above the age of 80 years old on average. Therefore, further studies investigating hip fracture and other parameters related to bone health should be conducted to ensure the observed association holds in younger age brackets as well. Finally, the study was conducted in participants from the Hong Kong Chinese population and association between hip fracture and risk of diabetes may not be observed in other populations. Therefore, further studies incorporating other parameters relating to bone health should be conducted in more diverse populations to improve our understanding on the cross-talk between bone health and glucose metabolism.

5. Conclusions

In conclusion, this study provides new insights into the association between bone health and the risk of T2DM. The findings suggest that hip fractures may have a protective effect against the development of T2DM. The observed associations highlight the complex relationship between bone and glucose metabolism, which warrants further investigation to better understand the underlying mechanisms and explore the clinical applications of such findings.

CRediT author statement

Suhas Krishnamoorthy: Conceptualization; data curation; formal analysis; validation; investigation; visualization; writing – original draft; writing – review and editing; methodology; software. **Casey Tze-Lam Tang:** Conceptualization; methodology; data curation; formal analysis; investigation; writing – original draft; software; visualization. **Warrington Wen-Qiang Hsu:** Investigation. **Gloria Hoi-Yee Li:** Writing – review and editing. **Chor-Wing Sing:** Writing – review and editing. **Xiaowen Zhang:** Investigation. **Kathryn Choon-Beng Tan:** Resources; project administration. **Bernard Man-Yung Cheung:** Resources. **Ian Chi-Kei Wong:** Supervision. **Annie Wai-Chee Kung:** Resources; project administration. **Ching-Lung Cheung:** Project administration; conceptualization; methodology; writing – original draft; writing – review and editing; supervision; resources; visualization; funding acquisition.

Data availability statement

Research data for the cohort study were retrieved from the Hong Kong Hospital Authority and can be accessed for research purposes through the application to HA Data Sharing Portal. The related information can be found online (https://www3.ha.org.hk/data).

Conflicts of interest

The authors declare no competing interests.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afos.2024.05.002.

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