



Visit-to-visit blood pressure variability and hip fracture risk in older persons

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Abstract

Summary We investigated the association between blood pressure variability measured by the coefficient of variation (CV) of blood pressure and hip fracture in older persons with diabetes. After excluding patients with acute complications and comorbidities, a positive association with similar magnitude of strength was found between BP variability and hip fracture, compared with that in the original analysis.

Introduction Hypertension is a risk factor of osteoporosis and hip fracture, but studies have yet to investigate whether blood pressure variability measured by the CV of blood pressure can predict hip fracture in older persons with diabetes.

Methods We conducted a retrospective cohort study on 21,160 patients who suffered from type 2 diabetes (age ≥ 50 years) and participated in the National Diabetes Care Management Program in Taiwan. The patients' 1-year variability in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the baseline and subsequent hip fracture incidence for 8.2 years were analyzed.

Results There were 937 recorded incident hip fractures. SBP-CV and DBP-CV were classified based on their tertiles. After multivariate adjustment was conducted, SBP-CV found to be a predictor of hip fracture, and its hazard ratio was 1.18 (95% CI 1.00–1.40) for the third tertile compared with the first tertile.

Conclusions Our study suggests SBP stability is a predictor for hip fracture incidence in older persons with type 2 diabetes.

Keywords Blood pressure · Diabetes · Hip fracture

Abbreviations

DM	diabetes mellitus
FPG	fasting plasma glucose
BP	blood pressure
NDCMP	National Diabetes Care Management Program

NHI	National Health Insurance
PIN	personal identification number
CAD	coronary artery disease
CVs	coefficients of variability
SBP	systolic blood pressure
DBP	diastolic blood pressure
HRs	hazard ratios
CI	confidence intervals
OAD	oral glucose-lowering drug

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Introduction

Hip fracture, which is the main clinical consequence of osteoporosis, is one of the most serious fracture types associated with severe pain, loss of quality-adjusted life years, morbidity, and death in men and women aged > 50 years [1, 2]. Osteoporosis affects hundreds of millions of people, particularly postmenopausal women, and imposes considerable cost burden on both individuals and the society in terms of healthcare expenditure. Hip fracture, which typically requires

hospitalization, accounts for the most important expenditures in fracture-related healthcare in Western societies [3].

Diabetes mellitus (DM) has been reported as a risk factor of osteoporosis and hip fracture [4, 5]. Hyperglycemia [6] and visit-to-visit variability in fasting plasma glucose (FPG) [7] are the predictors associated with hip fracture incidence. Limited studies have explored the factors associated with hip fracture incidence in older persons with type 2 diabetes. High blood pressure (BP) and impaired FPG are clustered metabolic factors and also are risk factors of cardiovascular diseases, indicating that hypertension or high BP is common in older persons with type 2 diabetes. In addition to high BP, visit-to-visit variability in BP based on measurements obtained in clinical settings has been shown to be associated with cardiovascular diseases and mortality in patients with type 2 diabetes [8]. It has been reported that hypertension is a risk factor for hip fracture [9] because of occurrence of falls due to fainting associated with hypotension secondary to therapy or diminished baroreflex sensitivity [10]. The onset of dizziness, which is a side effect of several BP medications, and signs of stroke due to high BP, such as loss of balance or coordination and trouble in walking, may result in a fall or a hip fracture. It has also been reported that hypertension has been associated with various alterations of calcium metabolism, which can result in decreased bone mass [11]. However, we comprehensively reviewed the literature and found that studies have yet to explore the association between visit-to-visit variability in BP and hip fracture in older persons with type 2 diabetes. Additional data should be obtained to portray the effects of visit-to-visit BP variability on hip fracture.

To examine the association between visit-to-visit BP variability and hip fracture in older persons with type 2 diabetes, we conducted a retrospective cohort study on the enrollees of the National Diabetes Care Management Program (NDCMP) in Taiwan. Using the NDCMP dataset, we could evaluate the association between visit-to-visit variability in BP and hip fracture in a large national population with type 2 diabetes, and follow-up visits were conducted at regular time intervals. BP was measured in accordance with a standardized protocol, and the outcomes were verified on the basis of the records of hospital admissions for approximately 8 years of follow-up.

Methods

Study population

We conducted a retrospective cohort study on 63,084 Chinese enrollees of the Taiwan NDCMP from 2002 to 2004. The index date was the entry date into the NDCMP. In Taiwan, the diagnosis of diabetes mellitus was based on the American Diabetes Association criteria (ICD-9-CM Code 250). The inclusion criteria were as follows: patients aged ≥ 50 years and

those who could be followed up during subsequent years. A total of 50,491 older patients satisfied the inclusion criteria. The exclusion criteria were as follows: type 1 diabetes older persons (ICD-9-CM Code 250.x1/x3), those with a hip fracture history, and those without more than two records of BP measurement. A total of 22,027 persons with type 2 diabetes fulfilled the eligibility criteria. We further excluded persons with missing covariate data. A total of 21,160 persons were assessed in the final analysis (shown in Fig. 1). This study was approved by the Ethical Review Board of China Medical University Hospital (CMUH102-REC3-016).

Data sources for baseline covariates

The National Health Insurance (NHI) program is a universal insurance system that was launched in 1995 by the Bureau of NHI, Ministry of Health and Welfare. The coverage rate of this program has reached approximately 99% of the Taiwanese population (23.74 million) after 1999, and more than 99.62% of Taiwanese residents were enrolled by the end of 2010 [12]. The NHI contracted all hospitals and 92% of clinics [13]. The NHI database includes the patients' demographics, diagnosis, prescription of ambulatory claims in clinics and hospitals, and ambulatory claims in hospitals. The accuracy of the claims data is assessed by the Bureau of NHI four times every year through auditing claims data by experts. These experts review every 50 to 100 randomly selected outpatient and inpatient claims of each hospital and clinic. If a false diagnostic report is identified by the Bureau of NHI, a severe penalty is imposed.

The inpatient admissions and ambulatory visits in 2002–2011 datasets were used to ascertain the hip fracture and chronic conditions. Every individual in Taiwan has a unique personal identification number (PIN), which is scrambled for security and privacy reasons by the National Health Insurance Research Database. We linked the NHI datasets with the NDCMP registry through the patients' PINs to determine an

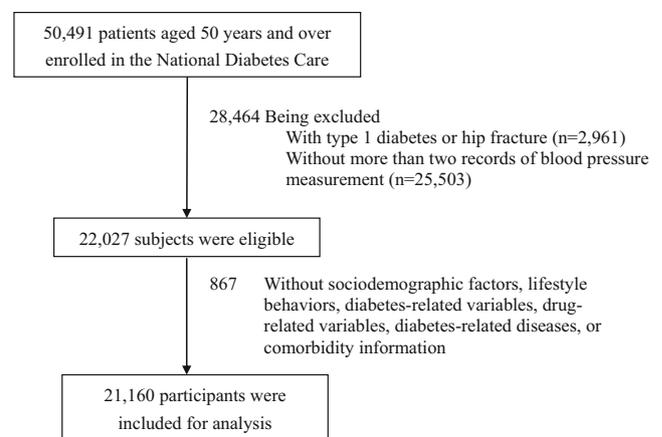


Fig. 1 Flowchart of recruitment procedures for the current study

individual's health status using codes of ICD-9-CM. The loss to follow-up bias can be negligible because the NHI program has pretty high coverage and low withdrawal rate. The ambulatory and inpatient claims data also provided data for all study subjects on glucose-lowering drug use, antihypertensive drug use (including diuretics, calcium channel blockers, renin-angiotensin system, and beta-blocking agents), chronic medical conditions, and corticosteroid use and the exposure period was 12 months prior to the cohort entry. The comorbidities included congestive heart failure (ICD-9-CM Codes 428, 398.91, and 402.x1), coronary artery disease (CAD, ICD-9-CM Codes 410–413, 414.01–414.05, 414.8, and 414.9), atrial fibrillation (ICD-9-CM Code 427.31), hyperlipidemia (ICD-9-CM Code 272), hypertension (ICD-9-CM Codes 401–405), hypoglycemia (ICD-9-CM Codes 2510–2512), chronic hepatitis (ICD-9-CM Codes 571, 572.2, 572.3, 572.8, 573.1–573.3, 573.8, and 573.9), obstructive pulmonary disease (490–496), cancer (ICD-9-CM Codes 140–149, 150–159, 160–165, 170–175, 179–189, 190–199, 200, 202, 203, 210–213, 215–229, 235–239, 654.1, and 654.10–654.14), and diabetic retinopathy (yes, no).

The NDCMP requires enrollees to undergo comprehensive assessments, including routine blood and urine tests, anthropometric measurements of height and weight, and disease and complication evaluations. A care manager records the patients' history or current diseases, medications, and lifestyle behaviors through a standardized computerized questionnaire. After an overnight 12-h fast, blood drawn from an antecubital vein was analyzed within 4 h collection. According to NDCMP, patients should be re-examined regularly every 3 or 6 months. The diabetes care quality of the NDCMP was improved through the use of a computerized tracking and recall system. This system instructs case managers to follow the managed care protocols managed by NHI Bureau. The combination of the case management nurses and the computerized system enhances the validity and completeness of the NDCMP data.

Outcome ascertainment

The PINs of the patients in ID file were linked with 2002–2011 inpatient claim records to ascertain the first primary or secondary hip fracture events (ICD-9-CM 820) and internal fixation or hemiarthroplasty operations (ICD-9-CM 79.15, 79.35, and 81.52). Excluded cases were persons with outcome events such as open hip fracture (ICD-9-CM 820.1, 820.10–820.12, 820.19, 820.9, 820.13, 820.22, 820.3, and 820.30–820.32), transport accidents (E800–E848), and pathological fracture (ICD-9-CM 733.14 and 733.15). We only considered a maximum of one hip fracture per patient included, thus, repeated hip fracture was not taken into account in the present study. The endpoint date of interest was the first day of hospitalization, loss to follow-up, or December 31, 2011. We

followed-up all eligible subjects from 1 year after the index date to the outcome event, death, withdrawal from the NHI program, or the end of 2011. We identified 937 persons with hip fracture, and the average follow-up period of entire cohort patients was 8.16 years.

Statistical analysis

We calculated the coefficients of variability (CVs) of the systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements of each patient within the first year of the index date from ambulatory visits only when more than two SBP and DBP measurements were available. The CV is the ratio of the standard deviation to the mean. SBP-CV and DBP-CV were then categorized into tertiles. The hazard ratios (HRs) were derived from the Cox proportional model to evaluate the association of SBP-CV and DBP-CV with the risk of hip fracture. The HRs and their 95% confidence intervals (CIs) were calculated using three multivariate models. The first multivariate model was adjusted for age (cont.) and gender (male/female). The second multivariate model was also adjusted for smoking (y/n), alcohol drinking (y/n), type of glucose-lowering drug used (no medication, oral glucose-lowering drug [OAD] only, two OAD-other, three OADs, more than three OADs, insulin monotherapy, and OAD plus insulin), diabetes duration (cont.), type of antihypertensive drug used (loop diuretics, thiazide diuretics, calcium channel blockers, renin-angiotensin system, and beta-blocking agents), use of corticosteroids (y/n), baseline obesity (body mass index $\geq 27\text{m}^2/\text{kg}$), fasting plasma glucose (cont.), HbA1c (cont.), and SBP and DBP (both cont.). The third multivariate model was further adjusted for congestive heart failure (y/n), cancer (y/n), CAD (y/n), hyperlipidemia (y/n), atrial fibrillation (y/n), hypertension (y/n), chronic hepatitis (y/n), chronic obstructive pulmonary disease (y/n), hypoglycemia (y/n), and diabetic retinopathy (yes/no). We reported *P* for linear trend across the SBP-CV and DBP-CV classes and tested the proportionality assumption by including an interaction term for the tertiles of SBP-CV and DBP-CV with person-year in the multivariate Cox models. The interaction between SBP-CV and DBP-CV was evaluated in terms of significance through likelihood ratio tests by entering their product terms into the full model. The significance level was set to 0.05 with two tails. Data were analyzed with SAS version 9.4 for Windows (SAS; Cary, NC, USA).

Results

Nine hundred and thirty-seven hip fracture cases were found in our cohort of older persons with type 2 diabetes during an average 8.2 follow-up years. The crude incidence rate was 5.4/1000 person-years and for women and men were 7.3 and 3.2/

1000 person-years, respectively. The crude incidence rates per 1000 person-years were 4.8, 5.1, and 6.4 for SBP-CV and 4.8, 5.1, and 6.5 for DBP-CV in the 1st, 2nd, and 3rd tertiles, respectively.

Table 1 shows the baseline characteristics according to the tertile subgroups of SBP-CV and DBP-CV, and Table 2 presents the incidence rates and HRs of hip fracture according to the tertile subgroups of SBP-CV and DBP-CV in the patients with diabetes. In comparison with those of the patients with the 1st tertile of SBP-CV ($\leq 4.5\%$), the age- and gender-adjusted HRs of the hip fracture of the patients with the 3rd tertile of SBP-CV (8.6%) were 1.20 (1.02, 1.42). After additional adjustments for lifestyle behaviors, medication use, and biomarkers were made, the association shown by SBP-CV was slightly weakened, but the 3rd tertile of SBP-CV remained significant. After the comorbidities were further adjusted, the risk of hip fracture of the patients with the 3rd tertile of SBP-CV was significant (adjusted HR 1.18 (1.00, 1.40), respectively). Similarly, the age- and gender-adjusted HRs of hip fracture were 1.21 (1.03, 1.43) for the patients with the 3rd tertile of DBP-CV ($\geq 9.4\%$) compared with those of the patients with the 1st tertile of DBP-CV ($< 4.7\%$). When all of the covariates were adjusted, the patients with the 3rd tertile of DBP-CV manifested a borderline significant increase in higher hip fracture risk [adjusted HR 1.18 (1.00, 1.39)] compared with those with the 1st tertile of DBP-CV. When SBP-CV and DBP-CV were treated as continuous variables, their effects remained similar (adjusted HR per 5% increase 1.08 (1.02, 1.15) for SBP-CV and 1.03 (0.98, 1.09) for DBP-CV).

We excluded persons with existence of comorbidities for sensitivity analyses to rule out the potential bias including hyperglycemic hyperosmolar nonketotic coma ($n = 381$), diabetic ketoacidosis ($n = 123$), CAD ($n = 2024$), hypoglycemia ($n = 64$), and all comorbidities ($n = 2592$). The patients with SBP-CV of $> 8.6\%$ exhibited similar significant HRs for the hip fracture of 1.20 (1.00, 1.44) while the effect of DBP-CV was at borderline significant [1.17, (0.98, 1.41), $P = 0.08$]. In order to rule out the impact of missing data on our study findings, we performed an additional analysis by using a multiple imputation approach to impute missing data and found similar findings (adjusted HR for 3rd tertile vs. 1st tertile 1.13 (1.01, 1.27) for SBP-CV and 1.11 (0.99, 1.24) for DBP-CV).

In order to examine whether the magnitude of the association between SBP-CV (or DBP-CV) and risk of hip fracture differs according to the level of DBP-CV (or SBP-CV), we examine the interaction between SBP-CV and DBP-CV. We did not find significant interaction effects ($P > 0.05$). Thus, we further examined the combined effects of SBP-CV and DBP-CV. Multivariate-adjusted HRs in the 1st tertile of SBP-CV was significantly linked to hip fracture in the patients with the 3rd tertile of DBP-CV (1.66, 1.24–2.21). The 3rd tertile of SBP-CV was also significantly associated with hip fracture

in the patients with the 2nd and 3rd tertiles of DBP-CV (1.49, 1.15–1.93; 1.48, 1.18–1.86; Fig. 2).

Discussion

This large-scale observational analysis on 21,160 older persons with type 2 diabetes mellitus from Taiwan Diabetes Study demonstrated for the first time that visit-to-visit SBP and DBP variability defined by CVs was positively associated with the risks of hip fracture. These associations persisted after adjustments were made for baseline SBP and DBP, hypertension status, type of antihypertensive drug used, and other cardiovascular risk factors. The joint effects indicated that individuals with SBP-CV of the 1st tertile and DBP-CV of the 3rd tertile, SBP-CV of the 3rd tertile and DBP-CV of the 2nd tertile, and SBP-CV of the 3rd tertile and DBP-CV of the 3rd tertile encountered hip fracture risks that increased by 66%, 49%, and 48%, respectively. After the patients with acute complications and comorbidities were excluded, our findings revealed a similar association of the levels of SBP-CV and DBP-CV with hip fracture incidence.

Based on the data of the Ministry of Health and Welfare and age distribution of NDCMP, there were an estimated 0.283 million person-years for diabetic patients who aged 50 years or older in the third tertile of SBP-CV in Taiwan every year. Assume all things being equal, 438 fewer hip fractures in this diabetic cohort would be expected if they were in the first tertile group, not in the third tertile group instead. In other words, 438 excess hip fracture events are attributable to the high variation in SBP. The attributable fraction among the exposed was 32.2%. Both measures indicated the negative effect of high variation in SBP may have been great.

Previous studies reported the risk factors of hip fracture in persons with type 2 diabetes and focused mainly on glucose control or glucose variability [6, 14, 15]. Although several observational studies have investigated the effect of visit-to-visit BP variability on the risks of cardiovascular outcomes [16–21], studies have yet to describe the influence of visit-to-visit BP variability on the risk of fracture in the general population, patients with hypertension, or persons with type 2 diabetes. Thus, our findings expanded the results of previous studies on the adverse outcomes of visit-to-visit BP variability on adverse outcomes in persons with type 2 diabetes and suggested that visit-to-visit SBP variability was associated with hip fracture in persons with type 2 diabetes mellitus.

The link between visit-to-visit BP variability and hip fracture can be explained by several possible mechanisms. First, the increase in BP variability may be a marker of arterial stiffness, which is related to the reduced elasticity of large arteries [22], and predictor of future vascular events, such as stroke and retinopathy. Stroke events may cause a sudden loss of balance or coordination and trouble in walking, resulting in

Table 1 Comparisons of baseline sociodemographic factors, lifestyle behaviors, diabetes-related variables, drug-related variables, and comorbidity according to tertiles of SBP-CV and DBP-CV in older persons with type 2 diabetes enrolled in the NDCMP, Taiwan

Variables	SBP-CV (%)			P value	DBP-CV (%)			P value
	≤4.5 (N=6917)	4.5–8.6 (N=6864)	≥8.6 (N=7379)		≤4.7 (N=7027)	4.7–9.4 (N=6953)	≥9.4 (N=7180)	
Sociodemographic factors								
Gender				0.4				0.9
Female	54.0	54.2	55.1		54.5	54.3	54.5	
Male	46.0	45.8	44.9		45.5	45.7	45.5	
Age (years) [†]	64.20 (8.5)	64.37 (8.4)	64.69 (8.3)	0.002	64.17 (8.4)	64.06 (8.3)	65.03 (8.5)	<0.001
Lifestyle behaviors								
Smoking	13.9	13.9	14.7	0.2	13.6	14.4	14.6	0.2
Alcohol drinking	7.9	7.9	8.3	0.6	7.3	8.6	8.3	0.01
Drug-related variables								
Antihypertensive drugs								
Renin–angiotensin system (RAS)	41.7	43.7	49.6	<0.001	41.5	44.5	49.0	<0.001
Beta blocking agents (BBs)	16.4	18.2	20.2	<0.001	16.5	19.4	19.0	<0.001
Calcium channel blockers (CCBs)	35.6	36.6	41.7	<0.001	34.3	38.5	41.3	<0.001
Diuretics								
Loop diuretics	5.3	6.0	6.9	<0.001	5.2	5.6	7.2	<0.001
Thiazide diuretics	11.4	11.8	14.6	<0.001	11.4	12.7	13.8	<0.001
Other	0.8	0.6	0.9	0.1	0.7	0.6	1.0	0.007
Use of corticosteroids	6.6	6.3	6.5	0.8	5.9	6.8	6.7	0.07
Diabetes-related variables								
Duration of diabetes (years) [†]	7.25 (6.7)	7.39 (6.8)	7.65 (6.9)	0.002	7.18 (6.7)	7.34 (6.7)	7.77 (7.0)	<0.001
Fasting glucose (mg/dL) [†]	170.18 (65.8)	170.1 (64.6)	172.73 (64.0)	0.02	170.5 (67.2)	170.14 (62.1)	172.45 (65.0)	0.07
HbA1c (%) [†]	8.14 (1.9)	8.13 (1.9)	8.24 (2.0)	<0.001	8.15 (1.9)	8.13 (1.9)	8.23 (2.0)	0.008
SBP (mmHg) [†]	134.85 (14.1)	135.36 (15.7)	137.75 (22.1)	<0.001	134.81 (15.5)	136.43 (17.0)	136.83 (20.5)	<0.001
DBP (mmHg) [†]	79.54 (9.3)	79.67 (9.8)	80.16 (12.1)	0.001	79.63 (8.0)	80.40 (9.2)	79.38 (13.4)	<0.001
Type of glucose-lowering drug use				<0.001				0.007
No medication	1.7	1.4	1.4		1.5	1.7	1.4	
One oral glucose-lowering drug	17.4	16.6	16.1		17.5	16.0	16.6	
Two oral glucose-lowering drugs	42.1	41.9	40.6		41.6	42.4	40.5	
Three oral glucose-lowering drugs	17.3	18.8	17.8		17.5	18.8	17.5	
>3 oral glucose-lowering drugs	4.4	4.8	5.5		4.6	4.8	5.3	
Insulin	3.3	2.7	3.2		3.3	2.7	3.2	
Insulin + oral glucose-lowering drug	13.7	13.8	15.4		14.0	13.5	15.4	
Comorbidity								
Obesity	36.1	36.6	34.1	0.004	36.3	36.3	34.1	0.007
CAD	9.2	9.5	10.9	0.002	8.9	9.9	10.8	<0.001
CHF	2.8	2.9	3.0	0.8	2.9	2.8	3.0	0.7
Cancer	2.2	1.9	2.2	0.3	2.1	2.1	2.1	1.0
Hyperlipidemia	26.4	25.2	26.1	0.3	27.0	26.1	24.7	0.005
Hypertension	48.6	48.6	52.2	<0.001	48.1	50.1	51.3	<0.001
Atrial fibrillation	0.6	0.5	0.6	0.8	0.5	0.6	0.7	0.2
Stroke	5.2	5.2	6.5	<0.001	5.2	5.3	6.4	0.002
Hypoglycemia	0.2	0.5	0.5	0.03	0.2	0.4	0.5	0.04
Number of measurement [†]	2.7 (0.9)	3.0 (0.9)	3.0 (0.9)	<0.001	2.7 (0.9)	3.1 (0.9)	2.9 (0.9)	<0.001

Differences in continuous variables were tested by ANOVA. Differences in categorical variables were tested by Chi-square test

SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; [†] mean (standard deviation)

a fall or a hip fracture, whereas retinopathy may lead to vision impairment and is reportedly related to hip fracture [23, 24]. Second, inflammation and oxidative stress may be the

underlying mechanisms of BP variability, hyperglycemia, and osteoporosis. Animal studies have suggested that an increased BP variability causes inflammation [25], and

Table 2 The hazard ratios (HRs) of hip fracture according to tertiles of SBP-CV and DBP-CV in diabetic patients enrolled in the NDCMP, Taiwan

Variables	n	Case	Person-years	IR (95% CI) ^a	Hip fracture HR (95% CI)		
					Model 1	Model 2	Model 3
SBP-CV							
1st tertile ($\leq 4.5\%$)	6917	273	56,671.58	4.82 (4.25, 5.39)	1.00	1.00	1.00
2nd tertile (4.5–8.6%)	6864	287	56,733.42	5.06 (4.47, 5.64)	1.01 (0.85, 1.19)	1.00 (0.85, 1.19)	1.01 (0.85, 1.19)
3rd tertile ($\geq 8.6\%$)	7379	377	59,172.02	6.37 (5.73, 7.01)	1.20 (1.02, 1.42)*	1.19 (1.01, 1.41)*	1.18 (1.00, 1.40)*
<i>P</i> for trend					0.02	0.03	0.04
SBP-CV (per 5% increase)	21,160	937	172,577.00	5.43 (5.08, 5.78)	1.09 (1.03, 1.15)**	1.08 (1.02, 1.15)**	1.08 (1.02, 1.15)**
DBP-CV							
1st tertile ($\leq 4.7\%$)	7027	275	57,880.00	4.75 (4.19, 5.31)	1.00	1.00	1.00
2nd tertile (4.7–9.4%)	6953	289	57,265.25	5.05 (4.46, 5.63)	1.06 (0.90, 1.26)	1.07 (0.91, 1.27)	1.07 (0.91, 1.27)
3rd tertile ($\geq 9.4\%$)	7180	373	57,431.76	6.49 (5.84, 7.15)	1.21 (1.03, 1.43)*	1.19 (1.01, 1.40)*	1.18 (1.00, 1.39)
<i>P</i> for trend					0.02	0.04	0.04
DBP-CV (per 5% increase)	21,160	937	172,577.00	5.43 (5.08, 5.78)	1.04 (0.99, 1.10)	1.04 (0.98, 1.09)	1.03 (0.98, 1.09)

^a Exact CIs for Poisson distribution

* $p < 0.05$; ** $p < 0.01$

Model 1 adjusted for age and gender

Model 2 adjusted for age, gender, type of antihypertensive drug use, type of diuretics, use of corticosteroids, smoking, alcohol drinking, diabetes duration, type of glucose-lowering drugs, obesity, baseline fasting plasma glucose, baseline HbA1c, baseline SBP, and baseline DBP

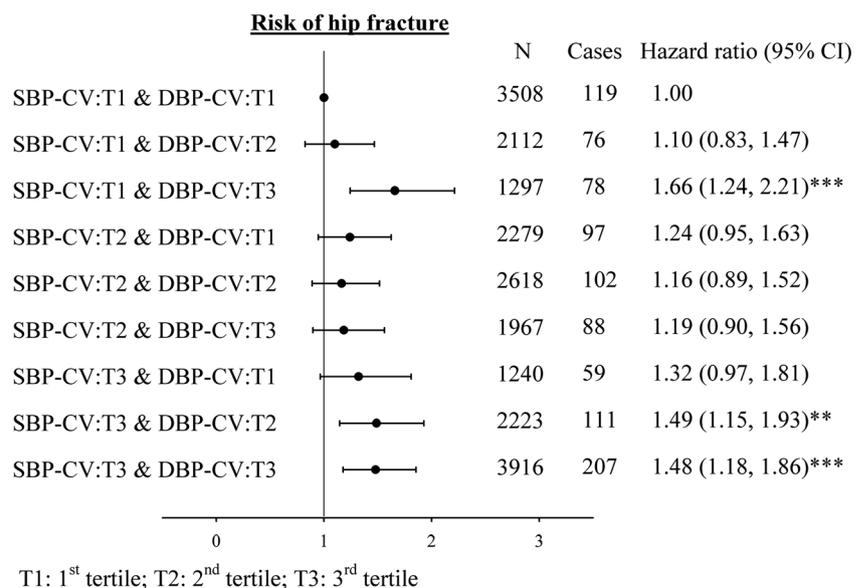
Model 3 adjusted for congestive heart failure, cancer, coronary artery disease, atrial fibrillation, hyperlipidemia, hypertension, stroke, and hypoglycemia in addition to variables in Model 2

IR, incidence density rate = number of incident cases/person-years \times 1000; SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, coefficient of variation; HR, hazard ratio

oxidative stress is a unifying feature of all contributing factors to hypertension [26]. Moreover, oxidative stress is one of the factors remarkably influencing bone mass [27]. Hyperglycemia also accompanies inflammation and oxidative stress. Clinical and molecular evidence has suggested that inflammation considerably influences bone turnover, inducing osteoporosis [28, 29]. In comparison with the nondiabetic

population, the patients with diabetes generally have higher bone mineral densities, and poorer bone quality [30, 31], and increased fracture risks. To eliminate the possibility of the confounding effects of hyperglycemia on the association between BP variability and hip fracture, we considered hyperglycemia in the multivariate analysis and found that BP variability is still significantly associated with hip fracture risk.

Fig. 2 The adjusted HR of hip fracture. The effects of SBP-CV and DBP-CV. SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, coefficient of variation; HR, hazard ratio; ** $p < 0.01$; *** $p < 0.001$



Fourth, BP variability might be an indicator of poor adherence to BP-lowering medications and multiple comorbidities treated by multiple medications, which might have played a role in the link to hip fracture. The risk estimates were similar to the original analyses and the sensitivity analysis that excluded patients who suffered from chronic conditions during the measurement period. Lastly, BP variability may be an indicator of increased risk and is not directly linked to a biological process in the body that results in an increased risk of hip fracture, or it is a marker of underlying mechanisms.

This work is the first and largest prospective study to demonstrate the independent association between visit-to-visit SBP and DBP variability and hip fracture risk in persons with type 2 diabetes mellitus. In Taiwan, BP is measured in routine clinical settings with an electronic BP sphygmomanometer and recorded in an electronic form. With the availability of computerized systems, the provision of visit-to-visit BP variability in routine clinical practice is feasible. Further studies are needed to provide evidence to confirm our study findings and to determine the optimal treatment option for persons with type 2 diabetes with high BP variability.

Our study has several limitations. First, our study sample was from persons with type 2 diabetes enrolled in the NDCMP. To evaluate whether our sample could be a representative of the national diabetes population, we compared the age and gender distributions in our study with those in the entire type 2 diabetes population and found similar distributions. The non-differential age and gender distributions indicated that our findings could be generalized to the population with type 2 diabetes in Taiwan. Second, our study design is observational. As such, the confounding effects of unadjusted covariates might exist. We adjusted as many confounders as possible to minimize the potential confounding effects, such as lifestyle behaviors and chronic complications like stroke, retinopathy, and neuropathy. We also excluded persons with comorbidities for sensitivity analysis to eliminate the possibility of residual confounding. Finally, the BP levels might be misclassified because of inter-clinical setting variation and accuracy. Nonetheless, no evidence indicated that this misclassification error was differential. The non-differential misclassification error would probably underestimate the effect if an association existed between BP variation and hip fracture.

Conclusion

Our study demonstrated that the SBP stability is associated with hip fracture. Based on the recommendations from the American Diabetes Association for fracture risk assessment and preventive program implementation in persons with type 2 diabetes, the prediction and prevention in older persons with type 2 diabetes may target at those with high SBP variability.

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Conflicts of interest None.

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