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ORIGINAL ARTICLE

Weight change and the risk of hip fractures in patients with type 2 diabetes: a nationwide cohort study

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Abstract

Summary Both weight gain and weight loss in type 2 diabetic population were associated with increased risk of hip fracture, while maintaining weight lowered the risk of hip fracture. Regarding the risk of hip fracture, we can propose active monitoring to maintain the weight of type 2 diabetes patients.

Introduction In type 2 diabetes, patients are often asked to control their weight in order to reduce their diabetic morbidity. The American Diabetes Association recommends that diabetic patients conduct high-intensity interventions for regulating diet, physical activity, and behavior to reduce weight, followed by long-term comprehensive weight maintenance programs. Although such weight control attempts are required in diabetic patients, there are few studies on the effect of weight change on hip fracture in this population. We aim to investigate the association between body weight change and the incidence of hip fracture in subjects with type 2 diabetes using large-scale, nationwide cohort data on the Korean population.

Materials and methods A total of 1,447,579 subjects (894,204 men and 553,375 women) > 40 years of age, who were diagnosed with type 2 diabetes, were enrolled in this study. Weight change within 2 years was divided into five categories: from weight loss ≥ 10% to weight gain ≥ 10%. The hazard ratios (HRs) and 95% confidence intervals for the incidence of hip fracture were analyzed, compared with the reference of the stable weight group (weight change < 5%).

Results Among 5 weight change groups, more than 10% weight loss showed the highest HR (HR, 1.605; 95% CI, 1.493 to 1.725), followed by more than 10% weight gain (HR, 1.457; 95% CI, 1.318 to 1.612). The effect of weight change on hip fracture risk was greater in males than in females, and those under 65 years of age were greater than those over 65 years of age. Baseline BMI did not play a role of weight change affecting the risk of hip fracture. The HR for hip fracture of subjects with regular exercise was lower than those without regular exercise.

Conclusions In the type 2 diabetes population, both weight gain and weight loss were significantly associated with a higher risk of hip fracture, whereas maintaining body weight reduced the risk of hip fracture the most.

Keywords Hip fractures · Type 2 diabetes · Weight change

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Introduction

Prevalence of obesity has increased steadily during the past half-century, leading to worldwide health concerns [1]. It is recommended by the World Health Organization (WHO) to use body mass index (BMI) as an indicator of obesity [2]. BMI was calculated as weight in kilograms divided by height in square meters. The World Health Organization recommendations for Asian populations were used to categorize individuals into five BMI groups. Among them, two groups with a BMI >25 (kg/m^2) are defined as obesity [3]. The higher the BMI, the higher a patient's risk is for metabolic diseases [4]. Among the risks of several diseases particularly increased by obesity, diabetes is well known for its association [5]. It is well known that being overweight or obese can induce type 2 diabetes, and the incidence of diabetes in adults with obesity is approximately 3–7 times that of adults with normal weight [6].

In the population without diabetes, several studies have shown the benefits of body weight reduction in preventing diverse diseases in obese people [7]. In regard to fractures, low BMI is associated with a significant increase in fracture risk [8]. Some population-based studies that investigated associations between weight change and fracture risk have shown that weight loss leads to increased risk of hip [9, 10], distal forearm [11], and frailty fractures [12], whereas weight gain serves as a protective factor for hip [9, 13], ankle [14], and distal forearm fractures [15].

Diabetes is a metabolic disorder, affecting nearly all organs and resulting in various complications [16]. Diabetic osteopathy is one of the complications of diabetes, and is characterized by decreased bone turnover and microarchitectural bone defects, leading to bone fragility and osteoporotic fractures [17]. It is well known that type 1 diabetes lowers bone mineral density and increases the risk of hip fracture [18, 19]. Type 2 diabetes is also reported to increase the risk of hip fracture, but the association is known to be less than that of type 1 diabetes. Vestergaard found that compared to those without diabetes, the relative risk (RR) for hip fractures in patients with type 1 diabetes was 6.94, and that for hip fractures in patients with type 2 diabetes was 1.38 [20]. Several [21–24], but not all [25, 26], studies have found that patients with type 2 diabetes are at an increased risk of hip fractures despite having higher bone mineral density (BMD) than non-diabetic subjects. Even pre-diabetes conditions have been reported to be associated with an increased risk of hip fracture [27]. Recently, there has been a growing appreciation of the relationship between diabetes and skeletal health. The worldwide incidence of hip fractures is expected to increase [28]. Hip fractures are a leading cause of mortality and morbidity in elderly individuals. The devastating complications associated with hip fractures create medical and financial burdens for society [29].

Recent studies have investigated whether intentional body weight loss reduces BMD and increases fracture in the population without diabetes [30, 31]. Type 2 diabetes patients are often asked to control their weight in order to reduce their diabetic morbidity. The American Diabetes Association recommends high-intensity interventions for regulating diet, physical activity, and behavior to reduce weight, followed by long-term comprehensive weight maintenance programs for diabetic patients [32]. However, there is a lack of research about fracture risk from weight change in the population with diabetes, although such weight control attempts are required in diabetic patients. Hip fracture is a representative osteoporotic fracture with significant adverse effects on public health. We aim to investigate the association between body weight change and the incidence of hip fracture in subjects with type 2 diabetes using large-scale, nationwide cohort data on the Korean population.

Research design and methods

Data source

The National Health Insurance Service (NHIS) is a mandatory social medical insurance system run by the Korean government. It is mainly supported by the contributions from the insured and the government subsidy. The NHIS covers approximately 97% of the population, and Medical Aid covers the remaining 3% of the low-income population. All healthcare providers are obliged to treat the insured, and the insured except the low-income group pay contributions monthly. As the NHIS operates on a fee-for-service system to pay healthcare providers, it is mandatory for all healthcare providers to submit the data regarding inpatients and outpatients, identification numbers, primary and secondary diagnoses classified according to the International Classification of Diseases-10th Revision (ICD-10), prescriptions, procedures, date of visits or hospitalization, and medical costs. The NHIS is in charge of collecting insurance contribution, providing health insurance benefits, managing the eligibility of the insured and making the medical service fee contract with representatives of healthcare providers. In addition, the NHIS operates the National Medical Checkup Program, which conducts a biannual standardized medical checkup for all of the insured who are 20 years old or older without copayment. Anthropometric measurements such as height, weight, body mass index (BMI) and waist circumference, systolic and diastolic blood pressure (BP), visual and hearing acuity, and laboratory tests such as fasting plasma glucose (FPG), total cholesterol (TC), serum creatinine, liver enzymes, urinalysis, and estimated glomerular filtration rate (eGFR) are included in the standardized medical checkup. Data on past medical history and health-related behaviors such as smoking status, alcohol

consumption, and regular exercise are also obtained through a standardized self-reported questionnaire. Detailed information about the Korean NHIS was previously introduced elsewhere [33].

The research protocol of this study was reviewed and approved by the Institutional Review Board (SSU-202003-HR-201-01), and was conducted in accordance with the tenets of the Helsinki Declaration. Since all data provided by the NHIS to researchers were anonymized, the need for informed consent was exempted.

Study population

Among the subjects who underwent health screenings from January 2009 to December 2012, we focused on patients with type 2 diabetes. Diagnosis of type 2 diabetes was confirmed according to the following criteria: (1) at least one claim per year under ICD-10 codes E11–14 and at least one claim per year for the prescription of antidiabetic medication (sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, or insulin) [34], or (2) fasting glucose level ≥126 mg/dL. Patients who were admitted to the hospital more than once or visited the outpatient clinic more than twice for type 2 diabetes were also included [35].

Among the 2,746,078 subjects diagnosed with diabetes who underwent health screening from January 2009 to December 2012, we excluded subjects aged < 40 (n = 210,885) and those who did not undergo a second health examination within 2 years from a health examination between January 2009 and December 2012 (n = 749,730). Subjects with missing data (n = 46,940) were excluded. Because health information data existed from 2002, subjects with a history of hip fracture during a washout period from 2002 to 2008 (n = 262,423) were excluded. In addition, subjects diagnosed with a new hip fracture within 1 year of follow-up (n = 28,521) were excluded. The reason for excluding the 1-year lag was because if the period from the index date to the occurrence of hip fracture is too short, it is difficult to determine whether it is caused by weight change, and the problem of reverse causation may also be raised. The final study population consisted of 1,447,579 subjects (Fig. 1). The study population was followed from the baseline (the date of second NHIS medical checkup) to the endpoint (new development of hip fracture), or December 31, 2018, whichever came first.

Study variables—the definition of BMI, obesity, and weight change

Height, weight, and waist circumference were measured while participants wore lightweight clothing. BMI (kg/m^2) was calculated as weight in kilograms divided by the square of height in meters. The World Health Organization recommendations for Asian populations were used to categorize individuals into five BMI groups: <18.5 kg/m^2 (underweight), 18.5–22.9 kg/m^2 (normal), 23.0–24.9 kg/m^2 (overweight), 25.0–29.9 kg/m^2 (class I obese), or ≥30 kg/m^2 (class II obese) [3]. The definition of obesity is a body mass index (BMI) >25 (kg/m^2) [3]. Abdominal obesity was defined as a waist circumference ≥ 90 cm in men and ≥ 80 cm in women [36]. We calculated weight changes within a 2-year interval according to the difference in weight values between the first and second health exams, expressed as a percentage. We defined ≤ 5% weight change as "stable weight" and categorized "weight change" into groups of 5% increments: (1) ≥10% weight loss, (2) 5–10% weight loss, (3) 5–10% weight gain, and (4) ≥10% weight gain.

Study variables—general health behaviors and physical activity variables

Using a standardized self-reporting questionnaire, we categorized smoking status as non-smokers, ex-smokers,

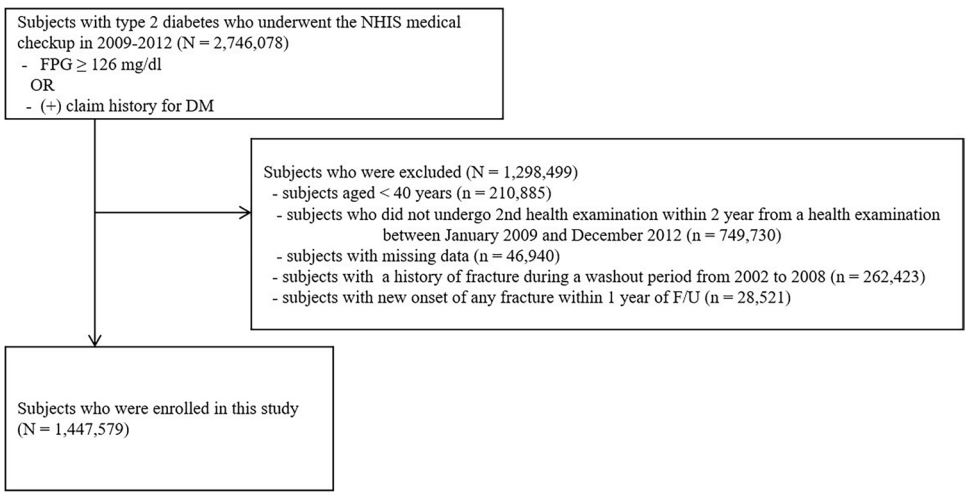


Fig. 1 Study design and disposition of subjects

or current smokers. Individuals who consumed ≥30 g of alcohol per day were considered as heavy alcohol drinkers [37]. Income level was dichotomized into <25% or ≥25% of the population. The physical activity level was assessed with self-report–structured questionnaires using a 7-day recall method [38]. The survey included 3 questions regarding the usual frequency (days per week) of (1) vigorous-intensity physical activity for at least 20 min, (2) moderate-intensity physical activity for at least 30 min, and (3) light-intensity physical activity for at least 30 min. Vigorous-intensity physical activity was defined as intense exercise that caused severe shortness of breath, including running and bicycling at high speed; moderate-intensity physical activity, as exercise that caused mild shortness of breath, including brisk walking and bicycling at usual speed; and light-intensity physical activity, as walking at a slow or leisurely pace. To calculate the metabolic equivalent task-minutes (MET-min), ratings of 3.0, 4.0, and 8.0 METs were assigned for light-intensity physical activity, moderate-intensity physical activity, and vigorous-intensity physical activity, respectively [39]. Physical activity–related energy expenditure was calculated in METs in minutes (MET-min) per week by summing the product of frequency, intensity, and duration. Regular exercise was defined as performing vigorous-intensity physical activity for ≥ 20 min at least three times per week or moderate-intensity physical activity for ≥ 30 min at least five times per week [40].

Study variables—definition of hip fracture and other comorbidities

The outcome variable of this study was the new occurrence of hip fracture after baseline. As a definite hip fracture requires hospitalization and operative treatment, hip fracture was defined when hospitalization under the primary diagnosis of ICD-10 code S72.0 (fracture of head and neck of femur) or S72.1 (pertrochanteric fracture) was confirmed.

Hypertension was defined as at least one claim per year under ICD-10 codes I10 or I11 and at least one claim per year for the prescription of an antihypertensive agent or measurement of systolic/diastolic blood pressure (BP) ≥ 140/90 mmHg were present. Dyslipidemia was defined as at least one claim per year for anti-dyslipidemia medication under ICD-10 code E78 or lab result of total cholesterol ≥ 240 mg/dL was present. Ischemic heart disease (IHD) was diagnosed with the self-questionnaire results for the history of acute myocardial infarction. We defined estimated glomerular filtration rate <60 mL/min/1.73m^2 as chronic kidney disease (CKD) [41]. The presence of osteoporosis was defined using ICD-10 code M80-82.

Statistical analysis

All statistical analyses were performed with the SAS software (version 9.4; SAS Institute, Cary, NC, USA). Results were considered statistically significant when the *P* value was less than 0.05. The baseline characteristics of the subjects are presented as mean values with standard deviations for continuous variables and as numbers with percentages for categorical variables. The differences in baseline characteristics were compared using the Student's *t*-test for continuous variables and the chi-square test for categorical variables. Subjects were categorized into 5 groups according to their weight change. The incidence rates (IRs) of hip fractures were calculated by dividing the number of incident cases by the total follow-up period duration and were expressed as the number of fractures per 1000 people per year. The association between the weight change categories and risk of hip fractures was evaluated with Cox proportional hazard regression models. For multi-variate analyses, model 1 included age and sex; model 2 included age, sex, smoke, drink, regular exercise, hypertension, dyslipidemia, and CKD; and model 3 included age, sex, smoke, drink, regular exercise, hypertension, dyslipidemia, CKD, insulin use, duration of diabetes ≥ 5 years, use of three or more oral hypoglycemic agents, fasting glucose level, height, and osteoporosis. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) using the normal group as reference. Subgroup analyses were conducted after categorizing the subjects according to sex, age, regular exercise, and exercise intensity (500 met/min and 1000 met/min). Age was divided into 2 groups: 40–64 years, and ≥65 years. In addition, *P* for interaction was evaluated for other variables, such as the presence of CKD, IHD, duration of diabetes ≥ 5 years, insulin use, or use of three or more oral hypoglycemic agents, abdominal obesity, obesity, and five BMI groups.

Results

Baseline characteristics

The baseline characteristics of participants are shown in Table 1. We identified 11,848 hip fractures among 1,447,579 subjects enrolled with type 2 diabetes. Compared with the weight loss groups, weight gain groups had greater proportions of men, smoking, and alcohol drinking. As for the weight change groups (i.e., weight loss, weight stable, and weight gain), the stable-weight group had a higher median value of MET-min per week, and a higher proportion of male, current smoker, heavy drinker, and patients with regular exercise. The stable-weight group

Table 1 Baseline characteristics of subjects

	Weight change					
	≤−10%	−10% to ≤−5%	−5% to ≤5%	5% to ≤10%	10% <	*P* value
N	46,621	185,654	1,086,966	99,879	28,459	
Hip fracture (percent: event/number)	830 (1.78)	1975 (1.06)	7637 (0.70)	1006 (1.01)	400 (1.41)	<.0001
Age						<.0001
40–64	26,813 (57.51)	119,730 (64.49)	757,859 (69.72)	66,861 (66.94)	18,169 (63.84)	
65≤	19,808 (42.49)	65,924 (35.51)	329,107 (30.28)	33,018 (33.06)	10,290 (36.16)	
Sex						<.0001
Male	21,784 (46.73)	101,712 (54.79)	696,625 (64.09)	58,185 (58.26)	15,898 (55.86)	
Female	24,837 (53.27)	83,942 (45.21)	39,0341 (35.91)	41,694 (41.74)	12,561 (44.14)	
Income (Q1)	11,463 (24.59)	43,757 (23.57)	256,486 (23.6)	25,243 (25.27)	7604 (26.72)	<.0001
Smoke						<.0001
Non	30,754 (65.97)	112,105 (60.38)	588,621 (54.15)	57,444 (57.51)	16,794 (59.01)	
Ex	7441 (15.96)	34,228 (18.44)	246,322 (22.66)	21,900 (21.93)	5810 (20.42)	
Current	8426 (18.07)	39,321 (21.18)	252,023 (23.19)	20,535 (20.56)	5855 (20.57)	
Drink						<.0001
Non	34,056 (73.05)	119,446 (64.34)	606,246 (55.77)	60,830 (60.9)	18,801 (66.06)	
Mild	10,090 (21.64)	52,868 (28.48)	382,368 (35.18)	30,988 (31.03)	7628 (26.8)	
Heavy	2475 (5.31)	13,340 (7.19)	98,352 (9.05)	8061 (8.07)	2030 (7.13)	
Regular exercise	10,298 (22.09)	44,172 (23.79)	263,471 (24.24)	21,512 (21.54)	5507 (19.35)	<.0001
BMI 5 level						<.0001
BMI <18.5	3554 (7.62)	4286 (2.31)	9989 (0.92)	698 (0.7)	222 (0.78)	
18.5 ≤ BMI <23	23,142 (49.64)	68,985 (37.16)	256,850 (23.63)	20467 (20.49)	5329 (18.73)	
23 ≤ BMI <25	10,119 (21.7)	50,471 (27.19)	28,9810 (26.66)	23,639 (23.67)	6241 (21.93)	
25 ≤ BMI <30	8717 (18.7)	55,251 (29.76)	460,747 (42.39)	45,217 (45.27)	12,669 (44.52)	
30 ≤BMI	1089 (2.34)	6661 (3.59)	69,570 (6.4)	9858 (9.87)	3998 (14.05)	
Hypertension	27,313 (58.59)	106,130 (57.17)	638,769 (58.77)	61,681 (61.76)	17,782 (62.48)	<.0001
Dyslipidemia	20,680 (44.36)	83,329 (44.88)	488,423 (44.93)	48,212 (48.27)	13,783 (48.43)	<.0001
Cancer	2647 (5.68)	5794 (3.12)	24,849 (2.29)	2877 (2.88)	993 (3.49)	<.0001
CKD	6302 (13.52)	19,830 (10.68)	105,203 (9.68)	12,229 (12.24)	4214 (14.81)	<.0001
IHD	6968 (14.95)	24,665 (13.29)	133210 (12.26)	13,419 (13.44)	3903 (13.71)	<.0001
Osteoporosis	9240 (19.82)	28,620 (15.42)	121,167 (11.15)	13,833 (13.85)	4409 (15.49)	<.0001
Insulin use	5667 (12.16)	16,494 (8.88)	81,947 (7.54)	11,916 (11.93)	4559 (16.02)	<.0001
Use of three or more oral hypoglycemic agents	8350 (17.91)	31,321 (16.87)	176,783 (16.26)	20,260 (20.28)	6175 (21.7)	<.0001
Duration of diabetes ≥ 5 years	18,428 (39.53)	72,315 (38.95)	418,346 (38.49)	40,943 (40.99)	11,799 (41.46)	<.0001
Met-min (median, Q1–Q3)	450 (0–900)	490 (0–960)	540 (90–980)	480 (0–900)	420 (0–800)	<.0001
Met-min ≥1000	10,403 (22.31)	44,698 (24.08)	266,116 (24.48)	21,789 (21.82)	5617 (19.74)	<.0001
Met-min ≥500	21,880 (46.93)	92,501 (49.82)	551,524 (50.74)	47,812 (47.87)	12,568 (44.16)	<.0001
Age	62.25 ± 11.2	60.6 ± 10.28	59.28 ± 9.89	59.9 ± 10.23	60.66 ± 10.84	<.0001
BMI	22.65 ± 3.22	23.91 ± 3.06	25.07 ± 3.11	25.61 ± 3.39	26.09 ± 3.85	<.0001
Waist circumference	80.83 ± 8.93	82.79 ± 8.36	85.43 ± 8.23	86.35 ± 9.06	86.95 ± 9.24	<.0001
Height	159.45 ± 9.23	161.2 ± 9.01	162.9 ± 8.74	161.79 ± 8.92	161.09 ± 9.19	<.0001
Weight	57.77 ± 10.6	62.32 ± 10.55	66.69 ± 10.82	67.2 ± 11.37	67.83 ± 12.09	<.0001
SBP	125.61 ± 15.97	126.51 ± 15.26	128.31 ± 15.05	129.33 ± 15.52	129.49 ± 15.79	<.0001
DBP	76.46 ± 10.19	77.2 ± 9.91	78.44 ± 9.86	78.67 ± 9.96	78.68 ± 10.09	<.0001

Table 1 (continued)

	Weight change					
	≤−10%	−10% to ≤−5%	−5% to ≤5%	5% to ≤10%	10% <	*P* value
N	46,621	185,654	1,086,966	99,879	28,459	
Glucose	133.42 ± 59.8	133.32 ± 49.86	132.75 ± 42.37	131.45 ± 42.33	132.42 ± 45.21	<.0001
Total cholesterol	183.85 ± 42.61	187.24 ± 43.09	189.98 ± 42.87	189.13 ± 42.54	189 ± 42.03	<.0001
HDL	52.92 ± 17.8	51.82 ± 16.11	50.84 ± 19.16	51.13 ± 28.87	50.91 ± 47.79	<.0001
LDL	105.11 ± 42.44	107.48 ± 43.62	108.33 ± 62.35	107.05 ± 64.6	107.37 ± 72.98	<.0001
FLI	24.66 ± 21.01	31.46 ± 22.92	40.78 ± 24.79	42.98 ± 25.58	44.35 ± 25.88	<.0001
*TG	113.25 (112.7–113.8)	122.92 (122.61–123.22)	138.07 (137.93–138.22)	139.78 (139.3–140.25)	139.4 (138.53–140.28)	<.0001
*ALT	20.71 (20.61–20.82)	22.45 (22.4–22.5)	25.31 (25.28–25.33)	25.48 (25.4–25.57)	24.74 (24.58–24.91)	<.0001
*AST	23.51 (23.42–23.6)	24.16 (24.11–24.2)	25.62 (25.61–25.64)	26.07 (26–26.14)	25.92 (25.78–26.05)	<.0001

Data are presented as mean ± standard deviation or proportions (%)

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FLI* fatty liver index, *TG* triglyceride, *Met-min* metabolic equivalent (MET)–minutes per week (MET-min/week)

*Geometrimean (95% CI)

had a lower proportion of subjects with ≥65 years of age, cancer, CKD, IHD, osteoporosis, insulin use, and use of three or more oral hypoglycemic agents. However, the following increased proportionally with weight: waist circumference, BMI, total cholesterol, proportion of subjects with obesity (BMI ≥ 25), low income (Q1), hypertension, and dyslipidemia. No trend was observed in age, height, systolic blood pressure, diastolic blood pressure, glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and the proportion of subjects with duration of diabetes for more than 5 years. The highest proportion of hip fractures (1.78%) was observed in the group with weight loss more than 10%, and the lowest proportion of hip fractures (0.70%) was observed in the group with stable weight: weight change between −5% and 5% (Table 1).

Hip fracture risk by weight change

The HRs of hip fracture in relation to weight change are shown in Table 2. In comparison to the stable-weight group, weight loss was associated with a greater hip fracture risk than weight gain per the equal changes in weight, after adjusting for all covariates, The group with weight loss ≥ 10% had the highest HR for hip fracture (HR, 1.605; 95% CI, 1.493 to 1.725) and the HRs for weight gain ≥ 10% and weight loss between 5 and 10% were 1.457 (95% CI, 1.318 to 1.612) and 1.237 (95% CI, 1.177 to 1.3), respectively. Kaplan–Meier estimates of cumulative incidence of hip fracture among patients with type 2 diabetes by the weight change categories are demonstrated in Fig. 2.

Table 2 Hazard ratio according to five categories of weight change

Weight change	*N*	Event	Duration*	IR†	Model 1; HR (95% CI)	Model 2; HR (95% CI)	Model 3; HR (95% CI)
≤−10%	46,621	830	23,5981.48	3.51723	1.661 (1.545,1.786)	1.615 (1.503,1.737)	1.605 (1.493,1.725)
−10% to ≤−5%	185,654	1975	982,912.91	2.00933	1.26 (1.199,1.324)	1.244 (1.184,1.308)	1.237 (1.177,1.3)
−5% to ≤5%	1,086,966	7637	5,975,095.9	1.27814	1 (ref.)	1 (ref.)	1 (ref.)
5% to ≤10%	99,879	1006	536,444.52	1.87531	1.29 (1.208,1.378)	1.265 (1.185,1.351)	1.234 (1.156,1.318)
10% <	28,459	400	148,209.19	2.69889	1.571 (1.421,1.738)	1.507 (1.362,1.667)	1.457 (1.318,1.612)

Model 1: adjusted for age and sex; model 2: adjusted for model 1 plus smoke, drink, regular exercise, hypertension, dyslipidemia and CKD; model 3, adjusted for model 2 plus insulin use, duration of diabetes ≥ 5 years, use of three or more oral hypoglycemic agents, fasting glucose level, height, and osteoporosis

HR hazard ratio, *CI* confidence interval

*Duration: person-years

†Incidence rate per 1000 person-years

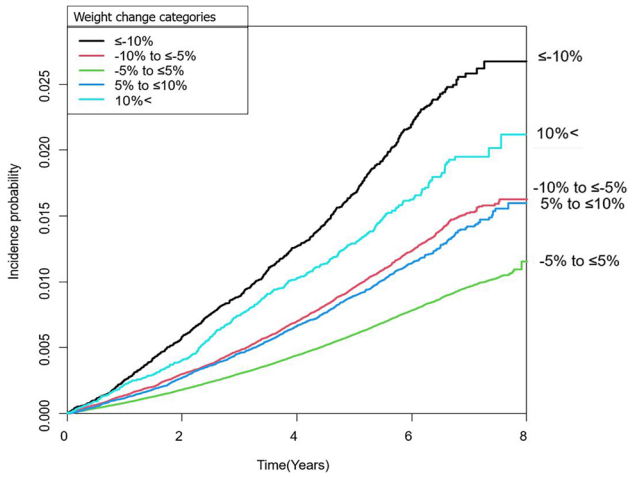


Fig. 2 Kaplan-Meier estimates of cumulative incidence of hip fracture among patients with type 2 diabetes by the weight change categories, based on unadjusted data

Hip fracture risk by weight change according to subgroups

We categorized participants by sex, age, five categories of BMI, presence of CKD and IHD, duration of diabetes ≥ 5 years, insulin use or use of three or more oral hypoglycemic agents, abdominal obesity (waist circumference ≥ 95 cm in male, ≥80 cm in female), and obesity (BMI ≥25). We also analyzed the HRs for hip fracture in the five weight change groups by forementioned categories, respectively. Results after adjusting covariates are summarized in Supplemental table S1. There was no significance of the *P* value for interaction regarding five categories of BMI, CKD, IHD, duration of diabetes ≥ 5 years, insulin use or use of three or more oral hypoglycemic agents, abdominal obesity, and obesity (Supplemental table S1).

For subgroup analysis by sex, the incidence rate per 1000 persons and event number of hip fractures were higher in females than in males. However, the increase in hip fracture risk was more evident in males, as the weight change increased (Table 3). Compared to the age 65 or older group,

Table 3 Incidence rates and hazard ratios of hip fractures according to the five categories of weight change by age and sex

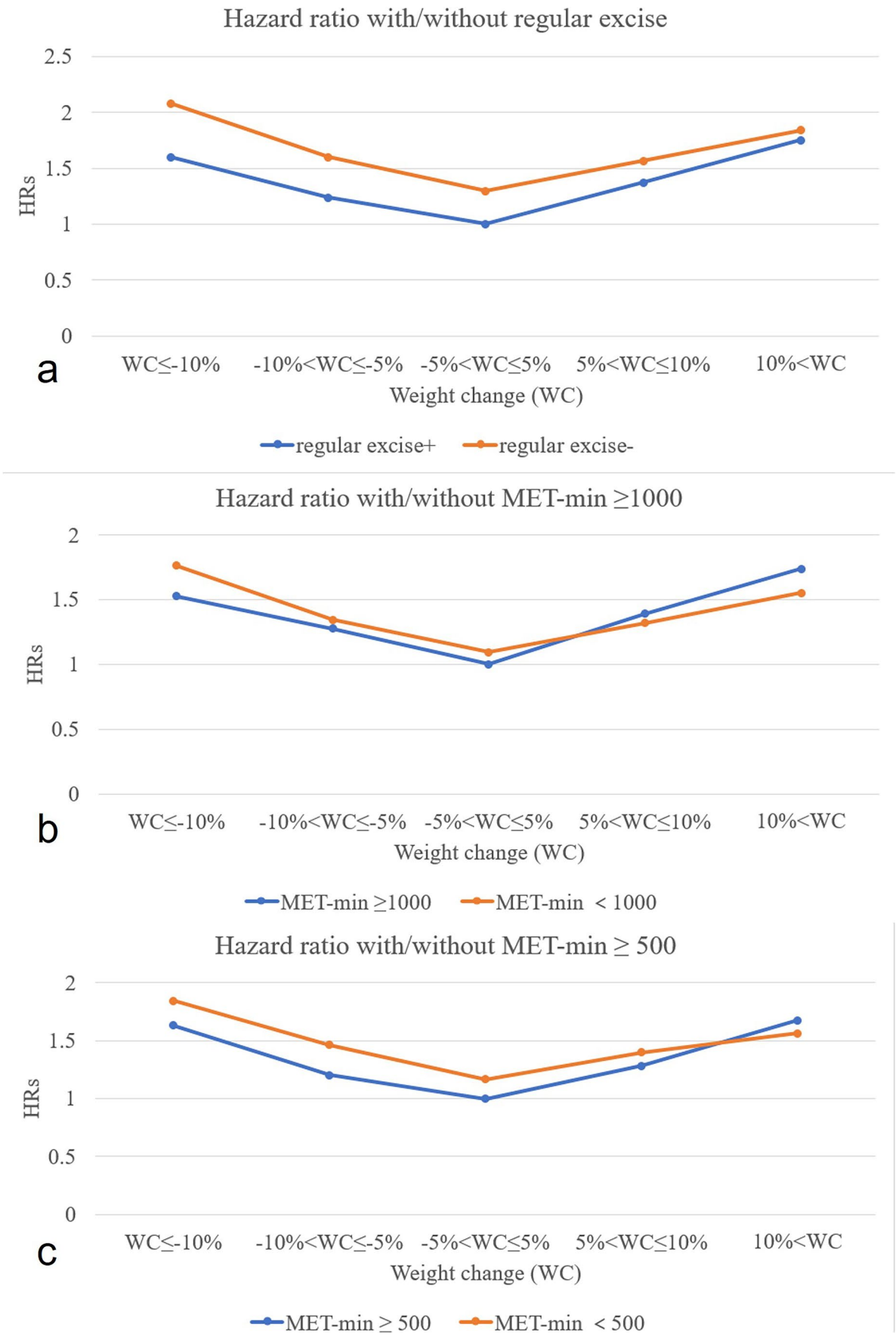
	Weight change	*N*	Event	Duration*	IR†	Model	*P* for interaction
Subanalysis by age							
Age 40–64	≤−10%	26,813	132	140,503.05	0.93948	1.976 (1.653,2.362)	0.025
	−10% to ≤−5%	119,730	389	646,214.98	0.60197	1.377 (1.233,1.538)	
	−5% to ≤5%	757,859	1729	4,236,333.18	0.40814	1 (ref.)	
	5% to ≤10%	66,861	222	365,216.08	0.60786	1.359 (1.181,1.564)	
	10%<	18,169	80	96,816.02	0.82631	1.697 (1.355,2.126)	
Age 65–	≤−10%	19,808	698	95,478.43	7.31055	1.538 (1.42,1.664)	
	−10% to ≤−5%	65,924	1586	336,697.93	4.71045	1.205 (1.14,1.274)	
	−5% to ≤5%	329,107	5908	1,738,762.73	3.39782	1 (ref.)	
	5% to ≤10%	33,018	784	171,228.44	4.57868	1.2 (1.114,1.293)	
	10%<	10,290	320	51,393.16	6.22651	1.4 (1.251,1.567)	
Subanalysis by sex							
Male	≤−10%	21,784	264	109,105.04	2.41969	2.047 (1.803,2.323)	<.0001
	−10% to ≤−5%	101,712	706	538,060.81	1.31212	1.375 (1.266,1.492)	
	−5% to ≤5%	696,625	3107	3,858,970.61	0.80514	1 (ref.)	
	5% to ≤10%	58,185	400	313,900.78	1.27429	1.372 (1.236,1.523)	
	10%<	15,898	146	82,819.73	1.76286	1.706 (1.445,2.015)	
Female	≤−10%	24,837	566	126,876.44	4.46103	1.423 (1.303,1.554)	
	−10% to ≤−5%	83,942	1269	444,852.1	2.85263	1.16 (1.09,1.234)	
	−5% to ≤5%	390,341	4530	2,116,125.3	2.1407	1 (ref.)	
	5% to ≤10%	41,694	606	222,543.73	2.72306	1.148 (1.055,1.25)	
	10%<	12,561	254	65,389.45	3.88442	1.313 (1.156,1.49)	

Model: adjusted for smoke, drink, regular exercise, hypertension, dyslipidemia, and CKD, insulin use, duration of diabetes ≥ 5 years, use of three or more oral hypoglycemic agents, fasting glucose level, height, and osteoporosis

HR hazard ratio, *CI* confidence interval

*Duration: person-years

†Incidence rate per 1000 person-years


Hazard ratio with/without regular excise
2.5
2
1.5
1
0.5
0
HRs
a
WC≤-10%
-10%<WC≤-5%
-5%<WC≤5%
5%<WC≤10%
10%<WC
Weight change (WC)
regular excise+
regular excise-
Hazard ratio with/without MET-min ≥1000
2
1.5
1
0.5
0
HRs
b
WC≤-10%
-10%<WC≤-5%
-5%<WC≤5%
5%<WC≤10%
10%<WC
Weight change (WC)
MET-min ≥1000
MET-min < 1000
Hazard ratio with/without MET-min ≥ 500
2
1.5
1
0.5
0
HRs
c
WC≤-10%
-10%<WC≤-5%
-5%<WC≤5%
5%<WC≤10%
10%<WC
Weight change (WC)
MET-min ≥ 500
MET-min < 500

◂**Fig. 3** Hazard ratio of hip fracture on weight change according to the presence of regular exercise, and exercise intensity (500 Met-min, 1000 Met-min). The reference group corresponds to stable weight (weight change < 5%), with regular exercise for **a**, with ≥1000 Met-min for **b**, or with ≥ 500 Met-min for **c**. The graphs are drawn based on adjusted HR measurement for age, sex, smoke, drink, regular exercise, hypertension, dyslipidemia, CKD, insulin use, duration of diabetes ≥ 5 years, use of three or more oral hypoglycemic agents, fasting glucose level, height, and osteoporosis

the incidence rate was lower in those under age 65, but the more the weight changed, the greater the risk of hip fracture (Table 3).

The HRs for the hip fracture of patients with regular exercise were lower than those without regular exercise. The difference was bigger in patients whose weight was reduced or maintained, and the difference in HR was small in patients who gained weight (Supplemental Table S2). To observe the effect of exercise intensity, subjects were classified as above and below 500 MET-min/week, and above and below 1000 MET-min/week, the effect of weight change on hip fracture was investigated. The difference in HRs between subjects with regular exercise and subjects without regular exercise was larger than the difference in HRs according to the intensity of exercise based on 500 MET-min/week and 1000 MET-min/week (Fig. 3).

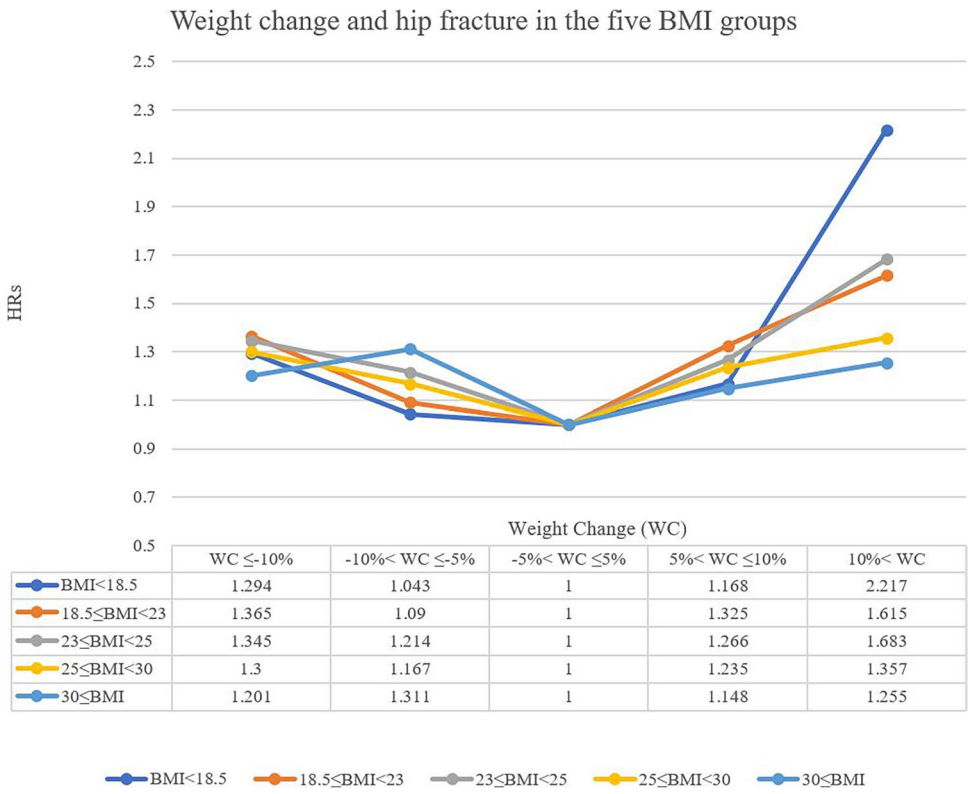
Hip fracture risk by weight change in five BMI categories

The HRs for hip fracture of weight change in the five BMI categories was also analyzed by adjusting for all covariates (Fig. 4). The value of *P* for interaction was 0.19, and the effect of weight change was not significantly affected by BMI (Supplemental table S1). Across all BMI categories, weight change ≥ 10% was associated with increased hip fracture risk. Among the weight gain ≥ 10% groups, the highest hip fracture risk was observed in subjects with BMI ≤18.5 kg/m^2 (HR, 2.217; 95% CI, 1.261 to 3.899) and the lowest hip fracture rate was observed in the subjects with BMI ≥ 30 kg/m^2 (HR, 1.255; 95% CI, 0.897 to 1.756). Among the weight loss ≥ 10% groups, the highest hip fracture risk was observed in subjects with normal BMI of 18.5 to 23 kg/m^2 (HR, 1.365; 95% CI, 1.233 to 1.51) and the lowest hip fracture risk was observed in the subjects with BMI ≥ 30 kg/m^2 (HR, 1.201; 95% CI, 0.568 to 2.539). In the underweight group (BMI <18.5 kg/m^2), both weight loss ≥10% and weight gain ≥10% were associated with increased hip fracture risk, but weight gain and weight loss of 5% to 10% did not show a correlation. Compared to the overweight and obese groups, the underweight and normal BMI groups had higher HRs of hip fracture regarding weight change more than 10%, and the weight gain group had higher HRs than the weight loss group. When BMI was low, the effect of weight change on hip fracture risk tended to be larger (Fig. 4).

Discussion

Weight loss has been documented to be related to bone loss [42] and increased fracture risk [9–13] in previous studies on the western nondiabetic populations. The Look AHEAD trial, a randomized trial testing the long-term health effects of intensive lifestyle interventions in 5145 persons with overweight/obesity and type 2 diabetes, reported that intentional body weight loss in older overweight/obese subjects with type 2 diabetes was not associated with an overall increased risk of fracture but was associated with a 39% increased risk of frailty fracture [43]. Similar to previous studies [9, 13], we demonstrated that weight loss of 10% or more significantly increased the risk of hip fracture as compared to stable-weight conditions. The mechanism behind the association between body weight change and adverse hip fracture events in diabetes cohort remains unclear. For the effect of weight loss on hip fracture, there are some possible explanations. First, body weight loss leads to decreased BMD in the general population as well as in type 2 diabetes patients. In the Framingham Osteoporosis Study, BMD measured at the hip or spine in 567 men and women aged 28–62 years declined with body weight loss of ≥ 5% from baseline [44]. This finding was also seen in patients with type 2 diabetes, where intentional body weight loss led to bone loss in the hip [45]. Second, body weight loss with loss of lean mass in particular may result in decreased muscle strength, leading to decreased physical activity, and increased risk of incident fall [46]. Since patients with diabetes are known to have sarcopenia and physical disability, and are prone to incident fall [47], the group with greater weight loss in our study may have included more sarcopenia patients. Third, as patients with diabetes receive diet therapy to improve glycemic control or lower obesity, greater weight loss may mean decreased intake of nutrients such as protein, calcium, and vitamin D, which are essential in maintaining bone strength [48]. The population study among Norwegian men and women also showed that weight loss of more than 3 kg was associated with a significant twofold increase in risk of hip fracture as compared to those who had body weight gain of 1.3–5.5 kg [49].

On the other hand, our study showed that weight gain of more than 10% is associated with the second highest hip fracture risk, in contrast to such nondiabetic population studies [9, 13]. Further studies are needed to determine how increased body weight increases the risk of hip fractures. One possible explanation is metabolic change with weight gain. After weight gain, rapid adipose tissue growth and hyperplasia occur owing to metabolic shifts that favor lipid



	WC ≤-10%	-10%< WC ≤-5%	-5%< WC ≤5%	5%< WC ≤10%	10%< WC
BMI<18.5	1.294	1.043	1	1.168	2.217
18.5≤BMI<23	1.365	1.09	1	1.325	1.615
23≤BMI<25	1.345	1.214	1	1.266	1.683
25≤BMI<30	1.3	1.167	1	1.235	1.357
30≤BMI	1.201	1.311	1	1.148	1.255

Fig. 4 Weight change and hip fracture in the five BMI groups, adjusted for age, sex, smoke, drink, regular exercise, hypertension, dyslipidemia, CKD, insulin use, duration of diabetes ≥ 5 years, use of three or more oral hypoglycemic agents, fasting glucose level, height, and osteoporosis

storage. Adipose tissue, which is metabolically active, can increase the production of leptin, cytokines, and adiponectin, potentially leading to adverse outcomes [50]. Weight gain could also be associated with abdominal fat accumulation [51]. Especially visceral fat can negatively affect insulin levels and cause inflammation [52]. In addition, one meta-analysis study demonstrated that abdominal obesity itself was associated with an increased risk of hip fracture [53].

In previous studies with nondiabetic populations, there were no associations regarding weight change and hip fracture risk by gender or age group [9, 12, 13]. However, there was a significant association with age and sex regarding weight change and hip fracture risk (Table 3). According to the subgroup analysis by sex, the incidence rate and absolute event values were much higher in females, but the effect on hip fracture risk by weight change was significantly higher in males than in females (Table 3). One possible reason for this disparity of the risk of hip fractures between the sexes is that males have larger bones and less fat tissue than females [54]. Since the weight of bone remains relatively constant compared to muscle or fat tissue during weight change, the effect of weight change on hip fracture may be more significant in males. In addition, a previous report demonstrated that males lose more muscle mass than females with weight loss, causing increased mechanical stress on bone [55]. For instance, male subjects with greater weight loss would be more prone to have sarcopenia, which is related to physical disability and consequent incident falls [47]. According to the subgroup analyses by age, the risk of hip fractures was higher in younger age groups. These results are consistent with previous studies [56, 57]. Some authors stated that the difference of the risk of hip fractures between young and old age groups comes from age- or menopause-related changes which overshadow the effect of diabetes itself on fracture risk [58].

Another interesting point revealed in this article is that the presence of regular exercise plays a role in decreasing HRs of hip fracture (Fig. 3). The first plot of Fig. 3 shows HRs between subjects with regular exercise and subjects without regular exercise. The second and third plots of Fig. 3 show HRs according to the intensity of exercise based on 500 MET-min/week and 1000 MET-min/week. The difference in HRs between subjects with regular exercise and subjects without regular exercise was larger than the difference in HRs according to the intensity of exercise based on 500 MET-min/week and 1000 MET-min/week. Therefore, it can be inferred that regular exercise is helpful in reducing hip fractures rather than just increasing the intensity of exercise for diabetic patients.

Contrary to our expectations, BMI did not play a role in affecting the risk of hip fracture (Supplemental Table S1). Nevertheless, the effect of weight change on the risk of hip fractures was slightly stronger in non-obese individuals than in obese individuals (Fig. 4). The interesting point is that, in subjects with BMI ≤18.5 kg/m^2, weight gain of more than 10% significantly increased hip fracture risk (Fig. 4).

Although the exact causality is unknown, a possible explanation is as follows: Since the body has a certain amount of skeletal bone weight, a 10% weight change in a subject with a low BMI will result in a greater change in fat tissue and muscle than a 10% weight change in a subject with a high BMI. In such situations, the effect of weight gain on hip fracture seemed to be maximized.

Our study has several notable strengths. We have a large sample size of > 1,400,000 individuals and a long follow-up period of >7 years. We believe this is the first study to investigate the association between weight change and hip fractures risk in patients with type 2 diabetes using nationwide cohort data. Various subgroup analyses were possible using this data, which provided interesting conclusions. The analyses were performed after adjusting substantial confounding variables, including age, sex, smoke, drink, regular exercise, hypertension, dyslipidemia, CKD, insulin use, duration of diabetes ≥ 5 years, use of three or more oral hypoglycemic agents, fasting glucose level, height, and osteoporosis, which may cause weight changes or BMI. Since the Korean society is a single ethnic society, it was possible to involve a homogeneous group in a nationwide study.

Despite these advantages, our study also has limitations. First, reverse causation may exist in our results because of the retrospective cohort design. To address this issue, this analysis was conducted excluding incident hip fracture during a washout period from 2002 to 2008, and new hip fractures within the first 1 year of follow-up. Second, causes of the body weight change could not be identified. It could be intentional or unintentional. For instance, unintentional weight loss is often related to underlying poor health. Increased risk of fracture may be due to underlying poor health causing the unintentional weight loss, rather than weight loss itself. For this issue, HR values were calculated by adjusting various health conditions. Third, there may be a misclassification bias. In concern of exclusion of insulin-dependent type 1 diabetes, we did not use the ICD-10 code E10 representing type 1 diabetes as an exclusion criterion. However, there is a possibility that subjects with type 1 diabetes still may have been enrolled in our study. Fortunately, East Asian countries, including the Republic of Korea, have the lowest incidence of type 1 diabetes in the world [59]. The prevalence of type 1 diabetes in the entire population of the Republic of Korea was reported to be from 0.017 to 0.021% [60]. The majority of diabetes is type 2 diabetes, and the proportion increases with age. We excluded subjects younger than 40 years in this study. Consequently, the possibility of inclusion of type 1 diabetes is minimal and was regarded insignificant. Fourth, due to lack of data in the Korean NHIS, the exact severity of type 2 diabetes based on glycated hemoglobin levels could not be taken into account. Instead, parameters such as use of three or more antidiabetic medications or insulin were used as proxy indicators for the severity of type 2 diabetes. Fifth, because the enrolled subjects were limited to the Korean population, future studies in other ethnic groups are needed to generalize our results. Sixth, by using only the NHIS claim database to search for hip fractures, without reviewing medical and radiologic records, traumatic hip fractures may have been included in our analyses. Seventh, the subject's comorbidity was not fully adjusted. We adjusted hypertension, dyslipidemia, CKD, and health-related behaviors. However, various medical conditions such as glucocorticoid use, pancreatitis, and various endocrinologic and rheumatologic diseases may have a considerable impact on bone density and severity of type 2 diabetes. Lastly, the details of body composition could not be identified from this database. Further studies will be required to research the correlation between body weight change in fat mass or lean body mass and the risk of fracture.

Conclusion

In type 2 diabetes population, regardless of the BMI, both weight gain and weight loss were significantly associated with a higher risk of hip fracture, whereas maintaining body weight reduced the risk of hip fracture the most.

In overweight or obese type 2 diabetic patients, although weight loss is associated with a higher risk of hip fracture, benefits of weight loss are likely greater than the costs from higher hip fracture risk [61]. When considering weight loss in overweight or obese type 2 diabetic patients, it should be appropriate to consider measures for fracture prevention, such as resistance training, retention of lean body mass, and supplementation of calcium and vitamin D to prevent bone loss from weight loss.

Contrary to the literature that weight gain had a protective effect on hip fracture in the nondiabetic population, it was found that weight gain was associated with higher hip fracture risk in the diabetic population in this study. Therefore, nonobese patients with type 2 diabetes should be advised to maintain their weight so as not to gain weight.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-022-06398-8.

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Declarations

Conflicts of interest None.

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Guarantor's statement K.H. and H.S.K. are the guarantors of this work and take responsibility for the integrity of the data and the accuracy of the data analysis.