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Association of DPP-4 activity with BMD, body composition, and incident hip fracture: the Cardiovascular Health Study

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Abstract

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Compliance with ethical standards The institutional review board (IRB) at each site approved the CHS methods, and all participants gave written informed consent. Augusta University's Office of Human Research Protection Assurance approved the use of human plasma samples previously collected as part of the CHS.

Conflicts of interest Authors Laura Carbone, Petra B Źková, Howard Fink, John Robbins, Monique Bethel, and Carlos Isales declare that they have no conflict of interest. William Hill is an inventor on provisional patent U.S.S.N. 61/712/708, Publication no. US-2014-0288010-A1 titled "Compositions and Methods for Increasing Stem Cell Survival." This is not a financial conflict.

Summary—There was no association of plasma DPP-4 activity levels with bone mineral density (BMD), body composition, or incident hip fractures in a cohort of elderly community-dwelling adults.

Introduction—Dipeptidyl peptidase IV (DPP-4) inactivates several key hormones including those that stimulate postprandial insulin secretion, and DPP-4 inhibitors (gliptins) are approved to treat diabetes. While DPP-4 is known to modulate osteogenesis, the relationship between DPP-4 activity and skeletal health is uncertain. The purpose of the present study was to examine possible associations between DPP-4 activity in elderly subjects enrolled in the Cardiovascular Health Study (CHS) and BMD, body composition measurements, and incident hip fractures.

Methods—All 1536 male and female CHS participants who had evaluable DXA scans and plasma for DPP-4 activity were included in the analyses. The association between (1) BMD of the total hip, femoral neck, lumbar spine, and total body; (2) body composition measurements (% lean, % fat, and total body mass); and (3) incident hip fractures and plasma levels of DPP-4 activity were determined.

Results—Mean plasma levels of DPP-4 activity were significantly higher in blacks (227 ± 78) compared with whites (216 ± 89) ($p = 0.04$). However, there was no significant association of DPP-4 activity with age or gender ($p = 0.14$ for both). In multivariable adjusted models, there was no association of plasma DPP-4 activity with BMD overall ($p = 0.55$ for all) or in gender stratified analyses ($p = 0.23$). There was also no association of DPP-4 levels and incident hip fractures overall ($p = 0.24$) or in gender stratified analyses ($p = 0.39$).

Conclusion—Plasma DPP-4 activity, within the endogenous physiological range, was significantly associated with race, but not with BMD, body composition, or incident hip fractures in elderly community-dwelling subjects.

Keywords

Body composition; Bone mineral density; Dipeptidyl peptidase IV; DPP-4; Epidemiology; Fracture

Introduction

Dipeptidyl peptidase IV (DPP-4), also called adenosine deaminase complexing protein-2, and T cell activation antigen CD26, is a highly conserved serine exopeptidase that cleaves X-proline dipeptides from the N-terminus of polypeptides. DPP-4/CD26 is found in eukaryotic organisms from drosophila to humans [1–5]. Confirmed substrates for DPP-4/CD26 in vivo include neuropeptides, chemokines, growth factors, and the incretin hormones [2, 3, 6, 7]. DPP-4/CD26 is a single-pass type II transmembrane protein that is regulated in terms of its expression, movement to the cell surface, activity, and the release of its extracellular portion as a soluble isoform (sCD26 or DPP-4) that is found in biological fluids such as plasma, where it is typically quantified in terms of activity or protein level [1, 3, 8].

DPP-4 plays a critical role in the regulation of insulin availability and glucose homeostasis largely via N-terminal cleavage of the incretin hormones glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), and glucose-dependent insulin tropic peptide (GIP) [9] [6,

10, 11]. Osteoblasts and osteoclasts that variably express receptors for GIP, GLP-1, and GLP-2, along with CD26 [12] and incretins, play an important role in the modulation of bone turnover, particularly postprandially [13, 14]. GIP and GLP-2 directly decrease bone resorption [15, 16], while the effects of GLP-1 on bone resorption are indirectly mediated through a calcitonin-dependent pathway [17]. GIP may also have anabolic actions on bone [18]. Further, DPP-4 may play a role in body composition since it is expressed and shed by adipocytes [19].

DPP-4 inhibitors were first introduced in 2006 in the USA for the treatment of type II diabetes mellitus. They are used as second-line agents in cases of inadequate glycemic control [20] and as an “add on” to insulin therapy particularly in elderly patients with renal insufficiency [21]. However, the relationship of use of these DPP-4 inhibitors to osteoporosis in persons with diabetes is conflicting [22–24], and the relationship of DPP-4 activity to body composition and incident hip fractures has not previously been reported. The confirmed and potential substrates of DPP-4/CD26 include a large number of factors that are known to affect bone homeostasis and energy balance; as such, the role of DPP-4 and its potential therapeutic regulation has drawn significant interest in addressing osteoporotic bone loss in both diabetic and non-diabetic patient populations [7]. The purpose of this study was to examine the endogenous association of plasma DPP-4 activity in elderly men and women with and without diabetes to bone mineral density (BMD) of the lumbar spine, total hip and femoral neck, body composition measurements (lean, fat, and total body mass), and incident hip fractures. We hypothesized that increased DPP-4 activity would be associated with increased risk of fracture, lower BMD, increased total body and fat mass, and decreased lean mass.

Methods

Participants

The Cardiovascular Health Study (CHS) is a longitudinal, community-based study of older men and women (age ≥ 65 years) designed to determine the factors that predict development and progression of cardiovascular disease [25]. Participants were recruited through random sampling from Medicare eligibility lists at four locations: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Allegheny County, Pennsylvania. The main cohort of 5201 participants was enrolled between June 10, 1989 and May 30, 1990. To increase minority representation, an additional 687 African-American participants were recruited from November 1992 through June 1993. Participants were excluded if they were institutionalized, required a proxy to complete informed consent, were planning to move out of the area within 3 years of recruitment, required a wheelchair in the home, were receiving hospice care, or were undergoing radiation or chemotherapy for cancer. In-person examinations were performed annually from 1989 to 1999 and again in 2005 to 2006. Telephone interviews were conducted semiannually from 1989 to 1999 and biannually thereafter. The total cohort included 5888 participants. Two of the four CHS sites, the Pittsburgh, Pennsylvania and Sacramento, California centers, performed dual energy x-ray absorptiometry (DXA) scans on 1591 participants during 1994–1995. The institutional review board (IRB) at each site approved the CHS methods, and all participants gave written

informed consent. Augusta University's Office of Human Research Protection Assurance approved the use of human plasma samples previously collected as part of the CHS.

Measurements

DPP-4 activity

Plasma samples were obtained from the year 7 visit (1994–1995) of CHS. These de-identified plasma samples were run in duplicate. Each assay plate contained a duplicate blank sample, along with a vendor supplied DPP-4 control sample for each plate that had been frozen at -80°C before use, a second DPP-4 control to which we added a DPP-4 inhibitor (P32/98) that was also vendor supplied frozen and that was thawed just before each plate was set up to run. Additionally, we added two control samples, which were plasma samples from two volunteers that had been aliquoted and frozen (-80°C) so they could be thawed just before use in order to assess coefficients of variation (CV). We noted that the values for these control samples appeared to be very consistent between each volunteer and across plates. Assays were started by the addition of $10\ \mu\text{L}$ H-Gly-Pro-pNA substrate, which had been equilibrated to room temperature and assessed at 405nm on the spectrophotometer at 30 min. The intra-assay CV for the DPP-4 control sample for the assay was 5.8% (mean 0.646, SD 0.036 absorbance unit (AU)). The inter-assay CV for the DPP-4 control sample was 10.1% (mean 0.619, SD 0.036 AU). Twenty-five of the 1536 samples had problems with either clouded plasma ($n = 19$) or hemolysis ($n = 6$); however, sensitivity analyses excluding these samples did not change the significance of the results.

Bone mineral density and body composition

Total hip, femoral neck, lumbar spine, and total body BMD were measured in 1591 participants at the 1994–1995 study visits using Hologic QDR-2000 densitometers (Hologic, Inc., Waltham, MA) and read centrally at the University of California San Francisco reading center using Hologic software, version 7.10. All scans were completed using the array beam mode. Standardized positioning and use of QDR software was based on the manufacturer's recommended protocol. Body composition measurements including total and percentage of lean and fat mass were also obtained [26]. A total of 1536 participants had analyzable hip and lumbar spine areal BMD and body composition data and plasma for DPP-4 analyses.

Fracture ascertainment

Incident hip fractures were defined by a hospital discharge International Classification of Diseases, Ninth Revision (ICD-9), code of 820.xx. CHS prospectively obtained all hospitalization data, including discharge summaries, from participants every 6 months. These data were checked against Medicare claims data to identify any hospitalizations not reported by participants. Follow-up for incident hip fracture began subsequent to the year 7 visit when plasma was collected that was used for the DPP-4 measurements and was continued to a hip fracture event, death, loss to follow-up, or end of follow-up on June 30, 2013. Hip fractures caused by motor vehicle accidents or severe injury were excluded.

Covariates

Covariates were selected a priori based on associations with osteoporosis (BMD or fracture) from the year 7 data of CHS (the same year as the DXA studies, plasma samples assayed for DPP-4, and start of analyses). Age, race, and gender were determined by participant self-report. Body weight was measured using a calibrated balance beam scale. Height was measured with a wall-mounted stadiometer. Height and weight were used to calculate body mass index (BMI) and change in BMI (from year 5 to year 7). Smoking history, alcohol use (0 drinks/week, 1–7 drinks/week, >7 drinks/week), highest level of education achieved (> 12th grade or <), and history of falls over the past year were obtained by participant self-report. Alcohol use was considered present in women if there were at least 7 drinks/week and in men at least 14 drinks/ week. Renal function was assessed by cystatin C-based estimated glomerular filtration rate (eGFR_{cys}) or if not available in CHS, eGFR was calculated from creatinine. Self-reported health status (excellent/very good vs. good vs. fair/poor) was obtained [27, 28]. Frailty status was as follows: frail (defined as three or more of the following: unintentional loss of 10 lb in the past year, self-reported exhaustion, weak grip strength, slow walking speed, and low physical activity), intermediate (defined as one or two of the above criteria), or not frail [29]. Prevalent cardiovascular disease (CHD) was defined as a history of angina, myocardial infarction, angioplasty, or coronary artery bypass graft. History of diabetes (use of insulin or oral hypoglycemic agents, non-fasting glucose 200, or fasting glucose level 126 mg/dL) was obtained. Both prevalent CHD and history of diabetes were adjudicated within CHS. Use of selected medications [oral corticosteroids, cardiac medications (angiotensin converting enzyme inhibitors (ACE), angiotensin-receptor blockers (ARBs), β -blockers, diuretics (loop, thiazide, potassium sparing, combination)), opioids, sedative hypnotics (benzodiazepines and other sedatives/ hypnotics), anticonvulsants/antidepressants, osteoporosis medications (estrogen, calcium and vitamin D supplements, SERMs, bisphosphonates, calcitonin), diabetes medications, and proton pump inhibitors was ascertained from a review of prescription bottle labels by interviewers [30].

Statistical analysis

We described the cohort and compared baseline participant characteristics across DPP-4 quartiles using linear trend tests for continuous variables and chi-square tests for categorical variables. Linear regression analysis was used to estimate the association between four BMD measures, five measures of body composition, and DPP-4. Time to hip fracture event was calculated as the interval in years from the baseline visit in 1994/1995 to the earliest date of first incident hip fracture, death, loss to follow-up, or end of follow-up on June 30, 2013. Cox proportional hazard models were used to estimate the hazard ratio (HR) of incident fracture associated with DPP-4. We explored the functional form of the DPP-4 with generalized additive models in both linear regression for BMDs and body composition measures and Cox regression for hip fracture and found no departures from linearity. We considered three nested models: unadjusted models; models adjusted for age, race, clinic site, and gender (minimally adjusted models); and fully adjusted models with age, race, clinic site, gender, smoking and alcohol use, BMI, change in BMI, frailty status, diabetes status, prevalent cardiovascular disease, self-reported health, and medication use.

Owing to differences in the natural history of BMDs, body composition and hip fractures between men and women, in addition to analyzing men and women combined, we a priori stratified our analyses by gender. Several sensitivity analyses were performed: History of falls was considered as an additional covariate; the analyses were limited to whites; the association of DPP-4 levels and BMD and body composition was stratified by history of diabetes mellitus; our cohort excluded the 25 samples of the 1536 who had either clouded plasma ($n = 19$) or hemolysis ($n = 6$); renal function was adjusted for; and finally, the association of DPP-4 and incident hip fractures was adjusted for total hip, lumbar spine, total body, and femoral neck BMD, in separate models. Analyses were conducted using R (R Development Core Team) [31].

Results

Participant characteristics

Baseline characteristics of the study population overall and by quartiles of DPP-4 activity are shown in Table 1. Approximately 10% of the population had diabetes mellitus ($n = 161$) including 82 women and 79 men. Diabetic drugs of the following classes were not used: thiazolidinediones, DPP-4 inhibitors, alpha-glucosidase inhibitors, or meglitinides.

Association of DPP-4 activity with race and gender

Mean plasma levels of DPP-4 activity were significantly higher in blacks (227 ± 78) compared with whites (216 ± 89) ($p = 0.04$). There was no significant association of DPP-4 levels with age ($p = 0.30$) or gender ($p = 0.14$).

Association of DPP-4 activity and bone mineral density

Univariate and multivariate associations of DPP-4 with BMD of the total hip, femoral neck, lumbar spine, total body, and body composition (total and % lean, total and % fat, and total body mass) and incident hip fractures [per increase of 100 AU] were determined for the overall population and stratified by gender. In unadjusted models; models adjusted for age, race, clinic site, and gender (minimally adjusted models); and fully adjusted models including age, race, clinic site, gender, smoking and alcohol use, BMI, change in BMI, frailty status, self-reported health, adjudicated self-reported prevalent cardiovascular disease (CHD) and diabetes, and medication use, there was no significant association of DPP-4 activity with total hip, femoral neck, lumbar spine or total body, BMD in overall models (Table 2), or in gender stratified analyses (Table 3).

Association of DPP-4 activity and body composition

DPP-4 activity was also not significantly associated with any body composition measurement including total lean, % lean, total fat, and % fat or total body mass in overall models (Table 4) or in gender stratified models (Table 5).

Association of DPP-4 activity and fractures

There were 169 incident hip fractures in the 1536 participants included in these analyses. There were only 13 hip fractures in the 161 participants with diabetes mellitus. The

association of DPP-4 activity and incident hip fractures is shown in Fig. 1. There was no significant association of DPP-4 activity with incident hip fractures in overall models or in gender-stratified analyses (Table 6). The addition of fall history or renal function as covariates did not significantly change the results in the BMD, body composition, or hip fracture analyses (data not shown) as well as analyses confined to whites were also similar to that of the whole cohort (data not shown). Finally, the addition of total hip, lumbar spine, total body, and femoral neck BMD to the hip fracture analyses in the overall model or stratified by gender did not materially affect the results (data not shown).

Association of DPP-4 activity with BMD and body composition in CHS participants with diabetes

There were 161 individuals with diabetes mellitus. In men with diabetes mellitus, an increase of 0.1 AU DPP-4 activity was associated with an average increase of 0.086 g/cm² in lumbar spine BMD. In women with diabetes mellitus, higher DPP-4 activity was significantly associated with lower lean body mass in unadjusted ($p = 0.03$) models with a trend in minimally adjusted ($p = 0.05$) models and with lower total mass in unadjusted models ($p = 0.04$) with a trend in minimally adjusted models ($p = 0.06$).

Additional sensitivity analyses

Additional sensitivity analyses excluding the 25 samples of the 1536 with either clouded plasma ($n = 19$) or hemolysis ($n = 6$) did not change the significance of the results (data not shown).

Discussion

Summary

In elderly community-dwelling men and women, basal DPP-4 activity was not significantly associated with BMD of the hip, lumbar spine, or total body; body composition measurements; or incident hip fractures. Results were similar in men and women and in analyses confined to whites only. Plasma levels of DPP-4 were higher in blacks than whites but were not related to either gender or age.

Clinical studies of DPP-4 and BMD

Human clinical studies show conflicting outcomes regarding DPP-4 and bone homeostasis [32, 33]. In agreement with our CHS findings, in a study that included 204 Japanese men with diabetes, serum DPP-4 levels were not significantly associated with BMD of the lumbar spine or femoral neck [34]. Additionally, in another analyses that included 124 postmenopausal Korean women, serum DPP-4 levels were not significantly associated with femoral neck or lumbar spine BMD; although, there was a significant association of higher DPP-4 levels with lower lumbar spine BMD when the analyses was confined to obese postmenopausal women [35]. We did not stratify by BMI; however, inclusion of BMI as a covariate in the analyses did not significantly change the findings. In contrast with our findings in CHS, in another study including 744 postmenopausal Chinese women with normal glucose tolerance, those in the highest quartile of DPP-4 activity had significantly lower lumbar spine and femoral neck BMD [36]. Our study differed from these studies [34–

36], in our larger sample size, racial and age composition including elderly black and white men and women and not Asians, and inclusion of both diabetics and non-diabetics.

DPP-4 activity and body composition

Adipose tissue, immune, and bone marrow cells are recognized sources of soluble DPP-4. DPP-4 has been reported to be an adipokine linking obesity to metabolic syndrome [19]. Circulating DPP-4 concentrations and activity have been reported to be higher in obese patients and in some patients with chronic hyperglycemia or type 2 diabetes and with inflammatory diseases [1, 6, 8] [19, 37, 38]. However, in our study of an older population, we did not see a general association of DPP-4 activity with diabetes or body composition. To our knowledge, this is the first report of the association of DPP-4 activity with body composition measurements by DXA. In contrast with the findings from CHS reported here, the relationship of DPP-4 to BMD has been reported to depend on BMI, with, in one study, only obese women having an inverse association between BMD and DPP-4 [35]. Relative to previous reports of use of DPP-4 inhibitors and body composition, in a small trial comparing a DPP-4 inhibitor (vildagliptin) and metformin to metformin and a sulfonylurea, there was preservation of lean body mass and significant decreases in total body weight, body mass index (BMI), fat mass, and tissue fat percentage in the DPP-4 inhibitor treated group compared with the sulfonylurea group [39]. Another DPP-4 inhibitor, sitagliptin, was also reported to decrease total body fat measured by DXA in patients with type 2 diabetes [40]. Although the findings in CHS do not suggest a relationship between DPP-4 levels and body composition, the physiological ranges of DPP-4 activity found in CHS may not reflect levels obtained with DPP-4 inhibitors [41].

DPP-4 activity and fracture risk

In CHS, there was no relationship of DPP-4 activity to incident hip fractures over the defined study period. To our knowledge, this is the first report of the association of DPP-4 activity with incident fractures of any kind. In the one study that did examine the relationship of DPP-4 levels with fracture, which included 204 Japanese men with diabetes, serum DPP-4 levels were significantly higher in those with multiple vertebral fractures [34]. This study differed from ours in that it examined vertebral and not hip fractures, was confined to Japanese men with severe diabetes, and most importantly, was only cross sectional in design. Although no patients in CHS were taking DPP-4 inhibitors, reports of the association of these medications with fractures are conflicting [7]. A meta-analysis assessing 28 randomized clinical trials (RCTs) enrolling 11,880 and 9175 patients for DPP-4 inhibitors suggested that there was a significant 40% reduction in the risk of fractures with DPP-4 inhibitors [24]. Further, the South Korean nationwide medical claim database was assessed for 207,558 subjects over age 50 being treated with anti-diabetes medications with a total of 5996 fractures observed. This included controls, patients receiving metformin, DPP-4 inhibitors, or a combination of both, as well as groups receiving other categories of diabetic medications. Compared to controls, the met-formin + DPP-4 inhibitor combination group had significantly reduced composite fracture risk and significantly reduced vertebral fracture risk in the unadjusted analysis [42]. In contrast, two recent meta-analyses assessing DPP-4 inhibitor use and fracture risk failed to find an association. Fu et al. compared 62 eligible RCTs with 62,206 participants, including 33,452 patients treated with DPP-4

inhibitors; they found that DPP-4 inhibitor use does not modify the risk of bone fracture compared with placebo or other anti-diabetic medications in patients with type 2 diabetes [43, 44]. Similarly, Mamza et al., identified 51 eligible RCTs for meta-analysis ($N = 36,402$) for comparison [44]. Thirty-seven of these studies compared DPP-4 inhibitor with placebo ($n = 23,974$), while 14 studies ($n = 12,428$) compared DPP-4 inhibitor with an active comparator: there was no significant association between DPP-4 inhibitor use and the incidence of fractures [44]. In a population-based cohort study from the UK Clinical Practice Research Datalink (CPRD) including over 200,000 patients with diabetes, DPP-4 inhibitors were not associated with fracture risk [23]. However, in our analyses in CHS, there were too few diabetes ($n = 161$) with only a limited number of hip fractures ($n = 13$) to examine the relationship of DPP-4 levels with incident fractures in diabetes.

DPP-4 activity and age and gender

That DPP-4 activity was not related to age or gender in CHS is in contrast to an earlier report that DPP-4 activity decreases significantly with age and is slightly lower in women than in men [45]. However, it should be noted that the CHS participants were significantly older (age > 65 years) than this previous study [45] in which the ages ranged between 19 and 61 years of age and may therefore not reveal an age related decline in DPP-4 activity compared to younger subjects.

Study strengths and limitations

This study has a number of important strengths. To start, this is the largest sample size to date to determine the relationship of DPP-4 activity with osteoporosis outcomes, which includes well measured covariates and a diverse population with men and women and both blacks and whites. To our knowledge, this is the first study to examine whether plasma DPP-4 activity is associated with body composition measurements in humans. It is also the first report of the relationship between DPP-4 levels and incident fractures and includes almost two decades of follow-up for fractures.

However, there are also a number of important limitations to consider. The physiological ranges of DPP-4 found in CHS may not reflect levels obtained with DPP-4 inhibitors; thus, we cannot extrapolate to determine whether use of DPP-4 inhibitors would have effects on bone. Both the number of subjects with hip fractures is low ($n = 169$) and the number of subjects with diabetes is lower than expected ($n = 161$) given the study subjects' age. This precludes determination of an association between hip fracture and diabetes in CHS. Height was not available at year 7; only weight was available, so year 5 heights were used to calculate BMI. Potentially important covariates that were not uniformly available in this dataset including history of hepatic disease, testosterone, and 25 hydroxy vitamin D were not included. However, even prior to covariate adjustments, there was no relationship between DPP-4 and osteoporosis. The BMD analyses were restricted to those who had a DXA measured, and there are significant differences in race, health status, physical activity, activities of daily living, medication use, cognition, and alcohol use between persons in CHS who received a DXA versus those who did not [46]. As such, the fact that all subjects had a DXA may bias the population towards those at risk for bone loss. Additionally, there were too few blacks to perform analyses separately in blacks. The measurements of DPP-4 were

only done at one time point; thus, whether changes in DPP-4 are associated with BMD, body composition or fracture is unknown. Additionally, we did not compare DPP-4 activity with total DPP-4 protein levels. Our cohort was elderly and included community-dwelling black and white men and women, and it is uncertain whether the same results would have been obtained in different populations, including younger groups.

Conclusions

In conclusion, DPP-4 activity was not shown to be associated with BMD, body composition, or hip fractures in elderly community-dwelling black and white men and women. However, further studies of the role of DPP-4/CD26 in regulating bone homeostasis and body composition are needed.

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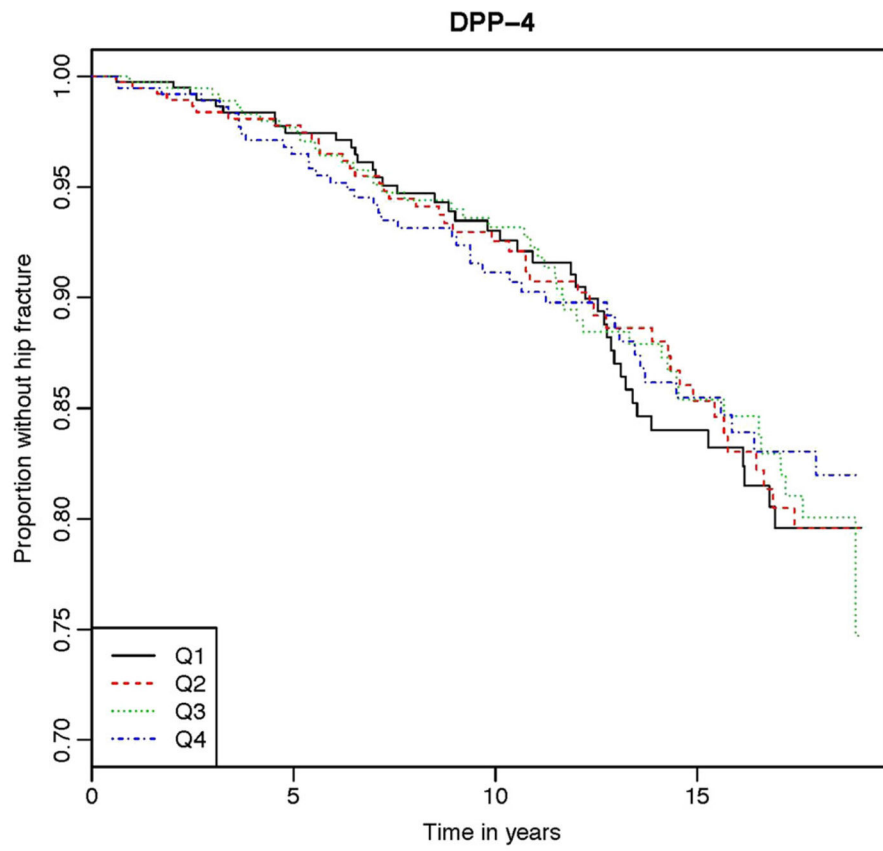


Fig. 1. Kaplan-Meier curve of hip fractures by DPP-4 quartile over time

Table 1

Baseline characteristics of study population by DPP-4 activity

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p value
Number	1536	394	376	384	382	
DPP-4 activity (AU × 1000 ± SD)	218 ± 87	21–58	159–203	204–261	262–1016	
Total hip BMD	0.83 ± 0.18	0.83 ± 0.17	0.84 ± 0.18	0.82 ± 0.18	0.83 ± 0.18	0.66
Lumbar spine BMD	1.02 ± 0.26	1.02 ± 0.25	1.04 ± 0.28	1.01 ± 0.24	1.01 ± 0.26	0.28
Total BMD	1.03 ± 0.16	1.03 ± 0.14	1.05 ± 0.16	1.02 ± 0.16	1.02 ± 0.16	0.14
Femoral neck BMD	0.7 ± 0.15	0.7 ± 0.14	0.71 ± 0.15	0.69 ± 0.15	0.71 ± 0.15	0.96
Age (years) Mean ± SD	76.32 ± 4.76	76.46 ± 4.27	75.81 ± 4.73	76.4 ± 4.96	76.57 ± 5.05	0.41
BMI (kg/m ²) Mean ± SD	26.86 ± 4.5	26.54 ± 4.38	26.85 ± 4.59	26.94 ± 4.5	27.11 ± 4.53	0.08
Change in BMI (kg/m ²) Mean ± SD	0.01 ± 1.37	0.15 ± 1.39	0.01 ± 1.46	0.02 ± 1.26	0.11 ± 1.34	<0.01
Male gender (%)	644 (41.9%)	184 (46.7%)	161 (42.8%)	147 (38.3%)	152 (39.8%)	0.08
Black race (%)	288 (18.8%)	50 (12.7%)	78 (20.7%)	78 (20.3%)	82 (21.5%)	<0.01
Education (12 grade) (%)	844 (55%)	223 (56.6%)	225 (60%)	207 (53.9%)	189 (49.6%)	0.03
History of diabetes (5)	161 (10.5%)	30 (7.6%)	40 (10.7%)	43 (11.2%)	48 (12.6%)	0.14
Prevalent cardiovascular disease (%)	244 (15.9%)	68 (17.3%)	66 (17.6%)	59 (15.4%)	51 (13.4%)	0.35
Self-reported health status (good %)	1227 (79.9%)	321 (81.5%)	302 (80.3%)	309 (80.5%)	295 (77.2%)	0.49
History of falls in the past year (%)	255 (16.6%)	72 (18.3%)	47 (12.5%)	66 (17.2%)	70 (18.3%)	0.10
Medication current use (%)						
Cardiac medications	565 (36.8%)	151 (38.3%)	141 (37.5%)	136 (35.4%)	137 (35.9%)	0.82
Osteoporosis medications	58 (3.8%)	18 (4.6%)	14 (3.7%)	13 (3.4%)	13 (3.4%)	0.8
Psychotropic medications	101 (6.6%)	26 (6.6%)	17 (4.5%)	26 (6.8%)	32 (8.4%)	0.2
Antidepressants	56 (3.6%)	10 (2.5%)	12 (3.2%)	14 (3.6%)	20 (5.2%)	0.23
Diabetes medications	120 (7.8%)	24 (6.1%)	24 (6.4%)	36 (9.4%)	36 (9.4%)	0.15
Opioids	58 (3.8%)	15 (3.8%)	11 (2.9%)	13 (3.4%)	19 (5%)	0.49
Proton pump inhibitors	34 (2.2%)	10 (2.25%)	12 (3.2%)	4 (1%)	8 (2.1%)	0.23
Oral corticosteroids	46 (3%)	17 (4.3%)	8 (2.1%)	7 (1.8%)	14 (3.7%)	0.12
Smoking status (%)						
Current	147 (9.6%)	32 (8.2%)	36 (9.7%)	31 (8.1%)	48 (12.6%)	0.39
Former	717 (47%)	184 (47.1%)	174 (46.8%)	181 (47.5%)	178 (46.8%)	

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p value
Never	660 (43.3%)	175 (44.8%)	162 (43.5%)	169 (44.4%)	154 (40.5%)	
Alcohol use, drinks per week (%)						0.5
0	702 (45.7%)	174 (44.2%)	166 (44.1%)	177 (46.1%)	185 (48.4%)	
1-7	601 (39.1%)	162 (41.1%)	153 (40.7%)	139 (36.2%)	147 (38.5%)	
>7	233 (15.2%)	58 (14.7%)	57 (15.2%)	68 (17.7%)	50 (13.1%)	
Renal function (cysGFR)	(N= 1480) 75.09 ± 18.29	N= 377 73.24 ± 17.83	N= 367 74.73 ± 18.66	N= 369 76.62 ± 18	N= 367 75.80 ± 18.56	0.02
Study site (%)						0.09
UC Davis	572 (37.2%)	150 (38.1%)	120 (31.9%)	148 (38.5%)	154 (40.3%)	
Pittsburg	964 (62.8%)	244 (61.9%)	256 (68.1%)	236 (61.5%)	228 (59.7%)	
Frailty status						0.95
Not frail	620 (45%)	153 (44%)	156 (46%)	164 (47%)	147 (43%)	
Intermediate	673 (48.8%)	175 (50.3%)	162 (47.8%)	164 (47%)	172 (50.3%)	
Frail	85 (6.2%)	20 (5.7%)	21 (6.2%)	21 (6%)	23 (6.7%)	

There is an unequal number of people in the DPP-4 quartiles due to ties in DPP-4 values AU absorbance units, SD standard deviation

Table 2

BMD of the total hip, femoral neck, lumbar spine, and total body by DPP-4 activity

	β	SE	95% CI	<i>p</i> value
Total hip BMD	-0.249 ^a	0.53	-1.288, 0.789	0.64
	-0.072 ^b	0.413	-0.881, 0.845	0.86
	0.079 ^c	0.391	-0.688, 0.845	0.84
Femoral neck BMD	-0.075 ^a	0.44	-0.788, 0.937	0.87
	-0.137 ^b	0.365	-0.578, 0.852	0.71
	0.203 ^c	0.353	-0.489, 0.896	0.57
Lumbar spine BMD	-1.072 ^a	0.759	-2.56, 0.416	0.16
	-0.969 ^b	0.69	-2.322, 0.384	0.16
	0.424 ^c	0.705	-1.806, 0.959	0.55
Total body BMD	-0.589 ^a	0.455	-1.481, 0.302	0.19
	-0.312 ^b	0.332	-0.963, 0.339	0.35
	0.035 ^c	0.34	-0.631, 0.701	0.92

BMD per increase of 0.1 AU of DPP-4

 β beta, SE standard error of the beta, CI confidence interval^a Unadjusted^b Age, race, clinic site, gender^c Age, race, clinic site, gender, smoking and alcohol use, BMI, change in BMI, frailty status, diabetes status, medication use, prevalent CHD, self-reported health

Table 3
BMD of the total hip, femoral neck, lumbar spine, and total body by DPP-4 activity stratified by gender

	Women				Men			
	β	SE	95% CI	p-val	β	SE	95% CI	p value
Total hip BMD	-0.353 ^a	0.564	-1.458, 0.752	0.532	0.806 ^a	0.733	-0.63, 2.241	0.27
	-0.318 ^b	0.507	-1.311, 0.676	0.531	0.243 ^b	0.693	-1.116, 1.601	0.73
	-0.13 ^c	0.467	-1.044, 0.785	0.781	0.273 ^c	0.679	-1.059, 1.604	0.69
Femoral neck BMD	-0.244 ^a	0.491	-1.206, 0.718	0.619	1.128 ^a	0.648	-0.142, 2.398	0.08
	-0.259 ^b	0.442	-1.126, 0.608	0.559	0.669 ^b	0.618	-0.542, 1.881	0.28
	-0.235 ^c	0.417	-1.052, 0.582	0.573	0.757 ^c	0.624	-0.465, 1.98	0.23
Lumbar spine BMD	-0.79 ^a	0.926	-2.604, 1.024	0.394	0.475 ^a	1.088	-2.608, 1.658	0.66
	-0.847 ^b	0.896	-2.602, 0.908	0.345	0.993 ^b	1.088	-3.125, 1.114	0.36
	-0.304 ^c	0.919	-2.105, 1.498	0.741	0.544 ^c	1.122	-2.743, 1.655	0.63
Total body BMD	-0.657 ^a	0.452	-1.542, 0.228	0.146	0.472 ^a	0.561	-0.627, 1.572	0.4
	-0.647 ^b	0.415	-1.461, 0.166	0.119	0.192 ^b	0.546	-0.878, 1.881	0.73
	-0.26 ^c	0.424	-1.091, 0.571	0.539	0.447 ^c	0.563	-0.656, 1.55	0.43

BMD per increase of 0.1 AU of DPP-4

β beta, SE standard error of the beta, CI confidence interval

^aUnadjusted

^bAge, race, clinic site, gender

^cAge, race, clinic site, gender, smoking and alcohol use, BMI, change in BMI, frailty status, diabetes status, medication use, prevalent CHD, self-reported health

Table 4

Body composition measurements by DPP-4 activity

	β	SE	95% CI	<i>p</i> value
Total lean	-0.205 ^a	0.302	-0.797, 0.386	0.50
	0.116 ^b	0.167	-0.211, 0.443	0.49
	0.022 ^c	0.158	-0.289, 0.332	0.89
Percent lean	-0.4 ^a	0.291	-0.97, 0.17	0.17
	-0.112 ^b	0.211	-0.526, 0.302	0.60
	0.035 ^c	0.147	-0.253, 0.323	0.81
Total fat	0.271 ^a	0.288	-0.295, 0.836	0.35
	0.101 ^b	0.268	-0.423, 0.626	0.71
	-0.135 ^c	0.132	-0.394, 0.124	0.31
Percent fat	0.4 ^a	0.291	-0.17, 0.97	0.83
	0.112 ^b	0.211	-0.302, 0.526	0.56
	-0.035 ^c	0.147	-0.323, 0.253	0.59
Total mass	0.065 ^a	0.418	-0.755, 0.885	0.88
	0.217 ^b	0.371	-0.511, 0.945	0.56
	-0.114 ^c	0.21	-0.526, 0.299	0.59

Body composition measurements per increase of 0.1 AU of DPP-4 β beta, SE standard error of the beta, CI confidence interval

^aUnadjusted

^bAge, race, clinic site, gender

^cAge, race, clinic site, gender, smoking and alcohol use, BMI, change in BMI, frailty status, diabetes status, medication use, prevalent CHD, self-reported health

Table 5

Body composition measurements by DPP-4 activity stratified by gender

	Women				Men			
	β	SE	95% CI	p value	β	SE	95% CI	p value
Total lean	-0.218 ^a	0.211	-0.196, 0.632	0.303	0.081 ^a	0.303	-0.513, 0.676	0.79
	-0.205 ^b	0.196	-0.18, 0.589	0.297	-0.037 ^b	0.286	-0.597, 0.522	0.90
	-0.083 ^c	0.179	-0.268, 0.434	0.644	-0.019 ^c	0.283	-0.575, 0.536	0.95
Percent lean	-0.223 ^a	0.296	-0.804, 0.358	0.452	0.048 ^a	0.302	-0.544, 0.693	0.88
	-0.306 ^b	0.291	-0.877, 0.265	0.294	0.139 ^b	0.299	-0.448, 0.725	0.64
	-0.051 ^c	0.196	-0.436, 0.334	0.795	0.134 ^c	0.216	-0.29, 0.558	0.54
Total fat	0.309 ^a	0.397	-0.47, 1.087	0.437	-0.089 ^a	0.358	-0.791, 0.613	0.80
	0.382 ^b	0.383	-0.368, 1.132	0.318	-0.25 ^b	0.352	-0.94, 0.44	0.48
	0.003 ^c	0.171	-0.333, 0.339	0.986	-0.263 ^c	0.204	-0.663, 0.136	0.20
Percent fat	0.223 ^a	0.296	-0.47, 1.087	0.452	-0.048 ^a	0.302	-0.639, 0.544	0.88
	0.306 ^b	0.291	-0.368, 1.132	0.294	-0.139 ^b	0.299	-0.725, 0.448	0.64
	0.051 ^c	0.196	-0.333, 0.339	0.795	-0.134 ^c	0.216	-0.558, 0.29	0.54
Total mass	0.526 ^a	0.544	-0.541, 1.594	0.334	-0.008 ^a	0.547	-1.081, 1.065	0.99
	0.587 ^b	0.514	-0.42, 1.593	0.254	-0.287 ^b	0.523	-1.313, 0.738	0.58
	0.086 ^c	0.086	-0.435, 0.607	0.747	-0.283 ^c	0.344	-0.958, 0.392	0.41

Body composition measurements per increase of 0.1 AU of DPP-4 β beta, SE standard error of the beta, CI confidence interval

^aUnadjusted

^bAge, race, clinic site, gender

^cAge, race, clinic site, gender, smoking and alcohol use, BMI, change in BMI, frailty status, diabetes status, medication use, prevalent CHD, self-reported health

Table 6

Incident hip fractures by DPP-4 activity

HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
1.045 ^a	0.877, 1.245	0.62	1.026 ^a	0.831, 1.268	0.809	1.071 ^a	0.776, 1.479	0.68
1.06 ^b	0.891, 1.262	0.51	1.041 ^b	0.845, 1.281	0.707	1.124 ^b	0.814, 1.553	0.48
1.122 ^c	0.925, 1.362	0.24	1.097 ^c	0.87, 1.383	0.433	1.222 ^c	0.839, 1.78	0.39

Incident hip fractures per increase of 0.1 AU of DPP-4

HR hazard ratio (Cox proportional hazards models were used to estimate the hazard ratio), CI confidence interval

^aUnadjusted

^bAge, race, clinic site, gender

^cAge, race, clinic site, gender, smoking and alcohol use, BMI, change in BMI, frailty status, diabetes status, medication use, prevalent CHD, self-reported health