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Serum uric acid is associated with incident hip fractures in women and men – Results from a large Austrian population-based cohort study

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ABSTRACT

Objectives: Serum markers that can be used to estimate the risk of bone fractures are rare, and findings for one candidate marker, uric acid, are heterogeneous. Our aim was to investigate the potential of serum uric acid (SUA) to predict hip fractures occurring in people aged 50 years and over.

Study design: During a medical prevention program over the period 1985–2005 in Vorarlberg, baseline data were collected on SUA levels and covariates (age, BMI, blood pressure, smoking status, diabetes, triglycerides and cholesterol) from 185,397 individuals, of whom 42,488 women and 35,908 men met the inclusion criteria of this population-based cohort study. Information on incident cancer and end-stage kidney disease was acquired from registries.

Main outcome measure: Incident hip fracture occurring in participants aged 50 years and over during the observation period 2003–2013.

Results: SUA was associated with a rise in female hip fracture risk by 6% per unit increase (HR 1.06, 95 %-CI 1.01−1.10), and risk in the highest vs. lowest SUA quartile was significantly increased (HR 1.17, 95 %-CI 1.01−1.35), but not at hyperuricemic (>5.7 mg/dl) vs. normouricemic (≤5.7 mg/dl) levels. In men, hip fracture risk rose by 15 % per unit increase (HR 1.15, 95 %-CI 1.08−1.22), and risk was significantly higher in the highest vs. lowest SUA quartile (HR 1.50, 95 %-CI 1.17−1.91) as well as at hyperuricemic (>7.0 mg/dl) vs. normouricemic (≤7.0 mg/dl) levels (HR 1.48, 95 %-CI 1.19−1.84).

Conclusions: Our results link SUA with increased risk of hip fractures, particularly in men.

1. Introduction

Hip fractures, the vast majority of which occur after the age of 50 as low-trauma fragility fractures, are amongst the most severe implications of osteoporosis [1]. Serum markers that predict hip fracture risk are scarce. Several parameters like osteocalcin, alkaline phosphatase, procollagen type 1 aminoterminal propeptide (PINP), and C-terminal telopeptide of type I collagen (CTX) reflect current metabolic activity of bone and are routinely used to monitor efficacy of anti-osteoporotic treatment [2], but their utility for predicting hip fractures is controversial [3,4]. In contrast, low serum 25-(OH)-vitamin D levels have been shown to predict long-term hip fracture risk [5]. Similarly, we have reported that hyperglycemia and hypertriglyceridemia predicted greater hip fracture risk in women and men, respectively, and increased total cholesterol was associated with reduced hip fracture risk in women, 5–10 years after baseline [6].

Uric acid is the final degradation product of purine nucleotides and excreted chiefly in urine but also via the intestine. It has been ascribed potent antioxidant properties [7], but pathologically elevated serum concentrations (hyperuricemia) are predisposing not only for gout but also for cardiovascular, metabolic, and renal disease [8]. Concerning possible effects on bone, most reports have demonstrated a beneficial role of higher serum uric acid (SUA) levels which has been attributed to antioxidant effects of SUA. However, also intra-cellular pro-oxidative

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effects of uric acid have been reported, and the association with hip fractures is ambiguous [9]. Notably, SUA is also implicated with chronic kidney disease [10] and dementia [11,12], risk conditions known to affect hip fracture risk [13,14]. In a previous meta-analysis, higher SUA levels have been correlated with increased BMD at the spine, total hip, and femoral neck, as well as with lower osteoporosis prevalence and fracture incidence [15]. Results therein on fracture incidence were, however, based on only a small number of studies, in particular for women [15]. Furthermore, results of the Osteoporotic Fractures in Men (MrOS) study showed that higher SUA levels were associated with significantly decreased risk for non-spine fractures and increased hip BMD which was, however, not paralleled by significant reduction in hip fracture risk [16]. Likewise, in the Rotterdam Study, although femoral neck BMD was increased at higher SUA levels, hip fracture risk was not significantly decreased [17]. By contrast, Mehta et al. [18] reported elevated hip fracture risk at both low and increased SUA concentrations in men, however, the association with low SUA was eliminated upon multivariate adjustment, and no SUA-dependent risk differences were found in women.

In our quest for serum markers that are associated with fracture risk and given the inconsistent epidemiological findings for the relation of SUA levels with hip fracture risk, we examined whether SUA levels could predict risk of future hip fractures occurring after the age of 50 years in a large, population-based cohort study with extensive follow-up time. Analyses were grouped according to gender and conducted considering both established risk-modifying covariates as well as serum parameters recently shown to modulate hip fracture risk [6].

2. Methods

2.1. Data acquisition and study design

From January 1985 until June 2005, all adult residents of Vorarlberg, the westernmost Austrian province, were invited to a voluntary health examination free of charge up to once a year in the context of the Vorarlberg Health Monitoring and Promotion Program (VHM&PP) [19]. More than 185,000 individuals, approximately two thirds of the inhabitants of the province, followed the invitation, undergoing a total of 716,679 health examinations. These individuals were followed up for the occurrence of hip fractures as identified by the ICD-10 codes S72.0, S72.1 and S72.2 in the period of January 1st, 2003 to December 31st, 2013 (Fig. 1). Only hip fractures occurring at the age of 50 years and above were considered with an exposure time of at least two years prior to fracture. All subjects who died before January 1st, 2003 as well as those with no health examination including SUA after 48 years of age were excluded from the study. Individuals entered the study at the first examination with available SUA and were required to be alive at 50 years (Fig. 1). Cancer diagnoses during the study interval 1985–2013 were identified from the Vorarlberg Cancer Registry. All first new diagnoses of invasive cancer were included, and diagnoses after hip fracture were excluded. In a sub-analysis, all patients with known end stage kidney disease (ESKD) at baseline or a diagnosis of ESKD until December 31st, 2013 were identified and excluded from the study population (292 patients of whom 113 women). This was achieved by linking the VHM&PP data with the Austrian Dialysis and Transplant Registry (OEDTR) where all patients receiving chronic renal replacement therapy (hemodialysis, peritoneal dialysis, kidney transplantation) in Austria have been enrolled since 1964 [20]. The Ethics Committee of

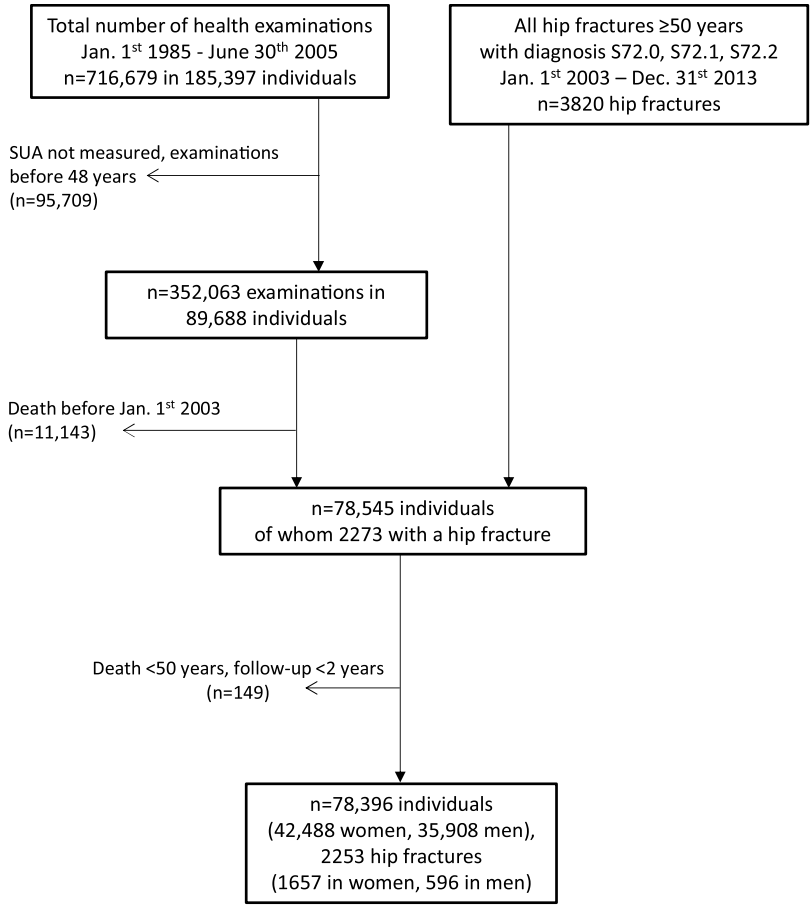

Fig. 1. Study flow chart; SUA, serum uric acid, hfx, hip fracture.

Vorarlberg approved the evaluation of the data, and all procedures were carried out in agreement with the Declaration of Helsinki.

2.2. Covariates, exposure and outcome

Medical examinations consisted of (i) a physical examination including measurement of body height and weight from which the BMI was calculated, and of blood pressure, (ii) a questionnaire to acquire information on smoking habits (classification as ex-, current and non-smoker), and (iii) the measurement of concentrations of blood serum parameters including uric acid, glucose, cholesterol, and triglycerides. Blood samples were taken either post-prandially (1985–1987) or after at least eight hours of fasting (1988–2005), and centrifuged, whereupon serum parameters were measured at 37 °C. Impaired fasting glucose was defined as blood glucose levels ranging from 100 to 125 mg/dl for fasting glucose, and from 180 to 199 mg/dl for post-prandial glucose. Individuals with fasting and post-prandial blood glucose levels ≥126 mg/dl and ≥200 mg/dl, respectively, were classified as diabetics. Serum uric acid (mg/dl) was treated either as continuous or discrete variable, because there were no *a priori* assumptions about its relationship with the outcome variable. Discrete categorization was done according to quartiles and to pathologic cut-off values. Quartile cut-off values were 3.6, 4.3, and 5.1 mg/dl for women and 4.9, 5.7, and 6.6 mg/dl for men. According to a commonly applied standard, hyperuricemia was defined as serum uric acid levels >5.7 mg/dl for women and >7.0 mg/ dl for men [21,22]. In addition, the occurrence or absence of malignant disease during 1985–2013 was treated as a binary covariate.

Other factors with potential influence on either SUA levels or hip fracture risk that we could not consider due to lack of information included 1) lifestyle-related ones (alcohol consumption, physical activity) and nutritional ones, 2) further serum parameters with long-term influence on bone health (vitamin D, glomerular filtration rate), 3) SUA-lowering drugs such as allopurinol, as well as cortisone, hormone replacement therapy (HRT), and anti-osteoporotic drugs affecting bone and thus hip fracture risk, and 4) disorders like polyarthritis, chronic obstructive pulmonary disease, and inflammatory bowel disease that affect bone status, as well as neurodegenerative disorders, degree of frailty, lower urinary tract symptoms, and urinary incontinence as risk factors for falls.

End point was hip fracture according to the ICD-10 code classes of S72 (comprising S72.0, fracture of femoral head and neck, as well as S72.1 and S72.2, per- and subtrochanteric fracture, respectively), which were discharge diagnoses of all hospitals in Vorarlberg between January 1st, 2003 and December 31st, 2013. Only the patients' first hip fractures in the study period were accounted for, and data were censored by date of death or last day of the study period (December 31st, 2013), whichever came first.

2.3. Statistical analysis

Kaplan–Meier plots served to display time to hip fracture in study participants who were normo- vs. hyperuricemic at baseline. Cox proportional hazards regression analysis was applied to obtain hazard ratios (HRs) with 95 % confidence intervals (CIs) for hip fracture incidence in models adjusted for age only and fully adjusted for all co-variates. Whether variables were normally distributed or not was checked as per Kolmogorov-Smirnov and Shapiro-Wilk tests, and the Mann-Whitney U- and χ^2 tests were applied to compare continuous and discrete variables, respectively. Triglycerides displayed a pronounced right-skewed distribution and were thus log transformed. HRs for

Table 1
Characteristics of the study population according to normal and elevated levels of serum uric acid for women and men separately.

	Women				Men			
	All	Normouricemia (≤5.7 mg/dl)	Hyperuricemia (>5.7 mg/dl)	*p*	All	Normouricemia (≤7.0 mg/dl)	Hyperuricemia (>7.0 mg/dl)	*p*
n	42,488	37,071	5417		35,908	30,249	5659	
Serum uric acid (mg/dl), mean ± SD	4.43 ± 1.21	4.11 ± 0.86	6.64 ± 0.92	<0.0001	5.75 ± 1.34	5.35 ± 0.99	7.91 ± 0.80	<0.0001
Age at health examination (years), mean ± SD	56.49 ± 7.64	56.05 ± 7.32	59.47 ± 8.98	<0.0001	54.93 ± 7.07	54.90 ± 7.04	55.10 ± 7.18	<0.05
BMI (kg/m^2), mean ± SD	26.28 ± 4.72	25.88 ± 4.48	29.00 ± 5.35	<0.0001	26.53 ± 3.69	26.24 ± 3.51	28.05 ± 4.24	<0.0001
Systolic blood pressure (mm Hg), mean ± SD	138.52 ± 21.75	137.23 ± 21.25	147.33 ± 23.10	<0.0001	137.71 ± 19.88	136.64 ± 19.55	143.41 ± 20.69	<0.0001
Diastolic blood pressure (mm Hg), mean ± SD	83.80 ± 11.01	83.31 ± 10.84	87.20 ± 11.59	<0.0001	84.60 ± 10.97	84.00 ± 10.76	87.83 ± 11.55	<0.0001
Triglycerides (mg/dl), median (IQR)	107 (78; 151)	103 (76; 143)	147 (105; 207)	<0.0001	131 (91; 195)	125 (88; 182)	176 (120; 264)	<0.0001
Total cholesterol (mg/dl), mean ± SD	237.57 ± 45.18	236.27 ± 44.40	246.48 ± 49.31	<0.0001	231.05 ± 44.99	228.94 ± 43.49	242.32 ± 50.85	<0.0001
Malignant disease (%)	7289 (14.64 %)	6235 (14.40 %)	1054 (16.29 %)	<0.0001	8530 (19.20 %)	7105 (19.02 %)	1425 (20.12 %)	<0.01
Diabetes status, n (%)				<0.0001				<0.0001
Normal blood glucose	33,173 (78.52 %)	29,568 (80.18 %)	3605 (67.16 %)		25,606 (71.68 %)	21,881 (72.70 %)	3725 (66.20 %)	
IFG	6751 (15.98 %)	5584 (15.14 %)	1167 (21.74 %)		7487 (20.96 %)	6051 (20.11 %)	1436 (25.52 %)	
Diabetes	2322 (5.50 %)	1726 (4.68 %)	596 (11.10 %)		2630 (7.36 %)	2164 (7.19 %)	466 (8.28 %)	
Smoking status, n (%)				<0.01				<0.0001
Non-smoker	34,816 (81.94 %)	30,373 (81.93 %)	4443 (82.02 %)		19,821 (55.20 %)	16,995 (56.18 %)	2826 (49.94 %)	
Ex-smoker	2515 (5.92 %)	2151 (5.80 %)	364 (6.72 %)		7729 (21.52 %)	6156 (20.35 %)	1573 (27.80 %)	
Current smoker	5157 (12.14 %)	4547 (12.27 %)	610 (11.26 %)		8358 (23.28 %)	7098 (23.47 %)	1260 (22.27 %)	
Hip fractures, n (%)	1657 (3.90 %)	1384 (3.73 %)	273 (5.04 %)	<0.0001	596 (1.66 %)	488 (1.61 %)	108 (1.91 %)	0.11

SD (standard deviation), BMI (body mass index), IQR (interquartile range), IFG (impaired fasting glucose).

cholesterol, systolic and diastolic blood pressure are each based on increments of 10 units owing to the wide distribution range of data. Analyses were stratified by gender throughout. HRs were considered statistically significant at the 95 % confidence level. All analyses were conducted using SPSS, version 25 (SPSS, Inc., Chicago, IL).

3. Results

Table 1 and Supplementary Table 1 describe characteristics of our study population. 42,488 women and 35,908 men were followed up for a median time of 18.9 years (IQR: 13.5–24.2 years) and 17.5 years (IQR: 12.6–23.1 years), respectively, in whom 1657 (3.90 %) and 596 (1.66 %) newly reported hip fractures, respectively, occurred between January 1st, 2003 and December 31st, 2013. Out of 5417 women and 5659 men with elevated SUA levels at baseline, 273 (5.04 %) and 108 (1.91 %), respectively, sustained a hip fracture. Mean age at health examination was higher in women than in men (56.5 ± 7.6 vs. 54.9 ± 7.1 years), in study participants with elevated vs. normal SUA levels (59.47 ± 8.98 vs. 56.05 ± 7.32 years in women, 55.10 ± 7.18 vs. 54.90 ± 7.04 years in men), and in subjects who did vs. did not sustain a hip fracture (63.11 ± 8.49 vs. 56.15 ± 7.44 years in women, 60.78 ± 8.59 vs. 54.82 ± 6.99 years in men). Mean age at hip fracture among women was 81.4 ± 8.2 years, and 77.3 ± 9.6 years among men. As Table 1 shows, hyperuricemic study participants had higher BMI, systolic and diastolic blood pressure, triglycerides, and total cholesterol at baseline and were more prone to malignant disease during the study interval than normouricemic participants. Moreover, normal blood glucose levels were less prevalent among hyperuricemic participants, and there were more ex-smokers among men with elevated SUA levels (Table 1). In study participants with a future hip fracture, BMI was decreased, and systolic blood pressure and diabetes prevalence were increased (Supplementary Table 1). Diastolic blood pressure, triglycerides, cholesterol and uric acid were higher, and smoking was less prevalent only in female participants (Supplementary Table 1).

In women, higher SUA levels were associated with a moderate increase in hip fracture risk (Table 2). In the fully adjusted regression model, risk rose by 6% for every unit increase in SUA (HR 1.06, 95 %-CI: 1.01−1.10). Split up into quartiles, participants in the highest vs. the lowest SUA quartile showed a 17 % increase in hip fracture risk (HR 1.17, 95 %-CI: 1.01−1.35) with adjustment for all covariates. In an additional analysis excluding all patients with known end-stage kidney disease (ESKD) at baseline or with diagnosis of ESKD until December 31st, 2013, almost identical results were obtained (Table 3).

In men, increase in SUA levels was associated with a greater rise in risk of hip fractures than in women (Table 2). In the fully adjusted regression model, there was a 15 % increase in risk for every unit SUA increase (HR 1.15, 95 %-CI: 1.08−1.22). Upon quartile categorization, hip fracture risk in the highest quartile rose to 49 % relative to the lowest (HR 1.50, 95 %-CI: 1.17−1.91) with adjustment for all covariates. Analysis upon exclusion of ESKD patients yielded very similar results (Table 3).

Supplementary Tables 2 and 3 present full results of the regression models for women and men including all covariates. Among those, BMI and total cholesterol were inversely, and diabetes, impaired fasting glucose (only in women), and current smoking were positively correlated with hip fracture risk.

Fig. 2 displays cumulative risk for incident hip fractures in Kaplan-Meier and Cox regression survival curves for normo- and hyperuricemic women and men. In the fully adjusted Cox regression models, hyperuricemic levels (>5.7 mg/dl for women, >7.0 mg/dl for men) were associated with statistically significantly increased hip fracture risk compared with normouricemia only in men (HR 1.48, 95 %-CI: 1.19−1.84) (Fig. 2, Table 2). Exclusion of ESKD patients did not result in different HRs in women and changed HRs only very slightly in men (Table 3).

4. Discussion

The findings of this large, population-based cohort study link increased SUA levels and hyperuricemia at baseline with elevated risk of future hip fractures occurring after the age of 50 years, being more pronounced in men than in women.

In various previous studies, increased SUA levels have been associated with higher BMD and reduced risk of incident fractures at various skeletal sites in both sexes [10,23,24]. Whereas results for hip BMD indicate a beneficial role of SUA, findings linking SUA and hip fractures are inconsistent. Elevated SUA was reported to be associated with increased total hip BMD that did not, however, decrease hip fracture risk

Table 2
Age-adjusted and fully adjusted Cox regression analyses of hip fracture (hfx) risk in women and men for increasing levels of serum uric acid as continuous as well as in quartiles, and for gender-specific cut-off values of hyperuricemia.

	Serum concentration	n (subjects)	n (hfx	Age-adjusted[a] HR (95 %-CI)	Fully adjusted[b] HR (95 %-CI)
Women					
Serum uric acid (continuous)		42,488	1657	1.05 (1.01−1.09)	1.06 (1.01−1.10)
Serum uric acid (quartiles)					
1st quartile	≤ 3.60 mg/dl	11,057	390	reference	
2nd quartile	3.61−4.30 mg/dl	10,816	394	1.06 (0.92−1.22)	1.08 (0.94−1.25)
3rd quartile	4.31−5.10 mg/dl	10,493	402	1.11 (0.97−1.28)	1.13 (0.98−1.30)
4th quartile	≥ 5.11 mg/dl	10,122	471	1.14 (1.00−1.31)	1.17 (1.01−1.35)
Normo- vs. Hyperuricemia					
normouricemia	≤5.7 mg/dl	37,071	1384	reference	
hyperuricemia	>5.7 mg/dl	5417	273	1.11 (0.97−1.26)	1.10 (0.96−1.27)
Men					
Serum uric acid (continuous)		35,908	596	1.11 (1.04−1.18)	1.15 (1.08−1.22)
Serum uric acid (quartiles)					
1st quartile	≤ 4.89 mg/dl	8824	142	reference	
2nd quartile	4.90−5.69 mg/dl	8860	138	1.04 (0.82−1.31)	1.09 (0.86−1.39)
3rd quartile	5.70−6.59 mg/dl	9082	153	1.17 (0.93−1.47)	1.26 (0.99−1.59)
4th quartile	≥ 6.60 mg/dl	9142	163	1.33 (1.06−1.67)	1.50 (1.17−1.91)
Normo- vs. Hyperuricemia					
normouricemia	≤7.0 mg/dl	30,249	488	reference	
hyperuricemia	>7.0 mg/dl	5659	108	1.37 (1.11−1.68)	1.48 (1.19−1.84)

[a] Adjusted for age at baseline.
[b] Adjusted for age at baseline, BMI, systolic blood pressure, diastolic blood pressure, triglycerides, cholesterol, malignant disease, diabetes and smoking status.

Table 3
Age-adjusted and fully adjusted Cox regression analyses of hip fracture (hfx) risk in women and men for increasing levels of serum uric acid as continuous as well as in quartiles, and for gender-specific cut-off values of hyperuricemia, upon exclusion of patients with end-stage kidney disease.

	Serum concentration	n (subjects)	n (hfx)	Age-adjusted[a] HR (95 %-CI)	Fully adjusted[b] HR (95 %-CI)
Women					
Serum uric acid (continuous)		42,375	1651	1.05 (1.01–1.09)	1.06 (1.01–1.10)
Serum uric acid (quartiles)					
1st quartile	≤ 3.60 mg/dl	11,048	390	reference	
2nd quartile		10,799	392	1.06 (0.92–1.21)	1.08 (0.93–1.24)
3rd quartile	4.31–5.10 mg/dl	10,470	400	1.10 (0.96–1.27)	1.12 (0.97–1.29)
4th quartile	≥ 5.11 mg/dl	10,058	469	1.14 (0.99–1.31)	1.17 (1.01–1.36)
Normo- vs. Hyperuricemia					
normouricemia	≤5.7 mg/dl	37,012	1380	reference	
hyperuricemia	>5.7 mg/dl	5363	271	1.11 (0.97–1.26)	1.10 (0.96–1.27)
Men					
Serum uric acid (continuous)		35,729	590	1.11 (1.05–1.18)	1.15 (1.08–1.23)
Serum uric acid (quartiles)					
1st quartile	≤ 4.89 mg/dl	8799	141	reference	
2nd quartile	4.90–5.69 mg/dl	8832	136	1.03 (0.81–1.30)	1.08 (0.85–1.37)
3rd quartile	5.70–6.59 mg/dl	9044	152	1.17 (0.93–1.47)	1.26 (0.99–1.59)
4th quartile	≥ 6.60 mg/dl	9054	161	1.33 (1.06–1.67)	1.51 (1.18–1.92)
Normo- vs. Hyperuricemia					
normouricemia	≤7.0 mg/dl	30,138	483	reference	
hyperuricemia	>7.0 mg/dl	5591	107	1.38 (1.12–1.70)	1.49 (1.20–1.86)

[a] Adjusted for age at baseline.
[b] Adjusted for age at baseline, BMI, systolic blood pressure, diastolic blood pressure, triglycerides, cholesterol, malignant disease, diabetes and smoking status.

in the MrOS study in men aged 65 years and older [16]. Likewise, in the Rotterdam Study devoid of gender stratification, increased SUA levels were associated with higher femoral neck BMD, thicker cortices, lower bone width and cortical buckling ratio in participants aged 55 years and older, but these differences did not translate into significantly reduced hip fracture risk [17]. Also gout for which hyperuricemia is a necessary predisposing condition has not been associated with altered hip fracture risk [25]. While the SUA-lowering drug allopurinol was shown to confer but a modest increase in hip fracture risk in a nationwide study among adult users in Denmark [26], after all in men, Basu et al. [27] found no association between allopurinol use and hip fracture incidence in patients >65 years referred to social services in Scotland. In stark contrast, male participants >65 years in the Cardiovascular Health Study were at elevated hip fracture risk in both the lowest and highest SUA quartiles relative to the lowest but one quartile, and statistical significance disappeared for the lowest quartile upon multivariate adjustment [18]. These results are in partial agreement with our findings, however, in the Cardiovascular Health Study no effect was observed in women. Heterogeneous results across study populations might be due to varying age and risk profiles, different follow-up periods, and adjustment for different co-variates.

Mechanistically, an ambivalent role of uric acid has been suggested, acting both as potent extracellular antioxidant compound in serum and as intracellular pro-oxidative reagent [9]. Accordingly, the protective effect of extracellular SUA on bone cells prevails under normouricemic conditions, whereas in hyperuricemia, urate transported into bone cells can trigger the formation of superoxide and free radicals leading to intracellular oxidative damage and inflammatory stress and consequently, disturbed bone remodeling [9]. However, no direct effect of uric acid on rodent osteoblast and osteoclast cells and a human osteocytic cell line could be detected in a recent investigation [28]. Alternatively, uric acid impairs expression and activity of the vitamin D anabolizing enzyme 25-(OH)D-1α-hydroxylase [29], and elevated SUA levels have been correlated with vitamin D insufficiency and deficiency [30], conditions that can impinge upon bone remodeling, also via ensuing secondary hyperparathyroidism [31]. Data of serum vitamin D levels to examine this mode of action were unfortunately not available from our study population. Furthermore, high SUA levels pose a risk for the development of chronic kidney disease [10,32], thus favoring osteoporosis and osteodystrophy with subsequent increased risk of hip fractures [13]. Conversely, impaired renal clearance can result in elevated SUA levels [33]. Nevertheless, we deem it unlikely that a high proportion of our study participants with increased SUA levels at baseline were suffering from chronic kidney disease or developed renal disease during follow-up, because our results remained robust after exclusion of ESKD patients. Also, neurodegenerative disorders that predispose to falls and therefore increase hip fracture risk [14] have been linked with SUA, however, results are inconclusive. While protective effects against Alzheimer's and Parkinson's disease have been reported [11], hyperuricemia was associated with lower prevalence of dementia only in the absence of cardiovascular risk factors [12], and higher uric acid levels might even raise the risk for vascular dementia [11]. Moreover, results of Mendelian randomization studies are conflicting with respect to the role of uric acid for Alzheimer's disease risk [34,35]. In view of these inconsistent findings, ascribing a possible role to dementia mediating SUA-related effects in our study would thus be speculative. Eventually, Mendelian randomization analyses failed to detect a causal relationship of urate levels with total femur BMD [36], nor with femoral neck and total hip BMD [37], suggesting the existence of confounding variables that might also underlie the association of SUA with (hip) fracture risk.

Hip fracture risk in response to increasing SUA levels was more pronounced in men than in women in our study. This gender difference can on the one hand be explained by men's increased average SUA concentrations and consequently higher quartile borders, and a higher threshold value for normouricemia, entailing higher fracture risk in the same quartiles and in hyperuricemia. On the other hand, when SUA was coded as continuous variable, we still observed a larger increase in hip fracture risk per unit among men than women. This finding might indicate the presence of more dominant risk factors than SUA among women that blur the effect of SUA on hip fractures, like postmenopausal estrogen deficiency [38]. The same argument was put forth by Mehta et al. [18] who in the Cardiovascular Health Study observed a trend towards higher hip fracture risk at high SUA levels among women on estrogen replacement therapy, but not in the entire female study cohort.

A number of limitations but also strengths apply to the present investigation. On the one hand, information was not available on relevant lifestyle-related risk factors like alcohol abuse and physical activity,

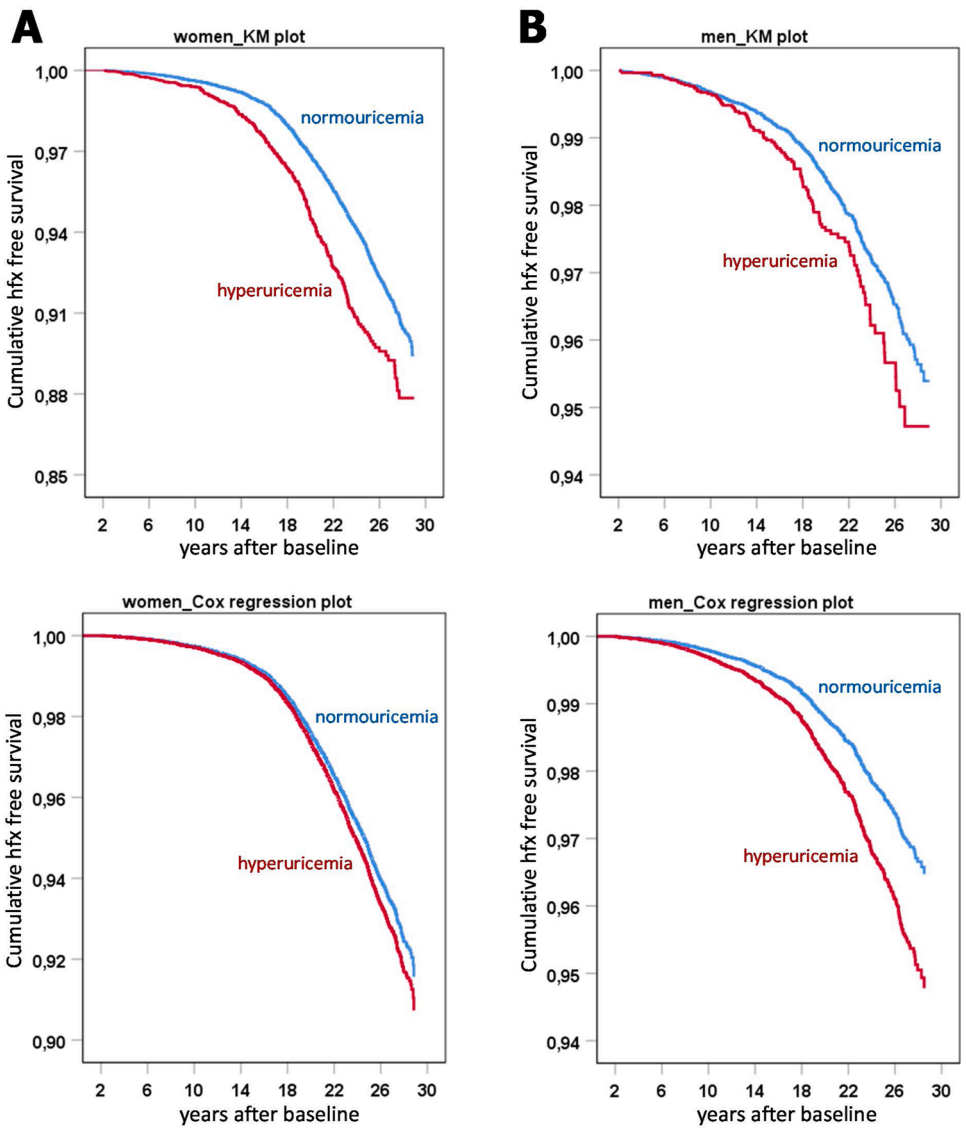

Fig. 2. Kaplan-Meier (KM) (above) and Cox regression (below) plots showing cumulative hip fracture (hfx) risk throughout the study interval in all 42,488 women (A, left) and all 35,908 men (B, right) who were normo- or hyperuricemic at baseline. The Cox regression model was fully adjusted for all variables, *i.e.* age at baseline examination, BMI, systolic and diastolic blood pressure, triglycerides, cholesterol, malignant disease, diabetes and smoking status.

neither on medications affecting SUA levels like allopurinol or affecting bone health like cortisone, HRT, and anti-osteoporotic drugs like bisphosphonates or denosumab, nor on other osteoporotic fractures. Also health conditions associated with increased risk of falls like frailty status, sarcopenia, occurrence of lower urinary tract syndrome and urinary incontinence were not known. Likewise, further bone health related laboratory parameters were not measured like vitamin D status and glomerular filtration rate. Another concern of every epidemiological study that spans a long interval like ours is with participants who are lost to follow-up due to relocation and/or admission to a hospital outside the study area. Apart from missed cases due to relocation, however, completeness of documented hip fracture cases in Vorarlberg can be assumed because of geographic and political factors [39]. Owing to large mountain ranges and borders with non-EU countries with a distinct social security system (Switzerland, Liechtenstein), treatment of hip fractures in neighboring regions is highly constrained. Next, observation intervals of the exposure (including covariates at baseline) and of the outcome events were overlapping by only one and a half years. Our study was thus blind to possible hip fracture events before January 1st, 2003, resulting in false negative classification or detection of a subsequent rather than the first hip fracture in a certain proportion of participants. There should, however, be no reason why among the false negatives the fraction of low and high SUA levels would deviate substantially from that of the cases between 2003 and 2013, there should hence be no major distortive impact on the results. In this regard, it may count as a strong argument for the validity and plausibility of results in our analysis that we found established risk and protective factors like diabetes, current smoking, and higher BMI. On the other hand, the large number of study participants and the long overall study period permitted us to analyze genders separately exhibiting each a considerable number of outcome events. In addition, we were able to identify and exclude patients with severe renal disease as a confounding factor for a SUA-related effect on bone. Finally, the analysis of SUA as continuous and discrete variable in quartiles and separated by gender-specific cut-off values for hyperuricemia provides details about clinically relevant concentration-dependent associations.

5. Conclusions

Collectively, we have demonstrated that high levels of serum uric

acid and hyperuricemia are associated with increased risk of hip fractures occurring after the age of 50 years. The risk was greater in men than in women which might reflect the dominant effect of postmenopausal estrogen deficiency on bone health. With respect to men, our results are in line with a previous finding [18], but generally at odds with various other studies reporting SUA in correlation with higher BMD and decreased risk of bone fractures. Among the covariates, diabetes and current smoking were positively, and cholesterol and BMI inversely associated with risk for hip fractures in women and men alike. It remains to be clarified by which mechanisms bone is affected by uric acid.

Contributors

Oliver Preyer contributed to the conception and design of the study, to the interpretation of results, drafted the manuscript, and critically revised the draft.

Hans Concin contributed to the conception and design of the study, to the interpretation of results, and critically revised the draft manuscript.

Gabriele Nagel contributed to the conception and design of the study, to the interpretation of results, drafted the manuscript, and critically revised the draft.

Emanuel Zitt contributed to the conception and design of the study, to the interpretation of results, drafted the manuscript, and critically revised the draft.

Hanno Ulmer contributed to the conception and design of the study, to the interpretation of results, and critically revised the draft manuscript.

Wolgang Brozek contributed to the conception and design of the study, conducted the data analysis, contributed to the interpretation of results, drafted the manuscript, and critically revised the draft.

All authors saw and approved of the final version of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

The Ethics Committee of Vorarlberg approved the evaluation of the data, and all procedures were carried out in agreement with the Declaration of Helsinki.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

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Appendix A. Supplementary data

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