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CALCIUM PYROPHOSPHATE DEPOSITION DISEASE AND ASSOCIATED MEDICAL CO-MORBIDITIES: A NATIONAL CROSS-SECTIONAL STUDY OF US VETERANS

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Abstract

Objective—Calcium pyrophosphate crystal deposition disease (CPDD) is a common cause of acute and chronic arthritis, yet there are few large epidemiologic studies of CPDD. We sought to characterize CPDD in the national Veterans Affairs (VA) population.

Methods—Patients with International Classification of Diseases, ninth revision (ICD-9) codes for CPDD seen at any VA medical center from 2010 through 2014 were matched by age and gender with control patients without CPDD, using data from the Department of Veterans Affairs Corporate Data Warehouse. We used multivariate analysis to compare the prevalence and odds ratios (OR; 95% confidence intervals [CI]) of various co-morbidities, substance use,medication exposures, and arthroplasties among patients with and without CPDD.

Results—We identified 25,157 patients with CPDD yielding a point prevalence of 5.2 per 1000. The average age was 68.1 ±12.3 years old and 95% were male. The strongest positive associations with CPDD were hyperparathyroidism (OR 3.35; 95% CI 2.96, 3.79), gout (2.82; 2.69, 2.95), osteoarthritis (2.26; 2.15, 2.37), rheumatoid arthritis (1.88; 1.74, 2.03), and hemochromatosis (1.87; 1.57, 2.24). Positive associations were also seen with higher odds for osteoporosis (1.26; 1.16, 1.36), hypomagnesemia (1.23; 1.16, 1.30), chronic kidney disease (1.12; 1.07, 1.18), and calcium supplementation (1.15; 1.06, 1.24). Negative associations were seen with proton pump inhibitors (0.58; 0.55, 0.60) and loop diuretics (0.80; 0.76, 0.84).

Conclusion—Using a large national dataset, we confirmed known CPDD associations, provided support for positive associations with rheumatoid arthritis, hypomagnesemia, and osteoporosis, and suggest potential novel negative associations with commonly used medications.

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Keywords

calcium pyrophosphate; pseudogout; chondrocalcinosis; veterans; osteoarthritis; rheumatoid arthritis; diuretics; proton pump inhibitors

Calcium pyrophosphate crystal deposition disease (CPDD) is acute or chronic arthritis caused by calcium pyrophosphate (CPP) crystals. Radiographic evidence of CPDD is present in up to 4% of the population over the age of 40 (1). A definite diagnosis of CPDD requires the presence of synovial fluid CPP crystals under polarizing light microscopy, and is further supported by the observation of chondrocalcinosis, a radiographic correlate of CPDD in cartilage. The epidemiology of CPDD remains poorly understood due in part to the absence of large studies of clinically significant CPDD. Prevalence studies, for example, have often been based on radiographic evidence of chondrocalcinosis alone. The majority of studies examining prevalence and comorbidities in CPDD are small, underpowered, or rely on a purely radiographic definition of the disease (1–3). To date, the largest epidemiologic study of CPDD included only 795 CPDD patients (4).

Some epidemiologic features and clinical associations of CPDD are well-supported by evidence, while other associations are speculative. CPDD is clearly associated with advanced age and is rare in patients under the age of 60 (1, 5). Metabolic conditions shown to have definite associations with CPDD include hemochromatosis (4), hyperparathyroidism, and hypophosphatasia (6). Associations with hypomagnesemia are largely based on case reports and a single small study (7). Similarly, an association of CPDD and gout is controversial. Two groups reported that chronic renal failure and loop diuretics, but not thiazide diuretics, were associated with higher rates/prevalence of CPDD (1, 4).

CPDD overlaps both epidemiologically and clinically with osteoarthritis (OA) and some other rheumatologic conditions. Interestingly, CPDD has also been reported in patients with rheumatoid arthritis (RA), but only case reports and case series support this association (8–11). While Rho et al. found no significant increase in RA among their cohort, this interesting reported overlap warrants further study (4). Recent work by Abishek et al. suggested an increased prevalence of osteoporosis in patients with chondrocalcinosis (12). Little is known about associations with CPDD and other common co-morbidities, such as diabetes, coronary artery disease, alcohol use, smoking, obesity, or commonly used medications.

We previously validated the high diagnostic accuracy of the International Classification of Disease (ICD)-9 codes for CPDD at one VA medical center, with 98% sensitivity and 78% specificity (13). The positive and negative predictive values were 91% and 94%, respectively (13). Using these diagnostic codes, we assembled a large, national CPDD cohort. Our objective was to identify patient characteristics, comorbid conditions, and medications associated with CPDD using national data from the Department of Veterans Affairs (VA) Corporate Data Warehouse.

METHODS

Study design and identification of patients and controls

We designed a cross-sectional study and queried the VA Corporate Data Warehouse (CDW) to identify all patients diagnosed with CPDD from 2010 through 2014 seen at any VA facility. We used the presence of ICD-9 codes defining CPDD (275.49 and 712.1–39) (Table 1) associated with an inpatient stay or outpatient visit to identify patients with CPDD. Only a single code was required for inclusion, and coding could have occurred any time in this 5 year interval. We matched CPDD patients 1:1 using age and gender to a control group of patients without diagnostic codes for CPDD, but with encounters at any VA facility during the same time period, 2010 through 2014.

Identification of co-morbidities and other conditions

For each cohort, during the same time period we determined the prevalence rates of several relevant co-morbidities including hyperparathyroidism, hemochromatosis, hypomagnesemia, and hypophosphatasia (Table 1). We also examined other potential associations with CPDD such as diabetes mellitus, chronic kidney disease, gout, RA, osteoporosis, Wilson's disease, and OA using ICD-9 codes for these conditions. Given uncertainty regarding the reliability of ICD-9 codes to identify hypomagnesemia, we also included patients who were prescribed magnesium supplements or exhibited low magnesium levels, as indicated by clinical lab results closest to the time of diagnosis.

Health behavior factors were also identified to compare cohorts. Alcohol and tobacco abuse data were obtained using ICD-9 codes (Table 1). Body mass index (BMI) was calculated using the patients' height and weight measurements recorded closest to the time of diagnosis. BMIs were categorized as underweight (<18.5), normal (18.5–24.99), overweight (25–29.99), obese (30–39.99), or morbidly obese (≥ 40).

We also investigated drugs that have been implicated in precipitating acute attacks of CPP crystal arthritis or were thought to influence the formation of CPP crystals. Pharmacy data extracted from the CDW allowed us to identify patients who received loop diuretics, thiazide diuretics, magnesium or calcium supplements, or proton-pump inhibitors (PPIs) from 2010–14. Finally, procedure codes were used to identify patients with and without CPDD who had undergone arthroplasty of the knee, hip, or shoulder (Table 1).

Statistical Analysis

To evaluate associations with CPDD, we compared the prevalence of co-morbidities, health behavior characteristics, medications, and arthroplasty status in our CPDD cohort and in the control group without CPDD. Odds ratios (OR) and 95% confidence intervals (CI) expressed as (OR; lower limit, upper limit of 95% CI) were estimated from univariate and then multivariable logistic regression analyses to provide us with a measure of association for each presumed risk factor. To address the potential impact of one co-morbid condition on another, we conducted a multivariate analysis to adjust for all covariates. All ORs cited in the text are multivariable-adjusted estimates. Due to the large size of our cohort, the

detectable effect size of our statistical tests was below clinical relevance; we therefore report the magnitude of the ORs to identify positive and negative associations with CPDD.

RESULTS

Cohort description

An estimated 5,082,696 veterans accessed care in the VA system in 2014. Among these veterans, we eliminated those without at least one VA encounter from 2010 through 2014. Using this population, we identified 26,287 unique patients with codes for CPDD. This suggests a prevalence rate of approximately 5.2 per 1000 patients in this adult, largely male population. Two sets of codes define CPDD (275.49 and 712.1–721.39) (Table 1). Of patients with CPDD, 7,991 (30%) had the 275.49 code, 6,345 (24%) had one of the 712.1–712.39 codes and 11,951 (45%) had both codes noted during the study period. Complete data were available for 25,157 CPDD patients, and this cohort was used for further analysis. The average patient with CPDD was 69 years of age, and 95% were male.

Comorbidity and health behavior associations

In Table 2, we show univariate and multivariate ORs of various comorbid conditions in the CPDD patient and control cohorts. There was significantly higher prevalence of various metabolic diseases associated with CPDD than in the controls. Hyperparathyroidism (OR 3.35; 95% CI, 2.96, 3.79) and hemochromatosis (OR 1.87; 95% CI, 1.57, 2.24) were strongly positively associated with CPDD. Hypomagnesemia was also positively associated with CPDD (OR 1.23; 95% CI, 1.16, 1.30) in our population. There was no positive association, but rather a negative association with hypothyroidism (OR 0.88; 95% CI, 0.83, 0.92). Analyses of hypophosphatasia and Wilson’s disease were impossible due the absence of significant numbers of cases of these rare diseases.

Several comorbidities and health behavior risk factors were also examined. We also found significantly higher prevalence of various rheumatic diseases in patients with CPDD than in the controls: OA (OR 2.26; 95% CI, 2.15, 2.37), RA (OR 1.88; 95% CI, 1.74, 2.03), and osteoporosis (OR 1.26; 95% CI, 1.16, 1.36), as shown in Table 2. Significant, less impressive associations were also noted with chronic kidney disease (OR 1.12; 95% CI, 1.07, 1.18). More subtle negative associations were noted with coronary artery disease (OR 0.76; 95% CI, 0.73, 0.79), congestive heart failure (OR 0.71; 95% CI, 0.67, 0.75), diabetes (OR 0.79; 95% CI, 0.76, 0.83), and hypertension (OR 0.77; 95% CI, 0.72, 0.82). Table 2 also reports the multivariate ORs for BMI, alcohol and tobacco abuse, and CPDD. Associations with BMI were non-linear and showed less CPDD in underweight (OR 0.84; 95% CI, 0.73, 0.96) and morbidly obese individuals (OR 0.87; 0.79, 0.95) vs. normal BMI, and more in the milder overweight and obese categories. Alcohol abuse (OR 0.62; 95% CI, 0.58, 0.65) and tobacco use (OR 0.73; 95% CI, 0.70, 0.76) were negatively associated.

Medication associations

Negative associations with CPDD were noted with use of the following medications (Table 3): PPI (OR 0.58; 95% CI, 0.55, 0.60); thiazide diuretics (OR 0.84; 95% CI, 0.81, 0.88); and loop diuretics (OR 0.80; 95% CI, 0.76, 0.84). We also noted a slight positive association of

calcium supplementation with CPDD (OR 1.15; 95% CI, 1.05, 1.24). Bisphosphonate use showed a negative association in multivariate analyses (OR 0.85; 95% CI, 0.78, 0.93).

Associations with Arthroplasty

Table 3 displays arthroplasty associations. Knee arthroplasties were more common in the CPDD cohort than in the control group (12.2% vs. 6.7%) even after controlling for the presence of OA in the multivariate model (OR 1.64; 95% CI, 1.53, 1.76). Hip and shoulder arthroplasty had insignificant or marginally significant ORs with multivariate analysis.

DISCUSSION

Using the largest representative US cohort of CPDD to date, we confirmed many known disease associations with co-morbid conditions and suggest new associations for further investigation. Much like the previous largest report of 795 UK patients with acute CPP crystal arthritis (pseudogout), hyperparathyroidism and OA were significantly associated with CPDD.(4). We provided data supporting the previously suspected associations of hypomagnesemia, osteoporosis, and RA with CPDD, and assessed potential associations with common conditions and medications advancing beyond that prior work. Hypothyroidism, congestive heart failure, hypertension, and diabetes were not associated with an increased prevalence of CPDD, and chronic kidney disease was only slightly more common in the CPDD cohort. In contrast to prior studies, we saw negative associations with usage of thiazide and loop diuretics (4). PPIs had a strong negative association with CPDD. We discuss these findings and their implications in the sections that follow.

Prevalence

Although this is not a population-based study, we present findings from one of the largest national US integrated health care systems (14). We estimate a prevalence of CPDD of 0.52% in the national veteran cohort. Rho et al. reported a prevalence of acute pseudogout of 0.17% in the UK general practice database of 4,484,066 persons (4). However, their study only included acute CPP crystal arthritis (pseudogout), a subgroup of the more comprehensive acute and chronic CPDD that we studied.

Rheumatologic associations

Our data illustrated the strong association of OA and CPDD. The link between OA and CPDD is complex. There is considerable overlap in the demographics, clinical manifestations, and even radiographic appearance between these two diseases. Twenty percent of patients thought to have classic OA, for example, also have CPP crystals in their synovial fluids (15) and articular tissues at the time of joint replacement surgery (16).

Similarly, gout and CPDD are strongly associated. Validation of codes for gout in the VA system support a relatively high accuracy of the ICD-9 codes (17), yet gout is over-diagnosed (18). While acute gout may mimic acute CPP crystal arthritis unless a careful synovial fluid crystal analysis is undertaken, evidence suggests that mixed crystals occur in about 5% of patients (19). Conditions such as increased levels of cations, low pH, the

inflammatory milieu, and prior joint damage may promote formation of both monosodium urate and CPP crystals (20)

An interesting association with RA was noted in our study. While some older research has shown either no association or a negative association between these two diseases (21, 22), more recent studies suggest otherwise. One study of 2,370 synovial fluids demonstrated that 8% of RA patients had CPP crystals in their synovial fluid samples (23), and in a similar study of hand joints, 19% of RA fluids contained CPP crystals (24). Chondrocalcinosis commonly occurs as a long-term consequence of joint injury. For example, repair of meniscal injuries resulted in a 5 fold increased risk of chondrocalcinosis in the operated knee compared to the un-operated side (25). CPDD may likewise occur concomitantly or as a complication of longstanding joint damage in OA or RA (26). It is possible that some of this overlap may also represent diagnostic mimicry. Examining prevalence rates of CPDD in an RA cohort could provide additional validation of this association. RA may not always be accurately coded in the VA medical record (27), and further work to unravel the relationship between CPDD and RA will be necessary.

Metabolic and medication associations

Hypomagnesemia has been previously associated with CPDD and we confirm this association here. Magnesium is a co-factor for enzymes that degrade CPP crystals (28) and increase CPP crystal solubility (29). We showed a significant association of hypomagnesemia with CPDD in this study, although the OR is smaller than that seen in previous work (7). One small cross-sectional study examining the prevalence of chondrocalcinosis in patients with hypomagnesemia demonstrated an OR of 13.5 in patients with low magnesium levels (7). Given that hypomagnesemia may be under-coded as an ICD-9 code, we included patients receiving magnesium supplementation and those with documented low magnesium levels during the observed period.

Interestingly, the use of PPIs was negatively associated with CPDD (OR 0.58; 95% CI, 0.55–0.60). This observation was noted despite a reported small risk for producing hypomagnesemia (30) and minimal effects of PPIs on fractional absorption of calcium (31). This negative association is plausible, but might not be etiologic. Notably, PPIs were the most commonly used medications among those studied in these cohorts and were used by 60.3% of CPDD patients and 71.9% of control group patients.

Confirming recent work by Abishek et al., osteoporosis was more common in the CPDD cohort than the controls (12). This observation supports the concept that CPDD may be a systemic disorder associated with dysregulated levels of pyrophosphate. Accumulation of pyrophosphate in cartilage matrix stimulates the formation of CPP crystals (32). Pyrophosphate is also a potent inhibitor of the calcium phosphate mineralization that is necessary for bone matrix formation. Calcium supplementation was also seen more commonly in the CPDD cohort than in controls. In our experience, patients often ask about the connection between calcium supplementation and CPDD, and this connection merits additional study. Interestingly, bisphosphonate usage was fairly unusual in both cohorts and showed differing effects for CPDD in univariate and multivariate models, suggesting the need for further study in relationship to osteoporosis and other factors.

Other comorbidity associations and diuretics

Weaker associations were noted with other comorbidities and behavioral factors. There was a small increased prevalence of chronic renal failure in the CPDD cohort. This has been implicated in one small study (4), but further studies are warranted. We showed weakly negative associations between CPDD and congestive heart failure, hypertension, and diabetes. There are no clear etiologic connections between these diagnoses and CPDD, and little in the literature suggests associations. Hypothyroidism also showed a negative association with CPDD, in contrast to previously reported possible positive associations. We found inconsistent associations with BMI and negative associations with tobacco or alcohol abuse, although the latter may have been under-ascertained using ICD-9 codes.

We were unable to confirm the findings of two prior studies that suggested a positive association of diuretics with CPDD (1, 4). In contrast, the use of loop diuretics was negatively associated with CPDD in this cohort (OR 0.80; 95% CI, 0.76, 0.84). This association may be related to the ability of these drugs to increase urinary calcium excretion (33), but this too needs additional confirmation.

Strengths and limitations

Strengths of this work obviously include the large national cohort, and investigation of comorbidity, health behavior, and pharmacy data. We have previously documented the accuracy of the codes for CPDD and it is unlikely that these codes are commonly over-used. Unfortunately, the common under-diagnosis of CPDD (15) makes it likely that true CPDD patients could be omitted from the disease cohort. In addition, it is possible that some of this cohort had asymptomatic radiographic chondrocalcinosis.

Other limitations of this work relate to the setting and cross-sectional study design. The VA selects for patients who were healthy enough in their late teens and early twenties to enroll in the armed services. Because older American veterans are predominantly male, we cannot comment on the gender distribution of CPDD in our patient cohort. There are also shortcomings of claims-based data. Exposures or illnesses that occurred decades earlier or in a non-VA setting may ultimately result in CPDD and these associations are not captured with this study design. The cross-sectional design also uncovers associations, which are not necessarily causal nor are they temporally sequenced. Confounding by indication or healthy adherer phenomena may have also influenced or led to associations with medications (34). Composite comorbidity and healthcare utilization were not compared between groups or controlled for in these analyses. However, similarly high frequencies of common diseases such as hypertension and diabetes mellitus in both the CPDD and control groups suggest similar disease burden between these two cohorts.

In conclusion, our study of CPDD in the national VA population confirms classic disease associations and epidemiology. We confirmed well-established disease associations with hyperparathyroidism and hemochromatosis, provided additional support for associations with RA, hypomagnesemia, and osteoporosis, and refute positive associations with loop diuretic use. Findings support recent associations with RA and osteoporosis, and possible novel negative associations of PPIs. Additional studies of risk factors and associations will

advance our understanding of CPDD pathogenesis and inform developing evidence-based treatment strategies for this common disease.

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SIGNIFICANCE AND INNOVATION

- Calcium pyrophosphate deposition disease arthritis commonly occurs in aging adults, including over 25,000 US veterans (0.09%) in this nationally representative sample.
- Classic risk factors are affirmed (e.g. hyperparathyroidisim, osteoarthritis, and hemochromatosis), and controversial associations including osteoporosis, hypomagnesemia, and calcium supplementation are noted.
- New associations are reported including a negative relationship between CPDD and use of proton pump inhibitors and loop diuretics.

Table 1

ICD-9 codes for conditions included in this study.

Diagnosis	ICD9 codes
Calcium Pyrophosphate Deposition disease	275.49, 712.1–712.39
Osteoarthritis	715.XX
Hyperparathyroidism	252.0–25208
Hemochromatosis	275.0–275.09
Hypothyroidism	244.xx
Hypomagnesemia	275.2
Diabetes Mellitus	249.xx, 250.xx
Chronic Kidney Disease	585.1–585.9
Gout	274.xx (excluding 274.11)
Rheumatoid Arthritis	714.0–714.4
Alcohol Abuse	303.90–303.93
Tobacco Abuse	305.1, V15.82
Coronary artery disease	414.xx
Congestive Heart Failure	428.xx
Hip Arthroplasty	V43.64
Knee Arthroplasty	V43.65
Shoulder Arthroplasty	V43.61
Wilsons	275.1
Osteoporosis	733.00–733.09
Hypertension	401.0–401.9

Table 2

Characteristics of Veterans with CPDD and age-matched controls (n= 50,314)

Characteristic	CPDD (n= 25,157)	%	Controls (n=25,157)	%
Age, mean, SD (range)	68.1±12.3	–	69.5±12.3	–
Male	23,899	95.0	23,899	95.0
Tobacco Use (ever)	10314	41.0	13324	53.0
Alcohol Abuse	3449	13.7	5632	22.4
BMI Underweight (<18.5)	460	1.8	661	2.6
Normal (18.5–24.99)	5720	22.7	6177	24.5
Overweight (25–29.99)	9126	36.2	8485	33.7
Obese (30–39.99)	8593	34.1	8290	32.9
Morbidly Obese (≥40)	1258	5.0	1544	6.1
Coronary Artery Disease	10224	40.6	12588	50.0
Congestive Heart Failure	5415	21.5	7493	29.8
Diabetes Mellitus	10525	41.8	12233	48.6
Chronic Kidney Disease	6347	25.2	5974	23.8
Hypertension	21298	84.7	22318	88.7
Osteoarthritis	21044	83.7	17669	70.2
Gout	8206	32.6	4015	16.0
Rheumatoid Arthritis	2370	9.4	1201	4.8
Hemochromatosis	405	1.6	213	0.9
Osteoporosis	2758	11.0	2251	9.0
Hyperparathyroidism	1227	4.9	429	1.7
Hypothyroidism	4031	16.0	4385	17.4
Hypomagnesemia	2460	9.8	2368	9.4
Bisphosphonates	2076	8.3	1902	7.6
Calcium	2015	8.0	1737	6.9
Diuretic-loop	6682	26.6	8422	33.5
Diuretic-thiazide	9619	38.2	10906	43.4
Proton Pump Inhibitor	15161	60.3	18093	71.9
Shoulder arthroplasty	301	1.2	198	0.8
Hip arthroplasty	1298	5.2	1005	4.0
Knee arthroplasty	3071	12.2	1682	6.7

Table 3

Odds ratios for associations of clinical and behavioral variables with CPDD (n= 50,314)*

Characteristic	Univariate OR	95% CI	Multivariate OR	95% CI
Tobacco Use (ever)	0.62	0.60, 0.64	0.73	0.70, 0.76
Alcohol Abuse	0.55	0.53, 0 .58	0.62	0.58, 0.65
BMI Underweight (<18.5)	0.75	0.66, 0.85	0.84	0.73, 0.96
Normal (18.5–24.99)	Referent		Referent	
Overweight (25–29.99)	1.16	1.11,1.22	1.08	1.03, 1.14
Obese (30–39.99)	1.12	1.07, 1.17	1.04	0.99, 1.1
Morbidly Obese ≥40	0.88	0.81, 0.96	0.87	0.79, 0.96
Coronary Artery Disease	0.68	0.66, 0.71	0.76	0.73, 0.79
Congestive Heart Failure	0.65	0.62, 0.67	0.71	0.67, 0.75
Diabetes mellitus	0.76	0.73, 0.79	0.79	0.76, 0.83
Chronic Kidney Disease	1.08	1.04, 1.13	1.12	1,07, 1.18
Hypertension	0.7	0.67, 0.74	0.77	0.72, 0.82
Osteoarthritis	2.17	2.08, 2.26	2.26	2.15, 2.37
Gout	2.55	2.44, 2.66	2.82	2.69, 2.95
Rheumatoid Arthritis	2.07	1.93, 2.23	1.88	1.74, 2.03
Hemochromatosis	1.92	1.62, 2.26	1.87	1.57, 2.24
Osteoporosis	1.25	1.18, 1.33	1.26	1.16, 1.36
Hyperparathyroidism	2.96	2.64, 3.3	3.35	2.96, 3.79
Hypothyroidism	0.9	0.86, 0.95	0.88	0.83, 0.92
Hypomagnesemia	1.04	0.98, 1.11	1.28	1.19, 1.36

*All characteristics, comorbidities, medications and arthroplasties listed in Table 2 were covariates in the multivariate analysis; age and sex were matched prior to analysis and not included in models.

Table 4

Odds ratios for associations with therapies in CPDD vs controls (n= 50,314)

Characteristic	Univariate OR	95% CI	Multivariate OR	95% CI
Medication				
Bisphosphonate	1.10	1.03, 1.17	0.85	0.78, 0.93
Calcium	1.17	1.10, 1.25	1.15	1.06, 1.24
Diuretic- Loop	0.72	0.69, 0.75	0.80	0.76, 0.84
Diuretic- Thiazide	0.81	0.78, 0.84	0.84	0.81, 0.88
Proton Pump Inhibitor	0.59	0.57, 0.61	0.58	0.55, 0.60
Joint Arthroplasty				
Knee	1.94	1.82, 2.07	1.64	1.53, 1.76
Hip	1.31	1.20, 1.42	1.02	0.93, 1.12
Shoulder	1.53	1.27, 1.83	1.22	1.0004, 1.48

* All characteristics, comorbidities, medications and arthroplasties listed in Table 2 were covariates in the multivariate analysis; age and sex were matched prior to analysis and not included in models.