Increased Fragility Fracture Rates in Older Men With Osteomyelitis

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In this study, we evaluated fracture incidence over a 10-year period among men with and without osteomyelitis from the Veterans Aging Cohort Study. Fracture incidence was significantly higher among those with osteomyelitis at all osteoporotic fracture sites after adjusting for key related risk factors. Future prospective studies are warranted.

Keywords. osteomyelitis; fracture incidence; inflammatory bone loss.

Osteomyelitis is characterized by inflammatory destruction of bone tissue, often resulting in chronic infection. *Staphylococcus aureus*, the most common pathogen, can invade and persist within osteoblasts, resulting in apoptosis and decreased osteoblast function [1], and can incite osteoclastogenesis through release of proresorptive cytokines [2]. The effects of increased osteoclast activation are likely greatest in the infected bone but may also have systemic skeletal effects. Pathological fractures occur with osteomyelitis, but its incidence is poorly quantified [3, 4], and no data exist regarding rates of systemic bone loss or fracture in this population. We utilized a well-characterized cohort to determine whether rates of fracture at major osteoporotic fracture (MOF) sites were higher in individuals with a history of osteomyelitis than without, taking into consideration established predictors of fractures.

METHODS

The Veterans Aging Cohort Study (VACS) is a prospective observational cohort of veterans with and without human

immunodeficiency virus (HIV) matched by age, sex, race/ethnicity, and geographic region [5]. This analysis includes men in VACS who were aged 50–70 years in 2000 and had data available to approximate 9 of the 11 risk factors (age, race/ethnicity, body mass index [BMI], history of previous fracture, current smoking, glucocorticoid use, rheumatoid arthritis, and/or alcohol use) utilized in FRAX, a validated fracture risk assessment tool [6]. FRAX calculates 10-year risk of fragility (or nontraumatic) fractures at MOF sites (spine, hip, humerus, or forearm). The accuracy of FRAX in men with HIV in VACS has previously been evaluated [7]. HIV infection, hepatitis C virus (HCV) infection, and diabetes were also included in the analysis since they are comorbidities associated with increased fracture risk.

Osteomyelitis cases were defined by the following *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9), codes in 2000 or prior: acute (730.0X), chronic (730.1X), and unspecified (730.2X, 730.8X, and 730.9) osteomyelitis, including the following sites: unspecified, shoulder region, upper arm, forearm, hand, pelvic region and thigh, lower leg, ankle, and foot. Validation was performed by randomly selecting 200 patients with and 200 patients without ICD-9-coded osteomyelitis for medical records review, among which 136 patients (69 with and 67 without osteomyelitis codes) had records sufficiently complete for inclusion. Among patients without ICD-9 codes for osteomyelitis, 66/67 had no evidence of osteomyelitis in their medical record. Among patients with an ICD-9 code for osteomyelitis, 44/69 had notes definitively confirming osteomyelitis and 5/69 had notes definitively ruling out osteomyelitis, but 20 had notes stating an indeterminate diagnosis of osteomyelitis. When we limited the dataset to patients with a definitive diagnosis (ie, excluding the 20 indeterminate cases), the overall agreement was 94.8%, with 97.7% sensitivity, 93.0% specificity, 89.8% positive predictive value (PPV), and an interrater agreement beyond chance (kappa) of 0.89. We also conservatively estimated an interrater kappa for all 136 patients (ie, classifying the 20 indeterminate cases as “no osteomyelitis by chart review”) and obtained an overall agreement of 80.9%, 97.8% sensitivity, 72.5% specificity, 6.8% PPV, with a kappa of 0.62. Fracture outcomes were defined using previously validated ICD-9 codes for hip, vertebrae, radius/ulna, and shoulder/upper arm fracture [8].

Statistical Analyses

We calculated fracture incidence for men with and without osteomyelitis based on the occurrence of a new fracture at the hip, radius/ulna, upper arm, or vertebrae over a 10-year interval (2000–2010) and compared variables across groups using *t* tests for continuous variables and χ^2 or Fisher exact tests for

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categorical variables. Logistic regression was utilized to assess whether osteomyelitis was predictive of fracture after adjustment for the FRAX variables and comorbidities described above for the overall cohort and stratified by HIV status. We performed separate sensitivity analyses after excluding all men with osteomyelitis in the pelvic region and lower extremities (to account for the influence of falls on fracture rates) and after limiting the analyses to men with a clinic visit in the VACS database after 2010 (to account for the influence of death or loss to follow-up).

RESULTS

Characteristics

A total of 42 924 males aged 50–70 years in 2000 were identified from the VACS database, including 24 451 with complete data for fracture-associated variables. At or before the index visit in year 2000, 2.13% (522/24451) of men had an osteomyelitis diagnosis. Men with osteomyelitis were slightly older (56.5 ± 5.7 vs 55.6 ± 5.4 years, $P < .001$), more likely to be black (54.0% vs 46.1%, $P < .001$), have a previous history of fracture (5.2% vs 1.9%, $P < .001$), have rheumatoid arthritis (6.7% vs 3.2%, $P < .001$), currently use alcohol (14.6% vs 10.6%, $P = .003$), have diabetes (35.8% vs 14.4%, $P < .001$), have HCV (24.7 vs 15.0, $P < .001$), and have HIV (35.6 vs 28.7, $P < .001$) compared to men without osteomyelitis. BMI and smoking rates were similar. With regard to chronicity, 19.5% were coded as acute osteomyelitis, 15.1% chronic, and 65.3% unspecified. The ankle/foot was the most common site of osteomyelitis.

Fracture Rates

Over the 10-year period, fractures were more common among men with osteomyelitis than those without (6.5% vs 3.8%, $P = .001$). Men with osteomyelitis at the hip, upper arm, and vertebrae but not the radius/ulna had more incident fractures at major osteoporosis sites. Among all but 2 individuals, the incident fracture occurred at a site distant from the osteomyelitis site.

Multivariable Model

Individuals with osteomyelitis had an increased odds of fracture: odds ratio (OR), 1.78 (95% confidence interval [CI], 1.25, 2.54) for fractures at any major osteoporotic site, OR, 2.01 (95% CI, 1.06, 2.80) at the hip; OR, 2.21 (95% CI, 1.16, 4.19) at the upper arm; and OR, 2.44 (95% CI, 1.19, 4.98) at the vertebrae (Table 1). In the multivariate model, osteomyelitis remained a significant predictor of MOF, with slight attenuation of the association. The models for fracture at other sites are shown in Table 1. History of previous fracture remained the strongest single predictor of fracture across all models.

In the stratified analysis, osteomyelitis correlated with fractures at any site, with an unadjusted OR for HIV+ and

Table 1. Logistic Regression Models Testing the Association of Osteomyelitis With Incident Fractures

Variable	Any Site	PValue	Hip	PValue	Upper Arm	PValue	Vertebrae	PValue
Model 1 (unadjusted)								
Osteomyelitis B ₁ (SE)	0.577 (0.181)	<.01	0.696 (0.326)	.03	0.7912 (0.3267)	.02	0.8898 (0.3655)	.01
Osteomyelitis odds ratio (95% confidence interval)	1.781 (1.250, 2.537)	...	2.005 (1.058, 3.798)	...	2.206 (1.163, 4.185)	...	2.435 (1.189, 4.983)	...
Model 2 (adjusted)								
Osteomyelitis (1 vs 0)	1.649 (1.154, 2.356)	<.01	1.762 (0.944, 3.289)	.08	1.950 (1.016, 3.744)	.04	2.428 (1.173, 5.029)	.02
Age (continuous)	1.001 (0.989, 1.014)	.83	...	<.01	0.986 (0.961, 1.013)	.31	0.990 (0.961, 1.021)	.53
Race (Asian vs black)	0.491 (0.068, 3.569)	.48	1.063 (1.041, 1.086)	...	...	...	4.195 (0.564, 31.174)	.16
Race (Hispanic vs black)	1.337 (1.041, 1.717)	.02	0.910 (0.526, 1.577)	.74	1.650 (0.986, 2.762)	.06	2.299 (1.302, 4.058)	<.01
Race (white vs black)	1.624 (1.410, 1.871)	<.01	1.437 (1.098, 1.881)	<.01	2.226 (1.652, 3.000)	<.01	2.615 (1.816, 3.767)	<.01
Body mass index	0.958 (0.944, 0.972)	<.01	0.898 (0.871, 0.925)	<.01	0.976 (0.948, 1.005)	.10	0.972 (0.939, 1.006)	.11
Previous fracture (1 vs 0)	4.202 (3.232, 5.464)	<.01	3.788 (2.368, 6.062)	<.01	5.409 (3.479, 8.410)	<.01	3.273 (1.752, 6.115)	<.01
Current smoker (1 vs 0)	0.955 (0.727, 1.254)	.74	1.224 (0.766, 1.955)	.40	0.948 (0.547, 1.641)	.85	0.645 (0.301, 1.385)	.26
Glucocorticoid use (1 vs 0)	3.996 (1.699, 9.397)	<.01	8.506 (3.138, 23.05)	<.01	4.135 (0.939, 18.22)	.06	...	...
Rheumatoid arthritis (1 vs 0)	0.969 (0.667, 1.409)	.87	0.751 (0.332, 1.700)	.49	0.810 (0.357, 1.836)	.61	1.103 (0.484, 2.510)	.82
Alcohol use (1 vs 0)	1.581 (1.315, 1.902)	<.01	1.788 (1.273, 2.511)	<.01	1.817 (1.273, 2.593)	<.01	1.524 (0.975, 2.384)	.06
Diabetes (1 vs 0)	1.117 (0.926, 1.348)	.25	1.430 (1.018, 2.009)	.04	1.206 (0.834, 1.745)	.32	0.908 (0.567, 1.454)	.69
Human immunodeficiency virus infection (1 vs 0)	1.153 (0.998, 1.333)	.05	1.132 (0.861, 1.488)	.38	1.249 (0.933, 1.670)	.13	0.924 (0.647, 1.319)	.66

Bolded characters represent variables for which $P < .05$.
Abbreviation: SE, standard error.

HIV- groups, respectively, of 1.852 (95% CI, 1.080, 3.178) and 1.672 (95% CI, 1.045, 2.676; *P* value for interaction = 0.78). In the multivariate model, the adjusted OR (aOR) remained significant for the HIV+ group, aOR = 1.883 (95% CI, 1.022, 3.227) but not for the HIV- group, aOR = 1.490 (95% CI, 0.923, 2.405).

Sensitivity Analyses

After excluding 219 men with osteomyelitis in the pelvic region or lower extremities, the rate of MOF remained greater in men with osteomyelitis than those without: 6.9% (21/303) vs 3.8% (901/23 929), *P* = .004. Among 15 876 men with a clinic visit after 2010, the MOF rates among men with (6.7%, 16/240) and without osteomyelitis (3.6%, 556/15 636) remained consistent (*P* = .010).

DISCUSSION

In this study, the rate of fragility fracture at any major osteoporotic site was 78% higher among men with osteomyelitis compared to those without. Rates were even higher for fractures at the hip, upper arm, or spine. This association was attenuated but remained statistically significant in the multivariable model adjusted for well-established fracture-associated risk factors, except at the hip. These are the first data to suggest that osteomyelitis is associated with a higher risk of fragility fracture systemically, not just at the site of infection.

Our stratified analysis suggested that the association between osteomyelitis and fracture may be stronger for men with HIV. However, in the aggregated analysis, HIV status was not independently associated with incident fracture when adjusted for other important fracture-associated risk factors nor was our interaction term for HIV status statistically significant.

Surprisingly, the association of osteomyelitis with systemic bone loss has not been examined in either animal models or humans. Chronic inflammation in the setting of osteomyelitis results in elevation of circulating inflammatory, proresorptive cytokines, such as RANKL, interleukin (IL)-1, IL-6, and tumor necrosis factor alpha, which may result in systemic bone loss and decreased bone strength [9], similar to the systemic bone loss observed with rheumatoid arthritis [10]. Bone specimens from patients with chronic osteomyelitis have been found to have higher levels of CD4+ and CD8+ T-cell activation than uninfected bones [11], and systemic inflammatory markers are known to increase with osteomyelitis. In support of our data, a recent retrospective study of 192 Korean patients (aged >60 years) with newly diagnosed pyogenic vertebral osteomyelitis and osteoporosis who were subsequently treated with bisphosphonates revealed that among patients for whom treatment was delayed (≥6 weeks after diagnosis), a decrease in bone

mineral density (BMD) was observed at the spine and hip 1 year following diagnosis [12].

Our study has several limitations. First, diagnosis of osteomyelitis is complex, and definitive diagnosis may be difficult to capture through chart review. Therefore, we cannot exclude the possibility that an ICD-9 code was assigned while the condition was being ruled out. However, if anything, we expect that such misclassifications would have biased our results toward the null, underestimating the impact of osteomyelitis on fracture rates. Second, we did not have access to data regarding BMD or falls. However, our sensitivity analysis suggested that falls may not fully account for the difference observed in fracture rates.

CONCLUSIONS

Our data suggest that osteomyelitis is an independent and important risk for future fragility fracture in older men. Further research is necessary to determine whether the mechanism is related to inflammation and systemic bone loss resulting in decreased bone strength or other comorbid factors such as HIV or deconditioning and increased fall risk. In addition to adequate antimicrobial therapy, fracture risk assessment and prevention measures may be necessary for patients with osteomyelitis.

Notes

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Potential conflicts of interest. E. H. has received honoraria from Gilead. M. T. Y. has served as a consultant for Gilead and Viiv. R. B. reports payments from Merck, Viiv Healthcare, and Napo Pharmaceuticals. All other authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Hamza T, Li B. Differential responses of osteoblasts and macrophages upon *Staphylococcus aureus* infection. *BMC Microbiol* 2014; 14:207.
2. Claro T, Widaa A, McDonnell C, Foster TJ, O'Brien FJ, Kerrigan SW. *Staphylococcus aureus* protein A binding to osteoblast tumour necrosis factor receptor 1 results in activation of nuclear factor kappa B and release of interleukin-6 in bone infection. *Microbiology* 2013; 159:147–54.
3. Gelfand MS, Cleveland KO, Heck RK, Goswami R. Pathological fracture in acute osteomyelitis of long bones secondary to community-acquired methicillin-resistant *Staphylococcus aureus*: two cases and review of the literature. *Am J Med Sci* 2006; 332:357–60.
4. Belthur MV, Birchansky SB, Verdugo AA, et al. Pathologic fractures in children with acute *Staphylococcus aureus* osteomyelitis. *J Bone Joint Surg Am* 2012; 94:34–42.
5. Fultz SL, Skanderson M, Mole LA, et al. Development and verification of a “virtual” cohort using the National VA Health Information System. *Med Care* 2006; 44:S25–30.

6. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* **2008**; 19:385–97.
7. Yin MT, Shiao S, Rimland D, et al. Fracture prediction with modified-FRAX in older HIV-infected and uninfected men. *J Acquir Immune Defic Syndr* **2016**; 72:513–20.
8. Womack JA, Goulet JL, Gibert C, et al; Veterans Aging Cohort Study Project Team. Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. *PLoS One* **2011**; 6:e17217.
9. Jones D, Glimcher LH, Aliprantis AO. Osteoimmunology at the nexus of arthritis, osteoporosis, cancer, and infection. *J Clin Invest* **2011**; 121:2534–42.
10. Güler-Yüksel M, Allaart CF, Goekoop-Ruiterman YP, et al. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis* **2009**; 68:330–6.
11. Kumar G, Roger PM, Ticchioni M, et al. T cells from chronic bone infection show reduced proliferation and a high proportion of CD28[−] CD4⁺ T cells. *Clin Exp Immunol* **2014**; 176:49–57.
12. Kim J, Kim SW, Lee SY, Kim TH, Jung JH. Bone mineral density in osteoporotic patients with pyogenic vertebral osteomyelitis: effect of early versus late treatment for osteoporosis. *Osteoporos Int* **2018**. doi: 10.1007/s00198-018-4695-2.