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Low bone density in patients receiving methadone maintenance treatment

Theresa W. Kim*, Daniel P. Alford, Alan Malabanan, Michael F. Holick, Jeffrey H. Samet

Boston University School of Medicine, Department of Medicine, 91 E. Concord Street, Ste. 200, Boston, MA 02131, USA

Abstract

Aim: To examine the frequency and severity of low bone mineral density (BMD) among patients enrolled in a methadone maintenance treatment (MMT) program and to ascertain risk factors for low BMD in this population.

Design: Cross-sectional.

Measurements: Data derived from standardized survey, medical record review, and dual energy X-ray densitometry (DXA).

Results: DXA results were below normal in 83% (76/92) of the study sample with T -scores < -2.5 (osteoporosis range) in 35% [32/92] and between -1.0 and -2.5 (osteopenia range) in 48% [44/92]. Risk factors for low BMD were common: tobacco use, 91%; heavy alcohol use, 52%; and HIV infection, 28%. Only 17% (16/92) were on medications that lower the risk of osteoporosis: estrogen ($n=5$), testosterone ($n=4$), calcium ($n=4$), and Vitamin D ($n=2$). None of the participants reported a known diagnosis of osteoporosis. In bivariate analyses, significant predictors of low BMD were: male gender ($p<0.001$), lower weight ($p=0.009$), and heavy alcohol use ($p=0.02$).

Conclusion: More than three quarters of this sample of patients in a MMT program had low BMD. Treatable conditions associated with low BMD were commonplace. Efforts to increase awareness of low BMD in MMT patients should be considered so that effective treatment may be employed to lower future fracture risk.

Keywords

Methadone maintenance; Epidemiology; Comorbidity; Bone metabolism

1. Background

Osteoporosis is a systemic disease, characterized by low bone mineral density (BMD) and micro-architectural deterioration, predisposing to fracture after minimal trauma or fall. Osteoporosis-related fractures are associated with physical functioning decline (Fink et al., 2003), impaired ambulation, and premature mortality (Johnell et al., 2004). Although effective treatment exists to reduce the risk of future fracture (Wilson, 2004), osteoporosis is underrecognized and undertreated (Neuner et al., 2003; Port et al., 2003; Wong et al., 2003).

*Corresponding author. author.theresa.kim@bmc.org (T.W. Kim).

This study examines whether osteoporosis occurs in patients with opioid dependence in methadone maintenance treatment (MMT) to an extent that suggests that efforts should be directed towards increasing its recognition and treatment.

Patients in MMT may be at higher risk for low BMD due to several reasons. First, direct opioid effects on bone metabolism may occur through inhibition of osteoblast functioning (Perez-Castrillon et al., 2000; Rosen et al., 1998), the cells responsible for new bone formation. Moreover, hypogonadism, a potential side effect of opioids (Daniell, 2004; Woody et al., 1988), is an important secondary cause of osteoporosis (Gennari et al., 2003; Mikhail, 2003). In addition to opioid-related effects, patients in MMT may have comorbid conditions associated with osteoporosis including HIV infection (Amiel et al., 2004; Mondy et al., 2003), tobacco dependence (Izumotani et al., 2003), and alcohol use disorders (Sampson, 2002). The objectives of this study were to evaluate BMD and risk factors for bone loss in patients receiving methadone for opioid dependence.

2. Methods

2.1. Study design and sampling

This was a cross-sectional study of participants recruited from the Boston Public Health Commission's Methadone Maintenance Treatment Program. Patients were excluded from the study if they were (1) pregnant due to radiation exposure during BMD measurement or (2) over 300lb. due to mechanical limitations of the dual energy X-ray densitometry (DXA) table.

2.2. Data collection

Research associates administered standardized interviews assessing the following: demographics; Vitamin D and calcium supplementation; tobacco, alcohol, and heroin use; and MMT enrollment duration. Medication information was obtained through medical record review.

BMD was assessed using DXA (QDR[®]4500W series; Hologic, Inc., Bedford, Massachusetts) of the lumbar spine (L1–L4), hip (excluding Ward' sregion) and forearm (distal one-third radius of non-dominant arm). DXA results are reported as *T*-scores, which are calculated by comparing an individual's BMD to a gender and race/ethnicity-matched, young adult reference population. *Z*-scores are calculated in a similar fashion to *T*-scores except that the reference population is also age-matched.

Study participants received a US\$ 40 gift certificate to a local supermarket. The Boston University Institutional Review Board approved the study protocol. An NIH Certificate of Confidentiality was obtained for added privacy protection.

2.3. Statistical analysis

Differences between BMD groups were tested using bivariate analyses of variance (ANOVA), Chi-square or Fisher's exact test as appropriate. *p*-Values, two-tailed, <0.05 were considered statistically significant. All statistical analyses were performed using SAS Version 8.2 (SAS Institute Inc., 2001).

3. Results

3.1. Sample characteristics

Characteristics of the study sample ($n=92$) are listed in Table 1. No statistically significant differences were found between the study sample and the entire MMT clinic population ($n=350$) in terms of age, gender, or race/ethnicity.

Median opioid use (i.e., heroin or prescription opioids) prior to enrollment in MMT was 14 years and duration of participation in MMT varied widely. One-third of women reported cessation of menses for more than one year; this subgroup had a median age of 42 years (range 31–59). Since women with opioid dependence may have menstrual cycle disruptions, including persistent amenorrhea unrelated to menopause (Schmittner et al., 2005), it is unclear whether these women were post-menopausal. Many participants had risk factors for osteoporosis. Tobacco use was almost universal and prolonged. Half the sample reported past regular use of “heavy” amounts of alcohol for years. About a quarter of the study sample reported HIV infection. Five participants had been prescribed oral steroid medications, drugs that are known to cause osteoporosis with chronic use.

Despite risk factors for osteoporosis, only 16% (15/92) of the sample was on medications that may help to decrease the rate of bone loss: estrogen ($n=5$), testosterone ($n=4$), calcium ($n=4$), Vitamin D ($n=2$), and bisphosphonate ($n=1$). No participant was aware of a history of osteoporosis.

3.2. DXA results

We used World Health Organization criteria to classify BMD as osteoporosis (T -score ≤ -2.5), osteopenia (T -score between -2.5 and -1.0) or normal (T -score ≥ -1) (World Health Organization, 2003). More than 3/4 of the study sample (83%, 76/92) met T -score criteria for either osteoporosis (35%, 32/92) or osteopenia (48%, 44/92) (Table 2). There were significant gender differences. Low T -scores were almost universal among the men (97%, 32/33) with the predominant abnormality, osteoporosis (61%, 20/33). In contrast, 75% (44/59) of the women had low T -scores with the predominant abnormality, osteopenia (54%, 32/59) rather than osteoporosis (20%, 12/59).

To assess risk factors for low BMD in this population, Z -scores were used to decrease the confounding effect of age on BMD. Low BMD (Z -score < -1.0) was significantly associated with the following (Table 3): male gender ($p<0.001$), lower weight ($p=0.009$), and more years of heavy alcohol use ($p=0.02$). There was a positive but non-significant relationship between longer duration of heroin use among those in the groups with lower Z -scores. Current heroin use, methadone dosage, and duration of MMT were not associated with lower BMD.

4. Discussion

We found that more than three quarters of patients recruited from one MMT clinic had abnormally low BMD. These findings indicate that patients in MMT programs may be at higher risk for fracture than the general population. Increased fracture risk in this population

has particular significance given the high rates of injuries (Rees et al., 2002) and worse physical functioning (De Alba et al., 2004; Friedmann et al., 2003) in individuals with addictions.

We also found that a high percentage had osteoporosis risk factors including almost universal tobacco use. Low BMD is yet another reason for continued tobacco cessation efforts in this population. Although excess body weight is considered protective of BMD, low BMD was found despite the overweight or obese character of the sample. The association between heavy alcohol use and low BMD is consistent with studies in other populations (Sampson, 2002; Turner, 2000).

BMD in patients with opioid dependence has received limited attention. Pedrazzoni et al., 1993 found lower lumbar BMD in “recent” heroin users (1–2 days after last use) compared to “former” heroin users (4–24 months since last use) in a cross-sectional study of 22 male heroin users. None of the subjects were receiving methadone. Arnsten et al., 2006 found that MMT was associated with low BMD in middle-aged women either with or at risk for HIV infection. The current study builds upon this work by examining men and premenopausal women in MMT. These studies’ findings and ours suggest that low BMD may be a common comorbidity in chronic opioid users.

An unexpectedly high proportion of the male sample had abnormal BMD. Other studies have found high rates of osteoporosis in men among patients with depression (Mussolino et al., 2004) and schizophrenia (Hummeretal., 2005). Reasons for this are unknown but may reflect the high prevalence of secondary causes of osteoporosis (Licata, 2003). These findings of exceptionally high proportions of patients in MMT with osteopenia or osteoporosis merit further examination in other cohorts since effective treatment is available (Wilson, 2004).

These results should be interpreted recognizing several limitations. Despite similar demographic characteristics between the MMT clinic population and study participants, patients with a family history of osteoporosis may have been more likely to participate, potentially overestimating of the prevalence of low BMD. Second, while this study included risk factors for low BMD not accounted for in previous studies of opioid-dependent patients, other issues such as genetic influences (Videman et al., 2002) and level of physical activity were not assessed. Third, we included multiple sites of BMD measurements in the results to better assess fracture risk, although peripheral DXA sites are generally not used for diagnostic classification. Finally, generalizability of the study’s findings is limited by recruitment from one MMT clinic.

Despite these limitations, these findings are relevant to recent efforts to increase effective linkage between addiction treatment and medical care for patients with substance use disorders (Institute of Medicine, 2006). These efforts are, in part, a response to the growing recognition of the frequency of cooccurring general health and substance use conditions (De Alba et al., 2004; Mertens et al., 2003) and unmet medical needs of patients engaged in addictions treatment (Saitz et al., 2004). Coordinated medical and addictions care, whether

by referral or co-located, has the potential to engage patients in risk reduction for osteoporosis and to reduce the incidence of osteoporotic fractures.

In summary, the majority of individuals examined in this methadone maintenance treatment program had low BMD. Treatable conditions associated with low BMD were commonplace including heavy alcohol use and smoking. Whether addressing osteoporosis risk factors or using bone-preserving medications within MMT settings or via referral to medical care would reduce the incidence of fractures is an area that merits further study.

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Table 1Characteristics of study participants recruited from a methadone maintenance treatment program ($n=92$)

Categorical variables	<i>N</i>	%
Race/ethnicity		
Black	44	48
Hispanic	12	13
White	36	39
BMI ^a		
<20	1	1
20–24	35	38
25–29	20	22
30	36	39
Female	59	64
Persistent amenorrhea ^b	19	21
Menses within past year	40	43
Tobacco		
Lifetime	87	95
Current	84	91
Former	3	3
Never	5	5
Heavy alcohol ^c		
Lifetime	47	52
Current	15	16
Former	32	36
Never	45	49
HIV infection	26	28
Continuous variables	Median	Range
Age, years	42	20–66
Lifetime heroin use, years	14	1–38
Methadone maintenance treatment, years	3	0–25
Current methadone dose, mg	77	3–140
Lifetime tobacco use, years	27	1–47
Lifetime heavy alcohol use, ^c years	7	1–35

^aWeight (lb.) $\times$ 703/height (in.).^bAssessed with the questions, “Aside from pregnancy and birth control medication, have you stopped having your period?” and “How old were you when you had your last period?”^cDefined as >3 drinks/occasion, >3 occasions/week for at least 1 year.

Table 2

Bone mineral density results for the total study sample and stratified by gender

<i>T</i> -score	Women (<i>n</i> = 59)	Men (<i>n</i> = 33)	Total (<i>n</i> = 92)
−1.0	15 (25%)	1 (3%)	16 (17%)
<−1.0 and >−2.5	32 (54%)	12 (36%)	44 (48%)
−2.5	12 (20%)	20 (61%)	32 (35%)

All sites measured by DXA were considered except Ward's area to classify BMD.

Table 3Bivariate analysis of variables associated with low bone mineral density^a

	Z-score ^a		p-Value
	-1.0 (n=33)	< -1 to -2.5 (n=44)	-2.5 (n=15)
Gender			
Male	3(9%)	15(45%)	15(45%)
Women			<0.001
Persistent amenorrhea	6(32%)	12(63%)	1(6%)
Menses with past year	18(45%)	20(50%)	2(6%)
Race/ethnicity			
Black	14(32%)	20(45%)	10(23%)
White	9(24%)	23(62%)	5(14%)
Hispanic	4(36%)	4(36%)	3(27%)
HIV infection			0.48
Yes	9(%)	12(46%)	6(23%)
No	24(%)	35(53%)	12(18%)
Recent heroin use			0.81
Yes	4 (21%)	12 (63%)	3 (16%)
No	23 (32%)	35 (48%)	15 (21%)
Age, mean (S.D.)	41.2 (6.9)	41.9 (10.3)	45.0 (9.2)
Weight (kg), mean (S.D.)	84.4 (17.1)	77.8 (15.2)	69.8 (10.9)
Tobacco, lifetime years, mean (S.D.)	26.0 (7.2)	26.2 (12.2)	29.3 (8.9)
Heavy drinking, lifetime years, mean (S.D.) ^b	3.3 (2.1)	9.5 (8.4)	11.6 (6.8)
Heroin, lifetime years, mean (S.D.)	11.7 (8.2)	13.8 (10.9)	17.5 (9.4)
MMT, lifetime years, mean (S.D.)	4.7 (4.2)	5.6 (5.3)	5.6 (6.6)
Methadone dosage (mg), mean (S.D.)	83.3 (37.6)	75.9 (31.2)	76.0 (33.9)

^a Z-score is the number of standard deviations that an individual's measured BMD is compared to an age-matched reference population.^b >3 drinks on >3 occasions per week for at least 1 year.