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Oral Opioids for Chronic Non-cancer Pain: Higher Prevalence of Hypogonadism in Men than in Women

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Abstract

The effect of chronic oral opioids on hypothalamus-pituitary-gonadal axis in women, and on bone mineral density (BMD) in men and women is not known. The objective of this cross-sectional study was to determine the effect of long-term oral opioids on gonadal status and BMD in male and female patients with chronic non-cancer pain (CNCP). We included 26 community-dwelling CNCP patients, 12 men and 14 premenopausal women, treated with oral opioids for at least one year. We obtained Visual Analogue Scale for pain score, BMD and plasma LH and FSH in all patients; menstrual history and estradiol in women; free androgen index and total and free testosterone in men. Men were older then women ($p < 0.05$) and had used opioids for a longer period (7.2 ± 3.8 and 4.1 ± 1.8 years, respectively; $p < 0.05$), but there was no difference in opioid dose or pain score between sexes. The prevalence of hypogonadism was high in men (75 %), while only 21 % of the women reported oligo- or amenorrhea indicating hypogonadism ($P < 0.01$, between sexes). Osteopenia was found in 50 % of men and 21 % of women (p = NS). We conclude that in CNCP patients receiving chronic opioid therapy there is a much higher prevalence of hypogonadism in men then in women. This needs to be considered clinical practice.

Keywords

opioids; hypogonadism; chronic pain; osteopenia/osteoporosis

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Introduction

Chronic non-cancer pain (CNCP), persisting at least 6 months, is common and affects up to 15–30% of the population. It is estimated that about 20 % of these patients do not experience sufficient pain control with non-opioid therapy and may benefit from chronic opioid therapy (Portenoy and Foley, 1986; MacQuay, 1999).

For over three decades it has been known that heroin and high dose methadone maintenance therapy can decrease testosterone levels in male patients (Azizi et al., 1973). This effect has been attributed to opioid-mediated suppression of gonadotropin secretion, and can be prevented by administration of naloxone, an opioid-receptor antagonist (Giri and Kaufman, 1994). Intrathecal opioid administration to CNCP patients results in decreased sex steroids in both male and female patients (Abs et al., 2000; Finch et al., 2000). Similar results have been found in male CNCP patients taking oral opioids (Daniell, 2002), but we are not aware of studies on the effect of oral opioids in female CNCP patients.

Hypogonadism is a well-known risk factor for decreased bone mineral density (BMD), and patients taking oral opioids chronically may therefore be at risk for decreased BMD. The association between opioid-use, causing hypogonadism, and BMD has mainly been studied in population studies. In 7 114 male and 7 532 female participants of the NHANES III study, Kinjo et al. (Kinjo et al., 2005) found a decreased BMD in opioid users, male and female combined, compared to nonusers. This study did not examine sex steroid levels, and could not determine if the decrease of BMD proceeded through hypogonadism. In two other population studies, use of opioids was associated with a 20–120 % increase of fracture risk in both women and men (Ensrud et al., 2003; Vestergaard et al., 2006). However, the increased fracture rate could be from frailty of patients, opioid medications, elevated risk of falls or impaired BMD. Information on BMD in CNCP patients taking opioids is limited to one retrospective study by Abs et al. (Abs et al., 2000), who found a tendency towards a decreased BMD in CNCP patients treated with intrathecal opioids. In the present study, we examined the effect of long-term oral opioids on gonadal function and BMD in both male and female patients with CNCP.

Subjects and Methods

Participants

Patients with severe chronic non-cancer pain, receiving oral and/or transdermal opioid treatment for at least one year, were eligible for participation. We included community-dwelling men aged 18–60 and premenopausal women aged 18–50 yrs. Patients were excluded if they were using oral contraceptives, estrogen preparations, testosterone, glucocorticoids, bisphosphonates, selective estrogen receptor modulators, calcitonin or parathyroid hormone. Patients were also excluded if they were pregnant, or if an osteoporosis-related fracture was the primary indication for their opioid use. The study was approved by the Health Research Ethics Board of the University of Western Ontario, and conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent before inclusion.

Procedures

A study physician who obtained data on medical and surgical history, current and past intake of drugs, dietary history and use of alcohol, cannabis and nicotine, and in women a detailed menstrual history saw all participants.

Pain severity was determined using a commonly used self-reported Visual Analogue Scale (VAS), with 0 indicating ‘no pain’, and 10 indicating ‘the worst possible pain’. Based on this, the pain severity in individual patients was classified as mild (VAS $\leq$3), moderate (VAS 4–6) or severe (VAS $\geq$ 7).

A physical exam was performed and included measurements of height, weight, body mass index, heart rate and blood pressure. All patients provided a fasting (between 8:00 and 10:00 AM) blood sample for measurement of TSH, free T4, free T3, alkaline phosphatase, LH, FSH, SHBG, prolactin, creatinine, and ALT. In men, we also measured the total and free testosterone and calculated the free androgen index, and in women, estradiol and progesterone. The between run coefficient of variation was 8.8 % for total testosterone, 10.4 % for estradiol, and 11.5 % for progesterone, and the lower limit levels of detection were 0.3 nmol/L, 40 pmol/L and 0.5 nmol/L, respectively.

To document presence of fractures, we performed X-Rays of the thoracolumbar spine, pelvis and hips. Bone mineral density (BMD) was measured using DEXA scans of the lumbar spine (LS) and proximal femur (PF) and results are presented as BMD (g/cm^2) and Z-scores. To evaluate for fracture risk, we also calculated T-scores. The same DEXA scanner was used for all participants, and was calibrated daily to phantoms.

Laboratory measurements

Total testosterone, estradiol, TSH, free T3, free T4, LH, FSH and prolactin were analyzed on serum using Bayer Centaur analyzer (Bayer Diagnostics, Terrytown, USA). Free testosterone was tested by manual radioimmunoassay using reagent kits from Diagnostic Systems Laboratories (Webster, Texas). SHBG was analyzed by competitive chemiluminescence on a fully automated Immulite 2000 analyzer (Diagnostics Products Corporation (Los Angeles, California). The free androgen index (FAI) was calculated by dividing total testosterone (nmol/L) by SHBG (nmol/L), then multiplying the ratio by 100 (Morley et al., 2002, pp. 554–559). Creatinine, ALT and Alkaline Phosphatase were measured on the Beckman CX7 analyzer (Fullerton, California).

Data and statistical analysis

To calculate daily opioid dose, all opioid doses were translated to oral morphine equivalent doses (http://www.rxfiles.ca/acrobat/cht-opioid.pdf). In men, hypogonadism was defined as a total serum testosterone below the age-specific normal range (9.1 nmol/L for age 20–49, and 6.3 nmol/L for age $\geq$ 50 years). For women, hypogonadism was defined based on the presence of amenorrhea or oligomenorrhoea, defined as less than 9 menstrual periods over the last year. Presence of hypogonadism was further evaluated by determination of the FAI in men, and serum estradiol and progesterone in women. Based on the BMD measurement, osteopenia was defined as $-1 >$ T-score ≥ -2.5, and osteoporosis as a T-score < -2.5.

All data are presented as mean ± SD unless specified otherwise. Comparisons between groups were conducted by the two sample independent T-test and, when appropriate, with the Mann-Whitney U test. The Chi-square test was used to assess relations between nominal variables. Associations between parameters were assessed by the Spearman correlation. Results were considered significant at a $P < 0.05$.

Results

Subjects

The charts of 83 consecutive patients visiting our Pain Clinic were initially evaluated (Fig. 1). Twenty-five patients were excluded either after chart review or after evaluation at the clinic: three patients had received opioid treatment for less than one year, two were on bisphosphonates, two were using testosterone therapy, six women were on oral contraceptive and 12 women were peri- or postmenopausal. Fifty-eight patients were eligible, 26 agreed to participate. All patients were evaluated between September 2005 and November 2006. Of the 26 patients included, nine patients had lumbar degenerative disc disease, eight patients had

chronic musculoskeletal pain, seven patients had chronic neuropathic pain and two patients had chronic visceral pain.

None of the patients included had thyroid or parathyroid disease, renal failure or a malignancy. Three patients had previously been diagnosed with depression, one male patient had diabetes mellitus type 2, one woman had Crohn's disease, and another woman with degenerative disc disease, fibromyalgia and pelvic pain had undergone a hysterectomy.

All patients were assessed by a study physician; their baseline characteristics are presented in Table 1. Subjects had used a daily morphine-equivalent dose of 679 ± 620 mg for a duration of 5.5 ± 3 years. Two patients were using a transdermal opioid, in one of them in combination with an oral opioid. In addition, the CNCP patients were taking multiple other medications. Individual VAS pain scores were available for 22 of 26 patients (12 women and 10 men); the mean score was 6.3 ± 1.8, with no difference between men and women (Table 1). Mild, moderate and severe pain was present in 4.5, 54.5, and 41.0 % of patients, respectively. Higher pain scores were associated with lower activity (rho = − 0.51, $P < 0.05$) and increased smoking (rho = 0.47; $P < 0.05$).

Menstrual function and hormone levels

The men were older and had used opioids for a longer period than the women but there was no difference in opioid dose between the two groups (Table 1). Results of measurement of hormones and menstrual function are presented in Table 2. For male participants, the total testosterone levels are shown in Fig. 2 (left panel). In male participants, total testosterone levels were below the age-specific reference range in 10 (83 %); the FAI was below the reference range in 9 (75 %) men. The free testosterone level was measured in 10 men and below the reference range in 40 %.

Three of 13 women reported oligo- or amenorrhoea. The patient who had undergone hysterectomy had an estradiol level of 349 pmol/L and was classified as eugonadal. Therefore, the prevalence of hypogonadism was 23 % in female participants. All women reported to have had regular periods before the start of opioids. The serum estradiol level was below 120 pmol/L in 5 (36 %) of 14 women (Fig. 2, right panel). The prevalence of hypogonadism, based on total testosterone levels in men and menstrual history in women, was statistically significantly higher in men than in women ($P < 0.01$).

To determine if gonadal status was affected by the severity of pain, we compared pain scores in relation to gonadal status, and found statistically significantly lower VAS scores in hypogonadal (5.6 ± 2.0) compared to eugonadal (6.9 ± 1.4) subjects ($P< 0.05$).

Bone mineral density and risk factors for osteoporosis

No vertebral compression fractures were reported either in the patients' history or on X-rays. There was a negative correlation between daily opioid dose and lumbar (rho = 0.4, $P < 0.05$) but not femoral BMD. In contrast, duration of opioid dose was positively correlated with femoral (rho = 0.58, $P < 0.01$) but not lumbar BMD. As there was a significant gender difference in duration of opioid treatment, we also analyzed male and female groups separately and did not find any statistically significant correlations. There was no difference in T- and Z-scores between men and women (Table 2). Individual T-scores for lumbar spine (LS) and proximal femur (PF) are presented in Fig. 3. A T-score below − 1.0 at at least one site was found in 9 (35 %) of the 26 participants, 6 (50 %) of men and 3 (21 %) of women (P = NS). There was no statistically significant association between pain scores and either T- or Z-scores.

Table 3 shows the prevalence of several known risk factors for osteoporosis in this patient group. Except for the prevalence of hypogonadism there was no difference between men and

women. More than 50 % of all participants were actively smoking, and there was a high prevalence of physical inactivity and insufficient calcium intake. In addition, the patients reported a high propensity to fall, with 16 % falling at least once a week and 50 % (4 of 9 men, and 6 of 11 women) falling at least once every 3 months.

Discussion

This study shows that in patients taking long-term oral opioids for chronic non-cancer pain there is a high prevalence of hypogonadism in men (83 %), while only 21 % of women had hypogonadism as indicated by oligo- or amenorrhoea. Further, osteopenia at lumbar and/or femoral site was present in 50 and 21 % of male and female participants, respectively. Importantly, there was no difference in daily opioid dose or pain score between sexes.

Previous studies in CNCP patients treated with intrathecal opioids have demonstrated a high prevalence of hypogonadism in both men and women (Abs et al., 2000; Finch et al., 2000), and only in men taking oral opioids (Daniell, 2002). The high prevalence of hypogonadism in men (82 %) corroborates the literature on the effects of opioids in men. In contrast, the prevalence of hypogonadism was only 21 % in women, which is a much lower than in previous studies in women receiving intrathecal opioids, which documented amenorrhea in 14 of 21 premenopausal women, and irregular periods with mostly anovulatory cycles in the remaining 7 women (Abs et al., 2000).

In this study, we found that the prevalence of hypogonadism was significantly lower in women than in men. In women, we defined hypogonadism based on self-reporting of oligo- or amenonorrhoea. This data is unlikely to be subject to recall bias, and regular periods in women are a powerful indicator of eugonadal status. However, as we did not know if the reported cycles were anovulatory or ovulatory, we also measured serum estradiol levels, the results are consistent with the gonadal status as indicated by the menstrual history.

At the time of the study design, we anticipated a high prevalence of oligo- and amenorrhea as had previously been documented in women receiving intrathecal opioids. In this study, therefore, we did not time the blood samples in relation to the menstrual cycle, which explains the high standard deviation of the progesterone levels. Future studies will need to time blood sampling in the follicular phase to document the prevalence of hypogonadism more precisely.

For male participants, the high prevalence of hypogonadism of 83 % was based on measurement of morning serum testosterone levels. This data is potentially subject to bias due to low levels of serum binding proteins. However, when using the FAI, which corrects for SHBG levels, the prevalence of hypogonadism was similar (75 %), indicating that low serum binding protein levels are not a major confounder in this study. Based on the measurement of free testosterone, only 40 % of men would be classified as hypogonadal. As reviewed by Vermeulen (Vermeulen, 2005), the measurement of free testosterone by radioimmunoassay is not reliable, therefore we submit that the assessment of hypogonadism based on total testosterone and FAI is more reliable.

Recently, Bliessener et al. (Bliesener et al., 2005) reported that treatment with buprenorphine, a partial opioid receptor agonist, did not decrease testosterone levels, this in contrast to the hypogonadal effect of high dose methadone. Their study only included a male population, and our results suggest that the potential beneficial effect of buprenorphine on pituitary-gonadal axis may only be minor in women. Of note, none of our patients was taking buprenorphine.

How can we explain the higher prevalence of hypogonadism in men than in women? The difference cannot be attributed to a difference in opioid dose or severity of pain, as we found lower, not higher pain scores in hypogonadal patients. Although the men had used opioids for

a longer period than the women, it is unlikely that this difference in duration of opioid therapy would explain the difference in hypogonadism. In our study, cannabis use was high in men, but absent in women. While toxicology reports suggest that marijuana extracts can interact with steroid metabolism (Watanabe et al., 2005), two clinical studies did not find any effect of chronic marijuana use on plasma testosterone levels (Friedrich et al., 1990; Block et al., 1991), suggesting that the difference between men and women can not be attributed to the cannabis use.

We are not aware of any other studies in humans looking at sex specific effects of oral opioids on the hypothalamic-pituitary-gonadal axis. Animal experiments have shown that morphine, in addition to its suppressive effect on gonadotropin release, also has a direct inhibitory effect on testicular testosterone secretion that is mediated by local opioid receptors in the testes (Adams et al., 1993). This additional suppressive effect on testosterone levels could contribute to the higher prevalence of hypogonadism in men compared to women. In contrast, the effect of opioids on ovarian steroid production has not been studied, but the mostly normal estradiol levels we observed argue against this. In the present study we found a T-score below − 1 in 35 % of this relatively young group of patients. T-scores compatible with osteopenia/osteoporosis were found in 55 % of men and 20 % of women. The difference between sexes was not statistically significant, although the data suggest more decreased BMD in men. In their retrospective study, Abs et al. (Abs et al., 2000) also found a tendency towards a decreased BMD in CNCP patients receiving opioids intrathecally. Of note, the median duration of opioid therapy was 5 years in our group, considerably longer than the mean of 27 months in the group study by Abs and colleagues. Little information is currently available on the effects of oral opioids on BMD. The cross sectional study by Kinjo et al. (Kinjo et al., 2005) was the first to show lower BMD scores in people receiving opioids, but no sex-specific data were presented. Other population studies have found an association between opioid use and fracture rate in women and in men (Ensrud et al., 2003; Vestergaard et al., 2006), but these studies can not determine if this effect is secondary to opioid-induced hypogonadism, or due to other factors including differences in fall frequency.

Kim et al. (Kim et al., 2006) found a high prevalence of osteopenia and osteoporosis of 48 % and 35 %, respectively, in patients receiving methadone maintenance treatment, with a decreased BMD particularly in men. A high prevalence of osteoporosis has also been found in men with depression (Mussolino et al., 2004) and schizophrenia (Hummer et al., 2005). Licata suggested that secondary causes of osteoporosis are particularly present in men (Licata, 2003). Except for hypogonadism, we did not find differences in known risk factors for osteoporosis men and women. In our study, we did not evaluate for growth hormone deficiency, which has been described in relation to intrathecal opioids administration (Abs et al., 2000), and may contribute to a decrease of BMD.

Several limitations need to be recognized with respect to this study. First, we did not include a control group of CNCP patients who are treated without opioids, and it is thus difficult to determine the effect of chronic pain itself versus the effect of opioids. Second, as these patients are recruited from a chronic pain clinic, they may represent a subgroup with more severe pain that is not well controlled. However, when we analyzed the relation between pain score and gonadal status or bone mineral density, we found a lower pain score in hypogonadal patients, but no association between pain score and bone density. Third, the number of study participants is small, the study is cross-sectional, and did not formally evaluate gonadal status before versus after start of opioids. Fourth, we did not evaluate for life-time alcohol use, which was a significant risk factor for osteopenia/osteoporosis in the study by Kim et al. (Kim et al., 2006). However, alcohol use is likely to be low in our patient group, since generally patients are not prescribed opioids if taking alcohol excessively. Despite these limitations, the relatively high prevalence of decreased BMD and the increased prevalence of hypogonadism particularly

in the male patients suggest that there may be an increased risk for future osteoporotic fractures, especially as opioid therapy may be given for several decades to this relatively young patient group. A pilot study in men with opioid induced androgen deficiency found improvement of androgen deficiency symptoms, sexual function, mood, depression, and hematocrit during testosterone treatment (Daniell et al., 2006). Prospective studies will need to determine the effect of hormone replacement on BMD.

This patient population is also characterized by a high prevalence of other risk factors for osteoporosis including active smoking, insufficient calcium intake, insufficient vitamin D levels and inactivity. All these factors need to be addressed by physicians taking care of this patient group. Attention may also be required for the increased fall frequency as reported by one-third of our patients, which is comparable to the fall frequency of 29 % found in much older community-dwelling elderly patients (O'Loughlin et al., 1993). Central nervous system effects of opioids, deconditioning, muscle weakness secondary to hypogonadism, pain and other factors may play a role. A study by Vestergaard and colleagues, (Vestergaard et al., 2006) showed an increased prevalence of fractures in opioid users, the authors speculated that this increased fall tendency was secondary to opioid induced CNS effects including dizziness.

In conclusion, the present cross-sectional study in patients taking oral opioids for chronic non-cancer pain suggests a high prevalence of hypogonadism and possibly osteopenia in men. In contrast, we did not find a major effect of chronic oral opiates on menstrual cycle in women. Further studies need to determine if these findings are associated with increased incidence of osteoporosis-related fractures in men, and to determine the mechanism why opiates affects males more than females.

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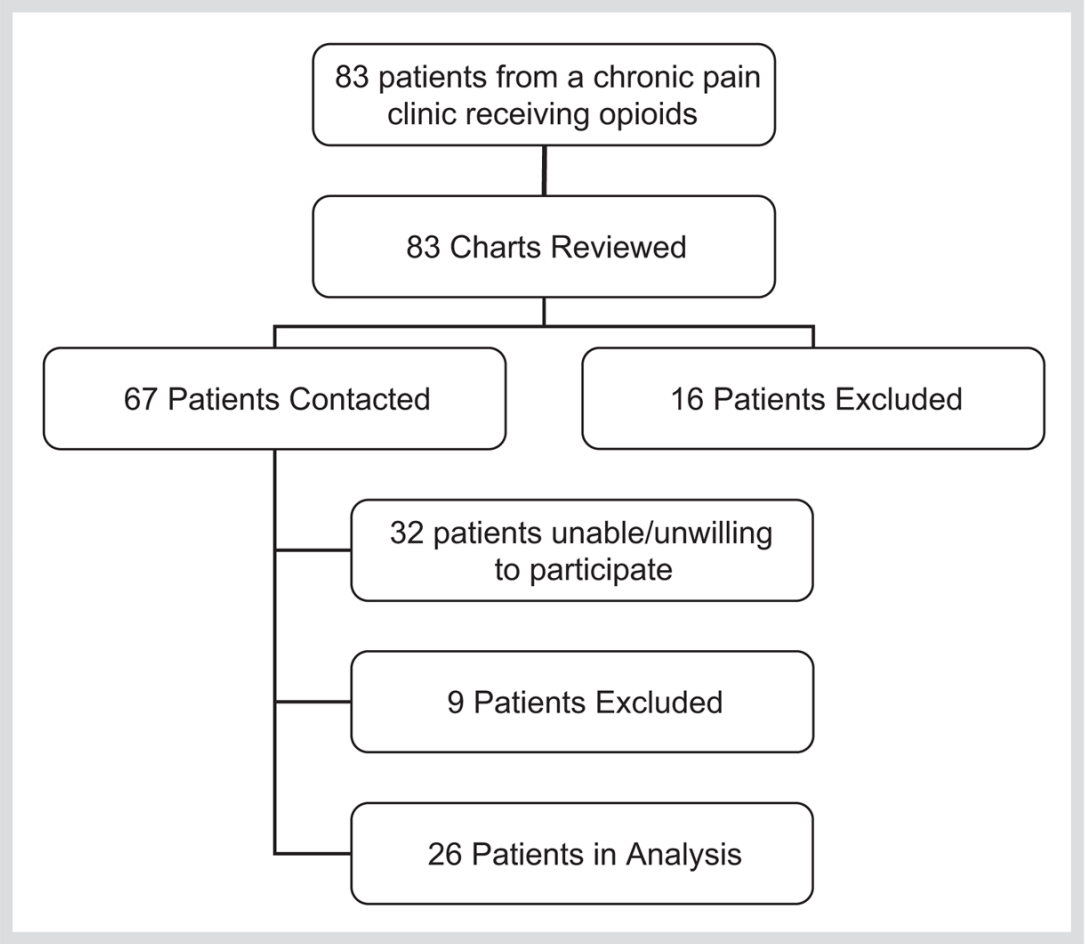

Fig. 1.
Recruitment flow chart. Specific reasons for exclusion are given in the text.

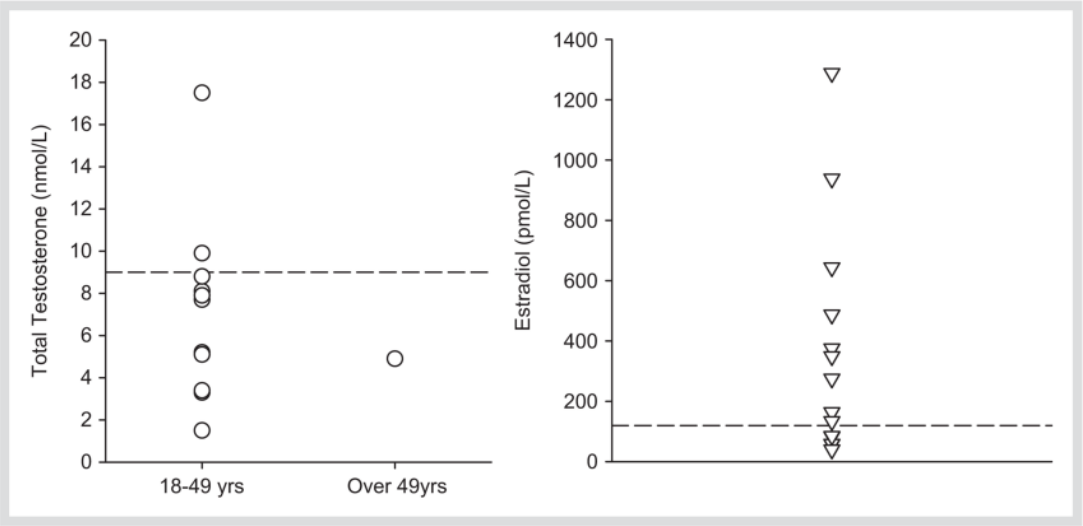

Fig. 2.

Total testosterone levels in men (circles; left panel) and estradiol levels in women (triangles; right panel). For men, the dashed lines indicate the lower end of the reference range for men aged 20–49 years, while the lower end of the reference range for men over 49 years of age is 6.1 nmol/L. For women, the dashed line represents the lower limit of normal estradiol throughout the menstrual cycle.

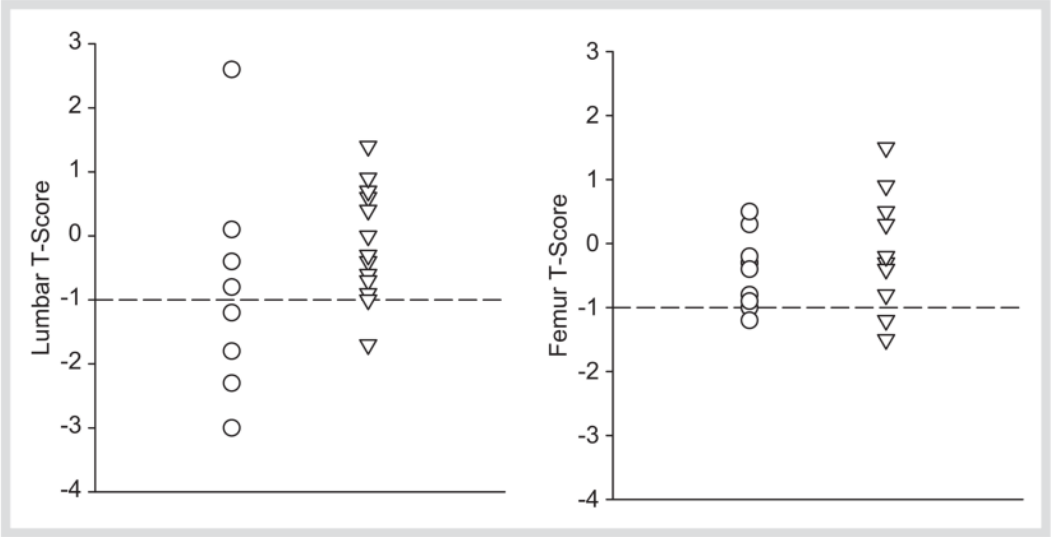

Fig. 3.

Sex-specific results of bone mineral density measurements in lumbar spine (left panel) and proximal femur (right panel). Men are represented by circles, women by triangles. The dashed lines represent the T-scores below which there is osteopenia/osteoporosis.

Table 1

Baseline Data

	Male (n = 12)	Female (n = 14)
age (years)	45.4 ± 5.5	38.6 ± 7.2[a]
BMI (kg/m^2)	29.0 ± 3.8	28.0 ± 7.3
systolic BP (mm Hg)	121 ± 11	114 ± 16
diastolic BP (mm Hg)	76 ± 9	71 ± 8
heart rate (beats/minute)	75 ± 12	71 ± 8
opioid dose (mg/d)	718 ± 524	646 ± 714
opioid duration (years)	7.2 ± 3.8	4.1 ± 1.8[a]
Visual Analogue Scale	5.8 ± 2.3	6.7 ± 1.2
smoking (packs/day)	0.35 ± 0.45	0.57 ± 0.55
alcohol (drinks/week)	0.6 ± 2.0	0.86 ± 2.1
cannabis (joints/week)	8 ± 21	0 ± 0

Data are presented as mean ± SD or n (%);

[a] = $P < 0.05$ (non-paired student t-test)

Table 2

Sex-Specific Results of Laboratory and Bone Density Measurements

	Male (n = 12)	Female (n = 14)	Reference range
TSH (mIU/L)	2.3 ± 0.9	1.9 ± 1.2	0.35–5.0
LH (IU/L)	2.2 ± 1.4	6.9 ± 7.0[a]	F 0.5–76; M 1.5–9
FSH (IU/L)	3.6 ± 1.4	6.3 ± 5.3	F 2–33; M 1–18
SHBG (nmol/L)	23 ± 10	56 ± 40[a]	F 18–144; M 7.2–100
total testosterone (nmol/L)	6.9 ± 4.2	N/A	M 9.1–55 20–49 yr 6.3–26 ≥ 50 yr
free testosterone (pmol/L)	19.3 ± 12.7	N/A	M 18–144 20–49 yr
free androgen index	24.9 ± 15.3	N/A	M 30–125
estradiol (pmol/L)	N/A	356 ± 374	F Fol 231–606 MP 536–1930 Lut 121–719
progesterone (nmol/L)	N/A	18 ± 29	F 0.5–89
prolactin (μg/L)	7 ± 3	15 ± 22	F 3–29; M 1–18
PTH (pmol/L)	4.0 ± 1.8	4.5 ± 2.4	1.1–6.0
creatinine (μmol/L)	96 ± 9	82 ± 11[a]	55–115
urine N-telopeptide (nmolBCE/mmolCr)	40 ± 19	37 ± 19	5–65
lumbar BMD (g/cm^2)	1.018 ± 0.157	1.063 ± 0.099	–
femur BMD (g/cm^2)	0.984 ± 0.082	0.920 ± 0.103	–
lumbar T-score	− 0.9 ± 1.4	− 0.1 ± 0.9	–
lumbar Z-score	− 0.7 ± 1.5	0.1 ± 0.9	–
femur T-score	− 0.4 ± 0.6	− 0.2 ± 0.8	–
femur Z-score	− 0.1 ± 0.5	0.0 ± 0.9	–

Data are presented as mean ± SD.

[a] = P < 0.05 (Student t-test)

F = Female; M = Male; Fol = Follicular phase; MP = Midcycle Peak; Lut = Luteal Phase

Table 3

Sex-Specific Prevalence of Risk Factors for Osteoporosis

Parameter	Men (n = 12)	Women (n = 14)	All subjects (n = 26)
hypogonadism*	10 (83 %)	3 (21 %)[a]	13 (50 %)
osteopenia (T-Score < − 1.0; at least 1 site)	6 (50 %)	3 (21 %)	9 (35 %)
active smoker	6 (50 %)	5 (36 %)	11 (42 %)
calcium intake < 1000 mg/d	11 (92 %)	8 (57 %)	19 (73 %)
inactivity (< 30 min exercise 3 times/wk)	8 (73 %)[#]	11 (79 %)	19 (73 %)
past or present Steroid use	1 (8 %)	2 (14 %)	3 (12 %)
family history of osteoporotic fractures	4 (33 %)	4 (29 %)	8 (31 %)

Data are presented as n (%),

[a] = p < 0.01 versus men (Chi-Square)

* Based on testosterone below age-specific reference range in men, and oligo- or amenorrhoea in women.

[#] based on n = 11 for men