ORIGINAL RESEARCH

Bone Mineral Density in Young Women on Methadone Substitution

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Abstract Little is known about bone mineral density (BMD) in patients with heroin addiction and subsequent methadone substitution. The goal of this study was to compare bone mass density of young HIV-negative women on long-term methadone treatment to a local group of young healthy women. Eleven women (aged 20–29) with previous heroin dependence and current methadone substitution (20–140 mg, median 60, daily) for 1.5–9 (median 3) years were compared to 30 healthy women (aged 20–28). Participants were examined with dual-energy X-ray absorptiometry of the lumbar spine (L2–L4), of the total proximal hip area, and of the femoral neck. Patients and controls had neither current nor lifetime underweight condition, had comparable ages at menarche, and did not differ significantly in current body mass index (21.9 ± 4.0, respectively, 20.5 ± 1.5 kg/m^2) in spite of a largely unhealthy lifestyle (cigarette, alcohol, and cocaine consumption in patients). Patients' total-hip parameters were marginally lower than those of controls (BMD $P = 0.054$, T score $P = 0.049$), whereas the femoral neck and lumbar spine parameters did not differ significantly between the two groups. Long-term methadone substitution in HIV-negative women seems to slightly affect bone mass density.

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The authors have stated that they have no conflict of interest.

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Interest in bone mineral density (BMD) in psychiatric patients has increased in recent years. Some studies have shown associations between psychiatric illnesses such as depression, schizophrenia, and personality disorders and diminished bone density [1–4]. Decreased BMD is known to occur in young women and men with, e.g., anorexia nervosa [5–9].

Analgesic therapy with opioids seems to induce the inhibition of gonadotropin-releasing hormone production, and chronic hypogonadism is an important cause of osteoporosis in both sexes [10]. In addition, opioids may contribute to increased fracture risk by directly interfering with bone formation [10–13].

Recent studies have reported an increased risk of fractures in postmenopausal women using narcotics [14]. A cross-sectional study also reported reduced BMD in middle-aged women with different central nervous system–active

medications and found reduced BMD in subjects with opioid intake [15]. The decreased BMD in a sample of young men with past and current heroin abuse and with a high rate of severe viral infections seemed to be caused by chronic heroin intake; however, it was hypothesized that bone mass could be regained by abstinence [16]. The assumption of low BMD in participants undergoing a methadone maintenance treatment was supported by another group. Their study sample consisted of men and women at different ages and of various ethnic groups who showed a high percentage of severe viral infections [17]. In general, previous studies did not discriminate between patients with and without viral infections.

Severe viral infections such as HIV appear to reduce BMD [18–21]. Since patients with opioid dependence often contract HIV infections, we investigated BMD in young HIV-negative women with previous heroin addiction and successive methadone substitution treatment during a period of at least 18 months in order to avoid this confounding factor. In addition to that, we compared the BMD of this group to a local age-matched group of healthy young women under the hypothesis that the patient group would show a lower BMD compared to controls.

Materials and Methods

Subjects

All 105 Caucasians in the pool of women with heroin dependence under treatment at the Psychiatric University Hospital of Zurich were initially contacted. The diagnosis of heroin dependence was made at this institution according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [22]. Only 47 of these women indicated interest in participating. Inclusion criteria were (1) age <30 years, (2) previous heroin consumption of >4 years, and (3) subsequent methadone substitution for >1 year. The inclusion criteria reduced the number of potential participants to 24.

Exclusion criteria were (1) HIV infection (positive HIV serology at recruitment); (2) current or lifetime underweight in adult age (body mass index [BMI] <18 kg/m^2), because underweight can negatively influence bone metabolism; and (3) pregnancy, because of the altered hormonal household and radiation exposure of dual-energy X-ray absorptiometry (DXA).

Finally, a total of 11 women aged 20–29 years were recruited. Participants completed a questionnaire on sociodemographic and anthropometric data, menstrual status, use of medications, hormonal substitution or contraceptives, as well as intake of vitamins, minerals, and calcium products. The questionnaire also included questions on participants' physical activity patterns such as postural and nonpostural sports and hours of sport per week. The therapeutic setting did not envisage that participants were not consuming heroin any longer since starting methadone substitution.

The most important patient data are listed in Table 1. The duration of heroin consumption ranged from 4 to 15 (median 7) years, and the duration of methadone substitution ranged from 1.5 to 9 (median 3) years.

A total of 30 healthy female medical or psychology students without any substance dependence aged 20–28 years were recruited as controls; the other inclusion and exclusion criteria were the same as in the patient group (Table 1).

Informed consent was obtained by all participants. The study was approved by the local ethics committee and designed in accordance with the ethical guidelines of Helsinki.

Measurement of BMD by DXA

All patients and controls were examined according to the following imaging protocol: DXA of the lumbar spine (L2–L4), of the nondominant total proximal hip, and of the femoral neck area was performed by means of a Hologic QDR 4500 R device (Hologic, Waltham, MA). The BMDs of the lumbar spine (L2–L4), of the total proximal hip area, and of the femoral neck were expressed in grams per centimeter squared. Analogous to a previous study [23], values were also expressed as T and Z scores in absolute numbers as defined in 1994 by the World Health Organization (WHO; number of standard deviations below or above the mean BMD value of young Caucasian women at peak bone mass and of Caucasian women of the same age, respectively).

The precision of the DXA measurements and the coefficients of variation at the level of the lumbar spine and the hip were 1 and 1.5%, respectively. Measurements were performed on the same scanner for each patient by the same experienced technician and according to the quality standards as defined by the International Society for Clinical Densitometry (www.ISCD.org). Similar to a previous study, T and Z scores were almost identical, differing by ≤0.1; therefore, we considered T scores only [23].

Data Analysis

The WHO has provided guidelines for the definition of osteoporosis, osteopenia, and normal bone density in postmenopausal women assessed by DXA. In clinical practice these criteria are commonly used in premenopausal women as well [5, 7]. Thus, we examined our data using WHO criteria in order to allow comparisons with the

Table 1 Characteristics of patient and control groups

Variable	Patients ($n = 11$)	Controls ($n = 30$)	P
Age (years)	24.5 ± 3.3	22.8 ± 2.1	0.147
BMI (kg/m^2)	21.9 ± 4.0	20.5 ± 1.5	0.230
Age at menarche (years)	12.8 ± 2.0	13.3 ± 1.5	0.364
Oral contraceptive use (% of n)	36.4	53.3	0.484
Oral contraceptive intake duration (months)	5.8 ± 4.3	22.7 ± 18.3	0.032
Total physical activity (hours/week)	9.5 ± 6.0	2.8 ± 3.2	<0.001
Weight-bearing activity (hours/week)	0.6 ± 1.3	4.6 ± 3.8	<0.001
Current smoking (% of n)	90.9	40	0.005
Smoking (cigarettes/week)	194.4 ± 91.1	34.5 ± 40.5	<0.001
Current or lifetime alcohol use (% of n)	63.6	23.3	0.026
Current or lifetime hashish use (% of n)	63.6	3.3	<0.001
Current or lifetime cocaine use (% of n)	54.5	0.0	<0.001
Lifetime amenorrhea (% of n)	81.8	0.0	<0.001
Duration of amenorrhea (months)	18.4 ± 15.5	0.0	–
Age at onset of heroin intake (years)	15.1 ± 2.1	–	–
Duration of heroin intake (years)	7.5 ± 3.0	0.0	–
Heroin quantity (g/day)	6.8 ± 2.2	0.0	–
Age at onset of methadone intake (years)	21.2 ± 4.1	–	–
Duration of methadone intake (years)	3.7 ± 2.9	0.0	–
Daily methadone dose (mg)	63.8 ± 37.7	0.0	–

Data are presented as mean ± SD unless otherwise noted

scientific literature and to provide information on the clinical severity of bone deficiency in the study sample.

Differences between patients and controls were tested using t, Mann-Whitney U, or Fisher's exact test with Freeman–Halton extension when appropriate [24]. P values, two-tailed, <0.05 were considered statistically significant. Correlation coefficients were determined where needed. Statistical analyses were performed using SPSS for Windows, version 12 (SPSS, Inc., Chicago, IL; 1989–2003).

Results

As listed in Table 1, patients and controls did not differ with regard to age, BMI, age at menarche, and intake of oral contraceptives. However, women on methadone substitution had a significantly longer duration of physical activity per week than controls ($P < 0.001$), although their weight-bearing activity, e.g., jogging, lasted significantly less. Furthermore, women on methadone substitution were far heavier smokers than controls ($P < 0.001$).

Table 2 shows the parameters characterizing BMD of patients and controls, according to the DXA measurements (BMD as well as T score). The total-hip parameters showed a marginally significant difference between patients and

controls (BMD $P = 0.054$, T score $P = 0.049$). The femoral neck and lumbar spine parameters did not differ significantly between the two groups. The duration of heroin and methadone intake showed no correlation with any BMD parameter.

According to the WHO definitions of osteopenia (DXA T score ≤-1.0 SD and >-2.5 SD) and osteoporosis (DXA T score ≤-2.5 SD), the DXA examination of the femur/hip yielded nine patients (82%) with normal bone density and two (18%) with osteopenia. DXA measurements of the lumbar spine identified five patients (45%) with normal bone density, five (45%) with osteopenia, and one (10%) with osteoporosis. In controls, DXA examination of the femur yielded 27 women (90%) with normal bone density and three women (10%) with osteopenia. Measurements of the lumbar spine identified 22 controls (74%) with normal bone density, seven (23%) with osteopenia, and one (3%) with osteoporosis. No statistically significant difference was found for the distribution of osteopenia and osteoporosis between patients and controls.

Discussion

In this cross-sectional study, the BMD of a small group of women in their third life decade who had been on

Table 2 BMD in patient and control groups

DXA	Patients ($n = 11$)			Controls ($n = 30$)				
	Mean ± SD	t^a $df = 10$	P	Mean ± SD	t^a $df = 29$	P	F (1,39)	P
Femoral neck BMD	0.83 ± 0.10	–		0.89 ± 0.12	–	–	2.084	0.157
T score femoral neck	−0.18 ± 0.89	−0.679	0.513	0.34 ± 1.12	1.668	0.106	1.940	0.172
Total-hip BMD	0.90 ± 0.09	–		0.98 ± 0.12	–	–	3.961	0.054
T score total hip	−0.33 ± 0.71	−1.529	0.157	0.33 ± 0.97	1.835	0.077	4.118	0.049
Lumbar spine BMD	0.97 ± 0.09	–		1.02 ± 0.12	–	–	1.149	0.290
T score lumbar spine	−0.89 ± 0.80	−3.714	0.004	−0.57 ± 1.06	−2.944	0.006	0.830	0.368

[a] One-sample t-testing difference from 0

methadone substitution for ≥18 months showed a marginally significant difference compared to a local age-matched healthy control group. This difference was evident at the nondominant total-hip area. Regarding the other localizations, we found no significant differences, which confirms our hypothesis only partially.

Women on methadone substitution had several factors with a putative negative influence of BMD, for which we expected a severe deficit of BMD in the patient group. Opiod intake (heroin and methadone) over a long period of time can induce hypogonadism in young women and subsequently amenorrhea. In the present study, the large majority of patients were amenorrheic; this endocrinological misbalance is a well-known negative factor for BMD metabolism [25–30]. Furthermore, the patient group had a high alcohol intake and high nicotine abuse, both factors having also a negative influence on BMD [31–33]. Some opioids seem also to compromise bone metabolism [10, 11, 13]. Thus, despite these numerous assumed negative influences on BMD, the group with methadone substitution interestingly did not show a severely pathological BMD.

At this point, it is important to consider that different opioids—heroin and methadone—could exert different influences on BMD [34]. In this regard, the study of Wilczek and Stepan needs to be cited [35]. Here, the authors investigated BMD and bone metabolism in a small sample of heroin-addicted young men and women at baseline and after 1 year of methadone maintenance. Based on their results, the authors hypothesized that prolonged heroin addiction could be associated with accelerated bone turnover and osteopenia, whereas methadone maintenance could restore altered bone turnover [35]. Obviously, to test this hypothesis, longitudinal studies in subjects with heroin and, separately, methadone intake are required.

Probably because of the absence of HIV infection, which is very frequent in persons undergoing heroin or methadone substitution therapy, the results of the present study are less dramatic than those of Pedrazzoni et al. [16] and Kim et al. [17], who both reported that opioid intake causes severe loss of BMD. Pedrazzoni et al. examined the consequences of chronic heroin intake, without methadone substitution, on BMD in young men with drug use duration ranging 1–2 years, but 60% of the sample had serological evidence of HIV and 80% of HBV infection. The high presence of severe viral infections may exert an additional negative effect on bone metabolism [18–21, 36–38]. Kim et al. also showed a low BMD in women and men of different ethnicities (median age 42 years, range 20–66) on methadone maintenance treatment over a wide range of durations (median duration 3 years, range 0–25). In this heterogeneous sample 28% of the participants were HIV-positive. The broad age and ethnicity spectrum as well the presence of HIV infection and the very long heroin intake weaken the plausibility of comparison with the results of the present study.

The presence of a local control group of age-matched women represents, therefore, a strength of the present study because this healthy group permits a real comparison with subjects who have very similar life conditions and who live in the same macroenvironment. On the other hand, it is conceivable that medicine and psychology students, due to their health-related education, could lead a particularly healthy lifestyle, although the distribution of the BMD parameters showed that at least 10% of the control group had in some locations at least osteopenia, thus indicating a relatively broad range of BMD values. Due to the scarce normative data, BMD values of young healthy women could well range as in our control group. It must be noted that there is a paucity of normative data on BMD in general in young, healthy women. Furthermore, the exclusion of subjects with a lifetime history of underweight is also a positive aspect of the study because low BMI can cause bone loss in healthy young people [39].

Nevertheless, these results have an explorative character. Certainly, the very small sample size is a central limitation of the study. Still, the marginal difference found for the total-hip parameters should not cause a large risk of overlooking a real difference, if the presence of a lowered

BMD in at least one location is considered abnormal. Also, it cannot be excluded that the patient sample could have other psychiatric pathologies possibly leading to BMD reduction. Furthermore, the lack of analysis of bone metabolism markers in blood and/or urine did not permit a deeper insight into factors influencing BMD. However, these additional assessments were omitted in order not to jeopardize the limited compliance of the patient group. Indeed, subjects with drug addiction often abhor medical assessments and procedures to a major extent [40].

In conclusion, the findings of this study suggest that BMD in young women on methadone substitution therapy and previous heroin use may only marginally differ from an age- and gender-matched healthy local control group. The effect of methadone on bone metabolism in young people is largely unclear and merits thorough investigation. Despite the severe compliance problems, it is necessary to carry out long-term follow-up studies in young patients under methadone treatment. Better knowledge of predictive and risk factors for BMD in young individuals with addiction problems would permit an improvement of prevention and treatment.

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