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A comparison of bone quality and its determinants in young opioid-dependent women with healthy control group

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ABSTRACT

Background: Little is known about bone quality and its determinants in patients with opioid addiction. The goal of this study was to compare bone quality and its determinants in young opioid addicted women with a local group of young healthy women.

Method: Using cross-sectional design, 104 women (mean age 29.9 yrs, range: 20–40 yrs, SD = 7.8) with previous opioid addiction and current methadone substitution (3–30 mg, daily) for 1–16 weeks were compared to 117 healthy women (mean age 31.0 yrs, range: 20–40 yrs, SD = 5.9). Bone quality was examined with quantitative ultrasound. Anthropometric characteristics (body weight, fat free mass (FFM), fat mass) were obtained by bioelectrical impedance analysis. Substance use and other risk factors for low bone quality were assessed by questionnaire-based interviews.

Results: More than one-quarter (34%) of patients had osteopenia (n = 31) or osteoporosis (n = 4), compared to 16% of the healthy control group having osteopenia (n = 18). Bivariate correlation analysis demonstrated that age, body weight, and FFM correlated with bone quality ($p < 0.05$) in healthy women, which were not found in patients. Multivariate analyses showed that in healthy controls, the determinants of bone quality were age, body height, physical activity, and BMI, but in patients, the determinant of bone quality was duration of drug intake.

Conclusions: Long-term opioid dependence in young women may lead to low bone quality. Efforts to increase awareness of low bone quality in young opioid addicted women should be considered so that effective treatment may be employed to lower future fracture risk.

1. Introduction

Osteoporosis is a systemic disease, characterized by a progressive loss of bone quality and micro-architectural deterioration, predisposing people to fractures after minimal trauma or falling (Rachner et al., 2011). Several risk factors, such as advanced age, low body mass index (BMI) and life-style factors as well as decreased mobility, have been reported to be the determinants of bone quality in the general population (Lima et al., 2009; Morin et al., 2009).

Low bone quality has been found among illicit drug users and opioid users on methadone maintenance treatment (MMT) both in men and women. A cross-sectional study in Switzerland reported a high prevalence of low bone mineral density (BMD) in 144 long-term opioid-dependent men (Gotthardt et al., 2016). Kim et al. (2006) reported that more than three quarters of the sample of patients (33 men, 59 women) with opioid dependence had low BMD. However, contrasting studies exist. For example, Grey et al. (2011) found that BMD in 83 opioid dependent patients (48 men, 35 women) was lower than normal throughout the skeleton in men, but not women. In general, studies focusing on young opioid-dependent women are limited, and the effect of opioid dependent on bone quality in young women is unclear and merits thorough investigation (Milos et al., 2011).

Several potential mechanisms have been proposed to analyze the bone quality in the opioid-dependent people. Some reports found that chronic abuse of opioid drugs may be associated with altered bone metabolism and reduced trabecular bone mass (Perez-Castrillon et al., 2000). Other researches established that opioids abuse can suppress hypothalamic secretion of gonadotropin-releasing hormone and consequently decreases the level of gonadal hormones (Katz and Mazer, 2009), and chronic hypogonadism is a prominent cause of osteoporosis in both sexes (Seeman, 2002). Moreover, life-style factors and comorbidities associated with long-term opioid consumption, such as smok-

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ing, alcohol use disorders and lower physical activity level may influence bone quality in young opioid dependent women (Slemenda et al., 1989). To our knowledge, body composition was an important determinant of bone status (Ding et al., 2016). Increased mechanical loads stimulate bone formation and suppress resorption, whereas unloading has the opposite effect (Ehrlich and Lanyon, 2002; Rodan, 1997). Body weight (BW) and fat-free mas (FFM) were found to have positive relationship with bone quality (Morin et al., 2009; Lima et al., 2009). However, it's uncertain that if these relationships also exist in patients with opioid addiction, and what's the difference compared with young healthy women.

Within a large cohort of young opioid dependent women and a healthy control group, the aim of our study was (1.) to evaluate bone quality in patients comparing with the healthy controls, and (2.) to find the determinations (among the risk factors) to bone quality in young opioid dependent women and in the healthy controls, so that the therapeutic interventions may be employed to prevent or treat drug-induced osteoporosis.

2. Material and methods

2.1. Design, participants and recruitment process

This was a cross-sectional study of long-term opioid dependent women living in the middle area of China. 206 Subjects were recruited from the Women's Specific Drug Rehabilitation Center of Anhui Province between November 2015 and March 2016. Inclusion criteria were:1.) newcomers (within 4 months), 2.) age 20–40 years, 3.) previous drug consumption of > 3 years.

After the medical examination and the questionnaire-based interviews, the exclusion criteria reduced the number of potential participants to 135. Exclusion criteria were: 1.) HIV infection; 2.) Individuals with history of fractures in previous 24 months; 3.) type 1 diabetes; 4.) significantly impaired renal or hepatic function, or chronic kidney disease; 5.) pregnancy, because of the altered hormonal household.

Patients not willing to participate or who had withdrawn consent were also excluded. Finally, a total of 104 patients aged 20–40 years were recruited.

Meanwhile, a total of 117 age- and BMI-matched healthy women were used as control group to compare bone quality and anthropometric data. All controls were recruited from Anhui province and assessed in Anhui National Physical Fitness Monitoring Center in Hefei of Anhui province. All subjects answered the questionnaires regarding lifestyle, medical history, and current medication. Individuals with history of fractures in previous 24 months, type 1 diabetes, significantly impaired renal or hepatic function, and chronic kidney disease were excluded. Women not willing to participate or who had withdrawn consent were also excluded.

All participants provided informed consent, and the study was conducted in accordance with the guidelines in Institute and Intelligent of Machines, Chinese Academy of Science. The study was approved by appropriate institutional research ethics committee.

2.2. Questionnaires – background characteristics

The questionnaires-based interviews were taken to obtain more information about patient group and healthy controls. The questionnaires include six parts: medical history, history of drug use, physical activity level, nutritional calcium intake, smoking status, and education level, as shown in Table 1. The history of drug use was taken only in patient group.

In order to ensure accuracy in survey results, we told all the subjects the purpose of this survey. The answers of patients were compared with medical examination and the official data, and any discrepancies would be confirmed by the individuals.

Table 1
Questionnaires to the Patient and Control group.

Questions	Data Type
Medical history:	
1. Individuals with history of fractures in previous 24 months	0 = No 1 = Yes
2. Pregnancy	0 = No 1 = Yes
3. Type 1 diabetes	0 = No 1 = Yes
4. Significantly impaired renal or hepatic function, or chronic kidney disease	0 = No 1 = Yes
History of drug use (Patients only):	
1. Type of drug use: (1) Heroin, opium, morphine, and other opiates (2) Cocaine (3) Marijuana (4) Amphetamines (5) Hallucinogens (6) Other drugs	Multi selection
2. Age at onset of drug intake (year)	Quantitative
3. Duration of drug intake (years)	Quantitative
4. Frequency of drug use: (1) 3–7/week or more; (2) 1–2/week; (3) 1–2/month; (4) seldom	Single selection
5. Way of drug use: (1) injection (2) non injection	Single selection
6. Duration of methadone intake (weeks)	Quantitative
7. Daily methadone dose (mg)	Quantitative
8. Duration of drug intake (years)	Quantitative
Physical activity level:	
1. Average physical activity (20 min brisk walking, fitness training or sport) (hours/week)	Quantitative
Nutritional calcium intake:	
1. Diet habit: (1) well-balanced diet, regular intake of calcium-rich foods (2) Occasionally intake of calcium-rich foods (3) Low nutritional calcium intake, seldom intake of calcium-rich foods	Single selection
Smoking status:	
(1) often (2) occasionally (3) seldom	Single selection
Education level:	
1. Years of education (years)	Quantitative

2.3. Measurements of anthropometric characteristics

Body height (BH) was measured to the nearest 0.1 cm using a stadiometer (GMCS-I, XinDongHuaTeng Corp., China). BW, FFM, and fat mass (FM) were measured by bioelectrical impedance analyzer (BX-BCA-100, Broshare Technology Corp., Hefei, China); the REG. NO. of BX-BCA-100 in the China Food and Drug Administration (CFDA) is 2210038. In addition to abstinence from diuretics, alcohol, intense exercise and fluids as detailed earlier, subjects emptied their bladder 30 min before the bioelectric impedance analyses (BIA) measurement was taken. Subjects stood on bare feet with the heel and toe of each foot in contact with the metal footpads, with arms hanging on each side, lightly holding the analyzer handgrips. Coefficient of variance (CV) of the impedance measure was 0.4%. Values obtained from BIA were supported by skinfold measurements using harpenden calipers.

2.4. Measurements of bone quality

Bone quality was assessed by a quantitative ultrasound (QUS) device (BX-BDI-500A, Broshare Technology Corp., Hefei, China). The REG. NO. of BX-BDI-500A in CFDA is 20152230048. Speed of sound (SOS; m/s) and broadband ultrasound attenuation (BUA; dB/MHz) were measured on the right calcaneus with the subjects in an upright seated position. The stiffness-index (SI), a combination of SOS and BUA, is calculated by the system according to the following formula: $SI = 0.67 \times BUA + 0.28 \times SOS–420$ (Njeh et al., 1997) and has a lower precision error than either SOS or BUA alone. In general, SI value impresses the bone quality as measured by QUS, and higher SI value indicates better bone health. Meanwhile, values were also expressed as T-score, which was generated based on the SI in QUS device (Liu et al., 2012). Bone health of subjects was classified into normal (T-score more than −1.0), osteopenia (T-score between −2.5 and −1.0), and osteoporosis (T-score less than −2.5). The measurement took 5 min

for each subject. The precision of the QUS measurements was determined using 20 measurements of each of 10 subjects aged between 20 and 40 years. The values for SOS, BUA and SI varied in the range 1489–1623 m/s, 42–133 dB/MHz and 62–130, respectively, and the respective standard deviations were between 4 and 11 m/s, 1 and 5 dB/MHz and 1 and 4. The calculated coefficients of variation were 0.4%, 2.0% and 2.5% for SOS, BUA and SI, respectively.

2.5. Statistical analysis

Age, anthropometric characteristics and SI were expressed as mean ± standard deviation. The level of statistical significance was set at a P value less than 0.05. Student's *t*-test was used for comparison of means and quantitative data between patients and controls. P values, two-tailed, < 0.05 were considered statistically significant. Correlation coefficients were determined where needed. The association of the outcome with each of the relevant factors was explored using linear regression. In a step further, relationships between the outcomes and factors of interest and potential determinants, including age, BH, BW, BMI, FFM, FM, duration of drug intake, and physical activity were investigated using multivariable linear regression. All statistical analyses were conducted using SPSS for Windows, Version 22.0 (IBM Corp., Armonk, NY).

3. Results

3.1. Characteristics of participants

As listed in Table 2, patients and controls did not differ with regard to age, BW, and BMI. Patients and controls showed significantly different with regard to BH, FFM, and FM (P < 0.05). However, the patients had a significantly shorter duration of physical activity per week than controls (P < 0.001). The percentage of low nutritional calcium intake was higher in patients than controls. The years of education in patients was significantly less than controls (P < 0.001).

Table 2
Characteristics of the patient and control group.

Variable	Patients (n = 104)	Controls (n = 117)	*P*
Age(years)	29.9 ± 7.8	31.0 ± 5.9	0.157
Body height (cm)	162 ± 5.2	161 ± 4.3	0.013
Body weight (kg)	62.1 ± 9.9	59.2 ± 10.1	0.210
Body mass index (kg/m^2)	23.8 ± 2.7	22.9 ± 3.7	0.192
Fat Free mass (kg)	42.9 ± 3.4	41.4 ± 3.4	0.032
Fat mass (kg)	20.0 ± 5.0	17.9 ± 7.3	0.019
Physical activity (hours/week)[a]	1.9 ± 2.9	4.2 ± 4.8	0.000
Low nutritional calcium intake (% of n)	25.9%	9.1%	0.000
Years of education (years)	4.7	12.6	0.000
Smoking (% of n)	95%	3%	0.000
SI[b]	95 ± 12	101 ± 15	0.000
T-Score	−0.5 ± 0.7	−0.2 ± 0.8	0.000
Heroin, opium, morphine, and other opiates (% of n)	85%	–	–
Cocaine and other drugs (% of n)	62%	–	–
Multi substances (% of n)	48%	–	–
High frequency of drug use[c]	87%	–	
Age at onset of drug intake (year)	22.3 ± 4.7	–	–
Injecting drug users (% of n)	41%	–	–
Duration of methadone intake (week)	7.3 ± 4.2	–	–
Daily methadone dose (mg)	16 ± 5	–	–
Duration of drug intake (years)	6.2 ± 2.9	–	–

[a)]Physical activity: 20 min brisk walking, fitness training or sport
[b)]SI indicates stiffness index, SI = 0.67 × BUA + 0.28 × SOS–420;
[c)]High frequency of drug use: 3–7/week or more.

Table 3
Bone quality results for the study sample stratified by patient and control group.

Bone status	T-Score	% of Patients (numbers)	% of Controls (numbers)
		N = 104	N = 117
Osteoporosis	< = −2.5	4 (4)	0 (0)
Osteopenia	< −1.0 and > −2.5	30 (31)	17 (20)
Normal	> = −1.0	66 (69)	83(97)

Furthermore, there were more smokers in patients than in the healthy controls (P < 0.001), and the bone quality (SI and T-Score) was lower in patients than in the healthy controls. What else, in patients, 85% used heroin, opium, and other opiates, 48% used more than one substance, and 41% were intravenous opioid users.

The data are shown as mean ± standard deviation; *P* value determined by student's *t*-test for differences in the basic characteristics of patients and healthy controls.

3.2. Osteopenia and osteoporosis in patients and controls

Table 3 shows the bone quality results for the study sample stratified by patient and control group. In the patients, 66% of patients (n = 69) with normal bone quality, and 4% of patients (n = 4) were diagnosed as having osteoporosis and 30% of patients (n = 31) were diagnosed with osteopenia. In healthy controls, QUS examination of the calcaneus yielded 83% women (n = 97) with normal bone quality and 17% (n = 20) with osteopenia, and none with osteoporosis. Overall, 34% of those young patients had low bone quality, which was twice as high as the ratio (17%) of low bone quality in the healthy controls.

3.3. Anthropometric characteristics and bone quality

Table 4 shows the bivariate correlation analysis of bone quality (SI) against age and anthropometric characteristics in patients and healthy control women. There was a negative correlation between age and SI in healthy controls, and positive correlations between SI and anthropometric characteristics (BH, BW, and FFM) were also found in the controls. However, those correlations were not found in opioid-dependent women.

Table 5 shows the multiple linear regression analysis for the prediction of bone quality in patients and healthy control women. Relationships between bone quality and factors of potential determinants (including age, BH, BW, BMI, FFM, FM, physical activity, duration of drug intake) were investigated using multivariable linear regression. In patients, duration of drug intake was the most important positive predictor for SI (P < 0.05). In the healthy control women, BH, age, physical activity, and BMI were the positive predictors of bone quality (P < 0.05).

Table 4
Bivariate correlation analysis of bone quality (SI) against age and anthropometric characteristics.

	SI of Patients	SI of Controls
	N = 104	N = 117
Age	0.120	−0.264**
Body height	0.094	0.265**
Body weight	0.032	0.205*
Body mass index	−0.012	0.124
Fat free mass	−0.148	0.260**
Fat mass	0.123	0.162

SI indicates stiffness index, SI = 0.67 × BUA + 0.28 × SOS–420; *P < 0.05, **P < 0.001.

Table 5
Multiple linear regression analysis for the prediction of bone quality (SI) in patients and healthy control women.

Dependent Variable	Independent Variable	Standard β	p
SI[a] of Patients			
Model1	Duration of drug intake (years)	−0.407	0.000
	Body height	0.092	0.908
	Age	0.241	0.097
	Body weight	−0.079	0.960
	Fat mass	0.167	0.105
	Physical activity (hours) [b]	0.186	0.059
	Fat-free mass	−0.193	0.097
	Body mass index	0.056	0.968
	R = 0.566		
SI of Controls			
Model1	Body height	0.560	0.013
	Age	−0.231	0.025
	Physical activity (hours)	0.144	0.029
	Body mass index	0.137	0.036
	Fat-free mass	0.291	0.052
	Body weight	0.963	0.064
	Fat mass	−1.654	0.673
	R = 0.430		

[a)]SI indicates calcaneal bone stiffness, SI = 0.67 × BUA + 0.28 × SOS–420.
[b)]Physical activity: 20 min brisk walking, fitness training or sport.

4. Discussion

4.1. Main findings

We found that 34% of young women (29.9 ± 7.8 yrs) with opioid dependence had abnormally low bone quality. Data on the effect of illicit drug use on bone quality of young women are limited. Kim et al. (2006) reported that 74% of the women, median age of 42 years, with a history heroin use (14 yrs) and now MMT (3 yrs) had osteopenia and osteoporosis. Our data showed a lower prevalence of osteopenia and osteoporosis than the result of Theresa et al. It may be due to our sample's lower average age and lower duration of drug intake. Meanwhile, Fraser et al. (2009) found that in patients who received long term opiates to relieve the pain, osteopenia was reported in 21% of women (38.6 ± 7.2 yrs). The prevalence of osteopenia and osteoporosis was higher in our samples. It may be due to a regular intake of opiates for treatment in samples of Fraser et al. Moreover, in our study, the prevalence of low bone quality in patients was twice as high as compared to our healthy control women, and the average T-score of patients was much lower than that of healthy control women. Therefore, our results conformed the high prevalence of low bone quality in young women with illicit drug use.

Additionally, the risk of fracture is largely determined by two factors: 1.) peak bone quality achieved at skeletal maturity in early adulthood, and 2.) subsequent age- and hormone-related bone loss (Eisman et al., 1993; Hansen et al., 1991). Therefore, our findings indicated that young women with opioid dependence may be at a higher risk for fracture now and in the future than the general population.

Body composition was an important determinant of bone quality in general population (Lima et al., 2009). Our results further proved this point of view that FFM was more important than FM to bone quality of young women, though a substantial body of evidence indicated that FM may had beneficial effects on bone (Reid et al., 1992). Higher BW, FFM, and BMI lead to greater mechanical load on bone that results a better bone quality (Ehrlich and Lanyon, 2002). Meanwhile, as an important component of FFM, muscle contractions can produce mechanical stress, and the mechanical stress on bone would activate osteoblasts and increase bone formation (Schiessl et al., 1998). However, opioids may be involved in the reduction of osteocalcin, and directly interact with bone metabolism (Daniell, 2004; Rosen et al., 1998). Bone mass and quality in adults are maintained locally by the balance between osteoclastic bone resorption and osteoblastic bone formation (Takai et al., 1998). Drug addiction may tip the balance through decreasing the level of gonadal hormones, altering bone metabolism and other mechanism that has not yet been discovered (Katz and Mazer, 2009).

On the other hand, we found that the duration of drug intake (years) was the most important determinant of bone quality of young opioid dependent women. This was in accordance with the result on 144 men (44.2 ± 8.0) with long-term opioid dependence in Switzerland (Gotthardt et al., 2016), but we further supported this point of view in young women. Kay et al. (2010) reported that substance abuse in women yielded a higher risk of a variety of health problems than substance abuse in men. Opioid intake over a long period of time often induces hypogonadism owing to central suppression of hypothalamic secretion of gonadotropin-releasing hormone, and hypoestrogenism has been reported to be related with decreased bone quality, and would lead to osteopenia or osteoporosis (Meczekalski et al., 2010). In addition, as listed in Table 2, drug consumption is usually accompanied by specific risky life styles such as cigarette smoking, low physical activity, low dietary intake of calcium, and these risky life styles will make individuals more prone to bone loss (Gerdhem and Obrant, 2002).

4.2. Implications for the treatment of opioid dependence

The findings of our study are of importance because it could be helpful for rehabilitation centers to offer treatment programs. Increasing physician awareness of low bone quality in young opioid addicted women, especially in the long term drug addicted women, will allow for monitoring of bone health and therapeutic interventions to prevent or treat drug-induced osteoporosis.

In addition, we found several body composition parameters (BW, and FFM) and physical activity level had positive relationships with bone quality in young healthy control women, which may provide the guidance for the health services and treatment of opioid dependent women. Therefore, we put forward a research hypothesis that increasing the degree of FFM, and BMI through special physical training program could be a treatment for improving the bone health of women with drug addiction at the stage of recovery during detoxification in which stage the patients would not take the MMT. However, a prospective study should be taken to determine whether this is the case.

4.3. Strengths and limitations

The strengths of our study are that similar studies focusing on young opioid dependent women are scarce. Additionally, the presence of a local control group of age-matched women permits a real comparison with subjects who have very similar life conditions and who live in the same macro environment. However, our results should be interpreted in light of several limitations. Firstly, it is important to consider that different opioids (such as heroin and methadone) could exert different influences on bone quality. Thus, in our studies, we only choose the samples with long terms of drug addiction (> 4 years) and short term of MMT (within 4 months). Secondly, other issues such as serum concentrations of total testosterone, luteinizing hormone (LH) and sex hormone-binding globulin (SHBG) were not measured. Thirdly, we did not include measurements of bone status at other sites or use additional techniques such as DXA. However, QUS measurement has become an important modality for the assessment of osteoporosis status (Liu et al., 2012; Njeh et al., 1997).

4.4. Conclusions

In conclusion, our study confirmed the need of specific treatments for improving bone health in young opioid dependent women. We also provided cross-sessional evidence that higher levels of physical activity, FFM, and BMI were beneficial to bone quality in young healthy women.

However, further research should be undertaken to confirm these findings and to investigate whether such an approach could improve bone health of young opioid women at the stage of recovery during detoxification, and whether such an approach could also be used in adolescent or elders.

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Ethical approvals

The study was approved by the local Institutional Review Board. All study participants were given written informed consent after the study was explained to them.

Contributors

Zenghui Ding on all aspects of the study and paper writing. Ming Jiang contributed to data collection. Xu zhou played a key role in service user engagement. Xi Wang, Yang Xu and Zuchang Ma led on the statistical analyses. Yanyan Chen and Yining Sun wrote sections of the paper, with input from Xi Wang & Yang Xu. All authors contributed to the design of the study and approved the final draft of the manuscript.

Conflict of interest

There are no financial or other relations that could lead to a conflict of interest.

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