Insecure attachment style predicts low bone mineral density in postmenopausal women. A pilot study

Lo stile di attaccamento insicuro è un fattore di rischio di ridotta densità minerale ossea in donne in menopausa. Uno studio pilota

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SUMMARY. Introduction. Major depressive disorder (MDD) and osteoporosis are two common disorders with high morbidity and mortality rates. Conflicting data have found associations between MDD and low bone mineral density (BMD) or osteoporosis, although causative factors are still unclear. A pilot study was designed with the aim to assess the relationship between MDD and BMD in postmenopausal women with MDD compared to healthy volunteers. We hypothesized that attachment style (AS) mediated this relationship. **Methods.** The sample was made of 101 postmenopausal women, 49 with MDD and 52 age-matched healthy volunteers. Structured clinical interview and Beck Depression Inventory (BDI) were performed to assesse MDD. AS was evaluated using the Relationship Questionnaire (RQ). BMD was measured by dual energy X-ray absorptiometry. **Results.** The univariate analysis showed that women with MDD had lower BMD values as compared to healthy volunteers. In the regression models MDD diagnosis and BDI score were not significant predictors of low BMD. The "preoccupied" pattern of insecure AS was a significant, independent predictor of decreased BMD in all skeletal sites: lumbar spine (p=0.008), femoral neck (p=0.011), total hip (p=0.002). **Conclusion.** This is the first study exploring the relationship between AS, MDD and BMD. Our results support the link between MDD and low BMD. We found that insecure AS was a risk factor for decreased BMD, regardless of depression. Insecure AS may play a role in the relationship between MDD and BMD or may constitute a risk factor itself. Therapeutic interventions focused on AS could improve psychiatric disorders and physical diseases related to low BMD.

KEY WORDS: attachment style, bone mineral density, major depressive disorder, osteoporosis, postmenopausal women.

RIASSUNTO. Introduzione. La depressione maggiore (MD) e l'osteoporosi sono malattie ad alta prevalenza nel genere femminile, associate a morbosità e mortalità. Sebbene alcuni studi abbiano dimostrato un'associazione tra MD, ridotta densità minerale ossea (BMD) e osteoporosi, non sono stati chiariti i meccanismi causali. Lo stile di attaccamento insicuro è stato messo in relazione con la patogenesi e il decorso di malattie croniche come la MD e le malattie cardiovascolari. Obiettivo di questo studio pilota è esplorare la relazione tra MD e BMD. Si ipotizza che lo stile di attaccamento possa agire da mediatore. **Metodi.** Il campione è formato da 101 donne in menopausa, 49 con MD e 52 controlli sani. La diagnosi di MD è stata formulata con l'intervista clinica e la Beck Depression Inventory. Lo stile di attaccamento è stato esplorato usando il Relationship Questionnaire, la BMD con la Mineralometria Ossea Computerizzata con tecnica DXA (Dual energy X-ray Absorptiometry). **Risultati.** L'analisi univariata ha mostrato che le donne con MD avevano valori di BMD inferiori rispetto ai controlli sani. Nelle analisi di regressione multipla la MD non è emersa come predittore significativo di ridotta BMD. Lo stile di attaccamento insicuro "preoccupato" è risultato un predittore significativo di ridotta BMD in tutti i siti scheletrici misurati con la DXA: colonna vertebrale lombare (p=0,008) e segmenti femorali: "femoral neck" (p=0,011), "total hip" (p=0,002). **Conclusioni.** Questo è il primo studio che esplora il possibile ruolo di MD e stile di attaccamento sulla BMD. Lo stile di attaccamento è risultato un predittore di ridotta BMD, indipendentemente dalla MD. L'attaccamento insicuro potrebbe avere un ruolo nella patogenesi dell'osteoporosi anche indipendente dalla MD. Se questi risultati saranno confermati, gli interventi terapeutici focalizzati sullo stile di attaccamento potrebbero contribuire al miglioramento della comorbilità psichiatrica e medica legata all'osteoporosi.

PAROLE CHIAVE: stile di attaccamento, depressione, menopausa, donne, osteoporosi, densità minerale ossea.

INTRODUCTION

Major depressive disorder (MDD) and osteoporosis are two common disorders with high morbidity and mortality rates[1]. According to the World Health Organization (WHO), it has been estimated that by 2020, MDD will be one of the leading causes of years lived with a disability[2]. It is worth noting that this development is not only attributed to depression itself, approximately half of the patients with MDD have at least one co-morbid either psychiatric or medical illness[3]. Major depression has been associated with accelerated bone loss leading to the development of low bone mineral density (BMD) and osteoporosis[4-6]. Even though, some data investigating the effects of depression on BMD have yielded divergent results, accounting for the exclusion of MDD from recognized cause of osteoporosis[7]. Given that 20%-30% of postmenopausal women with osteoporosis have a secondary cause, diagnosing secondary osteoporosis is mandatory to provide appropriate interventions[8]. Two main factors might explain the failure in demonstrating a putative link between MDD and low BMD. The first of these factors is methodological. As clearly suggested by a recent meta-analysis, a significant association between MDD and lower BMD was found among women diagnosed by a psychiatrist, compared to self-reported screening questionnaires[9]. The second factor is about the etiology of the association between MDD and BMD. In subjects with MDD, the role of various causative factors of low BMD has been discussed. These include the hypothalamic-pituitary-adrenal (HPA) axis hyperactivity[10], imbalance of inflammatory cytokines[11], impairment in gonadal hormones levels, lifestyle[12], and antidepressant intake[13]. In this study we aimed at investigating the possible contribute of further psychiatric variables in determining the interplay within MDD and decreased BMD. In particular, we focused on adult attachment style (AS). Adult attachment style is conceived as an attribute of the personality arisen from early life experiences with caregivers and representing the style of relating in adult close relationships. According to AS theory[14], people differ in the degree to which they believe close others will be supportive and available in times of need. Therefore, through previous relationships, people develop different "internal working models" of their close relationships that include sets of expectations, beliefs, and desires about whether the other will be responsive and whether the self is worthy of love[15]. These distinct working models lead by example in adult relationships and help individuals manage daily life stressors[16]. A growing literature made out the association between AS and MDD. A secure AS is needed for healthy development[17]. Insecure AS is an established factor that underlies the development and the course of MDD[18]. Furthermore, AS has been linked to the development of different diseases and non-communicable diseases, such as cardiovascular diseases, physical pain, and gastroduodenal ulcers[19]. AS may influence the course of chronic diseases by means of biological pathways, attitudes to support-seeking, and other illness-related behaviors[20,21]. To the best of our knowledge, there are no published studies investigating a potential link between AS and BMD. The present pilot study aimed at confirming whether MDD is a risk factor for low BMD among postmenopausal women, and exploring the mediating role of insecure AS.

MATERIALS AND METHODS

Participants

From September 2012 to September 2013, postmenopausal women with a MDD diagnosis from the outpatient program at "Tor Vergata" University Psychiatry Clinic were considered for the study. Inclusion criteria were a current depressive episode and being less than 70 years of age. Exclusion criteria were a history of eating disorders and, in the six months prior to the study, a history of alcohol and/or substance abuse. Postmenopausal HV of comparable ages and socio-economic status without a personal and familial history of psychiatric disorders were recruited as controls. To counter a potential confounding effect of bone turnover, three additional exclusion criteria in both groups were introduced: a history of rheumatoid arthritis, vitamin D deficiency[22], and chronic use of corticosteroids. Of the 101 women enrolled in the study, the 49 affected by a current episode of MDD comprised the MDD group and the 52 healthy postmenopausal women comprised the HV group. All women with MDD were medicated with SSRIs.

All study procedures and protocols were approved by the University Intramural Ethical Committee. Participants were provided written and oral information about the study prior to enrollment and were informed that they could withdraw from the study at any point, without detriment.

Measures

All participants were administered an accurate, semi-structured clinical interview in order to identify predictors of low BMD, including current smoking habit, diagnosed osteoporosis, type 1 diabetes, hyperthyroidism, and antidepressant drug therapy in the six months prior to the study.

Experienced clinical psychiatrist administered the Mini-Plus International Neuropsychiatric Interview (MINI-Plus) to verify the diagnosis of MDD or the absence of psychiatric disorders[23].

The Beck Depression Inventory (BDI) was administered to measure the severity of current depressive symptoms. BDI is a 21 item self-report instrument using a four-point scale ranging from 0 (symptom not present) to 3 (symptom very intense). Women were asked to place a mark next to the statement best describing how they felt over the week prior to the study for each of the 21 items[24].

Adult AS was assessed using the Relationship Questionnaire (RQ). Participants were instructed to interpret the questionnaire in reference to all their close relationships with peers (whether romantic or not). The RQ is a single-item measure comprising four short paragraphs, each describing a prototypical attachment pattern as it applies in close adult peer relationships. For each of the four descriptions, the respondents indicate how well it describes or relates to themselves on a seven-point rating scale. RQ provides a four-category model of AS based on the four combinations obtained by dichotomizing the subject's mental representations of the self (self "internal working model" on one axis) and the subject's image of the other (other "internal working model" on the orthogonal axis) into "positive" and "negative," based on their interpersonal relationships. This yields four attachment patterns: secure (positive self, positive other), preoccupied (negative self, positive other), fearful (negative self, negative other), and dismissing-avoidant (positive self, negative other)[25-27].

BMD was measured by Dual energy X-ray absorptiometry (DXA) at three skeletal sites, lumbar spine (L1-L4) and the prox-

imal femur (femoral neck, total hip). According to WHO, DXA is the gold standard method of measuring BMD and has widespread use because of its reliability, non-invasiveness, minimal radiation exposure, and short-term procedure preparation requirements. BMD determination is the main tool for assessing osteoporosis.

Statistical analysis

Since the DXA indices showed a non-normal distribution, we logarithmically transformed these variables to obtain a better approximation to a Gaussian curve, achieving appropriate equivalence to a normal distribution (Kolmogorov-Smirnov test, $p>0.2$). We conducted t-tests and chi-square tests to compare differences between HV and MDD groups. Pearson's product-moment correlation analysis was performed for DXA indices and age, years since menopause, RQ scales, and total BDI score for the whole sample, HV-, and MDD group. Finally, multiple forward stepwise regression analysis was used to identify significant independent predictors of DXA indices by selecting independent variables among those that were found to be significant in the univariate and correlation analyses. Statistical significance was set at $p<0.05$.

RESULTS

Descriptive and univariate analysis of socio-demographic and clinical characteristics are reported in Table 1. Compared to the HV group, the group with MDD had a higher total BDI score and lower BMD values.

Correlation analysis

In the whole sample, significant negative correlations were found between "fearful" RQ scale and BMD values of the three skeletal sites: lumbar spine ($p=0.008$), femoral neck ($p=0.019$), and total hip ($p=0.017$). We also found significant negative correlations between "preoccupied" RQ scale and BMD values of two of the three skeletal sites: femoral neck ($p=0.013$), and total hip ($p=0.024$) among all participants. The correlation analysis yielded different results when MDD and HV groups were analyzed separately. For the MDD group, a significant negative correlation was found between "fearful" RQ subscale and femoral neck ($p=0.008$) and total hip BMD values ($p=0.031$) and between the "dismissing" RQ subscale and femoral neck BMD values ($p=0.023$). No significant correlations were found for HV group. Furthermore, the relationships between BMD values and MDD onset, as well as between duration and episode number were not significant (Table 2).

Regression analysis

We developed three regression models, one for each region of BMD measurement (dependent variable). Years since menopause, total BDI score, "preoccupied," "fearful," and "dismissing" RQ scales, and the grouping factor "HV vs. MDD" were entered into the regression models as independent variables. Results of the regression analyses are reported in Table 3. The regression models were able to significantly predict BMD values for spine (L1–L4), femoral neck, and total hip, explaining 6% to 18% of the variance. The "preoccupied" RQ scale was an independent significant predictor in the three regression models. Years since menopause emerged as significant predictor in the femoral neck and total hip regression models. Other variables did not significantly predict BMD values in the three regression models.

Table 1. Descriptive and univariate statistics of socio-demographic and clinical characteristics.

	HV (n = 52)	MDD (n = 49)	Statistics
age	58.04 (±6.65)	60.02 (±6.51)	t_{99}=-1.512, p=0.134
years since menopause	9.08 (±6.90)	11.06 (±8.46)	t_{99}=-1.295, p= 0.198
smoke	50%	33%	χ^2_1=3.125, p=0.078
osteoporosis familiarity	27%	41%	χ^2_1=2.181, p=0.140
hypertension	35%	37%	χ^2_1=0.049, p=0.824
thyreopathy	29%	27%	χ^2_1=0.068, p=0.795
diabetes	6%	14%	χ^2_1=2.051, p=0.152
RQ – confident	27%	19%	χ^2_3=4.078, p=0.252
RQ – preoccupied	19%	25%	
RQ – fearful	12%	25%	
RQ – dismissing-avoidant	42%	31%	
MDD onset	–	40.76 (±11.33)	–
MDD duration	–	19.27 (±9.37)	–
MDD episode number	–	2.18 (±0.49)	–
BDI	3.94 (±2.75)	20.37 (±8.48)	t_{99}=-13.260, p<0.0001
L1-L4 BMD	1.11 (±0.23)	1.03 (±0.15)	t_{99}=2.013, p=0.047
femoral neck BMD	0.85 (±0.14)	0.80 (±0.10)	t_{99}=1.855, p=0.067
total hip BMD	0.93 (±0.16)	0.86 (±0.14)	t_{99}=2.495, p=0.014

Data are showed as percentages and means (SDs).
HV: Healthy Volunteers; MDD: Major Depressive Disorder; BDI: Beck Depression Inventory; RQ: Relationship Questionnaire; BMD: Bone Mineral Density.

DISCUSSION

Our results showed that the group of women with MDD had lower BMD values compared to the HV. No differences were found between the two groups for other established risk factors of low BMD, such as family history of osteo-

Table 2. Correlation analysis results between DXA BMD scores and age, years since menopause, RQ subscales and BDI total score in whole sample, in Healthy Volunteers (HV) and in Major Depressive Disorder (MDD). Significant correlations are showed in bold (p<0.05); correlation values with a statistical trend (p<0.1) are in Italic.

WHOLE SAMPLE	**BMD L1-L4**	**BMD femoral neck**	**BMD total hip**
age	r=-0.056	r=0.085	r=0.056
	p=0.579	p=0.397	p=0.580
years since menopause	r=0.121	**r=-0.221**	**r=-0.202**
	p=0.227	**p=0.026**	**p=0.043**
RQ1 SECURE	r=0.043	r=-0.080	r=-0.066
	p=0.671	p=0.426	p=0.511
RQ2 PREOCCUPIED	**r=-0.262**	**r=-0.234**	**r=-0.238**
	p=0.008	**p=0.019**	**p=0.017**
RQ3 FEARFUL	*r=-0.179*	**r=-0.247**	**r=-0.224**
	p=0.073	**p=0.013**	**p=0.024**
RQ4 DISMISSING	r=-0.093	*r=-0.180*	r=-0.039
	p=0.354	*p=0.071*	p=0.697
BDI	*r=-0.195*	*r=-0.166*	**r=-0.277**
	p=0.051	*p=0.098*	**p=0.005**
HV	**BMD L1-L4**	**BMD femoral neck**	**BMD total hip**
age	r=0.089	*r=-0.262*	r=0.087
	p=0.529	*p=0.060*	p=0.540
years since menopause	r=-0.152	**r=-0.326**	r=-0.173
	p=0.282	**p=0.018**	p=0.221
RQ1 SECURE	r=-0.012	r=-0.031	r=0.008
	p=0.930	p=0.825	p=0.955
RQ2 PREOCCUPIED	r=-0.207	r=-0.140	r=-0.199
	p=0.141	p=0.321	p=0.158
RQ3 FEARFUL	r=-0.116	r=-0.010	r=-0.075
	p=0.413	p=0.943	p=0.597
RQ4 DISMISSING	r=0.054	r=-0.058	r=0.005
	p=0.706	p=0.684	p=0.971
BDI	r=-0.161	r=-0.024	**r=-0.288**
	p=0.256	p=0.868	**p=0.038**

(Continued)

(Continued) - Table 2.

MDD	**BMD L1-L4**	**BMD femoral neck**	**BMD total hip**
age	r=-0.108	r=-0.004	r=-0.106
	p=0.461	p=0.978	p=0.470
years since menopause	r=-0.152	r=-0.205	**r=-0.295**
	p=0.296	p=0.157	**p=0.040**
depression onset	r=-0.272	r=-0.278	r=-0.166
	p=0.058	p=0.054	p=0.253
depression duration	r=0.255	r=0.273	r=0.275
	p=0.078	p=.054	p=0.056
episode number	r=-0.007	r=0.142	r=0.064
	p=0.961	p=0.331	p=0.665
RQ1 SECURE	r=0.051	r=-0.157	r=-0.189
	p=0.728	p=0.282	p=0.193
RQ2 PREOCCUPIED	*r=-0.277*	*r=-0.276*	r=-0.230
	p=0.054	*p=0.055*	p=0.111
RQ3 FEARFUL	r=-0.193	**r=-0.377**	**r=-0.308**
	p=0.184	**p=0.008**	**p=0.031**
RQ4 DISMISSING	*r=-0.239*	**r=-0.324**	r=-0.140
	p=0.098	**p=0.023**	p=0.337
BDI	r=0.008	r=-0.022	r=-0.123
	p=0.956	p=0.881	p=0.400

porosis, thyroid diseases, hypertension, diabetes, and smoking. Afterwards, the results of the present study support the hypothesis that MDD represents an important though often disregarded risk factor for osteoporosis.

In this study, we adopted a rigorous recruitment procedure. Diagnosis of MDD included but was not restricted to self-report questionnaire[28]. For instance, we enrolled a sample of women whose clinical diagnosis was first developed through a self-report scale (the BDI) and then confirmed by a semi-structured interview (the MINI-Plus) conducted by the same psychiatrist. Moreover, we employed a sample of postmenopausal women, HV and with MDD, with the intent to minimize possible confounding factors such as hormonal, nutritional, and physical ones, which might be different before and after menopause[29].

The correlation analysis demonstrated that women with insecure AS, with preoccupied and fearful patterns, showed decreased BMD at the three skeletal sites (lumbar spine, femoral neck, and total hip). However, when analyzing the MDD group and the HV group separately, we found a significant correlation between insecure AS and BMD in the MDD group but not in the HV group. This result supported our hypothesis, that insecure AS influenced BMD only in women with MDD.

Table 3. Results of forward stepwise multiple regression models in whole sample. As reported in the table footnotes, all models were significant in predicting DXA indexes. For each model, β and p values were reported for the significant predictors.

	BMD L1-L4[a]	**BMD femoral neck[b]**	**BMD total hip[c]**
years since menopause		β=-0.274	β=-0.387
		p=0.004	p<0.0001
BDI			
RQ2 PREOCCUPIED	β=-0.262	β=-0.244	β=-0.299
	p=0.008	p=0.011	p=0.002
RQ3 FEARFUL			
RQ4 DISMISSING			
HV vs. MDD			

[a] adjR^2=0.060, $F_{1,99}$=7.322, p<0.0003; [b] adjR^2=0.112, $F_{2,98}$=7.310, p=0.001; [c] adjR^2=0.178, $F_{2,98}$=11.816, p<0.0001.

Finally, we wanted to determine the most suitable predictors of decreased BMD in the whole sample of the study. The regression models for the sample included the following variables as possible risk factors for decreased BMD: years since menopause, the four AS subscales (secure, preoccupied, fearful, and dismissing), current depression severity (measured by BDI total score), and the "HV vs. MDD" grouping variable. Surprisingly, both MDD diagnosis and depression severity, were not significant predictors of low BMD. We found instead that age and insecure AS were significant and independent predictors of low BMD. Therefore, insecure AS but not depression was found to be a risk factor for low BMD. This result pointed out that neither depressive symptoms nor MDD influenced BMD values. Older postmenopausal women with insecure AS were more likely to show a decreased BMD at all skeletal sites.

At this stage, we can speculate about pathogenic pathways of low BMD in women with insecure AS. For instance, AS system is a psychological framework contributing to the stability and the flexibility of individual's participation in affective relationships[30]. In this perspective, due to the fact that AS is pervasively involved in all social situations, insecure AS may specifically, and perhaps more than secure AS[31], contribute to a wider range of pathogenic processes involved in reduced BMD. Individuals with insecure AS are deeply affected by their significant relationships, which evoke high levels of anxiety and fears of being abandoned[32]. Accordingly, it has been suggested that the way in which partners perceive and provide feeling to each other influences their cortisol responses[33]. A recent study supported the hypothesis that these links are different in women compared to men[34]. Data had consistently shown an increase in cortisol levels among individuals with insecure AS[35]. Therefore, those with insecure AS easily experienced social interactions as stressful, resulting in the activation of a chronic hyper-surveillance mechanism to deal with the intimidating environment, as perceived by them[36-38]. Through epigenetic pathways, this process could potentially modulate HPA axis activity, a principal stress-response system in humans, leading to the sustained release of cortisol[39]. Glucocorticoid is a well-documented cause of secondary osteoporosis, both in animal and in human models[40]. In individuals with insecure AS, HPA axis hyperactivity and imbalanced cortisol levels may cause changes in bone cell activity that affect expected bone turnover through the suppression of bone formation and the increase of bone resorption[41]. This cascade of events may result in decreased BMD. Further studies, including blood tests or saliva tests for the measure of cortisol levels and the possible HPA axis imbalance, are needed in order to understand the role of insecure AS on BMD, and to examine other factors influencing bone metabolism.

We acknowledge a main limitation of this study. Previous researches reported the association between antidepressant therapy and low BMD, independently from the effect of depression[42,43]. Antidepressant therapy could have been a confounding variable that we did not account, influencing the relation between MDD and BMD.

CONCLUSIONS

Our results suggest that insecure AS is a risk factor for lower BMD, regardless of depression. Attachment style, a psychological variable involved in all human relationships, may play a significant role in the complex interplay between depression and osteoporosis or may constitute a risk factor itself. Confirming or elucidating the influence of insecure AS could help us to comprehend the relationship between depression, AS, and BMD or osteoporosis. As osteoporosis and MDD are widespread disabling disorders, therapeutic interventions targeting insecure AS may further reduce the burden of these two diseases[44].

If the relationship between insecure AS and low BMD will be confirmed, we might expect that these therapeutic programs could be effective not only in improving psychiatric disorders but also physical diseases related to reduced BMD[45].

Conflict of interest: the authors declare that have no conflict of interest. The authors declare that the current study was conducted in conformity with the Helsinki Declaration concerning human rights and informed consent was obtained from each participant.

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