Increased Risk of Osteoporosis in Depressive Patients with Erectile Dysfunction: A Cross-sectional Study from Malaysia

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Background: Depression imposes numerous changes on depressive men, promoting for low bone mineral density (BMD) and erectile dysfunction (ED), yet no published data on exploring the possible association between these two disorders among depressive men. We therefore investigated whether low BMD is associated with ED among depressive men and highlighted the possible mutual underlying factors that might give rise to these two disorders in this specific group of patients. Materials and Methods: In this cross-sectional study, 119 depressive men were recruited and their sociodemographic and clinical characteristics were obtained. Erectile function was evaluated using the 5-item International Index of Erectile Function. All patients received a calcaneal BMD scanning. Chi-square test was conducted to determine if a significant association exists between ED and low BMD. Results: Of the study participants, ninety patients reported ED, while 29 patients reported no ED. Within the ED group, there was a significantly higher proportion of patients with low BMD compared to the non-ED group (85.6% vs. 62.1%, P = 0.006). In addition, among younger participants (i.e., aged <50 years old), the difference in T-score between ED patients (Md = −2.2, n = 41) and non-ED patients (Md = −1.3, n = 20) was significant (P = 0.001); but held no significance among older participants. Conclusions: While our findings are considered preatory, we reported that low BMD was significantly associated with ED in depressive men and that only among young depressive patients, BMD was significantly lower in ED patients compared to non-ED patients. More research investigating these findings and the possible underlying mechanisms for such association are warranted.

Keywords: Bone mineral density, depression, erectile dysfunction, men, osteoporosis

INTRODUCTION

Low bone mineral density (BMD) and microarchitectural deterioration are the two main characteristics of osteoporosis, which predispose an individual to fragility fractures and functional disability.[1] While it is mainly asymptomatic, osteoporosis is a progressive systemic disease with an estimation that more than 200 million people internationally are currently being affected.[2] As the population ages, the prevalence of osteoporosis in men is increasing. Even so, osteoporosis among male patients is overlooked, and its sequelae are unappreciated.[3] Erectile dysfunction (ED) is “the inability to attain and/or maintain penile erection sufficient for satisfactory sexual intercourse.”[4] The high prevalence of ED can be read from the results of several studies that were conducted across various populations,[5] pointing it as a significant public health problem that considerably affects men’s quality of life, with an estimation of more than 150 million men worldwide being affected.[6]
Depression is a prevailing mood disorder characterized by sadness, loss of interest, low self-worth, sleep or appetite disturbance, feelings of tiredness, and poor concentration. Depression afflicts more than 350 million people globally; it had also been ranked as the 11th greatest cause of disability and mortality in the world. Furthermore, the literature is overwhelmed with reports citing depression as a disease associated with a lot of other diseases, such as diabetes mellitus (DM), hypertension, and cardiovascular diseases (CVDs), and osteoporosis and ED are no exceptions.

The biological and behavioral changes, which transpire in depressive patients, adversely influence the bone health and sexual functioning of these patients. For instance, depressive patients have been reported with dysregulations in the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-gonadal (HPG), sympathoadrenal (SA), and somatotrophic axes. In addition, depressive patients have higher free serotonin levels and elevated inflammatory biomarkers. Moreover, these patients tend to practice unhealthy lifestyle, such as smoking and physical inactivity. Through these changes, depression might promote the development of osteoporosis and ED as well.

In fact, various studies documented a significant association between depression and osteoporosis. It is even proposed that such association is more remarkable in men than in women. Several mechanisms have been postulated to explain the composite relationship between depression and osteoporosis, suggesting for different underlying biological, behavioral, and medical factors.

By the same token, the association between depression and sexual dysfunction is well established, with a relatively high prevalence of ED among depressive men. While the link between depression and ED considered multifactorial, scholars, in an effort to gauge the connection between both, propose several factors, which include psychosocial, biological, and medical constructs.

Given that depression imposes several mutual risk factors for the development of osteoporosis and ED, we hypothesized that, among depressive men, there is possibly a relationship between low BMD and ED. With the present study, we aimed to explore the hypothesized association between the two disorders in question among our depressive patients. To the best of our knowledge, no published reports have been offered in investigating such association between bone health and erectile function among depressive men although two recent studies documented an increased risk for osteoporosis in patients with ED, but not among depressive men.

In addition, the study meant to shed light on the shared etiological pathways and risk factors for bone loss and ED that are specifically appertained to depressive men.

**Materials and Methods**

**Study design and participants**

This study is an observational cross-sectional study that was conducted at three psychiatric departments, from three general hospitals in Malaysia. The inclusion criteria included only adult male patients, who were diagnosed with major depression disorder (MDD) for at least 3 months before the investigation. The diagnosis had to be confirmed by the departments’ psychiatrists as per the Malaysian Guidelines in the Management of MDD, which adopts internationally accepted diagnostic criteria, i.e., the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition or the International Classification of Diseases, Tenth Revision. Since steroids and thyroxin had been proposed to be involved in osteoporosis development, a patient was excluded from the study if he had current and lifetime history of corticosteroids or thyroid hormone, as well as therapy for osteoporosis, including Vitamin D or calcium supplements.

First, we scrutinized the records of the included psychiatric departments and identified 356 male patients with depression. From those patients, we recruited the study participants while considering their eligibility for enrollment based on our inclusion/exclusion criteria. All procedures performed in this study were in accordance with the ethical standards of the Medical Research Ethical Committee, Ministry of Health, Malaysia (approval number: NMRR-14-310-19812, dated October 21, 2014), and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All participants provided written informed consents after the study had been fully explained. To ensure participants’ confidentiality, results of data analysis were displayed without proclaiming of any information that denotes participants’ identities. The final sample gathered was accumulated over consecutive admissions to the participating psychiatric units over almost 10 months (from May 2015 to March 2016).

**Measures**

**Sociodemographic and clinical information**

This included patient’s age (in years), weight and height, basic clinical characteristics (i.e., comorbidities, medications), current alcohol consumption, as well as current smoking status.

**Bone mineral density measurement**

To measure the peripheral BMD, all participants underwent calcaneal quantitative ultrasound (QUS)
scanning, using OsteoSys SONOST-3000 manufactured by OsteoSys Co., Ltd., Seoul, Korea. Indeed, QUS method offers an alternative way for bone status evaluation when the limited access to the dual-energy X-ray absorptiometry (DXA) is an issue, and the aim is to screen for osteoporosis. Based on the recommendations of the International Society of Clinical Densitometry, the only accepted QUS measure for defining clinically the status of bone health is the calcaneal QUS.[20] Besides, the measured calcaneal BMD by QUS was efficient and analogous to the measured hip BMD using DXA in hip fracture prediction.[21]

To ensure that the QUS device was generating accurate measures, daily calibration of the device was performed by means of a phantom provided by the manufacturer. The device uses the ultrasound pulse penetration technique that computes the speed of sound.[22] Subsequently, the T-score is instantly derived. The T-score, which is used to describe the BMD, is defined as the number of standard deviations above or below the mean BMD of a healthy, young adult. According to the WHO diagnostic criteria for osteoporosis, peripheral BMD measured in this study gave an estimation of the osteoporotic condition of the participants as per the followings: A T-score of −1 or more denotes normal BMD, whereas a T-score < −1 indicates low BMD with unhealthy bone condition; i.e., osteopenic (−1 > T-score > −2.5) or osteoporotic (T-score ≤ −2.5) bone status.[23]

**Erectile function measure**

The 5-item International Index of Erectile Function (IIEF-5) was used to evaluate erectile function, with a maximum score of 25.[24] Using a cutoff score of <22 points, the IIEF-5 showed a sensitivity of 98% and a specificity of 88% for the detection of ED presence and its severity. Accordingly, a score of 22 or more indicates normal erectile function, whereas lower score denotes ED of increasing severity. In this study, we used the translated and validated Malay version of the IIEF-5, which possesses favorable measuring properties in research domain and clinical practice.[25]

**Statistical analysis**

Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Descriptive statistics were used to report patients’ characteristics. For inferential analysis, Chi-square test or Fisher exact test was used for categorical variables, whereas for continuous variables, independent sample t-test or Mann–Whitney U-test was used. The significance of statistical analyses was deemed at P < 0.05 (two-tailed).

**RESULTS**

**Study sample**

A total of 167 depressive men were approached, forty patients of them did not fit our inclusion criteria while eight refused to participate. Hence, 119 patients were finally recruited. Of the study participants, 90 patients (75.6%) had ED, while 29 patients (24.4%) had normal erectile function.

**Comparison of the two groups of the study participants**

Table 1 demonstrates the sociodemographic and clinical characteristics of ED patients versus non-ED patients. The yield of T-score values showed that within the ED group, the proportion of patients who had low BMD (85.6%) was significantly greater than the proportion of patients who had low BMD (62.1%) in the non-ED group, \(\chi^2[1, 119] = 7.51, P = 0.006, \phi = 0.25\). In addition, there was a higher proportion of DM among ED patients compared to non-ED patients \(\chi^2[1, 119] = 4.49, P = 0.034\). There were no statistical differences between the two groups with respect to any other characteristics under consideration.

**T-scores of patients with erectile dysfunction versus patients without erectile dysfunction**

Between-group difference of the T-score values returned a statistically significant difference in T-scores between ED group \(Md = −2.2, n = 90\) and non-ED group \(Md = −1.3, n = 29\), \((U = 678, Z = −3.9, P < 0.0001)\). Furthermore, patients were categorized into two groups based on their age, while considering an age of 50 years old as a cutoff point.[26] Sixty-one patients were younger than 50 years old (51.3%) whereas 48.7% of the study participants aged 50 years old or more \((n = 58)\). We revealed a statistically significant between-group difference in T-score among younger patients, but not the elderly patients [Table 2]. Younger patients with ED showed a statistically significant lower T-scores \(Md = −2.2, n = 41\) compared to those with no ED \(Md = −1.3, n = 20\), \((U = 187, Z = −3.4, P = 0.001)\).

**DISCUSSION**

In the current study, examining the association between ED and low peripheral BMD in depressive men revealed a significant result with a small-sized effect. Depressive patients with ED had a significantly higher rate of low BMD compared to non-ED patients; thus, they were more prone to develop osteoporosis. Noticeably, younger participants with ED had lower BMD compared to younger participants with no ED; however, this significant difference was not observed among older participants, which was in parallel with the findings of a population-based study by Wu et al. in 2016, among nondepressive participants.[17]
Table 1: Demographic and clinical characteristics of the 119 study participants

| Characteristic                  | ED group (n=90), n (%) | Non-ED group (n=29), n (%) | P     |
|--------------------------------|------------------------|----------------------------|-------|
| Age (years), mean (SD)         | 50.0 (11.7)            | 46.9 (8.4)                 | 0.12* |
| BMI (kg/m²), median (range)    | 25.4 (16.5-36.6)       | 25.9 (16.3-39.4)           | 0.13  |
| Low BMD                       | 77 (85.6)              | 18 (62.1)                  | 0.0006|
| Current alcohol consumers     | 28 (31.1)              | 12 (41.4)                  | 0.31  |
| Current smokers               | 30 (33.3)              | 11 (37.9)                  | 0.65  |
| Use of antidepressants        | 82 (91.1)              | 25 (86.2)                  | 0.48  |
| Other medications             |                        |                            |       |
| Antihypertensives             | 7 (7.8)                | 1 (3.4)                    | 0.69  |
| Antihyperlipidemics           | 7 (7.8)                | 3 (10.3)                   | 0.70  |
| Comorbidities                 |                        |                            |       |
| DM                             | 27 (30.0)              | 3 (10.3)                   | 0.034 |
| HTN                            | 32 (35.6)              | 6 (20.7)                   | 0.17  |
| Hyperlipidemia                | 10 (11.1)              | 3 (10.3)                   | 1.0   |

Values are n (%) except for patient’s age and BMI. Significant P values are in bold. *Independent sample t-test, †Mann–Whitney U-test, ‡Low peripheral BMD as defined by T-score < −1, †Chi-square test, §Fisher’s exact test, §Most frequent. ED: Erectile dysfunction, SD: Standard deviation, BMI: Body mass index, BMD: Bone mineral density, DM: Diabetes mellitus, HTN: Hypertension.

Table 2: Between-group (i.e., erectile dysfunction and nonerectile dysfunction) differences in T-score, according to age (N=119)

| Age    | Groups                | T-scores | P*     |
|--------|-----------------------|----------|--------|
|        | Mean  | SD    | Median | Range  |        |
| <50 years | ED  (n=41) | −2.0 | 0.9   | −2.2   | −3.6-0.5| 0.001  |
| old   | Non-ED (n=20)        | −1.3 | 0.8   | −1.3   | −3.1-1.0| 0.001  |
| ≥50 years | ED  (n=49) | −2.2 | 1.0   | −2.3   | −4.1-0.9| 0.102  |
| old   | Non-ED (n=9)         | −1.6 | 1.1   | −1.6   | −3.7-0.4| 0.102  |

Significant P values are in bold. *Mann–Whitney U-test. SD: Standard deviation; ED: Erectile dysfunction.

These findings confirmed our hypothesis that low BMD is associated with ED among depressive men. In part, our findings concur with the findings of two recent studies, which revealed a significant association between low BMD and ED among their participants;[6,17] however, current study differs in the nature of the sample being studied, in that we focused on depressive men.

In fact, the research aiming to explore the link between the reduced BMD and ED is in its first steps, in addition, such link is likely to be complex. Yet, previous researchers had put their efforts to suggest for the underlying mutual pathways that bring about ED and osteoporosis in men,[6,17] but not specifically in depressive men. As a result, in an attempt to elucidate the mutual etiologies and risk factors for low BMD and ED among depressive men, the postulated mediating mechanisms of the two disorders, which might in part explicate their association among this group of patients, were provided while considering the major contributing factor, i.e., depression.

First, depressive patients have an activated HPA and SA axes, consequently, corticotropin-releasing factor is hypersecreted, which further centrally activates these two axes, resulting in higher cortisol levels.[11] Cortisol reduces the proliferation and differentiation of osteoblasts and promotes for osteoblasts and osteocytes apoptosis. It also increases urinary calcium excretion, while minimizing its absorption by the gut.[27] All these changes will result in reduced BMD, making a depressive patient at risk for osteoporosis. On the other hand, failure to initiate or retain relaxation of the corporal smooth muscle tissue can result from the autonomic sympathetic overactivation, which eventually leads to ED.[28] Moreover, the increased cortisol expedites vascular injury of endothelial cells;[29] it also suppresses the production of testosterone by the Leydig cells in the testicle, which subsequently causes ED.[30] Testosterone production can also be suppressed in depressive men owing to the dysregulated HPG axis.[11] It is known that sex steroids are key elements in the pathogenesis of male osteoporosis, as testosterone can stimulate osteoblast proliferation and reduce the apoptosis of osteocytes and osteoblast, which enhance bone formation.[31] ED patients have lower serum testosterone, whose level was found to be inversely associated with the incidence of ED.[32]

Through enhancement of the activity of osteoclasts, inflammatory biomarkers such as C-reactive protein, interleukin (IL)-6, IL-1, and tumor necrosis factor-alpha lead to increased bone resorption.[33] Observations from various studies revealed a negative correlation between IIEF-5 scores and the levels of several inflammatory markers.[34] Since depression is considered as an inflammatory state, it is not uncommon that higher levels of such biomarkers had been reported in depressive patients.[13]
Another interesting finding among depressive patients is the reduced growth hormone (GH) secretion with the disrupted somatrophic axis.[11] GH exerts its effect on bone remodeling through stimulation of the activity and proliferation of both osteoblasts and osteoclasts promoting for bone formation and resorption, respectively. As a result, there is an increase in bone remodeling; however, the net effect is that bone accumulation eventuate.[35] Equally important, it is possible that the reduced GH in depressive men may contribute in ED, as GH may facilitate both venous constriction and smooth muscle relaxation required for penile erection.[36]

When discussing bone health and erectile rigidity among depressive men, serotonin is of great interest. Depressive patients have demonstrated reduced concentration of platelet and neuronal serotonin,[27] resulting in higher level of circulating free serotonin.[12] The effect of serotonin on osteogenesis, through binding to the 5-hydroxytryptamine (5-HT) receptor 1b, varies based on its origin, in which the brain-originated serotonin stimulates bone formation, while the gut-derived serotonin inhibits bone formation.[14] However, the excess of free serotonin seen in depressive men might adversely affect bone mass through suppression of osteoblast proliferation.[38] The effect of the elevated serotonin bioavailability extends to inhibit sexual functioning as well, in which the serotonin-activated 5-HT2 and 5-HT3 receptors result in diminished sexual desire, erection, ejaculation and orgasm.[39,40]

Importance of the role of nitric oxide (NO) in bone health and penile erection has been studied by several scholars. NO can inhibit the proliferation of osteoclasts, which in turn suppresses bone resorption.[61] It is also known that NO is a crucial mediator in the penile erection, given its role in cavernosal smooth muscle relaxation.[42] Although NO levels has been revealed to be high in depressive patients[43,44] but, nonetheless, antidepressants-treated depressive patients showed reduced NO levels compared to control subjects.[45]

Another imperative issue affecting BMD and erectile function is the unfavorable health behaviors practiced by depressive men, which are known risk factors for osteoporosis and ED. It is reported that decreased physical activity, increased rate of smoking, and alcohol consumption, as well as poor nutrition and less daylight exposure, which result in lower levels of Vitamin D, all can negatively afflict BMD and possibly involved in osteoporosis development.[14] Likewise, physical inactivity adversely affects erectile function, and smoking and drinking alcohol are also related to ED incidence.[46,47] In addition, the reduced level of Vitamin D can contribute to endothelial dysfunction, which in turn increases the risk for ED development.[17]

Depression is frequently regarded as a disease associated with numerous disorders such as CVDs, type 2 DM, hypertension, and hyperlipidemia.[10] These diseases are known to be associated with osteoporosis[12,48-50] and ED[46] and might in part account for the relationship between these two disorders. Not to mention that certain medications consumed by depressive patients such as glucocorticoids, antihyperlipidemias, most of the antihypertensive medications, and specifically, antidepressants may accelerate bone loss[14,33,50,51] and precipitate ED.[46]

Focusing on antidepressants, it is worth mentioning that there is a significant evidence to support the relationship between the use of antidepressants and increased fracture risk, which was imputed to the influence of antidepressants on BMD.[14] In addition, 30%-60% was the estimate for the incidence of antidepressants-associated sexual dysfunction in several studies.[39]

The current study has several limitations. First, dietary habits, which may vary in the recruited patients, were not assessed. Consequently, remaining confounding possibly subsists since insufficient nutrition may affect BMD[52] and ED as well.[53] Second, owing to the cross-sectional design, one cannot conclude a causal relationship between ED and low BMD in depressive men. Our findings also cannot be generalized owing to the relatively small sample size and the convenience sampling technique that we adopt for patients’ recruitment. Finally, since the current gold standard method for osteoporosis diagnosis is the DXA,[54] further confirmation with this technique is advocated.

**Conclusions**

An important finding of this study was not only supporting an incipient idea of the association between low BMD and ED but also extending it by providing an empirical evidence for such association among a particular population, that is, depressive men. Another key point is that low BMD is lower in depressive patients with ED compared to those with no ED, which is significant among the young, but not the elderly participants. Second, clinicians involved in the management of depressive men should pay heed to the probable comorbidity of ED as well as the potentially increased risk for osteoporosis in these patients.

Despite the limitations of this study, our results surface a new question about the possible association between ED and low BMD among depressive men given the
shared risk factors and the possible common underlying etiologies. Finally, we hope that our findings, together with those from the two preceding studies, will stimulate other interested scholars to further investigate such association in larger cohorts more profoundly.

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**Conflicts of interest**

There are no conflicts of interest.

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