Can depression influence bone density?

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INTRODUCTION: The link between depression and lowered bone mineral density (BMD) has been investigated using varying methods of BMD quantification (mainly DEXA and CT scans) and disparate tests of depression. The anatomical regions chosen for assessment of BMD also differ across studies. These distinct research methods have contributed to inconsistent results. There is therefore a great deal of controversy surrounding the depression-BMD debate.

Evidence to contradict findings of a link between depression and low BMD is found in the work of Yazici, *et al.,*[1] who found that mild to moderate depression in premenopausal females did not cause osteoporosis. Yazici and colleagues do suggest that factors such as duration of depression, number of episodes and cortisol levels may confound data. Reginster, Deroisy, Paul, Hansenne and Ansseau[2] also refute a link between depression and low BMD. There are also however, a number of works offering supporting evidence for the link.[3-7] The argument therefore continues over whether depression is a potential cause of osteoporosis, or whether the two are discrete clinical entities.[1]

The mechanism underlying the possible link between depression and low BMD also has need of elucidation. Brown, Varghese and McEwen[8] have proposed cortisol as a mediator in the relationship between depression and osteoporosis. The present study takes up this proposal and supplements it with the notion that the effectors of this relationship may also include pro-inflammatory cytokines.

Bone is built and maintained through the continual process of remodelling, which is mediated by a number of factors, including glucocorticoids and cytokines. Glucocorticoids and pro-inflammatory cytokines are linked to the activation of osteoclast activity and, therefore, resorption. The release of these substances is influenced by the HPA axis. One common finding in depression is hypercortisolaemia. Pro-inflammatory cytokines upregulate cortisol release. In a healthy person, increased cortisol levels are part of a negative feedback loop, which inhibit pro-inflammatory cytokine release. However, many depressed patients exhibit an unusual combination of hypercortisolaemia with concomitant excessive pro-inflammatory cytokine levels.[9-13] The dysregulation in the HPA axis that precedes or that is induced by depression is largely suspected of influencing BMD.[14] Figure 1 illustrates a proposed relationship between depression and BMD loss.

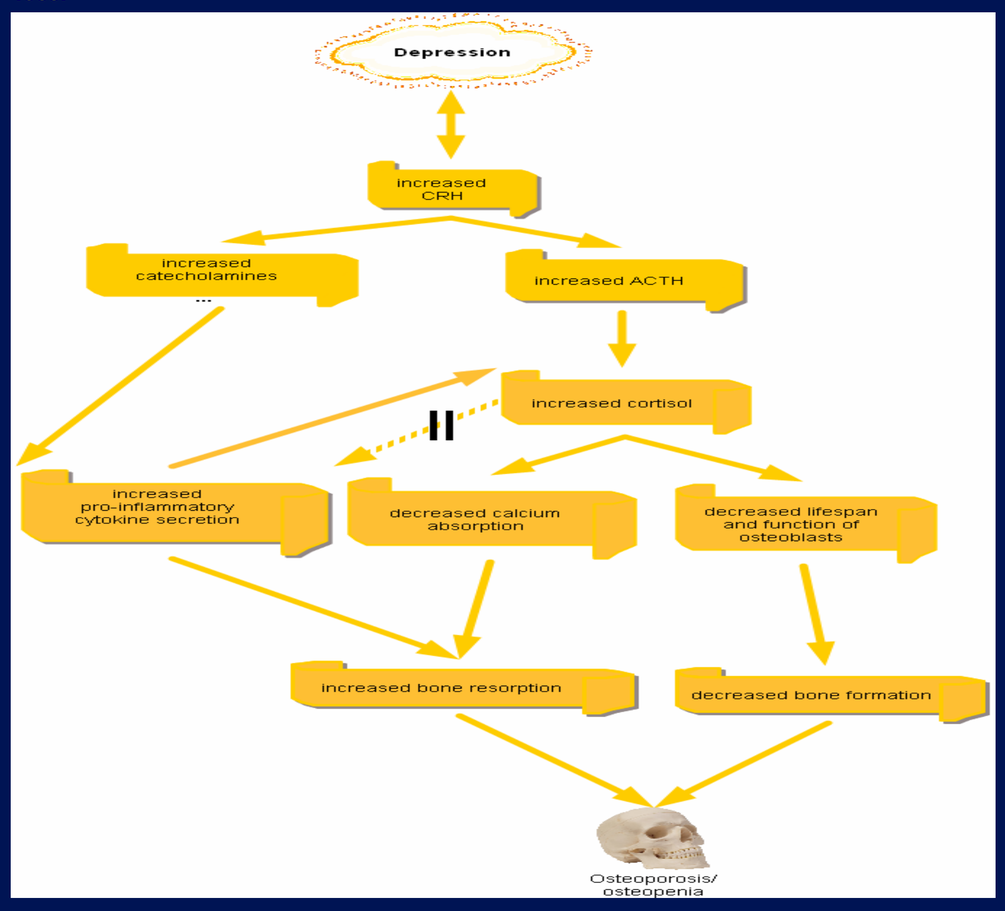

Figure 1 A proposed relationship between depression, low bone mineral density (BMD) and cortisol

AIM: The aim of this study was to investigate the possible association between depression and low BMD in premenopausal females.

METHOD: The study has two starting points (Study 1 and Study 2). The approaches to each are summarised in Table 1.

Table 1: The focal points and measures of Studies 1 and 2

	Study 1	Study 2
Focus	Do depression levels differ between premenopausal women with normal and low BMD?	Does BMD differ between premenopausal women that have been diagnosed with severe, recurrent major depression and their healthy cohorts?
Measures	BMD (DEXA); depression (Beck Depression Inventory, called the BDI[a] and the Psychological General Well-being Scale, abbreviated to PGW)[a]; 24-hour salivary cortisol (via ELISA)	As for Study 1, plus bone turnover markers (bone specific alkaline phosphate [BSAP], osteocalcin, urine pyridinoline cross-linked C-telopeptide [β-CrossLaps] and deoxypyridinoline [DPD] and cytokines [L-1β and TNFα via ELISA])
Sample	Random, volunteers, 3 recruitment sites, N=40	Psychiatric unit, volunteer controls from recruitment sites, N=9
Difficulties	Volunteer recruitment, time, finance-limited	

[a]: depression is indicated by a low PGW depression subscale score or by a high BDI score.

RESULTS of Study 1

Table 2: Demographics of the sample in study 1

Variable	Mean	SD	Minimum	Maximum
Age (years)	25.8	5.2	20	37
Height (cm)	167	6.6	155	178
Mass (kg)	60.9	9.0	40	80
BMI	21.7	3.1	15.6	30.1
Alcohol intake (units)	1.3	1.9	0	7

After collating the descriptive data from the questionnaires and the DEXA readings, two groups of subjects were identified – those with low BMD and those with normal BMD. All three readings for BMD were considered, namely total lumbar BMD, left femoral neck BMD and total left femoral BMD. Subjects with normal BMD on all three readings were classed in Group 1 and the rest of the subjects in Group 2. This was done to differentiate those with one or more low BMD readings from those with normal BMD. A Mann-Whitney test was executed to confirm that this division of groups was sound and that the groups did in fact differ significantly on BMD. The results of the test are noted in Table 3.10. DEXA results for the left femoral neck, the left femoral total and the total lumbar spine all varied significantly from Group 1 to Group 2, as did their T-scores: the difference between the two groups on the left femoral neck BMD showed a p-value of 0.0004 and 0.0008 on the T-score. The differences on the left femoral total score, the total lumbar spine score and their respective T-scores were all significant at $p < 0.0001$. This confirms that the division of groups was sound.

Table 3 Significant differences between premenopausal women (N=40) with normal (Group 1) and low (Group 2) BMD in Study 1

Characteristics	Group 1 (N=26)					Group 2 (N=14)					p-value
	Mean	SD	SEM	Min	Max	Mean	SD	SEM	Min	Max	
Age (y)	25.9	5.2	1.026	20	36	25.6	5.4	1.444	20	37	0.954
BMI (kg/m²)	22.6	3.1	0.616	18.4	30.1	20.0	2.1	0.571	15.6	22.3	0.032
Alcohol intake (alcohol units)	1.1	1.9	0.381	0	7	1.8	1.7	0.448	0	4	0.127
BDI raw score	7.6	6.9	1.349	0	32	5.7	5.9	1.581	0	21	0.249
PGW depression raw score	12.4	1.9	0.369	8	15	12.4	2.4	0.635	7	15	0.749

Significant correlations ($p \leq 0.05$) were found in Group 1 between left femoral neck T-score and BMI ($r = 0.388$; $p = 0.050$); left femoral total T-score and BMI ($r = 0.455$; $p = 0.019$); lumbar T-score and age ($r = 0.479$; $p = 0.013$). However, these correlations not strong. What they do indicate though, is that in females with normal BMD: the higher the left femoral neck BMD , the higher the BMI and that the older the female (range 20-37 years), the higher the lumbar BMD score. A significant correlation was found in Group 2 between left femoral neck T-score and the depression score on the PGW scale ($r = 0.669$; $p = 0.009$). This indicates that, with regard to women that fall into the low BMD category, the left femoral neck BMD is higher in females with low depression.

RESULTS of Study 2:

Table 4: Demographics of the women with severe, recurrent major depression (Group 1) and controls (Group 2) in Study 2

Variable	Mean	Median	Minimum	Maximum	Range	Interquartile range
Age: Group 1 (years) N=5	26.6	28	23	29	6	3
Age: Group 2 (years) N=4	25.5	23	23	33	10	5
BMI: Group 1 N=5	25.6	24.7	21.7	31.2	9.6	1.4
BMI: Group 2 N=4	21.9	21.4	20.2	24.8	4.6	2.9
Alcohol Intake (units): Group 1 N=5	3.6	2	0	11	11	3
Alcohol Intake (units): Group 2 N=4	2.5	1.5	1	3	2	5

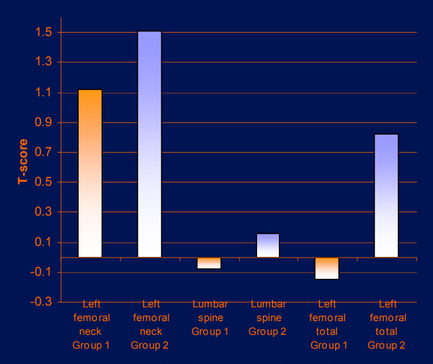

Figure 2: DEXA T-scores for Groups 1 and 2

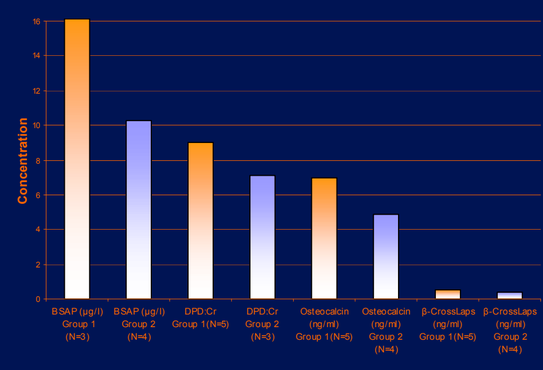

Figure 3: Bone turnover markers for Groups 1 and 2

A trend is noted of lower BMD, higher bone turnover and higher cortisol for Group 1 relative to the controls. In addition, Group 1's median IL-1β reading (14.669pg/ml) is well above the normative value of 4.721pg/ml. This indicates very high levels of this pro-inflammatory cytokine. There is also a great deal of variability between subjects (range and interquartile range = 11.374 and 7.982, respectively). However, the group's median TNFα reading is within the normative range (1.333).

SUMMARY: In Study 1: depressed patients were only moderately depressed ; cortisol levels were within normal range; only femoral neck T-score and depression correlation was significant ($r=0.669$; $p=0.009$). Study 2: depressed patients were diagnosed with severe, recurrent major depression; cortisol and IL-1β were elevated in these patients.

DISCUSSION: The degree of depression differed between the two studies. In contrast to Study 1, patients in Study 2 suffer from clinically diagnosed recurrent major depression. While Study 2 indicates a trend of association between depression, BMD and cortisol, Study 1 offers no substantial evidence for such a link. It appears therefore, that the effect of depression on bone density is dependent on the intensity and duration of depression and this may explain the marked differences in Study 1 and Study 2's results. IL-1β and cortisol may be instrumental in this form of BMD loss . This data should be supplemented with longitudinal studies and larger samples that are more representative of the population to resolve the question of whether or not depression can influence BMD.

REFERENCES
1. Yazici AE, Bagis S, Tot S, Sahin G, Yazici K, Erdogan, C. Bone mineral density in premenopausal women with major depression. Joint Bone Spine 2005; 72: 540-543.
2. Reginster JY, Deroisy R, Paul I, Hansenne M, Ansseau M. Depressive vulnerability is not an independent risk factor for osteoporosis in postmenopausal women. Maturitas 1999; 33: 133-137.
3. Schweiger U, Weber B, Deuschle M, Heuser I. Lumbar bone mineral density in patients with major depression: Evidence of increased bone loss at follow-up. American Journal of Psychiatry 2000; 157(1): 118-120.
4. Robbins J, Hirsch C, Whitmer R, Cauley J, Harris T. The association of bone mineral density in an older population. Journal of the American Geriatrics Society 2001; 49: 732-736.
5. Yazici KM, Akinci A, Sütçü A, Özçazar L. Bone mineral density in premenopausal women with major depressive disorder. Psychiatric Research 2003; 117: 271-275.
6. Mussolino M, Jonas, BS, Looker A. Depression and bone mineral density in young adults: results from NHANES III. Psychosomatic Medicine. 2004; 66(4): 533-537.
7. Kahl KG, Greggersen W, Rudolf S, Stockelhuber BM, Bergmann-Koester CU, Dibbelt L, Shweiger U. Bone mineral density, bone turnover, and osteoprotegerin in depressed women with and without borderline personality disorder. Psychosomatic Medicine 2006; 68:669-674
8. Brown ES, Varghese FP & McEwen BS. Association of Depression with Medical Illness: Does cortisol play a role? Biological Psychiatry 2004; 57:911-917.
9. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Molecular Psychiatry 2002; 7: 254-275.
10. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. Brain, Behavior, and Immunity 2007; 21: 374-383.
11. Parker KJ, Schatzberg AF, Lyons DM. Neuroendocrine aspects of hypercortisolism in major depression. Hormones and Behavior, 2003; 43, 60-66.
12. Yirima R, Goshen I, Bajayo A, Kriesel T, Feldman S, Tam J, Trembovler V, Csernus V, Shohami E, Bab I. Depression induces bone loss through stimulation of the sympathetic nervous system. Proceedings of the National Academy of Sciences of the USA, 2006; 103(45): 16876-16881.
13. Eskandari F, Martinez PE, Torvik S, Phillips TM, Sternberg EM, Mistry S, Ronsaville D, Wesley R, Toomey C, Sebring NG, Reynolds JC, Blackman MR, Calis KA, Gold PW, Cizza G. Premenopausal, Osteoporosis Women, Alendronate, Depression (POWER) Study Group. Low bone mass in premenopausal women with depression. Archives of Internal Medicine 2007; 167(21):2329-2336.
14. Simon NM, McNamara K, Chow CW, Maser RS, Papkostas GI, Pollack MH, Nierenberg AA, Fava M, Wong KK. A detailed examination of cytokine abnormalities in Major Depressive Disorder. European Neuropsychopharmacology 2008; 18: 203-233.