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Serotonin-norepinephrine reuptake inhibitor therapy in late-life depression is associated with increased marker of bone resorption

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Abstract

Purpose—Antidepressants have been associated with increased bone loss and fractures in older adults in observational studies, but the mechanism is unclear. We examined the effects of a serotonin-norepinephrine reuptake inhibitor, venlafaxine, on biomarkers of bone turnover in a prospective treatment study of late-life depression.

Methods—76 individuals aged 60 and older with current major depressive disorder received a 12-week course of venlafaxine XR 150-300mg daily. We measured serum C-terminal cross-linking telopeptide of type I collagen (β-CTX) and N-terminal propeptide of type I procollagen (P1NP), measures of bone resorption and formation, respectively, before and after treatment. We then analyzed the change in β-CTX and P1NP within each participant. Venlafaxine levels were measured at the end of the study. We assessed depression severity at baseline and remission status after treatment.

Results—After 12 weeks of venlafaxine, β-CTX increased significantly, whereas P1NP did not significantly change. The increase in β-CTX was significant only in participants whose depression did not remit (increase of 10% in non-remitters versus 4% in remitters). Change in β-CTX was not correlated with serum levels of venlafaxine or norvenlafaxine.

Conclusion—Our findings suggest that the primary effect of serotonergic antidepressants is to increase bone resorption. However, such an increase in bone resorption seemed to depend on whether or not participants' depression remitted. Our results are in agreement with prior observational studies reporting increased bone loss in older adults taking serotonergic

antidepressants. These negative effects on bone homeostasis could potentially contribute to increased fracture risk in older adults.

INTRODUCTION

One in seven community-dwelling older adults and up to half of nursing-home residents are prescribed antidepressants.[1, 2] This high rate of antidepressant use is potentially concerning, if there are issues with their safety in older adults. One critical issue is whether antidepressants, particularly serotonergic antidepressants (selective serotonin-reuptake inhibitors [SSRIs] and serotonin-norepinephrine reuptake inhibitors) negatively impact bone health in older adults.

There is substantial evidence linking serotonergic antidepressants to adverse bone health. Several *in vitro* and rodent studies suggest that antidepressants have negative skeletal effects, such as impaired bone formation and increased bone resorption, [3-8] though a few studies suggest beneficial effects of antidepressants.[9-12] In human observational research, several cross-sectional and prospective studies have reported an association between the use of antidepressants and declines in bone mineral density (BMD),[13-20] though other studies have found an absence of an association between antidepressant use and BMD. [21-24] Antidepressant use has also been associated with increased risk of fracture. [25-27]

The mechanism by which antidepressants impact bone health appears primarily via serotonergic pathways. Several serotonin (5-hydroxytryptamine; 5-HT) receptor subtypes, including the serotonin transporter (5-HTT), have been identified in osteocytes, osteoblasts and osteoclasts.[7] The mechanism of action of different classes of antidepressants appears to produce differential skeletal effects: several rodent and human observational studies have reported negative skeletal effects with serotonergic antidepressants (i.e. SSRIs, which block the 5-HTT) but not with noradrenergic antidepressants (i.e. tricyclic antidepressants, which block the norepinephrine transporter).[3, 5, 14, 17, 19] To date, no studies have examined the effects of serotonin-norepinephrine reuptake inhibitors, commonly-prescribed antidepressants which have a potency for 5-HTT similar to that of SSRIs. In summary, both animal and epidemiologic studies have reported an association between serotonergic antidepressant use and declines in BMD, suggesting that these antidepressants increase bone turnover. However, these studies have not yet confirmed the mechanism of this association. They also lack details on participant characteristics that might account for this association and they are potentially confounded by depression: several other studies have reported greater declines in BMD in participants with a history of depression, even after controlling for antidepressant use.[16, 20, 21, 28-35]

Because studies have suggested a correlation between antidepressant treatment and increased bone loss and fractures, we assessed bone turnover markers before and after treatment of late-life depression with venlafaxine, a serotonin-norepinephrine reuptake inhibitor. Venlafaxine was chosen based on prior research experience with it as an efficacious medication, both for treatment-naïve individuals and those nonresponsive to SSRIs.[36] Biochemical markers can detect rapid changes in bone resorption and formation, so they are well-suited to monitor potential short-term effects of a pharmacologic treatment

on bone remodeling, whereas changes in BMD may take months or years before they can be detected.[37, 38] Since venlafaxine is highly potent for 5-HTT, we hypothesized that we would observe a negative impact on bone health with an increase of beta-isomerized C-terminal cross-linking telopeptide of type I collagen (β-CTX) -- a marker of bone resorption —and a decrease of N-terminal propeptide of type I procollagen (P1NP) --a marker of bone formation--during treatment of late-life depression. We also investigated whether changes in β-CTX and P1NP varied as a function of whether or not participants attained remission from depression and were correlated with serum venlafaxine and norvenlafaxine levels.

METHODS

Participants

Data are from a prospective treatment study of late-life depression in which all participants were treated with venlafaxine (extended release capsules), conducted at three sites: University of Pittsburgh, University of Toronto/Centre for Addiction and Mental Health, and Washington University. Between July 2009 and June 2011, we recruited participants aged 60 and older presenting with a current major depressive episode of at least four weeks duration , as established by the Structured Clinical Interview for DSM-IV Axis I disorders[39] plus at least moderate depressive symptoms as defined by a score ≥15 on the Montgomery-Asberg Depression Rating Scale (MADRS).[40] The study protocol was approved by the institutional review boards of the three institutions, and all participants provided written informed consent. We excluded patients with: lifetime bipolar or chronic psychotic disorder; dementia; Mini-Mental Status Examination[41]≤20; alcohol or substance abuse within the past 6 months; unstable medical illness; treatment with corticosteroids; or contraindication to venlafaxine. From 122 participants, we assayed bone turnover markers in 76 participants who met the following additional criteria: completion of the acute treatment phase with detectable venlafaxine serum level; pre- and post-treatment serum collected within the recommended time-frame of 8:00 am to 11:00 am.[42]Of these 76, 30 were taking an SSRI or serotonin-norepinephrine reuptake inhibitor, and 6 were taking another antidepressant (bupropion or mirtazapine) at the time of consenting for the study and had these gradually tapered and discontinued, with no doses for at least two weeks prior to the baseline assessment.

Assessment

Participants underwent a comprehensive assessment at baseline, including assessment of global cognitive function and comorbid physical illness.[43, 44] Depressive symptoms were assessed before and during treatment using the MADRS.[40] Since depression status might affect bone turnover,[16, 20, 21, 28-34] we classified participants as either “remitters” (MADRS≤10 at end of the treatment phase) or “non-remitters” (MADRS>10).

Antidepressant Pharmacotherapy Protocol

Participants received open-label venlafaxine XR for 12 weeks starting with a dose of 37.5 mg/day, titrated to a target dose of 150 mg/day over two weeks. After six weeks of treatment, non-remitters (MADRS > 10) had their dose of venlafaxine XR increased (in 37.5-75 mg increments) to a maximum of 300 mg/day, while remitters stayed on the same

dose. At any time during treatment, participants who demonstrated distressing side effects could have their dose reduced or a slower titration. Adherence to venlafaxine was rated by asking participants at each visit whether they had missed any pills since the previous visit; by this measure, adherence was very high: at 93% of visits, participants reported missing no pills, 3% of visits missing 1 pill, 3% of visits missing 2 pills, and 1% of visits missing 3-4 pills.

Assays

Before treatment with venlafaxine and after 12 weeks of treatment, blood samples were obtained after an overnight fast. All samples were collected prior to 11:00 am and immediately cold-centrifuged and stored at – 80 °C until analysis. To examine bone resorption, we measured serum β -CTX, a product of collagen breakdown with an electrochemiluminescence immunoassay (β-Crosslaps/ serum, Core Diagnostics) with intra and interassay coefficients of variation (CV) of 1.0-1.3% and 1.1-1.6%, respectively. To examine bone formation, we measured serum P1NP with a radioimmunoassay (RIA; Core diagnostics) with an intra and interassay CV's of 6.1-7.9% and 4.3-4.7%, respectively. Serum venlafaxine and O-desmethylvenlafaxine (norvenlafaxine) were measured by an LC/MS/MS method developed at the CAMH Clinical Laboratory on the TSQ (triplequadruple) mass spectrometer (ThermoFisher). Briefly, 100 μL serum was extracted with ethyl acetate at alkaline pH. The dried extract was reconstituted and chromatographed on Kromasil C18 column with ammonium acetate-acetonitrile-formic acid mobile phase. Deuterated (D6) venlafaxine was used as internal standard. MS/MS analysis was in ESI positive mode, and the following mass transitions were monitored: 284→121 for D6-venlafaxine; 278→121 for venlafaxine; 264 → 107 for O-desmethylvenlafaxine. Assay was linear between 1-1000 ng/mL. The intra and interassay CV's were <10% for both venlafaxine and norvenlafaxine.

Analysis

Statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). Descriptive statistics for the entire study population were reported as means ± standard deviations (SD). Given the length of the current depressive episode in this sample (see Results: Participant Characteristics), we treated baseline results as a stable reflection of a chronic depressed state; therefore, our analyses assume that any changes in bone biomarker levels from pre- to post-treatment reflected either a direct pharmacological effect of venlafaxine, or an indirect effect via changes in depression. Therefore, our primary analysis was a within-subject change from pre- to post-treatment with paired *t* tests. Group differences were analyzed with *t* tests. The relationship of pre- and post-treatment markers of bone turnover was analyzed with Pearson correlation coefficients.

RESULTS

Participant Characteristics

The mean age was 68.9 (SD 6.8) years; most participants were female (64%) and Caucasian (91%). All females were post-menopausal. The mean baseline body mass index (BMI) was 30.4 (SD 6.9), and the mean post-treatment BMI was 29.6 (SD 6.4), not significantly

changed from baseline. Use of medications potentially affecting bone turnover was as follows: 26% took vitamin D, 21% took calcium, 5% took bisphosphonates and 5% took estrogen. No users of calcium, vitamin D supplements, bisphosphonates or estrogen discontinued such treatment during the study; and no non-users commenced treatment with these agents during the study. The mean Cumulative Illness Rating Scale for Geriatrics score was 10.2 (SD 3.9), reflecting moderate medical comorbidity. The mean baseline Repeatable Battery for the Assessment of Neuropsychological Status score was 94.5 (SD 18.0), indicating that this was a cognitively intact sample.

Baseline severity of depression was moderate, with mean MADRS score 26.9 (SD 5.5). The mean age of onset of depression was 38.0 (SD 23.6) years. The majority (75%) of participants had recurrent depression. The current depressive episode was chronic for participants: mean and median duration was 428 weeks (SD 860; median 76).

Bone Biomarker Changes

Figure 1 shows changes in P1NP and β-CTX from pre- to post-treatment. After 12 weeks of treatment with venlafaxine, β-CTX levels increased significantly from mean 390.3 (SD 202.0) to 421.5 (SD 218.2) pg/mL; t=2.33, N=76, p=0.02), whereas the change in P1NP level was not significant (reduction from 46.6 (SD 18.7) to 44.7 (SD 18.9) μg/L; t=-1.55, N=76, p=0.12).

To assess test-retest reliability, we examined pre- and post-treatment correlations of P1NP and β-CTX. Pre-treatment levels of both β-CTX and P1NP were highly correlated with their post-treatment levels (r=0.85, p< 0.001 and r=0.84, p<0.001, respectively), indicating good test-retest reliability.

Exploratory Subgroup Analyses

We examined whether changes in β-CTX differed in various subgroups based on demographics or co-prescribed medications that may impact bone metabolism (i.e., estrogen, bisphosphonates, calcium and vitamin D). Mean changes in β-CTX did not differ significantly between males and females: 38.7 (SD 97.0) vs. 27.1 (SD 126.8) pg/mL; t=-0.41, p=0.68. Due to the small number of minority participants, we did not perform sub-group analysis based on race. Mean changes in β-CTX did not differ significantly between participants taking one or more bone-protective medications (N = 26) and those not taking any bone-protective agent (N = 50): 34.8 (SD 125.0) pg/mL vs. 29.3 (SD 113.1) pg/mL; t=0.19, p=0.84. Since levels of β-CTX and P1NP have been reported to vary between seasons,[42, 45] we analyzed whether differences in pre- and post-treatment levels of β-CTX and P1NP could be explained by this seasonal effect; the mean changes in β-CTX levels did not differ significantly between groups for whom pre-treatment β-CTX was collected in winter or in another season --β-CTX: 48.4 (SD 132.1) vs. 31.5 (SD 122.2) pg/mL; t=- 0.40, df=37, p=0.69 -- P1NP: -0.7 (SD 12.1) μg/L vs. +1.0 (SD 10.2); t=0.44, df=37, p=0.66.

Finally, we examined whether pre-study antidepressant medication may have influenced the results. Of the 76 participants, 30 (39%) were taking an SSRI or serotonin-norepinephrine reuptake inhibitors at the time of consent, which were tapered and discontinued for at least two weeks prior to the baseline blood draw. These 30 who were tapered off of pre-study

serotonin antidepressants had a significant increase in β-CTX (change in β-CTX +50.7, SD 127; t=2.2, p=0.036) while the 46 who were not tapered off such antidepressants did not (change in β-CTX +18.5, SD 109; t=1.1, p=0.26). Further, the 30 who had pre-study serotonin antidepressants had a significant decrease in P1NP (-5.8, SD 9.6; t=3.3, p=0.003) while the 46 who did not had no significant change in P1NP (0.6, SD 10.8; t=0.4, p=0.71). We could not find any clinical or demographic variable that differentiated these two populations. A repeated-measures mixed model including time, pre-study serotonergic antidepressant, and their interaction found that the increase in β-CTX in the sample remained significant (model data for time: F=6.4, df=1,74, p=0.013; for pre-study antidepressant group: F=.71, df=1,74, p=0.40; for the interaction: F=1.4, df=1,74, p=0.24).

Remitter versus Non-Remitter Analysis

Remission from depression (final MADRS score<10) was achieved by 29 (38.2%) of the 76 participants, a rate similar to previous research with venlafaxine in late-life depression.[36] Figure 2 shows changes in P1NP and β-CTX in the remitters and non-remitters. β-CTX increased significantly only in non-remitters with an increase in β-CTX of 10% in non-remitters (mean change = 40.8 [SD 119.3] pg/mL; t=2.34, N=47, p=0.02), vs. 4% in remitters (15.7 [SD 112.3] pg/mL; t=0.75, N=29, p=0.46). No significant change was observed in P1NP for either nonremitters or remitters.

We examined whether any covariate differing between remitters and non-remitters could explain the difference in β-CTX change between these two groups. There were differences in gender: of the 29 participants who remitted, 23 (79.3%) were female and 6 (20.7%) were male. A total of 46.9% of females and 22.2% of males were considered remitters (χ^2 =4.5, p=0.03); however, as mentioned above, gender was not a predictor of bone biomarker changes. Baseline levels of β-CTX were not significantly different in non-remitters and remitters. Baseline depression severity (MADRS) scores were significantly higher in non-remitters than in remitters (28.1 (SD 5.3) vs. 24.9 (SD 5.4); t=2.50, p<0.05). However, baseline depression severity (MADRS) scores were not significantly correlated with changes in β-CTX (r=0.04, p=0.72). Final depression severity (MADRS) scores were not significantly correlated with changes in β-CTX (r=0.12, p=0.29). The change in depression severity (MADRS) scores were not significantly correlated with changes in β-CTX (r=0.11, p=0.37). Age of depression onset and mean duration of depressive episode were not statistically different in non-remitters and remitters. Another difference between the groups was that, as expected given the treatment protocol requiring a dosage increase in non-remitters, the mean final venlafaxine dose was significantly higher in non-remitters than in remitters: 282.5 (SD 42.0) mg/day vs. 206.9 (SD 64.7) mg/day; t=5.60, p<0.001. However, the mean final venlafaxine levels were not significantly different between non-remitters and remitters: 215.0 (SD 188.3) ng/mL vs. 172.8 (SD 168.1) ng/mL; t=0.99, p=0.33; similarly, norvenlafaxine levels were not significantly different between non-remitters and remitters: 331.1 (SD 137.3) ng/mL vs. 291.8 (SD 176.6) ng/mL; t=1.09, p=0.28; finally, the sums of venlafaxine and norvenlafaxine levels were not significantly different between non-remitters and remitters: 546.1 (SD 239.1) ng/mL vs. 464.6 (SD 318.8) ng/mL; t=1.27, p=0.21. Thus, we assessed whether the difference in venlafaxine exposure could explain the difference in β-CTX between remitter and non-remitter groups: venlafaxine dose was not correlated with

the change in β-CTX in either remitters (r=0.05, p=0.79) or non-remitters (r=0.11, p=0.45); venlafaxine levels were not correlated with the change in β-CTX in either remitters (r=-0.22, p=0.25) or non-remitters (r=0.02, p=0.88); similarly, norvenlafaxine levels were not correlated with the change in β-CTX in either remitters (r=-0.18, p=0.37) or non-remitters (r=-0.03, p=0.82); finally, the sums of venlafaxine and norvenlafaxine levels were not correlated with the change in β-CTX in either remitters (r=-0.22, p=0.27) or non-remitters (r=-0.00, p=0.99). Since change in weight may influence bone turnover markers, we compared change in BMI between remitters and non-remitters. The mean changes in BMI did not differ significantly between remitters and non-remitters: -0.69 (SD 1.96) vs.-0.86 (SD 3.93); t=-0.22, p=0.82. Similarly, baseline measures of medical comorbidity and cognition did not differ between remitters and non-remitters --mean CIRS-G scores: of 10.9 (SD 4.2) vs. 9.7 (SD 3.7); t=-1.38, p=0.17 --mean RBANS scores: 94.5 (SD 20.1) vs. 94.4 (SD 13.6); t=0.05, p=0.96.

Finally, we examined remitter status as a function of whether participants had been on a pre-study serotonin antidepressant; the two were not associated ($\chi 2$=0.07, p=0.79) and the remitter vs. nonremitter difference remained when dichotomized by pre-study antidepressant (β-CTX change for nonremitters on a pre-study serotonin antidepressant: +56.8 [SD 130.8]; for nonremitters not on a pre-study serotonin antidepressant: +30.8 [SD 112.7]; for remitters on a pre-study serotonin antidepressant: +41.6 [SD 125.4], for remitters not on a pre-study serotonin antidepressant: +2.6 [SD 101.9]). Thus, pre-study antidepressant status did not have any effect on the differences between non-remitters and remitters from depression in terms of β-CTX change.

DISCUSSION

In a prospective treatment study of late-life major depression, we found that treatment with venlafaxine, a serotonin-norepinephrine reuptake inhibitor, was associated with increased levels of β-CTX, a marker of bone resorption, without a compensatory increase in P1NP, a marker of bone formation. These findings suggest a net negative impact on bone metabolism, consistent with the results of the majority of observational studies reporting an association of serotonergic antidepressant use with greater declines in BMD in older adults. [14-20]

To our knowledge, this study is the first prospective clinical study to examine the effects of serotonin-norepinephrine reuptake inhibitor treatment on bone turnover markers in older adults. Our study adds to prior observational results in three major ways: first, our sample was well-characterized clinically. We used a standardized diagnostic instrument and a validated rating scale to confirm that all participants had a diagnosis of Major Depressive Disorder with depressive symptoms of at least moderate severity. We were also able to clarify whether participants' depressive episodes remitted with treatment. Also, we documented the exact duration and dose of antidepressant exposure, which we evaluated with serum drug levels, as well as adherence and switch from previous antidepressants. As a result, we were able to delineate pharmacological effects of antidepressant from the effects of the depressive illness or other issues with a level of precision not achievable in large observational studies.

Second, our study provides new information regarding the mechanism by which antidepressants affect bone metabolism. Our study assessed the effects of venlafaxine, a serotonin-norepinephrine reuptake inhibitor. While its potency at the 5-HTT is less than other SSRIs and it also inhibits the norepinephrine transporter, venlafaxine is considered serotonin selective because its potency at the 5-HTT is more than 100 times its potency at the norepinephrine transporter.[46] In addition, appreciable noradrenergic effects of venlafaxine are dose-dependent, yet we found no correlation between venlafaxine serum levels and change in bone turnover markers in our study. Therefore, we attribute the skeletal effects of venlafaxine primarily to its serotonergic properties.

Our findings suggest that the increased rate of bone loss with serotonergic antidepressants is primarily mediated via increased bone resorption. Serotonergic antidepressants may increase bone resorption by exerting their effects on osteoclasts via the serotonin transporter or other types of serotonin receptors, including subtypes 1B, 2A, 2B, 2C and 4. [10, 47] The substantial role of 5-HTT inhibition on bone health was supported by a study in mice demonstrating a negative skeletal phenotype from administration of fluoxetine and from a null mutation in the gene encoding for 5-HTT. [6] Serotonergic antidepressants may also enhance the differentiation of osteoclast precursors: an in vitro study reported that administration of low-dose fluoxetine resulted in increased differentiation of cells into osteoclast-like cells and increased their bone-resorption activity.(16) However, this same study and another in vitro study reported the opposite effect with higher doses of fluoxetine. [10, 47] In addition to the aforementioned peripheral effects, enhancing serotonin signaling in the central nervous system may alter various hormones, indirectly affecting bone metabolism.[6, 48] Finally, although effects on bone formation failed to reach significance in our study, it is also possible that serotonergic antidepressants decrease bone formation: in vitro and mice studies have reported inhibition of proliferation of osteoblasts and decreased bone formation with high dose fluoxetine. [6, 10] The potential role of norepinephrine-transporter inhibition is less clear. Several rodent and human observation studies have failed to find an association between noradrenergic (tricyclic) antidepressants and skeletal effects. [3, 5, 14, 17, 19]

A third new finding is that remission from depression apparently counteracts the direct pharmacological effect of venlafaxine on β-CTX. We observed a significant increase in β-CTX with venlafaxine treatment in non-remitters and no significant change in remitters. This difference cannot be explained by the higher doses of venlafaxine received by non-remitters, as venlafaxine and norvenlafaxine serum levels did not differ between groups and were not correlated with the change in β-CTX. Rather, our findings suggest a complex interaction between depression status, serotonergic antidepressant use, and bone metabolism. SSRIs and serotoninnorepinephrine reuptake inhibitors may increase bone resorption through a direct pharmacological effect, but effective treatment of major depression may provide an offsetting effect. This offsetting effect may have several explanations. For instance, depression remission may result in increased physical activity or reduced immobility. Also, negative biological effects of depression (e.g., elevation in cortisol or pro-inflammatory cytokines) may reverse with remission.[49, 50]

We found that treatment with venlafaxine *increased* β-CTX, but only in participants whose depression did not remit. To date, only one other prospective clinical study has examined the relationship between bone turnover markers and antidepressants. In that study, treatment with the serotonin reuptake inhibitor escitalopram significantly *decreased* β-CTX levels, but only in participants whose depression improved.[51] It is possible that escitalopram and venlafaxine have differential effects on β-CTX: although both have the main pharmacological effect of blocking the 5-HTT, venlafaxine also blocks the norepinephrine transporter albeit to a much lower degree.[46] Taken together, both studies suggest that negative skeletal effects of serotonergic antidepressants are not observed when such treatment leads to remission of depression.

While some research has suggested a dose-response relationship between serotonergic antidepressants and bone metabolism,[6, 10] we did not find a significant correlation of venlafaxine or norvenlafaxine levels, or dose, with change in bone turnover markers. One reason for this lack of correlation may be that all participants in our study received at least 150 mg/day of venlafaxine in order to ensure optimal treatment. In many settings, including observational studies, patients often receive lower (and possibly subtherapeutic) doses of antidepressants.[52] It is possible that a dose-response relationship may exist at doses lower than that used in our study.

One unexpected finding from this study was that change in both β-CTX and P1NP were associated with whether participants had been tapered off of a different serotonin reuptake inhibitor (either SSRI or serotonin-norepinephrine reuptake inhibitor) prior to starting in the study. In those individuals, β-CTX increased by a greater degree and P1NP decreased. We could not identify any clinical or demographic characteristic to explain these findings, and this covariate did not change our main results. Nevertheless, it appears that either coming off of a serotonin reuptake inhibitor may produce a rebound effect on bone biomarkers, or individuals with prior treatment resistance to serotonin reuptake inhibitors may have particularly deleterious bone marker changes. In either event, this is a limitation in the interpretation of our findings, given the bone remodeling extends over 6-9 months; future studies need to control for pre-study or pre-observation antidepressant use when examining bone biomarker changes during treatment with an antidepressant.

In this study, more females remitted from depression than males, and this difference was significant. However, gender differences in remission do not explain the differences in β-CTX between remitters and non-remitters: mean changes in β-CTX did not differ significantly between males and females.

Our study had some limitations. We did not have a placebo-control group; each participant served as their own control. Participants in our study had a median depression duration of 76 weeks. Since the participants in our study were stably depressed, the change in β-CTX observed over the course of this 12-week study should not be attributed to the effects of ongoing depression. This is supported by the fact that baseline β-CTX levels were not correlated with baseline depression severity or with depression remission status. Our findings cannot be attributed to non-adherence to venlafaxine treatment: one participant was excluded from the analysis due to treatment non-adherence (detected by nondetectable

venlafaxine levels); all other participants both had detectable venlafaxine levels and reported a high level of adherence. However, it is possible (albeit unlikely) that the non-remitted sample had increased bone turnover due to some other naturalistic or study-induced change, rather than the venlafaxine. Additional research in this area ought to include a randomized design with a non-serotonin reuptake inhibitor control such as Cognitive-Behavioral Therapy. We had inadequate power to detect whether depression remission status was a moderator of bone turnover marker change (i.e., whether the “difference in the differences” of β-CTX between remitters and non-remitters was significant) or to detect other possible moderators of the outcome of interest. A much larger study would be needed to detect such moderator effects.[53] Our study may also be underpowered to detect a smaller but potentially clinically significant medication effect on bone formation, as we saw a numerical but not statistically significant decrease in P1NP. Another potential limitation was the use of self-report to document venlafaxine adherence (although we also excluded individuals with no detectable venlafaxine in their blood). Finally, a longer follow-up would be required to assess whether the bone turnover changes we detected lead to bone loss and/or increase the risk of fracture.

In conclusion, this is the first study showing that antidepressant treatment in older adults was associated with an increase in β-CTX, a bone resorption marker. Our findings should not prompt clinicians to cease prescribing antidepressants to older adults because achieving remission from depression appeared to attenuate the negative skeletal effects of antidepressant treatment. It is also likely that untreated depression has negative effects on bone health. However, treatment with serotonergic antidepressants may require closer monitoring of bone health, particularly for patients whose depression does not remit. Given the very high prevalence of serotonergic antidepressant use in older adults [1, 2] and the high public health impact of bone health in this age group, these issues constitute a major public health concern. Additional longer-term studies are needed to assess the interaction among depression, serotonergic antidepressant use, and bone turnover marker change, examine their ultimate effects on bone health and fracture risk, and determine who is at high risk for these effects.

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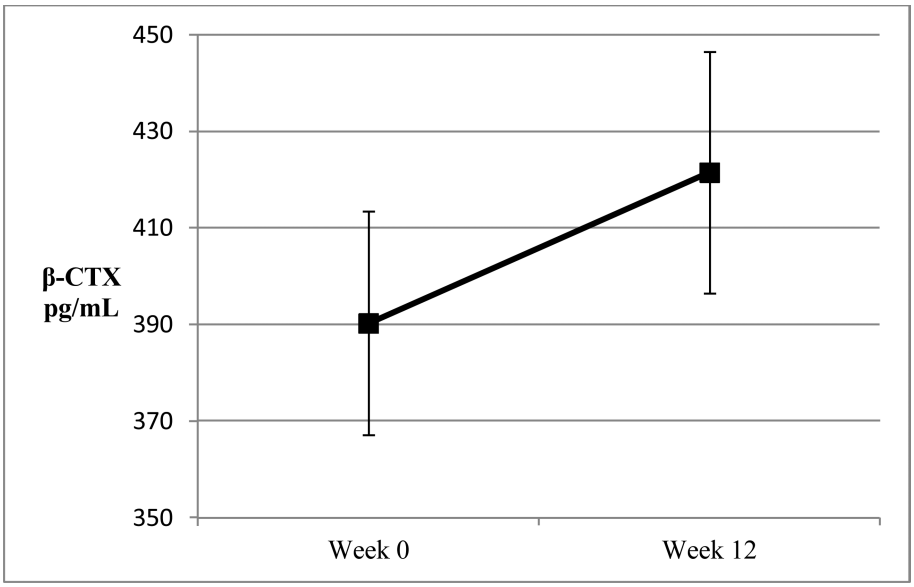

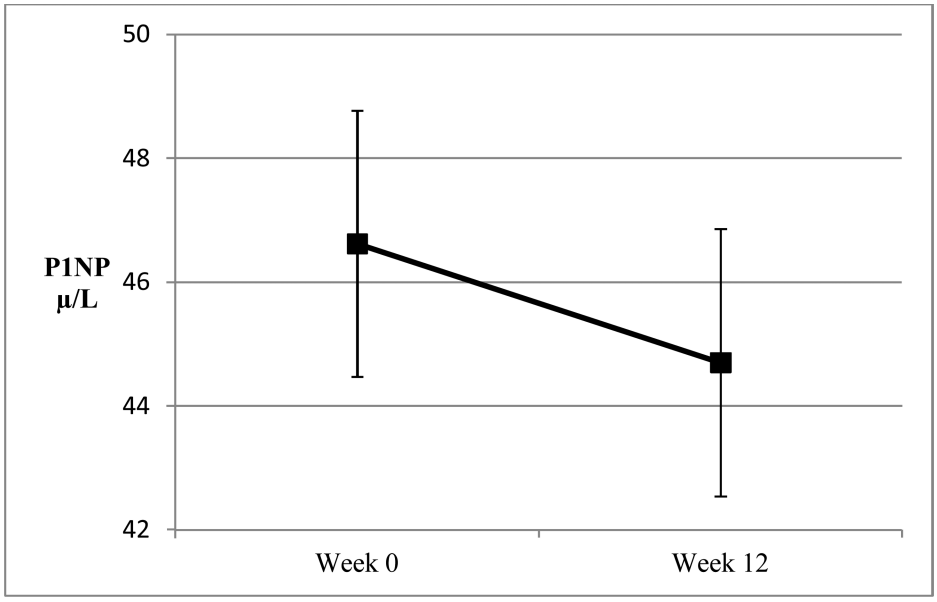

Figure 1. Pre- and post-treatment levels of (a) β-CTX and (b) P1NP for 76 participants

Figure 1a: β-CTX=serum C-terminal cross-linking telopeptide of type I collagen. Mean (SD) change in β-CTX = 31.2 (116.5) pg/mL, t = 2.33, p = 0.02. Standard error bars are shown.

Figure 1b: P1NP=N-terminal propeptide of type I procollagen. Mean (SD) change in P1NP = -1.9 (10.8) µg/L, t = -1.55, p = 0.12. Standard error bars are shown.

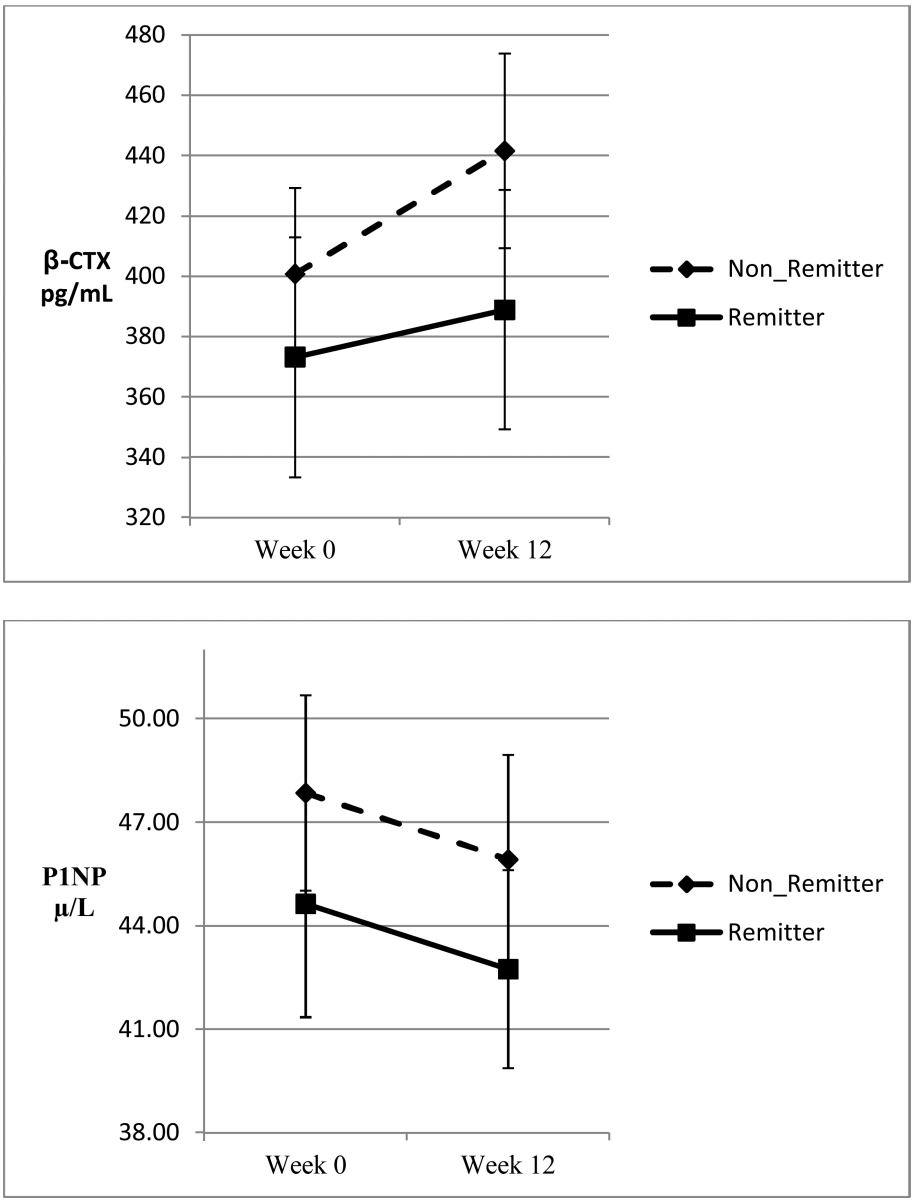

Figure 2. Pre- and post-treatment levels of (a) β-CTX and (b) P1NP in depression remitters and non-remitters

Figure 2a: β-CTX=serum C-terminal cross-linking telopeptide of type I collagen. Mean (SD) change in β-CTX: Non-Remitters = 40.8 (119.3) pg/mL, t = 2.34, p = 0.02. Remitters = 15.7 (112.2) pg/mL t = 0.75, p = 0.46. Standard error bars are shown.

Figure 2b: P1NP=N-terminal propeptide of type I procollagen. Mean (SD) change in P1NP: Non-Remitters = -1.9 (10.8) µg/L, t = -1.23, p = 0.23. Remitters = -1.9 (10.9) µg/L, t = -0.94, p = 0.36. Standard error bars are shown.