Psychiatry Research 276 (2019) 39–44

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Effect of selective serotonin reuptake inhibitors on markers of bone loss

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ARTICLE INFO

Keywords:
Osteoporosis
Bone loss
P1NP
β-CTX
pCREB
RANKL
Bone turnover
SSRI

ABSTRACT

Several preclinical and clinical studies show that selective serotonin reuptake inhibitors (SSRI's) are associated with bone loss and an increase in fracture risk, not many reports on their effect on bone turnover markers. This cross-sectional study evaluated the effect of SSRIs treatment on bone turnover markers in Indian population for the first time. Inclusion criteria were subjects of either sex and age 18–45 years undergoing treatment with an SSRI for at least 3 months, regardless of the indication. The results were compared with age-matched healthy controls. A total of 141 subjects were screened out of which 85 were enrolled, 44 in treatment and 41 in the control group. Serum Procollagen Type 1 Amino Terminal Propeptide (P1NP) levels were decreased in patients on SSRI treatment whereas no change was observed in the beta-C-terminal telopeptide (β-CTX) and receptor activator of nuclear factor kappa-B ligand (RANKL) levels suggesting that these drugs can reduce bone formation but not resorption. Patients on SSRI treatment also showed reduced pCREB levels indicating that reduced bone formation is possibly through the gut mediated pathway. Our study suggests that SSRIs treatment at therapeutic doses may have a deteriorating effect on bone requiring caution in patients with additional risk factors.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are one of the most extensively used antidepressants in the western world (Abrahamsen and Brixen, 2009). They are the treatment of choice for various psychiatric disorders because of their safety and efficacy (Mann 2005; Vaswani et al., 2003). There is an approximately two-fold increase in the prescription of SSRI antidepressants from the period of 1995 to 2011 due to the long period consumption of these drugs (Mars et al., 2017). Incidence from various clinical studies illustrates low bone mineral density (BMD) as a risk factor for bone fractures and osteoporosis development in a different population of the world (Hung et al., 2017; Sheu et al., 2015; Wang et al., 2016). Prior studies have shown the use of antidepressant medications, specifically selective serotonin reuptake inhibitors (SSRIs), to be inversely related to BMD (Feuer et al., 2015; Rauma et al., 2016; Rauma et al., 2015). A recent meta-analysis on 11 studies showed that SSRI administration is associated with reduced BMD (Zhou et al., 2018). Also, there have been a number of cross-sectional and cohort studies showing use of antidepressants, mainly SSRIs, to be associated with reduced BMD (Wadhwa et al., 2018). Contrary to these, a recent meta-analysis concluded that SSRIs are not associated with any significant changes in BMD (Schweiger et al., 2018), however only one of the study in this meta-analysis diagnosed major depressive disorder according to the structured clinical assessment.

The action of SSRI's on the bone is controversial as serotonin shows the opposing effect as per its origin, the brain-derived serotonin results in the bone formation and gastrointestinal tract derived serotonin results in bone resorption (Ducy and Karsenty, 2010) and this contrasting effect leads to overall bone health in patients on SSRIs treatment.

In addition to BMD measurements, bone turnover markers can be used to forecast the probability of fracture and establishment of osteoporosis in the near future (Kahl et al., 2006; Vasikaran et al., 2011). To the best of our knowledge, only three clinical studies of SSRIs on bone turnover markers could be found in the public domain. However, no study has been conducted in the Indian population until now to show any association between SSRIs and bone health.

The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommend that a marker of bone formation (serum procollagen type I N propeptide, s-PINP) and a marker of bone resorption (serum C terminal telopeptide of type I collagen, s-CTX) are used as reference analytes for bone turnover markers in clinical studies (Vasikaran et al., 2011), hence in the present work, we have measured these bone

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https://doi.org/10.1016/j.psychres.2019.04.006
Received 6 March 2019; Received in revised form 2 April 2019; Accepted 3 April 2019
Available online 03 April 2019
0165-1781/

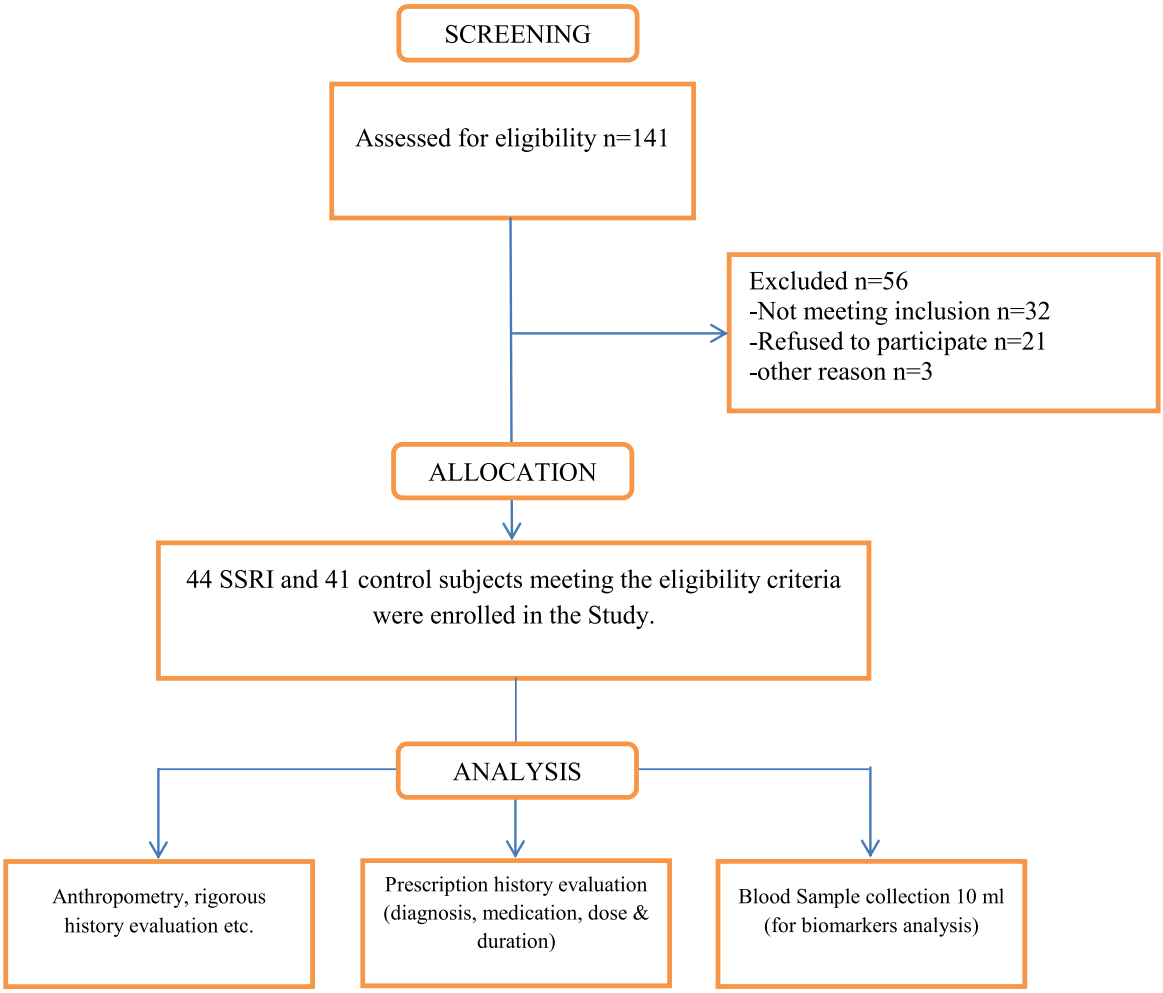

Fig. 1. Flow of participants.

turnover markers in patients undergoing treatment with SSRIs. cAMP responsive element binding protein (CREB) is a transcriptional factor that is present in various cellular part (mitochondria, cytoplasm or nucleus), as per the functional requirement. Serum and peripheral blood CREB levels have been studied in various disease groups versus the control in recent studies (Rojas et al., 2011; Tezel et al., 2012). CREB is a key transcriptional moderator of serotonin signaling in osteoblasts and serotonin (Yadav et al., 2008). RANKL has shown to be involved in the brain-derived serotonin effect of the bone (Ducy and Karsenty, 2010). Hence, we have measured serum levels of CREB and RANKL to check the connection between them and the SSRI treated patients.

Recently, we reported that one of the SSRI, fluoxetine treatment for 40 days resulted in reduced P1NP levels in Wistar rats without affecting β-CTX and that fluoxetine reduces bone formation possibly through reduced pCREB mediated by the action of gut serotonin in osteoblasts (Kumar et al., 2018). The present work was planned to confirm the preclinical findings in patients undergoing treatment with these antidepressants.

2. Methods

We followed the 'Strengthening the reporting of Observational Studies in Epidemiology'(STROBE) guidelines for reporting of data.

2.1. Study design and setting

This observational cross-sectional study was conducted in the psychiatric OPD setting of the Hakeem Abdul Hameed Centenary Hospital, Jamia Hamdard, New Delhi from the period of 28-Jul-16 to 04-May-17. Informed consent was taken at the time of enrollment for each subject. Data was collected for anthropometry, medication, vital signs, history of the disease, duration of treatment, dose of medication, exercise, age, sex, sun exposure, dairy product consumption, smoking, alcohol use, diabetes, education, employment, and marital status.

2.2. Participants

Inclusion criteria were subjects of either sex, with age 18–45 years (both inclusive), undergoing treatment with an SSRI for at least 3 months, regardless of the indication and ability to provide consent. SSRIs included fluoxetine, citalopram, escitalopram, sertraline, paroxetine, fluvoxamine while non-osteoporotic healthy subjects were enrolled in the control group. Subjects were excluded if they were having Hamilton depression score more than 19 (being in major depression category), pregnant and lactating, or having disease conditions like chronic inflammatory diseases, diabetes, hypo- or hyperparathyroidism, hypo- or hyperthyroidism, growth hormone deficiency, and other endocrine disturbances, history of childhood cancer, or prior transplantation, hepatic, renal, neoplastic, gastrointestinal, dermatological and endocrine disorders etc. The subjects are also excluded if they are on concomitant treatment with drugs that may affect bone health

such as steroids, anticoagulants (heparin), anticonvulsants, barbiturates, chemotherapeutic agents, glucocorticoids, gonadotropin-releasing hormone agonists, immuno-suppressants, lithium, long-acting progestin, proton pump inhibitors, pioglitazone etc. subjects on calcium supplements and vitamin-D.

2.3. Variables

Data sources/measurement: Prescription history of the subjects was thoroughly investigated. Adherence to the medication of subjects was monitored by all the past prescriptions, subjects were asked to bring the leftover prescribed medicines or containers to help in with correct recording of details and rigorous evaluation of clinical history investigations. The drug, its dose, and duration of treatment was transcribed from the prescription. Body mass index, blood pressure, pulse rate were measured and Hamilton depression scale was administered by the qualified medical professional.

2.4. Biasing parameter

As major depression itself causes bone loss (Schweiger et al., 2016a) so it is one of the major confounders in our study hence we have included patients with mild to moderate depression as assessed by Hamilton depression score less than 19 (moderate depression), which rules out the probability of the depression itself causing bone loss.

2.5. Study size

The sample size calculation was based on primary efficacy parameter of bone turnover markers i.e. P1NP and β-CTX (Diem et al., 2014) and calculated taking 95% confidence interval, power = 90, using statistical software STATA version 14.2. The sample size was calculated to be 25 in each (treatment and control) group. We recruited a total of 85 subjects with 44 in the treatment group and 41 in the control group as shown in Fig. 1.

2.6. Sample collection, and analysis of quantitative variables

Blood volume up to 10 ml was collected from each enrolled overnight fasting subjects. The whole blood was processed to extract serum and stored under low temperature as prescribed in the literature of enzyme-linked immunosorbent assay (ELISA) kits until analysis in batch. Validated ELISA test was performed for the serum concentration of bone turnover markers (P1NP & β-CTX), and for exploration of the possible mechanism (RANKL & pCREB).

2.7. Ethical considerations

The study was conducted after the approval of the protocol and other relevant documents from Jamia Hamdard institutional Ethics Committeeas per letter dated 30 May 2016.The study was carried out in accordance with the provisions of the current version of the ICH 'Guidance for Good Clinical Practices', ICMR 'Guidelines for Biomedical Research on Human Participants' and the principles enunciated in the Declaration of Helsinki (2013). This study has been registered in Clinical Trials Registry- India (CTRI) (http://ctri.nic.in/Clinicaltrials/login.php), reference no REF/2018/02/017517.

2.8. Statistical methods

The descriptive statistics were done using mean with standard deviation (SD) for quantitative variables and categorical variables were presented in frequencies along with respective percentages. The other statistical comparisons for quantitative variables was done using Student's '*t*'/ Mann–Whitney 'U' test and for categorical variables, Chi-Squared / Fisher's exact test was used as per the nature of data. Logistic regression analysis was carried out for treatment (SSRI user and control) with bone turnover markers and relevant significant variables (B.M.I. and exercise) and RANKL; other parameters were excluded being non-significant (age, systolic blood pressure, diastolic blood pressure, pulse rate, sun exposure, dairy product consumption, smoking, alcoholic, diabetes, and hypertension), or non-relevant (education, employment, and marital status). All statistical analyses will be performed by using SPSS software (Version 22, SPSS Inc., Chicago, IL, USA) and STATA version 14.2. The p-value less than 0.05 was considered as statistically significant.

3. Results

3.1. Study population characteristics

A total of 141 patients were screened, out of which 85 subjects meeting the eligibility criteria were enrolled in the study (44 in the treatment group compared with 41 subjects in the control group) as shown in Fig. 1. No statistical difference between the age, sex, systolic and diastolic blood pressure, pulse rate, sun exposure, dairy product consumption, smoking habits, diabetes history and history of hypertension was observed between the two groups. However, significant differences were discernible at the education level, employment status, marital status, and exercise and BMI variables in SSRI and control subjects. The most commonly prescribed medication was sertraline followed by fluoxetine and then escitalopram. Anxiety and depression were the two most common diagnoses for which medications were prescribed (table 1a and 1b).

3.2. Selective serotonin reuptake inhibitors and bone turnover markers

The distribution of serum concentration of bone turnover markers is depicted in Fig. 2 where data is represented in the box which shows the 1st and 3rd quartile while the whisker shows the minimum and maximum concentration of the data.

In patients undergoing treatment with selective serotonin reuptake inhibitors for 11.84 ± 8.00 months, there was significant decrease ($P = 0.015$) in the serum P1NP levels while no significant changes were observed in β-CTX level ($P = 0.881$) as shown in Table 2b.

3.3. Selective serotonin reuptake inhibitors and pCREB, RANKL levels

A highly significant reduction in the levels of the serum pCREB ($P < 0.001$) was observed in SSRI users whereas no change was observed in the serum levels of RANKL ($P = 0.993$).

3.4. Logistic regression model between the treatment and control group

Table 3 demonstrates the univariate and multivariate logistic regression analysis which was done for treatments between bone turnover markers and relevant significant variables. It was observed that a significant difference between the serum concentration of P1NP ($P = 0.04$) levels in the treatment group as compared to control group persisted even after controlling for exercise and BMI.

3.5. Outcome

SSRI users (after a mean duration of 11.84 months) reported a significant reduction in the bone formation marker P1NP as compared to healthy control while there was no change in the bone resorption markers, β-CTX, and RANKL. The reduction in P1NP remained significant even after controlling for confounders (exercise and BMI in our study). Additionally, a significant reduction in pCREB levels was also observed in patients undergoing treatment with SSRI.

Table 1a
Demographic and clinical characteristics of SSRIs user and control group.

Characteristic		SSRIs user (n = 44)	Control (n = 41)	P value
Sex	Female (n = 46, 54.1%)	24 (54.5%)	22 (53.7%)	0.935
	Male (n = 39, 45.9%)	20 (45.5%)	19 (46.3%)	
Age (years) (mean ± SD)		34.3 ± 8.4	33.2 ± 6.6	0.492
B.M.I. (kg/m^2) (mean ± SD)		25.9 ± 4.4***	23.1 ± 2.2	Less than 0.001
Systolic BP (mm/hg) (mean ± SD)		118.4 ± 5.6	119.6 ± 4.8	0.269
Diastolic BP (mm/hg) (mean ± SD)		78.4 ± 4.8	79.7 ± 4.0	0.216
Pulse rate (Beat/Min) (mean ± SD)		69.3 ± 4.9	69.7 ± 4.4	0.736
Sun Exposure (Min) (mean ± SD)		54.4 ± 50.6	35.8 ± 16.6	0.398
Education	≤ =12 (n = 40, 47.1%)	36 (81.8%)***	4 (9.8%)	Less than 0.001
	>12 (n = 45, 52.9%)	8 (18.2%)***	37 (90.2%)	
Employment	Unemployed (n = 53, 62.4%)	18 (40.9%)***	35 (85.4%)	Less than 0.001
	Employed (n = 32, 37.6%)	26 (59.1%)***	6 (14.6%)	
Marital status	Single (n = 40, 47.1%)	12 (27.3%)***	28 (68.3%)	Less than 0.001
	Married (n = 45, 52.9%)	32 (72.7%)***	13 (31.7%)	
Dairy product consumption	No (n = 50, 58.8%)	24 (54.5%)	26 (63.4%)	0.406
	Yes (n = 35, 41.2%)	20 (45.5%)	15 (36.6%)	
Exercise	HW + ≤5 KM (n = 56, 65.9%)	24 (54.5%)*	32 (78.0%)	0.022
	>5 KM (n = 29, 34.1%)	20 (45.5%)*	9 (22.0%)	
Smoking	No (n = 81, 95.3%)	40 (90.9%)	41 (100.0%)	0.117
	Yes (n = 4, 4.7%)	4 (9.1%)	0 (0.0%)	
Alcoholic	No (n = 85, 100%)	44 (100%)	41 (100%)	1.0
	Yes (n = 0, 0.0%)	0 (0%)	0 (0%)	
Diabetes	No (n = 82, 96.5%)	41 (93.2%)	41 (100.0%)	0.242
	Yes (n = 3, 3.5%)	3 (6.8%)	0 (0.0%)	
Hypertension	No (n = 82, 96.5%)	41 (93.2%)	41 (100.0%)	0.242
	Yes (n = 3, 3.5%)	3 (6.8%)	0 (0.0%)	

Abbreviations: B.M.I.= Body mass index; ≤ =12 = less than or equal to 12 years of Education; >12 = greater than 12 years of education; HW + ≤5 = Household work and less than 5 kms of walking per day; >5 KM= greater than 5 kms of walking per day. The data is represented by mean ± Standard Deviation for parametric and percentage for non-categorical variables, which was computed by 2 × 2 table using Chi-squared for the variables more than 5 and for variables less than 5, Fisher's exact test was used. *$P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq$ less than 0.001 when compared with control.

Table 1b
Characteristics of SSRIs individuals.

SSRI Arm		N	Mean/percentage
Duration of disease (Months) Mean ± SD SSRI		44	11.84 ± 8.667
Duration of drug usage (months) Mean ± SD		44	10.00 ± 8.305
Medication Used (n)	Sertraline	25	56.81%
	Fluoxetine	9	20.45%
	Escitalopram	7	15.90%
	Paroxetine	3	6.81%
Diagnosis (DSM V)	Anxiety	16	36.36%
	Depression	16	36.36%
	Mood Disorder	8	18.18%
	Compulsive Disorder	3	6.81%
	Schizophrenia	1	2.27%

Abbreviations: DSM V= The Diagnostic and Statistical Manual of Mental Disorders. The data is represented by the mean ± Standard Deviation for parametric and percentage for non-parametric variables.

4. Discussion

Though the association between SSRIs and fracture risk or SSRIs and reduced BMD has been confirmed in various cross-sectional, case-control and cohort studies, there is limited data available on their effect on bone turnover markers. The results from our study reported a significant reduction in the peripheral serum bone formation marker P1NP upon SSRIs treatment suggesting an increase in the bone loss while no significant changes were observed in the serum bone resorption markers, β-CTX, and RANKL.

A recent meta-analysis that analyzed 21 studies show that major depressive disorder is associated with decreased bone mineral density (Schweiger et al., 2016b) while only one of the study reported that depression do not have any impact on bone mineral density and bone turnover markers (Yazici et al., 2005). As per our literature review, we could not come across any study where mild to moderate depression has been linked to alterations in bone mineral density or bone turnover markers. In one of the studies, it was reported that mild depression did not have any effect on BMD in premenopausal women (Kavuncu et al., 2002). Hence, we excluded subjects if they were having Hamilton depression score more than 19 (being in major depression category) in order to rule out the confounding effects of major depression.

Our results are in agreement with a recent clinical study showing a highly significant reduction in serum levels of P1NP ($P > 0.006$) in SSRIs (average usage of 2.7 years) users as compared with non-users (Williams et al., 2018). However, this study also showed a reduction in

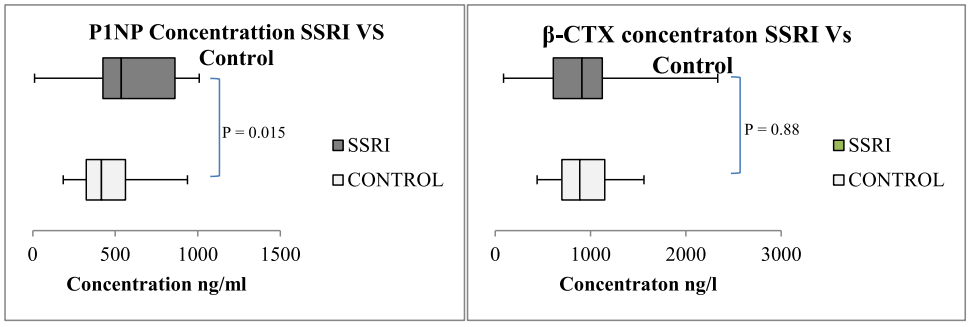

Fig. 2. Distribution of bone turnover markers concentration. Distribution of data represented in box plot and box ranges from quartile 1 (25%) to quartile 3 (75%) with whisker representing the minimum and maximum value of concentration. Median is indicated by a line across the box. *$P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq$ less than 0.001 when SSRI treated group compared with control using Mann Whitney U test.

Table 2
Serum biomarkers levels for P1NP, β- CTX, pCREB, and RANKL.

	Group	n	Mean (SD)	Mann–Whitney *U*	P
P1NP (ng/ml)	SSRI	44	475.37 ± 212.36*	625.00	0.015
	Control	41	595.49 ± 267.97		
β-CTX (ng/L)	SSRI	44	905.38 ± 268.42	885.00	0.881
	Control	41	931.31 ± 420.34		
pCREB (ng/L)	SSRI	44	497.08 ± 355.94***	326.00	Less than 0.001
	Control	41	959.03 ± 531.81		
RANKL (ng/L)	SSRI	44	92.46 ± 29.47	894.50	0.947
	Control	41	95.53 ± 38.48		

The concentrations of serum P1NP, β-CTX and pCREB are expressed in Mean + SD., which are analyzed by the Mann–Whitney *U* test. *$P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq$ less than 0.001 when SSRI treated group compared with control.
ng = Nanogram; ml = milliliter; *L* = Liter.

CTX levels which could be possibly related to the longer duration of their study. Our findings are also consistent with a preclinical study in rodents which reported that one of the SSRI fluoxetine, when administered in a dose of 10 mg/kg for 4 weeks, significantly reduces the bone formation marker osteocalcin while no change is seen in the resorption marker (CTX) (Bonnet et al., 2007). In a randomized clinical trial by Diem et al., however, it was reported that after 8 weeks of treatment, another SSRI escitalopram does not affect the bone turnover in the short term. It was also seen that there was a declining trend in the serum concentration of bone formation marker P1NP after 8 weeks of treatment and it is possible that the formation marker might have further declined if the subjects treated for a longer duration (Diem et al., 2014). The authors of the study, however, also confirmed that the results could not be generalized for other SSRIs usage for the long term. In fact, an in vitro study that compared the effect of various SSRIs on human osteoblast and osteoclast differentiation and function reported that except for citalopram, all other SSRIs including fluoxetine, sertraline, paroxetine, fluvoxamine inhibited ALP and bone mineralization by osteoblasts and induced apoptosis in both osteoblast and osteoclast (Hodge et al., 2013). The study suggested low bone deteriorating effects of citalopram, a racemic mixture of R and S-citalopram (escitalopram), than other SSRI's (Azorin et al., 2004). Another study reported an increase in the bone formation marker osteocalcin and reduction in the serum β-CTX level in the premenopausal women treated with escitalopram for 3 months suggesting escitalopram to have positive effects on bone (Aydin et al., 2011). Above findings reported for escitalopram are somewhat in agreement with our previous work on Wistar rats where we reported a differential profile of two SSRIs, fluoxetine and escitalopram, on bone turnover markers and microarchitecture. While fluoxetine reduced P1NP and deteriorated tibial bone microarchitecture, escitalopram was without any effect. Since the present work evaluated the effect of SSRIs as a class of drugs, reduced bone formation but not resorption is suggested.

Presence of the serotonin receptors and transporters in osteoblasts, osteocytes, and osteoclasts bone cells (Warden and Haney, 2008; Warden et al., 2010) provide evidence that serotonin has played an important role in bone metabolism thus causing the effect on the bone health. It has been previously reported that gastrointestinal tract derived serotonin, being a major source of serotonin in bone, acts on the Htr1b receptors on the osteoblast and through a PKA dependent pathway, inhibits cAMP response element binding protein (CREB) phosphorylation and expression, as a result, it inhibits osteoblastic proliferation leading to a decrease in bone mass (Ducy and Karsenty, 2010; Oury et al., 2010). We confirmed this mechanism of reduced bone formation in our study through a significant reduction in the pCREB level observed in SSRI treated group. However, measurement of pCREB levels in bone tissues would have been more specific rather than measurement of pCREB in serum so it is tough to explain the relevance of the CREB in sera with the amount of CREB phosphorylated in osteoblast. Further studies are required to confirm these observations.

Our study has limitations including the cross-sectional design so the future direction would be long term longitudinal follow-up of these participants. Another limitation is lack of BMD data and insufficient sample size that could have led to the non-significant findings between these markers and some of the potential covariates tested in the study. A higher sample size can also enable sub-group analysis to assess the effect of individual SSRI on bone biomarkers. The outcome of our study points toward an early indication of reduced bone formation with SSRIs treatment which is possibly mediated through gut serotonin. However, we need more randomized clinical studies to give better clarification of the risk or benefit involved in the treatment of most widely used selective serotonin reuptake inhibitors ina different population with

Table 3
Univariate and Multivariate Logistic regression model to show association of P1NP, β-CTX, RANKL.

	Control	Treatment (SSRI)	P Value	Univariate odds ratio 95% CI	Multivariate odds ratio 95% CI
P1NP					
>536.00	20 (51.22%)	31 (29.55%)	0.044	1	1
<536.01	21 (48.78%)	13 (70.45%)		2.50 (1.02–6.10)	16.27 (3.62–73.18)
B-CTX					
>733.00	21 (51.22%)	18 (40.91%)	0.341	1	1
<733.01	20 (48.78%)	26 (59.09%)		1.51 (0.64–3.57)	.829 (0.25–2.66)
RANKL					
>85.00	20 (48.78%)	20 (45.45%)	0.759	1	1
<85.01	21 (51.22%)	24 (54.55%)		1.14 (0.48–2.68)	2.10 (0 0.70–6.35)
BMI					
>25.0	33 (80.48%)	8 (19.51%)	0.01	1	1
≤25.1	23 (52.27%)	21 (47.72%)		3.58 (1.34–9.53)	5.83 (1.66–20.48)
Exercise					
>5.0 km	32 (78.04%)	9 (21.95%)	0.025	1	1
≤5.1 km	24 (54.54%)	20 (45.45%)		2.96 (1.14–7.64)	4.82 (1.36–17.09)

OD= Odds ratio, Cl=Confidence Interval, *$P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq$ less than0.001.

various other disease conditions.

Acknowledgments

We are grateful to UGC-SAP DRS-II support and the Jamia Hamdard Pharmaceutical Medicine Program in collaboration with Sun Pharmaceutical Industries ltd. for financial support. We also acknowledge the Psychiatry Department of HAH centenary hospital, Jamia Hamdard in providing the eligible subjects for the study. Special thanks to Dr. Bibhu Prasad Panda, for permission to do a part of work in Pharmaceutical Biotechnology Laboratory (Jamia Hamdard).

Conflict of interest

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.04.006.

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