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RESEARCH ARTICLE

Evaluation of jawbone morphology and bone density indices in panoramic radiographs of selective serotonin reuptake inhibitor users: a preliminary study

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Objectives: To assess the influence of selective serotonin reuptake inhibitor (SSRI) use on jawbone and bone mineral density by retrospective analysis of panoramic radiographs.
Methods: Radiographic and clinical records were sourced from the Division of Orthodontics and TMJD, Eastman Institute for Oral Health, University of Rochester. Randomly selected adults (20–65 years) were categorized into: "Active" (with history of SSRI use of >6 months) and a "Control" group. Panoramic indices: Klemetti index (KI), panoramic mandibular index, antegonial notching index, condylar pathology, mandibular cortical width (MCW) and mean ramus height were recorded. Frequency-weighted X^2 tests and multinomial regression controlling for age and gender were applied to categorical indices (KI, condylar pathology, antegonial notching index). Multivariate generalized linear modeling was applied to mean ramus height, MCW and panoramic mandibular index. Multiple regression analyses determined: (a) panoramic indices that best predicted SSRI use, and (b) independent predictors of KI category.
Results: 64 SSRI users and 48 Controls were assessed. SSRI users had significantly higher odds of having worse KI status than normal [mildly to moderately eroded cortex: odds ratio (OR) = 2.926, 95% CI (1.07–8.04) and severely eroded cortex: OR = 19.86, 95% CI (3.91–100.69)], more frequent flat condylar anatomy (right side: $p = 0.009$, left side: $p < 0.001$) but greater ramus height ($p = 0.001$) and mandibular cortical width ($p = 0.032$). Age, gender, SSRI use each significantly impacted KI. Only SSRI use significantly impacted condylar pathology, ramus height and MCW. KI category (OR = 1.3) was the best panoramic predictor of SSRI use. Conversely, KI category C3 was significantly predicted by SSRI use (OR = 31.2, $p = 0.002$), female gender (17.5, $p = 0.006$), and severe antegonial notching (OR = 1289, $p < 0.001$).
Conclusions: SRRI use was significantly associated with worse panoramic morphometric indices: KI, condylar pathology, ramus height, and MCW, where KI was its strongest predictor. Worse KI was independently predicted by SSRI use.
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Introduction

Depression is a major cause of disability worldwide, causing significant burden on society and the individual[1–3] with rising incidence.[4] At the same time, osteoporosis has been noted as an epidemic,[5] characterized by a reduction in bone mineral density (BMD), often with no discernible symptoms until an unexpected fracture.[6] Osteoporosis is a multifactorial disease[7], and one of its risk factors is depression.[8–10] Postulated mechanisms of depression-induced effects on bone metabolism include activation of hypothalamic corticotrophin-releasing hormone and elevated cortisol levels, sedentary lifestyle, vitamin D deficiency, parathyroid hormone disturbances and antidepressant use.[11] Antidepressants, in particular, selective serotonin inhibitors (SSRIs), have been associated with reduced BMD[12,13] and increased fracture rate.[14–17]As serotonin (5-HT) receptors are expressed on bone cells and impact bone homeostasis,[18–21] SSRIs may negatively impact BMD.[22] SSRIs may also affect extracellular bone matrix regulation,[23] and deleterious effects of SSRIs on bone may begin during embryonic development.[24–26] However, a negative impact of SSRIs on BMD has also been refuted.[27,28] While almost all research about impact of SSRIs use on bone has been in animal models or long bones in humans, not much is known their effects on the craniofacial skeleton. Recent studies have investigated the link between SSRI and dental implant outcomes, with conflicting findings.[29,30]

Diagnosis of osteoporosis is based on measurements of bone density. For this, the "gold-standard" method is dual-energy X-ray absorptiometry (DXA). However, DXA is not routinely performed and osteoporosis is often a "silent" disease, diagnosed only after a patient presents with fracture. Tools that enable non-invasive, cost-effective screening for osteoporosis or low BMD are likely to be clinically valuable, especially in at-risk populations. Panoramic radiology is frequently performed in the dental care setting and can be utilized as a cost-effective screening tool for reduced BMD, osteopenia or osteoporosis.[31–40] The panoramic indices; mandibular cortical width (MCW), panoramic mandibular index (PMI), and mandibular cortical erosion as indicated by Klemetti index (KI), have demonstrated clinical value in detecting low BMD and osteoporosis.[31] Although prescribing panoramic radiographs solely to detect osteopenia or osteoporosis is not recommended, screening them for reduced BMD could be the very first interception of the disease. A MCW of 3–4 mm has been recommended as an appropriate threshold to warrant referral for bone densitomertry.[31] A PMI cutoff value of ≤0.3 is shown to denote reduced BMD with an estimated sensitivity and specificity of >70%,[31] proving to be the most accurate linear index to screen for reduced BMD. The presence of moderate to severe cortical erosion as indicated by KI is also useful indicator of reduced BMD.[41] Overall, panoramic indices have shown moderate diagnostic accuracy in diagnosing hip-osteoporosis as measured by DXA.[42] In particular, a casual finding of a thin or eroded mandibular cortex merits further clinical and DXA investigations.[42] Screening panoramic radiographs could be an effective method to unravel drug associated adverse effects on bone quality. The present study aimed to measure panoramic radiomorphometric indices as related to SRRI use, in an attempt to investigate BMD and jawbone changes that may be associated with SSRI intake.

Methods and materials

Study design and inclusion criteria

The study was designed as a retrospective cohort study. The study protocol was approved by the Institutional Review Board of University of Rochester (IRB number: RSRB# 62666). The subjects were identified from the Axium™ electronic patient records database within Eastman Institute for Oral Health, University of Rochester, Division of Orthodontics and Orofacial pain. All panoramic radiographs have been obtained using a single panoramic machine: (Orthopantomograph OP100D™, Instrumentarium Dental Imaging®, Charlotte, NC). Adult subjects aged 20–65 were randomly selected and categorized on the basis of SSRI use as: an "Active" group: with history of SSRI consumption for more than 6 months and a "Control" group with no reported SSRI use.

The exclusion criteria were as follows:

(1) A documented history of consumption of hypertensive drugs or other drugs affecting bone metabolism including bisphosphonates, glucocorticoids, anticonvulsants, thyroxin, hormone replacement therapy, calcium, vitamin-D supplements, immunosuppressants and chemotherapeutic agents.
(2) History of diseases that alter bone metabolism such as hyperparathyroidism, multiple myeloma.
(3) History of malignancy not limited to the mandible or a benign lesion in the mandible.
(4) History of radiotherapy or resection and reconstruction to the mandible.
(5) History of maxillofacial trauma.
(6) Patients with skeletal deformity and asymmetry.
(7) Diagnosed temporomandibular joint disorders (TMD), condylar pathology or internal derangement of the temporomandibular joint.
(8) History of smoking or smokeless tobacco consumption.

Data Collection and radiographic indices

Panoramic radiographs for subjects meeting the inclusion and exclusion criteria were collected. Demographic data included age and gender. The disease category of subjects was coded for the purpose of blinding by B.G.

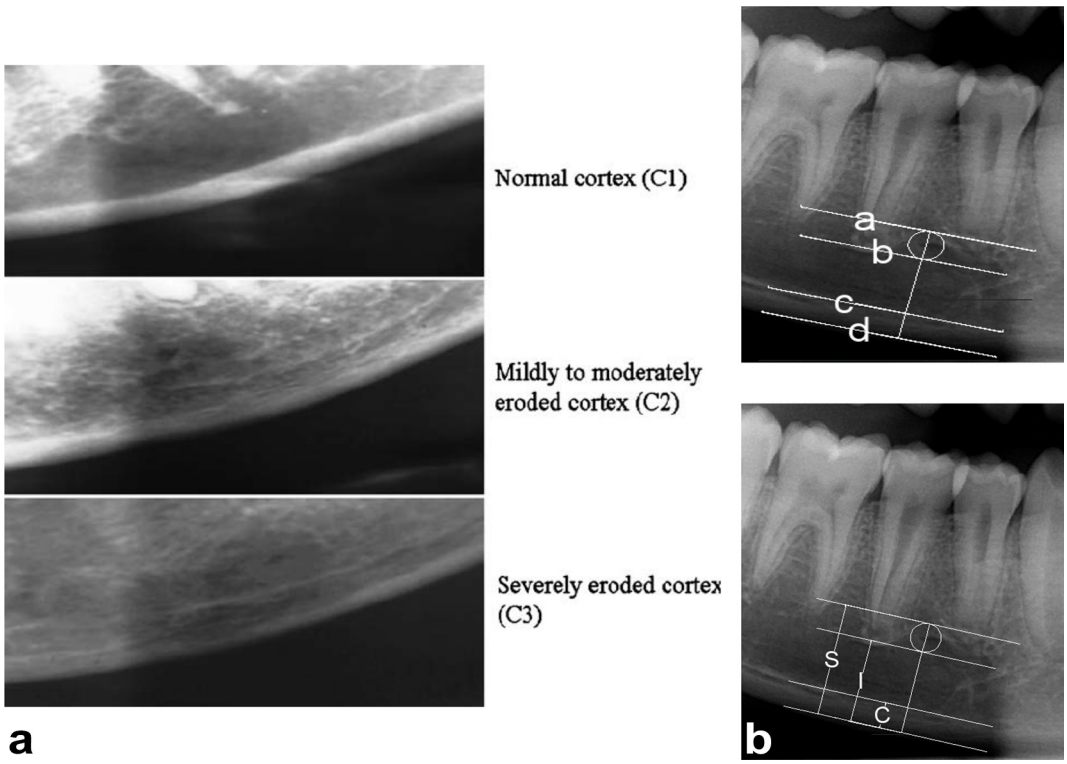

Figure 1 (a) (left): Schematic representation of categories of KI. Normal cortex [C1]: "The endosteal margin of the cortex is even and sharp on both sides". Mildly to moderately eroded cortex [C2]: "The endosteal margin shows semilunar defects (lacunar resorption) or appears to form endosteal cortical residues, one to three layers thick". Severely eroded cortex [C3]: "A clearly porous cortical layer." 1b (right): Schematic representation of PMI. Lines were drawn tangent to: the upper border of the mental foramen (a); the lower border of the mental foramen (b); the upper border of the mandible (c); the lower border of the mandible (d). The following were identified: distance between the lower border of the mandible and the inferior margin of the mental foramen (I); distance between the lower border of the mandible and the superior margin of the mental foramen (S); the width of the cortex (C). PMI was then computed as: C/I% (inferior PMI or PMIi) or C/S% (superior PMI or PMIs). KI, Klemetti index; PMI, panoramic mandibular index.

Radiographic measures were made by a single trained investigator (SS) who was blinded to the subject category. Three measurements were done for each side and the mean value recorded. Specific indices were measured as described before and included: KI,[37] MCW,[38] PMI[39], Antegonial notching index (AI), Ramus height and condylar pathology. The digital panoramic radiographs were imported into Adobe Autodesk™ AutoCAD™ 2015 software (Adobe photoshop™, Adobe systems incorporated, San Jose, CA and Auto CAD™, Autodesk Inc., San Rafael, USA: Product v. J.51.M.256). The morphometric analysis of the mandible was performed using radiographic viewer (Dolphin™) software. For each panoramic radiograph, the final values were calculated taking into account magnification error and the fixed dimension of the bite block width of 13 mm.

(1) KI:[41] mandibular cortical shape was determined by observing the mandible distally from the mental foramen bilaterally and categorized into one of three groups[41] as follows (Figure 1): normal cortex, the endosteal margin of the cortex is even and sharp on both sides [C1]; mildly to moderately eroded cortex, the endosteal margin shows semilunar defects (lacunar resorption) or appears to form endosteal cortical residues, one to three layers thick [C2]; severely eroded cortex, the cortical layer forms heavy endosteal cortical residues and is clearly porous [C3].
(2) Mandibular cortex width also known as mental index (MCW):[43] the thickness of the mandibular cortex was measured in the mental foramen region, along a line passing through the middle of the mental foramen and perpendicular to the tangent to the lower border of the mandible.
(3) PMI:[44] the PMI was defined as the ratio of the thickness of the inferior mandibular cortex in the mental region over the distance between the lower border of the mandible and either the inferior or the superior border of the mental foramen. Where the superior border of the inferior mandibular cortex was ill-defined/poorly defined, the smallest width of compact cortical bone lying below the mental foramen was measured as follows (Figure 2a,b).

- The mental foramen was identified
- Lines were drawn tangent to: the upper border of the mental foramen (a); the lower border of the mental foramen (b); the upper border of the mandible (c); the lower border of the mandible (d).

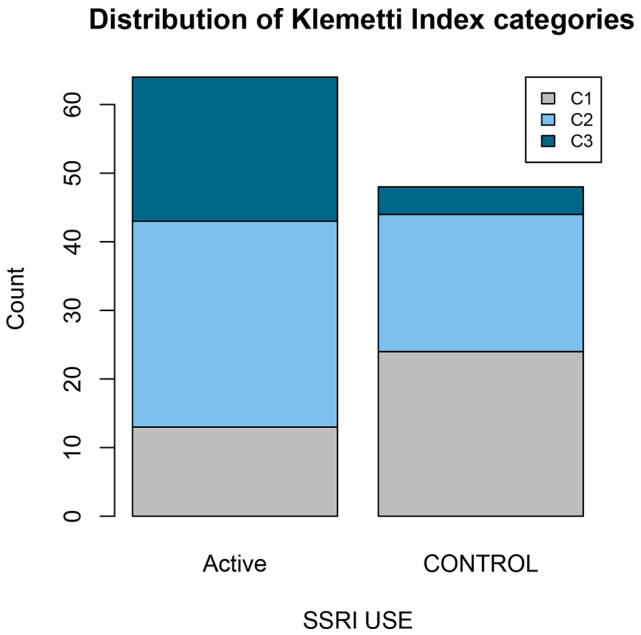

Figure 2 Distribution of Klemetti index categories in SSRI active and control groups. SSRI, selective serotonin reuptake inhibitor.

- The following were identified: distance between the lower border of the mandible and the inferior margin of the mental foramen (I); distance between the lower border of the mandible and the superior margin of the mental foramen (S); the width of the cortex (C). PMI was then computed as: C/I% (inferior PMI: PMI-i) or C/S% (superior PMI: PMI-s)

(4) Ramus height: the ramus height was obtained drawing lines parallel to the lower border of the mandible (c), the ramus (a) and the line tangent to the condyle and perpendicular to the parallel to the ramus (b) (Figure 3).

(5) Condylar pathology: any flattening or tipped back condyles, sclerotic changes in condyles, small condyles were considered in either side suggested some degenerative changes in the TMJ and categorized as: condylar pathology present, flat, or normal (Figure 4).

(6) AI[45]: a prominent antegonial notching has been associated with congenital or acquired changes in mandibular growth. The prominence of the antegonial notch was measured on the panoramic radiographs and categorized as normal, mild, moderate or severe (Figure 5).

Statistical analysis

All statistical analyses were done in the R statistical environment (v. 3.1.3).[46] Descriptive statistics were drawn for demographic and radiographic parameters. Frequency-weighted X^2 tests were used to compare distribution of gender and categorical radiographic outcome measures (distribution of KI categories, condylar pathology categories, AI) between active SSRI and control groups, while adjusting for unequal group sizes. Subjects were also categorized according to mean PMI-i (mean of right and left PMI-i) of <0.3 or ≥0.3 and the association with gender and SSRIs use was analyzed using frequency-weighted X^2 tests.

In order to explore the relationships between variables, correlation matrix analysis was performed. For this purpose, as the data contained variables of three types: continuous (age, mean ramus height, mean cortical width and PMI), polytomous (AI and condylar pathology) and dichotmous variables (gender, SSRI use, PMI <0.3); Spearman's correlation coefficient was

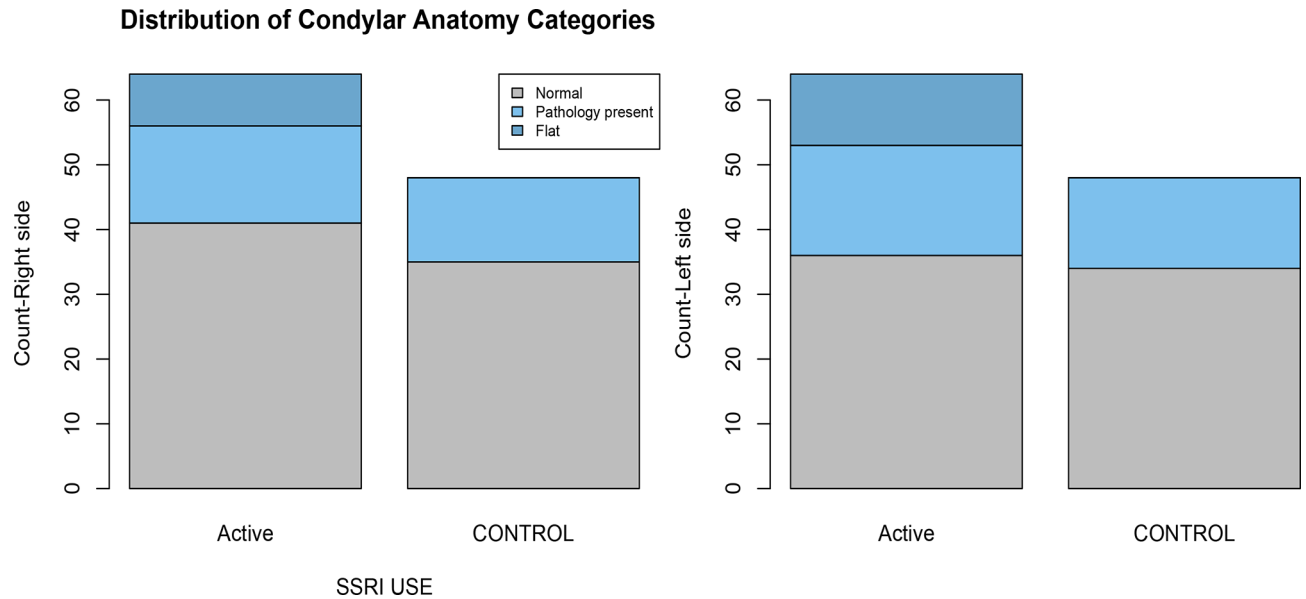

Figure 3 Distribution of condylar anatomy categories in SSRI active *vs* control subjects. SSRI, selective serotonin reuptake inhibitor.

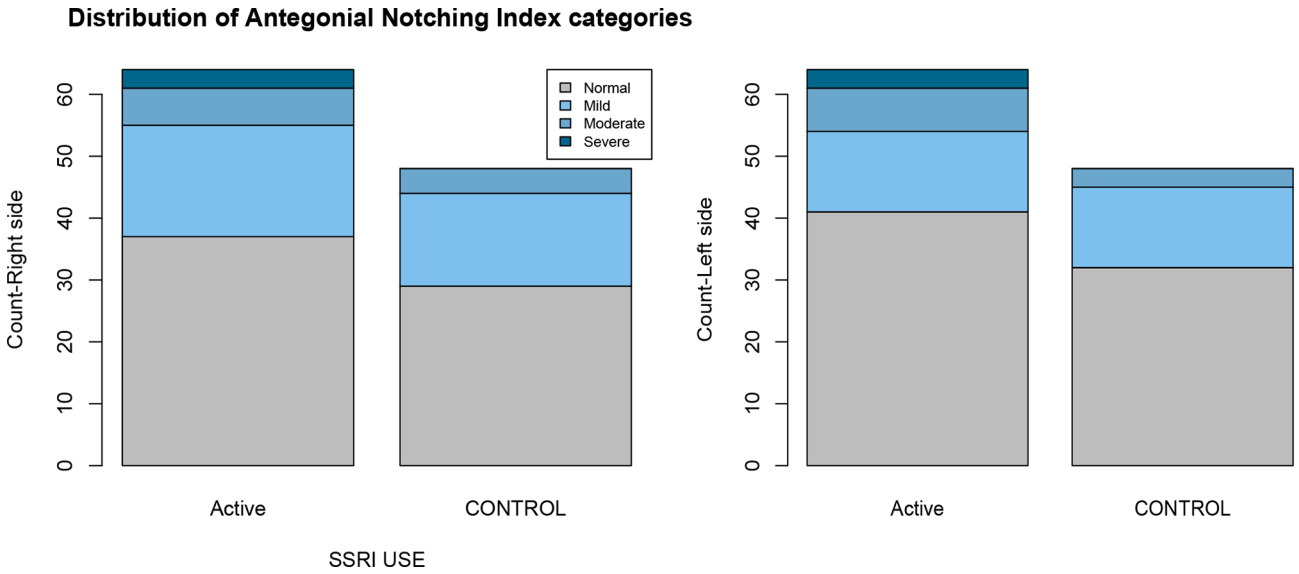

Figure 4 Distribution of antegonial notching index categories in SSRI active *vs* Control subjects. SSRI, selective serotonin reuptake inhibitor.

determined for the continuous variables, polychoric coefficient for the polytomous items, tetrachoric coefficient for the dichotomous items and a mixed correlation matrix was drawn.

Next, multinomial regression models (forward-stepwise) were constructed with SSRI use, age and gender as predictors and individual radiographic outcome variable: KI categories, antegonial notching (left and right) and condylar pathology categories (left and right) and similarly generalized linear modeling was performed for the continuous outcome measures: mean ramus height, mandibular cortical width and PMI-s and PMI-i for each side. In addition, a binary logistic regression was done for mean PMI-i of <0.3, with the same predictors.

To determine which panoramic indices were "best" and independently associated with SSRI use while accounting for age and gender, firstly, multiple regression modeling was performed with sub setting for

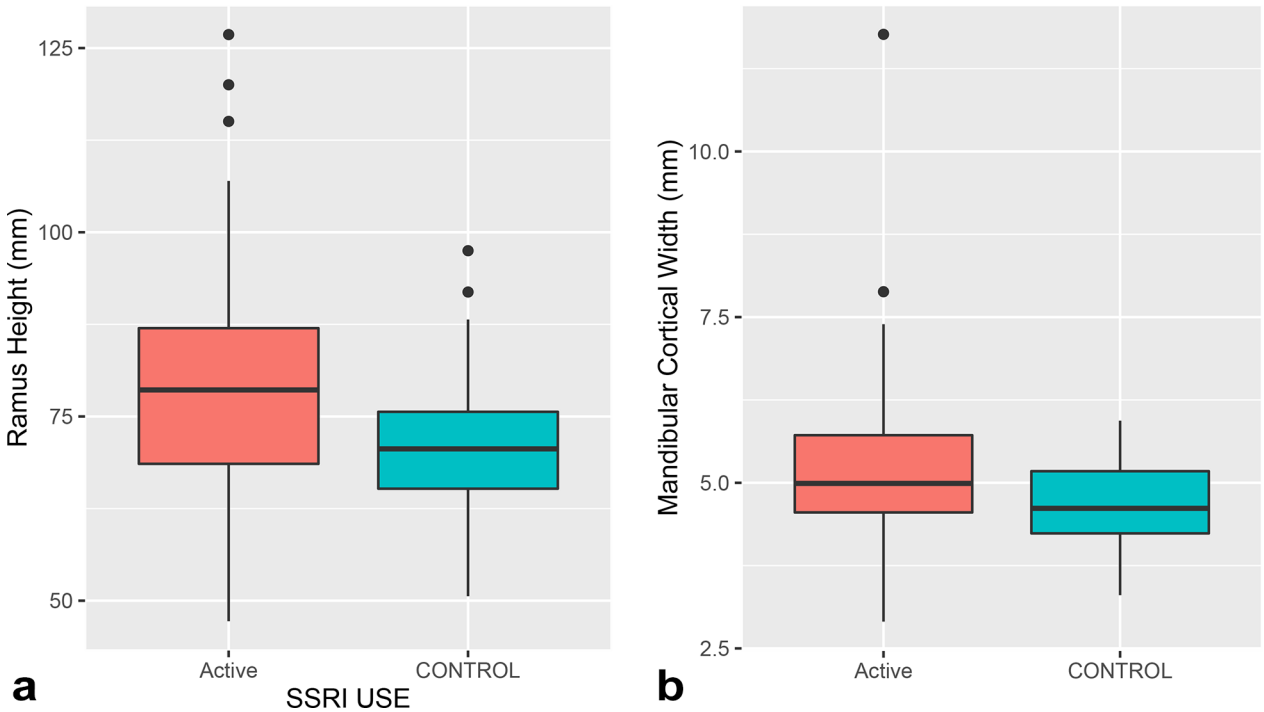

Figure 5 (a) Ramus height in SSRI active and control groups. (b) Cortical width in SSRI active and control groups (mean of right and left side values).

Table 1 Descriptive data for demographic and radiographic measurements in SSRI active and control subjects (mm)

	SSRI active (n = 64)		***Control (n = 48)***	
Age (years) Mean (standard deviation)	35.2 (11.9)		31.7 (9.7)	
Gender N (%) of females	53 (82.8%)		29 (60.4%)	
Klemetti index n (%) of C1, C2, C3	C1 = 13 (20.3%), C2 = 20 (46.9%), C3 = 21 (32.8%)		C1 = 24 (50.0%), C2 = 20 (41.6%), C3 = 4 (8.3%)	
	Right	**Left**	**Right**	**Left**
Antegonial notching index N (%) of normal, mild, moderate, severe erosion	mild = 18 (28.1%) moderate = 06 (9.3%) severe = 03 (0.04%) normal = 37 (57.8%)	mild = 13 (20.3%) moderate = 07 (10.9%) severe = 03 (0.04%) normal = 41 (64.1%)	mild = 15 (14.9%) moderate = 04 (0.1%) severe = 0 (0%) normal = 29 (60.4%)	mild = 13 (27.1%) moderate = 03 (0.1%) severe = 0 (0%) normal = 32 (66.6%)
Condylar pathology N (%) of none, present, flat	none = 41 (64%) present = 15 (23.4%) flat = 8 (12.5%)	none = 36 (56.3%) present = 17 (26.5%) flat = 11 (17.2%)	none = 35 (72.9%) present = 13 (27.0%) flat = 00 (0%)	none = 34 (70.8%) present = 14 (29.1%) flat = 00 (0%)
Ramus height (mm) Mean (SD)	79.65 (15.94)	80.2 (15.19)	70.5 (9.52)	71.06 (10.2)
Mandibular cortical width (mm) Mean (SD)	5.2 (1.48)	5.28 (1.32)	4.67 (0.67)	4.72 (0.78)
Panoramic mandibular indexi-i	0.38 (0.28)	0.36 (0.17)	0.34 (0.07)	0.35 (0.07)
Panoramic mandibular index-s	0.33 (0.33)	0.34 (0.38)	0.26 (0.05)	0.27 (0.05)
Mean panoramic mandibular index i[a]<0.3 n (%)	21 (32.8%)		12 (25%)	

SD, standard deviation; SSRI, selective serotonin reuptake inhibitor.
[a]Based on the mean of right & left PMIi.

selection of the model with lowest Akaike information criterion (AIC) value, which is a measure of goodness of fit. Here, SSRI use was applied as outcome and predictors analyzed were: age, gender, and selected panoramic indices that significantly correlated with any of the demographic variables. In the model selection process, multicollinear predictor variables with variance inflation factor ≥2 were first discarded followed by non-significant predictors until the lowest AIC value was reached. Odds ratios (ORs) for significant predictors were computed. Secondly, based on the above model, a multinomial regression analysis was conducted to determine if SSRI was an independent predictor of the determined best-related panoramic index, while accounting for confounding by age, gender and other panoramic indices.

As an ancillary analysis to identify the impact of different SSRI agents, the subset of data for SSRI users was used to build a proportional odds model with the selected panoramic index as dependent variable, using age, gender and type of SSRI agent as predictors.

Results

Descriptive values of demographic and radiographic measurements are summarized in Table 1. A total of 112 subjects: 64 active SSRI users and 48 controls were assessed. Mean age in active group was 35.2 (± 11.9) years and in the control group was 31.6 (± 9.7) years. No significant differences were noted in mean age between the two groups (independent sample's *t*-test, $p = 0.087$). The active group had 53 females (82.8%) and 11 (17.2%) males whereas the control group had 29 (60.4%) females and 19 (39.6%) males. Frequency-weighted X^2 tests controlling for difference in group sizes demonstrated females were significantly over represented among SSRI users (Pearsons X^2 statistic = 0.623, $p = 0.022$) with an OR of 1.379 [95% confidence interval (CI) (1.062–1792)] as compared to males. With regards to specific SSRI agents, among the 64 SSRI users, 20 used Citalopram, 20 used Sertraline, 13 used Escitalopram, 6 used Paroxetine and 5 used Fluoxetine.

Tables 2 and 3 show outcomes of correlation matrix analyses. Amongst the demographic variables; SSRI use correlated significantly with gender, which was significantly correlated to age. Age and gender were significantly correlated to KI category and PMI, respectively. SSRI use was correlated to several panoramic indices; namely; KI category, condylar pathology, mean ramus height and mean cortical width (Table 2). Amongst the panoramic indices, several significant correlations were notable. KI category significantly correlated with Antegonial notching index, mean cortical width and PMI. Mean ramus height and cortical width were

Table 2 Correlation matrix: independent variables and radiographic indices

Spearmans r (p-value)	*SSRI use*	*Age*	*Gender*
SSRI use	1	–	–
Age	0.20 (0.10)	1	–
Gender	**0.41 (0.01)**	**0.48 (<0.001)**	1
KI category	**0.5(<0.001)**	**0.23** (0.04)	−0.17 (0.38)
Antegonial notching	0.12 (0.14)	0.06 (0.61)	−0.27 (0.13)
Condylar pathology	**0.28** (0.04)	0.10 (0.46)	0.03 (0.79)
Mean ramus height	**0.40 (<0.001)**	−0.09 (0.48)	−0.04 (0.68)
Mean cortical width	**0.31(<0.001)**	0.09 (0.22)	0.07 (0.51)
PMI	0.13 (0.19)	0.07 (0.90)	**0.16 (<0.001)**
PMI <0.3	0.01 (0.95)	−0.04 (0.69)	0.48 (0.08)

KI, Klemetti index; PMI, panoramic mandibular index; SSRI, selective serotonin reuptake inhibitor.
Variables: age: continuous, SSRI use: categorical, levels: active/control; gender: categorical, levels: female/male; KI categories: categorical, levels: c1, c2 or c3; antegonial notching (highest score among left and right sides): categorical, levels: none, mild, moderate, severe; condylar anatomy (highest score among left and right sides): categorical, levels: normal, condylar pathology, flat. PMI: continuous, PMI <0.3: categorical; levels: yes, no.
[a]*p* value was significant at 0.05, significant values in bold font

similarly correlated. PMI was significantly correlated with mean cortical width, whereas PMI <0.3 was significantly correlated to Condylar pathology, mean ramus height, mean cortical width and PMI (Table 3).

The distribution of KI categories was significantly different between SSRI active and control groups (X^2 statistic = 13.165, p = 0.001) (Figure 2). The category C3 was significantly overrepresented in the SSRI Active group. Multinomial regression models (forward stepwise, reference category: C1) were constructed with SSRI use, age and gender as predictors and revealed significant effects for all predictors (Mc Fadden Pseudo R^2 squared = 0.143; X^2 statistic = 36.068, p < 0.001). As compared to C1, SSRI use had OR 2.926 [95% CI (1.07–8.04)] for category C2 and an OR of 19.86 [95% (CI 3.91–100.69)] for category C3.

Significantly greater number of subjects in the SSRI active group had flat condylar anatomy on both sides as compared to control subjects (right side: X^2 statistic = 6.41, p = 0.41; left side: X^2 statistic = 8.84, p = 0.012) (Figure 3). Multinomial regression modeling using age, gender and SSRI use, showed only SSRI use was significant in the final model (right side: Mc Fadden Pseudo R^2 = 0.053; X^2 statistic = 9.414, p = 0.009; left side: Mc Fadden Pseudo R^2= 0.143; X^2 statistic = 36.068, p < 0.001).

However, the distribution of antegonial notching categories for both left and right sides showed no significant differences between the two groups (right side: 3.207, p = 0.524; left side: 3.891, p = 0.424) (Figure 4). Multinomial regression modeling showed no significant effects of age, gender or SSRI use on the incidence of the antegonial notching category (right side: Mc Fadden Pseudo R^2= 0.040, X^2 statistic = 7.505, p = 0.585; Left side: Mc Fadden Pseudo R^2 = 0.086; X^2 statistic = 16.09; p = 0.187).

Multivariate generalized linear modeling controlling for age and gender revealed significant effects of SSRI use on mean ramus height (f statistic = 5.774; p = 0.001) (Figure 5a) and MCW (f statistic = 3.039, p = 0.032) (Figure 5b).

Generalized linear modeling with age and gender and SSRI use as predictors showed no significant impact upon panoramic mandibular indices (inferior PMI: f statistic = 0.687, p = 0.562; superior PMI = f statistic = 1.046; p = 0.375) (Figure 6). Similarly, binary logistic regression showed non-significant effect on mean PMI <0.3 (Mc Fadden Pseudo R^2 = 0.016, X^2 statistic = 2.141, p = 0.543) of age (OR = 1.00, p = 0.91), gender (OR for male gender = 0.49, p= 0.163) or SSRI use (OR for SSRI use present = 1.14, p = 0.762).

Multiple regression with model selection was initiated using as predictors: age, gender and panoramic indices that significantly correlated to demographic variables, including KI category, condylar pathology, mean ramus height, mean cortical width and PMI. The full and best-fit model results are summarized in Table 4. The best-fit model (AIC = 130. 25) showed significant impact of gender (OR = 1.4), KI (OR = 1.3) and mean ramus height (OR = 1.0) with low variance

Table 3 Correlation matrix of dependent variables (radiographic indices)a

Spearmans r (p- value)	*KI*	*Antegonial notching*	*Condylar anatomy*	*Mean ramus height*	*Mean cortical width*	*PMI*	*PMI <0.3*
KI category	1.00	**0.43 (<0.001)**	0.20 (0.14)	0.13 (0.21)	**0.37 (<0.001)**	**0.14** (0.03)	0.48 (0.06)
Antegonial notching	–	1.00	0.19 (0.26)	0.12 (0.34)	0.22 (0.06)	0.15 (0.37)	0.22 (0.15)
Condylar pathology	–	–	1.00	0.05 (0.68)	0.08 (0.54)	−0.14 (0.06)	**−0.32** (0.02)
Mean ramus height	–	–	–	1.00	**0.43 (<0.001)**	−0.22 (0.72)	**−0.23** (0.07)
Mean cortical width	–	–	–	–	1.00	**0.46 (<0.001)**	**0.41 (<0.001)**
PMI	–	–	–	–	–	1.00	**0.87 (<0.001)**
PMI <0.3	–	–	–	–	–	–	1.00

KI, Klemetti index; PMI, panoramic mandibular index.
[a]*p*-value significant at 0.05, Variables: KI categories: categorical, levels: c1, c2 or c3; antegonial notching (highest score among left and right sides): categorical, levels: none, mild, moderate, severe; condylar anatomy (highest score among left and right sides): categorical, levels: normal, condylar pathology, flat. PMI: continuous, PMI <0.3: categorical; levels: yes, no.

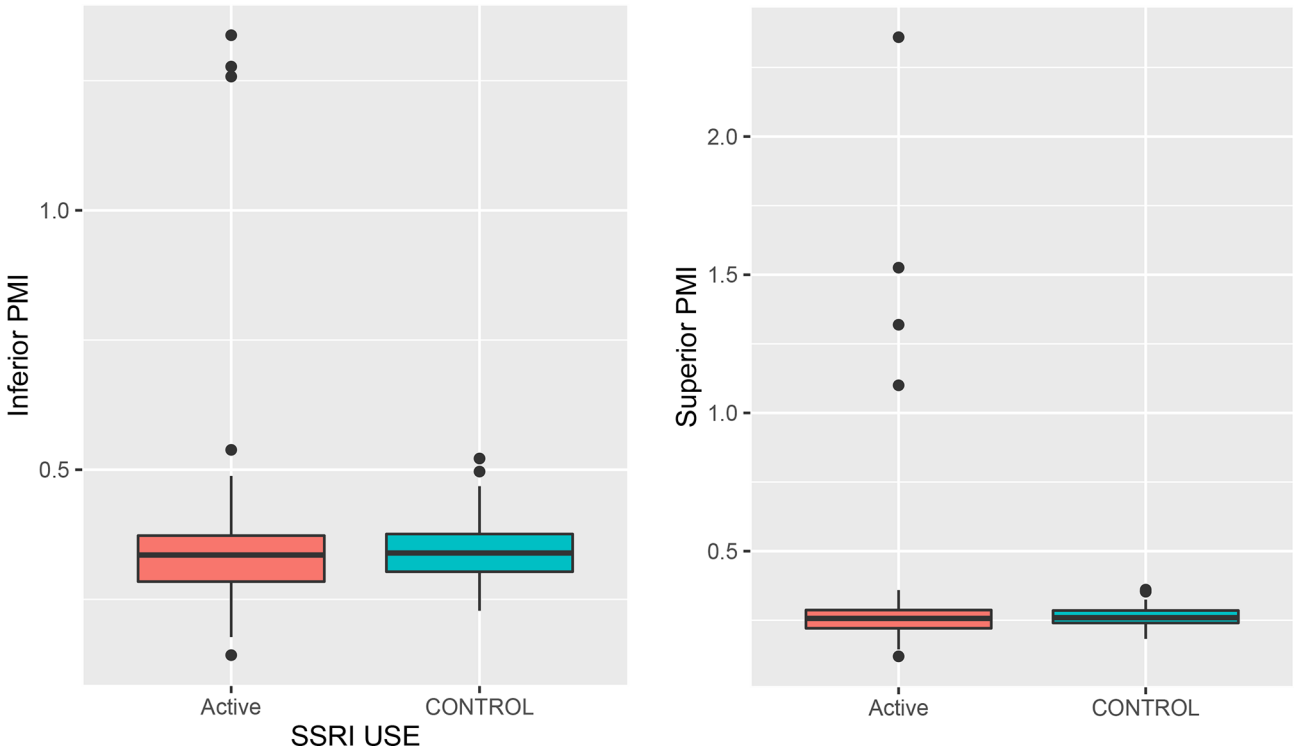

Figure 6 Inferior and superior panoramic mandibular index in SSRI active and control groups (mean of right and left side)

inflation values (<1.1) of each of these predictors indicating no multicollinearity. The KI was the selected as the "best-associated" panoramic index. Table 5 summarizes the multinomial regression performed with KI category as dependent variable. Here, KI category C1 was considered as the reference level. KI category C3 was significantly predicted by SSRI use (OR = 31.2, p = 0.002), female gender (17.5, p = 0.006), and severe antegonial notching (OR = 1289, p < 0.001). For SSRI users, the proportional odds model with SSRI type, age

Table 4 Multiple regression analysis to ascertain panoramic indices best associated with SSRI use

Full model[a]: SSRI use = age + gender + KI category + condylar anatomy + mean ramus height + mean cortical width + PMI				
Summary statistics: AIC = 133.9, likelihood ratio[b] = 8.97, p[b] ≤0.001				
Predictors	*VIF*	*Odds ratio*	*t-statistic*	*-pvalue*
Age	1.3	1.0	−0.06	0.95
Gender	1.2	1.4	3.36	0.001
KI category	1.3	1.3	4.08	<0.001
Condylar anatomy	1.1	1.1	1.79	0.07
Mean ramus height	1.6	1.0	3.40	0.001
Mean cortical width	2.0	0.9	−1.03	0.30
PMI	1.2	1.1	0.57	0.57
Final model[a] = SSRI use = gender + KI category + mean ramus height				
Summary statistics: AIC = 130.2, likelihood ratio[b] = 8.24, p^b = <0.001				
Predictors	*VIF*	*Odds ratio*	*t-statistic*	*p-value*
Gender	1.0	1.4	3.70	<0.001
KI category	1.0	1.3	4.47	<0.001
Mean ramus height	1.0	1.0	3.54	0.001

AIC, Akaike information criterion; KI, Klemetti index; PMI, panoramic mandibular index; SSRI, selective serotonin reuptake inhibitor.
[a]Dummy coding for variables: SSRI use: controls = 0, SSRI users = 1; gender: male = 0, female = 1; KI category: c1 = 1, c2 = 2, c3 = 3; condylar pathology: normal = 0, pathology present = 1, flat = 2.
[b]Likelihood test for model comparison with null model containing only intercept. Significant values in bold text.

Table 5 Multinomial regression analysis with KI category as dependent variablea

Full model[a]: KI = mean ramus height + SSRI use + age + gender + antegonial notching + condylar anatomy + mean ramus height + mean cortical width + PMI,		
Summary statistics: AIC = 189. 34, likelihood ratio[b] = 66.01, p[b] = <0.001		
Predictors	***Odds ratio for KI category C2 (p-value)***	***Odds ratio for KI category C3 (p-value)***
Age	0.98 (0.21)	1.06 (0.07)
Gender	1.3 (0.32)	**17.53 (0.006)**
SSRI use	**4.41 (0.02)**	**31.18 (0.002)**
Mean ramus height	0.94 (0.05)	0.98 (0.30)
Mean cortical width	2.60 (0.05)	2.30 (0.10)
PMI	61.89 (0.17)	1229.05 (0.30)
Antegonial notching		
Antegonial notching - normal	1.09 (0.44)	0.21 (0.05)
Antegonial notching - moderate	0.96 (0.49)	4.51 (0.13)
Antegonial notching- severe	**2568.51 (<0.001)**	**1289.07 (<0.001)**
Condylar anatomy		
Condylar anatomy - normal	0.22 (0.16)	0.40 (0.30)
Condylar anatomy -pathology present	0.46 (0.30)	0.29 (0.24)

AIC, Akaike information criterion; KI, Klemetti index; PMI, panoramic mandibular index; SSRI, selective serotonin reuptake inhibitor.
[a]Reference category: KI category C1.
[b]Likelihood test for model comparison with null model containing only intercept. Significant values in bold text.

and gender as predictors showed that for the outcome KI (reference category = C1), gender alone was a significant predictor (Wald statistic = 2.58, OR = 12.85, p = 0.009) but not age (Wald statistic = −0.08, OR = 0.91, p = 0.93) and type of SSRI (Escitalopram; Wald statistic = 0.67, OR = 1.66; p = 0.50, Fluoxetine; Wald statistic = 0.80, OR = 2.15, p = 0.42; Paroxetine; Wald statistic = −0.46, OR = 0.63, p = 0.64; Sertraline; Wald statistic = −0.12, OR = 0.91, p = 0.90).

Discussion

The primary purpose of this study was to investigate the association between the intake of SSRIs and panoramic mandibular indices, which have been widely assessed as indicators of skeletal BMD.[31–42] Skeletal BMD is also correlated to mandibular BMD,[45] which is similarly reflected by panoramic indices.[47] As jawbone BMD impacts local microarchitecture,[48] its loss is suggested as a risk factor for alveolar bone loss in periodontits[49] although the not conclusively. Despite their limitations, panoramic indices mentioned may serve as screening tools for the effect of SSRIs on jawbones and BMD due to their widespread availability. It is plausible that a negative impact on panoramic indices may reflect deleterious changes in skeletal and local BMD and possibly a greater susceptibility to related pathology such as periodontal disease. To our knowledge, this is the first study to report on the panoramic indices as related to clinical SSRI use. However, such an association needs to be evaluated in light of the fact that numerous local, systemic and environmental factors converge to influence bone condition and the exact clinical value of panoramic indices is yet undetermined.

Notably, there is scare dental literature regarding the implications of SSRIs on dental procedures and their outcomes.[29,30,50] The link between SSRI use and bone health however, is affected by several patient- and drug-related factors. These include age, gender, type of SSRI drug, dosage and duration of exposure and the mental health status of the patient.[16] The present study was limited to individuals in the age range of 20–65 years as the reliability of these indices in adolescents and older individuals could be lower, owing to the developmental stage and age associated decline which may be sharper after 60 years of age.[51] In the present study, females showed significantly higher odds of SSRI use, very likely reflecting the well-recognized gender differences in depression and anxiety disorders.[52] Therefore, both age and gender were used as independent predictors in the multivariate analyses. Increase in drug dosage and duration of exposure have both been associated positively with long bone fracture risk,[19,53] whereas others have noted that such risk peaked at about 8 months of SSRI consumption and remained elevated thereafter.[53] In the present study, a threshold of 6 months was used in an attempt to avoid confounding from very short durations of SSRI consumption.

In the correlation matrix analysis, increasing KI category was correlated with both SSRI use and age. After adjusting for age and gender, the KI index was significantly different between the SSRI active and control groups and SSRI users had an OR 2.926 [95% CI (1.07–8.04)] for category C2 over C1 and an OR of 19.86 [95% CI (3.91–100.69)] for category C3 over C1, as

compared to non-users. Considering moderate or severe cortical erosion is associated with osteopenia in 80% cases,[36] these findings can be clinically significant. Paradoxically, increasing KI was also positively correlated with mean MCW and ramus height. Correspondingly, both these parameters were noted as higher in SSRI users after controlling for demographic variables. MCW of <3 mm has low sensitivity but good specificity for individuals with reduced bone density.[36] For this cohort, the average MCW in both SSRI users and non-users was >3 mm, possibly indicating a low prevalence of overt osteopenia or osteoporosis.

A significant finding of correlation matrix analysis was several significant correlations of both demographic and panoramic indices. A limitation of the univariate analyses of panoramic indices in relation to SSRI use is that these do not take the noted collinearity into account. In order to ascertain the panoramic indices with independent effects on SSRI use, multiple regression analysis with model selection was performed. In best-fit model, KI category and mean ramus were significant predictors of SSRI use. A single unit rise KI category significantly increased the odds of SSRI use by 1.3, whereas mean ramus height had an OR of 1.0. Therefore, KI category was selected as the panoramic index of choice, and verified by multinomial regression with KI as dependent variable. This analysis showed SSRI use as an independent predictor of worse KI category C2 and C3, with increasing odds, after accounting for significant associations with demographic factor gender and panoramic index Antegonial notching index. Together, these results suggest that among the evaluated indices KI category showed "best" independent association with SSRI use. Therefore, it was the basis for subgroup analysis. Consistent with its association with poor BMD,[36] this finding suggest that further studies could preferentially assess KI as an panoramic indicator of SSRI related bone changes.

Differences have been noted in fracture risk associated with various SSRI agents.[54] However, an ancillary subgroup analysis the subset of data for SSRI users with ordinal KI categories as outcome showed no significant impact of different SSRI agents but found gender alone as a significant predictor of worse KI. It is likely that the small sample size and lack of information regarding dose and precise duration of exposure do not permit a dissection of specific drug related differences in the present study.

PMI has shown good sensitivity and specificity for low BMD at a cut-off of 0.3.[36] However, no statistical difference was determined in the PMI distribution between the control and SSRI groups. Using a cut-off of 0.3 in a binary logistic regression model, again no significant impact of SSRI use, age or gender was notable, although SSRI use showed a trend towards higher odds PMI of <0.3, there is need for further investigation in larger cohorts. Increased incidence of condylar flattening was found associated with SSRI use. While it is known that SSRIs can induce sleep bruxism and may exacerbate TMD,[55,56] these results may be seen as preliminary evidence that SSRIs' impact extends to condylar structure and wear. The association of SSRI with altered mandibular morphology warrants further investigations into effects of SSRI use on TMD, especially as antidepressants are used in treatment of TMD. Overall, the results of our preliminary study support the hypothesis that SSRIs use is associated with detrimental impact on BMD and craniofacial skeleton.

The findings must be viewed in light of several limitations inherent in the current study. The study design was a retrospective cohort and although demographic covariates were factored into the analyses, other potential confounders remained unaddressed. Several other factors not taken into consideration in this preliminary study included race, alcohol intake, levels of physical activity, obesity, and nutritional status, vitamin D and calcium deficiency. The standard diagnosis of low BMD is via DXA or CT Hounsfield units.[55] Linear measurements from panoramic radiographs have shown considerable heterogeneity[57] in screening efficacy for low BMD and so are often combined with other diagnostic tools, which were lacking in the present investigation. Furthermore, panoramic radiographs may present with unequal magnification and distortion based on patient positioning. Despite using the same machine and exposure parameters, unequal magnification may persist and may also occur in different regions of the same radiograph.[43,58] In the current retrospective study, the radiographs were obtained for routine purposes and not under standardized conditions. It is likely that differences in operator and acquisition parameters have a confounding effect. MCW index is affected by the condition/presence of the teeth in the region due to distribution of occlusion forces[59] that were not accounted for in the current study. Moreover, *a priori* sample size was computation was not done in this preliminary investigation owing to a lack of pilot data. In the light of these limitations, these findings may be considered preliminary in nature and form a basis for larger scale epidemiological studies. Further investigations utilizing prospective designs, standardized BMD measurement tools, larger and stratified sample sizes, and careful drug monitoring are in order to understand how SSRI drugs impact dentomaxillary structures and related conditions.

Conclusion

In summary, this preliminary study suggested that SSRI intake was associated with lower BMD as indicated by worse panoramic radiomorphometric indices and alterations in the mandibular bone morphology. Amongst the evaluated panoramic indices, KI had the best independent association with SSRI use.

References

1. Ustün TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. *Br J Psychiatry* 2004; **184**: 386–92. doi: https://doi.org/10.1192/bjp.184.5.386
2. Kessler RC. The costs of depression. *Psychiatr Clin North Am* 2012; **35**: 1–14. doi: https://doi.org/10.1016/j.psc.2011.11.005
3. Pratt LA, Ph D, Brody DJ. Depression in the U. *S. Household Population* 2014; **172**: 2009–12.
4. Bachmann CJ, Aagaard L, Burcu M, Glaeske G, Kalverdijk LJ, Petersen I, et al. Trends and patterns of antidepressant use in children and adolescents from five western countries, 2005-2012. *Eur Neuropsychopharmacol* 2016; **26**: 411–9. doi: https://doi.org/10.1016/j.euroneuro.2016.02.001
5. Borrelli J. Taking control: the osteoporosis epidemic. *Injury* 2012; **43**: 1235–6. doi: https://doi.org/10.1016/j.injury.2012.06.001
6. Varner JM. Osteoporosis: a silent disease. *Ala Nurse* 2012; **39**: 10–12.
7. Services H. *National Institutes of Health Updated October 2010 1*; 2010. pp. 1–2.
8. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Cauley JA, Whooley MA, et al. Depressive symptoms and rates of bone loss at the hip in older women. *J Am Geriatr Soc* 2007; **55**: 824–31. doi: https://doi.org/10.1111/j.1532-5415.2007.01194.x
9. Mussolino ME, Jonas BS, Looker AC. Depression and bone mineral density in young adults: results from NHANES III. *Psychosom Med* 2004; **66**: 533–7. doi: https://doi.org/10.1097/01.psy.0000132873.50734.7d
10. Jacka FN, Pasco JA, Henry MJ, Kotowicz MA, Dodd S, Nicholson GC, et al. Depression and bone mineral density in a community sample of perimenopausal women: Geelong Osteoporosis Study. *Menopause* 2005; **12**: 88–91. doi: https://doi.org/10.1097/00042192-200512010-00015
11. Cizza G, Primma S, Csako G. Depression as a risk factor for osteoporosis. *Trends Endocrinol Metab* 2009; **20**: 367–73. doi: https://doi.org/10.1016/j.tem.2009.05.003
12. Moura C, Bernatsky S, Abrahamowicz M, Papaioannou A, Bessette L, Adachi J, et al. Antidepressant use and 10-year incident fracture risk: the population-based Canadian Multicentre Osteoporosis Study (CaMoS). *Osteoporos Int* 2014; **25**: 1473–81. doi: https://doi.org/10.1007/s00198-014-2649-x
13. Warden SJ, Nelson IR, Fuchs RK, Bliziotes MM, Turner CH, Serotonin TCH. Serotonin (5-hydroxytryptamine) transporter inhibition causes bone loss in adult mice independently of estrogen deficiency. *Menopause* 2008; **15**: 1176–83. doi: https://doi.org/10.1097/gme.0b013e318173566b
14. Sansone RA, Sansone LA. SSRIs: bad to the bone? *Innov Clin Neurosci* **9**: 42–7.
15. Wu Q, Bencaz AF, Hentz JG, Crowell MD. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. *Osteoporos Int* 2012; **23**: 365–75. doi: https://doi.org/10.1007/s00198-011-1778-8
16. Eom CS, Lee HK, Ye S, Park SM, Cho KH. Use of selective serotonin reuptake inhibitors and risk of fracture: a systematic review and meta-analysis. *J Bone Miner Res* 2012; **27**: 1186–95. doi: https://doi.org/10.1002/jbmr.1554
17. Gebara MA, Shea MLO, Lipsey KL, Teitelbaum SL, Civitelli R, Müller DJ, et al. Depression, antidepressants, and bone health in older adults: a systematic review. *J Am Geriatr Soc* 2014; **62**: 1434–41. doi: https://doi.org/10.1111/jgs.12945
18. Battaglino R, Fu J, Späte U, Ersoy U, Joe M, Sedaghat L, et al. Serotonin regulates osteoclast differentiation through its transporter. *J Bone Miner Res* 2004; **19**: 1420–31. doi: https://doi.org/10.1359/JBMR.040606
19. Bliziotes MM, Eshleman AJ, Zhang XW, Wiren KM. Neurotransmitter action in osteoblasts: expression of a functional system for serotonin receptor activation and reuptake. *Bone* 2001; **29**: 477–86. doi: https://doi.org/10.1016/S8756-3282(01)00593-2
20. Westbroek I, van der Plas A, de Rooij KE, Klein-Nulend J, Nijweide PJ. Expression of serotonin receptors in bone. *J Biol Chem* 2001; **276**: 28961–8. doi: https://doi.org/10.1074/jbc.M101824200
21. Nam SS, Lee JC, Kim HJ, Park JW, Lee JM, Suh JY, et al. Serotonin inhibits osteoblast differentiation and bone regeneration in rats. *J Periodontol* 2016; **87**: 461–9. doi: https://doi.org/10.1902/jop.2015.150302
22. Haney EM, Warden SJ, Bliziotes MM. Effects of selective serotonin reuptake inhibitors on bone health in adults: time for recommendations about screening, prevention and management? *Bone* 2010; **46**: 13–17. doi: https://doi.org/10.1016/j.bone.2009.07.083
23. Cui C, Kaartinen MT, Serotonin KMT. Serotonin (5-HT) inhibits Factor XIII-A-mediated plasma fibronectin matrix assembly and crosslinking in osteoblast cultures via direct competition with transamidation. *Bone* 2015; **72**: 43–52. doi: https://doi.org/10.1016/j.bone.2014.11.008
24. Fraher D, Hodge JM, Collier FM, McMillan JS, Kennedy RL, Ellis M, et al. Citalopram and sertraline exposure compromises embryonic bone development. *Mol Psychiatry* 2016; **21**: 656–64. doi: https://doi.org/10.1038/mp.2015.135
25. Cray JJ, Weinberg SM, Parsons TE, Howie RN, Elsalanty M, Yu JC. Selective serotonin reuptake inhibitor exposure alters osteoblast gene expression and craniofacial development in mice. *Birth Defects Res A Clin Mol Teratol* 2014; **100**: 912–23. doi: https://doi.org/10.1002/bdra.23323
26. Correia-Leite de Marcelos PG, Regueira LS, Santiago-Jaegger IM, Cruz Perez DE, de Moraes Ramos-Perez FM, Evêncio Neto J, et al. Effects of treatment with fluoxetine on mandibular development: a morphological study in rats. *Acta Histochem* 2015; **117**: 582–9. doi: https://doi.org/10.1016/j.acthis.2015.05.005
27. Spangler L, Scholes D, Brunner RL, Robbins J, Reed SD, Newton KM, et al. Depressive symptoms, bone loss, and fractures in postmenopausal women. *J Gen Intern Med* 2008; **23**: 567–74. doi: https://doi.org/10.1007/s11606-008-0525-0
28. Westbroek I, Waarsing JH, van Leeuwen JP, Waldum H, Reseland JE, Weinans H, et al. Long-term fluoxetine administration does not result in major changes in bone architecture and strength in growing rats. *J Cell Biochem* 2007; **101**: 360–8. doi: https://doi.org/10.1002/jcb.21177
29. Chrcanovic BR, Kisch J, Albrektsson T, Wennerberg A. Is the intake of selective serotonin reuptake inhibitors associated with an increased risk of dental implant failure? *Int J Oral Maxillofac Surg* 2017; **46**: 782–8. doi: https://doi.org/10.1016/j.ijom.2017.01.016
30. Calciolari E, Donos N, Park JC, Petrie A, Mardas N. Panoramic measures for oral bone mass in detecting osteoporosis: a systematic review and meta-analysis. *J Dent Res* 2015; **94**(3 Suppl94): 17–27. doi: https://doi.org/10.1177/0022034514554949
31. Wu X, Al-Abedalla K, Rastikerdar E, Abi Nader S, Daniel NG, Nicolau B, et al. Selective serotonin reuptake inhibitors and the risk of osseointegrated implant failure: a cohort study. *J Dent Res* 2014; **93**: 1054–61. doi: https://doi.org/10.1177/0022034514549378
32. Jagelaviciene E, Kubilius R, Krasauskiene A. The relationship between panoramic radiomorphometric indices of the mandible and calcaneus bone mineral density. *Medicina* 2010; **46**: 95–103. doi: https://doi.org/10.3390/medicina46020014
33. Leite AF. Figueiredo PT de S, Guia CM, Melo NS, de Paula AP. Correlations between seven panoramic radiomorphometric indices and bone mineral density in postmenopausal women. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **109**: 449–56.
34. Gulsahi A, Paksoy CS, Ozden S, Kucuk NO, Cebeci AR, Genc Y. Assessment of bone mineral density in the jaws and its relationship to radiomorphometric indices. *Dentomaxillofac Radiol* 2010; **39**: 284–9. doi: https://doi.org/10.1259/dmfr/20522657
34. Neves FS, Oliveira LS, Torres MG, Toralles MB, da Silva MC, Campos MI, et al. Evaluation of panoramic radiomorphometric indices related to low bone density in sickle cell disease. *Osteo-*

poros Int 2012; **23**: 2037–42. doi: https://doi.org/10.1007/s00198-011-1810-z
35. Shakeel MK, Daniel MJ, Srinivasan SV, Koliyan R, Kumar JV. Comparative analysis of linear and angular measurements on digital orthopantomogram with calcaneus bone mineral density. *J Clin Diagn Res* 2015; **9**: ZC12–16. doi: https://doi.org/10.7860/JCDR/2015/13606.6163
36. Nakamoto T, Taguchi A, Ohtsuka M, Suei Y, Fujita M, Tanimoto K, et al. Dental panoramic radiograph as a tool to detect postmenopausal women with low bone mineral density: untrained general dental practitioners' diagnostic performance. *Osteoporos Int* 2003; **14**: 659–64. doi: https://doi.org/10.1007/s00198-003-1419-y
37. Taguchi A. Triage screening for osteoporosis in dental clinics using panoramic radiographs. *Oral Dis* 2010; **16**: 316–27. doi: https://doi.org/10.1111/j.1601-0825.2009.01615.x
38. Taguchi A, Sugino N, Miki M, Kozai Y, Mochizuki N, Osanai H, et al. Detecting young Japanese adults with undetected low skeletal bone density using panoramic radiographs. *Dentomaxillofac Radiol* 2011; **40**: 154–9. doi: https://doi.org/10.1259/dmfr/30045588
39. Devlin H, Karayianni K, Mitsea A, Jacobs R, Lindh C, van der Stelt P, et al. Diagnosing osteoporosis by using dental panoramic radiographs: the OSTEODENT project. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **104**: 821–8. doi: https://doi.org/10.1016/j.tripleo.2006.12.027
40. Klemetti E, Kolmakow S. Morphology of the mandibular cortex on panoramic radiographs as an indicator of bone quality. *Dentomaxillofac Radiol* 1997; **26**: 22–5. doi: https://doi.org/10.1038/sj.dmfr.4600203
41. Devlin H, Whelton C. Can mandibular bone resorption predict hip fracture in elderly women? A systematic review of diagnostic test accuracy. *Gerodontology* 2015; **32**: 163–8. doi: https://doi.org/10.1111/ger.12077
42. Ledgerton D, Horner K, Devlin H, Worthington H. Radiomorphometric indices of the mandible in a British female population. *Dentomaxillofac Radiol* 1999; **28**: 173–81. doi: https://doi.org/10.1038/sj.dmfr.4600435
43. Benson BW, Prihoda TJ, Glass BJ. Variations in adult cortical bone mass as measured by a panoramic mandibular index. *Oral Surg Oral Med Oral Pathol* 1991; **71**: 349–56. doi: https://doi.org/10.1016/0030-4220(91)90314-3
44. Pluskiewicz W, Tarnawska B, Drozdzowska B. Mandibular bone mineral density measured using dual-energy X-ray absorptiometry: relationship to hip bone mineral density and quantitative ultrasound at calcaneus and hand phalanges. *Br J Radiol* 2000; **73**: 288–92. doi: https://doi.org/10.1259/bjr.73.867.10817045
45. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2015. Available from: http://www.R-project.org/.
46. Horner K, Devlin H, Alsop CW, Hodgkinson IM, Adams JE. Mandibular bone mineral density as a predictor of skeletal osteoporosis. *Br J Radiol* 1996; **69**: 1019–25. doi: https://doi.org/10.1259/0007-1285-69-827-1019
47. Lindh C, Petersson A, Klinge B, Nilsson M. Trabecular bone volume and bone mineral density in the mandible. *Dentomaxillofac Radiol* 1997; **26**: 101–6. doi: https://doi.org/10.1038/sj.dmfr.4600217
48. Moeintaghavi A, Hosseinizarch H, Tabassi SM. The comparison of mandibular radiomorphometric indices in panoramic radiography between patients with chronic periodontitis and healthy individuals. *J Contemp Dent Pract* 2014; **15**: 461–5. doi: https://doi.org/10.5005/jp-journals-10024-1563
49. Pal S, Amrutesh S. Evaluation of panoramic radiomorphometric indices in Indian population Cumhuriyet. *Dent J* 2013; **16**: 273–81.
50. Gorman JM. Gender differences in depression and response to psychotropic medication. *Gend Med* 2006; **3**: 93–109. doi: https://doi.org/10.1016/S1550-8579(06)80199-3
51. van den Brand MWM, Samson MM, Pouwels S, van Staa TP, Thio B, Cooper C, et al. Use of anti-depressants and the risk of fracture of the hip or femur. *Osteoporosis International* 2009; **20**: 1705–13. doi: https://doi.org/10.1007/s00198-009-0849-6
52. Vestergaard P, Prieto-Alhambra D, Javaid MK, Cooper C. Fractures in users of antidepressants and anxiolytics and sedatives: effects of age and dose. *Osteoporos Int* 2013; **24**: 671–80. doi: https://doi.org/10.1007/s00198-012-2043-5
53. Drozdzowska B, Pluskiewicz W, Tarnawska B. Panoramic-based mandibular indices in relation to mandibular bone mineral density and skeletal status assessed by dual energy X-ray absorptiometry and quantitative ultrasound. *Dentomaxillofac Radiol* 2002; **31**: 361–7. doi: https://doi.org/10.1038/sj.dmfr.4600729
55. Pfeiffer P, Bewersdorf S, Schmage P. The effect of changes in head position on enlargement of structures during panoramic radiography. *Int J Oral Maxillofac Implants* 2012; **27**: 55–63.
56. Gulsahi A, Yüzügüllü B, Imirzalioglu P, Genç Y. Assessment of panoramic radiomorphometric indices in Turkish patients of different age groups, gender and dental status. *Dentomaxillofac Radiol* 2008; **37**: 288–92. doi: https://doi.org/10.1259/dmfr/19491030
57. Schulze R, Krummenauer F, Schalldach F, d'Hoedt B, d'Hoedt B. Precision and accuracy of measurements in digital panoramic radiography. *Dentomaxillofac Radiol* 2000; **29**: 52–6. doi: https://doi.org/10.1038/sj.dmfr.4600500
58. Van Cann EM, Koole R. Abnormal bleeding after an oral surgical procedure leading to airway compromise in a patient taking a selective serotonin reuptake inhibitor and a nonsteroidal antiinflammatory drug. *Anesthesiology* 2008; **109**: 568–9. doi: https://doi.org/10.1097/ALN.0b013e318182c88c
59. Rajan R, Sun YM. Reevaluating antidepressant selection in patients with bruxism and temporomandibular joint disorder. *J Psychiatr Pract* 2017; **23**: 173–9. doi: https://doi.org/10.1097/PRA.0000000000000227
60. Isa Kara M, Ertaş ET, Ozen E, Atıcı M, Aksoy S, Erdogan MS, et al. BiteStrip analysis of the effect of fluoxetine and paroxetine on sleep bruxism. *Arch Oral Biol* 2017; **80**: 69–74. doi: https://doi.org/10.1016/j.archoralbio.2016.12.013