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Original Article

Hylonome

Changes in volumetric BMD of radius and tibia upon antidepressant drug administration in young depressive patients

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Abstract

Objectives: To determine longitudinal changes in trabecular volumetric BMD (vBMD) at tibia and radius in young depressive patients under antidepressants using pQCT. **Methods:** PQCT data on 26 patients (22 females, 4 males) on serotonin re-uptake inhibitors (SSRI), and 14 patients (12 females, 2 males) on non-SSRI (10 SNRI, 4 TCA) were obtained at 4% and 66% of radius and tibia at baseline and at 12-month. Depression was assessed by Beck Depression Inventory (BDI) at baseline and follow-up. Wilcoxon tests were performed to find longitudinal changes in bone parameters within each group, Mann-Whitney tests to detect differences between groups. **Results:** The two groups were comparable with regard to age, height and BDI. None of the measured bone parameters changed in the SSRI group. In the non-SSRI group trabecular vBMD increased slightly but significantly from baseline to follow-up at radius and tibia ($p<0.03$). Between group differences were significant for trabecular BMD at the radius. BDI decreased significantly in both groups by the same amount. **Conclusions:** Bone properties were found to be stable over 12 months under therapy with SSRIs. Whether SNRI and TCA indeed increase trabecular vBMD need to be shown in larger cohort.

Keywords: SSRI, TCA, SNRI peripheral quantitative computed tomography, Bone geometry, Depression, BMD

Introduction

Selective reuptake inhibitors of Serotonin (5-hydroxytryptamine; 5-HT) and or Noradrenalin (norepinephrine) are frequently used in therapy for depression and particularly in chronic pain disorders such as somatoform pain syndrome[1]. The literature about the effect of serotonin, its inhibition of synthesis or reuptake is conflicting. Whereas most of the clinical longitudinal and cross-sectional studies found a reduction of BMD associated with SSRI therapy[2-6], some clinical[7,8] and basic science studies[9] did not show any difference in BMD nor did they find a change in bone formation and histomorphometry upon inhibition of serotonin synthesis.

Most of the large cohort studies cited above have had the limitation of confounding by indication. Because depression is also likely to have an adverse effect on bone integrity[10], BMD[11] and fracture rate[12], the effects of SSRIs on bone need to be compared to a similarly depressed population. A recent meta-analysis has analysed the widely documented association of depression and low bone mass and its clinical relevance[12]. Areal BMD of depressed subjects was found to be between 3.5% and 7.3% lower compared to non-depressed subjects, depending on skeletal site. Potential mechanisms for depression induced bone loss are a hypercortisolism due to a change in the set point threshold for negative feedback in the hypothalamic-pituitary-adrenal (HPA) axis[13]. Further involved mechanism are increased levels of pro-inflammatory cytokines[14,15] and radikals of oxidative stress (ROS).

Due to the interaction between antidepressants and depression, the most valid approach would be to compare bone changes between depressed patients on SSRIs to patients on other antidepressant medication and also to depressed patients on no medication. However, this is hardly possible in clinical practice, as patients with major depression are almost always treated with antidepressants. Further, except for one animal study[16], none of

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the previous studies assessed the contribution of changes in muscle mass/force to the changes measured in bone parameters.

The aim of this study was to assess the effect of 12 months of antidepressant therapy on volumetric BMD and bone geometry of the radius and tibia in young depressive patients and to compare agents belonging to the SSRI group to those of other anti-depressants. To reduce the influence of confounding factors, we have excluded post-menopausal subjects. We have quantified depression severity to assure comparability of the two drug groups and to assess the effect of changes in depression on bone. Changes in muscle volume at the forearm and lower leg were also measured and related to the changes in bone parameters in order to differentiate between the drugs' direct effects on bone and indirect effects via changes in muscle volume/force.

Methods

We have conducted a longitudinal study in young depressed patients assessing the influence of different antidepressant drugs on volumetric BMD and bone geometry at the distal epiphyses and shafts of the radius and tibia measured by pQCT over 12 months. In an additional cross-sectional study, we have compared baseline bone and soft-tissue parameters of the forearm and lower leg of our depressed patients to a healthy control group comparable with regard to sex, age, height and weight. The study protocol was approved by the Ethics committee of the Canton of Bern, and all subjects gave written informed consent.

Subjects

Depressed patients seen at the psychiatric private clinic Wyss in Münchenbuchsee, Switzerland were recruited. Inclusion criteria were age between 25 and 45 years, and starting or persisting therapy with an SSRI, SNRI or tricyclic antidepressant. All patients with depression seen for this study were patients with a first manifestation of moderate and severe disease. Therapy was tailored to additional symptoms such as sleeping disorders, for which TCAs were more likely to be used.

Exclusion criteria were menopause, previous therapy with an antidepressant other than the current one, therapy with bisphosphonates or glucocorticoids, bone metabolic diseases, hyper-/hypoparathyroidism, hyper/hypothyreoidism, chronic renal insufficiency, cancer, pregnancy or lactation.

Assessment of BDI

The Beck-Depression-Inventory (BDI) is a 21-item self-rating method that evaluates the severity of depressive symptoms during the last 2 weeks[17]. Each item is rated from 0 to 3.The total scores of the BDI range from 0 to 63, with higher scores indicating more severe depressive symptoms.

Bone measurements

Measurements were performed with a Stratec XCT 2000 scanner (Stratec Medical, Pforzheim, Germany). This peripheral quantitative computed tomography apparatus measures attenuation of x-rays which are linearly transformed into hydroxyapatit (HA) densities. Unlike some other pQCT scanners, the Stratec XCT 2000 is calibrated with respect to water which is set at 60 mg hydroxyapatite (HA), so that fat results in 0 mg HA[18]. HA equivalent densities are automatically calculated from the attenuation coefficients by employing the manufacturer's phantom which itself is calibrated with respect to the European Forearm Phantom (EFP; QRM, Erlangen, Germany)[18]. The effective radiation dose is indicated to be 0.2 μSv per scan and per scout view by the manufacturer.

Radius bone length was set equal to ulnar length, which was measured to the near-est 5 mm with a measuring tape by palpation from the olecranon to the ulnar styloid. Tibia length was determined from the medial knee joint cleft to the end of the medial malleolus. A scout view of the distal end of the tibia/radius was performed and the automated detection algorithm provided by the manufacturer was used to place the reference line at the distal bone end. At the radius scans were performed at 4% and 66% of the bone's total length measured from the reference line. At the tibia, the 4% scan at the distal epiphysis was performed using the scout view at the distal end. The 66% scan at the tibia could not be performed using the scout view at the distal tibia because of the limited translation distance of the pQCT unit. Therefore, an additional scout view was performed at the proximal tibia, where the reference line was placed on the medial plateau. From there, a scan was placed at 34% which corresponds to the skeletal site of 66% measured from the distal end. Slice thickness was 2.2 mm, and voxel size was set at 0.5 mm with a scanning speed of 20 mm/s.

Bone parameters measured by pQCT

Epiphyseal scans (4%): The periosteal surface of each bone's epiphysis was found by a contour algorithm based on thresholding at 180 mg/cm^3. CSA, and total BMD was determined. Concentric pixel layers were peeled off from the bone's perimeter until a central area covering 45% of the total bone CSA was left. From this central area, trabecular BMD was determined. Reproducibility determined at our laboratory in 9 subjects with 4 repeat measurements resulted in smallest detectable differences (1.96*SD) of 4.74 mg/cm^3 and 3.92 mg/cm^3 for trabecular BMD at the radius and tibia, respectively, and 11.68 mg/cm^3 and 5.39 mg/cm^3 for total BMD at the radius and tibia, respectively.

Diaphyseal scans (66%): The periosteal surface of the bone's diaphysis was found by a contour algorithm based on a threshold of 280 mg/cm^3. Total CSA (including the marrow CSA), and the polar bone strength strain index (SSIpol)[18] were calculated. Cortical bone was selected with an inner and outer threshold of 710 mg/cm^3. Of the selected area, cortical CSA and cortical BMD were calculated.

Soft tissue assessment

Of the diaphyseal scans at 66% of the forearm and lower leg, subcutaneous fat CSA was determined by selecting the area with thresholds 240 to +40 mg/cm^3 HA density after

Patients on SSRI (n=26)	Patients on SNRI (n=10)	Patients on TCA (n=4)
fluoxetine hydrochloride (1) paroxetine hydrochloride (5) citalopram hydrobromide (7) sertraline hydrochloride (3) escitalopram oxalate (10)	venlafaxine hydrochloride (7) duloxetine (3)	amitriptyline hydrochloride (3) trimipramine (1)

Table 1. Overview of antidepressant medications used in either SSRI, SNRI or TCA group.

	SSRI (n=26)		SNRI, TCA (n=14)		Mann-Whitney p-value
Females/males	22/4		12/2		
Age [yrs]	36.88	(8.74)	37.21	(7.95)	0.812
Height [cm]	167.54	(7.72)	168.36	(8.10)	0.705
Weight [kg]	68.58	(15.61)	79.21	(18.65)	0.039
Therapy Duration at baseline [months]	10.19	(34.64)	7.86	(6.27)	0.051
BDI at baseline	18.12	(7.97)	22.14	(11.15)	0.149

Table 2. Baseline characteristics of the SSRI and non-SSRI groups (means and sd in brackets, and p-values for Mann-Whitney tests).

smoothing the image, and muscle CSA was determined by subtracting the total bone CSA and subcutaneous fat CSA from the total limb CSA. The fat CSA/muscle CSA ratio was also calculated.

Data analysis

Subject characteristics as well as bone and soft-tissue parameters at baseline were compared between the two groups by non-parametric Mann-Whitney tests due to small sample size in the non-SSRI group. For the longitudinal changes within each group, baseline and follow-up values were compared by Wilcoxon tests. Longitudinal changes were compared between groups by Mann-Whitney tests. Within each group, Spearman correlations were performed between change in BDI and bone parameters found to differ between baseline and follow-up. For bone parameters with significant changes between baseline and follow-up, a linear regression between the respective bone parameters at the radius and tibia was also performed in order to evaluate systemic changes. Further, for bone parameters with significant changes between baseline and follow-up, bone changes were correlated to changes in muscle CSA of the particular limb. For the cross-sectional study, baseline soft-tissue data of all depressive subjects was compared to the group of healthy subjects by Mann-Whithey tests. Statistical analyses were performed using SPSS (Version 17.0).

Results

Subject parameters

A total of 56 depressive patients were recruited for the present study and performed baseline measurements. Of these, only 40 were willing to perform follow-up measurements after 12 months.

Of the 40 patients who completed the study 26 were on therapy with SSRIs, and 14 were on non-SSRIs as shown in Table 1. Baseline characteristics of the two groups are shown in Table 2. The two groups were comparable with regard to age, and height, but the non-SSRI group was 15.5% (p=0.04) heavier than the SSRI group and therapy duration at baseline tended to be 22.9% (p=0.05) longer in the SSRI group. Median BDI at baseline were with 18 in the SSRI group and 24 in the non-SSRI group also comparable (p=0.14). Mean duration to follow-up was with 14.1±1.5 months in the SSRI and 13.7±1.4 months in the non-SSRI group comparable between groups (p=0.44). At follow-up, BDI had improved significantly and similarly in both groups ($p \leq 0.01$) to a median of 6 in the SSRI and 9 in the non-SSRI group (p=0.176 for difference between groups). None of the bone and soft-tissue parameters differed between the two groups at baseline.

Within the SSRI group, none of the measured bone parameters at neither the radius nor tibia changed between baseline and follow-up (Table 3). Within the non-SSRI group, trabecular vBMD at the distal radius and tibia increased significantly by 1.8 % (p=0.021) and 1.0% (p=0.025), respectively. Results were comparable when paired t-tests were performed. Within the SSRI group 3 subjects had an increase in trabecular BMD at the radius exceeding the smallest detectable difference and one subject had a detectable decrease, while at the tibia 4 subjects had a detectable increase. In the non-SSRI group at both the radius and tibia 4 subjects had a detectable increase. When longitudinal changes were compared between groups, only trabecular vBMD at the radius was significantly different (p=0.032) between groups. Muscle and fat CSA at the forearm

		SSRI						SNRI & TCA					
			Baseline		Follow-up		Wilcoxon		Baseline		Follow-up		Wilcoxon
		N	Mean	SD	Mean	SD	p-value	N	Mean	SD	Mean	SD	p-value
Radius 4%	Total CSA [mm²]	18	331.83	65.99	331.89	65.99	.862	11	323.59	52.00	320.16	47.75	.285
	Total BMD [mg/cm³]	18	334.62	50.21	336.22	49.71	.199	11	344.46	38.39	348.87	34.04	.286
	Trab. BMD [mg/cm³]	18	176.29	38.80	176.78	39.64	.811	11	193.76	37.41	197.33	37.66	**.021**
Radius 66%	Total CSA [mm²]	12	120.25	21.28	122.19	19.44	.099	9	129.08	31.05	128.36	31.58	.594
	Cort. CSA [mm²]	12	74.63	12.32	75.56	11.61	.090	9	79.06	15.19	80.08	14.15	.122
	Cort. BMD [mg/cm³]	12	1164.90	33.74	1160.58	29.57	.117	9	1163.98	49.43	1157.38	39.41	.139
Tibia 4%	Total CSA [mm²]	24	1105.52	176.96	1105.21	180.23	.742	12	1078.69	135.51	1073.07	130.78	.182
	Total BMD [mg/cm³]	24	290.80	35.26	291.69	36.19	.109	12	308.10	30.91	311.08	29.71	.092
	Trab. BMD [mg/cm³]	24	223.67	38.92	224.26	38.65	.415	12	234.90	36.45	237.21	35.62	**.025**
Tibia 66%	Total CSA [mm²]	22	555.26	104.00	555.27	103.13	.876	10	507.85	70.58	509.60	70.07	.207
	Cort. CSA [mm²]	22	309.11	48.63	309.92	47.98	.269	10	292.38	31.09	293.13	30.42	.374
	Cort. BMD [mg/cm³]	22	1141.49	28.91	1139.57	27.63	.649	10	1134.33	49.11	1134.02	45.76	.959

Table 3. Bone variables at baseline and follow-up (mean and sd) in the two groups and p-values of Wilcoxon test within each group.

		SSRI							SNRI & TCA						
			Baseline			Follow-up		Wilcoxon		Baseline			Follow-up		Wilcoxon
		N	Mean	SD	N	Mean	SD	p-value	N	Mean	SD	N	Mean	SD	p-value
Forearm	Muscle CSA [mm²]	26	2828.3	707.1	13	2708.4	627.1	0.753	14	2770.3	706.4	9	2797.5	576.9	0.767
	Fat CSA [mm²]	26	1465.5	637.5	13	1376.2	425.4	0.064	14	1851.8	1021.7	9	1873.6	1004.4	0.678
	Fat CSA/Muscle CSA [%]	26	55.3	26.3	13	54.7	23.0	0.152	14	69.8	40.0	9	69.1	36.6	0.374
Lower leg	Muscle CSA [mm²]	23	6349.4	999.4	23	6234.0	941.4	0.563	11	6054.8	858.2	9	6043.8	1093.0	0.953
	Fat CSA [mm²]	23	2857.6	1182.7	23	2969.7	1175.9	0.316	11	3314.1	900.6	9	3248.2	752.4	0.401
	Fat CSA/Muscle CSA [%]	23	46.5	20.2	23	49.7	22.5	0.162	11	54.9	12.6	9	54.4	11.2	0.594

Table 4. Body weight as well as soft-tissue composition at the forearm and lower leg at baseline and follow-up in the two groups.

and lower leg did not change significantly within either group (Table 4), however, there was a trend for a decreased fat CSA at the forearm by 6.1% in the SSRI group (p=0.064).

Spearman correlations between change in BDI and change in trabecular BMD at the radius/tibia were not significant in neither group. However, there was a trend for decreasing BDI with an increase in trabecular BMD at the radius in the non-SSRI group (p=0.09) and with an increase in trabecular BMD at the tibia in the SSRI group (p=0.10). Spearman correlations between change in trabecular BMD and change in muscle CSA of the particular limb were also non significant in both groups. Linear regression between changes in trabecular BMD at the radius and tibia was not significant (p=0.75).

Discussion

This is the first longitudinal study measuring changes in bone properties upon antidepressant administration at the radius and tibia by pQCT. All measured densitometric and geometric bone properties at the radius and tibia were found to be stable over 12 months under therapy with SSRIs. Under therapy with SNRI and tricyclic antidepressants trabecular BMD at the distal radius and tibia increased slightly but significantly over 12 months. There were no significant relationships between changes in muscle CSA and trabecular BMD at either limb, indicating that increases in trabecular BMD were not caused by increased muscle mass.

Results of our study do not suggest that therapy with SSRIs leads to a measurable decrease in BMD or change in bone geometry within 12 months. A reason for the missing negative effect of SSRI on BMD in our study compared to previous longitudinal studies is the lower serotonergic activity of the majority of SSRIs used in our study. In our study most of the antidepressant medications prescribed were of moderate serotonergic activity, while other longitudinal studies used medications with high activity[3,4]. However, there was no correlation between serotonergic activity and loss of BMD in our study, possibly due to the fact that most 14-months changes

were minimal. Another reason for the missing negative effect of SSRI on BMD is the short observation time of fourteen months. Results of the only existing longitudinal study measured changes in areal BMD of the hip over a mean duration of 4.9 years in 198 SSRI, 118 TCA users and 2406 non-users[3]. The cited study found a yearly loss rate of 0.47% in non-users and users of TCA and a loss rate of 0.82% in SSRI users. However, the use of pQCT rather than dual x-ray absorptiometry (DXA) in our study permits a shorter observation time because this method is not subject to under- and overestimation of BMD due to changes in soft-tissue composition[19]. Another likely reason for the fact that we found no loss in BMD in SSRI users is the young age of our study population compared to the mean age of 78 years in the study by Diem and colleagues[3]. In addition, in our study we found only eight patients with a low BMD for age[20], in the elderly population studied by Diem et al. this proportion was probably higher.

It is unclear why non-SSRI users showed an increase in trabecular BMD at the radius and tibia. Interpretation should consider the fact that in both groups only in 4 subjects 14-month changes exceeded the smallest detectable difference based on reproducibility of measuring methodology. In the non-SSRI group bone data was included of 11 for radius and 12 subjects for tibia data only, therefore random effects cannot be excluded.

Strengths of the present study are the selection of a homogeneous study population of young patients with groups that were comparable with regard to baseline parameters (in particular depression level) and similar improvement of depression at follow-up, and the measurement methodology of pQCT that allows detailed assessment of volumetric BMD and cross-sectional bone geometry independent of surrounding soft-tissue changes over the observation period[19]. The possibility of also assessing muscle CSA allowed us to relate changes in bone parameters to changes in muscle mass, and thus excluding the indirect effect of antidepressant medication on bone via muscle mass.

Limitations of the present study was the small subject number and the fact that some subjects had started their particular medication before baseline measurements. In fact, the initial study protocol was to include antidepressant medication naïve patients, but the protocol had to be amended subsequently due to the fact that it proved to be impossible to recruit a sufficient number of antidepressant medication naïve patients. However, the two groups did not differ with regard to therapy duration at baseline nor subject number who had started their particular therapy before baseline, and the non-SSRI group showed significant increases in trabecular BMD at the radius and tibia despite the fact that some subjects had started therapy before baseline. Further, therapy duration was not a significant factor for any of the changes in bone parameters when entered as a covariate into an ANCOVA.

Conclusions

Bone properties at the radius and tibia were found to be stable over 12 months under therapy with SSRIs. Under therapy with SNRI and tricyclic antidepressants trabecular vBMD at the distal radius and tibia increased slightly over 12 months. Whether this small change is clinically relevant, given the long term precision of the method needs to be explored in larger prospective cohorts.

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