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ROLE OF BONE DENSITOMETRY IN PATIENTS TAKING SELECTIVE SEROTONINE REUPTAKE INHIBITORS: AN OBSERVATIONAL STUDY

Di Grezia, G.[1]; Prisco, V.[2*]; Iannaccone, T.[2]; Serra, N.[1]; Gatta, G.[1]

[1] Department of Radiology, University of Naples SUN
[2] Department of Psychiatry, University of Naples SUN

[*]viciprisco@gmail.com

Abstract

Purpose of the study were to evaluate the effect of selective serotonine reuptake inhibitor therapy on bone density in patients affected by panic disorder and and to detect a correlation with ostheoporosis risk factors such as treatment duration, body mass index and smoking. 27 postmenopausal female patients (age range 52-66 yo) diagnosed with panic and treated with selective serotonine reuptake inhibitors (escitalopram, citalopram or paroxetine) for at least 18 months were enrolled in this study. All patients underwent anamnesis for smoking, clinical exam, Body Mass Index and a bone densitometry with DEXA (Dual Energy X-ray Absorptiometry) examination of femoral neck and lumbar spine. We had a significant (p-value=$2.86 \cdot 10^{-4}$) and good linear correlation (R = 0.644) between BMD (body mineral density) and BMI (body mass index). There weren't significant differences in relation to therapy times, while paroxetine therapy was linked to the high osteoporosis score. In conclusion, Selective serotonin reuptake inhibitors therapy, in patients with panic disorder, is associated with a bone densitometry value that correspond to a condition of osteopenia/osteoporosis and an increased risk of pathological fractures.

Key words: SSRI, osteoporosis, fracture, bone densitometry

Introduction

Osteoporosis is a skeletal disease that is characterized by decrease in bone density and abnormality in bone structure, that causes an increase in the risk of bone fractures. The prognosis of patients who have been diagnosed with osteoporosis is grim as osteoporosis is a major risk factor for hip joint, spine, and radio-ulnar joint; therefore prevention is the most important factor in this disease [1]. It can be classified as either primary or secondary, like drug-induced osteoporosis due to the long-term use of glucocorticoids, thyroxine overdose, gonadotropin-releasing hormone (GnRH) agonists, aromatase inhibitors, thiazolidinediones, proton pump inhibitors, loop diuretics, anticoagulant drugs, tricyclic antidepressants, anticonvulsant and selective serotonin reuptake inhibitors (SSRI) [2]. Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter produced primarily in serotonergic neurons in the central nervous system (CNS). Its primarily role is to influence psychological and behavioural functions such as mood, anxiety, and sleep, and, as a consequence, it is a key factor in the pathophysiology of major depressive disorder (MDD) and other psychiatric illnesses [3].

A functional role for 5HT has been demonstrated in bone through the presence of neurotransmitters, receptors, and transporters in osteoblasts and osteoclasts. In knockout mice without the serotonin transporter has been evaluated significant decreases in bone density, impaired bone architecture, and bone mechanical properties. Possible mechanism to explain 5HT's negative effect on bone is the reduction in osteoblast activity, as a result of serotonin transporter inhibition, leading to lower bone densitometry (BMD) [4,5]. One of the few illnesses with greater disease burden than low bone mineral density (BMD) is depression. Both depression and antidepressants use have been identified as secondary causes of osteoporosis. Depression and anxiety disorders is one of the most important mental health problems and a leading cause of disability in postmenopausal women. SSRIs are considered as first-line therapy for the treatment of these disorders. The association between SSRIs use and fracture risk is a problem. However, the risk of fracture declined rapidly after discontinuation of SSRIs. In practice, assessment of risk factor for osteoporosis or fractures could be made taking into account age, gender, duration, and severity of depression, length of SSRI treatments, and other concurrent risk factors as body mass index and smoking [6].

Nicotine addiction is found in 25.8 % of the occurrence of anxiety disorders in the literature. It has been reported that nicotine helps in coping with stress by increasing the ACTH and cortisol levels and that tobacco consumption increases the risk of osteoporosis, hip fracture, and early menopause [7]. Furthermore osteoporosis is more prevalent in obese individuals. Studies have shown a positive correlation between BMD scores and the BMI to support the hypothesis that a higher BMI (Body Mass Index) is a protective factor for osteoporosis [8]. The objectives of our study are to evaluate the effect of SSRIs therapy on BMD in postmenopausal women who are diagnosed with anxiety disorder, especially DAP (Panic Attack disorder) diagnosed according DSM-V (Diagnostic and Statistical Manual of Mental Disorders- V- Ed.) to identify risk factors for osteoporosis along the duration of illness and therapy, previous fractures in patient anamnestic history, BMI and smoking.

Material and Methods

Twenty-seven postmenopausal female patients, aged between 52-66 yo, with a mean age of about 59 yo and standard deviation (*sd*) of about 4 y.o., diagnosed with panic disorder and treated with selective serotonine reuptake inhibitors (escitalopram, citalopram or paroxetine) for at least 18 months were enrolled in this study.

All patients underwent anamnesis for smoking, clinical exam Body Mass Index and a bone densitometry with DEXA (Dual Energy X-ray Absorptiometry) examination of femoral neck and lumbar spine. We evaluated also old fractures in these patients, the location and the time before therapy.

Results

Statistical analysis

The statistical analysis was performed by Matlab statistical toolbox version 2008 (MathWorks, Natick, MA, USA) for Windows at 32 bit.The statistical tests performed: Student T-test and Cohen's kappa test, were considered significant with p-value < 0.05.

Patients' mean age was 59 (range 52-66), mean BMI was 29.41 (range 17-41), mean BMD was -1.56 and the mean of the duration of the therapy was 15.63 months (range 12-18). We had a significant (p-value = $2.86 \cdot 10^{-4}$) and good linear correlation (R = 0.644) between BMD and BMI, i.e. the osteoporosis and body mass had a good linear connection. There was not statistically significant correlation between SSRI time and BMD (p:0.837), between SSRI time and BMI (p:0.847), SSRI time and age of the patient (0.463) or

between BMD or BMI and age (p: 0.563 and 0.9333, respectively) (Table 1A-B). Statistical analysis reveals that there is not a statistically significant correlation between smoke, BMD and old fractures (Table 2). In addition to verify the best/worse therapy, in Table 3 we had considered 4 subgroups, A = subgroup with FLUVOXAMINE therapy, P = subgroup with PAROXETINE therapy, E = subgroup with ESCITALOPRAM therapy and C = subgroup with CITALOPRAM therapy. From multicomparison test, it resulted that there weren't significant differences for therapy times, instead PAROXETINE therapy was the therapy more linked to the high osteoporosis score.

Discussion and conclusion

Panic disorder is a cronic disease with an incidence of 4-6%. SSRI are the antidepressant drugs most used for panic disorder. This therapy can cause sistemic disorders, such as osteoporosis. Patterson-Buckendahl et al. proved that anxiety disorder influence bone metabolism, because psychological stress can cause a reduction of osteocalcin level [9]. There are few studies on the effects of SSRI on bone mineral density and all authors described negative effects of these drugs on BMD. Some studies in literature support the hypotesis that serotonin carrier in bone cells has an important role for bone mass, structure and strenght [10,11]. The most frequent psichiatric comorbility founded in women with panic disorder are: major depression (62,4%) and dysthymia (40%). Depression may have effects on bone density altering hypothalamic-pituitary-adrenal axis and enhancing the output of proinflammatory cytokines such as IL-6 and TNF- α [12]. In our study we evaluated the effect of SSRI therapy on BMD in postmenopausal women with diagnosis of panic disorder and we identified the effect of disease duration and of the therapy on risk factors for osteoporosis, trying to identify the drug with a significant correlation. Between risk factors for osteoporosis we analized BMI, previous fractures and smoking habit. In literature, 25% of patients with anxiety disorder have nicotine addiction; nicotine helps to cope with stress enhancing ACTH production and cortisol. Nicotine consumption also increases osteoporosis risk [13,14]. In our study, bone mineral density in smoker women was lower than in non smokers. This result, however, is not statistically significant, even if there is a previous fracture in the history of the patient. In relation to BMI, our study, according to literature, shows a positive correlation between BMI and BMD, supporting the hypotesis that an higher BMI could be considered a protective factor for osteoporosis [15,16]. SSRI administration was associated with reduced BMD and increased fragility fracture risk. Other studies evaluated the effects of therapy with SSRI on BMD with similar results. Diem et al [17] described an increased bone loss in female patients treated with SSRI if compared with healthy controls. Ak et al. [18] pointed out, in patients with anxiety disorder, a BMD value significantly lower if compared with healthy patients. Furthermore, analyzing the effects of SSRI subgroups on BMD, in paroxetine group, bone density value was lower than citalopram and sertraline group. This difference can be related to disease duration and not to therapy duration, that was not statistically significant. Results of a big meta-analysis demonstrated that SSRI are associated to a moderate and significant increase of fracture risk. If we analyze case-control and cohort studies of the period between 1996 and 2011, relative fracture risk in patients treated with antidepression drugs, was 1.39 [19]. Limits of our study are the little sample of patients and a short therapy period. In future we can add other variables, such as nutritional data, ormonal parameters, physical activity, osteoporosis familiar history, calcium and D vitamin deficit.

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References

1. Richards JB, Papaioannou A, Adachi JD, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med 2007;167:188–194
2. Kang MI, Koh JM, Kim T, et al. Physician's guide for diagnosis and treatment of osteoporosis. Seoul: Korean Society for Bone and Mineral Research; 2008
3. Hubbard R, Farrington P, Smith C et al. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. American Journal of Epidemiology 2003; 158:1,77–84,
4. Battaglino R, Späte U et al. Serotonin regulates osteoclast differentiation through its transporter. Journal of Bone and Mineral Research 2004; 19: 9,1420–1431
5. Warden SJ, Bliziotes MM, Wiren KM et al. Neural regulation of bone and the skeletal effects of serotonin (5-hydroxytryptamine). Molecular and Cellular Endocrinology 2005; 242:1,1–9
6. Bruyère O, Reginster Y. Osteoporosis in patients taking selective serotonin reuptake inhibitors: a focus on fracture outcome. Endocrine 2015; 48(1):65-8
7. Ortego-Centeno N, Munoz-Torres M, Jodar E, Hernandez-Quero J, Jurado-Duce A, de la Higuera T-PJ. Effect of tobacco consumption on bone mineral density in healthy young males. Calcif Tissue Int. 1997;60(6):496–500
8. Lindsay R, Cosman F. Osteoporozis. In: Braundwald E, Fauci AS, Isselbacher KJ, editors. Harrison's principles of internal medicine. New York: McGraw- Hill; 2001,342

9. Patterson-Buckendahl P, Rusnak M, Fukuhara K, Kvetnansky R. Repeated immobilization stress reduces rat vertebral bone growth and osteocalcin. Am J Physiol Regul Integr Comp Physiol 2001;280(1):79–86
10. Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, Prior JC, Goltzman D. Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med 2007 167(2):188–194
11. Bab I., Yirmiya R. Depression, selective serotonin reuptake inhibitors, and osteoporosis. Curr Osteoporos Rep. 2010 ;8(4):185-91
12. Williams L, Pasco J, Jackson H, Litza Kiropoulos. Depression as a risk factor for fracture in women: A 10 year longitudinal study. Journal of Affective Disorders, 2016; 192, 34-40
13. Pomerleau OF, Pomerleau CS. Research on stress and smoking: progress and problems. Br J Addict 1991;86(5):599–603
14. Ortego-Centeno N, Munoz-Torres M, Jodar E, Hernandez-Quero J, Jurado-Duce A, de la Higuera T-PJ. Effect of tobacco consumption on bone mineral density in healthy young males. Calcif Tissue Int. 1997; 60(6):496–500
15. Jiang X, Good LE, Spinka R, Schnatz PF. Osteoporosis screening in postmenopausal women aged 50-64 years: BMI alone compared with current screening tools. Maturitas 2016;83:59-64
16. Bonnick, S., Harris, S., Kendler, D. et al, Management of osteoporosis in postmenopausal women. Position statement of the North Menopause Society: position statement. Menopause 2010;17:25–54
17. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Haney EM, Bliziotes MM, Ensrud KE. Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. Arch Intern Med. 2007 167(12):1240–1245
18. Ak E, Bulut SD, Bulut S, Akdağ HA, Öter GB, Kaya H, Kaya OB, Şengül CB, Kısa C. Evaluation of the effect of selective serotonin reuptake inhibitors on bone mineral density: an observational cross-sectional study. Osteoporos Int. 2015;26(1):273-9
19. Rabenda V, Nicolet D, Beaudart C. Relationship between use of antidepressants and risk of fractures. A metanalysis.Osteoporosis Int 2013;24(1):121-137

Table 1A. Table shows parameters and statistical tests for BMI, SSRI time, BMD and age

PZ	AGE	BMI	SMOKE	SSRI	SSRI MONTHS THERAPY	OLD FRACTURES	T SCORE
1	52	31	YES	FLUVOXAMINA	12	WRIST 10 YEARS BEFORE	-1,7
2	65	40	YES	PAROXETINE	16	HIP 2 MONTHS BEFORE	-2,6
3	55	32	YES	ESCITALOPRAM	16	NO	-1
4	60	18	YES	CITALOPRAM	12	NO	-1,5
5	60	20	YES	FLUVOXAMINA	18	NO	-1,7
6	55	26	NO	PAROXETINE	18	NO	-2,5
7	64	19	NO	PAROXETINE	16	RADIUS 1O MONTHS BEFORE	-2,7
8	58	23	YES	PAROXETINE	16	NO	-2,8
9	61	35	NO	FLUVOXAMINA	18	NO	-0,8
10	60	36	YES	ESCITALOPRAM	18	NO	-0,7
11	53	38	NO	CITALOPRAM	12	V METHATARSUS 5 MONTHS BEFORE	-1
12	56	27	NO	PAROXETINE	12	NO	-2,4
13	66	28	YES	CITALOPRAM	12	NO	-1,1
14	55	22	YES	FLUVOXAMINA	16	NO	-2,3
15	61	26	NO	PAROXETINE	16	NO	-2,7
16	59	33	YES	FLUVOXAMINA	18	HUMERUS 8 YEARS BEFORE	-0,9
17	62	33	YES	CITALOPRAM	18	NO	-0,7
18	57	40	NO	ESCITALOPRAM	18	NO	-0,8
19	63	18	NO	PAROXETINE	16	FEMUR 1 YEAR BEFORE	-2,7
20	62	38	NO	FLUVOXAMINA	16	NO	-0,6
21	56	32	YES	FLUVOXAMINA	12	NO	-1
22	54	36	YES	CITALOPRAM	16	NO	-0,8
23	64	41	YES	ESCITALOPRAM	12	NO	-0,5
24	58	27	NO	ESCITALOPRAM	18	NO	-0,7
25	59	34	NO	PAROXETINE	16	NO	-0,9
26	66	24	NO	PAROXETINE	18	HIP 6 MONTHS BEFORE	-2,9
27	52	17	YES	FLUVOXAMINA	16	NO	-2

Table 1B. Table shows parameters and statistical tests for BMI, SSRI time, BMD and age

Parameters	mean ± sd	range	Hypothesis	*R* (p-value)
BMI	29.41 ± 7.35	[17,41]	Correlation: SSRI time/BMD	-0.041 (0.837)
SSRI time	15.63 ± 2.31	[12,18]	Correlation: SSRI time/BMI	-0.039 (0.847)
			Correlation: SSRI time/Age	0.148 (0.463)
BMD	-1.56 ± 0.83	[-2.9,-0.5]	Correlation: BMD/BMI	0.644 ($2.86 \cdot 10^{-4}$)
Age	59.00 ± 4.21	[52, 66]	Correlation: BMD/Age	0.116 (0.563)
			Correlation: BMI/Age	0.0171 (0.933)

Legend: BMI (body mass index), SSRI time (selective serotonin reuptake inhibitors), BMD (bone densitometry) R = Pearson's linear correlation coefficient

Table 2. Table shows statistical tests for correlation between smoke and BMD and fractures and BMD and Smoke

Parameters	Present %	Absent %	Hypothesis	*k* (p-value)
Smoke	55.56 (15/27)	44.44 (12/27)	Correlation: Smoke/Fractures	-0.125 (0.642)
Old Fractures	25.92 (7/27)	74.08 (20/27)	Correlation: BMD/Fractures	0.20 (0.437)
BMD	51.85 (14/27)	48.15 (13/27)	Correlation: BMD/Smoke	0.033 (0.865)

Legend: k = Cohen's kappa; BMD (bone densitometry)

Table 3. Table shows parameters and statistical tests for patient's group

SSRI therapy groups	Time (mean ± sd)	BMD (mean ± sd)	Hypothesis	p-value
FLUVOXAMINA (F)	15.75 ± 2.49	-1.38 ± 0.63	$\mu_{time}(F) < \mu_{time}(P)$ $\mu_{BMD}(F) > \mu_{BMD}(P)$	≈ 1 0.0048
PAROXETINE (P)	16.00 ± 1.73	-2.47 ± 0.61	$\mu_{time}(F) < \mu_{time}(E)$ $\mu_{BMD}(F) < \mu_{BMD}(E)$	≈ 1 0.0512
ESCITALOPRAM (E)	16.40 ± 2.61	-0.74 ± 0.18	$\mu_{time}(F) > \mu_{time}(C)$ $\mu_{BMD}(F) < \mu_{BMD}(C)$	0.532 0.536
CITALOPRAM (C)	14.00 ± 2.83	-1.02 ± 0.31	$\mu_{time}(P) < \mu_{time}(E)$ $\mu_{BMD}(P) < \mu_{BMD}(E)$	≈ 1 0.00004
			$\mu_{time}(P) > \mu_{time}(C)$ $\mu_{BMD}(P) < \mu_{BMD}(C)$	0.246 0.00072
Student T-test with Bonferroni correction, for independent data			$\mu_{time}(E) > \mu_{time}(C)$ $\mu_{BMD}(E) > \mu_{BMD}(C)$	0.401 0.241