Effect of Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors on Trabecular Bone Score and Bone Mineral Density in Primary Fibromyalgia

Hesham S. Hamoud, Mohamed M. Ghait, Yasser A. Hussein, Muhammad M. Harb

Department of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Corresponding author: Muhammad M. Harb; **Mobile:** 01009952990; **Email:** Dr_2MH@Yahoo.com

ABSTRACT

Background: fibromyalgia is characterized by chronic widespread pain classified as primary and concomitant. **Aim of the Work:** this work aimed to determine the correlation between selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) usage and bone mineral density (BMD) and trabecular bone score (TBS) changes in primary fibromyalgia patients.

Patients and Methods: The present study was conducted on study on 100 Egyptian patients diagnosed as primary fibromyalgia categorized according to drug medication into two 2 groups, 50 patients on SSRIs and 50 patients on SNRIs, recruited from Rheumatology, Physical Medicine and Rehabilitation Departments at Al-Hussein and Sayed Galal, Al-Azhar University Hospitals. In addition to another 50 age matched the control group subdivided into 25 primary fibromyalgia patients not on those drugs and 25 healthy individuals selected by nurses and medical staff, after an informed consent from all subjects from June 2018 to December 2018. **Results:** DXA and TBS revealed that usage of SSRIs and SNRI was significantly associated with low BMD (Osteopenia and osteoporosis) specially spine BMD reduction with low TBS (partially degraded and degraded) particularly for old people. **Conclusion:** the present study provided evidence that usage of SSRIs or SNRI was significantly associated with low BMD (Osteopenia and osteoporosis) specially spine BMD reduction with low TBS (Partially degraded and degraded) particularly for old people and despite low BMD was found in the SRI users; it also found in 1[ry] fibromyalgia not on SRIs so 1[ry] fibromyalgia should also be considered as a contributing factor for low BMD.

Keywords: SSRI, SNRI, FMS, fibromyalgia, osteoporosis, TBS, BMD, bone mineral density, trabecular bone score.

INTRODUCTION

Fibromyalgia is characterized by chronic widespread musculoskeletal pain that often co-exists with sleep disturbances, fatigue, cognitive dysfunction, stiffness and tenderness to palpation at specific tender points. It has been classified as primary and concomitant. Primary fibromyalgia indicates that there is no underlying or concomitant medical condition that might have contributed to a patient's pain. Fibromyalgia is considered concomitant if another condition such as osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, or hypothyroidism is present and in turn contributes to a patient's pain or fatigue [1]. Fibromyalgia is associated with low level of physical activity and exercise, which may lead to an increased risk of osteoporosis resulting in a substantial impact on quality of life [2]. Selective serotonin reuptake inhibitors represent a class of commonly used antidepressants. They act by preventing the reuptake of 5-hydroxytryptamine (5-HT) (Serotonin) through the inhibition of the 5-HT transporter (5-HTT) which is located on the presynaptic neuron, thereby increasing levels of 5-HT within the synaptic cleft and modulating neurochemical signaling [3]. Usage of SSRIs was significantly associated with lumbar spine BMD reduction, particularly for old people [4]. Two SNRI's have gained FDA approval for the management of fibromyalgia Duloxetine and Milnacipran [5], CaMoS study found an elevated danger of fractures in individuals who used SSRI or SNRI, even after controlling other multiple risk factors for osteoporosis [6]. Currently, DXA (Dual-energy X-ray absorptiometry) scan was used to assess BMD and FRAX assessment tool to predict 10-year probability of hip fracture, the diagnosis of osteoporosis rests on a real bone mineral density (BMD) measurement using DXA. Microarchitecture of cancellous bone was a determinant for bone strength which can't be measured

via DXA [7]. Trabecular bone score (TBS) is a texture parameter related to bone microarchitecture providing skeletal information that is not captured from the standard BMD measurement. It measures the variations in gray-level texture from 1 pixel to the next across 2 dimensional images, Trabecular bone score (TBS) seems to be an amazing surrogate noninvasive method for assessing microarchitecture texture of vertebral bone than DXA scans in routine scientific practice which will fulfill the definition of osteoporosis [8] .Recent data showed a significant added and independent predictive value of lumbar trabecular bone score (TBS) over bone mineral density (BMD) alone in the estimation of fracture risk in both women and men [9].

AIM of the WORK

This work aim to determine the correlation between selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) usage and bone mineral density (BMD) and trabecular bone score (TBS) changes in primary Fibromyalgia patients.

PATIENTS and METHODS

The present cross sectional study was conducted on a Hundred (100) Egyptian patients diagnosed as primary fibromyalgia divided according to drug medication into two 2 groups, 50 patients on SSRIs and 50patients on SNRIs, recruited from Rheumatology, Physical Medicine and Rehabilitation departments at Al-Hussein and Sayed Galal, Al-Azhar University Hospitals. In addition to another 50 age matched the control group subdivided into 25 primary fibromyalgia patients not on those drugs and 25 healthy individuals selected by nurses and medical staff, after an informed consent from all subjects from June 2018 to December 2018..An approval was obtained from the medical ethics committee of Al-Azhar University before starting this study. All the patients were informed about the study procedures and a written consent was obtained from all of them. The subjects were categorized into three groups**.** Group A: 50 1[ry] fibromyalgia patients on SSRI. Group B: 50 1[ry] fibromyalgia patients on SNRI. Group C: 50 individuals as a the control group subdivided into: group C-1: 25, 1[ry] fibromyalgia patients non SRIs-users and group C-2: 25) healthy individuals.

Patient's selection

A) Inclusion criteria for group A and B:

All fibromyalgia patients had to fulfill 2010 ACR diagnostic criteria of fibromyalgia and On SSRI or SNRIs for at least 6 months

B) Exclusion criteria:

Age of participants was < 30 years or > 65 years rheumatoid arthritis and collagen diseases (SLE, SS, MCTD, etc.), systemic diseases e.g. hypothyroidism, TB, hepatic, renal, etc., patients on glucocorticoids for more than 6 months, chronic obstructive pulmonary disease including asthmatics IBD, autoimmune hepatitis and celiac diseases, history of traumatic vertebral fractures hospitalization due to alcohol or drug addiction pregnant or lactating women.

I-Full medical history taking:

Personal history about, name, age, sex, residence, occupation, marital status, special habits of medical importance, in addition to menstrual history and obstetric history including number of labors and abortions for female patients.

History of present illness: onset, course and disease duration. To assess risk factors and prognostic factors for osteoporosis, including age, menopausal age, anthropometric variables, physical activity (hours per week spent on jogging, gymnastics,cycling,swimming and standing/walking on the job), previous and present illnesses, gynecological history, and use of drugs, vitamin supplements, alcohol and tobacco, constitutional symptoms as fatigue, fever and loss of weight, musculoskeletal manifestations as morning stiffness, joint pain, swelling, redness, hotness and muscle pain or weakness, mucocutaneous manifestations as rash, photosensitivity, alopecia, oral ulcers, Raynaud's phenomena, skin ulcers and splinter hemorrhage, gastrointestinal manifestations as anorexia, epigastric pain, nausea, vomiting, diarrhea and constipation. renal manifestations as loin pain, hematuria, dysuria, urgency, frequency, polyuria or oliguria, puffiness of the eye lids and swelling of the lower limbs. Somatic symptoms : muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia,

depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Past history: past history of chronic diseases, medications, surgery, allergy, blood transfusion or hospital admission, rheumatologic diseases, DM or other metabolic diseases, cardiac, kidney or liver diseases.

Family history: family history of RA cases or other autoimmune diseases.

II- Examination: general examination, examination of scalp, eye and skin, cardiac examination, chest examination, abdominal examination, neuropsychiatric examination and articular examination. All joints were examined as follow: inspection: overlying skin color, muscle wasting, deformity and swelling. Palpation: temperature, tenderness and swelling (soft tissue or effusion). Movement: both active and passive movement was done, with observation of pain, crepitus and protecting muscle spasm with local examination, inspection for skin changes such as discoloration, scar or rashes, swelling either generalized or localized.

Palpation: warmth, swelling either generalized or localized, synovial hypertrophy, bony enlargement, crepitus, clicking of the joint with motion.

III- Assessment of tender points according to the ACR 1990 criteria:

Table 1: fibromyalgia tender points according to the ACR 1990 criteria

Right			Left		
Site	Yes	No	Site	Yes	No
Low cervical region			Low cervical region		
2nd Rib			2nd Rib		
Occiput			Occiput		
Trapezius			Trapezius		
Supraspinatus			Supraspinatus		
Lateral epicondyle			Lateral epicondyle		
Gluteal			Gluteal		
Greater trochanter			Greater trochanter		
Knee			Knee		
Total		18			

Score interpretation: the patient must feel pain in 11 of 18 tender point sites on digital palpation (Performed with a force of~4kg/cm2) and had a history of widespread pain (present for at least 3 months) to be considered.

IV- Assessment according to ACR 2010 diagnostic criteria of fibromyalgia:

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

- ✓ Widespread pain index (WPI) ≥ 7 and symptom severity (SS)

scale score ≥ 5 or WPI $\geq 3–6$ and SS scale score ≥ 9.

- ✓ Symptoms have been present at a similar level for at least 3months.
- ✓ The patient does not have a disorder that would otherwise explain the pain.

Investigations:

C.B.C. analyzed using Sysmex Kx-21 N automated cell counter.

E.S.R (assay by Westergren method) & C.R.P (assay by BioMed-CRP latex agglutination method).Erythrocyte sedimentation rate (ESR): by Westergren method. The reading of first hour was taken.

Liver function tests: ALT, AST and Bilirubin, analyzed using Hitachi Cobas C 311 automated analyzer.

Kidney function tests: urea and creatinine, analyzed by using Hitachi Cobas C 311 automated analyzer.

Blood sugar: fasting blood glucose and 2-hours post prandial blood glucose level by Hitachi Cobas C 311 automated analyzer.

Autoimmune profile: including RF, ANA, were detected by an enzyme-linked immune-sorbent assay (ELISA).

E. Bone Quantity Assessment The procedure:

Assessment of bone mineral density measured by dual-energy X-ray absorptiometry at lumbar spine, left proximal femur and left distal forearm.

Type of apparatus:

GE Medical System (GE-Lunar Prodigy Primo), Madison, WI, USA , Brand: GE-Lunar, Model: Prodigy Primo, SN: 35156

Bone Mineral Density (BMD) or bone mass was one of the predictors of fracture. With the availability of high precision bone densitometers, the World Health Organization has established criteria for diagnosing osteoporosis.

The diagnostic score (T-score) was related to bone mass in young healthy women. Bone mineral density (BMD) above -1 SD (standard deviation) is normal, BMD between -1 and -2.5 SD is assigned to osteopenia, while below -2.5 SD is the diagnostic criterion for osteoporosis (T-score) BMD is preferably measured by dual energy X-ray absorptiometry (DXA).

The World Health Organization has defined the following categories based on bone density:

Normal bone	T-score greater than -1
Osteopenia	T-score between -1 and -2.5
Osteoporosis	T-score less than -2.5
Severe Osteoporosis	T-score less than -2.5 and history of fracture

Procedure:

A- For measuring spine BMD:

- The patient lies supine on the scan table. The scan arm and detector move to the approximate start position and the program turns on the laser light.

- Put the patient's leg on the support block until the patient's thighs are at 60-90 angle. The support block helps to separate vertebrae and straightens the lower back.

- Put the laser light approximately 5cm below the patient's navel and in the same longitudinal plane as the patient's midline.

- The program automatically labels L1 to L4.

B- For measuring femur BMD:

- The patient lies flat on the scan table. The scan arm and detector move to the approximate start position and the program turns on the laser light.

- Position the laser light midway between the anterior superior iliac spine and the pubic tubercle.

- The program automatically labels head and neck of the femur and greater trochanter.

C- For measuring distal forearm BMD:

- The patient sits on a chair and put the forearm on the scan table in pronated position. The scan arm and detector move to the approximate start position and the program turns on the laser light.

- Put the laser light midway the wrist joint.

- The program automatically labels the distal forearm.

  A definition of common terms shown on the report:

- BMD (Bone Mineral Density): The BMD value gives a Measurement of bone mineral found in the region of interest. BMD is measured in grams per centimeter squared (g/cm^2).

- **Area:** This value identifies the area of the scan region measured in cm2.

- **T- Score (% young adult).:** This value compares a patient's BMD with the expected peak bone mass for a subject of approximately 20-40 years old.

- **Z- Score (% Age- Matched):** This value compares a patient's BMD with the expected values of the reference group of the same age and gender.

El-Hussien University Hospital
Rheumatology and Physical Medicine Department,
Phone: (___) ___-___

Patient:	Ali Zidan, Zainab			Referring Physician: Dr. M. Harb	
Birth Date:	14/06/1978	Age:	40.2 years	Patient ID:	1005
Height:	165.0 cm	Weight:	75.0 kg	Measured:	03/09/2018 11:04:57 AM (15 [SP 2])
Sex:	Female	Ethnicity:	Hispanic	Analyzed:	03/09/2018 11:07:06 AM (15 [SP 2])

Spain AP Spine: L1-L4 (BMD)
YA T-score   AM Z-score
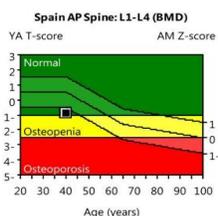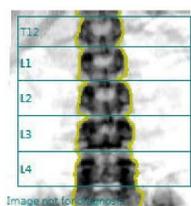
Region	BMD (g/cm²)	Young-Adult T-score	Age-Matched Z-score
T12	0.890	-	-
L1	0.944	1.6-	2.1-
L2	0.990	1.8-	2.3-
L3	1.208	0.1-	0.6-
L4	1.158	0.5-	1.0-
L1-L2	0.969	1.7-	2.2-
L1-L3	1.059	1.0-	1.5-
L1-L4	1.087	0.9-	1.3-
L2-L3	1.106	0.9-	1.4-
L2-L4	1.124	0.7-	1.2-
L3-L4	1.182	0.3-	0.8-

Spain Left Femur: Total (BMD)
YA T-score   AM Z-score
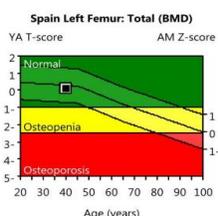
| Region	BMD (g/cm²)	Young-Adult T-score	Age-Matched Z-score
Neck	0.897	0.7-	0.9-
Wards	0.713	1.5-	1.7-
Troch	0.853	0.6	0.2
Shaft	1.230	-	-
Total	1.017	0.1	0.1-

Spain Left Forearm: Radius 33% (BMD)
YA T-score   AM Z-score
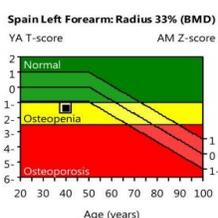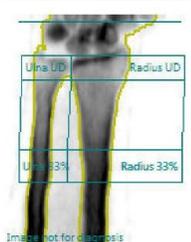
Region	BMD (g/cm²)	Young-Adult T-score	Age-Matched Z-score
Radius UD	0.463	0.0	0.0
Ulna UD	0.277	-	-
Radius 33%	0.755	1.4-	1.4-
Ulna 33%	0.750	-	-
Both UD	0.390	-	-
Both 33%	0.753	-	-
Radius Total	0.550	2.1-	2.1-
Ulna Total	0.506	-	-
Both Total	0.534	-	-

Statistically 68% of repeat scans fall within: 1SD (± 0.010 g/cm² for AP Spine L1-L4); (± 0.012 g/cm² for Left Femur Total); (± 0.020 g/cm² for Left Forearm Radius 33%); Spain (ages 20-40) AP Spine Reference Population (v113); Spain (ages 20-40) Femur Reference Population (v113); Spain (ages 20-40) Forearm Reference Population (v113); AP Spine Matched for Age, Weight (females 25-100 kg), Ethnic; Left Femur Matched for Age, Weight (females 25-100 kg). Ethnic; Left Forearm Matched for Age, Ethnic; Lunar calibrat on in use.; World Health Organization - Definition of Osteoporosis and Osteopenia for Caucasian Women: Normal = T-score at or above 1.0- SD: Osteopenia = T-score between 1.0- and 2.5- SD; Osteoporosis = T-score at or below 2.5- SD; (WHO definitions only apply when a young healthy Caucasian Women reference database is used to determine T-scores.)
Date created: 03/09/2018 11:12:06 AM 15 [SP 2]; Filename: ali_zz_amzgep7j9k.dfx; AP Spine: 76:1.50:22.24:27.0 0.00:10.50 0.60x1.05 20.6:%Fat=27.1%; 0.00:0.00 0.00:0.00; Scan Mode: Standard;OneScan; 42.0 µGy; Left Femur: 76:1.50:22.74:27.0 0.00:10.68 0.60x1.05 17.0:%Fat=28.9%; 0.00:0.00 0.00:0.00; Neck Angle (deg)= 63; Scan Mode: Standard; 42.0 µGy; Left Forearm; 76:0.15:50.03:12.0 0.00:6.20 0.60x1.05 4.4:%Fat=38.9%; 0.00:0.00 0.00:0.00; Forearm Length: 26.3 cm; Scan Mode: Standard;Not seated; 2.0 µGy

GE Healthcare   Page: 1 of 1   Lunar Prodigy Primo
                                                                PR+351560

Figure 1: DXA report

F-Trabecular Bone Score (TBS) of lumber spine

Assessment of Trabecular Bone Score (TBS) of lumber spine using TBS iNsight ® software (Version 2.0), distributed by Med-Imaps and installed on (GE Lunar: Prodigy), High TBS value means that the bone microarchitecture is dense and well-connected, with little space between spans. Conversely, a low TBS value means that the bone microarchitecture is incomplete, with large spaces between spans. In clinical practice, TBS is calculated in a few seconds, using images obtained during BMD examination along with the software TBS iNsight®, which is installed

directly onto bone densitometer. Trabeculometry is the measurement of TBS, and trabeculography is the color map of local TBS values on the L1-L4 vertebrae, TBS $\geq$ 1.350 is normal while as partially degraded when $1.200 <$ TBS < 1.350 and degraded when TBS $\leq$ 1.200.

AI-Hussien University Hospital

DEXA & TBS Unit
Rheumatology, Physical Medicine and Rehabilitation Department
- Cairo

Patient :	Ragab abdelmahfouz, Zinat	Patient ID:	
Date of birth:	12/03/1965 53.5 years	Acquisition date:	23/09/2018
Height / Weight:	145.0 cm / 69.0 kg	Prescribing doctor:	Dr.M.Harb
Gender / Ethnicity:	Female / Hispanic		

SPINE TBS REPORT

TBS reference graph
Reference population: European

TBS L1-L4:1.234

TBS Mapping

TBS Values High

TBS Values Low

Non diagnostic image

Additional results

Region	TBS	BMD	BMD T-Score
L1	0.960	0.884	-2.1
L2	1.148	0.973	-2.0
L3	1.381	1.010	-1.7
L4	1.447	1.006	-1.7
L1-L4	1.234	0.973	-1.8
L1-L3	1.163	0.962	-1.8
L1-L2	1.054	0.932	-2.0
L2-L4	1.325	0.997	-1.8
L2-L3	1.264	0.993	-1.8
L3-L4	1.414	1.008	-1.7

Comments

The TBS is derived from the texture of the DEXA image and has been shown to be related to bone microarchitecture and fracture risk.
This data provides information independent of BMD value; it is used as a complement to the data obtained from the DEXA analysis and the clinical examination
The TBS score can assist the health care professional in assessment of fracture risk and in monitoring the effect of treatments on patients across time.
Overall fracture risk will depend on many additional factors that should be considered before making diagnostic or therapeutic recommendations.
The software does not diagnose disease or recommand treatment regimens. Only the health care professional can make these judgments.
DXA file: "RagabZ_y05ifp7j9k.dfx" (TBS analysis done on 23/09/2018, version 2.1.0.0)
Before accepting this report, the user is held accountable for ensuring that the DXA examination has been carried out:
 - by the osteodensitometer GE-Lunar Prodigy Primo (# 351560)
 - after the latest TBS iNsight calibration, the 03/03/2014 11:03:40 AM.

TBSiNsight   medimaps

Figure 2: TBS report

Statistical analysis: Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done: A one-way analysis of variance (ANOVA) when comparing between more than two means. Post Hoc test: Least Significant Difference (LSD) was used for multiple comparisons between different variables. Independent-samples t-test of significance

was used when comparing between two means. Chi-square (x2) test of significance was used in order to compare proportions between qualitative parameters. Pearson's correlation coefficient (r) test was used to assess the degree of association between two sets of variables. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: Probability (P-value): P-value <0.05 was considered significant. P-value <0.001 was considered as highly significant. P-value >0.05 was considered insignificant

.**RESULTS**

Table 1: comparison between groups according to the demographic data

Data	SSRI *(n=50)*	SNRI *(n=50)*	Control FMS *(n=25)*	Healthy control *(n=25)*	F/x2#	p-value
Age (years)						
Mean±SD	45.08±9.49	45.50±4.49	44.76±9.11	45.12±8.47		
Range	30_60	37_55	30_60	31_60	0.054	0.983
<45 years	24 (48.0%)	25 (50.0%)	12 (48.0%)	12 (48.0%)		
≥45 years	26 (52.0%)	25 (50.0%)	13 (52.0%)	13 (52.0%)		
Height (cm)						
Mean±SD	154.78±8.16	154.71±10.63	156.99±6.24	158.44±9.85	1.294	0.279
Range	140_190.5	140_190.5	145_170	122_176		
Weight (kg)						
Mean±SD	77.86±20.89	79.09±23.70	78.54±17.54	81.46±14.53	0.176	0.913
Range	27.2_115	27.2_115	27.2_100	40.8_112		
BMI [wt/(ht)^2]						
Mean±SD	33.03±8.59	33.28±10.14	31.82±6.77	32.72±6.66	0.170	0.917
Range	11.7_46.2	11.71_46.22	11.7_40.8	15.4_46.4		
Obesity						
Normal	9 (18.0%)	11 (22.0%)	2 (8.0%)	2 (8.0%)		
Overweight	4 (8.0%)	3 (6.0%)	8 (32.0%)	5 (20.0%)	4.200#	0.072
Obese	37 (74.0%)	36 (72.0%)	15 (60.0%)	18 (72.0%)		

According to the demographic data; all subjects were Egyptian with age ranged from 30 to 60 years old.

As regard the comparison between the groups according to demographic data, there was no statistically significant difference between them.

I- Comparison between groups according to L1-L4 BMD and BMC.

Table 2: comparison between the groups according to AP lumber spine L1-L4 BMD and BMC

	SSRI *(n=50)*	SNRI *(n=50)*	Control FMS *(n=25)*	Healthy control *(n=25)*	ANOVA	p-value
AP Spine L1-L4 BMD						
Mean±SD	0.99±0.13	1.10±0.15a	1.06±0.15a	1.21±0.09abc	15.477	<0.001**
Range	0.74_1.38	0.61_1.44	0.74_1.29	1.09_1.40		
AP Spine L1-L4 BMC						

Mean±SD	48.63±9.15	57.94±9.67a	52.66±10.31	60.36±9.22ac	11.920	<0.001**
Range	35.00_72.15	33.64_80.00	33.76_71.48	46.85_79.13		

As regard the comparison between the groups according to AP lumber spine L1-L4 BMD and BMC. There was highly statistically significant difference

Table 3: comparison between the groups according to L1-L4 T-score and z-score

L1-L4	SSRI (*n=50*)	SNRI (*n=50*)	Control FMS (*n=25*)	Healthy control (*n=25*)	F/x2#	p-value
L1-L4 T-Score						
Mean±SD	-1.94±1.04	-2.31±0.83a	-1.08±1.21ab	0.09±0.73abc	39.542	<0.001**
Range	-3.70_1.51	-4.68_-1.12	-3.65_0.77	-0.84_1.64		
Normal	9 (18.0%)	0 (0.0%)	14 (56.0%)	25 (100.0%)		
Osteopenia	20 (40.0%)	29 (58.0%)	6 (24.0%)	0 (0.0%)	88.795#	<0.001**
Osteoporosis	21 (42.0%)	21 (42.0%)	5 (20.0%)	0 (0.0%)		
L1-L4 Z-Score						
Mean±SD	-1.35±1.07	-0.75±1.35a	-0.86±1.28a	-0.02±1.03abc	6.974	<0.001**
Range	-3.36_2.55	-4.34_2.79	-2.66_1.53	-1.71_2.55		
Normal	17 (34.0%)	30 (60.0%)	13 (52.0%)	21 (84.0%)		
Osteopenia	26 (52.0%)	15 (30.0%)	10 (40.0%)	4 (16.0%)	18.594#	0.005*
Osteoporosis	7 (14.0%)	5 (10.0%)	2 (8.0%)	0 (0.0%)		

As regard the comparison between the groups according to L1-L4 T-score and z-score. There was highly statistically significant difference between groups according to L1-L4 T-score and Z-score.

Table 4: comparison between the groups according to TBS L1-L4

TBS L1-L4	SSRI (*n=50*)	SNRI (*n=50*)	Control FMS (*n=25*)	Healthy control (*n=25*)	F/x2#	p-value
TBS L1-L4						
Mean±SD	1.32±0.16	1.28±0.23	1.46±0.19ab	1.44±0.17ab	7.361	<0.001**
Range	0.94_1.71	0.27_1.61	0.99_1.75	0.79_1.63		
TBS L1-L4						
Degraded	12 (24.0%)	11 (22.0%)	2 (8.0%)	1 (4.0%)		
Partially degraded	8 (16.0%)	11 (22.0%)	3 (12.0%)	1 (4.0%)	13.678#	0.033*
Normal	30 (60.0%)	28 (56.0%)	20 (80.0%)	23 (92.0%)		

As regard the comparison between groups according to TBS L1-L4, there was a highly statistically significant difference between groups according to TBS L1-L4.

Table 5: comparison between the groups according to left femur total BMD and BMC

	SSRI (*n=50*)	SNRI (*n=50*)	Control FMS (*n=25*)	Healthy control (*n=25*)	ANOVA	p-value
Left Femur Total BMD						
Mean±SD	0.89±0.18	0.99±0.17a	0.97±0.11a	1.04±0.12abc	6.001	<0.001**
Range	0.49_1.78	0.74_1.78	0.75_1.14	0.78_1.28		
Left Femur Total BMC						
Mean±SD	27.02±4.44	30.20±5.48a	30.40±4.69a	32.63±4.49abc	8.437	<0.001**
Range	14.67_34.46	19.75_45.70	20.47_37.23	23.43_42.07		

As regard the comparison between the groups according to left femur total BMD and BMC there was highly statistically significant difference between groups according to left femur total BMD and BMC.

As regard the comparison between groups according to left femur total T-score and z-score, there was highly statistically significant difference between groups according to left femur total T-score and Z-score

Table 6: comparison between groups according to left femur total T-score and z-score

	SSRI (n=50)	SNRI (n=50)	Control FMS (n=25)	Healthy control (n=25)	F/x2#	p-value
Left Femur Total T-Score Mean±SD Range	-0.90±1.47 -4.28_6.48	-0.07±1.43a -2.14_6.48	-0.23±0.93ab -2.05_1.12	0.32±0.96abc -1.84_2.34	5.907	<0.001**
Left Femur Total T-Score Normal Osteopenia Osteoporosis	23 (46.0%) 25 (50.0%) 2 (4.0%)	37 (74.0%) 13 (26.0%) 0 (0.0%)	20 (80.0%) 5 (20.0%) 0 (0.0%)	23 (92.0%) 2 (8.0%) 0 (0.0%)	22.198#	<0.001**
Left Femur Total Z-Score Mean±SD Range	-0.88±1.39 -3.03_6.43	-0.39±1.41a -2.77_6.43	-0.25±0.91ab -1.81_1.81	0.10±0.91abc -1.65_2.07	3.758	0.012*
Left Femur Total Z-Score Normal Osteopenia Osteoporosis	25 (50.0%) 24 (48.0%) 1 (2.0%)	35 (70.0%) 14 (28.0%) 1 (2.0%)	19 (76.0%) 6 (24.0%) 0 (0.0%)	24 (96.0%) 1 (4.0%) 0 (0.0%)	17.866#	0.007*

Table 7: comparison between groups according to left forearm total T-score and Z-score

	SSRI (n=50)	SNRI (n=50)	Control FMS (n=25)	Healthy control (n=25)	F/x2#	p-value
Left Forearm Total T-Score **Mean±SD** **Range**	-1.97±1.49 -5.57_2.01	-0.89±1.64a -5.57_3.12	-0.95±1.82ab -5.19_2.37	-0.29±1.18abc -2.05_1.79	7.820	<0.001**
Left Forearm Total T-Score **Normal** **Osteopenia** **Osteoporosis**	15 (30.0%) 17 (34.0%) 18 (36.0%)	27 (54.0%) 15 (30.0%) 8 (16.0%)	12 (48.0%) 9 (36.0%) 4 (16.0%)	15 (60.0%) 10 (40.0%) 0 (0.0%)	17.095	0.009*
Left Forearm Total Z-Score **Mean±SD** **Range**	-1.65±1.47 -5.57_2.01	-0.81±1.63a -5.57_3.12	-0.69±1.78ab -5.19_2.37	-0.13±1.14abc -2.05_2.49	6.175	<0.001**
Left Forearm Total Z-Score **Normal** **Osteopenia** **Osteoporosis**	17 (34.0%) 19 (38.0%) 14 (28.0%)	28 (56.0%) 14 (28.0%) 8 (16.0%)	14 (56.0%) 7 (28.0%) 4 (16.0%)	19 (76.0%) 6 (24.0%) 0 (0.0%)	15.221	0.019*

As regard the comparison between groups according to left forearm total T-score and Z-score, there was highly statistically significant difference between groups according to left forearm total T-score and left forearm total Z-score.

Table 8: comparison between age <45 years versus ≥45 years according to T-score and Z-score in SSRI group

SSRI	<45 years		≥45 years		t-test	
	Mean	**±SD**	**Mean**	**±SD**	**t**	**p-value**

L1-L4 T-Score	-1.58	1.08	-2.26	0.89	5.982	0.018*
L1-L4 Z-Score	-1.25	1.16	-1.45	1.00	0.413	0.524
Left Femur Total T-Score	-0.54	1.74	-1.23	1.10	2.843	0.098
Left Femur Total Z-Score	-0.62	1.74	-1.12	0.94	1.636	0.207
Left Forearm Total T-Score	-1.47	1.58	-2.43	1.27	5.671	0.021*
Left Forearm Total Z-Score	-1.25	1.60	-2.01	1.26	3.530	0.046*

This table showed statistically significant difference between age <45 years and ≥45 years according to L1-L4 T-score, Left Forearm Total T-Score and Left Forearm Total Z-Score.

DISCUSSION

According to **White and Harth[10]** Fibromyalgia was second only to osteoarthritis among new consults and it was the only disorder perceived by a majority (69.3%) with increased in frequency within the practices over the previous 5 years. FM now also appears to account for a significant percentage of patients seen in family practice clinics 2.1%, general medicine clinics 5.7% and hospitals 7.5%. **Carville et al. [10]** (SNRIs) duloxetine and milnacipran had been approved by the US Food and Drug Administration for the management of fibromyalgia and appear to be more effective in relieving fibromyalgia symptoms than are the SSRIs. **Atzeni[12]** reported that (SSRIs) such as citalopram, fluoxetine, escitalopram, fluvoxamine, paroxetine, and sertraline may be helpful in treating depression and/or anxiety symptoms, they are superior to placebo in treating the key FM symptoms of pain, fatigue, or sleep dysfunction.

Cosman[13] reported that BMD testing was a vital component in the diagnosis and management of osteoporosis. BMD has been shown to correlate with bone strength and is an excellent predictor of future fracture risk. DXA measurements must be performed by appropriately trained technologists on properly maintained instruments. DXA scans are associated with the risk of exposure to radiation mostly trivial amounts.

According to **Mateos[14]** the association between fibromyalgia and osteoporosis was theoretically sound, since some risk factors were common for both fibromyalgia and osteoporosis. Gender is an example, as the two diseases are more frequent in women. In a study of **Moura and his colleagues [15]** they found that selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) usage may increase the risk of falls, decrease bone mineral density (BMD), and result in subsequent fractures even after controlling for multiple risk factors. The present study provided evidence that usage of SSRIs or SNRI is significantly associated with low BMD (osteopenia & osteoporosis) specially spine BMD reduction with low TBS (Partially degraded and degraded) particularly for old people, and despite low BMD was found in the SRI users; it also found in 1ry fibromyalgia not on SRIs so 1ry fibromyalgia should also be considered as a contributing factor for low BMD. These results are in accordance with those of **Zhou[4]** who concluded that SSRIs and SNRIs have a reducing effect on BMD, and in accordance with **Upala[2]** concluded that FMS is associated with decreased BMD at the lumbar spine (L2–L4) compared with normal individuals. Hence, we recommend eliminating other risk factors to avoid osteoporosis and take calcium and vitamin D in daily recommended doses for preventing osteoporosis, also switch old patients on SSRIs user for fibromyalgia to another regimen.

CONCLUSION

The present study provided evidence that usage of SSRIs or SNRI was significantly associated with low BMD (Osteopenia and osteoporosis) specially spine BMD reduction with low TBS (Partially degraded and degraded) particularly for old people and despite low BMD was found in the SRI users; it also found in 1ry fibromyalgia not on SRIs so 1ry

fibromyalgia should also be considered as a contributing factor for low BMD.

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