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Feasibility of Low Intensity Pulsed Ultrasound to Improve FRAX® Results in Postmenopausal Osteoporotic Femur

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Abstract : *Objectives:* The aim of this study was to investigate the efficacy of low intensity pulsed ultrasound on the results of fracture risk assessment tool (FRAX®)of osteoporotic femoral neck in postmenopausal women. *Methods:* Thirty six postmenopausal women with low femoral neck bone mineral density ageing between 45 to 75 years with BMI between 28.2 to 45.7 kg/m^2 participated in this study. They were assigned randomly into one study group (18Osteopenic subjects: with a T-score between –1.0 and –2.5, and18 Osteoporotic subjects: with a T-score at or below –2.5) as each subject was her control in a single group pretest posttest study design. All participants received the treatment of low intensity pulsed ultra sound (LIPUS) for successive six months. Both 10-years probability of major osteoporotic hip fracture and 10-years probability of hip fracture were assessed by FRAX® desktop individual entry model (version 3.91). The participants were tested twice; before and after the application of LIPUS therapy. *Results:* The statistical analysis revealed that there was a statistically significant decrease of both 10-years probability of major osteoporotic hip fracture and 10-years probability of hip fracture in the post-treatment condition compared with the pre-treatment ($p<0.05$). Moreover, there was a more significant improvement of FRAX® results in osteopenic subgroup compared to FRAX® results in osteoporotic subgroup ($p<0.05$). *Conclusions:* low intensity pulsed ultrasound therapy may be considered as one of the most helpful methods of physiotherapy in management of low bone mineral density in postmenopausal women.

Keywords : Osteoporosis; Low Intensity Pulsed Ultrasound; Fracture risk assessment tool; FRAX®.

Introduction

Osteoporosis, literally “porous bone”, is a disease characterized by weak bone. It is a major public health problem, affecting hundreds of millions of people worldwide, predominantly postmenopausal women[1]. Fragility fractures cause physical disability, impaired quality of life, increased mortality and higher health-care cost[2]. There are several clinical conditions that require enhancement of bone regeneration either locally or systemically, and various methods are currently used to augment or accelerate bone repair, depending on the

healing potential and the specific requirements of each case. Knowledge of bone biology has vastly expanded with the increased understanding at the molecular level, resulting in development of many new treatment methods[3].

The WHO developed two 10-years probabilities of fracture models (FRAX®): one for hip fracture and one for major osteoporotic fracture (hip, spine, wrist, or shoulder). FRAX® uses nine clinical risk factors to estimate the 10-yr probability of fracture: age, sex, body mass index, parental history of hip fracture, exposure to systemic glucocorticoids, history of prior fragility fracture, current smoking, three or more units of alcohol per day, and the presence of secondary osteoporosis[4]. FRAX® can identify postmenopausal women at highest risk of incident major osteoporotic fracture and incident radiographic vertebral fracture. The addition of bone mineral density (BMD) information to clinical risk factor assessment improved fracture risk prediction[5].

Low intensity pulsed ultra sound (LIPUS) is a form of mechanical energy transmitted transcutaneously by high frequency acoustic pressure waves. The intensity of LIPUS (30mW/cm^2) is within the range of ultrasound intensities used for diagnostic purposes (1–50 mW/cm^2) and is regarded as non-thermal and non-destructive. The LIPUS device produces a 200 μs burst of 1.5 MHz acoustic sine waves, that repeats at a modulation frequency of 1 kHz, and provides a peak pressure of 30mW/cm^2. Bone cells are sensitive to strains caused by physical loading. Mechanoreceptors convert biophysical stimuli into biochemical responses that alter gene expression and cellular adaptation. Mechanical adaptive modeling can promote bone tissue formation by a proliferative response or by a direct anabolic effect on bone cells[6].

The micro-mechanical stress produced by LIPUS may provide a surrogate for the forces normally applied on bone by physical loading according to Wolff's law. Although the strain induced by LIPUS at the tissue level is several orders of magnitude lower than the peak strains generated by functional load bearing, high frequency low magnitude strains can result in strong regulatory signals to bone tissue. LIPUS increases prostaglandin E2 production via the induction of cyclooxygenase-2 in MC3T3-E1 osteoblastic cells in vitro[7].

2. Patients, instrumentation and Intervention protocols

2.1. Patients

Thirty six postmenopausal females with early diagnosed low femoral neck bone mineral density ageing between 45 to 75 years with BMI between 28.2 to 45.7 kg/m^{2}were encouraged to participate in this study. Subjects were selected randomly from visitors of osteoporosis laboratory at faculty of Physical Therapy – Misr University for Science and technology (MUST), they were assigned randomly into one study group, each subject was her control in a single group pretest posttest design: (18 osteopenic participants: with a T-score between –1.0 and –2.5, and 18 osteoporotic participants: with a T-score at or below –2.5). Subjects who were receiving hormonal replacement therapy or any medications may affect the BMD were excluded from this study. All participants received 20 minutes of LIPUS treatment over the anatomical site of neck of femur, three times per week for successive six months[8]. Both 10-years probability of major osteoporotic hip fracture and 10-years probability of hip fracture were assessed by FRAX® desktop individual entry model (version 3.91). The participants were tested twice; before and after the application of LIPUS therapy. Double blind evaluation was conducted for each woman individually before and after six months of treatment[9].

2.2. Instrumentation

2.2.1. For evaluation

Dual Energy X-ray Absorptiometry (DXA) for bone density assessment which includes large machine (central devices) that consists of padded platform and a mechanical arm like devise (scanner) that emit low dose X-ray on the area of measurement. The equipment combined with computer in which its software is able to determine bone mineral density. Dual Energy X-ray Absorptiometry (DXA) is the standard of measuring bone mineral content using very low dose of radiation while producing bone mineral density using bone mineral content (gm) by the area of bone measured (cm^2)[10].

FRAX® desktop individual entry model (version 3.91): gives the 10-year probability (in percentage %) of a hip fracture and major osteoporotic hip fracture according to the T-score for femoral neck BMD. It is universally accessible on the Internet: www.shef.ac.uk/FRAX.

2.2.2. For treatment

The OSTEOTRON III is a very Low Intensity Pulsed Ultra Sound (LIPUS); non-invasive (LIPUS); two channels; can be used in a digital display of cumulative hours of treatment; a single probe capable of both1 MHz or 3 MHz output is used according to treatment objectives and areas: 1 MHz for a deep area and 3 MHz for superficial area. The probe BNR (beam non-uniformity ratio), a key factor in the efficacy and safety of ultrasound therapy, is 3.1–3.5 (IEC) [11].

2.3.Intervention protocols

2.3.1. For evaluation

Dual Energy X-ray Absorptiometry (DXA) technique was used to measure BMD of the femoral neck point using bone mineral content in gram (gm) by measured area (cm^2). During this test, each woman was allowed to lie on a padded platform for a few minutes while an imager (a mechanical arm-like device) passes over the woman without touching her, it emit radiation through the exposed part of the woman body (the proximal femur). The equipment converted the information received by the detector in the mechanical arm like device into an image of the hip. The results were reported as a total amount of bone per unit of the skeleton area[12].

DXA outcome results of each woman with her own data and current risk factors were introduced to FRAX® desktop individual entry model (version 3.91): gives the 10-year probability (in percentage %) of a hip fracture and major osteoporotic hip fracture according to the T-score for femoral neck BMD[5, 13].Both 10-years probability of major osteoporotic hip fracture and 10-years probability of hip fracture were assessed by FRAX® desktop individual entry model. All participants were tested twice; before and after the application of LIPUS therapy for both right and left lower limbs[9].

2.3.2. For treatment

All participants received 20 minutes of LIPUS treatment over the anatomical site of neck of femur, three times per week for successive six months[8]. Each subject received the application of LIPUS while lying in side position. The head of LIPUS were placed on the area of the femoral neck of both right and left lower limbs separately as bilateral hip measurements using DXA are recommended to avoid underestimating the BMD status of postmenopausal women and to extend the application of BMD[14].

3. Data analysis

It was intended to compare between the “pre-treatment” and “post-treatment” conditions "within-subject effect" for both 10-years probability of major osteoporotic hip fracture and 10-years probability of hip fracture variables in the tested group. T-tests were conducted to reveal the changes within subjects to determine whether there were significant differences in the set of dependent variables across the two experimental subgroups which received LIPUS treatment.

4. Results

All statistical measures were performed using the Statistical Package for Social science (SPSS) program version 18 for windows. Prior to final analysis, data were screened for normality assumption, and presence of extreme scores. This exploration was done as a pre-requisite for parametric calculation of the analysis of difference.

4.1. Demographic data of patients

Although there is a significant difference between osteopenic and osteoporotic groups in age, weight and body mass index (BMI), this shouldn’t be a problem since the effectiveness of the treatment is measured in this paper through the relative difference which is the difference between pre and post FRAX® values relative to the pre FRAX® value so the two subgroups can be compared without worrying about the initial criteria. What matters was how much decrease in FRAX® results happened in relation to the initial FRAX®. Relative difference was calculated as follows:

Relative Difference = (post value - pre value) / pre value

The demographic data of the participants are shown in (Table 1).

Table (1): Initial subjects criteria in both groups

Variable	Osteopenic subgroup		Osteoporotic subgroup		t-value	p-value
	Mean	SD	Mean	SD		
Age (Yrs)	57.78	8.30	64.06	9.13	2.1	0.03*
Weight(Kg.)	87.19	12.50	98.11	13.52	2.5	0.01*
Height(cm)	163.56	3.82	162.39	4.78	0.8	0.4
BMI(Kg/m^2)	32.78	4.84	37.33	5.91	2.5	0.01*

SD: Standard deviation *Significant at p-value<0.05

4.2. Ten-years probability of major osteoporotic hip fracture

Statistical analysis using the results of paired t-test in Table (2), revealed that there was a significant difference (p-value = 0.0001) between pre and post mean values of FRAX® (major osteoporotic hip fracture risk probability) in each subgroup. Post mean was less than pre mean in both subgroups, but the relative difference between pre and post means was larger in Osteopenic subgroup than Osteoporotic subgroup which means that the LIPUS treatment is more effective in decreasing FRAX®(major osteoporotic hip fracturerisk probability) values in Osteopenic group. This conclusion is also apparent in Figure (1).

Table (2):Comparison between pre &post mean values of FRAX® (major osteoporotic hip fracture risk probability) in Osteopenic and Osteoporotic subgroups.

FRAX® (major osteoporotic hip fracture risk probability)	Osteopenic subgroup		Osteoporotic subgroup	
	Mean	SD	Mean	SD
Pre-treatment	6.66	3.71	23.10	10.59
Post-treatment	5.97	3.29	22.26	10.59
Relative Difference	-0.1		-0.03	
Paired t-value	4.6		4.1	
p-value	0.0001*		0.0001*	

SD: Standard deviation *Significant at p-value<0.05

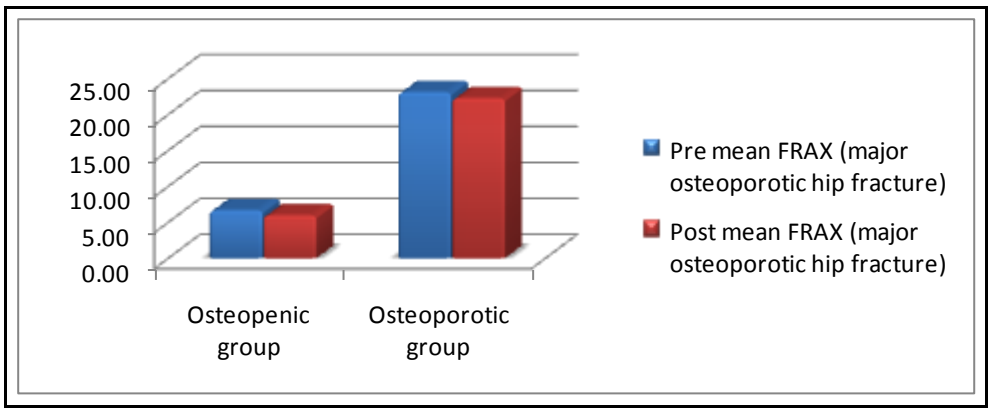

Figure (1): Comparison between pre & post mean values of FRAX® (major osteoporotic hip fracturerisk probability) in Osteopenic and Osteoporotic subgroups.

4.3. Ten-years probability of hip fracture

Statistical analysis using the results of paired t-test in Table (3), revealed that there was a significant difference (p-value = 0.0001) between pre and post mean values of FRAX® (hip fracture risk probability) in each subgroup. Post mean was less than pre mean in both subgroups, but the relative difference between pre and post means is much larger in Osteopenic subgroup than Osteoporotic subgroup which means that the LIPUS treatment is more effective in decreasing FRAX® (hip fracture risk probability) values in Osteopenic group .This conclusion is also apparent in Figure (2).

Table (3): Comparison between pre &post mean values of FRAX® (hip fracture risk probability) in Osteopenic and Osteoporotic subgroups.

FRAX® (hip fracture risk probability)	Osteopenic subgroup		Osteoporotic subgroup	
	Mean	SD	Mean	SD
Pre-treatment	0.91	0.75	10.60	6.89
Post-treatment	0.64	0.55	9.98	6.93
Relative Difference	-0.29		-0.05	
Paired t-value	4.25		4.3	
p-value	0.0001*		0.0001*	

SD: Standard deviation *Significant at p-value<0.05

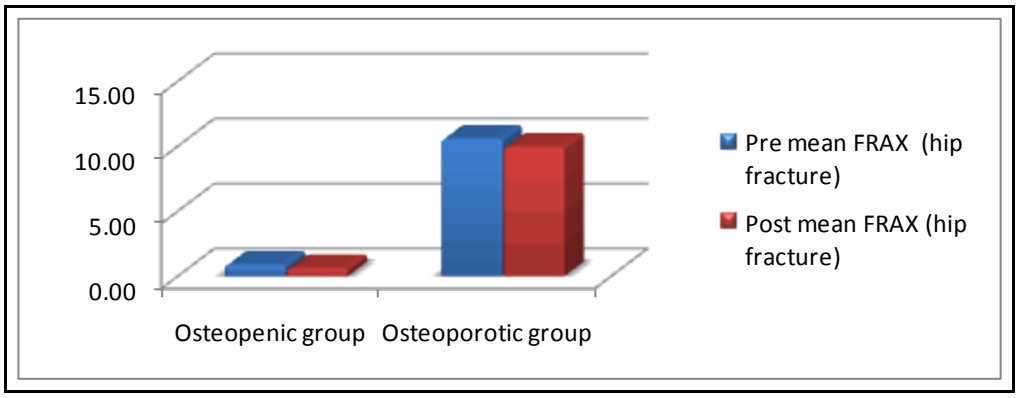

Figure (2): Comparison between pre & post mean values of FRAX® (hip fracture risk probability) in Osteopenic and Osteoporotic subgroups.

4.3. Relative differences between Osteopenic and Osteoporotic subgroups

Statistical analysis using the results of Independent samples t-test in Table (4); revealed that there was a significant difference between mean values of the relative difference in FRAX® (hip fracturerisk probability)and FRAX®(major osteoporotic hip fracturerisk probability) of Osteopenic subgroup and Osteoporotic subgroup. The difference was larger in the Osteopenic subgroup. In Figure (3) it is clear that the relative difference in both variables of FRAX® was larger in the Osteopenic subgroup. The difference between the two groups in FRAX® (hip fracturerisk probability) was much more than FRAX®(major osteoporotic hip fracturerisk probability).

Table (4):Comparison between Osteopenic and Osteoporotic subgroups.

Groups	Relative Difference in FRAX® hip fracturerisk probability (between pre and post)		Relative Difference in FRAX® major osteoporotic hip fracture risk probability (between pre and post)	
	Mean	SD	Mean	SD
Osteopenicsubgroup	-0.23	0.22	-0.09	0.08
Osteoporotic subgroup	-0.09	0.12	-0.04	0.05
Difference	0.14		0.05	
Independent samples t-value	3.39		2.98	
p-value	0.001*		0.004*	

SD: Standard deviation *Significant at p-value<0.05

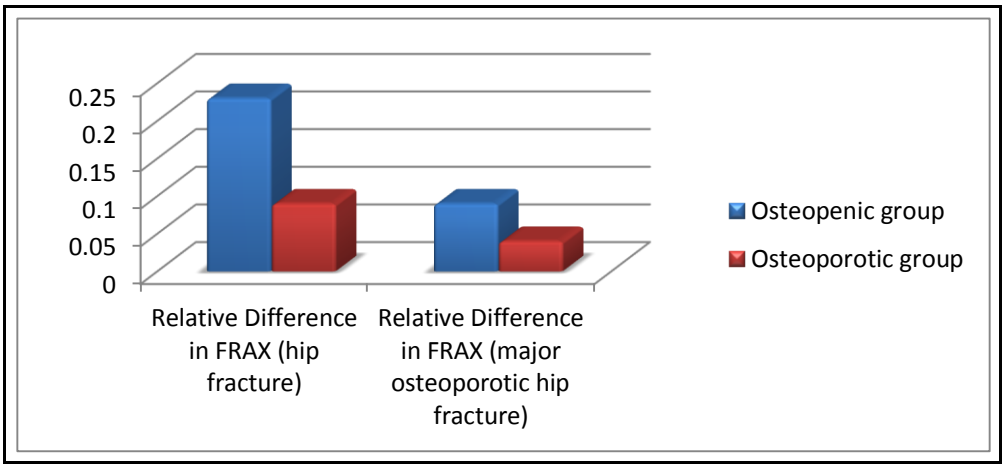

Figure (3): Comparison between Osteopenic and Osteoporotic subgroups.

5. Discussion

The aim of the present study was to investigate the efficacy of low intensity pulsed ultrasound on the results of FRAX® of osteoporotic femoral neck in postmenopausal women. Thirty six postmenopausal women with low femoral neck bone mineral density participated in this study. They were assigned randomly into one study group and two study subgroups according to World Health Organization (WHO) criteria of defining low bone mineral density:18Osteopenic subgroup: with a T-score between –1.0 and –2.5, and18 Osteoporotic subgroup: with a T-score at or below –2.5)[15]. Dual Energy X-ray Absorptiometry (DXA) before and after six months of treatment which gives indication about the bone mineral content (gm) per the area (cm^2) of the examined bone. DXA is characterized by fast scan time, low radiation dose and excellent precision and accuracy[9].

The FRAX® algorithms give the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (hip, shoulder, forearm, or clinical spine fracture, but not radiological spine fracture without symptoms) [16]. The fracture risk variables are entered on the Web site. Femoral neck BMD can additionally be entered as a T-score. The obvious application of FRAX® is for the assessment of individuals to identify those who would be candidates for pharmacological intervention, and it has been widely used since the launch of the Web site. There are also challenges to be faced in the assessment of pharmacological agents for drug registration and in health economics. FRAX® is available in 58 models for 53 countries and in multiple languages[17].

Bone stimulation represents a $500 million market in the United States. The use of electromagnetic stimulation in the treatment of fractures is common; however, the efficacy of this modality remains uncertain[18].There is ample literature that supports that LIPUS can be utilized to enhance cell proliferation and differentiation, matrix production with the differentiated cells, gene transfection for cell differentiation as well as tissue repair both in vitro and in vivo. The optimum LIPUS treatment time and dose is still yet to be studied. The potential applications of LIPUS in tissue engineering could be used for bone, cartilage, skin, nerve, and possibly teeth tissue engineering[19].

Lim et al. (2011) have showed that LIPUS may improve the microarchitectural characteristics, material properties and mechanical strength in the osteoporotic bone, leading to decrease in bone fracture risks, while Lam et al. (2012) confirmed that daily ultrasound treatment significantly increased the rate of union and the volumetric bone mineral density in the neurally intact rats[20, 21].Handolin, (2006) found that low intensity ultrasound did not have any effects on radiological bone morphology, bone mineral density or clinical outcome in fixed lateral malleolar fractures 18 months after the injury, while Leung et al. (2004) found that LIPUS should be recommended in fractures with poor healing potential, while Schofer et al. (2010) demonstrated significantly greater progress toward bone healing after LIPUS treatment compared to no LIPUS treatment in subjects with established delayed unions of the tibia[22, 23, 24].

Our study revealed that the LIPUS treatment has statistically significant efficacy in both osteopenic and osteoporotic criteria of low BMD of femoral neck. It decreases both parameters of FRAX® in both groups. However, the relative decrease is larger in the Osteopenic group making the treatment more effective in the Osteopenic criteria especially for FRAX® (hip fracture risk probability) where there is an apparent difference in efficacy of treatment in both subgroups since the treatment is much more effective in the Osteopenic group. It was also noted that the relative decrease in FRAX® (hip fracture risk probability) is much more than the relative decrease of FRAX® (major osteoporotic hip fracture risk probability) in both groups.

5. Conclusion

On the bases of the present data, it is possible to conclude that the low intensity pulsed ultra sound (LIPUS) is an effective therapeutic modality for improving BMD at the femoral neck region in postmenopausal women, as well as improving the results of FRAX®.

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