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Bone mineral density in response to radial extracorporeal shock wave after thyroidectomy

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To evaluate the response of bone mineral density to radial extracorporeal shock wave therapy (rESWT) in patients suffering from osteoporosis after thyroidectomy.60 participants their ages ranged from 25- 45 years from both sexes. The participants were randomized into two groups, a study group (n= 30) and a control group (n=30). The study group received rESWT in addition to routine medical treatment while the control group received routine medical treatment only. The study group received two sessions per week for 8 weeks. T-score levels were measured as an indicator of the bone mineral density with dual-energy X-ray absorptiometry (DXA) for both groups before and after treatment. Post-treatment there was a significant increase in bone mineral density of forearm and femur in both groups compared with pre-treatment. There was a significant increase in BMD of forearm and femur of the study group compared with that of the control group ($p < 0.01$). Radial extracorporeal shock wave therapy is an effective, safe and pain-free modality for improving bone mineral density in patients with osteoporosis after thyroidectomy.

Keywords: Radial Extracorporeal Shock Wave, Bone Mineral Density, Osteoporosis, Dual Energy X-ray Absorptiometry, Thyroidectomy

INTRODUCTION

Thyroidectomy is a surgical procedure to remove either a part or the whole thyroid gland for treating thyroid goiter, adenoma, and thyroid malignancy. Distinctive kinds of thyroidectomy including partial, subtotal, or total are used to remove a part, most, or all of the thyroid tissue, respectively (Parangi and Phitayakorn, 2011).

Deficiency of calcitonin and thyroxin treatment postoperatively with suppressive doses were the major factors to cause bone loss after total thyroidectomy (Frilling and Hertl, 2001 and Capelli et al., 2004) and in patients with partial thyroidectomy (Hung et al., 2018). To prevent recurrence of thyroid cancer, thyroxin treatment is usually required to maintain the subclinical hyperthyroid status or euthyroid status. It has been associated with a decrease in BMD and increased risk of osteoporosis (Moon et al., 2016 and Papaleontiou et al., 2016).

As most biologically active calcitonin is produced by C-cells, which are located in the centre of each lobe of the thyroid, also partial thyroidectomy causes a relative calcitonin deficiency and there is evidence of reduced serum calcitonin levels after surgery (Gam et al., 1991 and Cummings et al., 1995).

Osteoporosis is a disease characterized by decreased bone strength. Women are susceptible to develop osteoporosis four times more than men. It is most commonly affect post-menopausal women but also affects men and women with major risk factors associated with decrease BMD. Its main clinical signs are vertebral and hip fractures. Fractures also can occur at any skeletal site (Suman et al., 2013).

Fractures after minimum trauma is the most common complication after osteoporosis. They are called fragility fractures as a result of exposure to a force equal to or less than that occurred during falling from standing (Center et al., 2007). The most common sites of fracture are hip, forearm and the vertebral bodies. Hip fractures are associated with increased rate of mortality and morbidity (Burge et al., 2007).

Drugs used for treating osteoporosis (approved by Food and Drug Administration (FDA) improve BMD and increase the mechanical strength of the bone. Although, there are many disadvantages to these drugs, such as it need a long time, low efficacy and a potential negative side effects (Khan et al., 2017). So, it is essential to find lifelong treatment, and the high costs justify the search for alternative treatments (Van der Jagt et al., 2009).

Radial shock waves are produced ballistically by enhancing a bullet to hit an applicator, then converts the kinetic energy into radically expanding pressure waves. Focused shock waves characterized by focusing on a specific point. On the other hand, rESWT is characterized by a larger treatment area, that cause radiation of the waves to cover wide pathology zone (Gerdesmeyer et al., 2004).

The most common effects of shock waves are mechanical by reflection with pressure, production of tension forces at different resistance levels and the production of cavitation bubbles in the contact medium, which produce shear forces by high velocity liquid streams (Delacretaz, 1995 and Delius et al., 1998).

Extracorporeal shock wave therapy has been used for the treatment of various musculoskeletal conditions such as plantar fasciitis, a vascular necrosis of femoral head, calcifying tendinitis, and lateral epicondylitis (Gerdesmeyer et al., 2008 and Wang et al., 2005). Moreover, ESWT has been used to enhance bone healing, and it has been used as a treatment of delayed non-union fractures (Valchanou and Michailov, 1991).

Many studies have shown a positive effect of shock waves on bone formation by one of the following underlying mechanisms:

Extracorporeal shock wave will enhance the expression of growth factors (Link et al., 2013 and Rosso et al., 2015). Mechanical stimulation by extracorporeal shockwave therapy has proven to stimulate proliferation, migration and activation of osteoblasts (Martini et al., 2003 and Martini et al., 2006). Extracorporeal shock wave therapy is also involved in intense formation of new cortical bone, in growth of neovascularisation and promotion of bone morphogenetic protein (Wang et al., 2002 and Wang et al., 2003). It also induces nitric oxide liberation in bone cells and stimulates osteogenesis through core binding factors (Zaragoza et al., 2006). ESWT stimulates bone formation by micro-damages, such as microfractures of trabeculae, subperiosteal haemorrhage, periosteal detachment, and bone marrow hypoxia (Zhao et al., 2015).

After shock wave application, dose-dependent stimulation of bone cells in vitro was observed, with a minimum threshold energy essential to affect on bone cell growth. Stimulation of bone cell depends on the total amount of applied energy, instead of single physical parameters like energy flux density or number of impulses (Kusnierczak et al., 2000).

Extracorporeal shock wave therapy (ESWT) can be classified into two different energy influx levels. Low-energy flux application ($<$0.2 mJ/mm2) is generally well tolerated, with mild to moderate discomfort. High-energy flux applications ($>$0.2 mJ/mm2) which require local anesthesia (Rompe et al., 2007).

In the previous studies, focused shock waves were applied to a small area. In osteoporosis the skeletal sites that require to be treated are much larger than the points that focused shock wave therapy was applied on. So, it is difficult to apply focused shock wave therapy for the treatment of osteoporosis. USWT have a treatment zone of 3.8 cm in diameter, allowing treatment of larger area of skeletal sites that are susceptible to fracture in osteoporotic patients (Van der Jagt et al., 2011).

No previous study has been conducted to evaluate the response of bone mineral density to repeated intervention of radial extracorporeal shock wave in patients with osteoporosis after thyroidectomy, as the previous studies investigated focused ESWT and the effect of single application of UFESW on osteoporosis animals. So, this study evaluated the efficacy of radial shock waves on improving bone mineral density in patients with osteoporosis after thyroidectomy.

MATERIALS AND METHODS

Study design

This is a randomized control double-blinded, pre-test and post-test design study evaluating the effect of radial ESWT on bone mineral density in patients suffering from osteoporosis after thyroidectomy.

Subjects

The participants were selected from endocrinal surgery department at Kasr Al Ainy Teaching Hospital, Cairo University, Egypt. Sample size calculation was performed by using G* POWER statistical software (version 3.1.9.2; Franz Faul, Universitat Kiel, Germany) [31] and revealed that the appropriate sample size for each group n=30 with a power= 0.80, α=0.05, β=0.2 and medium effect size. Inclusion criteria: Their ages ranged from 25-45 years, their body mass index (BMI) ranged from 25 to 28 kg/m² and patients after thyroidectomy with T score ≤ −2.5 at femur and forearm. Exclusion criteria: Patients who received any drugs that affect bone metabolism (glucocorticoids, heparin and warfarin), patients had any gonadal disease that affects hormonal balance, orthopaedic or neurological abnormality in hip or forearm and patients who had contraindications for ESWT (heart pacemaker, cardiac pathologies, hemorrhagic disease, cancer, thrombus formation, skin diseases in the treated areas, acute and massive joint effusion and bone infections).

Randomization process

60 participants were selected according to the inclusion criteria. Patients were randomly allocated to either group (Shock wave or control) by a blinded and independent research assistant by opening sealed envelopes that contained a computer-generated randomization card. The researcher and patients were blinded as to on which group they were allocated. Randomization and blinding were used to prevent bias.

Group A (Shock wave group) received radial ESWT (twice per week) in addition to routine medical intervention (Pisphosphonates, calcium and vitamin D) and group B (control group) received routine medical intervention (Pisphosphonates, calcium and vitamin D) only.

Data collection

Data were collected during the period from January 2017 to April 2018. Assessment was performed before and after treatment for both groups. Bone mineral density was assessed by using dual-energy X-ray absorptiometry (DXA).

Assessment

Generally, the most common method of assessment of osteoporosis is to use DXA scans of the central skeleton to measure BMD of hip and lumber vertebra. Central DXA scans most commonly used to identify osteoporosis, assessment of fracture risk, and to evaluate response to treatment (Johnell et al., 2005).

During a DXA assessment, a patient is exposed to an irradiated X-ray beam of two different energies, which allows bone attenuation separation from soft tissue attenuation. It is highly important that facilities that perform DXA examinations identify that the main output of this test is quantitative. A quality-control program must be followed to be sure that the data obtained falls within accepted ranges for precision and accuracy (Choplin et al., 2014).

The dual-energy X-ray absorptiometry used to measure the BMD, T-score, and Z-score. The T-score used for assessment of patient's status: normal, low BMD, or osteoporosis (Kanis et al., 2008). T-scores are measured by calculating the difference between the measured BMD and the mean BMD in normal young adults, according to sex and ethnic population, this difference is expressed according to the standard deviation of the young adults (Blake and Fogelman, 2007). Osteoporotic patients have T-score below or equal to −2.5. Osteopenic patients have T-score between −1.0 and −2.5. If all of the T-scores were above −1.0, BMD was considered as normal (Chang, 2017).

BMD of the femur (total hip) and forearm was measured using dual energy X-ray absorptiometry (DEXA; Lunar Corporation, Model DP3, Madison, WI, USA) pre and post- treatment. The study was approved by the local ethical committee of Faculty of Physical Therapy, Cairo University. All subjects signed an informed consent for participation in the study.

Intervention

Radial ESWT was applied with a Swiss Dolorclast shock wave device (EMS Electro Medical Systems, Nyon, Switzerland). The patients were positioned in the bed with hip joint in an external rotation position and forearm in supinated position and rested on the bed. Then, the coupling gel was applied as a contact medium at the skin to reduce the loss of shock wave energy with the following parameters: (0.16 mJ/mm2, 4 Hz, total 2000 impulses) for each site. The treatment was repeated twice /week for 8 weeks. There was no side effects at the application sites.

Statistical analysis

Descriptive statistics and t-test were conducted for comparison of subject characteristics between both groups. Mixed

MANOVA was conducted to compare the mean values BMD of forearm and femur between the study and control groups as between group comparison and between pre and post-treatment in each group as within group comparison. Post-hoc tests using the Bonferroni correction were carried out for subsequent multiple comparison. The level of significance for all statistical tests was set at $p < 0.05$. All statistical analysis was conducted through the statistical package for social studies (SPSS) version 19 for windows (IBM SPSS, Chicago, IL, USA).

RESULTS

Subject characteristics:

Table (1) showed the mean ± SD age, weight, height and body mass index of study and control groups. There was no significant difference between study and control groups in age, weight, height and BMI ($p > 0.05$).

Effect of treatment on bone mineral density:

As shown in (table 2) mixed MANOVA revealed that there was a significant interaction of treatment and time (Wilks' Lambda = 0.17; F= 134.4, $p < 0.001$). There was a significant main effect of time (Wilks' Lambda = 0.08; F= 299.53, $p < 0.001$).There was no significant main effect of treatment (Wilks' Lambda = 0.94; F = 1.72, p = 0.18).

Within group comparison:

There was a significant increase in BMD of forearm and femur according to T- score post-treatment in both groups compared with that pre-treatment ($p < 0.001$). (table 2).

Between groups comparison:

There was no significant difference in BMD pre-treatment between both groups ($p > 0.05$). Comparison between groups post-treatment revealed a significant increase in BMD of forearm and femur of study group compared with that of control group ($p < 0.01$). (Table 2) and (Figure 1).

Table (1): Comparison of subject characteristics between study and control groups:

	x̄±SD		MD	t- value	p-value
	Study group	Control group			
Age (years)	37.56± 5.69	38.76± 5.11	-1.2	-0.85	0.39*
Weight (kg)	70.7± 2.85	71.03± 2.73	-0.33	-0.46	0.64*
Height (cm)	162.9± 4.57	164.53± 4.09	-1.63	-1.45	0.15*
BMI (kg/m²)	26.69± 1.73	26.28± 1.58	0.41	0.96	0.33*

x̄, Mean; SD, Standard deviation; MD, Mean difference; p value, Probability value; *, Non significant.

Table (2): Mean BMD of forearm and femur pre and post treatment in study and control groups:

	Study group			Control group			Between groups	
	Pre	Post		Pre	Post		Pre	Post
BMD (g/cm²)	x̄±SD	x̄±SD	P value	x̄±SD	x̄±SD	P value	P value	P value
Forearm	-3.17 ± 0.58	-2.72 ± 0.55	0.001**	-3.24 ± 0.6	-3.16 ± 0.61	0.001**	0.65*	0.006**
Femur	-3.04 ± 0.52	-2.52 ± 0.53	0.001**	-2.98 ± 0.48	-2.87 ± 0.44	0.001**	0.62*	0.008**

x̄, Mean; SD, standard deviation; p-value, level of significance; * Non significant; ** Significant

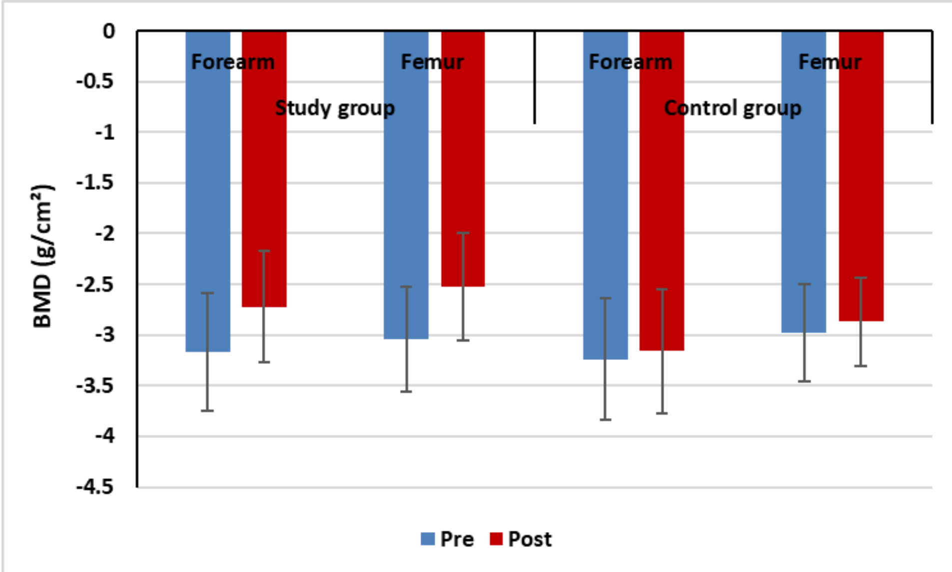

Figure (1): Mean value of BMD of femur and forearm pre and post-treatment in both groups.

DISCUSSION:

Thyroidectomy could be followed by bone loss as a result of increase release of an endogenous of thyroxin, overenthusiastic thyroid therapy following surgery, deregulation of bone resorption as in case of deficiency of calcitonin, or combination of these factors (Cummings et al., 1995 and Lawrence and Rais, 2005).

One of the most frequent complications of thyroid surgery is postoperative hypocalcemia, due to postoperative, transient or permanent hypoparathyroidism, mainly due to compromise of the vascularisation of the parathyroid glands or the inadvertent resection of these (Gac et al., 2007).

Results of this study revealed a significant improvement of BMD in response to 8 weeks of intervention of radial ESWT in patients with osteoporosis after thyroidectomy in femur and forearm. The biological mechanism of ESWT in bone healing was assessed by many studies and revealed that ESWT accelerates healing of fractures by stimulation of neovascularisation, angiogenesis and osteogenesis growth factors (Wang et al., 2008). ESWT enhance bone formation, accelerate healing of fractures and increase BMD and bone mineral content (BMC). Osteogenesis can also be stimulated in the non-pathologically altered bone using ESWT. Shock wave therapy could be an option in patients suffering from impaired bone quality such as osteoporosis (Gerdesmeyer et al., 2015). Also, ESWT have a direct effect in bone gene expression, and neovascularisation which accelerates healing of delayed unions fractures, a vascular necrosis and osteochondritis dissecans (Leal et al., 2015). Extracorporeal shock wave therapy can be used instead of surgery in many orthopaedic disorders to avoid the surgical risks, with low complication rates (Wang, 2012).

Previous in vivo studies argued that unfocused extracorporeal shock wave therapy can be used in the local treatment of osteoporosis in different skeletal sites especially when combined with a medical treatment with bisphosphonates, It is proved that UESW increases bone mass and improved biomechanical properties. It can be applied without use of anesthesia at the sites which are susceptible to osteoporotic fracture (Van der Jagt et al., 2013 and Van der Jagt et al., 2009). Unfocused ESW could stimulate formation of new bone and preferable changes in micro architecture of osteoporotic bone. Also, at the same total energy, low-intensity shockwaves with more shocks were more preferable for stimulating the cellular activities than high-intensity shockwaves with less shocks. So, UESW treatment is an effective modality to prevent local osteoporosis (Tam et al., 2009). It was proved that rESWT is effective for treatment of larger treatment area by enhancing new bone formation in normal bone. Radial ESWT is applied repeatedly for three to six interventions with treatment free intervals from 4–8 weeks. Osteogenesis was enhanced significantly by rESWT already after the first week of shock wave treatment. So, rESWT is considered a new option in the therapy of osteoporosis as it can be effectively applied for treatment of larger areas (Gollwitzer et al., 2013). ESWT improves trabecular architecture in metaphyseal femur in osteoporotic rats after repeated applications for 5 weeks of shockwaves. This effect was more obvious after combined therapy which is a common approach in the treatment of multifactorial diseases, as osteoporosis (Lama et a., 2017). Moreover, unfocused ESWT produced damage to bone and bone-marrow accompanied by increased bone formation, thicker cortices, trabecular bone volume, formation of de novo trabecular structures, and an increased adipocytes in bone marrow. Unfocused extracorporeal shock waves can be used for local treatment of osteoporosis (Van der Jagt et al., 2011).

Other studies evaluate the effect of single session of high energy SWT, slightly focused HESW and roughly focused SWT on bone formation as follows:

High-energy shock wave therapy (HESWT) can cause damage to tendon and paratendon by increasing the diameter and fibrinoid necrosis, whether low-energy shockwaves did not produce tendon damage. Also, it can cause an inflammatory response in the peritendinous area. These changes were observed after 4 weeks of shock wave treatment (Maier et al., 2002 and Rompe et al., 1998). Osteoporotic rats were treated once with roughly focused ESWT. There were increase in collagen, osteoblasts, and ossification, osteoprotegerin (OPG) and bone morphogenetic protein-2 (BMP-2) expression levels in response to the treatment. Increase of OPG prevents loss of bone and reduces osteoporosis (Huang et al., 2016). Slightly focused HESW therapy has been proved to stimulate inflammation reaction, local vascularisation, intramembranous ossification and endochondral bone formation, and promote healing of fracture (Rodola et al., 2002). Slightly focused HESWT with the energy flux density of 0.26 mj/mm2, 1 Hz and 2000 shocks is effective on improving healing of osteoporotic fracture in rats by stimulating callus formation, promoting the reconstruction and the spatial structure of trabecular bone, and improving the biomechanical characteristics of healed bone (Chen et al., 2015). Single application of ESWT is an effective non-invasive approach for improvement of the local BMD in the femoral neck osteoporosis after menopause and could be a better method for reduce the risk of osteoporotic fractures. The effects of ESWT are dose related (Shi et al., 2017).

This is the first study that investigates the effect of repeated interventions (8 weeks) of radial ESWT in patients suffering from osteoporosis after thyroidectomy. As the previous studies investigate the effect of focused ESW on osteoporosis and the effect of single application of UFESW on osteoporotic animals.

There were some potential limitations to this study including small sample size for each group, there was no follow-up period to investigate the long term effect and changes of BMD after repeated application of rESWT and there were no comparison of repeated intervention of rESWT and single session of HESW.

CONCLUSION

From the results of the current study it can be concluded that repeated intervention for 8 weeks of radial ESWT is an effective, non-invasive, safe and pain free modality for treatment of local osteoporosis after thyroidectomy as it can cover large treatment area rather than focusing on specific points and to avoid complications of HESW.

CONFLICT OF INTEREST

The author declared that the present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

NMA designed and performed the study, also performed data analysis and wrote the manuscript. Then read and approved the final version.

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