Exercise versus Estrogen Therapy in Osteoporotic Postmenopausal Women with Endothelial Dysfunction

Mervat El-Sergany[*1], Abeer Shahba[2] and Lamia Al-Ahwal[3]
Departments of Rheumatology & Rehabilitation[1], Internal Medicine[2] and Obestetric & Gynecology[3], Faculty of Medicine, Tanta University, Tanta, Egypt
[*]sergany3@hotmail.com

Abstract: Both exercise and estrogen augments bone metabolism and endothelial function in postmenopausal women. Osteoprotegrin (OPG) appears to represent the molecular link between bone resorption and vascular calcification.This study was conducted to determine the effects of acute bouts of dynamic exercise and oral estrogen on serum osteoprotegrin (OPG) and endothelial dependent flow mediated dilatation of brachial artery (FMD); to assess if these two interventions independently or together achieve same improvement and finally to find any relation between OPG and FMD. Twenty early osteoporotic postmenopausal women with endothelial dysfunction, their mean age (53±9 years) and 20 healthy premenopausal female controls with mean age (29±2 years) were included. All subjects were subjected to assessment of OPG and FMD before the beginning of the study. Then OPG and FMD were quantified after 60 minutes of treadmill exercise for one hour, this protocol was repeated after 4 weeks of oral estrogen therapy .We found that serum OPG was elevated significantly in postmenopausal women after exercise(post-ex) approximating double baseline value (4.8±0.3 vs 2.9±0.3). There was a significant difference between OPG level post exercise and estrogen (post ex-est) vs post estrogen (post-est) alone (5.3±0.2 vs 4.3±0.2) while there was no significant difference between post exercise (post-ex) versus post-est (4.8±0.3 vs 4.3±0.2). Regarding FMD there was a significant difference between post-ex vs baseline (11.4±0.4 vs 6.1±0.5), post-est vs baseline (11.5±1.5 vs 6.1±0.5), also between post ex-est and baseline value (10.5±1.6 vs 6.1±0.5) , while there was no significant difference between all interventions . Our results suggested that both exercise and estrogen augment bone metabolism and vascular reactivity to nearly equal values. So, this study reinforces the importance of exercise as a non pharmacological and alternative to oral estrogen in postmenopausal women and consider exercise as one of the mechanisms that protect against osteoporosis and atherosclerosis.
[Exercise versus Estrogen Therapy in Osteoporotic Postmenopausal Women with Endothelial Dysfunction Mervat El-Sergany, Abeer Shahba and Lamia Al-Ahwal. Journal of American Science 2010;6(10):1154-1159]. (ISSN: 1545-1003).
Keywords: estrogen augments; bone metabolism; endothelial function; postmenopausal women; Osteoprotegrin (OPG); flow mediated dilatation of brachial artery (FMD);

1. Introduction:

After the onset of menopause, there is an increase in age related osteoporosis (Shargorodsky et al; 2009) and impairment of endothelial function (Verdis et al ; 2000).

Both exercise and estrogen therapy augment bone metabolism (West et al . 2009) and endothelial function (Harvey et al; 2005).

Osteoprotegrin (OPG) appears to represent the molecular link between bone resorption and vascular calcification, and may help to explain the high prevalence of atherosclerosis and osteoporosis in postmenopausal women (Saunders, 2009). OPG increases bone mineral density by its well established capacity to inhibite osteoclast differentiation and regulate bone remodeling. The production of OPG protein in endothelium and vascular smooth muscle cell exerting antiapoptotic effects on endothelial cells, protecting them from cell death and regulate vascular inflammation and immunity (Shargorodsky et al;2009) .

Saunders, (2009) concluded that, while the effect of exercise appeared to improve arterial flow mediated vasodilatation (FMD).it may also be evident that the number of endothelial progenitor cells were increased in trained patients

Recently, alternations in bone remodeling have been demonstrated in amenorrheic women (De souza, 2008). Furthermore, numerous investigators have demonstrated that exercising women who are estrogen deficient have negative alternations in bone turnover markers and /or BMD (De souza, 2008).

Published controlled trials of estrogen administration for prevention of CVD have produced negative results (Hodis et al; 2003). However, estrogen has multiple complex pleiotropic effects on the CV system that may exert both beneficial and adverse events (Harvey et al; 2005).

Thus alternative interventions must be explored to protect against osteoporosis and endothelial dysfunction in early postmenopausal period.

The aim of this study was to determine the effects of acute bouts of dynamic exercise and oral

estrogen on serum OPG and FMD; to assess if these two interventions independently or together achieve same improvement and finally to find any relation between OPG and FMD.

2. Patients and Methods

Twenty post menopausal women with early osteoporosis and endothelial dysfunction attending the outpatient clinic of Rheumatology & Rehabilitation and Internal Medicine Departments, Tanta University Hospitals Egypt, were included in this study. Their mean age was (53±9 ys). Twenty healthy premenopausal women were studied as controls; their mean age was (29±2 ys).

All subjects were neither sedentary nor extremely fit.

Exclusion criteria:
-Age above 60 years.
-Secondary osteoporosis
-Coronary heart disease
-Unbalanced endocrine disease
-History of gynacologial or breast cancer
-Abnormal vaginal bleeding
-On hormonal therapy before enrollment in the study
-Any chronic disease (R.A, SLE, thyroid disease etc)
-Deep vein thrombosis or peripheral vascular disease
-Creatinine > 1.5 mg/dl or liver enzyme twice the upper normal value.

All postmenopausal women were with early osteoporotic changes as suggested by BMD (T score at the hip and/or spine between -1 and -2.5) and had a history of amenorrhea for least 12 months. Ovarian hormonal level [follicle stimulating hormone and estrogen] was assessed to confirm menopausal status.

All premenopausal women (controls) were without cardiovascular risk factors and have normal endothelial function (normal FMD). They were examined gynecologically to exclude any uterine or breast cancer or vaginal bleeding. They have regular menstrual cycle averaging (25-35) days, non was receiving any oral contraceptive formulation and were studied during follicular phase which defined as day 5 to 13 of menstrual cycle. Pregnancy was excluded by a negative B human chorionic gonadotropin test.

All included subjects premenopausal and post menopausal underwent.

1- Through clinical examination
2- Standard 12 ECG lead was carried out of all subjects to detect any abnormalities in the heart rate and rhythm.
3- Echocardiogrfaphy and Doppler assessment for evaluation of left ventricular dimention, left ventricular function (systolic and diastolic).

Biochemical parameters:

Blood sampling for full chemistry and metabolic parameters, including fasting glucose, lipid profile, calcium, phosphorus, PTH, creatinine, Albumin, and serum osteoprotegerin (OPG) were performed. Serum OPG was assayed Using Sandwich Enzyme Linked Immunosorbent Assay (ELISA) provided by sigma (St. Louis, MO).

Bone Mineral density (BMD):

Bone status was evaluated at the lumbar spine and femoral neck at the time of the study using dual energy X-ray absorbiometry (DEXA) (9 Hologic ODR 1000/w, Waltham, MA, USA) osteopenia and osteoporosis were defined according to the criteria of World Health Organization. Osteoporosis is defined as a bone mineral density T scores at the hip and /or spine below -2.5. Osteopenia is defined as a T score between -1 and – 2.5, and established osteoporosis as a T score below – 2.5 in the presence of one or more fragility fractures.

Study protocol:

Baseline values (OPG and FMD) were acquired in the morning with all subjects (premenopausal and postmenopausal) resting supine. Then postmenopausal women were exercised on treadmill for a total of one hour to provide similar exercise loads, the speed and grade of treadmill exercise were adjusted to maintain the Heart rate at 60% of each individual's VO_2 max, as calculated from previously obtained cardiopulmonary stress test (Hara and Floras, 1995). Post exercise measurements commenced at 60 minutes after exercise. .Heart rate and arterial BP were recorded continuously throughout the study

In postmenopausal subjects, this protocol was repeated 4 weeks after treatment with open-labeled oral estradiol 2mg/day. Subjects were instructed to take this estrogen at the same time every morning. After completion of the study protocol, women with uterus in situ were prescribed medroxyprogesterone acetate 10mg tablets once daily for a period of 12 days to convert the endometrium from the follicular to the secretory state.

Assessment of endothelial function by flow mediated dilatation (FMD)(Chan et al ; 2003):

Endothelial function was assessed non invasively using high external vascular ultrasound (10 MHZ) under a ray transducer connected to a vivid 7 dimention ultrasound machine Briefly, the test was performed in the morning in a quite room and subjects were fasted. The brachial artery was scanned 5-15 cm above cubital fassa. Resting diameter was measured then blood pressure cuff

inflated to > 200mm Hg for 4.5 minutes. A second image 30 seconds before cuff deflation and conlinued for 2 minutes. FMD was calculated as follows:
(post deflation diameter – resting diameter)/resting diameter X 100.
The endothelial function was considered normal if FMD% is within 2 standard deviation of the mean FMD of control group.

Statistical analysis:

Using SPSS program, version 10 descriptive statistics for continuous variables were expressed as mean and standard deviation. Comparison between groups was done by paired t-test. Correlation between variables was done by Pearson's correlation method. Results were considered significant at P<0.05 and non significant at P > 0.05.

3-Results:

This study was conducted on 20 early osteoporotic post menopausal women with endothelial dysfunction and 20 healthy premenopausal controls. Demographic and clinical data of patients and controls are shown in table (1).

Table (1) show that there was no significant difference between patients and controls regarding body mass index (BMI), cardiovascular risk factors and serum OPG (P>0.05), but there was significant difference regarding, FMD, and BMD (P<0.05).

There was significant elevation of serum OPG post-exercise versus pre-exercise (4.8±0.3 vs 2.9±0.3) and post exercise versus premenopausal value (4.8±0.3 vs 2.22±0.3), but there was no significance difference between post exercise OPG and post estrogen OPG (4.8±0.3 vs 4.3±0.2).There was significance difference between post exercise & estrogen versus post estrogen alone (5.3+0.2 vs 4.3+0.2) (table 2). Regarding FMD there was a significant difference between post ex, post-est and post ex-est versus baseline value (11.4±0.4, 11.5± 1.5 and 10.5±1.6 versus 6.1±0.5) respectively ,while there was no significant difference between all interventions (table 2).

In the present study, there was positive correlation between OPG and FMD (r=0.82, P<0.001) post exercise, and also positive correlation between serum OPG and FMD (r=0.38 P<0.003) post estrogen. (data not shown).

Table (1): Demographic and clinical characteristics of patients and controls

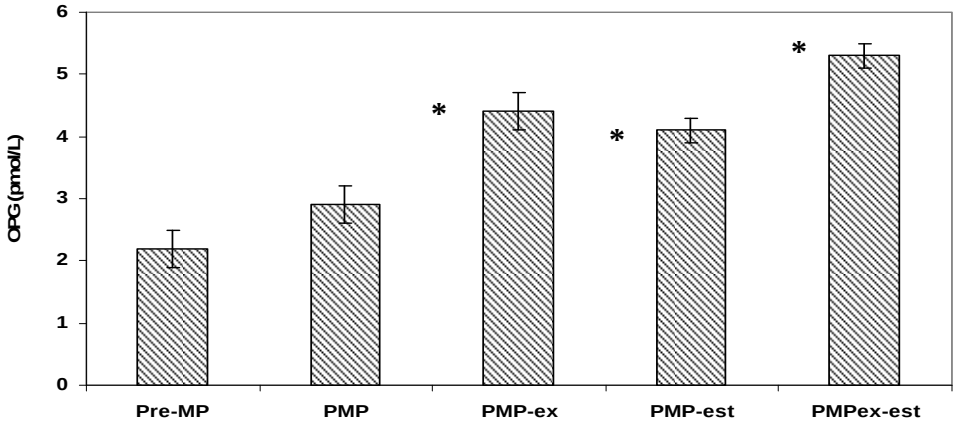
	Patients	**Controls**	**P**
Age (ys)	53±9	29.1±2	S
Weight (kg)	57.8±2.6	59.9±1.0	NS
Hight (cm)	162.5±1.9	167.1±0.8	NS
BMI (kg/m2)	22.3±0.9	21.8±0.3	NS
Smoking (%)	0%	0%	NS
Fasting glucose (%)	85±7	83±2	NS
Mean arterial press. MAP (mmHg)	78±1	76±3	NS
Albumin (mg/dl)	3.9±0.1	4.0±0.2	NS
Creatinine (mg/dl)	1.0±0.2	0.9±0.2	NS
PTH (pg/ml)	65±45	64.2±49	NS
OPG(pmol/L)	2.9±0.3	2.22±0.3	NS
T score (l_2-l_4)	-1.9±0.0.2	-0.8±0.1	S
FMD %	6.1±0.5	12±0.5	S

BMI: body mass index; PTH: parathyroid Hormone; OPG: serum osteoprotegrin; FMD: brachial artery flow mediated dilatation

Table (2): Mean arterial pressure(MAP), heart rate(HR) flow mediated dilatation(FMD) and osteoprotegrin(OPG) post ex, post est, and post ex & est

	Pre ex pre est	Post ex	Post est	Post ex post est	Controls
MAP	78±1	73±1	75±3	60±3	75±6
HR (beat/min)	61±3	76_2	75±2	71±2	68±3
Baseline (mm) measurements	33.4±3.6	33.1±1.8	32.1±1.3	33.1±1.4	33.9±1.9
Post occlusion measurments (mm)	35.41±2.5	36.9±1.6	35.8±1.5	36.6±1.3	39.1±1.8
The absolute changes in brachial artery.	2.01±02	3.9±0.3	3.7±0.6	3.5±0.5	4.1±0.4
FMD (%)	6.1±0.5	11.4±0.4**	11.5±1.5**	10.5±1.6**	12±0.5
Serum OPG (Pmol/L)	2.9±0.3	4.8±0.3*	4.3±0.2*	5.3±0.2*	2.22±0.3

*statistically significant difference versus baseline value and premenopausal value p<0.05
**statistically significant difference versus baseline value p<0.05



Fig(1): Serum OPG in premenopausal women and in early osteoporotic post menopausal women with endothelial dysfunction before and after exercise & estrogen replacement. Values are mean ± SD p*<0.05versus PMP baseline and premenopausal value .There was a significant difference between post estrogen and exercise versus post estrogen alone but there was no significant difference between post estrogen and post exercise. Pre-MP, premenopausal; PMP, postmenopausal baseline; PMP-ex, postmenopausal post exercise: PMP-est; postmenopausal post estrogen, PMP-ex-est, postmenopausal post exercise and estrogen.

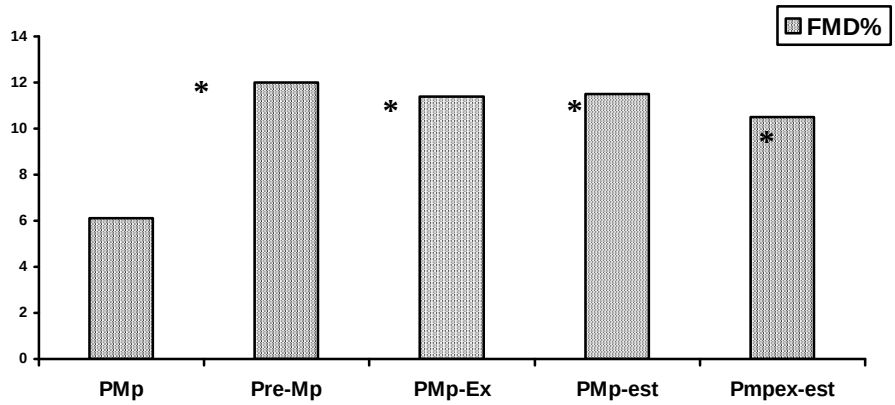


Fig.(2): Flow mediated dilatation (FMD) in premenopausal women and in early osteoporotic postmenopausal women with endothelial dysfunction before and after exercise and estrogen replacement. . Values are mean ± SD. *P < 0.05 vs PMP baseline. There was significant difference between all interventions and baseline value. But there was no significant difference in FMD in PreMP and either PMP-ex, PMP-est, or PMP-est-ex. *PMP*, postmenopausal, *PreMP*, premenopausal; baseline; *PMP-ex*, postmenopausal post exercise; *PMP-est*, postmenopausal post-estrogen replacement; *PMP-est-ex*, postmenopausal post-estrogen replacement and exercise.

4-Discussion

Estrogen and exercise both impact bone metabolism and serum OPG. Mechanical strain & various types of stress and strain on osteoblasts cells have been reported to significantly increase OPG levels (Kim et al; 2006).

Serum OPG functions as a decoy receptor (Holen et al ; 2006) and aids in regulating bone loss by blocking the actions of the RANKL/RANK interaction (Wietzmann and Pacifici , 2006) .OPG is proving to be important in the pathogenesis of bone loss in postmenopausal women (Hofbauer and Schoppet , 2004)

Ziegler *et al*; (2005) in his study for the evaluation of the effects of running (long or short distance) , reported acute increase in serum OPG immediately after running, suggesting the positive effect of exercise on OPG. Moreover West *et al* ;(2009) observed that exercising menstruating women had significantly high OPG compared to sedentary menstruating women, highlighting the

positive effects of exercise training on serum OPG. These results are in accordance with our results.

In this study, post exercise OPG level was significantly elevated comparing to baseline value and controls (P<0.05), but it was non significantly elevated comparing to post estrogen therapy (P> 0.05) There was significant difference between post exercise & estrogen versus post estrogen alone. The absence of estrogen enhances the ratio of RANKL/OPG, promoting osteoclastogenesis and consequently the acceleration of bone loss (Hofbauer and Schoppet , 2004).

Estrogen, a steroid with direct effects on bone metabolism, is another important contributer to bone health in women (Boyle et al ; 2003).

Regarding the effect of estrogen on serum OPG, we found that serum OPG value was nearly similar to post exercise value, denoting that moderate intensity weight bearing exercise can substitute oral estrogen therapy in early osteoporotic postmenopausal women. Our results are similar to that reported by Kahl *et al; (2005)* where he studied anorexia nervosa patients (while there was estrogen deficiency) ,he found elevation of bone resorption and consequent suppretion in OPG. Also West *et al* (2009) concluded same results.

Grinspoon *et al*· (2003) reported no differences in OPG between amenorrheic women on estrogen therapy versus women on placebo therapy. Also Herrmann and Herrmann (2004) concluded that exercising premonopausal atheletes, when compared to sedentary controls, had suppressed serum OPG. These finding are discordant with our findings. However results remain equivocal (Munoz et al., 2007 and Galusca et al., 2008).

This study investigates also the acute effects of a single bout of dynamic exercise on brachial artery dilatation (FMD) in early osteoporotic postmenopausal women with endothelial dysfunction. Consistent with Taddei *et al* ;(1996) and Harvey *et al (2005)*, our study showed that at baseline rest, endothelium dependent FMD was significantly impaired in postmenopausal women compared to healthy premenopausal women. After a single bout of dynamic exercise the FMD was significantly augmented approximating the value of healthy premenopausal controls. At the same time after four weeks of oral estrogen FMD was significantly elevated to a value approximating healthy premenopausal controls.

On the other hand, FMD was not augmented further by concurrent use of estrogen with exercise. So, in postmenopausal women acute dynamic exercise and oral estrogen effectively and independently normalize FMD, However when applied concurrently, the action of the two interventions were not additive. Our findings are similar to data reported by Stathokostals *et al* (2008), who concluded that there was no difference in maximum aerobic power (Max Vo2) in healthy exercising postmenopausal women taking HRT versus women not taking HRT. These results support the concept that potential benefit of Hormone Replacement Therapy (HRT) on cardiovascular function was not additive to the potential benefits of exercise. Furthermore, this study is in agreement with Attipo *et al* (2008), who investigated whether postmenopausal women on HRT would experience a greater reduction in oxidative stress (endothelial dysfunction) after 24 weeks of aerobic exercise compared to women not taking HRT by measuring level of plasma barbituric acid reductive substances as an indicative of oxidative stress. They concluded that aerobic exercise training significantly decreased oxidative stress in postmenopausal women regardless using HRT or not.

In the present study we found a positive correlation between OPG and FMD either post exercise or estrogen.

Suggesting a potential link between OPG and vascular inflammation. These results are consistent with those reported by Shargorodsky *et al*; (2009) while these results are discordant with those reported by Mangiafico et al; (2008).

5. Conclusion:

Our results suggest that both exercise and estrogen augment bone metabolism and vascular reactivity to nearly equal values. So, this study reinforces the importance of exercise as a non pharmacological and alternative method to oral estrogen in early postmenopausal women and consider it as one of the mechanisms that protect against osteoporosis and atherosclerosis.

6. Recommendation:

For every postmenopausal women regular moderate intensity weight bearing exercise must be continued to maintain improvement in your health. However, you don't have to spend hours in the gym to reap the benefits of exercise, but regular performance of daily activities (walking, bicycle riding and climbing stairs instead of the elevator) for half an hour per day or 3 lots of 10 minutes per day instead, this will increase your bone health and blood flow from your heart

Corresponding author
Mervat El-Sergany

Departments of Rheumatology & Rehabilitation, Faculty of Medicine, Tanta University, Tanta, Egypt
sergany3@hotmail.com

7. References:

1. Attipo S, Park JY, Fenty N, Phares D, Brown M.(2008): Oxidative sress levels are reduced in postmenopausal women with exercise training regardless of hormone replacement therapy status. J Women Aging; 20 (1-2):31-45.
2. Boyle WJ, Simonet WS, Lacey DS, (2003): Osteoclast differentiation and activation, Nature; 423:337-42.
3. Chan C, Harvey PJ, Picton P, et al (2003): Short term blood pressure, noradrenergic, and vascular effects of nocturnal hemodialysis .hypertention ; 42;925-31.
4. De SouzaMJ ,WestSL, Jamal SA, et al (2008):The presence of both an energy deficiencyand estrogen deficiency exacerbatealternations of bone metabolism in exercising women .Bone 43(1):140-8
5. Galusca B, Zouch M, Germain N, et al (2008): Constitutional thinness: unusual human phynotype of low bone quality. j Clin Endocrinol Metab ;93 :110-7
6. Grinspoon SK, Friedman AJ, Miller KK, Lippman J, et al (2003): Effects of a triphasic combination oral contraceptive containing /ethinyl estradiol in biochemical markers of bone metabolism in young women with osteopenia secondary to hypothalamic amenorrhea .J Clin Endocrinol Metab ;88:3651-6
7. Hara K, Floras JS, (1995): Influence of naloxone on sympathetic nerve activity, systemic and calf heamodynamicsand ambulatory blood pressure after exercise in mild essential hypertention .J Hypertens; 13:447-61
8. Harvey, Paula J., Peter E, Picton, Winnie S, et al(2005): Exercise as an alternative to oral estrogen for amelioration of endothelial dysfunction in postmenopausal women Am Heart J ;149:291-7.
9. Herrman M, Herrman W, (2004): The assessment of bone metabolism in female elite endurance atheletes by biochemical bone markers .clin chem. Lab med; 42:1384-9.
10. Hodis HN, Mack WJ, Azen SP, et al.(2003): Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med 2003; 349:535-45.
11. Hofbauer LC, Schoppet M, (2004): Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular disease .JAMA; 292:490-5.
12. Holen I, Shipman CM, (2006): Role of osteoprotegerin (OPG) in cancer. Clin Sci(Lond);110:279-91 .
13. (13)Kahl Kg, Rudolf S, Debbelt L, et al (2005): Decreased osteoprotegerin and increased bone turnover in young female patients with major depressive disorder and a life time history of anorexia nervosa. Osteoporos Int ;16;424-9
14. Kim CH, You L, yellowely CE, et al (2006): Oscillatory fluid flow-induced shear stress decreases osteoclastogenesis through RANKLE and OPG signaling. Bone .39:1043-7
15. Mangiafico RA , Alagona C , Pennici P, et al (2008): Increased augmentation index and central aortic blood pressure in osteoporotic postmenopausal women . Osteoporosis Int; 19:49-56.
16. Munoz –Calvo MT, Barrios V, Garcia D alvaro MT , et al (2007): Maintained malnutrition produces a progressive decrease in OPG/RANKL ratio and leptin levels in patients with anorexia nervosa Scand J Clin Lab Invest ; 67: 387-93 .
17. Saunders, M. (2009): More evidence for the benefits of exercise in CVDs, and even in heart failure. www.sciencedaily. com Retrieved 3 June,
18. Shargorodsky M; Luchish A; Boaz M; et al (2009):Osteoprotegrin as an independent marker of subclinical atherosclerosis in osteoporotic postmenopausal women.Atherosclerosis 20:.608-611.
19. Stathokostals, L., Kowalchuk, J., Petrella, R. and Paterson DH :(2008): Maximal and sub maximal aerobic fitness in post menopausal women: influence of hormone replacement therapy. Appl. Physiol. Nutr. Metab. 1 Feb . 33:922-928.
20. Taddei Irr'virdis A, Ghiadoni L, et al.(1996): Menopause is associated with endothelial dysfunction in women. Hypertension; 28:576 -82.
21. Verdis A, Ghiadoni L, Pinto S, et al (2000): Mechanisms responsible for endothelial dysfunction associated with acute estrogen deprivation in normotensive women .Circulation; 101:2258-63.
22. West L; Jennifer L; and Mary Jane De Souza (2009): The effect of exercise and estrogen on osteoprotegerin in premenopausal women. Bone 44:137-144.
23. Wietzmann MN, Pacifici R, (2006): Estrogen deficiency and bone loss, an inflammatory tale .J Clin Invest 116:1186-94.
24. Ziegler S, Niessener A, Richter B, et al (2005):Endurance running acutely raise plasma osteoprotegerin and lower plasma receptor activator of nuclear factor kappa B ligand. Metabolism;54:935-8.

9/1/2010