

## A Review on Some Physiological Studies Related to Osteoporosis

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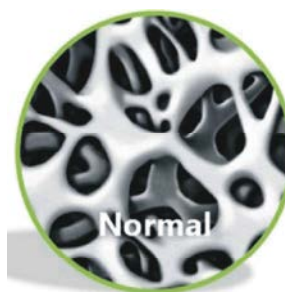
**Abstract:** Osteoporosis is a disease of the bones. It happens when you lose too much bone, make too little bone or both. As a result, bones become weak and may break from a minor fall or, in serious cases, even from simple actions, like sneezing or bumping into furniture. Breaking a bone is a serious complication of osteoporosis, especially when you're older. Broken bones due to osteoporosis are most likely to occur in the hip, spine and wrist, but other bones can break too. Broken bones can cause severe pain that may not go away. Osteoporosis also causes some people to lose height. When osteoporosis causes the bones of the spine, called vertebrae, to break or collapse, it affects their posture and become stooped or hunched. Osteoporosis is responsible for two million broken bones and \$19 billion in related costs every year. By 2025, experts predict that osteoporosis will be responsible for approximately three million fractures and \$25.3 billion in costs each year. Therefore, the present review explain what is osteoporosis, types, causes, signs and symptoms. In addition, to the previous studies demonstrate the effect of estrogen treatment or folic acid supplementation in menopause ovariectomized rats on some physiological and biochemical parameters and their relations to osteoporosis, then finally how to treat osteoporosis and preventing it.

**Key words:** Osteoporosis • Bones • Estrogen • Folic acid • Physiological and biochemical parameters

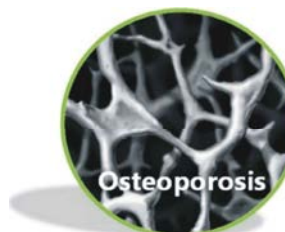
### INTRODUCTION

Osteoporosis is a condition that affects the bones, causing them to become weak and fragile and more likely to break (fracture). These fractures most commonly occur in the spine, wrist and hips but can affect other bones such as the arm or pelvis. Osteoporotic bone fractures are responsible for considerable pain, decreased quality of life, lost workdays and disability. Up to 30% of patients suffering a hip fracture will require long – term nursing – home care. Elderly patients can develop pneumonia and blood clots in the leg veins that can travel to the lungs (pulmonary embolism) due to prolonged bed rest after the hip fracture. Osteoporosis has even been linked with an increased risk of death. Some 20% of women with a hip fracture will die in the subsequent year as an indirect result of the fracture. In addition, once a person has experienced a spine fracture due to osteoporosis, he or she is at very high risk of suffering another such fracture in the near future (next few years). About 20% of postmenopausal women who experience a

vertebral fracture will suffer a new vertebral fracture of bone in the following year. Osteoporosis is affecting about 200 million in worldwide [1].

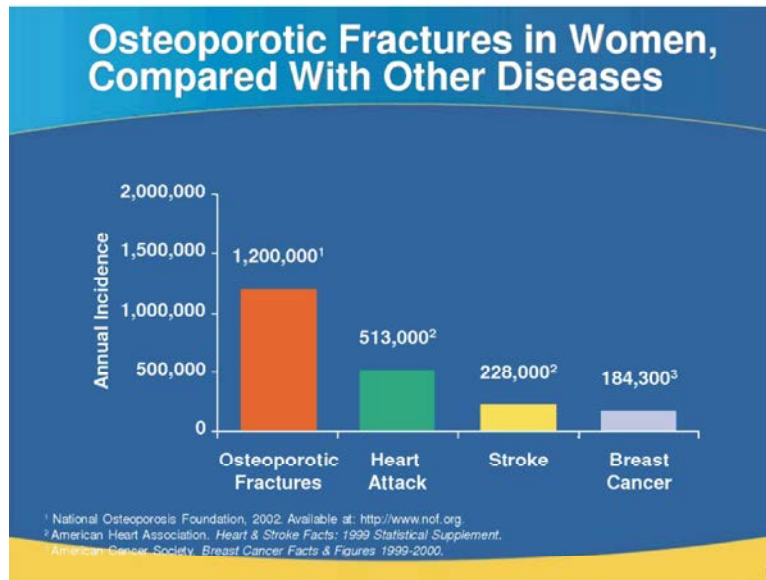


Normal bone

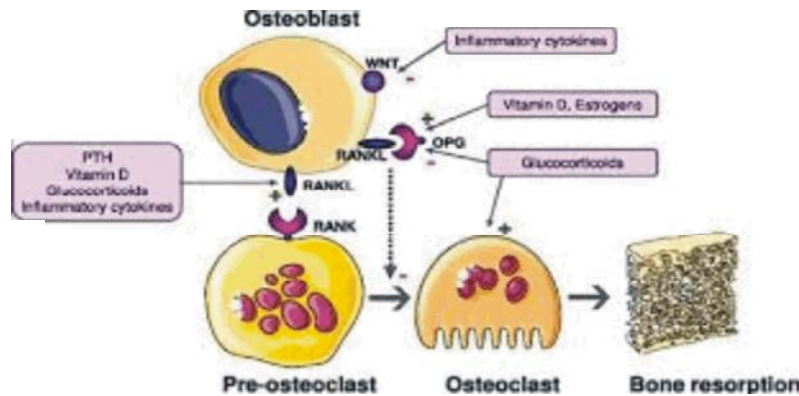


Osteoporotic bone

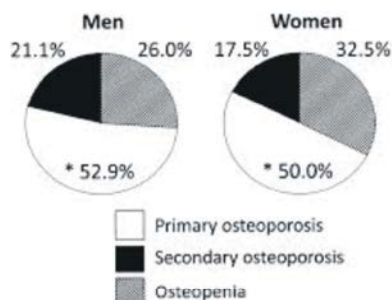
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**What is Osteoporosis ?:** Osteoporosis is a disease characterized by low bone mass and deterioration of bone tissue. This leads to increased bone fragility and risk of fracture (broken bones), particularly of the hip, spine, wrist and shoulder. Osteoporosis is often known as (the silent thief) because bone loss occurs without symptoms. Osteoporosis is sometimes confused with osteoarthritis, because the names are similar. Osteoporosis is a bone disease; osteoarthritis is a disease of the joints and surrounding tissue.

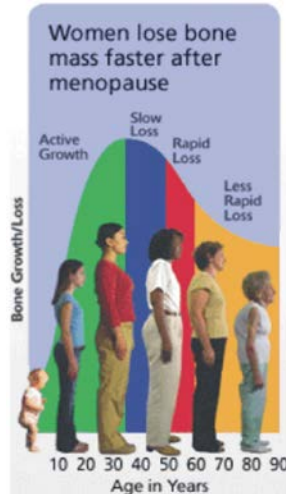


**Types of Osteoporosis:** The disease may be classified as primary type 1, primary type 2, or secondary. The form of osteoporosis most common in women after menopause is referred to as primary type 1 or postmenopausal osteoporosis. Primary type 2 osteoporosis or senile osteoporosis occurs after age 75 and is seen in both females and males at a ratio of 2: 1. Secondary osteoporosis may arise at any age and affect men and women equally. This form results from chronic predisposing medical problems or disease, or prolonged use of medications such as glucocorticoids, when the disease is called steroid – or glucocorticoid- induced osteoporosis.



**What Causes Osteoporosis ?:** In childhood, bones grow and repair very quickly, but this process slows as you get older. Bones stop growing in length between the ages of 16 and 18, but continue to increase in density until you are in your late 20s. From about the age of 35, you gradually lose bone density. This is a normal part of ageing, but for some people it can lead to osteoporosis and an increased risk of fractures. Other things that increase the risk of developing osteoporosis include:

- Diseases of the hormone producing glands—such as an over active thyroid gland (hyperthyroidism).
- A family history of osteoporosis
- Long-term use of certain medications that affect bone strength or hormone levels, for example, oral prednisolone
- Malabsorption problems
- Heavy drinking and smoking

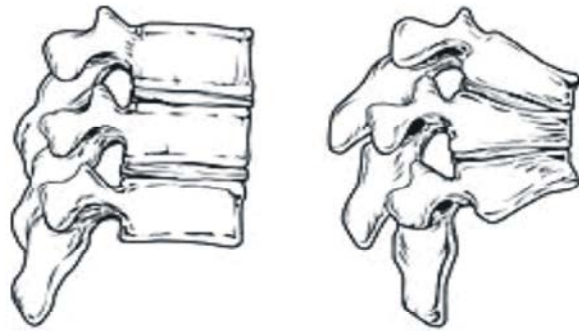


#### What Are Osteoporosis Signs and Symptoms?:

Osteoporosis is an age-related disorder that causes the gradual loss of bone density and strength. When the thoracic vertebrae are affected, there can be a gradual collapse of the vertebrae. This results in kyphosis, an excessive curvature of the thoracic region. Osteoporosis itself has no symptoms; its main consequence is the increased risk of bone fractures. Osteoporotic fractures occur in situations where healthy people would not normally break a bone; they are therefore regarded as fragility fractures. Typical fragility fractures occur in the vertebral column, rib, hip and wrist.



Illustration depicting normal standing posture and osteoporosis



Normal vertebrae

Bone loss amplifies curvature

**Risk Factors:** Ovarian hormone deficiency is a major risk factor for osteoporosis in women [2, 3]. Although there are several FDA-approved medications to either prevent or reverse osteoporosis, women continue to look for safer and more feasible preventative and therapeutic alternatives [4]. In postmenopausal women, the rate of bone turnover increases with the rate of bone resorption exceeding that of bone formation which results in net bone loss [5]. Risk factors for osteoporotic fracture can be split between non-modifiable and modifiable.

#### Non-Modifiable:

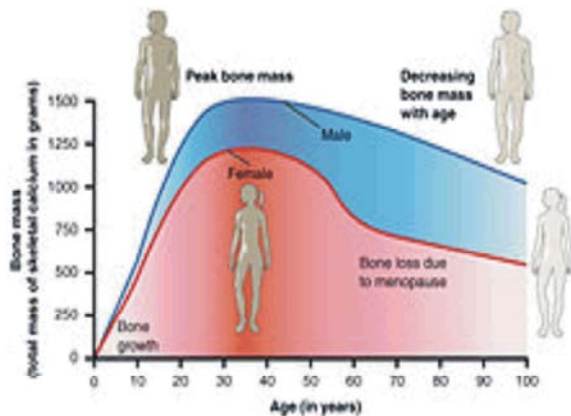
- The most important risk factors for osteoporosis are advanced age (in both men and women) and female sex; estrogen deficiency following menopause or oophorectomy is correlated with a rapid reduction in bone mineral density, while in men, a decrease in testosterone levels has a comparable (but less pronounced) effect [6, 7].

**Race:** While osteoporosis occurs in people from all ethnic groups, European or Asian ancestry predisposes for osteoporosis [8].

**Heredity:** Those with a family history of fracture or osteoporosis are at an increased risk; the heritability of the fracture, as well as low bone mineral density, are relatively high, ranging from 25 to 80%. At least 30 genes are associated with the development of osteoporosis [9].

- Those who have already had a fracture are at least twice as likely to have another fracture compared to someone of the same age and sex [10]. Early menopause /hysterectomy is another predisposing factor.

**Build:** A small stature is also a non-modifiable risk factor associated with the development of osteoporosis.



Bone density peaks at about 30 years of age.  
Women lose bone mass more rapidly than men.

#### Modifiable

**Excess Consumption of Alcohol:** Although small amounts of alcohol are probably beneficial (bone density increases with increasing alcohol intake), chronic heavy drinking (alcohol intake greater than three units/day) probably increases fracture risk despite any beneficial effects on bone density [11,12].

**Vitamin D Deficiency [13, 14]:** Low circulating vitamin D is common among the elderly worldwide [15], mild vitamin D insufficiency is associated with increased parathyroid hormone (PTH) production. PTH increases bone resorption, leading to bone loss. A positive association exists between serum 1, 25-dihydroxycholecalciferol levels and bone mineral density, while PTH is negatively associated with bone mineral density.

**Tobacco Smoking:** Many studies have associated smoking with decreased bone health, but the mechanisms are unclear. Tobacco smoking has been proposed to inhibit the activity of osteoblasts and is an independent risk factor for osteoporosis [11, 16]. Smoking also results in increased breakdown of exogenous estrogen, lower body weight and earlier menopause, all of which contribute to lower bone mineral density.

**Malnutrition:** Nutrition has an important and complex role in maintenance of good bone. Identified risk factors include low dietary calcium and/or phosphorus, magnesium, zinc, boron, iron, fluoride, copper, vitamins A, K, E and C (and D where skin exposure to sunlight provides an inadequate supply). Excess sodium is a risk

factor. High blood acidity may be diet –related and is a known antagonist of bone [17]. Some have identified low protein intake as associated with lower peak bone mass during adolescence and lower bone mineral density in elderly populations [15]. Conversely, some have identified low protein intake as a positive factor, protein is among the causes of dietary acidity. Imbalance of omega-6 to omega-3 polyunsaturated fats is yet another identified risk factor [18].

**High Dietary Protein:** Research has found an association between diets high in animal protein and increased urinary calcium [19-21] and have been linked to an increase in fractures [22]. However, the relevance of this observation to bone density is unclear, since higher protein diets tend to increase absorption of calcium from the diet and are associated with higher bone density [23] indeed, it has recently been argued that low protein diets cause poor bone health [24], no interventional trials have been performed on dietary protein in the prevention and treatment of osteoporosis.

**Underweight/Inactive:** Bone remodeling occurs in response to physical stress, so physical inactivity can lead to significant bone loss [15]. Weight bearing exercise can increase peak bone mass achieved in adolescence and a highly significant correlation between bone strength and muscle strength has been determined [25]. The incidence of osteoporosis is lower in overweight people [26].

**Endurance Training:** In female endurance athletes, large volumes of training can lead to decreased bone density and an increased risk of osteoporosis [27] This effect might be caused by intense training suppressing menstruation, producing amenorrhea and it is part of the female athlete triad [28]. However, for male athletes, the situation is less clear and although some studies have reported low bone density in elite male endurance athletes [29], others have instead seen increased leg bone density [30, 31].

**Heavy Metals:** A strong association between cadmium and lead with bone disease has been established. Low -level exposure to cadmium is associated with an increased loss of bone mineral density readily in both genders, leading to pain and increased risk of fractures, especially in the elderly and in females. Higher cadmium exposure results in osteomalacia (softening of the bone) [32].

**Soft Drinks:** Some studies indicate soft drinks (many of which contain phosphoric acid) may increase risk of osteoporosis, at least in women. Others suggest soft drinks may displace calcium-containing drinks from the diet rather than directly causing osteoporosis [33].

**Effect of Homocysteine on Bone Resorption:** The results of Ziakk *et al.* [34] demonstrate significant relations between homocysteine (Hcy) and markers of organic and inorganic bone resorption, suggesting a mechanistic role of Hcy in bone metabolism. Hcy is thought to play an important role in the development of osteoporosis and fracture and methionine synthase reductase is an enzyme involved in the conversion of Hcy to methionine and certain genetic polymorphisms leading to reduced the enzyme activity may cause hyperhomocysteinemia [35].

The increase in plasma homocysteine levels with menopause suggests a close relationship between homocysteine metabolism and estrogen status [36]. Hyperhomocysteinemia (HHcy) has been suggested to have adverse effects on bone and HHcy in rats induces accumulation of Hcy in bone tissue that is accompanied by bone loss [37].

Hyperhomocysteinemia is an independent risk factor for arteriosclerosis, recurrent thromboembolic complications and osteoporosis. After menopause, a high level of total homocysteine seems to be secondary to the altered hormonal status. Hormone replacement therapy (HRT) limits the development of coronary artery disease through a variety of mechanisms. One such mechanism is through affecting homocysteine metabolism. Folate and vitamin B12 deficiencies are considered to be major risks for hyperhomocysteinemia. This study, therefore, was undertaken by El-Swefy *et al.* [38] to examine whether lowering homocysteine with HRT or folic acid in ovariectomized rats could attenuate cardiovascular complications. Sixty sexually mature female Wistar rats were ovariectomized. Three weeks later, they were treated with estradiol (15 µg/kg (-1), every two weeks, I.M.) or folic acid (90 µg daily, orally), either alone or in a combined form for four weeks. In addition, groups of ovariectomized rats (positive control) and healthy rats (negative control) were given cotton seed oil. In ovariectomized rats, hyperhomocysteinemia was established and associated with significant increments of both atherogenic indexes (total cholesterol/HDL, low density lipoprotein cholesterol (LDL)/HDL) and susceptibility of their non HDL to oxidation. However, plasma NO, serum folate and estradiol levels significantly decreased. HRT and folic acid significantly reduced total

homocysteine and susceptibility of non HDL to oxidation and increased plasma NO content. Moreover, a significant negative correlation was found between total homocysteine versus folate and estradiol ( $r = -0.5$ ,  $P < 0.01$ ;  $r = -0.25$ ,  $P < 0.05$ , respectively). Meanwhile, a positive correlation with the susceptibility of lipoprotein to oxidation was observed ( $r = 0.85$ ,  $P < 0.001$ ). In conclusion, a low folate level is found to be associated with elevated total homocysteine. Folic acid supplementation, either individually or in a combined form with HRT, has a beneficial effect in low estrogen status subsequent to ovariectomy.

The study of Magyar and Fel [39] evaluate the effects of hormone replacement therapy (HRT) with or without the addition of vitamin B supplementation on serum Hcy levels and their relationship to bone metabolism in postmenopausal women. They revealed that Hcy levels significantly decreased in vitamin B6 treated group but HRT alone significantly increase Hcy level.

**Relation Between Estrogen and Calcium with Osteoporosis:** Exogenous hormones are used worldwide by more than 100 million women yearly as hormonal contraception or postmenopausal hormonal therapy [40]. Hormone replacement therapy improves Homocysteine metabolism in postmenopausal women and this effect seems to be independent of vitamin status and may have positive implication for prevention of osteoporosis [41].

The risk of developing osteoporosis increases with age and is higher in women than in men. Among the many possible contributors to primary osteoporosis, estrogen and calcium deficiencies and they are considered to be the most important causes Coxam [42]. During menopause bone remodeling is increased and agents that suppress bone resorption can stabilize bone mass Canalis [43]. Estrogen is usually thought to maintain bone mass by inhibiting bone resorption and formation.

Estrogen deficiency at menopause increased bone turnover with loss throughout the skeleton. A number of theories have been proposed including imbalanced turnover at the level of basic multicellular unit of bone remodeling with a greater level of bone resorption relative to bone formation [44]. Estrogen replacement therapy is claimed to reduce bone turnover, increase bone mineral density and decreases vertebral and hip fractures rates [45, 46]. Folic acid supplementation reducing an elevated homocysteine levels. So, folic acid and vitamin B may help to reverse the problems associated with hyperhomocysteinemia [47].



Al-Sowyan and Mahmoud [48] studied the effect of estrogen treatment, folic acid supplementation on bone markers in ovariectomized (Ovx) rats. Ovariectomized rats showed insignificant increase in serum Ca<sup>2+</sup> and osteocalcin levels with significant decrease in serum vitamin D3 (vit. D3) and significant increase in alkaline phosphatases activity and homocysteine levels. Estrogen treatment of ovariectomized rats showed a significant decrease in serum homocysteine (Hcy) levels, alkaline phosphates activity accompanied with insignificant decrease in serum Ca<sup>2+</sup>, vit D3 and osteocalcin than ovariectomized rats. Supplementation of folic acid to ovariectomized rats induced significant increase in osteocalcin and decreased Hcy levels, insignificant changes in serum Ca<sup>2+</sup>, vit D3 and alkaline phosphates than ovariectomized control rats, while combined treatment of ovariectomized rats with estrogen and folic acid exhibit better action on bone turnover with marked decrease in Hcy level. They concluded that, supplementation of folate with estrogen treatment has a beneficial effect for menopausal women to avoid osteoporosis and fracture.

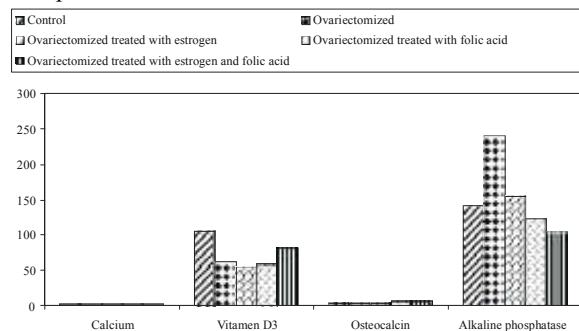


Fig. 1: Effect of folic acid administration on serum calcium (mmol/l), vit. D3 (ng/ml), osteocalcin (ng/ml) and alkaline phosphatase activity (u/l) in normal rats, Ovariectomized and Ovariectomized treated with estrogen [47]

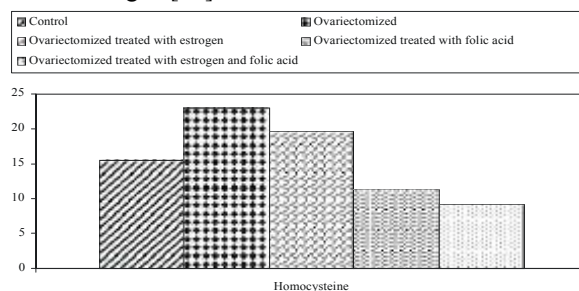


Fig. 2: Effect of folic acid administration on serum homocysteine levels (Umol/L) in normal rats, Ovariectomized and ovariectomized treated with estrogen [47]

The effect of ovariectomy, estrogen replacement therapy and vitamin B6 supplementation on homocysteine levels and parameters of bone biomarkers were investigated by AL-Sowyan [49]. The data from this study showed that indices of both bone resorption and formation increased markedly after ovariectomy. Serum homocysteine (Hcy) level, vitamin D3 and alkaline phosphatase activity were higher with insignificant changes in serum calcium and osteocalcin level in ovariectomized control compared with control healthy rats. Oral estrogen administration to ovariectomized rats induced higher concentration of serum Hcy when compared to normal control rats. While, Hcy concentration, alkaline phosphatase were decreased with insignificant decrease in serum Ca<sup>2+</sup>, vit D3 and increased osteocalcin level compared with ovariectomized control group. Supplementation of vit B6 alone to ovariectomized rats induced significant increase in osteocalcin accompanied with insignificant changes in serum Ca<sup>2+</sup> and alkaline phosphates. Vit D3 significantly increased in vit B6 treated rats than ovariectomized control rats. Combined treatment of ovariectomized rats with estrogen and vit B6 induced insignificant decrease in serum Ca<sup>2+</sup> and return its level to normal value, accompanied with significant increase in vit D3 and osteocalcin with decreased activity of alkaline phosphatase compared with ovariectomized group. The prevention of osteoporosis by identifying risk indicators as well as the development of new treatment strategies are major issues. Homocysteine is not only a risk factor, but also a player in bone metabolism. However, this trial suggests that Hcy lowering therapy may prevent bone loss in postmenopausal women.

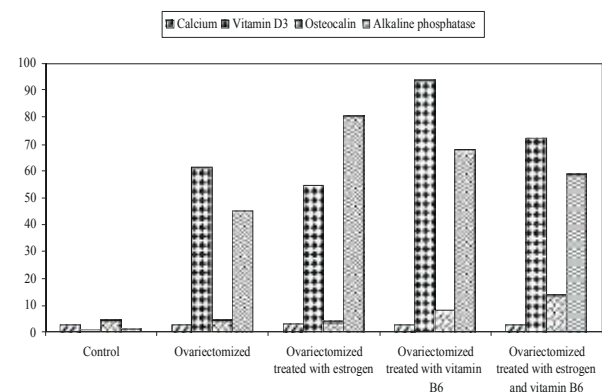


Fig. 3: Effect of vitamin B6 administration on serum calcium(mmol/L), vitamin D3, osteocalcin (ng/ml)and alkaJin phosphatase activity (U/L) in normal rats, ovariectomized and ovariectomized treated with estrogen(ng/ml)... [49]

### Effect of Vitamin E on Lipid Profile in Ovariectomized

**Rats:** Vitamin E, a fat-soluble antioxidant [50-52], has been of particular interest due to its ability to suppress the production of certain proinflammatory mediators such as prostaglandins of the E series (PGE), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL) -1 and IL-6 [53-57] that have been linked to increased bone loss [58-60, 61] and protect against oxidative damage caused by oxygen-derived free radical (ODFR) [52, 62]. The relationship between vitamin E and bone has been studied to some extent. Xu *et al.* [63] reported that vitamin E maintains normal bone growth and bone modeling in young animals and protects cartilage against cellular lipid peroxidation. They also found that supplemental vitamin E increased bone mass by lowering the concentrations of free radicals that stimulate bone resorption and suppress bone formation. Vitamin E also reduced the ODFR stimulation of osteoclastic bone resorption [64]. Furthermore, the administration of  $\alpha$ -tocopherol was shown to suppress the production of ODFRs in the early stages of fracture healing in rabbits [65], increase the activity of antioxidant enzymes in Ovx rats [66] and enhance bone fracture healing in its early [67] and late phases [68] in Ovx rats and in male rats [69]. In addition, the results of a population study by Melhus *et al.* [70] indicated the important role of adequate intake of dietary vitamin E in reducing the risk of hip fracture in current smokers. Another cross-sectional study suggests that vitamin E may uncouple bone turnover in postmenopausal women, causing an increase in the rate of bone formation while having no effects on the rate of bone resorption [71]. Collectively, these observations suggest that vitamin E positively influences skeletal health.

The risk of cardiovascular disease drastically increases at the onset of menopause, in part, because of rise in blood cholesterol and unfavorable changes in lipid profile. Lucas *et al.* [72] investigate the dose-dependent effects of vitamin E supplementation on lipid parameters in ovariectomized (ovx) rats. Ovariectomy tended to decrease HDL cholesterol and increase other lipid parameters. Vitamin E did not have any significant effects on serum lipid parameters. Liver total lipids were notably increased in ovx animals and supplementation with vitamin E at 525 IU/Kg of diet was able to significantly reduce liver total lipids by 13%. These alterations on liver fatty acid profiles were unaffected by vitamin E. The findings of this study suggest that vitamin E supplementation moderately improves lipid parameters in ovarian hormone-deficient rats.

The effect of menopause induced by ovariectomy of rats on serum level of lipid profile and homocysteine (Hcy) were studied by AL-Sowyan [73]. The author revealed that ovariectomized rats showed a significant increase in serum homocysteine, total cholesterol, LDL-c and triglycerides, with significant decrease in HDL-c levels than normal control. Oral estrogen administration to ovariectomized rats, induced significant reduction of Hcy, total cholesterol, LDL-c levels than ovariectomized control group. Folic acid supplementation to ovariectomized rats revealed, significant decrease in serum Hcy, LDL-c with insignificant increase in HDL-c, while combined treatment of estrogen and folic acid resulted in significant decrease in Hcy and significant increase in triglycerides levels versus ovariectomized rats.

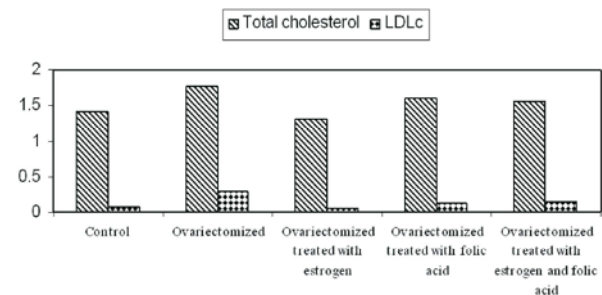


Fig. 4: Effect of folic acid administration on serum lipid profile levels (mmol m<sup>-1</sup>) in normal rats, ovariectomized and ovariectomized treated with estrogen.....[73].....

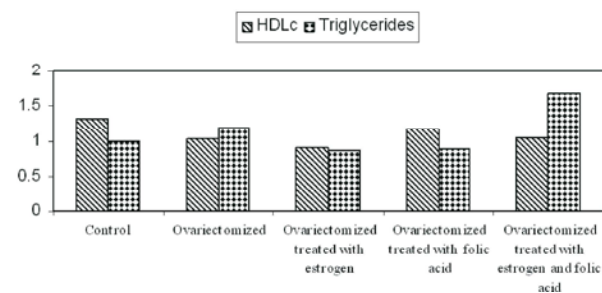


Fig. 5: Effect of folic acid administration on serum lipid profile levels (mmol m<sup>-1</sup>) in normal rats, ovariectomized and ovariectomized treated with estrogen

Feresin *et al.* [74] examined the dose-dependent effect of vitamin E in reversing bone loss in ovariectomized (Ovx) rats. They revealed that animals receiving medium dose (Ovx +525 mg /kg diet; MD) and high dose (Ovx+ 750 mg/kg diet; HD ) of vitamin E had increased serum alkaline phosphatase compared to the Ovx-control group. Bone histomorphometry analysis

indicated a decrease in bone resorption as well as increased bone formation and mineralization in the OvX groups supplemented with MD and HD of vitamin E. Microcomputed tomography findings indicated no effects of vitamin E on trabecular bone of fifth lumbar vertebrae. Animals receiving HD of vitamin E had enhanced fourth lumbar vertebra quality as evidenced by improved ultimate and yield load and stress when compared to OvX-control group. These findings demonstrate that vitamin E improves bone quality, attenuates bone resorption and enhances the rate of bone formation while being unable to restore bone density and trabecular bone structure.

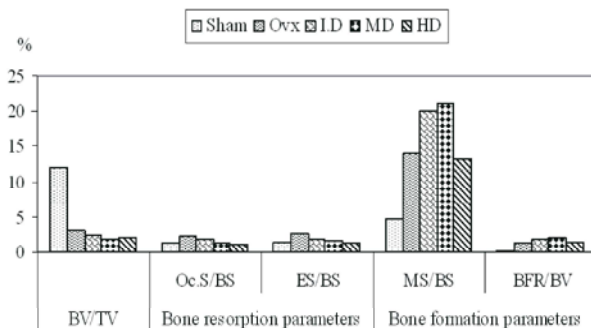


Fig. 6: Effects of ovariectomy (Ovx) and three doses of vitamin E: low dose (LD, 300 mg/kg diet), medium dose (MD, 525 mg/kg diet) and high dose (HD, 750 mg/kg diet) on the proximal tibia metaphysis cancellous bone cellular activity [74]

**Effect of Vitamin K on Bone Loss in Ovariectomized Rats:** Vitamin K<sub>2</sub> (menatetrenone) has been used for the treatment of osteoporosis in Japan. Kobayashi *et al.* [75] investigated the effects of ovariectomy (Ovx) and vitamin K<sub>2</sub> on the calcium (Ca) balance in 20-week-old female Fischer rats. Vitamin K<sub>2</sub> (31 mg/kg per day) was given to animals as a dietary supplement. At weeks 4 and 8 after Ovx, a Ca balance study was performed for 5 days. The intestinal Ca transport was determined using the everted gut-sac technique at week 9. The Ca balance was poorer in the OvX-control group than in the sham-control group at weeks 4 and 8 after Ovx. The Ca balance improved significantly in the vitamin K<sub>2</sub> groups as compared with the sham and OvX control groups. The intestinal Ca transport decreased due to Ovx and was higher in the vitamin K<sub>2</sub> administration groups than in the sham and OvX control groups, but not to a significant extent. The bone mineral density in the femoral metaphysis as well as the cortical area and cortical thickness in the femoral diaphysis in the OvX control group were lower

than in the sham-control group. The administration of vitamin K<sub>2</sub> significantly inhibited an OvX induced decrease in cortical area and cortical thickness in the femur. These findings suggest that the poor Ca balance observed in OvX rats may be improved by vitamin K<sub>2</sub>; vitamin K<sub>2</sub> may be involved in preventing bone loss *in vivo*.

Vitamin K (VK) exists in multiple forms that share common biochemical structures to support VK-dependent protein carboxylation. Vitamin K may benefit bone by carboxylating the bone protein, osteocalcin. The unique side chains of the menaquinones (MK<sub>n</sub>) may further enhance K bone benefits. Therefore, Moreines *et al.* [76] studied the role of vitamin K in bone and differential abilities of MK<sub>n</sub> and VK<sub>1</sub> to benefit bone. To assess this, ovariectomized (OVX) rats were randomized to 6 dosing groups of 16/group [Sham OVX (SOVX); OVX; OVX + Bisphosphonate (BP) (100ig/kg/100ig/mL saline sc); OVX + VK<sub>1</sub>; OVX + MK<sub>4</sub>; and OVX + MK<sub>7</sub>] for 12 weeks. Equimolar doses of 107 mg K<sub>1</sub>/kg, 147 mg MK<sub>4</sub>/kg and 201 mg/kg MK<sub>7</sub> were added to vitamin K deficient diets daily. As expected, OVX significantly increased weight and decreased bone strength vs. SOVX ( $p < 0.05$ ). OVX failed to significantly alter serum or bone vitamin K concentrations vs. SOVX. BP significantly increased bone strength and bone mineral density (BMD) vs. OVX ( $p < 0.05$ ). However, VK failed to prevent bone loss. VK<sub>1</sub> supplementation significantly increased serum/bone concentrations of VK<sub>1</sub> vs. The concentrations of MK<sub>4</sub> or MK<sub>7</sub> following their supplementation ( $p < 0.05$ ). Osteoporosis is characterized by loss of bone density and strength. Improved bone quality has been observed in ovariectomized rats fed diets containing orange pulp which is rich in antioxidants and contains vitamin C. Strong [77,78] investigate whether drinking vitamin C solution improves bone quality in ovariectomized (OVX) rats once bone loss has occurred.

**Anticarcinogenic and Antioxidant Effects of Propolis Aqueous extract against Ehrlich Ascites Carcinoma (EAC) Cells bearing Mice** The results clearly suggest that the propolis treated group may effectively normalize the impaired antioxidant status in EAC-treated groups. The propolis exerted rapid protective effects against lipid peroxidation by scavenging of free radicals by reducing the risk of EAC induced cancer.

The effect was more pronounced in 4<sup>th</sup> group compared to 5<sup>th</sup> one [79].

The total leucocytes count was decreased in the animals which received irinotecan as anticancer drug.



While combination with propolis, WBCs count was increased [80].

It could be promote cellular immune response and would be expected as the component drugs of new type of immune potentiator [81] Erythrogram that revealed a significant reduction in RBCs count in the 2<sup>nd</sup> group that could be as a result of suppressive effect of Erlich ascites carcinoma in MCV and MCHC i.e (macrocytic normochromic anemia) this may be due to deficiency of thiamine in the liver and blood of mice bearing Ehrlich ascites carcinoma which play an important role in folate metabolism leading to indirect decrease in folic acid in the body [82].

**Physiological and Pharmacological Investigation**  
The Effects of Ciprofloxacin on GIUT, 1, 2, 3, 4 & 5 Activities; Since the effects of ciprofloxacin on cellular glucose transport remain unknown, in this study we tested the hypothesis that ciprofloxacin inhibit GLUTs function and disturb cellular glucose transport [83].

The newer fluoroquinolones have broad –spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration favorable safety and tolerability profiles. Anew four –generation classification of the quinolone drugs takes into account the expanded anti-microbial spectrum of the more recently introduced fluoroquinolones and their clinical indications [84].

Ciprofloxacin associated seizures occur most commonly in patients with special risk factors that may cause accumulation of drug (high doses of the drug, old age, renal insufficiency and drug interactions) or that may decrease the threshold of epileptogenic activity [85]. The bactericidal action of quinolones promote the generation of lethal hydroxyl radicals in both Gram –negative and Gram positive bacteria, despite the stark differences in their primary drug –target interactions (9 In the present study, it was ensured that serum glucose and fructose levels were significantly increased after ciprofloxacin treatment. Symptoms of high blood glucose include increased thirst and frequency urination with ciprofloxacin treatment [86].

**Effect of Vitamin C on Bone Quality:** In this study, rats were subjected to sham operated or OVX and fed a common diet for 120 days. Sixty days after the surgical procedure, the ovariectomized rats were divided to two groups, OVX group or OVX group drinking solution containing vitamin C (1mg/1 ml). At the end of the study rats were euthanized, blood was collected for the plasma

antioxidant capacity and 5<sup>th</sup> lumbar vertebrae and right femur bones were collected for bone quality. The plasma antioxidant capacity, 5<sup>th</sup> lumbar and femur density and strength, calcium and magnesium were reduced ( $p < 0.05$ ) in the OVX treatment group compared to the sham group. The addition of vitamin C to drinking water increased ( $p < 0.05$ ) the antioxidant capacity to the level of the sham group. But, the density of the 5<sup>th</sup> lumbar and femur in the vitamin C group significantly increases ( $p < 0.05$ ) compared to the OVX group while it never reached those of the sham group. In contrast, femoral strength and the calcium concentration of the vitamin C group were not different from those of the OVX group, while, the calcium concentration of the 5<sup>th</sup> lumbar in the vitamin C group was significantly higher ( $p < 0.05$ ) in the OVX group to the level of the sham group. In conclusion, beneficial effects of drinking vitamin C solution on bone quality may be related to improved antioxidant status in ovariectomized rats.

**Treating Osteoporosis:** Treatment for osteoporosis is based on treating and preventing fractures and using medication to strengthen your bones. However, the decision about what treatment, if any, will depend on risk of fracture. This will be based on a number of things such as the results of DEXA scan and age.

**Preventing Osteoporosis:** It is important that people at risk of osteoporosis take steps to help keep bones healthy and reduce their risk of developing the condition. This may include:

- Regular exercise
- Healthy eating
- Lifestyle changes such as quitting smoking and reducing alcohol intake

**Living with Osteoporosis:** If person are diagnosed with osteoporosis, there are steps they can take to reduce their chances of a fall, such as removing hazards from their home and having regular sight and hearing tests.

There are ways to help the recovery from a fracture. This might include:

- Hot or cold treatments, with warm baths or cold packs.
- Electrical device, which is thought to reduce pain by stimulating the nerves.
- Relaxation techniques.

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