

Impact of omeprazole on bone remodeling in normal and ovariectomized Wistar rats

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Abstract. – BACKGROUND: Several epidemiologic studies have suggested the association between therapy with proton pump inhibitors (PPIs) and bone fractures.

AIM: This study aimed at evaluating the effect of omeprazole on bone in normal and ovariectomized Wistar rats and the possible mechanisms involved.

MATERIALS AND METHODS: 56 rats were divided into 3 main groups. Normal group; further subdivided into normal control group and two groups which were treated with omeprazole in two doses (20, 40 mg/kg/day i.p). Sham operated group. Ovariectomized group; further subdivided into ovariectomized control group, and two groups which were treated with omeprazole in two doses (20, 40 mg/kg/day i.p). Rats were treated for the last 4 weeks of the total 8 weeks of the experiment. Urine hydroxyproline, serum osteocalcin, TNF- α and IL-6 and bone mineral content were assessed. Omeprazole effects on the endothelial dependent and independent relaxation were determined.

RESULTS: Omeprazole in normal and ovariectomized rats produced significant reduction in bone formation, tibia calcium content and serum TNF- α and IL-6. Omeprazole in ovariectomized rats produced a dose dependent decrease in bone resorption. Isolated aortic rings from ovariectomized/omeprazole treated rats exhibited reversal of the endothelial dysfunction that observed with ovariectomized rats.

CONCLUSIONS: PPIs might induce both positive and negative effects on bone remodeling. Although these drugs might have the potential to inhibit bone resorption, through suppression of pro-inflammatory cytokines and improvement of endothelial function, yet these effects are counteracted by their inhibitory effects on the gastric proton pump with reduction in calcium absorption and bone formation.

Key Words:

Bone formation, Bone resorption, Hydroxyproline, Omeprazole, Osteocalcin Osteoporosis, Ovariectomized rat.

Introduction

Osteoporosis is a common chronic progressive degenerative systemic skeletal disease, which leads to increased bone fragility. Increased bone fragility is associated with increased risk of low trauma fractures of all bones leading to a decrease in the quality of life, disability and even death¹. Increase in the frequency of osteoporosis and its complications show that there are currently no reliable methods of drug treatment and prevention of this disease². We are in need to evaluate the effect of drugs especially those used for long term on bone, to reduce the occurrence of osteoporosis and or its deterioration.

Bone is a dynamic tissue; it is continuously remodeled by a balance between resorption of old bone by osteoclasts and synthesis of bone matrix and mineral deposition by osteoblasts³. Proton pump inhibitors (PPIs) are potent acid-suppressive medications commonly used for management of acid-related diseases such as peptic ulcer and gastro-esophageal reflux disease (GERD). Since long-term therapy with these medications is being increasingly common⁴, concerns have been raised about their long-term safety profile⁵.

The impact of PPIs on bone remodeling is quite controversial. This controversy arises from the findings that an acid secreting proton pump is expressed on plasma membrane of bone resorbing osteoclasts and its inhibition prevents bone loss in rats⁶. Although the osteoclast V-type ATPase is different from the parietal H/K ATPase yet omeprazole has been reported to inhibit it with resultant suppression of bone resorption⁷. These findings are in contrast with several epidemiologic studies which have suggested an association between PPIs use and hip, wrist and spine fractures⁸.

From the foregoing the current study was conducted to evaluate the effect of omeprazole administration on bone in normal and ovariectomized rats.

tomized Wistar rats. Ovariectomy is an excellent animal model that correctly emulates the important clinical feature of the estrogen depleted human skeleton and the response of therapeutic agents⁹. The effects of omeprazole on biochemical markers of bone resorption and formation were investigated. Biochemical markers of bone resorption and formation are sensitive markers that reflect the different processes involved in bone metabolism by detecting the activity of osteoclasts and osteoblasts¹⁰. Osteocalcin is an osteoblast-specific non-collagenous protein. It forms about 10% of non-collagenous proteins of the bone matrix and generally serves as a specific marker for osteoblast activity and bone formation¹¹. Ninety percent of hydroxyproline liberated during the degradation of bone collagen is metabolized in the liver and excreted in the urine. Urinary hydroxyproline measurement is usually considered to reflect bone resorption¹².

Blood flow plays a significant role in bone remodeling and reparative regeneration of bone tissue¹³, and several experimental and clinical studies have shown that endothelial dysfunction with reduced bone perfusion is related to osteoporosis^{14,15}; hence, the effect of omeprazole on endothelial function was also investigated. Finally changes in levels of TNF- α and IL-6, both of which are known to be involved in osteoporosis and endothelial dysfunction, were also determined.

Materials and Methods

Drugs and Chemicals

Omeprazole (Risek Vial 40 mg, Gulf Pharmaceutical Industries {Julphar, Ras Al Khaimah, UAE}, dissolved in distilled water), sodium pentobarbital, L-phenylephrine hydrochloride and acetylcholine were purchased from Sigma Chemicals (St. Louis, MO, USA).

Animals

Female Wistar rats (weighing 225 to 250 g) supplied by the Holding Company for Biological Products & Vaccines VACCERA, Helwan, Egypt. The rats were housed in an animal room with a temperature (22 °C) and lighting (12 h light-dark cycle) control. An adaptation period of 1 week was allowed before initiation of the experimental protocol. All animal procedures were approved by the Pharmacology Animal Ethics Committee, Faculty of Medicine Ain Shams University which adheres to the international guidelines.

Study Design

Fifty six rats were divided into three main groups. The first was the normal group; which further subdivided into 3 subgroups with 8 animals in each group; normal control group which was treated with i.p. injection of distilled water, two normal/omeprazole groups which were treated with i.p omeprazole in two doses (20, 40 mg/kg/day)^{16,17}. The second was sham operated group (8 animals). The third was ovariectomized (OVX) group which further subdivided into 3 subgroups with 8 animals in each group; OVX control group which was treated with i.p. injection of distilled water, two OVX/omeprazole groups which were treated with i.p omeprazole in two doses (20, 40 mg/kg/day). Treatments were started 4 weeks after ovariectomy so all rats were treated for the last 4 weeks of the total 8 weeks of the experiment.

Ovariectomy

Following the method outlined by Lasota and Danowska-Klonowska¹⁸, the ovary was resected bilaterally through longitudinal, dorsal midline skin incision in which each female rat was anesthetized with sodium pentobarbital (40 mg/kg, i.p.)¹⁹. Sham-operated animals underwent the same procedure as the ovariectomized rat but without resection of the ovaries.

Outcomes Measured

Urine Collection and Urine Hydroxyproline Measurement

At the end of the 8th week rats were housed in metabolic cages for 8 hours to collect urine samples. Hydroxyproline was measured using, Enzyme-linked Immunosorbent Assay Kit for rat hydroxyproline (HYP) ELISA Kit (Shanghai Crystal Clay Biotech Co., Ltd. China).

Blood Collection and Parameters Measurements

At the end of 8th week of the study, rats were under sodium pentobarbital anesthesia, blood was collected from retro-orbital plexus using heparinized capillary tubes. The plasma samples were separated by centrifugation (15 min, 5000 rpm) and then were stored at -80°C until they were analyzed for:

- Plasma osteocalcin level: using Immunoradiometric Assay (IRMA) for the Quantitative Determination of Rat Osteocalcin Levels (Immunotopics, Inc. San Clemente, CA, USA)

- Plasma TNF-alpha level was measured using Rat TNF-alpha ELISA Kit (KOMA Biotech Inc, Seoul, South Korea).
- Plasma IL-6, using Rat IL-6 ELISA kits (Immuno-Biological Laboratories, Inc. Minneapolis, MN, USA)

Bone Mineral Content

Right tibia removed from each experimental animal was ashed at 700°C for 7 h. For bone calcium and phosphorus measurement, ash was dissolved in 6 M hydrochloric acid (1 ml of acid for 50 mg of ash). After neutralization with sodium hydroxide and suitable dilution, Calcium was measured by spectrophotometer using the Calcium assay kit (Cayman Chemical Company, Ann Arbor, MI, USA). Phosphorus was measured by spectrophotometer. The method described previously by Fisher and Higgins²⁰, using Quantichrom phosphate assay kit (quantitative colorimetric phosphate determination; BioAssay Systems, Hayward, CA, USA).

Rats' Aortic Ring Preparations

The thoracic aorta was removed and carefully dissected from the surrounding tissue then placed in a Petri dish containing Krebs solution continuously bubbled with 95% O₂ and 5% CO₂. The aorta was cut into 2 rings, each measuring 6-7 mm in length. The endothelium was removed from one ring by gently rubbing the luminal surface with stainless steel wire. The endothelium was left intact on the other ring. Each ring was mounted between 2 hooks made of stainless steel wire in a 15 ml organ bath filled with modified Krebs solution consisting of (mM) NaCl 118, KCl 4.7, CaCl₂ 2.5, MgSO₄ 1.2, KH₂PO₄ 1.2, NaHCO₃ 25, glucose 11 continuously gassed with 95% O₂ and 5% CO₂ and temperature was adjusted to 37°C²¹. An initial 4 g resting tension was applied to the rings, which were allowed to equilibrate for 1-2 hours, during which time they were rinsed with Krebs solution every 20 minutes and temperature was maintained at 37°C. Isometric responses were measured with a force displacement transducer (K30, Hugo Sacks Electronics, Freiburg, Germany) connected to a bridge coupler type 570 and the trace were displayed on a two-channel recorder (Lineacorder, HSE, WR 3310).

1. To assess vascular reactivity, aortic rings were sensitized by being repeatedly contracted with 0.4 μM of phenylephrine until two repro-

ducible contractions were obtained, and then a cumulative dose-response curve was constructed by cumulative addition of phenylephrine (10⁻¹⁰ M-10⁻⁴ M) to the bath. Finally, the maximum contractile response (E max) and mean effective concentration 50 (EC₅₀) were determined for each curve.

2. To assess endothelium dependent relaxation, after reaching the plateau of the phenylephrine induced submaximal pre-contraction, the rings were relaxed by exposure to a stepwise increase in acetylcholine (Ach) concentration (10⁻⁹ M-10⁻⁴ M). The percent of relaxation in phenylephrine induced pre-contraction was then obtained for the different animal groups and computed.
3. To assess endothelium independent relaxation, the previous steps were repeated but relaxations were induced in the aortic rings using increasing concentrations of sodium nitropruside (1 nM-10 μM). The percent relaxation in phenylephrine induced pre-contraction was determined for all groups and computed.

Statistical Analysis

Statistical analysis was carried out using Graphpad prism, software program, version 5.0 (2007). Inc., CA, USA. All values in the results were expressed as means ± SD. For all parameters, statistical difference among more than 2 groups was determined using one way analysis of variance; ANOVA followed by Tukey's Multiple Comparison Test. *p* values < 0.05 were considered statistically significant.

In the experiment of phenylephrine induced contraction, all doses were transformed into Log value and the contractile responses for each preparation were expressed as a percentage of the maximum response achieved by each ring separately, which is considered in this cases, the 100% response of that particular ring, the next step was to plot the log concentration against the responses expressed as percentages, in a linear regression curve, then the EC50 as mean±SD for each group were determined.

Results

The Effect of Omeprazole on Urine Hydroxyproline and Plasma Osteocalcin

Administration of omeprazole in normal rats in a dose of (20 mg/kg) exhibited an increase in bone resorption as evidenced by the significant

increase in the urine hydroxyproline level and decreased bone formation manifested by significant decrease in plasma osteocalcin level in comparison to normal control group. Omeprazole 40 mg/kg produced a non-significant increase in urine hydroxyproline level and produced a significant decrease in bone formation. Ovariectomized (OVX) rats exhibited an increase in bone turn over as evidenced by significant increase in both bone resorption and bone formation in comparison to sham operated animals. Omeprazole administration to OVX rats in doses 20 and 40 mg/kg produced a dose dependent decrease in both bone resorption and bone formation in comparison to OVX rats. (Data shown in Table I).

The effect of Omeprazole on Bone Minerals content

As shown in Figure 1, A-B, administration of omeprazole in 2 doses (20, 40 mg/kg) in normal rats produced a significant ($p < 0.05$) decrease in tibia calcium content and insignificant effect on phosphorous content compared to the normal control group with a non-significant ($p > 0.05$) difference between the 2 doses of omeprazole. OVX rats exhibited insignificant ($p > 0.05$) decrease on both calcium and phosphorous contents compared to sham operated rats. Administration of omeprazole (20, 40 mg/kg) to OVX rats produced a significant decrease in both calcium and phosphorous contents when compared to OVX rats with insignificant difference between the 2 treated groups.

The Effect of Omeprazole on Plasma TNF- α

Administration of omeprazole in normal rats with the 2 doses (20, 40 mg/kg) produced a significant ($p < 0.05$) decrease in plasma TNF- α level by

40%, 61.5% respectively in comparison to normal group with insignificant difference between the 2 treated groups. OVX rats exhibited marked increase in TNF- α by 584.7% in comparison to sham operated group. Treatment with omeprazole (20, 40 mg/kg) in OVX rats showed dose dependent decrease in its level by 69.4%, 78.7% respectively in comparison to OVX rats (Figure 2A).

The effect of Omeprazole on Plasma IL-6

Omeprazole (40 mg/kg) administration in normal rats produced a significant decrease in plasma level of IL-6 by 63.8% in comparison to normal rats. Although treatment with omeprazole (20 mg/kg) showed non-significant decrease in IL-6 level in comparison to normal group, there is insignificant difference between 2 treated groups in normal rats. OVX rats exhibited a significant elevation in plasma IL-6 by 155.7% in comparison to sham operated group. A dose dependent decrease in IL-6 plasma levels was observed in omeprazole (20, 40 mg/kg) by 43.3%, 64.5% respectively in comparison to OVX rats (Figure 2B).

The Effect of Omeprazole on Vascular Reactivity

As shown in Table II OVX rats in comparison to sham operated rats exhibited increase in the contractile response to phenylephrine as evidenced by significant increase in maximal contractile response (E_{max}) and significant reduction in the effective concentration 50 (EC_{50}). Omeprazole administration in the 2 doses (20 and 40 mg/kg) produced a significant reduction of this increased contractile response. As regards endothelial dependent relaxation, treatment of OVX rats with omeprazole (20, 40 mg/kg) produced a significant improvement of Ach percent relax-

Table I. The effect of omeprazole administration on urine hydroxyproline and plasma osteocalcin levels in normal and ovariectomized Wistar rats.

Animal groups (n=8)	Normal (N)	N/Omep (20 mg/kg)	N/Omep (40 mg/kg)	Sham Operated	Ovariectomized (OVX)	OVX/Omep (20 mg/kg)	OVX/Omep (40 mg/kg)
Urine hydroxyproline (mg/dl)	15.50 \pm 3.28	30.50 \pm 6.1 (96.8%)*	21.20 \pm 1.12 (36.8%)	22.40 \pm 2.56 (471%) [#]	127.9 \pm 4.17 (-25.8%) [§]	94.9 \pm 9.57 (-51.1%) [§]	62.57 \pm 4.38 (-34.1%) [†]
Plasma osteocalcin (ng/ml)	29.52 \pm 7.66	9.27 \pm 0.81 (-68.6%)*	5.33 \pm 0.40 (-82%)*	32.87 \pm 2.39	60.17 \pm 3.62 (83.1%) [#]	41.17 \pm 3.59 (-31.6%) [§]	25.10 \pm 1.98 (-58.3%) [§] (-39%) [†]

Data are mean \pm SD, n = number of animals, Omep = omeprazole. One way ANOVA followed by Tukey's Multiple Comparisons test: * $p < 0.05$, compared to normal group. [#] $p < 0.05$ compared to sham operated group, [§] $p < 0.05$ compared to OVX group, [†] $p < 0.05$ compared to OVX/Omep (20 mg/kg) treated group.

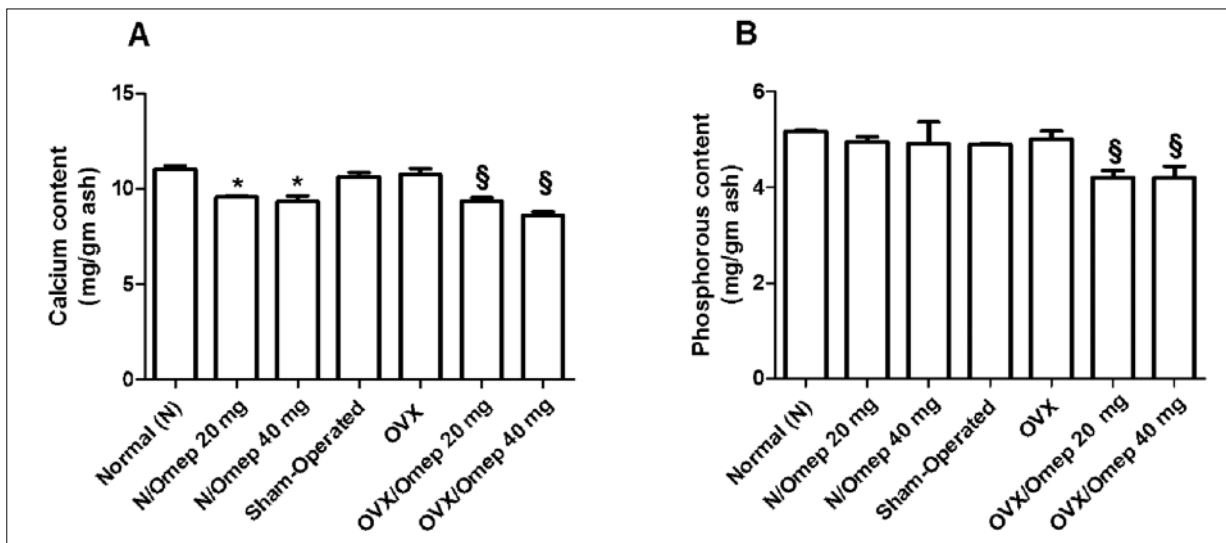


Figure 1. A, B, The effect of omeprazole administration on bone calcium and phosphorous contents in normal and ovariectomized Wistar rats. Number of animals = 8, OVX = ovariectomized, Omeprazole = omeprazole. Data are expressed as mean \pm SD. One way ANOVA followed by Tukey's Multiple Comparisons test. * $p < 0.05$, compared to normal group, [§] $p < 0.05$ compared to OVX group.

ation which was significantly decreased in OVX rats when compared to sham operated group. Meanwhile OVX rats exhibited insignificant effect on endothelial independent relaxation in comparison to sham operated group; the same results were obtained from omeprazole treated groups when compared to OVX rats.

Discussion

In the present study, OVX rats exhibited increase in bone turnover as evidenced by significant increase in both bone resorption and formation, in consistency with Picherit et al²². It was surprising that the tibia calcium and phosphorous

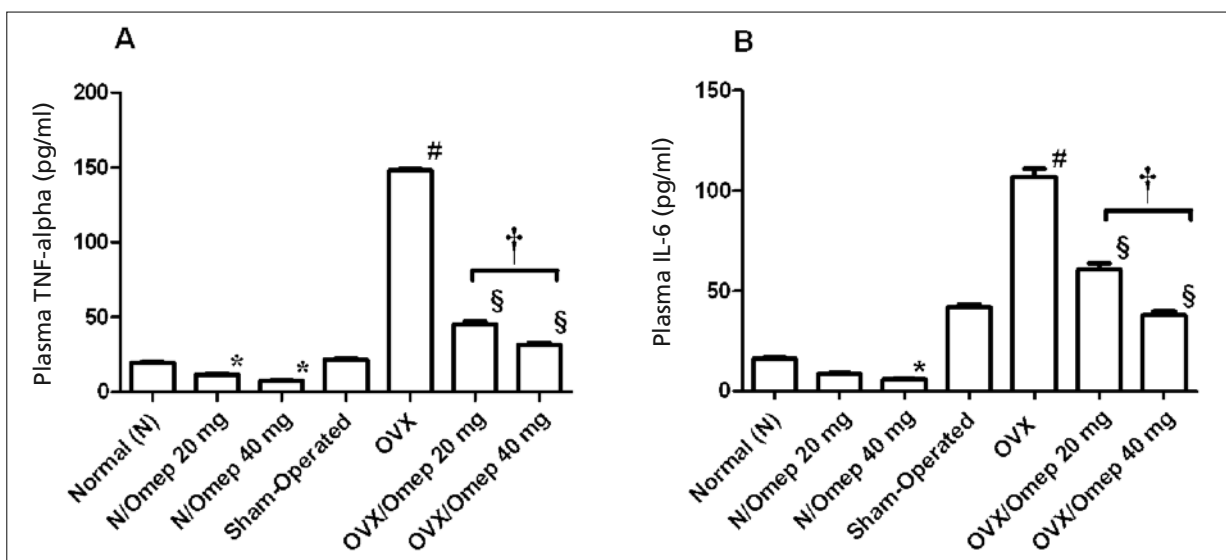


Figure 2. A, B, The effect of omeprazole administration on plasma tumor necrosis alpha (TNF- α) and interleukin-6 (IL-6) in normal and ovariectomized osteoporotic Wistar rats: Data are mean \pm SD, number of animals = 8, Omeprazole = omeprazole, OVX = ovariectomized. Data are expressed as mean \pm SD. One way ANOVA followed by Tukey's Multiple Comparisons test: * $p < 0.05$, compared to normal group, [#] $p < 0.05$ compared to sham operated group, [§] $p < 0.05$ compared to OVX group, [†] $p < 0.05$ compared to OVX/Omep (20 mg/kg) treated group.

Table II. The effect of omeprazole administration on vascular reactivity (contractile and relaxant responses) in normal and ovariectomized Wistar rats.

Animal groups (n=8)	Normal (N)	N/Omep (20 mg/kg)	N/Omep (40 mg/kg)	Sham Operated	Ovariectomized (OVX)	OVX/Omep (20 mg/kg)	OVX/Omep (40 mg/kg)
EC ₅₀ for Phenylephrine (μM)	0.98 ± 0.29	0.57 ± 0.18	0.63 ± 0.12	0.73 ± 0.18	0.01 ± 0.001 [#]	0.83 ± 0.25 [§]	0.69 ± 0.09 [§]
E _{max} for Phenylephrine (gm)	0.36 ± 0.03	0.45 ± 0.05	0.64 ± 0.24	0.63 ± 0.1	1.03 ± 0.31 [#]	0.37 ± 0.07 [§]	0.50 ± 0.09 [§]
Ach relaxation (%)	98.0 ± 2.37	91.2 ± 6.51	92.28 ± 4.06	96.0 ± 4.73	55.75 ± 7.39 [#]	78.88 ± 7.69 [§]	94.0 ± 6.99 ^{§,†}
Sodium nitroprusside relaxation (%)	96.0 ± 5.44	94.67 ± 5.96	95.33 ± 4.93	95.33 ± 4.93	99.0 ± 0.89	98.33 ± 1.37	97.67 ± 1.03

Data are mean ± SD, n = number of animals, EC₅₀ = effective concentration 50, E_{max} = maximal contraction, Ach = acetylcholine, Omep = omeprazole One way ANOVA followed by Tukey's Multiple Comparisons test: **p* < 0.05, compared to normal group. [#]*p* < 0.05 compared to sham operated group, [§]*p* < 0.05 compared to ovariectomized (OVX) group, [†]*p* < 0.05 compared to OVX/Omep (20 mg/kg) treated group.

contents were insignificantly changed when compared to sham operated group. These findings disagree with Shuid et al²³ who reported that lumbar bone calcium content was decreased in OVX rats. This difference could be explained by the site where the calcium content was measured, since in cortical bone of the mid-shaft or diaphysis of long bones as tibia, ovariectomy was reported to stimulate periosteal bone growth²⁴, while the mid-diaphyseal endosteum in the OVX rat was found to exhibit increased bone resorption²⁵. It seems that bone lost at the endosteum adjacent to marrow is being replaced on the adjacent periosteum. Kimmel and Wronski²⁶ demonstrated that post-OVX femoral shaft failed to demonstrate changes in bone mineral content. In contrast Yu et al²⁷ reported that the mandibular bone mineral density four weeks after ovariectomy had an increase compared to sham group. At 12 and 20 weeks after the operation, the mandibular bone mineral density (BMD) of the OVX group had a decreasing trend. These results indicate that different parts of the osteoporotic body differ in the BMD.

In this work normal and OVX rats treated with omeprazole (20, 40 mg/kg/day) for four weeks exhibited a significant reduction in bone formation as evidenced by a decrease in osteocalcin. This reduction was dose dependent in OVX rats. As for bone resorption, normal rats treated with omeprazole 20 mg/kg/day exhibited an increase in bone resorption. In contrast OVX rats treated with omeprazole in both doses exhibited a significant dose dependent decrease in bone resorption. In addition administration of omeprazole in

normal and OVX rats induced a significant decrease in tibia calcium content and OVX rats exhibited a significant decrease of phosphorous contents compared to their corresponding control groups.

Conflicting results on the effects of PPIs on bone remodeling have been reported by several investigators. In a case control study Zojaji and Bonehy²⁸ reported that short-term administration of omeprazole has no significant effect on bone density and did not increase the incidence of osteopenia and osteoporosis. Meanwhile Cui et al²⁹ reported that long term omeprazole treatment of young male rats induced reduced bone mineral contents and bone mineral density. In addition Yang et al³⁰ indicated that the risk of hip fracture was significantly higher among patients prescribed long-term high-dose PPIs and the strength of the association increased as the period of PPI therapy is prolonged.

Many hypotheses were raised to explain the effect of PPIs on bone. PPIs may inhibit calcium absorption, secondary to lack of HCl which is essential for its absorption³¹. PPIs induced hyper-gastrinaemia may also induce hyperparathyroidism with resultant increase in resorption³².

In contrast Farina and Gagliardi³³ reported that the suppressive effect of omeprazole on bone resorption is through modulation of V-type H⁺-AT-Pase activity of osteoclast acid-producing systems which maintain bone turnover. Indeed Mizunashi et al³⁴ reported that omeprazole can suppress bone resorption with a potentially protective effect of osteoclastic proton pump inhibi-

tion, which may attenuate some of the negative effects of gastric acid suppression of PPIs on calcium absorption. Accordingly an acid-secreting proton pump is expressed on the plasma membrane of bone-resorbing osteoclasts and its inhibition prevents bone loss in rats⁶. Although the osteoclast ν -type ATPase is different from the parietal H⁺/K⁺-ATPase, Tuukkanen and Vaananen⁷ reported that omeprazole inhibits it.

In this work, the significant or the insignificant reducing effect of omeprazole on both TNF- α and IL-6 in rats can explain its effect on reducing bone resorption. Tumor necrosis factor alpha (TNF- α) is considered as one of the osteotropic factors. It does not directly activate osteoclasts but rather stimulate osteoblasts to secrete cytokines³⁵. Activated osteoblasts secrete TNF- α ³⁶, and IL-6³⁷. These cytokines act directly on osteoclast progenitor cells and induce differentiation into mature osteoclasts³⁸. IL-6 also seems to play a major role in the activation process of immature osteoclasts³⁷. Animal studies showed that OVX mice did not develop osteoporosis if an antibody to IL-6 was administered³⁹. Even more, IL-6 knockout mice, ovariectomy in these mice does not cause osteoporosis, indicating that IL-6 is essential for the bone loss caused by estrogen deficiency⁴⁰.

As effect of PPIs on bone blood flow may also have an impact on their effects on bone remodeling. Micro-vessels of the bones are formed only of endothelium with no muscle or connective tissue layers. Consequently, it is the endothelium that mediates the entire humoral regulation of exchange between osteoblasts, osteoclasts and the blood⁴¹. In the present work endothelium dependent relaxation which is mainly mediated by nitric oxide (NO) was impaired in OVX rats, while endothelium-independent relaxation with sodium nitroprusside was similar in both OVX and control group. This indicates that endothelial release of NO was impaired, but the sensitivity of vascular smooth muscle to NO was not altered. This endothelial dysfunction through impaired vasodilatation or enhanced vascular tone may lead to reduced blood flow and bone perfusion. These observed findings are supported by those of Prisby et al⁴², who by using radiolabeled microspheres, demonstrated a 21% reduction in metaphyseal blood flow in old rats compared with young rats. The reduction in blood flow was associated with impaired endothelium-dependent vasodilatation and decreased NO

bioavailability. Griffith et al⁴³ demonstrated that reduced bone perfusion occurs in synchrony with reduced bone mineral density and is most likely the result of impaired endothelial function after ovariectomy.

Vascular tissues isolated from OVX rats treated with omeprazole (20, 40 mg/kg/day) exhibited a significant improvement of endothelial function. These data are consistent with those of Kelicen et al²¹ who reported that omeprazole-induced concentration dependent relaxation in rat aortic rings was dependent on endothelium. These results could be explained by the observed reducing effect of omeprazole on both TNF- α and IL-6, as both can affect endothelial nitric oxide synthase (eNOS). Indeed two of the most potent inhibitory stimuli for eNOS expression in vascular endothelial cells are TNF- α which inhibits eNOS expression⁴⁴ and IL-6 which decreases eNOS activation⁴⁵.

In spite of the observed improvement of endothelial function after omeprazole administration in OVX rats, yet the drug failed to improve bone condition, so we can conclude that endothelial dysfunction is not likely however, to be the sole cause of reduced bone perfusion.

Conclusions

We observed that PPIs might induce both positive and negative effects on bone remodeling. Although these drugs might have the potential to inhibit bone resorption, through suppression of pro-inflammatory cytokines and improvement of endothelial function, yet these effects are counteracted by their inhibitory effects on the gastric proton pump with reduction in calcium absorption and decreased bone formation. Further research is required to screen different PPIs for their differential effects on gastric versus osteoclastic PPs in an attempt to develop PPIs with improved activity on osteoclastic PP and consequently less risk of inducing osteoporosis on prolonged use.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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