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Effect of omeprazole, pantoprazole and famotidine on rat bones

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Abstract: Acid-suppressive drugs usage is widespread in osteoporotic patients. An association between gastric acid suppressants and increased any-site fractures risk has been found denoting the possible effects of chronic use of omeprazole, pantoprazole (PPIs) and famotidine (H_2 receptor antagonist). Forty eight (48) female Sprague–Dawley rats were used, they were divided into two main groups. group A. (7-week old), group B. (7-month old). Each main group was subdivided into four subgroups. omeprazole, pantoprazole, famotidine treated and received drugs orally/ day (successive 3 months), and control. Then, blood was collected for serum calcium, alkaline phosphatase, estradiol, and osteocalcin levels. Femurs were processed for histopathology. Omeprazole or pantoprazole administration produced bone loss (low serum calcium, elevated alkaline phosphatase, and osteocalcin and decrease in cortical and trabecular bone thickness). These drugs have no effect on serum estradiol level. The effects of these drugs on bone tissue were more prominent in old rats. On the other hand, famotidine produced bone changes only in old rats. It could be concluded, omeprazole or pantoprazole induces bone lesions which are more prominent in old age. Famotidine affects only old age. This is may be due to calcium deficiency resulted from prolonged gastric acid suppression.
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Keywords. acid-suppressive drugs, H_2 receptor antagonists (H_2RA), proton pump inhibitors (PPIs), osteopor osis.

Running head acid-suppressive drugs and osteoprosis

Introduction

Osteoporosis is a chronic progressive degenerative systemic skeletal disease, which leads to bone fragility associated with a risk of low trauma fractures of all bones [1]. Osteoporotic fractures are a serious health problem among the elderly [2, 3].

Acid-suppressive drugs (ASDs) represent the second leading medication worldwide in terms of sales [4]. Proton pump inhibitors (PPIs) and H_2 receptor antagonists (H_2RAs) are the most popular ASDs available [5]. These drugs are indicated in the management of several acid-related gastrointestinal disorders [6].Omeprazole and pantoprazole are the most frequently used PPIs clinically . These drugs can reduce gastric acid secretion by up to 98% , irreversibly deactivating the proton pump (H+/K+ ATPase) of the gastric parietal cells [7]. H_2RAs (cimetidine, ranitidine, famotidine) competitively inhibit H_2 receptors, have similar effects to PPIs, although they are less potent, blocking only 70% of gastric acid production [8,9].

The use of ASDs is widespread in osteoporotic patients to counteract inflammation and ulceration of esophagus and stomach caused by prolonged use of antiresorptive medications especially bisphosphonates[10]. It has been suggested a possible association between PPIs use and increased fracture risk [11-14]. While, others have not observed any fracture risk with the use of PPIs [15-19]. The data on the effects of H_2RAs are conflicting too [5, 12, 20].

Several mechanisms of this association have been proposed in theory, such as the possibility that PPIs decrease calcium-absorption, leading to bone mineral density (BMD) loss [11], or they decrease magnesium absorption, which is important to bone health [21], other studies suggest that these agents can cause hyperparathyroidism by acid suppression and lead to decrease in BMD [22].

In this study, it was aimed to clarify the possible effects of chronic use of omeprazole , pantoprazole and famotidine on adult and old female rat.

Materials and methods.

Animals.

Forty eight (48) female Sprague–Dawley rats were used in this study. 24 of them are adult (7-week old, each of them weighing 120-150 g), the other 24 are old (7-month old, each of them weighing 250-300 g). Animals were obtained from the medical experimental research center (MERC) at Mansoura Faculty of Medicine, they were put in similar optimum housing conditions with free access to food and water. Animals were kept in cages at a room with controlled temperature 26 °c and on a 12-h light–dark cycle. The local animal ethics committee has approved all experimental procedures. Rats were randomly divided into 8 groups (n=6 per group). Group (A) represents adult rats, Group (B) represent old age rats.

Each main group was subdivided into four subgroups. Control subgroups in which rats were given oral carboxy methylcellulose, Omeprazole treated subgroups. rats received omeprazole (Healsec 40 mg capsules from BORG pharmaceutical Inc.) at a dose of 10 mg/kg of body weight per day [23] , Pantoprazole treated subgroups. rats received pantoprazole (Pantoloc 40 mg tablets from Medical Union Pharmaceuticals "MUP") at a dose of 3 mg/kg of body weight per day [23], Famotidine treated groups. rats received famotidine (Famotin 40 mg tablets from Memphis Co. for Pharm. & Chem. Ind.) at a dose of 3 mg/kg of body weight per day [24].These drugs were dissolved in 0.5% carboxy methylcellulose solution and given daily for successive 3 months by oral gavage.

Samples collection.

At the end of the experimental period, animals were sacrificed by thiopental high dose (50mg/kg). The blood was collected from carotid arteries. Then, centrifuged at 4000 rpm for 15 min at 4°C where the clear sera were separated then stored at –20°C until measurement of serum calcium, alkaline phosphatase, estradiol, and osteocalcin levels. Femurs were collected and processed for histopathological examination.

Serum measurements.

Calcium level was measured by calcium colorimetric kits (Spinreact, S.A. / S.A.U. Ctra. Santa Coloma, Spain). Alkaline phosphatase level was measured by alkaline phosphatase kits (AGAPPE Diagnostics Switzerland Gmbh). Estradiol (E2) level was determined by Estradiol ELISA kits (Biosource Europe S.A, Nivelles, Belgium). Rat osteocalcin ELISA kits were used in this study for measurement of serum osteocalcin level.

Bone histomorphometrical analysis.

Femurs were removed, dissected free of soft tissue, fixed with 10 % buffered neutral paraformaldehyde for 24 hour at 4°C then decalcified in EDTA (Ethylenediaminetetraacetic acid) solution for 2 weeks. Once decalcified, the specimens took after routine histological handling and were embedded in paraffin. Paraffin sections (5 µm thick) from the metaphysis and the diaphysis of the femurs were deparaffinized then processed for hematoxylin and eosin staining (H/E) and viewed under the light microscope [25]. Osteoporotic changes in the bones were graded from 0 to 3 as indicated by the following schedule[26]. Grade 0. Bone with normal structure, Grade 1. Slight osteoporotic changes. Bone showing early osteoporotic changes, namely osteocytic activation (hypertrophy of osteocytes and enlargement of their lacunae) and hypertrophy of endosteal cells, Grade 2. Moderate osteoporotic changes. Beside the above changes, appearance of resorption cavities in the compact bone, Grade 3. Severe osteoporotic changes. Many resorption cavities in the diaphysis with the larger cavities containing bone marrow spaces and the compact bone becoming significantly thinner.

Image analysis procedure.

Slides were digitized using Olympus® digital camera installed on Olympus® microscope with 1/2 X photo adaptor, using 40X objective. The resulted images were analyzed on Intel® Core I3® based computer using Video Test Morphology® software (Russia) with a specific built-in routine for distance measurement.5 images were taken for each sample, 5 measurements for cortical and trabecular bone thickness were taken by using line measurement tool.

Statistical analysis.

Data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 17.0. Descriptive statistics were calculated in the form of Mean ± SD (Standard deviation) for quantitative parametric data and in the form of median and range (Minimum – maximum) for quantitative non-parametric data. In the statistical comparison between different groups, the significance of difference was tested using ANOVA (Analysis of variance) to compare between more than two groups of numerical parametric data followed by post-hoc tukey test for comparison between two groups. Kruskal-Wallis test was used to compare between more than two groups of non- parametric data followed by mann-whitney test for comparisons between two groups. P value <0.05 was considered statistically significant in all analyses and P value <0.001 was considered highly significant in all analyses.

Results.

Biochemical results.

- Effect of omeprazole, pantoprazole, and famotidine on serum calcium level in adult and old age female rats.

Omeprazole and pantoprazole administration to adult and old age female rats produced highly significant decrease ($p< 0.001$) in serum calcium level as compared with control group but serum calcium level in pantoprazole groups is still significantly lower than omeprazole groups while famotidine administration to adult female rats produced non-significant change ($P = 0.69$) in serum calcium level as compared with control group but administration to old female rats produced moderate significant decrease ($P < 0.01$) in serum calcium level as compared with control group, and is still significantly higher than omeprazole group ($p= 0.001$) and pantoprazole group ($p < 0.001$) (table 1, 2).

- Effect of omeprazole, pantoprazole, and famotidine on serum alkaline phosphatase level in adult and old age female rats.

Omeprazole and pantoprazole administration to adult and old age female rats produced highly significant increase ($p< 0.001$) in serum alkaline phosphatase level as compared with control group but serum alkaline phosphatase level in pantoprazole groups is still significantly higher than omeprazole groups while famotidine administration to adult female rats produced non-significant change ($P = 1$) in serum alkaline phosphatase level as compared with control group but administration to old female rats produced moderate significant increase ($P < 0.01$) in serum alkaline phosphatase level as compared with control group and is still significantly lower than omeprazole group ($p= 0.001$) and pantoprazole group ($p < 0.001$) (table 1, 2).

- Effect of omeprazole, pantoprazole, and famotidine on serum estradiol level in adult and old age female rats.

Omeprazole, pantoprazole, and famotidine administration to adult and old age female rats produced non-significant change ($p = 0.2$) in serum estradiol level as compared with control group (table 1, 2).

- Effect of omeprazole, pantoprazole, and famotidine on serum osteocalcin level in adult and old age female rats.

Omeprazole and pantoprazole administration to adult and old age female rats produced highly significant increase ($p < 0.001$) in serum osteocalcin level as compared with control group but serum osteocalcin level in pantoprazole groups is still significantly higher ($p = 0.01$) than omeprazole group while famotidine administration to adult female rats produced non-significant change ($p=0.99$) in serum osteocalcin level as compared with control group but administration to old female rats produced moderate significant increase ($P < 0.01$) in serum osteocalcin level as compared with control group and is still significantly lower than omeprazole group ($p= 0.029$) and pantoprazole group ($p < 0.001$) (table 1 , 2).

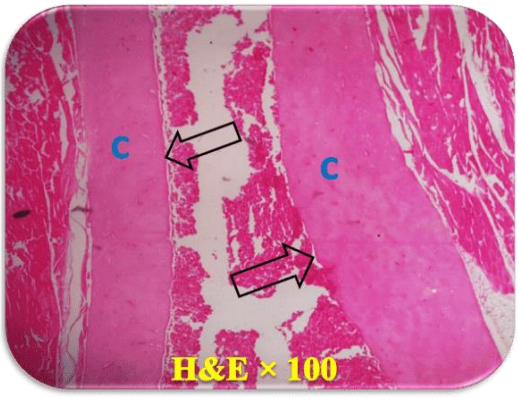

Fig. 1(A)

Fig. 1(C)

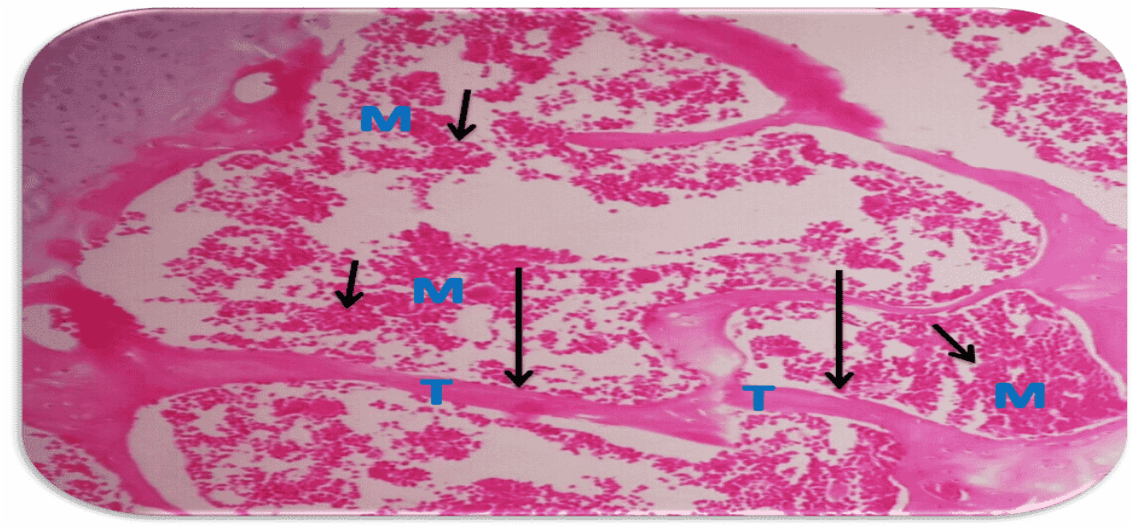

Fig. 1(B)

Fig.1. Normal histological appearance of the femur of adult female rats (Grade 0)
The proximal metaphysis of the femur formed of an outer shell of cortical bone and inner trabecular bone.
A: Cortical (C) bone (empty arrows) consisted of bone lamellae that are covered by periosteum and lined with endosteum. B: Trabecular (T) bone composed of regular bone lamellae (long arrows) enclosing average thickness marrow spaces (M) (short arrows).C: Average size osteocytes (O) resided in their lacunae in between the lamellae (curved arrows).

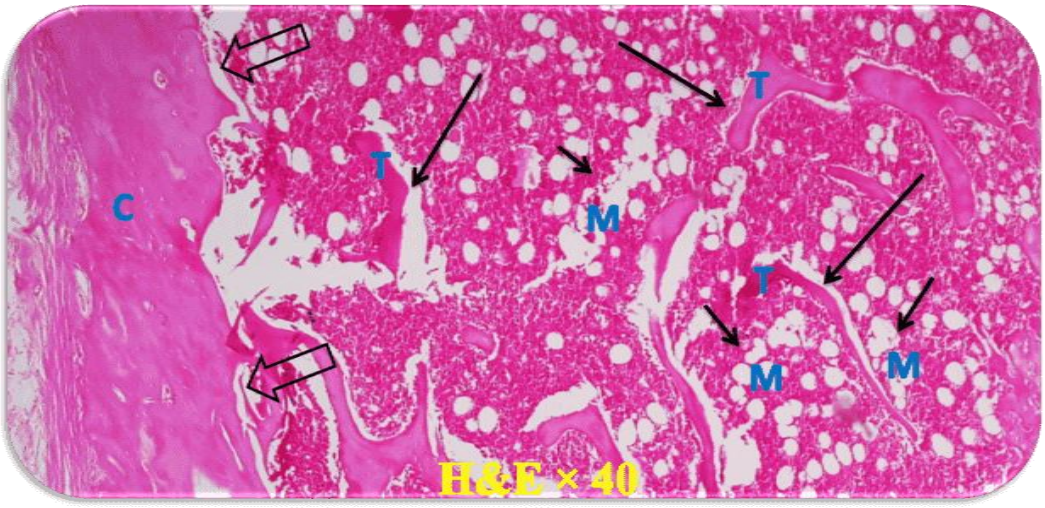

Fig. 2(A)

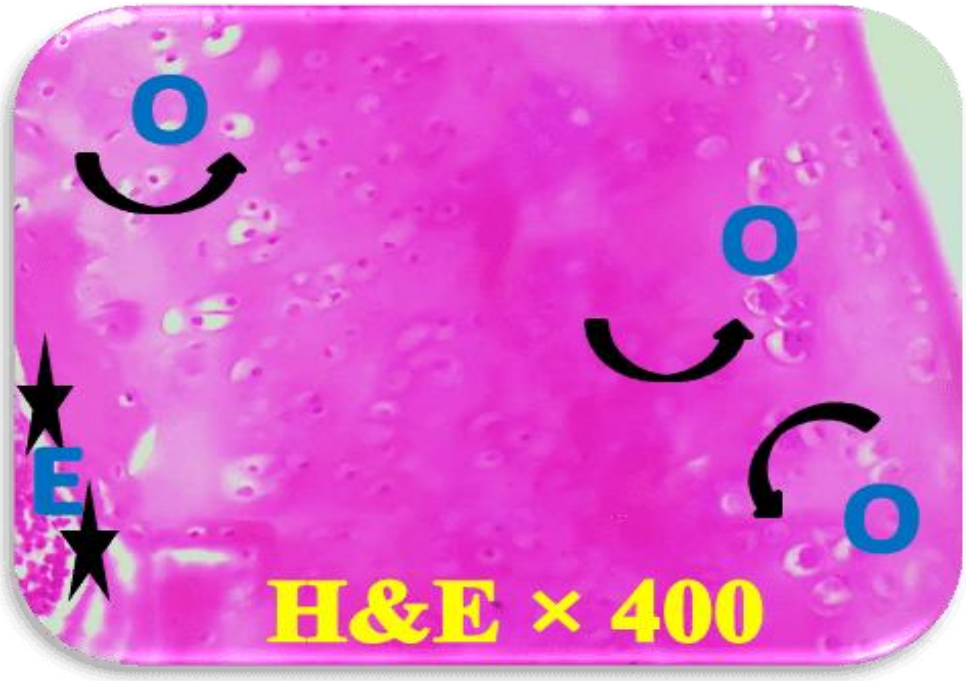

Fig. 2(B)

Fig.2. Histopathological findings in omeprazole treated adult female rats (Grade 1)
A: Significant decrease in cortical (C) bone thickness (empty arrows). Significant decrease in trabecular (T) bone thickness (long arrows) with wide marrow spaces (M) filled with fat tissue (short arrows).B: Hypertrophy of osteocytes (O) and enlargement of their lacunae (curved arrows) with hypertrophy of endosteal cells (E) (stars).

Fig. 3(A)

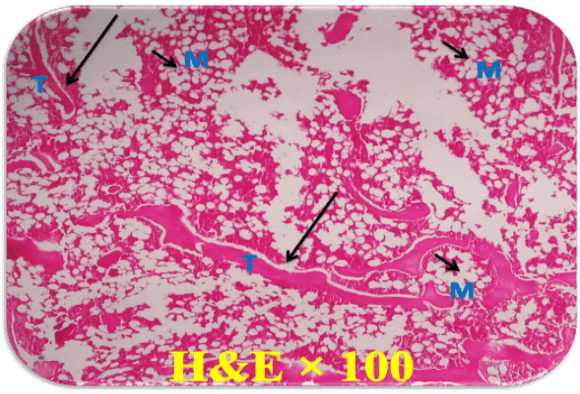

Fig. 3(B)

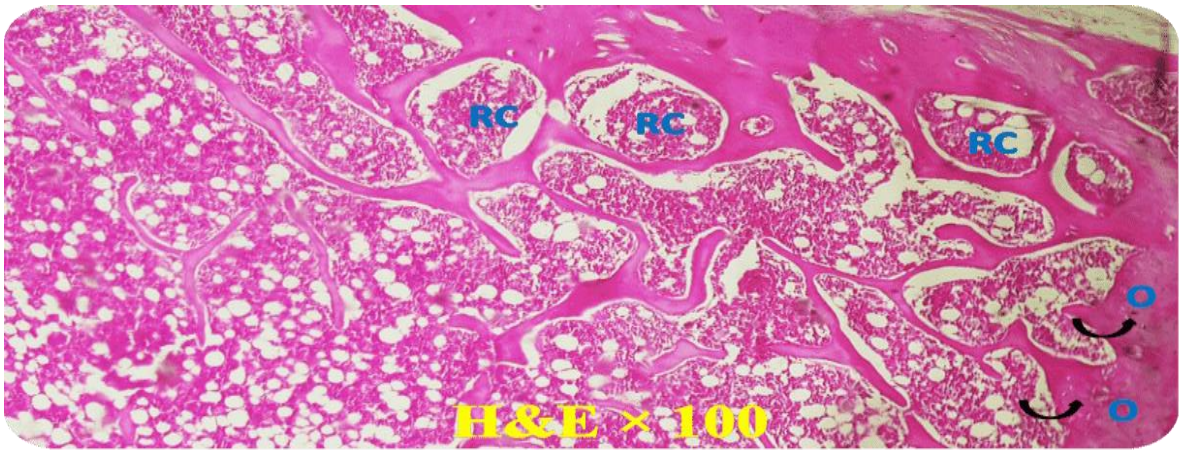

Fig. 3(C)

Fig.3. Histopathological findings in pantoprazole treated adult female rats (Grade 2)
A: Significant decrease in cortical (C) bone thickness (empty arrows) with loss of continuity.
B: Significant decrease in trabecular (T) bone thickness (long arrows) with wide marrow spaces (M) filled with fat tissue (short arrows).C: Hypertrophy of osteocytes (O) and enlargement of their lacunae (curved arrows). Resorption cavities (RC) filled with bone marrow spaces are detected.

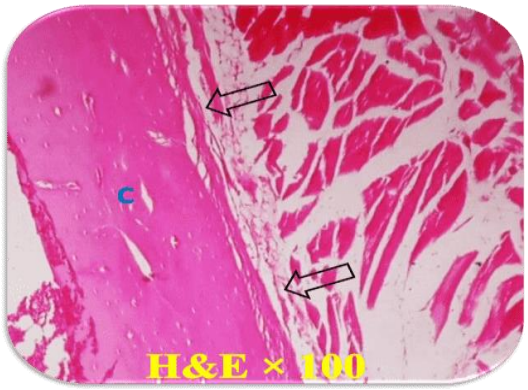

Fig. 4(C)

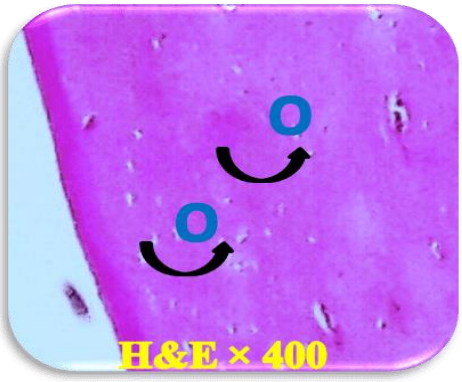

Fig. 4(A)

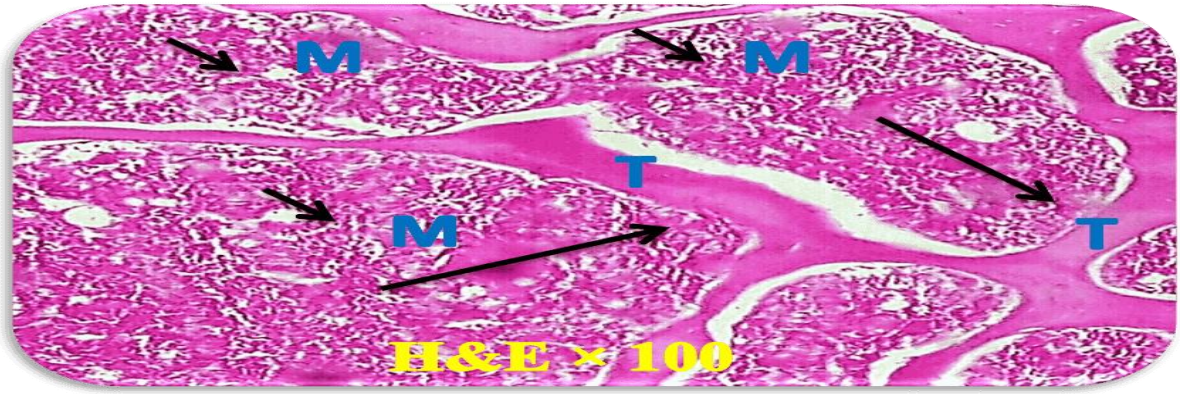

Fig. 4(B)

Fig.4. Histopathological findings in famotidine treated adult female rats (Grade 0)

A: Average cortical (C) bone thickness (empty arrows).B: Average trabecular (T) bone thickness (long arrows) with average size marrow spaces (M) (short arrows).C: Average size osteocytes (O) resided in their lacunae (curved arrows).

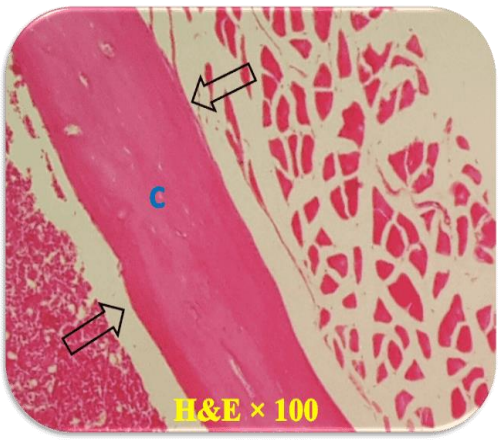

Fig. 5(A)

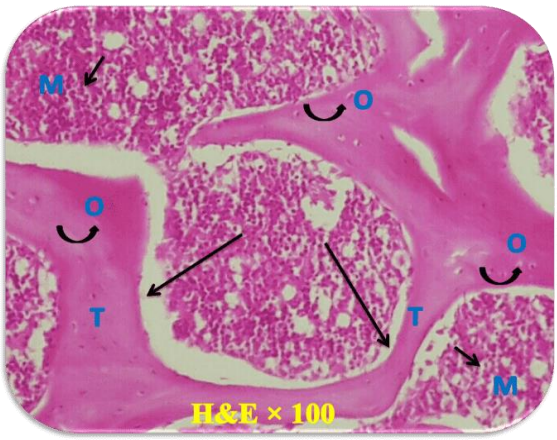

Fig. 5(B)

Fig.5. Normal histological appearance of the femur of old female rats (Grade 0)

A: Cortical (C) bone (empty arrows) consisted of bone lamellae that are covered by periosteum and lined with endosteum. B: Trabecular (T) bone composed of regular bone lamellae (long arrows) enclosing average thickness marrow spaces (M) (short arrows). Average size osteocytes (O) resided in their lacunae in between the lamellae (curved arrows).

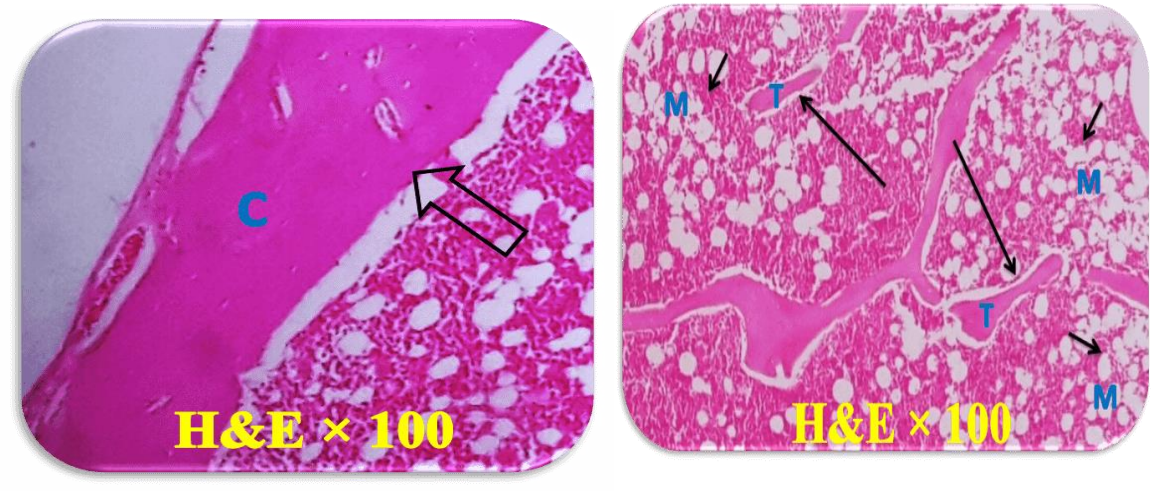

Fig. 6(A) **Fig. 6(B)**

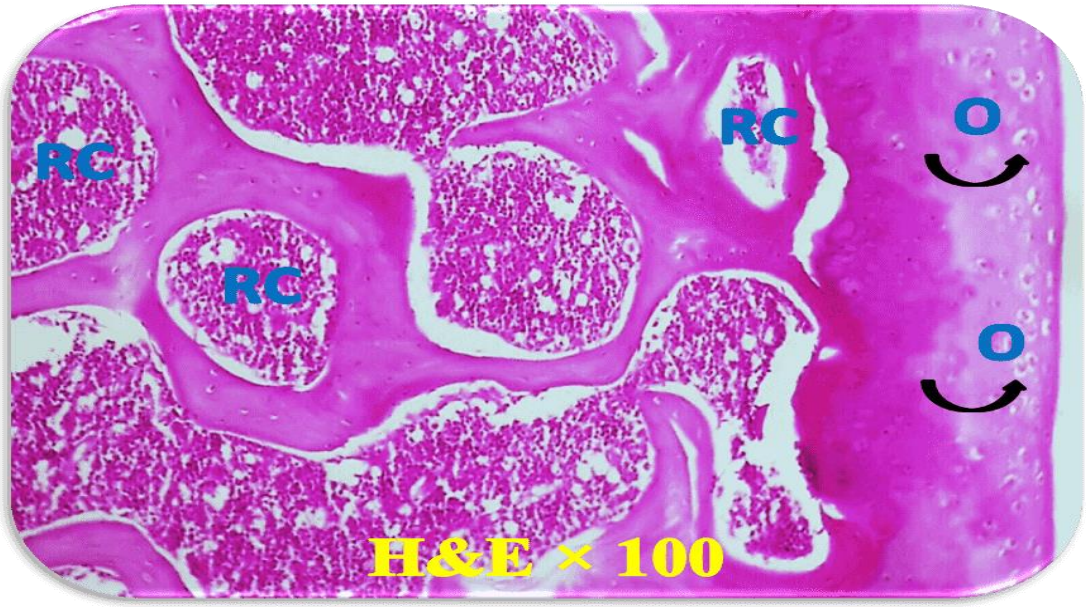

Fig. 6(C)

Fig.6. Histopathological findings in omeprazole treated old female rats (Grade 2)
A: Significant decrease in cortical (C) bone thickness (empty arrows). B: Significant decrease in trabecular (T) bone thickness (long arrows) with wide marrow spaces (M) filled with fat tissue (short arrows). C: Hypertrophy of osteocytes (O) and enlargement of their lacunae (curved arrows) with appearance of resorption cavities (RC) filled with bone marrow spaces.

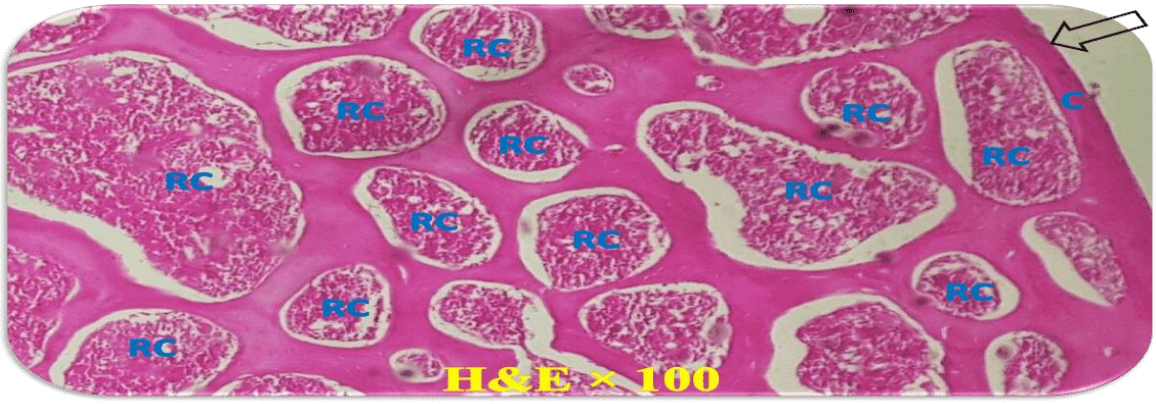

Fig. 7(A)

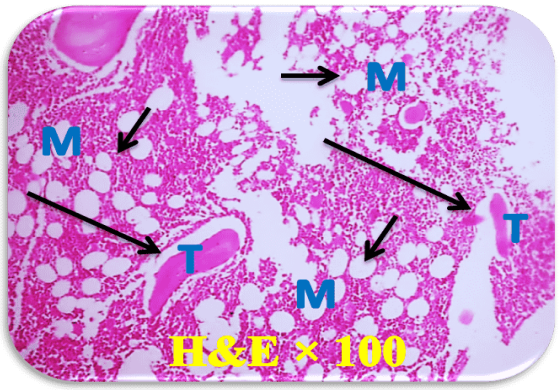

Fig. 7(B)

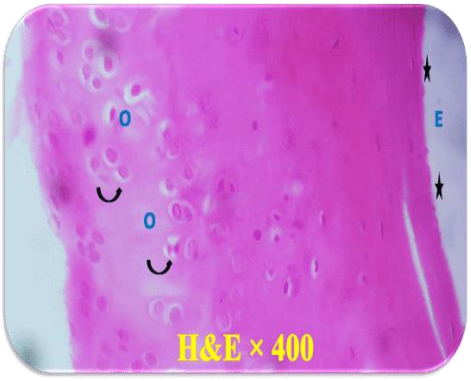

Fig. 7(C)

Fig.7. Histopathological findings in pantoprazole treated old female rats (Grade 3)
A: Significant decrease in cortical (C) bone thickness (empty arrows) with appearance of resorption cavities (RC) filled with bone marrow spaces. B: Significant decrease in trabecular (T) bone thickness (long arrows) with wide marrow spaces (M) filled with fat tissue (short arrows). C: Hypertrophy of osteocytes (O) and enlargement of their lacunae (curved arrows) with hypertrophy of endosteal cells (E) (stars).

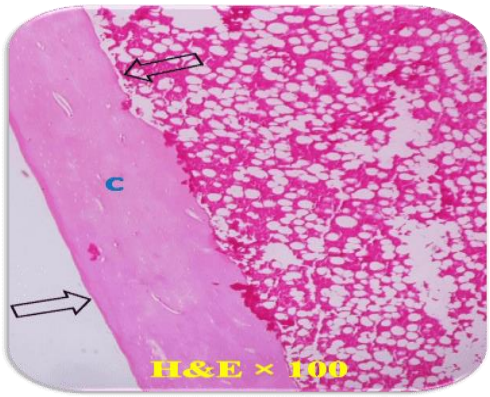

Fig. 8(A)

Fig. 8(C)

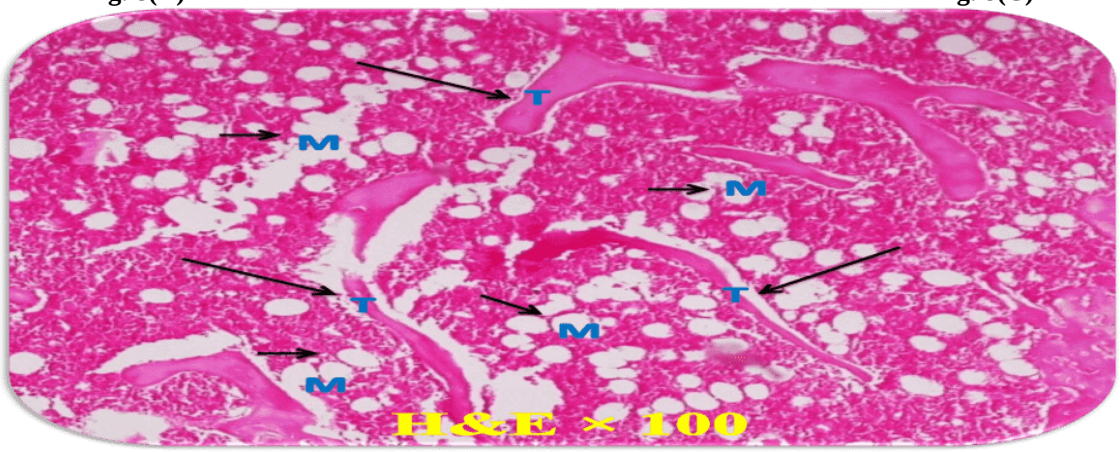

Fig. 8(B)

Fig.8. Histopathological findings in famotidine treated old female rats (Grade 1)

A: Significant decrease in cortical (C) bone thickness (empty arrows). B: Significant decrease in trabecular (T) bone thickness (long arrows) with wide marrow spaces (M) filled with fat tissue (short arrows). C: Hypertrophy of osteocytes (O) and enlargement of their lacunae (curved arrows) with hypertrophy of endosteal cells (E) (stars).

Table 1. Effect of omeprazole, pantoprazole, and famotidine on serum calcium, alkaline phosphatase, estradiol and osteocalcin levels in adult female rats

		Control group	Omeprazole group	Pantoprazole group	Famotidine group
Serum calcium (mg/ dl)	**Mean ± SD**	11.00 ± 0.89	8.50 ± 0.55 [a]	6.5 ± 0.54 [a b]	10.50 ± 1.05 [b c]
Serum alkaline phosphatase (IU/L)		130.00 ± 20.76	164.5 ± 12.88 [a]	198.00 ± 8.69 [a b]	130.50 ± 12.76 [b c]
Serum estradiol (Pg/ ml)		60.50 ± 15.91	47.50 ± 11.57	51.3 ± 5.15	60.00 ± 12.41
Serum osteocalcin (ng/ml)		12.00 ± 2.00	19.66 ± 2.8 [a]	26.5 ± 5.08 [a b]	12.50 ± 2.66 [b c]

Data are presented as means ± SD and were analyzed by one-way ANOVA followed by post-hoc tukey test for comparison between groups.

Superscript letters indicate significant differences between groups at (**P < 0.05**):

a: significance in relation to control group.

b: significance in relation to omeprazole group.

c: significance in relation to pantoprazole group.

Table 2. Effect of omeprazole, pantoprazole, and famotidine on serum calcium, alkaline phosphatase, estradiol and osteocalcin levels in old female rats

		Control group	Omeprazole group	Pantoprazole group	Famotidine group
Serum calcium (mg/ dl)	**Mean ± SD**	10.00 ± 1.41	6.92 ± 0.21 [a]	5.52 ± 0.55 [a b]	8.50 ± 0.55 [a b c]
Serum alkaline phosphatase (IU/L)		103.50 ± 8.55	145.67 ± 5.79 [a]	163.50 ± 8.41 [a b]	125.17 ± 8.08 [a b c]
Serum estradiol (Pg/ ml		32.50 ± 8.38	27.50 ± 6.16	24.50 ± 2.74	30.00 ± 5.33
Serum osteocalcin (ng/ml)		5.00 ± 0.89	10.17 ± 2.56 [a]	14.33 ± 0.82 [a b]	7.50 ± 1.05 [a b c]

Data are presented as means ± SD and were analyzed by one-way ANOVA followed by post-hoc tukey test for comparison between groups.
Superscript letters indicate significant differences between groups at (P < 0.05):
a: significance in relation to control group.
b: significance in relation to omeprazole group.
c: significance in relation to pantoprazole group.

Table 3. Histomorphometric parameters of the femur of adult female rats after administration of omeprazole, pantoprazole, and famotidine

		Control group	Omeprazole group	Pantoprazole group	Famotidine group
Hypertrophy of osteocytes & endosteal cells*	**Present %**	0.0% (n=0/6)	66.7% (n=4/6)	83.3% (n=5/6)	0.0% (n=0/6)
Resorption cavities at compact bones*		0.0% (n=0/6)	0.0% (n=0/6)	83.3% (n=5/6)	0.0% (n=0/6)
Significant thin cortical bone*		0.0% (n=0/6)	0.0% (n=0/6)	0.0% (n=0/6)	0.0% (n=0/6)
Grade ♦	**Median (Minimum-Maximum)**	0.00 (0.00-0.00)	1.00 (0.00-1.00)[a]	2.00 (1.00-2.00)[a b]	0.00 (0.00-0.00)[b c]

* Test used: Chi-square
♦ Test used Kruskal Wallis test followed by mann-whitney for pairwise comparisons.
Superscript letters indicate significant differences between groups at (P < 0.05):
a: significance in relation to control group.
b: significance in relation to omeprazole group.
c: significance in relation to pantoprazole group.

Table 4. Histomorphometric parameters of the femur of old female rats after administration of omeprazole, pantoprazole, and famotidine

		Control group	Omeprazole group	Pantoprazole group	Famotidine group
Hypertrophy of osteocytes & endosteal cells*	**Present %**	0.0% (n=0/6)	83.3% (n=5/6)	83.3% (n=5/6)	66.7% (n=4/6)
Resorption cavities at compact bones*	**Present %**	0.0% (n=0/6)	66.7% (n=4/6)	100% (n=6/6)	0.0% (n=0/6)
Significant thin cortical bone*	**Present %**	0.0% (n=0/6)	0.0% (n=0/6)	100 % (n=6/6)	0.0% (n=0/6)
Grade ♦	**Median (Minimum-Maximum)**	0.00 (0.00-0.00)	1.50 (1.00-2.00)[a]	3.00 (2.00-3.00)[a b]	1.00 (0.00-1.00)[a b c]

* Test used: Chi-square
♦ Test used Kruskal Wallis test followed by mann-whitney for pairwise comparisons.
Superscript letters indicate significant differences between groups at (P < 0.05):
a: significance in relation to control group.
b: significance in relation to omeprazole group.
c: significance in relation to pantoprazole group.

Table 5. Effect of omeprazole, pantoprazole, and famotidine on cortical and trabecular thickness of the femoral bones of adult female rats by image analysis

Groups (n=6)	Cortical bone thickness (µm) Mean ±SD	Trabecular bone thickness (µm) Mean ±SD
Control group	65 ± 10.3	28± 6.4
Omeprazole group	46 ± 7.4 [a]	16± 3.9 [a]
Pantoprazole group	30 ± 6.7 [a b]	7± 2.6 [a b]
Famotidine group	59 ± 8.1[b c]	25± 3.6 [b c]

Data are presented as means ± SD and were analyzed by one-way ANOVA followed by post-hoc tukey test for comparison between groups.
Superscript letters indicate significant differences between groups at (P < 0.05):
a: significance in relation to control group.
b: significance in relation to omeprazole group.
c: significance in relation to pantoprazole group.

Table 6. Effect of omeprazole, pantoprazole, and famotidine on cortical and trabecular thickness of the femoral bones of old female rats by image analysis

Groups *(n=6)*	Cortical bone thickness (µm) Mean ±SD	Trabecular bone thickness (µm) Mean ±SD
Control group	59.6 ± 12.6	26.4± 4.3
Omeprazole group	31.3 ± 6.3 [a]	12.9± 3.2[a]
Pantoprazole group	16.4 ± 4.7 [a b]	6.2 ± 1.8 [a b]
Famotidine group	46.2 ± 7.3 [a b c]	19.3± 3.9 [a b c]

Data are presented as means ± SD and were analyzed by one-way ANOVA followed by post-hoc tukey test for comparison between groups.
Superscript letters indicate significant differences between groups at ($P < 0.05$):
a: significance in relation to control group.
b: significance in relation to omeprazole group.
c: significance in relation to pantoprazole group.

Discussion.

Osteoporosis is a common chronic progressive degenerative systemic skeletal disease, which leads to increased bone fragility that is associated with increased risk of low trauma fractures of all bones [1]. Many risk factors are related to fractures including including medication classes that have been associated with increased fracture risk include antidepressants, antipsychotics, antidiabetic agents, and opiate agonists[27- 29] .

Proton pump inhibitors (PPIs) and histamine -2 receptor antagonists (H_2RAs) are the most popular acid-suppressive drugs (ASDs) [5]. These drugs are indicated in the management of several acid-related gastrointestinal disorders, including. duodenal ulcer, gastric ulcer, and gastroesophageal reflux disease (GERD) [6]. The use of ASDs is widespread in osteoporotic patients to counteract inflammation and ulceration of esophagus and stomach either caused by prolonged use of antiresorptive bisphosphonates [10] or by nonsteroidal anti-inflammatory drugs (NSAIDs) used for pain management in fractures [30].

There is a possible association between PPIs use and increased fracture risk [11, 13]. Although another studies have not observed any risk in hip fracture [15, 19].

In this study, the aimed was to clarify the possible effect of chronic use of PPIs (omeprazole, pantoprazole) and H_2RAs (famotidine) on adult and old female rat bones for successive 3 months .

In the present study, omeprazole or pantoprazole administration to adult or old age female rats induced bone lesions that are explained by a significant biochemical and histopathological changes as compared with control groups . On the other hand, famotidine administration produced mild changes only in old rats.

In the present study, serum calcium level in both adult and old female rats was significantly decreased by omeprazole or pantoprazole administration as compared with control groups (pantoprazole produced greater changes more than omeprazole). On the other hand, famotidine caused mild decrease in serum calcium level only in old age female rats.

There are several explanations for the risk of fractures with PPIs, which seems to be more prominent than with H_2RAs [12]. Some suggest that PPIs have deleterious effects on calcium absorption leading to increased risk of bone fractures. In addition, secondary hypergastrinemia due to acid suppression by PPIs may induce hyperparathyroidism and result in increased bone resorption[31].Prolonged PPIs use has been shown to worsen vitamin B_{12} absorption and subsequently hyperhomocysteinemia and interfering with collagen crosslinking, and bone strength [32].

Histamine may also be involved in bone metabolism regulation. Histamine receptors are expressed on osteoblastic and osteoclastic cells [33]. Studies have already been reported that cimetidine has been shown

to prevent osteoclast differentiation and shows antiresorptive effect in estrogen-deficient rats[34-35] .

Calcium to be absorbed into the small intestine, it has to be dissociated from its complexes by the acidic environment in the stomach [36]. Impaired calcium absorption as a result of reduced gastric acid leads to compensatory physiologic responses including secondary hyperparathyroidism. PTH increases the rate of osteoclastic bone resorption. Over time, this would lead to an increase in the rate of skeletal turnover and increase the risk of fracture [31, 37 - 41].

In the present study, serum alkaline phosphatase level in both adult and old female rats was significantly increased by omeprazole or pantoprazole administration as compared with control groups (pantoprazole produced greater changes more than omeprazole). On the other hand, famotidine caused mild increase in serum alkaline phosphatase only in old female rats Alkaline phosphatase (ALP) is the most commonly used biomarker of bone formation and considered a sensitive marker of increased bone turnover in osteoporosis [42-44- 45].

In the present study, omeprazole, pantoprazole, and famotidine administration to either adult or old rats produced non-significant change in serum estradiol level as compared with control groups [34,46]. Estradiol level decreased with aging . This decline with aging leads to increased bone remodeling rate, both bone resorption and formation, with the balance moved in favor of bone resorption, causing progressive loss of bone mass and strength [47 -51]..

Osteocalcin (OC) is an osteoblast- specific protein. OC is released from the bone matrix into blood during bone resorption, suggesting that osteocalcin is a marker of bone turnover [52-53].
In the present study, serum ostocalcin level in adult and old female rats was significantly increased by omeprazole or pantoprazole administration as compared with control groups (pantoprazole produced greater changes more than omeprazole). On the other hand, famotidine caused mild increase in serum osteocalcin only in old rats. [54-56].

Omeprazole and pantoprazole groups showed signs of osteoporosis (pantoprazole more than omeprazole) as compared with control groups. On the other hand, famotidine groups revealed signs of osteoporosis only in old rats but less than omeprazole and pantoprazole groups. Increased bone resorption in the present study is explained by enlargement of the resorption area on trabecular surface and cortical thinning, primarily by enhancing osteoclast lifespan and decreasing osteoclast apoptosis [50]. Also, the contraction or even the loss of some trabeculae is produced by resorption of some connecting trabeculae [57]. Hypertrophy of endosteal cells suggests increased activity of these cells which is related to the resorptive process [58 -62] .

In the present study, the unfavorable effect of pantoprazole on rat bones was stronger than that of omeprazole [59, 63]. The possible explanation is that pantoprazole demonstrates a significantly faster onset of action [64], higher bioavailability [65], and slower restoration of the proton pump activity than omeprazole results in prolonged and potent suppression of gastric acid secretion [66].

The effect of omeprazole or pantoprazole on old female rat bones was stronger than that of young rats most probably due to associated risk factors of osteoporosis that are more evident with age such as atrophy of gastric mucosa and calcium malabsorption as a result of estradiol decline with age. More over ,there may be some mechanisms of compensation for PPIs effects on bone metabolism especially in young age [67-68].

In the present study, the unfavorable effect of PPIs on rat bones was stronger than famotidine which causes bone changes only in old female rats. This is in agreement with previous studies reported that the risk fracture was significantly greater with PPIs use than H_2RAs [11].

Acid suppression in the stomach caused by PPIs is significantly greater and lasts longer compared with H_2RAs since their effect is irreversible. Thus, if impaired calcium absorption caused by acid suppression is associated with an increased risk of fracture, this should be most abundant with PPIs use. Perhaps more prolonged exposure is necessary to see effects on fracture risk with less potent acid inhibitors such as H_2RAs, and the risk will be more pronounced with advancing age due to associated risk factors [69-70].

Conclusions.

In conclusion, omeprazole and pantoprazole administration to either adult or old female rats for successive 3 months produced bone loss , these effects are more prominent in old rats. On the other hand, famotidine administration to either adult or old female rats for 3 months produces bone loss in old rats .

Conflicts of interest

No potential conflict of interest relevant to this article was reported

No financial contributions to the present work.

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