The Egyptian Rheumatologist xxx (xxxx) xxx

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

journal homepage: www.elsevier.com/locate/ejr

# Potential effectiveness of exenatide in experimentally-induced osteoporosis

Osama M. Abu Taleb [a,*], Marian Y. Wissa [a], Rahma K. Abou El Nour [b], Hesham A. Awad [a], Nahed M. Moussa [a]

[a] Medical Pharmacology Department, Faculty of Medicine, Cairo University, Egypt
[b] Medical Histology Department, Faculty of Medicine, Cairo University, Egypt

ARTICLE INFO

*Article history:*
Received 30 May 2019
Accepted 9 June 2019
Available online xxxx

*Keywords:*
Osteoporosis
Vitamin D
Exenatide
Ovariectomy
Experimentally-induced

ABSTRACT

*Aim of the work:* To study the possible protective and therapeutic effects of exenatide on experimentally-induced osteoporosis in adult ovariectomized female albino rats.

*Materials and methods:* The study included 40 mature female albino rats, matched for age and weight (150–250 gm). Osteoporosis was experimentally-induced by bilateral ovariectomy (OVX) and the animals were left untreated for 6 weeks. Rats were divided into 4 groups: Sham group (group-I), ovariectomized (OVX) non-treated (group-II), prophylactic exenatide (group-III: received 1 μg/kg/d SC for 6 weeks immediately after ovariectomy) and treated group-IV (Left untreated for 6 weeks after ovariectomy then received treatment for 8 weeks) was subdivided into subgroup-IVa: treated with exenatide in a dose of 1 μg/kg/d SC and subgroup IVb: treated with vitamin Din a dose 0.25 μg/day orally for 5 days/week. Serum bone-specific alkaline phosphatase (BsALP) level was measured and bone histomorphometry assessed.

*Results:* Non-treated rats showed a significant elevation of BsALP level by 182%, reduction of cortical thickness by 36% and osteocyte number by 29% compared to Sham group-I. Rats of prophylactic exenatide, therapeutic exenatide and therapeutic vitamin D showed a significant reduction of BsALP level by 62.4%,62.5% and 62.2%, respectively, increase of the cortical thickness by 38.7%, 29.4% and40.9% respectively and osteocyte number by 29%,26% and 42%, respectively compared to OVX non-treated group-II. The mean BsALP in group IV improved to levels comparable to Sham group-I. There was no significant difference in all previous results between groups-III and IVa or IVb.

*Conclusion:* Exenatide has a potential prophylactic and therapeutic role in the management postmenopausal osteoporosis. The non-inferiority of exenatide to vitamin D in treatment of osteoporosis is deduced.



## 1. Introduction

Osteoporosis is defined by low bone mass and microstructural deterioration. It is an escalating public health problem due to increase life expectancy and the resulting bone fractures represent a significant burden in terms of morbidity, mortality and cost. It is a silent multifactorial disease and proper estimation can help identity those at risk and permit prophylactic treatment before its occurrence [1]. The risk of osteoporosis is increased in postmenopausal females, owing to increased rate of bone remodeling due to estrogen deficiency and increased osteoclast life span [2].

Gastrointestinal hormones have been proved as modulators of bone growth and remodeling [3]. Furthermore, activation of glucagon like peptide-1 (GLP-1) receptors has been shown to enhance bone formation in rats [4]. Yet, the direct effects of exogenous GLP-1 analogues on bone turnover in postmenopausal females remain unclear [5]. Vitamin D is essential for calcium absorption and bone mineralization. It is well-established that prolonged and severe vitamin D deficiency leads to rickets in children and osteomalacia in adults [6]. The aforementioned highlights the importance of early prevention and treatment of these diseases especially in post menopausal females who represent one of the most vulnerable groups at risk. Experimentally-induced osteoporosis significantly elevated serum bone-specific alkaline phosphatase (BsALP), decreased serum calcium, bone mineral density and cortical thickness and significantly increased presence of fractures, bone defects and periosteal irregularity [7].

Peer review under responsibility of Egyptian Society of Rheumatic Diseases.
* Corresponding author.
*E-mail address:* osamaabutaleb2016@hotmail.com (O.M. Abu Taleb).

https://doi.org/10.1016/j.ejr.2019.06.003
1110-1164/

Please cite this article as: O. M. Abu Taleb, M. Y. Wissa, R. K. Abou El Nour et al., Potential effectiveness of exenatide in experimentally-induced osteoporosis, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.06.003

Exenatide is a synthetic peptide sharing 53% sequence homology with GLP- 1 and has been used as an agonist of mammalian GLP-1 receptor (GLP-1RA) for the treatment of type 2 diabetes. Compared to conventional treatments, GLP-1RAs not only have an advantage in lowering blood sugar, but have also been reported to confer cardio protection [8] and neuroprotection [9] hence with a potential anti-depressant effect. Furthermore, GLP-1 receptors have been shown to promote bone formation indicating an anabolic effect [4].

The aim of this work was to study the possible protective and therapeutic effects of exenatide on experimentally-induced osteoporosis in adult ovariectomized (OVX) female albino rats.

## 2. Material and methods

The study included 40 mature female albino rats, matched for age and weight (150–250 gm). Animals were harbored in Research Institute of Ophthalmology, Egypt on a 12-h light/dark cycle in a fully ventilated room, fed with standard laboratory diet and allowed water ad libitum. All experimental procedures were performed under a protocol approved by the Cairo University Institutional Animal Care and Use Committee (CU III F 49 17 CU-IACUC) and according to the ethical standards.

Rats were divided into 4 groups (8 animals in each group and in the 2 subgroups of group IV) as follow: Group-I (control; Sham surgery without removing the ovaries); Group II (OVX non-treated); rats in groups-I and II were left untreated for 6 weeks then given distilled water orally for 8 weeks; Group-III (OVX prophylactic) rats were given exenatide (1 μg/kg/d) subcutaneously (SC) [10] for 6 weeks immediately after ovariectomy followed by distilled water for 8 weeks; Group-IV (OVX treated) where treatment was started 6 weeks after ovariectomy and continued for 8 weeks. Group-IV was further subdivided into subgroup Iva treated with exenatide (1 μg/kg/d) subcutaneously (SC) [10] and subgroup-IVb treated with 1α OH-D3 orally for 5 days/week (0.25 μg/day) [11].

The drugs used in the study included 1α OH-vitamin D3 (LEO-Denmark), supplied as 0.2 μgm/ml oral drops and exenatide (Byetta; Lilly company-USA) supplied as 1.2 mg prefilled pen. BsALP kit (Randox Laboratories LTD) was used for colorimetric determination of serum BsALP (IU/L).

Ovariectomy was performed in groups II, III and IV according to the technique described by Pytlik et al. [12]. At the end of experiment venous blood samples were collected from the rats tail vein [13]. Samples were incubated at 37°C until blood clotted then centrifuged for separation of serum for measurement of the total and BsALP [14]. Animals were sacrificed at the end of the experiment, one of the hind limbs was separated, the femur was fixed in 10% formalin solution (El-Gomhorya pharmaceutical company) for histopathological examination [15].

Bone histomorphometry was carried out according to Kim et al. [15] method: after fixation of the femur, 30 μm cross-sections were decalcified in 10% nitric acid for 6 hr, then dehydrated with alcohol and embedded in xylene and paraffin and cut into 4 μm thick sections. Each section was stained with Hematoxylin- Eosin (H&E). The cortical thickness and osteocyte number in the femur were measured by quantitative image analysis system. The data were obtained using Leica Qwin 500 image analyzer computer system. The image analyzer consisted of a colored video camera, colored monitor, hard disc of IBM personal computer connected to the microscope, and controlled by Leica Qwin 500 software. The image analyzer was first calibrated automatically to convert the measurement units (pixels) produced by the image analyzer program into actual micrometer units. The cortical bone thickness and osteocyte number were measured in each specimen using the interactive measuring menu with an objective lens of magnification 4 i.e. of total magnification 40. Twenty readings were obtained for each specimen; 10 on the lateral and 10 on the medial cortical bone.

### 2.1. Statistical analysis

Statistical Package of Social Science (SPSS) software version 21 was used. Data was summarized using minimum, maximum, mean, and standard deviation for all quantitative variables. Comparison between groups was performed using one way analysis of variance (ANOVA) test with post hoc least significant difference (LSD) test which was designed for exploration of the differences among means to provide specific information on which means are significantly different from each other. P values < 0.05 were considered significant.

## 3. Results

The changes in the BsALP in the different groups studied are shown in table 1. There was a significant increase in the mean serum level in the OVX non-treated group compared to the control. The levels were nearly normalized in the exenatide prophylactic and treated groups. The BsALP values were comparable ($p > 0.05$) among the prophylactic group and the 2 treated subgroups.

Bone histomorphometry revealed mature bone of the mid shaft of femur in the Sham group-I. Sections obtained from OVX group-II showed multiple osteolytic lesions. Osteoporotic cavities with severe bone loss accompanied by deterioration of bone microarchitecture and fractures were observed with many osteoclasts which appeared as large, multinucleated cells with acidophilic cytoplasm present on the surface of fractured bone undergoing resorption. There were few osteocytes with absence of well organized lamellated appearance of bone matrix (Fig. 1).

Sections obtained from the prophylactic exenatide group showed that most of the bone tissue was immature (woven) with non organized lamellated appearance and many randomly arranged osteocytes, thickening of periosteum and irregular endosteum lining. The presence of irregular space within the bone tissue (resorption canal) indicative of bone remodeling near the endosteum was noted (Fig. 2).

Sections obtained from exenatide treated group-IVa showed irregularity in bone thickness and contained immature (woven) bone. There were many osteocytes that were randomly arranged. Some areas showed mature bone and there was irregularity in the endosteum lining and thickening of the periosteum with partial separation. While in those treated with vitamin D most of the bone sections exhibited Haversian system and a thickened

**Table 1**
Changes in the mean serum bone-specific alkaline phosphatase (BsALP) in the different studied groups (n = 8/group).

| Groups | BsALP (IU/L) in studied groups (n = 8/group) | | |
|---|---|---|---|
| | Mean ± SD | % increase compared to I | % reduction compared to II |
| I (Sham control) | 136.1 ± 6 | – | 64.6% |
| II (OVX non-treated) | 384.4 ± 56.1[a] | 182.6% | – |
| III (prophylactic exenatide) | 144.3 ± 7.5[b] | 6.1% | 62.4% |
| IVa (treated exenatide) | 144.2 ± 5.4[b] | 6% | 62.5% |
| IVb (treated vitamin D) | 145.7 ± 4.1[b] | 7.1% | 62.2% |

BsALP: bone-specific alkaline phosphatase, OVX: ovariectomized.
[a] = Significant at $p < 0.05$ compared to Sham group-I.
[b] = significant at $p < 0.05$ compared to OVX non-treated group-II.

Please cite this article as: O. M. Abu Taleb, M. Y. Wissa, R. K. Abou El Nour et al., Potential effectiveness of exenatide in experimentally-induced osteoporosis, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.06.003

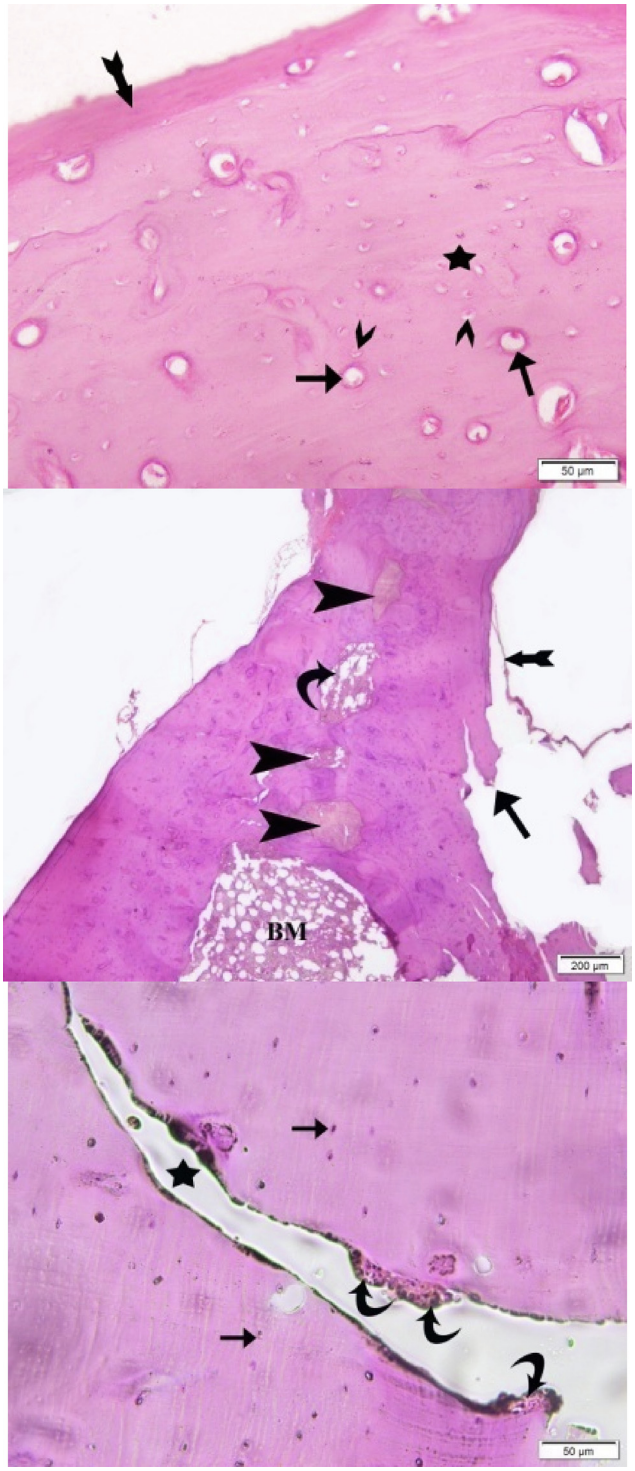


**Fig. 1.** A photomicrograph of the mid shaft of the femur of Sham group-I (transverse section) (UPPER) showing mature bone units (osteons) and Haversian systems (arrows). Between the lamellae are lacunae in which osteocytes are present (arrow heads). Note the External Circumferential Lamellae (arrow with bifid tail) & there are Interstitial Lamellae -(star) (H&E ×200); (MIDDLE) OVX non-treated-II showing multiple osteolytic lesions (arrow heads) accompanied by deterioration of bone microarchitecture (curved arrow). The outer fibrous layer of the periosteum is separated (arrow with bifid tail). Area of bone necrosis is also seen (arrow). (H&E ×40) (LOWER) OVX non-treated group-II showing: Break in continuity of bone (fracture) (star). Note the presence of many osteoclasts (curved arrows). Note the presence of few osteocytes (arrow) with absence of well organized lamellated appearance of bone matrix. (H&E ×200).

periosteum. A small area of immature bone could also be seen (Fig. 3).

Measurement of mean cortical thickness (Table 2) in the studied sections revealed a significant decrease in the OVX non-treated group-II compared to the Sham group-I. The mean cortical thickness of the prophylactic group and the exenatide treated group-IVa or the vitamin D treated group-IVb showed a significant reduction by 10.6%, 16.7% and 9.3% respectively compared to Sham group-I and a significant increase by 38.7%, 29.4% and 40.9% respectively compared to OVX non-treated group-II. The highest mean cortical thickness was observed in vitamin D group-IVb followed by the prophylactic exenatide group-III.

The osteocyte number (Table 3) was significantly reduced in the OVX non-treated group-II by 29% compared to Sham group-I. The mean number of osteocytes of prophylactic group and the exenatide treated group or vitamin D treated group significantly increased by 29%, 26% and 42% respectively compared to Sham group-I, denoting active bone formation, while it showed a significant increase by 91%, 82.6% and 112%, compared to OVX non-treated group-II.

The mean cortical thickness or osteocyte number were comparable ($p > 0.05$) among the prophylactic group and the 2 treated subgroups.

## 4. Discussion

Osteoporosis is a systemic skeletal disease characterized by reduced bone mass, predisposing to fragility and fractures. It affects an enormous number of people, of both sexes and all races, and its prevalence will increase as the population ages [16].

The present work was designed to study the possible effects of exenatide and vitamin D on experimentally-induced osteoporosis in adult ovariectomized female albino rats. Vitamin D was chosen as the standard traditional treatment for osteoporosis. Ovariectomy model for induction of osteoporosis was mentioned by Kalu [17] to be an ideal animal model for postmenopausal women's bone loss in old age. In comparison to Sham group-I, the OVX non treated group-II showed a significant increase in the mean serum level of BsALP, reduction in cortical thickness and number of osteocytes in the examined rat femur bones with the appearance of multiple osteolytic lesions, osteoporotic cavities, area of bone necrosis, breaks in the continuity of bone (fracture) and appearance of many osteoclasts, denoting detrimental effects on bone density and the occurrence of osteoporosis. This is in agreement with the findings of others [7,18–20]who reported marked increase of bone turnover markers and worsening of bone histomorphometry after ovariectomy. Additionally, Shin et al. [21] detected higher levels of BsALP eight weeks after ovariectomy in rats indicating increased bone turnover due to menopause–induced estrogen deficiency. Moreover, Biver and colleagues [22] found the serum level of BsALP higher in osteoporotic rats compared to controls. This could be explained by the depletion of estrogen which largely can be prevented by estrogen replacement [18]. The two most important cell types for bone homeostasis are the bone-resorbing osteoclasts and the bone-forming osteoblasts. Both cell types express estrogen receptors [20]. Ovariectomy model in rats mimics estrogen deficiency in humans; this estrogen deficiency increases osteoclast formation and therefore supports bone resorption. Shortage of estrogen also induces apoptosis of osteoblasts [23]. This leads to an imbalance between osteoblastic bone formation and osteoclastic bone resorption, favoring bone loss and resulting in marked osteoporotic changes and bone fractures [24].

Please cite this article as: O. M. Abu Taleb, M. Y. Wissa, R. K. Abou El Nour et al., Potential effectiveness of exenatide in experimentally-induced osteoporosis, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.06.003

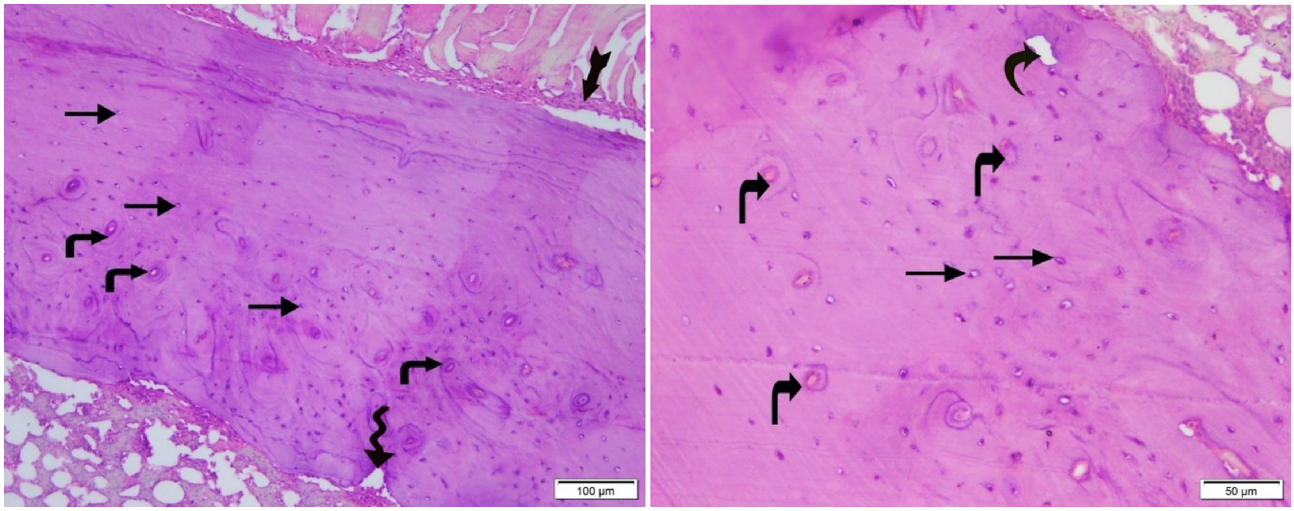


**Fig. 2.** A photomicrograph of the mid shaft of the femur of prophylactic exenatide group-III (LEFT) showing immature (woven) bone which display non organized lamellated appearance (right angle arrows). There are many osteocytes (arrows) that randomly arranged. There is thickening in outer fibrous layer of the periosteum (arrow with bifid tail). Note the presence of irregular endosteum lining the bone (spiral arrow) (H&E ×100). (RIGHT) prophylactic exenatide group-III showing: Immature (woven) bone (right angle arrows). There are many osteocytes (arrows) that are randomly arranged. Note the presence of irregular space (curved arrow) within the bone tissue (resorption canal) near the endosteum. (H&E ×200).

Singer and Eyre [25]claimed that after menopause bone resorption markers increase due to estrogen deficiency and bone formation markers increase as a compensatory mechanism to fill the higher number of resorption cavities, and as a result, there is an increase in their serum levels. Serum level of BsALP significantly increased in postmenopausal women and in those who underwent ovariectomy denoting the imbalance of bone homeostasis and the development of osteoporosis [26]. The significant elevation of BsALP in ovariectomized rats was reported by others [27,28].

Cortical and trabecular morphometric parameters and histopathology of femur bones were severely altered by ovariectomy with reduction of bone cortical thickness and osteocyte number, appearance of osteolytic lesions and derangement of the bone Haversian system [27,28]. Also, Palumbo et al. [29] detected obvious bone mass reduction in ovariectomized rats. Similarly, Yoon et al. [30] observed that cortical bone mineral density, cortical thickness and osteocyte number were significantly lower in the ovariectomized rats compared to normal control.

This study also showed that vitamin D treated rats showed a significant reduction in serum level of BsALP and improvement of bone histomorphometry parameters with the appearance of well organized Haversian system and thickened periosteum compared to OVX non treated group-II. Only small areas of immature bone were seen. This is in agreement with the findings from other studies [31–33] who reported that treatment with vitamin D markedly improved bone mineral density and cortical thickness in osteoporotic rats. This could be explained by the fact that inadequate vitamin D intake over long periods of time can lead to bone demineralization. Vitamin D deficiency leads to decreased calcium absorption and ultimately the release of calcium from the bones in order to maintain circulating calcium concentrations. Continuous bone turnover and resorption weakens the architecture of bones and increases fracture risk via secondary hyperparathyroidism ultimately leading to the development of osteomalacia and osteoporosis [32].

This study also showed that exenatide either as a prophylactic or a treatment strategy in rats lead to a significant reduction in serum level of BsALP and improvement of bone histomorphometry parameters compared to OVX non-treated group-II. The improvement of serum level of BsALP was even comparable to Sham group-I. The examined sections showed many osteocytes randomly arranged with the appearance of mature bone Haversian system. This is in agreement with Yamada et al. [34]who mentioned that GLP-1 receptor knockout mice had increased bone breakdown, suggesting that the GLP-1 signaling pathway had an antiresorptive effect. Nuche et al. [4] claimed that activation of GLP-1 receptors has been shown to promote bone formation in streptozotocin-induced type 2 diabetic and fructose-induced insulin resistant rats, indicating an anabolic effect. Furthermore, Ma et al. [35] stated that exenatide prevented the loss of bone mass in OVX rats, enhanced bone strength, and prevented the deterioration of trabecular microarchitecture. They explained the anti-osteoporotic effect of exenatide by the fact that it not only inhibited bone resorption by increasing the osteoprotegerin (OPG)/receptor activator of NF-kB ligand (RANKL) ratio, but also promoted bone formation. They added that exenatide had a direct dual anti-osteoporotic effect in aging and estrogen deficiency-induced osteopenia and that exenatide treatment dramatically increased bone mineral density and protected against the deterioration of trabecular bone structure. Furthermore in humans, it has been suggested that aging lowers the levels of osteoblast differentiation and enhances adipogenesis [36]. The differentiation of bone marrow mesenchymal stem cells (BMMSCs) to osteoblasts or adipocytes may be a crucial process in bone remodeling. GLP-1 receptors are expressed on BMMSCs and stimulate their proliferation and differentiation to osteoblasts and inhibit differentiation to adipocytes in human. Thus, exenatide is claimed to promote osteogenesis and suppress adipogenesis via its target receptor [37]. This is in contrast to Bollag et al. [38] who claimed that GLP-1 receptor agonists have no effect on bone homeostasis as GLP-1 receptors were not present on osteoblasts or osteoclasts.

Osteoporosis is characterized by decreased trabecular and cortical bone formation relative to resorption, resulting in bone fragility and increased risk of fractures. A limited number of approved therapeutic molecules are available to activate bone formation. Therefore, there is a need for anabolic drugs that promote bone matrix formation [39]. With the emergence of novel antidiabetic treatments, prospective studies are required to evaluate their effects on bone health and identify which treatments may require co-treatment with anti-osteoporosis medications [40]. Taking into consideration its preferable mechanism of action, tolerability and safety, exenatide has a promising potential as an alternative to

Please cite this article as: O. M. Abu Taleb, M. Y. Wissa, R. K. Abou El Nour et al., Potential effectiveness of exenatide in experimentally-induced osteoporosis, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.06.003

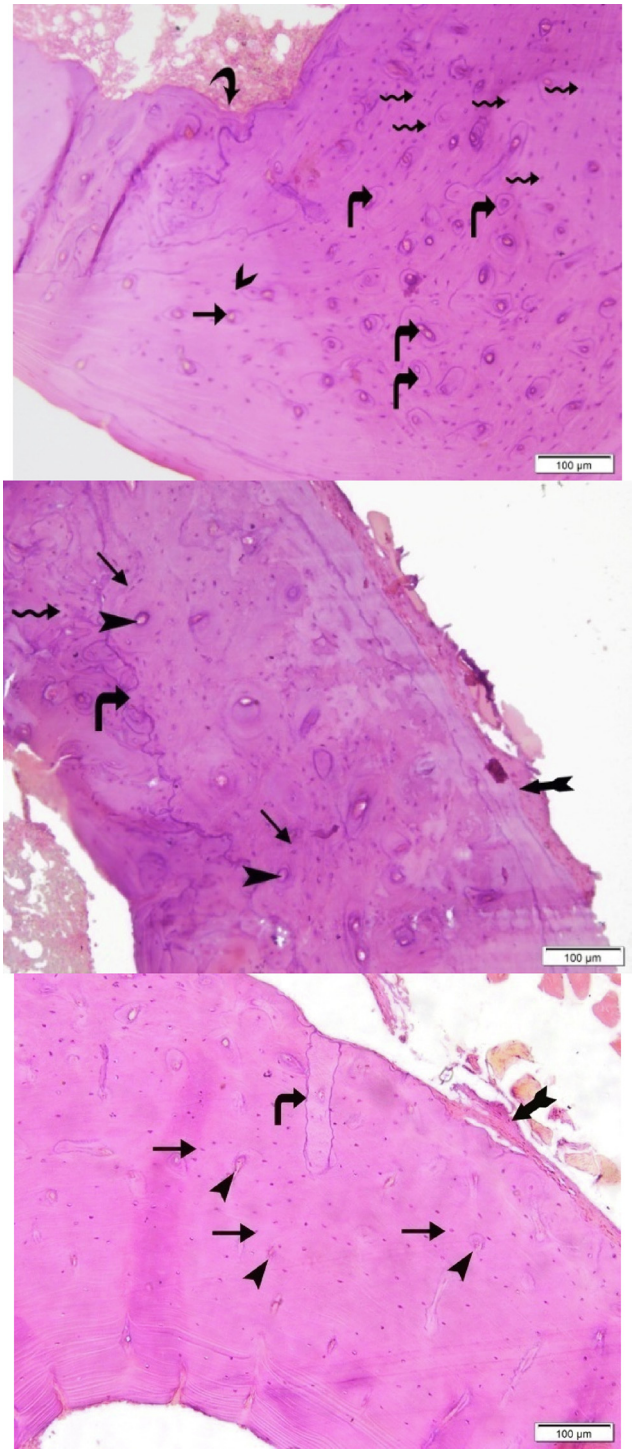


**Fig. 3.** (UPPER) A photomicrograph of the mid shaft of the femur of exenatide treated group-IVa showing an irregularity in the thickness of the bone containing immature (woven) bone (right angle arrows). There are many osteocytes (spiral arrows) randomly arranged. Note the presence of mature bone showing Haversian system formed of central vascular canal (arrow) and concentrically arranged bone lamellae with osteocytes inside their lacunae (arrow head). Note the presence of irregular endosteum (curved arrow). (H & E ×100). (MIDDLE) exenatide treated group-IVa showing immature (woven)bone (right angle arrows). There are many osteocytes randomly arranged (spiral arrow). Note the presence of Haversian system which is formed of Haversian Canal (arrow heads) and concentrically arranged bone lamellae with osteocytes inside their lacunae (arrows). Thickened outer fibrous layer of periosteum (arrow with bifid tail) can also be seen with partial separation (H&E ×100). (LOWER) A photomicrograph of the mid shaft of the femur of vitamin D treated group-IVb showing Haversian Canals (arrow heads) and concentrically arranged bone lamellae around the Haversian canal with osteocytes inside their lacunae (arrows). Thickened periosteum can also be seen (arrow with bifid tail). Note the presence of a small area of an immature bone (right angle arrow). (H&E ×100).

**Table 2**
Changes in the mean cortical thickness (µm) in the different studied groups (n = 8/group).

| Groups | Cortical thickness (µm) in studied groups (n = 8/group) | | |
|---|---|---|---|
| | Mean ± SD | % reduction compared to I | % increase compared to II |
| I (Sham control) | 581.02 ± 5.41 | – | 55.3% |
| II (OVX non-treated) | 374.74 ± 6.83[a] | 36% | – |
| III (prophylactic exenatide) | 519.02 ± 16.10[a,b] | 10.6% | 38.7% |
| IVa (treated exenatide) | 484.02 ± 9.6[a,b] | 16.7% | 29.4% |
| IVb (treated vitamin D) | 527.77 ± 21.97[a,b] | 9.3% | 40.9% |

OVX: ovariectomized.
[a] = Significant at $p < 0.05$ compared to Sham group-I.
[b] = significant at $p < 0.05$ compared to OVX non-treated group-II.

**Table 3**
Changes in the mean number of osteocytes in the different studied groups (n = 8/group).

| Groups | Number of osteocytes in studied groups (n = 8/group) | | |
|---|---|---|---|
| | Mean ± SD | % change compared to I | % change compared to II |
| I (Sham control) | 34.5 ± 5.48 | – | 49% |
| II (OVX non-treated) | 23.1 ± 2.92[a] | 29% | – |
| III (prophylactic exenatide) | 44.1 ± 5.36[a,b] | 29% | 91% |
| IVa (treated exenatide) | 42.6 ± 9.29[a,b] | 26% | 82.6% |
| IVb (treated vitamin D) | 48.9 ± 2.84[a,b] | 42% | 112% |

OVX: ovariectomized.
[a] = Significant at $p < 0.05$ compared to Sham group-I.
[b] = significant at $p < 0.05$ compared to OVX non-treated group-II.

traditionally used anti-osteoporotic drugs. Exenatide improves trabecular bone mass by increasing bone formation and could protect against the development of skeletal complications associated with type II diabetes mellitus [41].

*In conclusion,* exenatide represents a potentially promising protective and therapeutic tool in the management of postmenopausal osteoporosis. Additionally, it can be deduced that exenatide, either as a prophylactic or a treatment strategy possesses potent anti-osteoporotic effects against osteoporosis-induced by ovariectomy in rats. They are as effective as vitamin D for improving bone mineral density. This drug provides a new opportunity for developing novel therapeutic approaches for treatment of osteoporosis. However, further clinical trials are needed to prove its effectiveness in humans with osteoporosis. It is further recommended to determine the therapeutic effectiveness of use of exenatide in diabetic patients with osteoporosis and to also investigate the effect of its combination with other conventional drugs used for treatment of osteoporosis especially in diabetic patients.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of Competing Interest

None.

## References

[1] Gheita TA, Hammam N. Epidemiology and awareness of osteoporosis: a viewpoint from the Middle East and North Africa. Int J Clin Rheumatol 2018;13 (3):134–47.

[2] Gates BJ, Sonnett TE, Duvall CA, Dobbins EK. Review of osteoporosis pharmacotherapy for geriatric patients. Am J Geriatr Pharmacother 2009;7:293–323.
[3] Ma X, Hui H, Liu Z, He G, Hu J, Meng J, et al. Poly-GLP-1, a novel long-lasting glucagon-like peptide-1 polymer, ameliorates hyperglycaemia by improving insulin sensitivity and increasing pancreatic beta-cell proliferation. Diabetes Obes Metab 2009;11(10):c953–65.
[4] Nuche-Berenguer B, Moreno P, Portal-Nunez S, Dapia S, Esbrit P, Villanueva-Penacarrillo ML. Exendin-4 exerts osteogenic actions in insulin-resistant and type 2 diabetic states. Regul Pept 2010;159(1–3):61–6.
[5] Brubaker PL. Incretin-based therapies. Mimetics versus protease inhibitors. Trends Endocrinol Metab 2007;18(6):240–5.
[6] Weitzmann NM, Pacifici R. Estrogen deficiency and bone loss: an inflammatory tale. J Clin Invest 2006;116:1186–94.
[7] Osman AS, Labib DA, Omar AI. Do acid suppressive drugs (pantoprazole and ranitidine) attenuate the protective effect of alendronate in estrogen-deficient osteoporotic rats? The Egyptian. Rheumatologist 2018;40(2):99–106.
[8] Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–705.
[9] Holscher C. Potential role of glucagon-like peptide-1(GLP-1) inneuroprotection. CNS Drugs 2012;26:871–82.
[10] Kolterman OG, Kim DD, Shen L, Ruggles JA, Nielsen LL, Fineman MS, et al. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. Am J Health SystPharm 2005;62(2):173–81.
[11] Lindgren JU, Lindholm TS. Effect of 1-alpha-hydroxyvitamin D3 on osteoporosis in rats induced by oophorectomy. Calcif Tiss Intl 1979;27:161–4.
[12] Pytlik M, Kaczmarczyk-Sedlak I, Sliwiński L, Janiec W, Rymkiewicz I. Effect of concurrent administration of alendronate sodium and retinol on development of changes in histomorphometric parameters of bones induced by ovariectomy in rats. Pol J Pharmacol 2004;56:817–24.
[13] Schermer S. The blood morphology of laboratory animals 3rd edition.1967;137–69.
[14] Naik RB, Gosling P, Price CP. Comparative study of alkaline phosphatase isoenzyme, bone histology and skeletal radiography in dialysis bone disease. British Med J 1977;1:1307–10.
[15] Kim JH, Mosekilde L, Duan Y, Zhang XZ, Tornvig L, Thomsen JS, et al. The structural and hormonal basis of sex differences in peak appendicular bone strength in rats. J Bone Miner Res 2003;18:150–5.
[16] Chang W, Friedman SM. Hip fracture management. Hosp Med Clin 2013;2(3):e399–421.
[17] Kalu DN. The ovariectomized rat model of postmenopausal bone loss. Bone Miner 1991;15(3):175–91.
[18] Couse JF, Lindzey J, Grandien K, Gustafsson JA, Korach KS. Tissue distribution and quantitative analysis of estrogen receptor α (ERα) and estrogen receptor β (ERβ) mRNA in the wild-type and ERα-knockout mouse. Endocrinology 1997;138:4613–21.
[19] Ankrom MA, Patterson JA, d'Avis PY, Vetter UK, Blackman MR, Sponseller PD, et al. Age-related changes in human oestrogen receptor α function and levels in osteoblasts. Biochem J 1998;333:787–94.
[20] Bodine PV, Henderson RA, Green J, Aronow M, Owen T, Stein GS, et al. Estrogen receptor α is developmentally regulated during osteoblast differentiation and contributes to selective responsiveness of gene expression. Endocrinology 1998;139:2048–57.
[21] Shin YH, Cho DC, Yu SH, Kim KT, Cho HJ, Sung JK. Histomorphometric analysis of the spine and femur in ovariectomized rats using micro-computed tomographic scan. J Korean Neurosurg Soc 2012;52:1–6.
[22] Biver E, Chopin F, Coiffier G, Brentano TF, Bouvard B, Garnero P, et al. turnover markers for osteoporotic status assessment. A systematic review of their diagnostic values at baseline in osteoporosis. Joint Bone Spine 2012;79(1):20–5.
[23] Manolagas SC, Kousteni S, Jilka RL. Sex steroids and bone. Recent Prog Horm Res 2002;57:385–409.
[24] McNamara LM. Perspective on post-menopausal osteoporosis establishing an interdisciplinary understanding of the sequence of events from the molecular level to whole bone fractures. J R Soc Interface 2010;7(44):353–72.
[25] Singer FR, Eyre DR. Using biochemical markers of bone turnover in clinical practice. Clev Cl J 2008;75:739–50.
[26] Pedrazzoni M, Alfano FS, Girasole G, Giuliani N, Fantuzzi M, Passeri M. Clinical observations with a new specific assay for bone alkaline phosphatase: a cross-sectional study in osteoporotic and pagetic subjects and a longitudinal evaluation of the response to ovariectomy, estrogens, and bisphosphonates. Calcif Tissue Int 1996;59(5):334–8.
[27] Hatem M, Mohammed MA, Salim SA, Kamal EH. The antidepressant bupropion exerts alleviating properties in an ovariectomized osteoporotic rat model. Acta Pharmacol Sin 2015;36(2):209–20.
[28] Mukaiyama K, Kamimura M, Uchiyama S, Ikegami S, Nakamura Y, Kato H. Elevation of serum alkaline phosphatase (ALP) level in postmenopausal women is caused by high bone turnover. Aging Clin Exp Res 2015;27(4):413–8.
[29] Palumbo C, Ferretti M, Bertoni L, Cavani F, Resca E, Casolari B, et al. Influence of ferutinin on bone metabolism in ovariectomized rats. I:role in preventing osteoporosis. J Bone Miner Metab 2010;27:538–45.
[30] Yoon KH, Cho DC, Yu SH, Kim KT, Jeon Y, Sung JK. The change of bone metabolism in ovariectomized rats: analyses of micro CT scan and biochemical markers of bone turnover. J Korean Neurosurg Soc 2012;51:323–7.
[31] Lambrinoudaki I, Chan DT, Lau CS, Wong RW, Yeung SS, Kung AW. Effect of calcitriol on bone mineral density in premenopausal Chinese women taking chronic steroid therapy. A randomized, double-blind, placebo controlled study. J Rheumatol 2000;27:1759–65.
[32] Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocrinol Rev 2001;22:477–501.
[33] Meier C, Meinhardt U, Greenfield JR, De Winter J, Nguyen TV, Dunstan CR, et al. Serum cathepsin K concentrations reflect osteoclastic activity in women with postmenopausal osteoporosis and patients with Paget's disease. Clin Lab 2006;52:1–10.
[34] Yamada C, Yamada Y, Tsukiyama K, Yamada K, Udagawa N, Takahashi N, et al. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. Endocrinology 2008;149(2):574–9.
[35] Ma X, Meng J, Jia M, Bi L, Zhou Y, Wang Y, et al. Exendin-4, a glucagon-like peptide-1 receptor agonist, prevents osteopenia by promoting bone formation and suppressing bone resorption in aged ovariectomized rats. J Bone Mineral Res 2013;28(7):1641–52.
[36] Abdallah BM, Kassem M. New factors controlling the balance between osteoblastogenesis and adipogenesis. Bone 2012;50(2):540–5.
[37] Lee HM, Joo BS, Lee CH, Kim HY, Ock JH, Lee YS. Effect of glucagon-like peptide-1 on the differentiation of adipose-derived stem cells into osteoblasts and adipocytes. J Menopausal Med 2015;21(2):93–103.
[38] Bollag RJ, Zhong Q, Phillips P, Min L, Zhong L, Cameron R, et al. Osteoblast-derived cells express functional glucose-dependent insulinotropic peptide receptors. Endocrinology 2000;141(3):1228–35.
[39] Marie PJ, Kassem M. Osteoblasts in osteoporosis: past, emerging, and future anabolic targets. Eur J Endocrinol 2011;165:1–10.
[40] Picke AK, Campbell G, Napoli N, Hofbauer LC, Rauner M. Update on the impact of type 2 diabetes mellitus on bone metabolism and material properties. Endocr Connect 2019;8(3):R55–70.
[41] Pereira M, Gohin S, Roux JP, Fisher A, Cleasby ME, Mabilleau G, et al. Exenatide improves bone quality in a murine model of genetically inherited type 2 diabetes mellitus. Front Endocrinol (Lausanne) 2017;8:327.

Please cite this article as: O. M. Abu Taleb, M. Y. Wissa, R. K. Abou El Nour et al., Potential effectiveness of exenatide in experimentally-induced osteoporosis, The Egyptian Rheumatologist, https://doi.org/10.1016/j.ejr.2019.06.003