Effect of Blocking L-Type Calcium Channels on Bone in Ovariectomy Model of Osteoporosis in Rats

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Abstract

Background: Calcium channel blockers are widely used in many cardiovascular diseases. These diseases are common in old age persons suffering from osteoporosis. However, the impact of calcium channel blockade on osteoporosis is still controversial. This study investigated effect of calcium channel blockers on bone metabolism in an ovariectomized rat model of osteoporosis.

Methods: 50 female white albino rats were divided into 5 equal groups: Sham operated control, ovariectomized, Ovariectomized + Diltiazem treatment, Ovariectomized + Verapamil treatment and Ovariectomized + Amlodipine treatment groups. At the end of the experiment, femora were examined for length, dry weight wet weight, ash weight calcium and phosphate levels. Serum concentrations of calcium, phosphate, osteocalcin (BGP), Carboxy-terminal collagen crosslinks (CTX) and alkaline phosphatase activity (ALP) were measured.

Results: In ovarictomized rats, treatment for eight weeks with Diltiazem, Verapamil or Amlodipine calcium channel blockers induced a significant increase in bone-dry weight, ash weight and bone calcium content reflecting an increase in bone density and mineral content when compared with control groups. They also significantly decreased serum concentrations of calcium, phosphate, osteocalcin, carboxy-terminal collagen crosslinks and alkaline phosphatase. However, amlodipine treated animals had significantly lower bone-dry weight, ash weight and bone calcium content and significantly higher serum concentrations of calcium, phosphate, osteocalcin, carboxy-terminal collagen crosslinks and alkaline phosphatase when compared with the other two CCB groups.

Conclusion: All the examined types of calcium channel blockers have possible beneficial effects in osteoporotic animals. The benzothiazepine (Diltiazem) and phenylalkylamines (verapamil) subtypes of calcium channel blockers induced a significant improvement in all bone markers. The dihydropyridine (Amlodipine) subtype had similar protective effect however, it was significantly lower than the other two CCBs.

Key Words: Calcium channel blockers – Osteoporosis – Ovariectomy – Verapamil – Diltiazem – Amlodipine.

Introduction

OSTEOPOROSIS is now considered as the most common metabolic bone disorder. Overtime, it leads to increased rate of bone turnover, loss of normal bone architecture, disturbed proper mineralization and subsequently increasing the incidence of fractures [1]. It has been reported that the critical balance between the bone forming cells “osteoblasts” and the bone resorbing cells “osteoclasts” is what determines bone mass [2].

Aging is typically accompanied by decreased power of movement and several hormonal changes. These two factors are considered the main contributors to the development of osteoporosis in elderly patients among other less common factors and diseases [3].

Post-menopausal ovarian hormone deficiency is considered the most common cause of age related osteoporosis is. After menopause, there is increased bone turnover with an imbalance between bone formation and bone loss leading to net bone loss [4]. This postmenopausal osteoporosis has become a major health problem with significant morbidity and mortality [5].

The ovarictomized (OVX) model of osteoporosis in the rat is a useful method to study the effectiveness of different agents for the prevention and for the treatment of bone loss [6].

Several clinical and experimental studies have linked hypertension to an increase in the rate of loss in bone mineral density [7,8,9]. Due to the high prevalence of hypertension it was reported that anti-hypertension medications are the top prescribed medications worldwide. Calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors are generally the most widely prescribed drugs for the treatment of hypertension [10].
Calcium channel blockers (CCBs) are used in the treatment of many diseases, including hypertension, arrhythmia, angina pectoris, myocardial infarction, peripheral vascular diseases, etc. [11].

Five classes of compounds have been identified as calcium channel blockers: Phenylalkylamines, dihydropyridines, benzothiazepines, diphenylpiperazines, and a diarylaminopropylamine. At present, verapamil (a phenylalkylamines); diltiazem (a benzothiazepine); and several (dihydropyridines) as nifedipine, amlodipine, felodipine, and nicardipine, nisoldipine, are approved for clinical use in the United States [12].

The calcium channel family has been found to be largely expressed in bone cells. Hence, it is suggested that modulation of their activity can affect bone metabolism [13]. Moreover, it was reported that, the L-type calcium channels are probably the major source of calcium signaling inside osteoblasts. This finding raised the question whether the blockade of calcium channels with their specific antagonists, could have adverse effects on bone metabolism [14].

Several clinical and experimental trials had been performed to show the effects of CCBs on bone [15-17]. However, the results were contradictory and non-conclusive.

The aim of this study was to investigate the effect of blocking L-Type calcium channels; will have either a positive or a negative effect on bone loss and different bone markers in an ovariectomized rat model of osteoporosis.

Material and Methods

Animals:

In the period from 25 August 2016 to 3rd January 2017, at the Physiology Department, Faculty of Medicine, Zagazig, the current study was performed using 50 female adult albino rats 12-15 weeks old with body weight 200-250gm. Animals were obtained from the animal house of Faculty of Veterinary Medicine of Zagazig University and were kept in clean steel wire cages (10/cage) in the Physiology Research Laboratory in Faculty of Medicine of Zagazig University under hygienic conditions.

Rats were kept on normal diet, which consisted of mixed commercial rat chow supplied in separate clean containers. All animals were kept at room temperature, on a 12-hour light/dark cycle with free access to water. The rats were allowed to accommodate to laboratory conditions for two weeks before the start of experiments. Rats were numbered and randomized (according to their body weight) into five groups, each containing 10 rats:

- Group 1 = Sham-operated control Group (SHAM).
- Group 2 = Ovariectomized group with no medication (OVX).
- Group 3 = Ovariectomized group plus dihydropyridine CCB (Amlodipine) in a dose of 0.5mg/ rat/day orally (OVX+A) [18].
- Group 4 = Ovariectomized group plus phenylalkylamines CCB (Verapamil) in a dose of 8mg/kg orally (OVX+V) [19].
- Group 5 = Ovariectomized group plus benzothiazepine CCB (Diltiazem) in a dose of 1mg/kg IP (OVX+D) [20].

After the ovariectomy or sham surgeries, all the groups were allowed to recover for 2 weeks. Then they were treated with the study drugs or vehicle for eight weeks then all animals were anaesthetized, sacrificed to obtain blood and bone samples.

At the end of the experiment, femora were examined for length, dry weight wet weight, ash weight calcium and phosphate levels. Serum concentrations of calcium, phosphate, osteocalcin, Carboxy-terminal collagen crosslinks (CTX) and alkaline phosphatase activity (ALP) were measured.

Ovariectomy:

Ovariectomy was performed under anesthesia with a thiopental sodium injection 20mg/kg, intraperitoneally. Bilateral incisions were performed in rats at both right and left flanks under ether anesthesia. The peri-ovarian fatty tissue was identified and exteriorized. For prevention of subsequent hemorrhage, the arterial blood vessels were clamped by an artery forceps. Above the clamped area, both ovaries were removed out by cutting using a scalpel. Muscles and skin were stitched separately.

After the ovariectomy, the rats were given ibuprofen 10mg/kg ibuprofen as an analgesic for 2 days and 1.75mg/kg amoxicillin to prevent to infections [21].

Sham Group: Bilateral incisions were performed in rats at both right and left flanks under the same anesthesia. Ovaries were exposed then muscles and skin were stitched separately as above but without removing the ovaries [21].
Sampling of blood:
At the end of the experimental period and after overnight fasting, at 8:00a.m, blood samples (8ml/rat) were obtained, allowed to clot for 2 hours at room temperature before centrifugation for 20 minutes at approximately 500 rpm [22]. The separated serum was stored at –20°C until the time of measurement.

Bone mineral content:
After disecting both femurs, the soft tissues around the femur bones were removed and the femur was weighed (Wet Weight). The femur bone was dried overnight at 100°C then weighed again (Dry Weight).

The femur was then incenerated for 12 hours at 1000°C in Muffle apparatus to obtain the ash. The ash was weighed, solubilized with 6 N HCL and quantitatively transferred into volumetric flask then completed to 100ml with 6 N HCL. The solutions were used for analysis of calcium and phosphorus content in bone ash [23].

Laboratory analysis:
Estimation of Serum Osteocalcin (BGP) and Carboxy-terminal collagen crosslinks (CTX) levels were done by enzyme-linked immune-sorbent assay (ELISA) method using ELISA kits supplied by USCN Life Science Inc. - Wuhan, Hubei, PRC.

Estimation of serum alkaline phosphatase activity:
Activity of alkaline phosphatase was determined by a colorimetric method using kits purchased from USCN Life Science Inc. - Wuhan, Hubei, PRC.

Estimation of serum calcium and phosphate levels:
Concentrations of calcium and phosphate in serum samples were determined spectrophotometrically using specific diagnostic reagent kits (BioMérieux, France).

Estimation of bone calcium and phosphate content:
Calcium and phosphate content in bone ash was determined using atomic absorption spectrophotometer [23].

Statistical analysis:
Results are presented as mean ± standard deviation. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences, version 22 (IBM SPSS Inc., Chicago, IL, United States).

Repeated measures of analysis of variance (ANOVA) statistical analysis were applied followed by the least significant difference (LSD) post hoc test. p-value <0.05 was considered to be statistically significant.

Results
Body weight:
In this study, it was found that initial body weight (mean ± SD) was 215.1 ± 16.190, 219.1 ± 17.387, 217.0±21.985, 214.7±21.884 and 210.8±15.576 in SHAM, OVX, OVX+D, OVX+V and OVX+A groups respectively.

While, final body weight was 289.8±27.495, 294.6±32.239, 280.4±19.213, 285.6±8.746 and 282.9±21.641 in the same groups respectively.

Final body weight was significantly higher than initial body weight in all groups. However, there was no significant difference in body weight between the diverse groups at the end of the study period (Fig. 1).

![Body weight](image)

Sham operated control (SHAM). Ovariectomized (OVX), Ovariectomized + Diltiazem treatment (OVX+D), Ovariectomized + Verapamil treatment (OVX+V) and Ovariectomized + Amlodipine treatment (OVX+A) groups.

Fig. (1): Initial and final body weights in all study groups.

Serum and bone minerals:
Ovariectomy (OVX) induced a significant increase in serum calcium and phosphate levels when compared to control (SHAM) Group (p<0.001, p<0.001). Calcium channel blockade by Verapamil (OVX+V) and diltiazem (OVX+D) treatment reversed these effects and was apple to induce a significant reduction in serum calcium (p<0.001, p<0.001), and phosphate levels (p<0.001, p<0.001) when compared to OVX group. Moreover, both verapamil and diltiazem treated groups were insigificantly different from control (SHAM) group. Amlodipine, treatment partially reversed the effects...
of ovariectomy on serum calcium and phosphate, which were significantly lower than OVX group ($p<0.028$, and was significantly higher than SHAM, OVX+D and OVX+V groups ($p<0.001$, $p<0.001$, and $p<0.001$) (Table 1).

Ovariectomy (OVX) induced a significant decrease in bone ash calcium levels when compared to control (SHAM) Group ($p<0.001$). Calcium channel blockade by Verapamil (OVX+V), and diltiazem (OVX+D) treatment reversed these effects and was apple to induce a significant increase in bone ash calcium ($p<0.001$, and $p<0.001$) when compared to OVX group. Moreover, both verapamil and diltiazem treated groups were insignificantly different from control group. Amlodipine (OVX+A) treatment partially corrected the effects of ovariectomy on bone ash calcium, which was higher than OVX group but, it was still significantly lower than SHAM, OVX+D and OVX+V groups ($p<0.001$, $p<0.001$, and $p<0.001$) (Table 1).

Ovariectomy either alone or in the presence of three types of calcium channel blockers had no significant effect on bone ash phosphate levels when compared to sham operated control group (Table 1).

| Table 1: Levels of serum calcium (Ca), serum phosphorous (P), bone calcium (Ca) and bone phosphorous (P) in all groups. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Serum Ca (mg/dL) | Serum P (mg/dL) | Bone Ca (mg/g ash) | Bone P (mg/g ash) |
| SHAM            | 9.93            | ±0.755           | 3.33            | ±0.603          | 11.21           | ±0.480          | 6.58            | ±0.323          |
| OVX             | 13.94 a         | ±0.842           | 6.10 a          | ±0.242          | 8.24 a          | ±0.527          | 6.27            | ±0.410          |
| OVX+D           | 9.84 b, a, b, c | ±0.709           | 3.09 b, a, b, c | ±0.391          | 11.03 b, a, b, c| ±0.580          | 6.23            | ±0.692          |
| OVX+V           | 9.96 b, a, b, c | ±0.580           | 3.23 b, a, b, c | ±0.372          | 10.85 b, a, b, c| ±0.615          | 6.21            | ±0.609          |
| OVX+A           | 11.42 a         | ±1.684           | 4.96 a          | ±0.903          | 9.82 a          | ±1.690          | 6.35            | ±0.512          |

All Data expressed as Mean ± SD, in Sham operated control (SHAM), Ovariectomized (OVX), Ovariectomized + Diltiazem treatment (OVX+D), Ovariectomized + Verapamil treatment (OVX+V) and Ovariectomized + Amlodipine treatment (OVX+A) groups.

A: Significant vs. control (SHAM) group.  
B: Significant vs. OVX group.  
C: Significant vs. OVX+L group.

Bone turn over markers:

Ovariectomy (OVX) induced a significant increase in serum Osteocalcin (BGP), Carboxy-terminal collagen crosslinks (CTX) and Alkaline Phosphatase activity (ALP) levels when compared to control (SHAM) Group ($p<0.001$, $p<0.001$ and $p<0.001$). Calcium channel blockade by Verapamil (OVX+V), and diltiazem (OVX+D) treatment reversed these effects and was apple to induce a significant reduction in serum Osteocalcin (BGP) ($p<0.001$ and $p<0.001$), Carboxy-terminal collagen crosslinks (CTX) ($p<0.001$ and $p<0.001$) and Alkaline Phosphatase activity (ALP) ($p<0.001$ and $p<0.001$) when compared to OVX group. Moreover, both verapamil and diltiazem treated groups were insignificantly different from control group. Amlodipine (OVX+A) treatment partially corrected the effects of ovariectomy on serum GBP, CTX and ALP, and their values were significantly lower than OVX group ($p<0.001$), but they were still significantly higher than SHAM, OVX+D and OVX+V groups ($p<0.001$, $p<0.001$, and $p<0.001$) (Table 2).

| Table (2): Serum levels of bone turn over markers, Osteocalcin (BGP), Carboxy-terminal collagen crosslinks (CTX) and Alkaline Phosphatase (ALP) in all study groups. |
|-----------------|-----------------|-----------------|
| BGP (ng/ml)     | CTX (ng/ml)     | ALP (ng/ml)     |
| SHAM            | 701.1           | 58.8            | 122.5           |
| ±131.984        | ±6.017          | ±20.898         |
| OVX             | 1195.5 a        | 83.6 a          | 186.7 a         |
| ±202.254        | ±13.227         | ±40.384         |
| OVX+D           | 731.1 b, a, b, c| 57.3 b, a, b, c| 119.3 b, a, b, c|
| ±184.876        | ±6.216          | ±17.639         |
| OVX+V           | 751.7 b, a, b, c| 60.2 b, a, b, c| 123.3 b, a, b, c|
| ±201.260        | ±6.026          | ±15.720         |
| OVX+A           | 976.8 a         | 99.6 a          | 150.8 a         |
| ±200.532        | ±7.219          | ±35.042         |

All Data expressed as Mean ± SD, in Sham operated control (SHAM), Ovariectomized (OVX), Ovariectomized + Diltiazem treatment (OVX+D), Ovariectomized + Verapamil treatment (OVX+V) and Ovariectomized + Amlodipine treatment (OVX+A) groups.

A: Significant vs. control (SHAM) group.  
B: Significant vs. OVX group.  
C: Significant vs. OVX+D group.

Bone morphometry:

Ovariectomy either alone or in the presence of three types of calcium channel blockers had no significant effect on femur length or femur wet weight when compared to sham operated control group (Table 3).

Ovariectomy induced a significant reduction femur dry weight and femur ash weight when compared to control (SHAM) Group ($p<0.001$, and $p<0.001$). Calcium channel blockade by Verapamil (OVX+V) and diltiazem (OVX+D) treatment reversed these effects and was apple to induce a significant increase femur dry weight ($p<0.001$ and $p<0.001$), and femur ash weight ($p<0.001$ and $p<0.001$) when compared to OVX group. Moreover,
both verapamil and diltiazem treated groups were insignificantly different from control group. Amlodipine (OVX+A) treatment partially corrected the effects of ovariectomy on bone ash weight, which was higher than OVX group but, they were still significantly lower than SHAM, OVX+D and OVX+V groups (p<0.00 1, p<0.00 1, and p<0.00 1). Femur dry weight in amlodipine group was higher than OVX group but, it was still lower than control, verapamil and diltiazem treated groups. However, these differences did not reach statistical significance (Table 3).

In this study, it was found that ovariectomy (OVX group) induced marked changes in bone parameters indicating the development of osteoporosis when compared to sham operated control group. Eight weeks after ovariectomy there was no significant changes in femur, length or femur wet weights but there was a significant reduction in femur dry weight and ash weight. This indicates decreased mineral density of bone, which was proved by the significant reduction in bone ash calcium levels. These bone changes were reflected on serum parameters, as there was a significant increase in serum calcium, phosphate, and carboxy-terminal collagen crosslinks (CTX) indicating increased osteoclastic activity and increased bone resorption. Moreover, there were a significant increase in serum osteocalcin (BGP) and alkaline phosphatase activity (ALP) levels, which are indicators of osteoplastic activity.

These results agree with other studies, which documented the effects of ovariectomy on bones. Moreover, in a rat model of osteoporosis, the effects of ovariectomy were examined in detail, significant bone loss after ovariectomy occurs in the proximal tibial metaphysis after 14 days, in the lumbar vertebral body after 60 days, and in the femoral neck after 30 days.

In this study, it was found that treatment of ovariectomized rats with three different subtypes of calcium channel blockers have a general protective effect on bone turnover in osteoporotic rats. It was found that treatment with diltiazem (OVX+D) and verapamil (OVX+V) exerted a significant protective effect against ovariectomy induced bone changes. Both verapamil and amlodipine induced a significant increase in the femur dry weight, femur ash weight and bone ash calcium when compared to OVX group. In addition, they induced a significant reduction in serum calcium, phosphate, osteocalcin, carboxy-terminal collagen crosslinks and alkaline phosphatase levels when compared to OVX group. All these parameters were insignificantly different from control group.

On the other hand, the effect of Amlodipine treatment (OVX+A) was similar but modest compared to the other two calcium channel blocker subtypes. It was found that amlodipine induced a significant increase in the, femur ash weight and bone ash calcium, and a significant reduction in serum calcium, phosphate, osteocalcin, carboxy-terminal collagen crosslinks and alkaline phosphatase levels when compared to OVX group. However, these results were still statistically dif-

### Table (3): Bone morphometry parameters in all groups.

<table>
<thead>
<tr>
<th></th>
<th>Femur Length (mm)</th>
<th>Femur Wet weight (mg)</th>
<th>Femur Dry weight (mg)</th>
<th>Ash Weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAM</td>
<td>38.43 ± 0.422</td>
<td>834.0 ± 32.083</td>
<td>581.6 ± 25.039</td>
<td>359.4 ± 21.319</td>
</tr>
<tr>
<td>OVX</td>
<td>38.15 ± 0.572</td>
<td>810.6 ± 40.363</td>
<td>548.8 ± 26.645</td>
<td>310.1 ± 25.044</td>
</tr>
<tr>
<td>OVX+D</td>
<td>38.27 ± 0.313</td>
<td>827.1 ± 37.572</td>
<td>578.5 ± 27.758</td>
<td>365.5 ± 21.439</td>
</tr>
<tr>
<td>OVX+V</td>
<td>38.26 ± 0.357</td>
<td>842.7 ± 38.199</td>
<td>573.1 ± 22.990</td>
<td>361.8 ± 22.220</td>
</tr>
<tr>
<td>OVX+A</td>
<td>38.14 ± 0.409</td>
<td>806.8 ± 38.067</td>
<td>562.2 ± 24.004</td>
<td>335.1 ± 31.635</td>
</tr>
</tbody>
</table>

All Data expressed as Mean ± SD, in Sham operated control (SHAM), Ovariectomized (OVX), Ovariectomized + Diltiazem treatment (OVX+E), Ovariectomized + Verapamil treatment (OVX+V) and Ovariectomized + Amlodipine treatment (OVX+A) groups.

- a Significant vs. control (SHAM) group.
- b Significant vs. OVX+D group.

## Discussion

Three main subtypes of calcium channel blockers are commonly used in modern medical practice. These include diltiazem a benzothiazepine, verapamil a phenylalkylamine and amlodipine a dihydropyridine. The present study was performed to detect the effect of blocking L-Type calcium channels on bone turnover in an ovariectomized rat model of osteoporosis.

In this study, it was found that all animals significantly gained weight during the study; however, no statistically significant differences were observed among the mean final body weights of the sham-operated control, ovariectomized untreated or treated groups. This indicates that ovariectomy alone or combined with the test drugs did not affect food intake. These results agree with Bastos et al., [9].
ferent from control group and the other two calcium channel blockers.

These results agree with Zaidi et al., [27] who reported that calcium channel blockers have a positive effect on bone remodeling. Some studies found that treatment with calcium channel blockers was associated with a reduced risk of fracture [28,29]. Moreover, in one study, subgroup analysis by type of calcium channel blockers indicated the reduced risk of fracture was more pronounced in the users of non-dihydropyridine than in the users of dihydropyridine [28]. An old study reported that diltiazem treatment could prevent bone resorption but without affecting serum, calcium levels [30]. Besides, in OVX, mice that were intra-gastrically administered benidipine (DHP calcium channel blocker), bone parameters (trabecular thickness, bone mineral density, and trabecular number) in the distal femoral metaphysis were significantly increased compared with control OVX mice [31].

These protective effects can be explained by the reports that calcium channel blockers can regulate growth and differentiation of osteoblasts and stimulates the function of these cells [32]. In addition, this might exert a direct inhibition of osteoclast function and/or suppression of PTH secretion and subsequent inhibition of osteoclast activity [17,33].

In contrast, a study reported that bone mineral density (BMD) was unaffected by CCB [34]. In the same context, another study also reported that Amlodipine treatment had neither a positive nor a negative effect on bone healing in a rat model of tibial defect [35].

A study on bone density of teeth in males above 55 years reported that the values of subjects treated with calcium channel blockers were worse than the control group in all measured areas, and there was no statistically significant difference in any region between the control and study groups [36]. A review article also concluded that these agents are unlikely to have any clinically important effects on bone [37].

Moreover, another study, found that calcium channel blockers exerted negative effects on bone. This study reported a two-fold higher risk of fracture in calcium channel-blocker users when compared to control [38].

These differences may be due to different study protocols whether on humans or animals and due to wide variability in study periods.

**Conclusion:**

Calcium channel blockers have a bone protective effect that is more significant in non-dihydropyridines. This can suggest them as a preferred line of treatment in hypertensive or coronary heart disease patients suffering also from osteoporosis. However, more research is needed involving larger groups to validate these results.

**Conflict of interests:**

The author declares no Conflict of interests.

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Effect of Blocking L-Type Calcium Channels on Bone in Ovariectomy Model

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تأثر إغلاق فنوات الكالسيوم طويل المفعول على العظام في نموذج هشاشة العظام الناتج عن استنسل المبيض في الفئران

مقدمة: يعتبر مرض هشاشة العظام الآن أكثر اضطرابات العظام الأوروبية شيوعاً، وسرعان وقت، فإنه يؤدي إلى زيادة معدل تحلل العظام، وفقدان بنية العظام العامة، وأثقل الرسوم البيانية في العظام بالانتقالي زيادة احتمالية حدوث الكسور، ويرافقه الشكوك حول الحاجة إلى استخدام مضادات الكاسبيوم في العلاج المضمن العظام. بعض الأدوية، مثل الحقيلة، أمور لم تكن قد وصلت إلى المراحل الأولية في علاج العديد من أمراض القلب والأوعية الدموية مثل إرفاق ضغط الدم وقصور الرنين الناجية. هذه الدراسات تشير أيضاً إلى أن هناك منع عناوين من هشاشة العظام، ولكن حتى الآن لا زال تأثير المفاعلات الكاسبيوم على العظام غير مثبت. وقد صُممت هذه الدراسة لبحث تأثير إغلاق فنوات الكالسيوم طويل المفعول على العظام في نموذج هشاشة العظام الناتجة عن استنسل المبيض في الفئران.

Material and Methods: أجريت هذه الدراسة على 50 فئران، من الذكور والإناث، ذات الوزن بين 200 إلى 250 جم، وقسمت الجزء

وفي نهاية فترة التجربة تم التضحية بالفئران واختارت عينة الدم كما تستخرج عظام الفخذ. حيث قياس الوزن الكلبي والجهاز لعظام الفخذ.

نتيجة: تم إعداد مفاعلات الكالسيوم من نوع الكاربوكسيل، ويتضمن تأثير إيجابي على هشاشة العظام الناتجة عن استنسل المبيض.

الاستنتاجات: مفاعلات فنوات الكالسيوم من نوع الكاربوكسيل، كاربوكسيل، ويتضمن تأثير إيجابي على هشاشة العظام الناتجة عن استنسل المبيض في الفئران البيضاء.