

Study the Therapeutic Role of Zinc and Vitamin D3 in Juvenile Male Rats with Zinc Deficiency; Hormonally and Histologically

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Abstract

The current experience was carried out to evaluate the impacts of Zinc and VitD3 on the thyroid gland, and testicular functions as well as bone tissue architecture in rats with zinc deficiency, forty juvenile rats were used, and Zinc deficiency was induced within a dose of 30 mg/kg of 1,10 phenanthroline dissolved in 0.5 ml of DMSO. Rats were distributed into four groups: group I. Rats served as control without zinc deficiency, was received 1ml of saline, group II with zinc deficiency considered as positive control, was received 1ml of saline, group III with deficiency, was treated with zinc 20mg/kg, group IV with Zn deficient, was treated with Vit D3 at a dose of 500 IU/kg, all groups treated orally for 30 days consecutive, our findings indicating that zinc deficiency caused to elevated TSH and T4 while lowered T3 values, markedly decreased in testosterone, FSH and LH, whereas histopathological alteration in bone its representing by loss of trabecular mass and atrophy of the osteoblast were observable, while the administration of zinc and Vit D led to improvement thyroid and sexual hormones as well osteoblast activity. In Conclusion zinc deficiency causing harmful impacts on thyroid gland, spermatogenesis and bone mineralization, while the administration of zinc and Vitamin D results in improvement hormone levels and restoration of the histopathological changes in the bone.

Key words; Zinc deficiency, Thyroid gland, Bone tissue.

Introduction

Zinc is the most commonly trace element which is required in the smallest quantities in humans and animals to optimal biological processes and maintain a healthy life, it plays important roles in the immune, cell proliferation, apoptosis, growth and reproduction as well defense against free radicals and repairing of DNA disrupt since more than three hundred proteins contains on Zinc; Which is primarily for regulating cellular processes integrity, and all body metabolism involved ATP utilization, and performance of work (1,2); Zn plays a crucial part in spermatogenesis process, improve the fertility via controlling protein expression that correlated to Sperm Maturation and helps maintain sperm motility; It is as well play an important role in thyroid hormone metabolism (3,4)., Additionally, Reports indicate to zinc's antioxidant capabilities and, its ability to shield tissue from oxidative damage and it has a stimulatory impact on osteoblastic bone formation and mineralization (5,6).

Zinc insufficiency; is interestingly seen as a very prevalence public health issue, especially in poor Countries (7). Many developmental have shown that zinc insufficient can cause development disorders, bone growth retardation, and, poorl defenses against DNA disruption which becomes persons vulnerable to deoxyribonucleic acid-disrupting materials as well as cognitive impairment (8,9 ,10). Reduce Zn values in the cells can worsen stressful damage and interaction with p53's ability to bind with deoxyribonucleic acid and then repair deoxyribonucleic acid; Zinc

insufficiency could directly disrupted DNA and, finally increase their hazard of induced cancer (11). Zinc deficiency increasing germ cell apoptosis and suppressive spermatogenesis and, fertilization arrest (12). Zn insufficiency is concomitant with several types of muscle abnormalities in embryo and offspring growing indicating to physiological role of Zn in the development and Mineralization of the Bones(3). Also, Zn insufficiencies can impair thyroid gland action and inhibit the spermatogenesis process

Vit D3; belongs to the secosteroids type, it controls the homeostasis of Ca and P and strings the bones, it is synthesized as Vit D3 from the skin or ingested as Vit D2 from diet (13). The body requires very few amounts of vitamins ; Vit D3 plays several biological activities via the binding and activation of Vit D receptors (VDR), it has a pleiotropic role on target cells and systems, its insufficiency results in damage to metabolic processes and, vital bodily functions (14). Vit D3 plays important role in male reproductive system since the expression of VitD Receptors and Vit D metabolizing enzymes was demonstrated in the testes also spermatozoa (15). Vitamin D has potent effect on the immune system and is probable to affect the thyroid during its immunomodulatory impacts (16). Vitamin D has an impact on bones during the stimulation of osteoblasts which release the enzyme ALP contributing to elevation in the Phosphate concentration and calcium ion all of this enhances to mineralization (17). The current experience was carried out to evaluate the impacts of Zinc and VitD3

supplementation on the thyroid gland and, testicular functions as well as architecture bone tissue in juvenile male rats with zinc deficiency.

Materials and Methods

Animals model: 40 juvenile male Albino rats (30) days of age, initially weighing (55-65gm) were used in the current experience. Juvenile rats were put in the cages of the animal's room within standard conditions at temperature (25 ± 2 °C), illuminated for 12hrs light / dark cycles with free access to tap water in plastic bottles with stainless-steel sipper tubes and fed a commercial diet during the experiment duration, after adaptation for seven days, the Zinc deficiency induction in juvenile rats.

Procedure

Inducing of Zinc deficient: Zinc deficient induced with injection of 1,10 phenanthroline at a dose 30 mg/kg I. P (18), dissolved with 0.5 ml of dimethyl sulphoxide next twelve hrs fasted animals, the Zinc value was estimated to according method of (19) next twenty-four hrs from 1,10 phenanthroline injected, the value of Zn below (1 µg/ml) indicating ZD induced, juvenile animals were divided into (4) groups, ten juvenile animals each, as follows; group I (intact rats), rats served as normal control(without zinc deficiency), animals received saline 1ml; group II(with ZD), as a positive group, animals received saline 1ml, group III (with ZD); animals treated with zinc sulfate 20mg /kg. b.w dissolved in(1ml) of saline, according to(20), group IV(with ZD),

animals treated with 500 IU/kg of vitamin D3, dissolved in 1ml of saline, according to (21), orally treatment for 30 days consecutive.

Sampling: Upon completion of the experience period, the samples of blood were collected and prepared for hormone investigation. Animals were fasted overnight, (2 ml) of blood was taken via myocardial - puncture from each male rat in the experimental animals after anesthesia by ether and blood was put into tubes without-heparin and left in slant positions to allow the formation of the a clot. Then then, the blood sample was centrifuged at 10³rpm for ten mins for separated serum and put in the tubes (Eppendorf), and then kept in a Freezer at (-20° C) till hormones estimation.

Hormones Analysis: The concentration of thyroxine, triiodothyronin as well as thyroid-stimulating hormone was assessed depending on the method (20). While the values of testosterone (T) and gonadotrophin hormones (FSH, LH), were assayed according to (22).

Histological analysis: 30 days after starting the experience, the rats were sacrificed while still under anesthetized ether, the specimens of bone tissue were taken from the all animals, the bones were cleaned from the surrounding musculature and fixed in neutral solution (formalin) with concentration 10% for one day thereby decalcification by immersed in formic acid(23) until softening, then washed with running tap water for 3 days, the tissue then put in ethanol within a graded concentrations for dehydrated and

following by dealcoholization by xylol , and embedded in paraffin wax and blocking, the histological sections were sectioned with thickness 5 μ m by a microtome and dewaxed , rehydration and, stained with H&E stain. We examined the sections to explore any changes in histopathology.

Analysis of Statistical: the outcomes are expressed as mean $\pm$ SD, to evaluate statistically the significance of the experimental findings by the one-way analysis of variance (ANOVA), findings were considered significant when P value < 0.05.

Results

The outcomes The outcomes clarified in Table (1) revealed there was significant increase in TSH and T4 values concomitant with significant decrease in T3 values in animals with zinc deficiency as compared to intact animals, whereas the results exhibit a significant decline in value of TSH along with improve values of T4 and T3 after treatment with zinc and Vit D3 as compared to positive and negative group. The data indicated in Table (2) exhibit there was a significantly decline in the value of testosterone and LH along with non-statically difference in values of FSH as compared to their values in the normal group. As seen the administration of zinc and Vit D3 resulted in significant increase in testosterone values and restored the values of both FSH and LH to proximately normal. as shown Histological alterations in femur bone in rats with zinc deficiency in(Fig 2), involved loss of trabecular mass especially compact bone and altered osteoclast activity

in the bone tissue were evaluated by atrophy in osteoblast and then decrease in bone density as compared to femur bone in rats without zinc deficiency in(Fig1) which characterized by normal architecture bone tissue showing normal compact (black star), spongy bone(black arrow) normal osteoblast (red arrow), osteoclast(yellow arrow) and normal trabecular (green arrow). Whereas the administration of zinc and Vit D cause to restoration these histological changes which including significantly improve in the trabecular mass (compact and spongy bones), improve bone density as well improve tissue remodeling and semi normal trabecular mass with normally distribution of osteoblast and osteoclast (red arrow) with good appearance of compact and spongy bone as shown in (Figs 3and4), the above changes in femur bone as comparison to femur bone in (Fig 2).

Discussion

As seen current data indicate that diminish zinc level lead to hypothyroidism is expressed through remarkably increased thyrotropin and thyroxine in concurrently with notable diminished triiodothyronine in albino rats zinc insufficiency comparison to normal rats , this might be attributed to diminish the action of 5- deiodinase in hepatic tissue consequent resulted lowering in transform of thyroxine to triiodothyronine; at other point, in return triiodothyronine requires the Zinc to complete its biological activity (24), these outcomes are agreed with those results described by(25) which indicating that the development of subclinical hypothyroidism by zinc deficiency. On the other hand, (26)

who reported that the thyrotropin produces because a greater releasing TRH from its secretagogue via stimulating its receptor-TRH-R1 expressed in the thyrotroph cells in pituitary gland results in improved TSH release or due to diminished value of triiodothyronine results in detachment of a nuclear- thyrotropin receptor from the thyrotropin gene developer, in such a way that the expression of the hormone is uninhibited. Another work (27) which found that zinc deficiency can be responsible for more activation of thyrotropin produced by increasing TRH through suppression of PPII activity due to zinc deficiency in rats was observed, above results are in parallel to findings in our study. According to results, the administration of zinc sulfate and vitamin D causes an improvement in thyroid stimulating hormone and thyroid function this might be ascribed to the antioxidant impacts displayed by it (10, 16). These outcomes agree with those results described by previous reports (28, 20) that have shown that Zn plays an important part in T4 and T3 metabolism as well as the transformation of T4 to T3. On the other hand, zinc impacts deiodinase action via its ability to elevate the value of GPX of the albino rats suffering from hypothyroidism to prevent the progressive stressful impact. This was supported by earlier work on the prostate in rat exposure to PCBs that recorded restoration of the values of T3, T4 and TSH by simultaneous Zn sulphate administration with the PCBs causing an increase in antioxidant enzymes (29). Moreover, the improvement levels of T4 and T3 hormones in rats with Zn insufficiency treated with Vit D3 because of lowered liver deiodinase 3

actions that diminished the destruction of the T4 ,and T3 hormones of the hepatic tissue (30). Our findings are supported, by, (31) who revealed that Vit D3 administration to diabetic rats causes a marked improvement in thyroid status, the impact because of the action of Vit D3 in the elevation of deiodinase 2 expression, and thereby transforming the thyroxine for triiodothyronine. Another work was reported by (32) who showed that the administration of VD effectively ameliorated TT3, fT3, TT4, and fT4 values in concomitant with markedly diminished in serum TSH and Tg-Ab values in arsenic-exposed rats. The above observations are in parallel with the outcome in our study.

As according we result demonstrated that significantly lowered testosterone levels with in concomitant decreased in LH and FSH levels in zinc deficiency rats compared to rats without zinc deficient, this impact might be due to mal-function of the luteinizing receptor action regulating the produce and stored of T and damage of the interstitial cells; Where T is bio - synthesized or is a result a losing in the efficiency of the sex hormone - binding consequently losing of a key protein and enzyme mediating the responses for Luteinizing hormone (33,34). Our outcomes were confirmed by results described by (35) who reported that zinc deficiency causes impaired spermatogenesis. This may be attributed to increased superoxide radical activity and oxidative stress along with increased proinflammatory cytokines. A Previous study was done by (36) which revealed that during the, maturity of rats, Zn

deficiency reduces the activity of Dcp and may cause a delay in sexual maturity. Along the same line, the releasing of gonadotropin hormone is altered by Zn deficiency. (37) Found that gonadotropin hormone values lowered in Zn deficient can be attributed to damage to the pituitary gland and lowered output of GnRH from the hypothalamus, this observation is in line with our outcomes. The treatment with Zn and Vit D3 to rats led to restoration of the harmful impacts of Zn insufficient for the pituitary–testicular- axis caused increasing the values of steroid(T) and gonadotropin hormones normal limited approximately through their anti-inflammatory and antioxidant properties (38,39). We outcomes in parallel with findings obtained by other researchers (40) who observed that Zinc may increase testosterone values. This may be attributed to zinc coupling with proteins further stimulating 2Nrf2, hence neutralizing prooxidative and, inflammatory intranuclear and extranuclear pathways. Moreover, zinc intake causes an increase in interstitial cell count of the testes of male Rabbits, this elevates T biosynthesis and increases spermatozoa count in the testes (41). In another research (42) it was mentioned that the serum LH, FSH, and Testosterone values markedly increased in co-treatment of cisplatin in conjugation with Zn administration relative to cisplatin]-treated rats only. All the above results inconsistent with the findings in this study. From we findings clarify that vitamin D3 has ameliorated effec on the hypothalamus - pituitary- testicular axis led to enhancing steroid and gonadotropin hormones biosynthesis this can be attributed to Vit D

possess potent properties as antioxidant, anti-inflammatory and antiapoptotic (43,44). These findings agree with those obtained by (45) who revealed that VitD3 administration for one month remarkably increased values of Testosterone; likely during up-regulation of steroidogenesis-related genes in rats testis which exposed to cisplatin. A previous work reported that Vit D3 stimulates Testosterone Formation in the Leydig cells exerted via promotion of the IGF-1 signaling pathway; this impact could be mediated VDR-dependent actions in testes (46). These observations supported with our findings. Along same line, in another work by (47) who reported that vitamin D3 improve gonadal- function by enhancing pituitary action is exerted by (PPAR-c,/TGF-b1/NF-jB)- signaling pathway in diabetic rats.

The histological alterations in femur bone its representing by loss of trabecular mass and atrophy of the osteoblast in rats femur bone with zinc deficiency inas compared to femur bone in rats without ZD which characterized by normal architecture bone tissue, this illustrates impairing bone formation by suppression osteoblast proliferation and differentiation might be attributed to elevation of oxidative stress and pro- inflammatory cytokines levels in concurrently with depletion of endogenous antioxidant status results in apoptosis of the osteoblasts, and osteocytes as well the osteogenesis and mineralization process slowdown (48,49). Along the same line, zinc deficiency causes dropped levels of calcium and phosphorus in bone tissue consequently impairment in bone

mineralization and loss architecture (50,51). The obvious alleviated in the bone architecture in male rats treated within the administration of Zinc sulfate, and VitD3 which manifested by decreased the spaces, significantly improved the tissue remodeling and semi normal trabecular mass with normal distribution of osteoblast and osteoclast, this may be attributed to the zinc and Vit D possesses potential anti-inflammatory and antioxidant activities

(52,53). In another study by (54) who revealed that ZnHA-NPs supplementation in minimum doses have stimulatory potential impacts in the preventive and therapeutic, of osteoporosis in OVX rats. Also (55) mentioned that Zn administration with high concentration reduced pro-inflammatory mediators via suppressing the; I κ B kinase (IKK)- α /NF- κ B, signaling pathway, these observations are consistent with our findings.

Table (1) the effect of zinc sulfate and Vit D3 on TSH, T4 and T3 hormones in male rats with zinc deficiency.

Groups	TSH μ IU/L	T3 μ IU/L	T4 μ IU/L
Negative Control	0.88 $\pm$ 0.05 b	1.61 $\pm$ 0.02 a	6.36 $\pm$ 0.06 c
ZD Positive control	1.47 $\pm$ 0.21 a	0.71 $\pm$ 0.07 d	8.00 $\pm$ 0.19 a
ZD Treated with Zinc 20mg/ kg	0.80 $\pm$ 0.01 b	1.53 $\pm$.040 b	6.48 $\pm$ 0.12 bc
ZD Treated with VD3 500 IU/ kg	0.74 $\pm$ 0.07 b	1.38 $\pm$ 0.03 c	6.56 $\pm$ 0.19 b

Findings are expressed as Mean $\pm$ SD, the symbol represent statistical difference at $p < 0.05$ value comparison to health animals

Table (2) the effect of zinc sulfate and Vit D3 on reproductive hormones (Testosterone , FSH, LH) in male rats with zinc deficiency.

Group	FSH mIU/ml	LH mIU/ml	T pg/ml
Negative Control	4.28 $\pm$ 0.22 NS	1.02 $\pm$ 0.07 a	2.55 $\pm$ 0.20 a
ZD Positive control	4.09 $\pm$ 0.08NS	0.83 $\pm$ 0.02 c	1.53 $\pm$ 0.02 c
ZD Treated with Zinc 20mg/ kg	4.25 $\pm$ 0.17NS	0.96 $\pm$ 0.06 ab	2.21 $\pm$ 0.14 b
ZD Treated with VD3 500 IU/ kg	4.22 $\pm$ 0.12NS	0.90 $\pm$ 0.03 b	2.13 $\pm$ 0.14 b

Findings are expressed as Mean $\pm$ SD, the symbol represent statistical difference at $p < 0.05$, value comparison to health animals

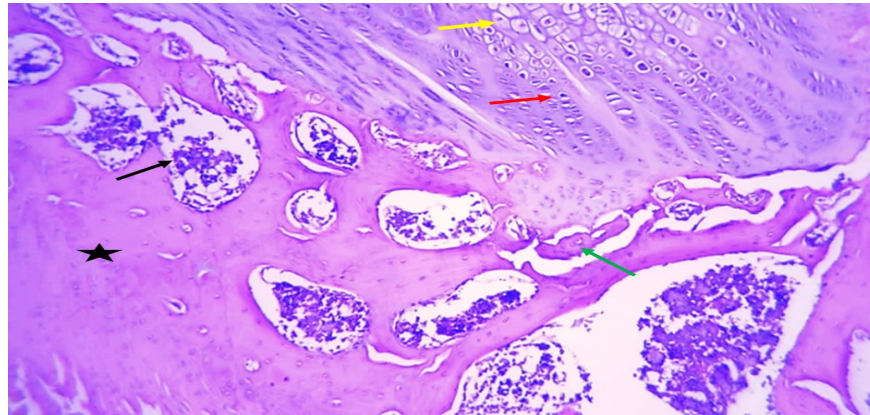


Figure (1): section of femur bone from intact rats (normal control) shows normal architecture of bone tissue including normal compact (black star), spongy bone (black arrow) normal osteoblast (red arrow), osteoclast (yellow arrow) and normal trabecular (green arrow) H&E stain 100X

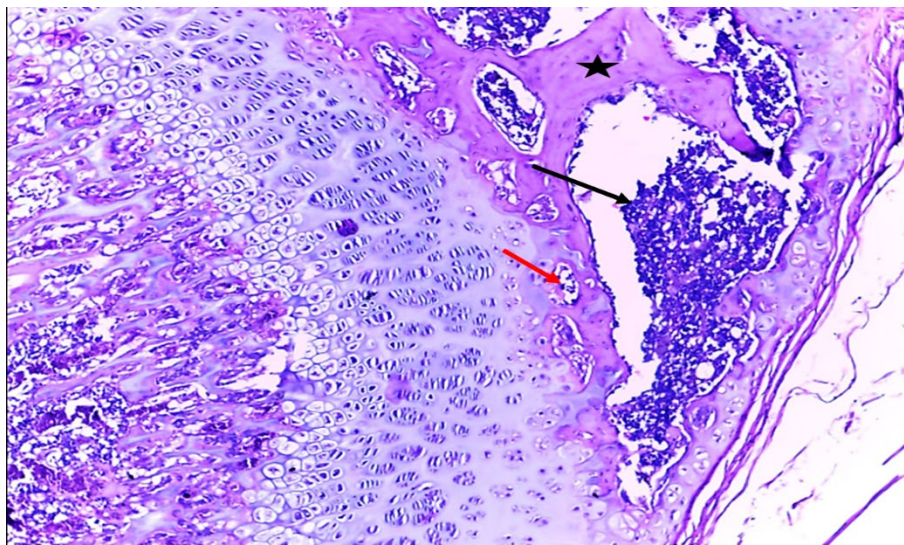


Figure (2): section of femur bone from rats with zinc deficiency shows loss of trabecular mass especially compact bone (black star) and, altered osteoclast action in the bone tissue were assessed by slight atrophy cells (red arrow) also there were (mild-sever) atrophy in osteoblast and then reduction in bone density and large spaces in spongy bone structure (black arrow). H&E stain 100X

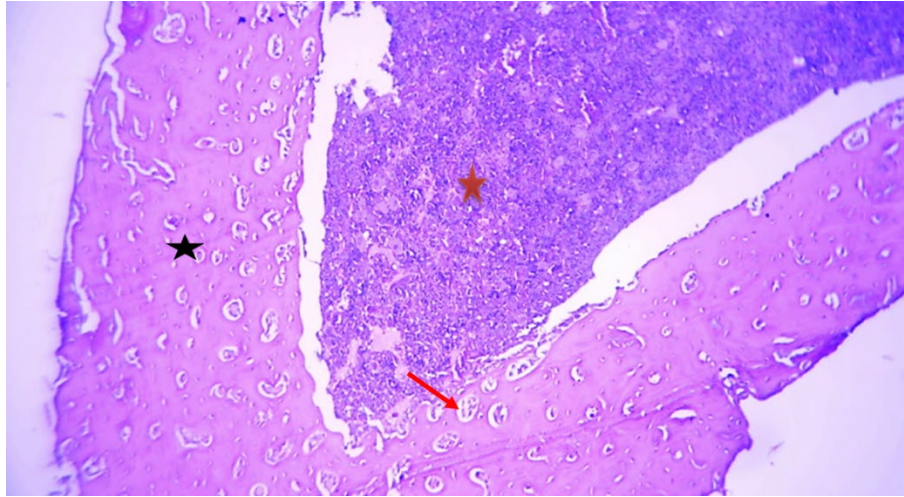


Figure (3): section of femur from rats treated with Zinc sulfate shows significantly improve in the tissue remodeling and semi normal trabecular mass with normally distribution of osteoblast and osteoclast (red arrow) with good appearance of compact and spongy bone(black and red star). H&E stain 100X

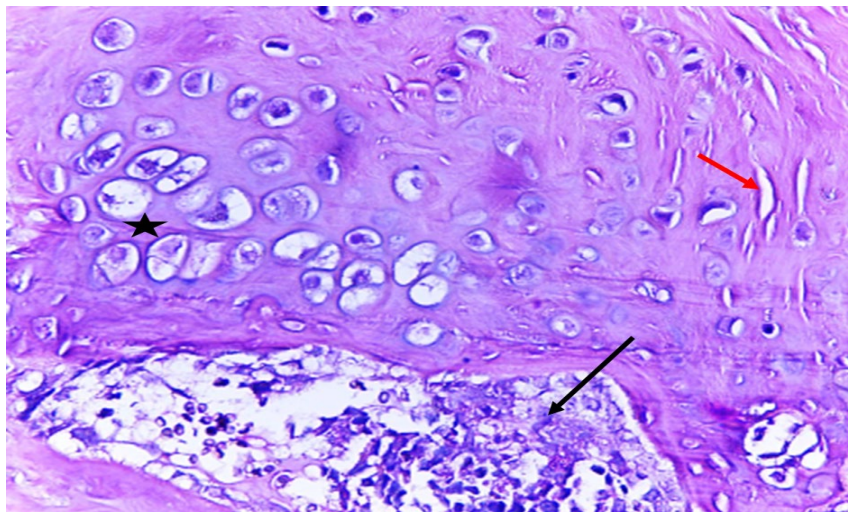


Figure (4): section of femur bone from treated rats with Vit D3 shows significant improved in the trabecular mass which include compact bone (black star), spongy bone(black arrow) , spongy bone there was decreased in the spaces and highly improved in the bone density and trabeculae (red arrow). H&E stain 400X

Conclusion

we concluded from outcomes that zinc deficiency causing harmful impacts on thyroid gland, spermatogenesis and bone mineralization, while the administration of

zinc and Vit D resulted in improvement hormones level and restoration the histopathological changes in bone.

Conflicts of interest

The authors declare that there is no conflict of interest.

Ethical Clearance

This work is approved by The Research Ethical Committee.

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دراسة الدور العلاجي للزنك وفيتامين د3 في ذكور الفئران الصغيرة المصابة بنقص الزنك هرمونيا

ونسيجيا

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الخلاصة

تم إجراء التجربة الحالية لتقييم تأثيرات الزنك وفيتامين د3 على الغدة الدرقية ووظائف الخصية وكذلك بنية أنسجة العظام في الفئران التي تعاني من نقص الزنك، وتم استخدام أربعين فأراً صغيراً، وتم تحريض نقص الزنك بجرعة 30 مجم / كجم من 1،10 فينانثرولين مذاب في 0.5 مل من ثنائي ميثيل سلفوكسيد. تم توزيع الفئران إلى أربع مجموعات: المجموعة الأولى. الفئران التي كانت بمثابة مجموعة تحكم سالبة بدون نقص الزنك، وتلقت 1 مل من المحلول الملحي، المجموعة الثانية التي تعاني من نقص الزنك اعتبرت مجموعة تحكم إيجابية، وتلقت 1 مل من المحلول الملحي، المجموعة الثالثة التي تعاني من نقص الزنك، وعولجت بالزنك 20 ملغ / كجم، المجموعة الرابعة التي تعاني من نقص الزنك، وعولجت بفيتامين د3 بجرعة 500 وحدة دولية / كجم، جميع المجموعات عولجت عن طريق الفم لمدة 30 يوماً متتالية، تشير نتائجنا إلى أن نقص الزنك تسبب في ارتفاع هرمون TSH و T4 بينما انخفض قيم T3 ، وانخفاض ملحوظ في هرمون التستوستيرون و FSH و LH ، في حين لوحظت تغيرات نسيجية مرضية في العظام تمثلت في فقدان الكتلة الإسفنجية وضمور الخلايا العظمية، بينما أدى تناول الزنك وفيتامين د إلى تحسن في هرمونات الغدة الدرقية والهرمونات الجنسية وكذلك نشاط الخلايا العظمية. استنتجنا من النتائج أن نقص الزنك يسبب قصور الغدة الدرقية ، ويُنَبِّط تكون النطف وتمعدن العظام، بينما يؤدي الزنك وفيتامين د إلى تحسين مستوى الهرمونات و اصلاح التغيرات المرضية في بنية العظام.

الكلمات المفتاحية: نقص الزنك، الغدة الدرقية، نسيج العظم.