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Original Research Article

Effect of Vitamin D3 on Hormonal and Histological Changes in Thyroid Gland Caused by Hyperprolactinemia of Male laboratory Rats (*Rattus norvegicus*)

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ABSTRACT

Hyperprolactinemia is commonly known as abnormal levels of prolactin hormone in the blood due to endocrine disorder. The study aimed to eliminate hyperprolactinemia affecting the thyroid gland by treating it with vitamin D supplements. Eighteen male rats *Rattus norvegicus* were divided into three groups of six rats each : The first group received normal saline for 42 days . The second group, rats were given 5 mg/kg metoclopramide by intraperitoneal injection for hyperprolactinemia induction for 14 days. The third group, hyperprolactinemic rats received 2.5 mg/kg vitamin D3 by intraperitoneal injection for 28 days. After the end of experimental (42 days), hormonal parameters (prolactin hormone, Triiodothyronine hormone (T3), and Thyroxine hormone(T4) , Thyroid stimulating hormone(TSH) were measure, and the thyroid gland was removed, processed and examine for histomorphological changes. The result of the study revealed a significant decrease (P≤0.01) in prolactin and TSH levels and a significant increase (P≤0.01) in T3 and T4 levels in Group 3 (Hyperprolactinemia group treated with vitamin D) compared with Group 2(Hyperprolactinemia group). Histological examination of sections of the thyroid gland of the group treated with vitamin D3 showed significant restoration compared to the hyperprolactinemia rats, throughout. Thyroid follicles became larger, containing dense colloidal material, in the group given Vitaim D 3 and structures of thyroid follicles. The study concluded that vitamin D3 had a protective effect on thyroid gland by stabilizing T3, T4, and TSH hormones levels and restoration of histological architectures and thyroid follicles became larger, containing dense colloidal material, with presence normal thyrocytes remarkably.

***Keywords*:** Medicinal plants; Morocco; Moulay Yaâcoub; Plants; Phytotherapy

Introduction

Hyperprolactinemia is an increase in the concentration of prolactin in the blood as a result of disorders in the pituitary gland.[1-2] The most common cause of hyperprolactinemia is the presence of tumors in the pituitary gland or the use of certain drugs.[3]. Among the drugs that lead to an increase in the level of prolactin in the blood is metoclopramide, [4-5] which is a common drug used to increase the movement of the digestive system and empty the stomach. Metoclopramide was first described by Jastin-Besaucon and Lavillen in 196.[6] Its long-term use leads to hyperprolactinemia.[7] Hypothyroidism is a dysfunction that leads to a deficiency in the secretion of T3 and T4 hormones that occurs as a result of an increase in the secretion of the thyroid-stimulating hormone (TSH), which is secreted from the pituitary gland. This disease affects both males and females.[8] Vitamin D is an element of the nutrients that the body needs. It is synthesize by subcutaneous cells from an inactive chemical compound related to the vitamin through exposure of the skin to ultraviolet radiation and has a function in the physiological commitment of the element calcium. Vitamin D can be obtained from some foodstuffs in fatty.[9] There is a major role for vitamin D in treating hypothyroidism and restoring hyperplasia to normal and it has a role in restoring the normal levels of T3 and T4 hormones.[10]

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The study evaluated the use of vitamin D3 in the restoration of damaged histological architectures components of thyroid tissue.

Materials and Methods

Animals

All protocols of experimental animals were applied according to Authorized guidelines of care and use of laboratory animals in education faculty for pure science /Thi-Qar university. This study was gotten approval by Thi-Qar university ethical committee for animal research(Issue7/30/439-Date11/10/2022).

Eighteen male rats *Rattus norvegicus* (200 - 250 ± 50g) were use in the study. The rats were put in the animal house in the college of Education Pure Sciences in Thi-Qar university under standard conditions of temperature (22 ± 25)ºC and lighting (12:12hr light: dark cycle) for two weeks before and during the study , The rats were maintained on rat feed and tap water *ad-libitum*.

Experimental design

The animals were randomly divided into 3 groups (6 rats in each group) as follows:

Group1: (negative control): received normals saline (N.S) intraperitoneal (IP) injection for 35 days.

Group2: (Hyperprolactinemia group): The animals received a single dose of metoclopramide (MC) 2.2 mg/Kg b.wt to induce hyperprolactinemia daily by intraperitoneal injection for 14 days according. [11]

Group3: (Hyperprolactinemia group treated with vitamin D) Received 0.5 mL of Vitamin D for 28 days by intraperitoneal injection (5 µg/kg b.wt).[12]

At the end of the experiment, animals of each group were anesthetize by ether and sacrificed, thyroid gland of all groups were removed and kept in 10% formalin for histopathological study.

Biochemical analysis

Determination of serum prolactin, T3,T4 and TSH levels

Prolactin (PRL), Triiodothyronine (T3), Thyroxin (T4) and Thyroid-stimulating hormone (TSH) were determined using commercial kits (Elisa, Monobind ,U.S.A.).

After being removed from the refrigerator, the necessary reagents were left at room temperature for 30 minutes. For each sample (control) that will be examined, use one PRL strip and one SPR from the kit.

The "PRL" code on the gadget served as the test's unique identifier. The sample was pipetted, calibrated, or regulated into a volume of 200µl.

SPRs and strips were placed into the device's places that were shown on the screen by Elisa. It is important that the color labels on the SPRs and Reagent strips match the assay code. According to the Operator's Manual's instructions, the assay was started.The instrument executes every assay step automatically. In 40 minutes or less, the assay will be finished.The SPRs and strips were removed from the instrument when the assay was finished.The T_3, T_4, D3, and TSH hormones underwent the same procedure.

Histopathological study

Thyroid samples were fixed in a 10% formalin solution for 48 hours. They were then processed (washed with water, passed through escalating grades of alcohol, cleaned in xylene, and imbedded in paraffin wax at 70 ^{0}C).5m of tissue thickness was put on clean glass slides and stained with hematoxylin and eosin. [13-14]

Statistical analysis

The results of the study were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's test. All statistical calculations were carried out by the aid of the statistical package SPSS V. 23(SPSS Inc.). The data were express as means ± standard error (Mean ± SE) .[14]

Results and Discussion

The results of the study showed an increase in prolactin levels (Figure 1), which led to an imbalance in the secretion of thyroid hormones, which led to a defect in the secretion of the thyroid gland that led to a deficiency in the secretion of T3 and T4 hormones (P≤0. 01) (Figures 2-3). With this deficiency, the pituitary gland increased the secretion of thyroid-stimulating hormone (TSH) (Figure 4).[15] In addition, the vitamin D level decreased in the hyperprolactinemia group (Figure 5), and this deficiency may be attributed to thyroid dysfunction.[16-17] However, the results of vitamin D treatment showed a decrease in the prolactin level in the vitamin D group. Vitamin D plays an important role in increasing the absorption of calcium into the blood, and when the level of calcium rises, this leads to a decrease in the level of the hormone prolactin, which inhibits the production of prolactin by the pituitary gland.[18-19] This study demonstrated the role of vitamin D in improving the pathological changes of the thyroid gland and balancing its secretions so that the levels of thyroid hormones return to their normal levels, compared to the hyperprolactinemia group9.The study showed that the hyperprolactinemia group had fusion in many follicles and the formation of a vacuole inside the cytoplasm, and many follicles were devoid of colloid material, and vascular congestion was observed these results are consistent with previous report (Figures 7) .[20] The study showed that the group treated with vitamin D had thyrocytes that consisted of many follicles, that the layer of simple cubic cells that make up the follicles was full of colloidal substances, and that the cell sizes ranged from large to medium to small. The results of the histological examination of the thyroid gland treated with vitamin D showed that the cells were near to their normal state where the tissue were near to the negative group (Figure 6), as the follicles appeared to be filled with colloidal matter and the vacuoles disappeared inside the cytoplasm (Figure 8), indicating the role of vitamin D in tissue repair.

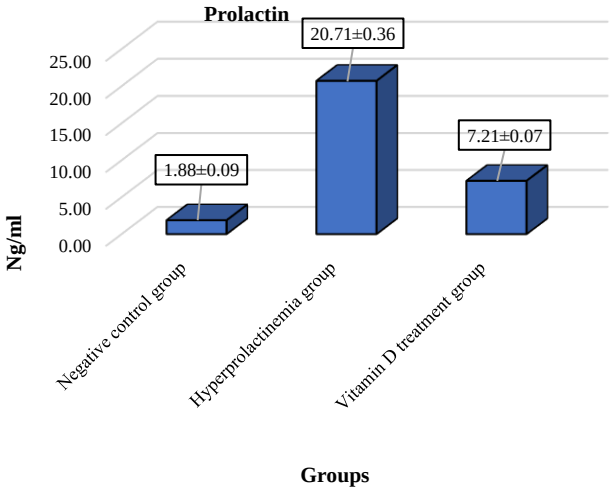

Figure: PRL hormone level in all groups

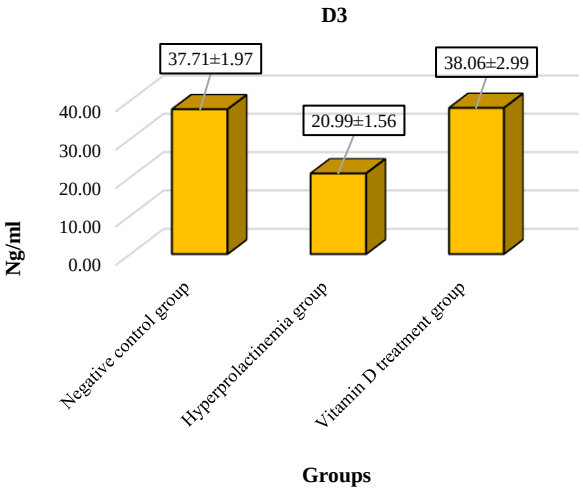

Figure: Vitamin D hormone level in all groups

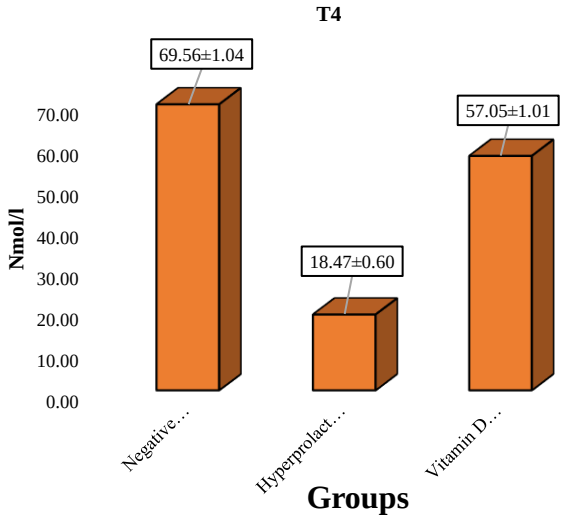

Figure: T_4 hormone level in all groups

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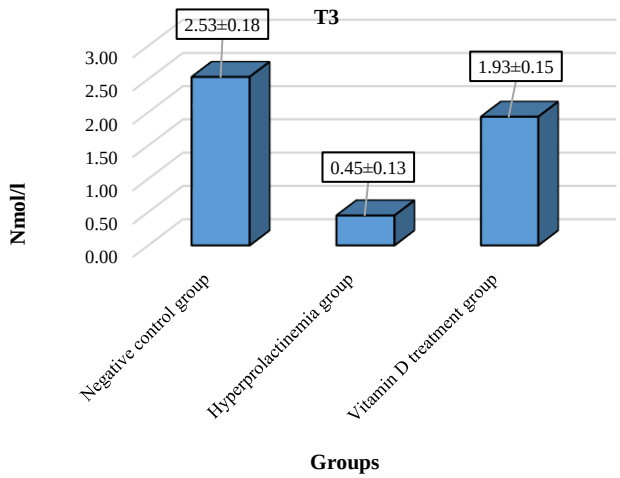

Figure: T_3 hormone level in all groups

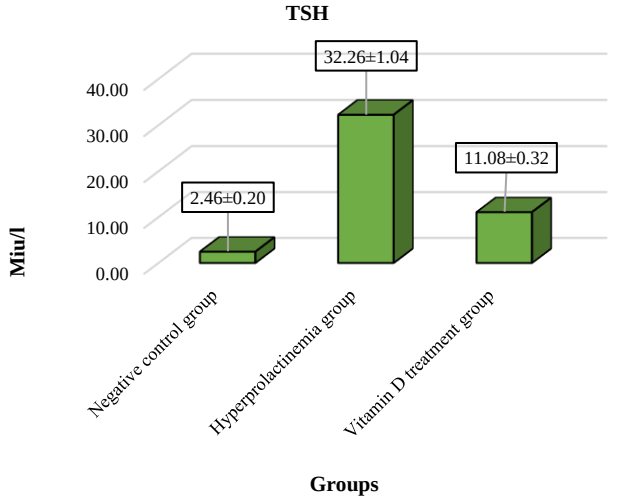

Figure: TSH hormone level in all groups

Conclusion

The results of this study indicate the occurrence of hypothyroidism as a result of hyperprolactinemia, as the study showed a decrease in thyroid hormones T4 and T3 and an increase in TSH, and our study proved the effectiveness of vitamin D in treating hypothyroidism and protecting its tissues.

The first involves having the same genomic impact as other steroid hormones by directly through the nuclear VDR, starting and controlling gene expression . The manifestation of this impact typically takes hours or days. The second is non-genomic and has a quicker biological impact Vitamin D produces its non-genomic action by activation of protein kinases, modification of the electrical state of cells, and stimulation of ion channels by another receptor, known as 1,25D3-membrane-associated, rapid response steroid-binding receptor (MARRS).

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

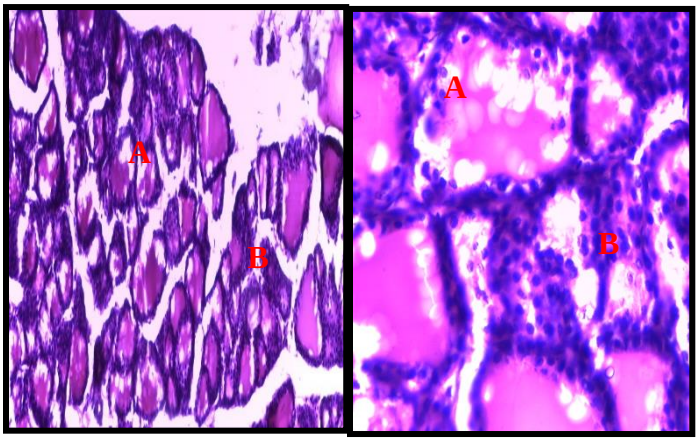

Figure 6: normal histostructures of thyroid gland tissues in the control group showing normal structure of thyrocytes and normal appearance of follicles (A) with colloids (B) Photomicrograph (100 X) and (400 X) (left and right) respectively.

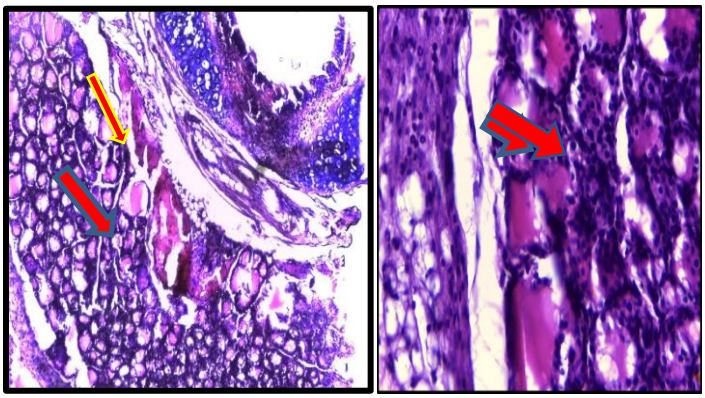

Figure 7: histostructures of thyroid gland tissues in the hyperprolactinemia group showing vacuolated cytoplasm (thin arrows), fusion of some follicles (thick arrows), empty of some follicles with no colloid (double arrows) and (A) congestion of the blood vessel. Photomicrograph (100 X) and (400 X) (left and right) respectively

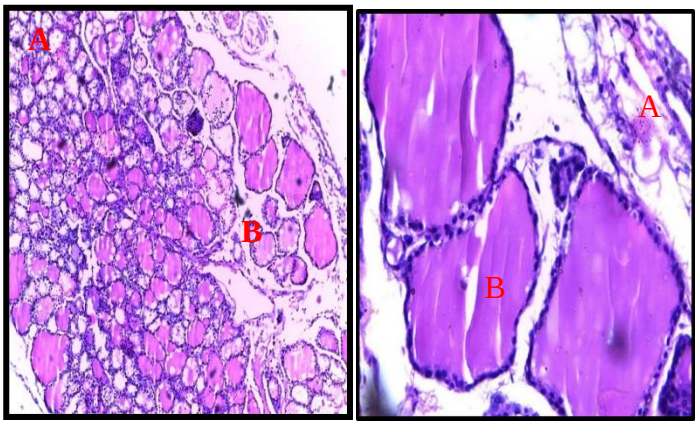

Figure 8: Histostructures of thyroid gland tissues in the in vitamin D3 -treated group showing normal follicles full of colloid (A) and homogeneous colloidal (B). Photomicrograph (100 X) and (400 X) (left and right) respectively

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