Regulation of Fibroblast Growth Factor 23 (FGF23) by Thyroid Hormones in Levothyroxin-Induced Hyperthyroidism and the Role of Vitamin D_3 in Bone Remodeling

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Abstract

Background: Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that plays a crucial role in regulating phosphate homeostasis and vitamin D_3 metabolism. Thyroid hormones influence bone remodeling and mineral balance; however, the interaction between thyroid hormone imbalances and FGF23 remains incompletely understood.

Objective: This study aimed to investigate the effect of levothyroxine-induced hyperthyroidism on thyroid hormones (T3 and TSH) and serum FGF23 levels, as well as to evaluate the role of vitamin D_3 and calcium supplementation in mineral metabolism.

Methods: Thirty Wistar rats were divided into six groups (n = 5 each): a control group, a levothyroxine (50 μg/kg) treatment control group, a high-dose levothyroxine (200 μg/kg) group with calcium (400 mg/kg), a high-dose vitamin D_3 (1000 IU) group, and a high-dose vitamin D_3 (1000 IU) and vitamin K_2 (30 mg/kg) combination group. After one month, serum levels of T3, TSH, FGF23, calcium, phosphorus, and vitamin D_3 were measured using ELISA and spectroscopic methods.

Results: High doses of levothyroxine significantly increased T3 levels (3.103 ± 0.2035 ng/mL vs. 1.626 ± 0.0894 ng/mL, $P < 0.001$ in the control group) with a marked decrease in TSH levels (1.840 ± 0.2320 ng/mL vs. 3.864 ± 0.293 ng/mL in the control group, $P = 0.036$). Additionally, FGF23 levels were significantly elevated in the high-dose group (164.6 ± 7.273 pg/mL vs. 114.3 ± 9.450 pg/mL in the control group, $P < 0.001$). Vitamin D_3 and calcium supplementation also contributed to the reduction of FGF23 levels and improved mineral metabolism.

Conclusion: Levothyroxine-induced hyperthyroidism leads to elevated FGF23 levels, suggesting a regulatory axis between the thyroid gland and FGF23. Vitamin D_3 supplementation reduces this response and supports mineral balance, highlighting its potential as a preventative strategy for protecting bone health in hyperthyroidism.

Keywords: Levothyroxine, hyperthyroidism, FGF23, thyroid hormones, vitamin D_3, bone remodeling.

تنظيم عامل نمو الأرومة الليفية 23 (FGF23) بواسطة هرمونات الغدة الدرقية في فرط الدرقية المُستحث بالليفوثيروكسين ودور فيتامين D3 في إعادة تشكيل العظام

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الملخص

الخلفية :يُعد عامل نمو الأرومة الليفية 23 (FGF23) هرمونًا مُشتقًا من العظام يلعب دورًا مهمًا في تنظيم توازن الفوسفات واستقلاب فيتامين .D3 تؤثر هرمونات الغدة الدرقية في إعادة تشكيل العظام وتوازن المعادن، إلا أن العلاقة بين اضطرابات هرمونات الغدة الدرقية و FGF23لا تزال غير مفهومة بشكل كامل.

الهدف :هدفت هذه الدراسة إلى تقييم تأثير فرط نشاط الغدة الدرقية المُستحث بالليفوثيروكسين على هرمونات الغدة الدرقية (T3 و TSH) ومستويات FGF23 في المصل، بالإضافة إلى دراسة دور فيتامين D3 ومكملات الكالسيوم في استقلاب المعادن.

المنهجية :تم تقسيم ثلاثين جرذًا من نوع ويستر إلى ست مجموعات (5 حيوانات لكل مجموعة): مجموعة سيطرة، مجموعة معالجة بالليفوثيروكسين (50 ميكروغرام/كغم)، مجموعة جرعة عالية من الليفوثيروكسين (200 ميكروغرام/كغم) مع الكالسيوم (400 ملغم/كغم)، مجموعة فيتامين D3 بجرعة عالية (1000 وحدة دولية)، ومجموعة مشتركة من فيتامين D3 (1000 وحدة دولية) وفيتامين K2 (30 ملغم/كغم). بعد شهر واحد، تم قياس مستويات T3 و TSH و FGF23 والكالسيوم والفوسفور وفيتامين D3 في المصل باستخدام تقنيات ELISA والطرق الطيفية.

النتائج :أدت الجرعات العالية من الليفوثيروكسين إلى زيادة معنوية في مستويات T3 (3.103 ± 0.2035 نانوغرام/مل مقارنة بـ 1.626 ± 0.0894 نانوغرام/مل في مجموعة السيطرة، ($P < 0.001$)، مع انخفاض ملحوظ في مستويات TSH (1.840 ± 0.2320 نانوغرام/مل مقارنة بـ 3.864 ± 0.293 نانوغرام/مل في مجموعة السيطرة، ($P = 0.036$). كما لوحظ ارتفاع معنوي في مستويات FGF23 في مجموعة الجرعة العالية (164.6 ± 7.273 بيكوغرام/مل مقارنة بـ 114.3 ± 9.450 بيكوغرام/مل في مجموعة السيطرة، $P <$ 0.001). من جهة أخرى، ساهمت مكملات فيتامين D3 والكالسيوم في خفض مستويات FGF23 وتحسين استقلاب المعادن.

الاستنتاج :يؤدي فرط نشاط الغدة الدرقية المُستحث بالليفوثيروكسين إلى زيادة مستويات FGF23 ، مما يشير إلى وجود محور تنظيمي بين الغدة الدرقية و FGF23. كما أن مكملات فيتامين D3 تقلل من هذه الاستجابة وتدعم توازن المعادن، مما يبرز دورها المحتمل كإستراتيجية وقائية للحفاظ على صحة العظام في حالات فرط الدرقية.

Introduction:

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone secreted primarily by osteoblasts. It plays a key role in regulating phosphate homeostasis and vitamin D_3 metabolism by increasing renal phosphate excretion and inhibiting 1,25-dihydroxyvitamin D synthesis (1). Abnormal FGF23 levels are associated with various metabolic bone disorders, chronic kidney disease, and cardiovascular complications (23). Thyroid hormones, particularly triiodothyronine (T3) and

thyroxine (T4), are key regulators of bone remodeling, influencing the activity of both osteoblasts and osteoclasts (4). Furthermore, hyperthyroidism accelerates bone turnover, contributing to decreased bone mineral density and an increased risk of fractures (5, 6). Disruption of thyroid function also leads to alterations in calcium and phosphorus balance, although the mechanism linking thyroid hormones to FGF23 remains unclear (7, 8). Previous studies have suggested an interaction between the thyroid and FGF23. Lin et al. (2019) reported alterations in FGF23 levels and mineral metabolism in patients with Graves' disease who have normal thyroid function, indicating that thyroid status may influence FGF23 secretion (9). Hyperthyroidism is also associated with disturbances in vitamin D_3 metabolism, which in turn is closely linked to FGF23 regulation (10, 11). Vitamin D3 supplementation can affect FGF23 concentration under various physiological conditions. A study by Kamelian et al. (2018) showed that cholecalciferol treatment significantly modified FGF23 levels in individuals with vitamin D_3 deficiency (12). Furthermore, Salem et al. (2023) demonstrated that D_3 supplementation alleviated hyperthyroid cardiomyopathy in rats (13). Despite these findings, the direct effect of levothyroxine-induced hyperthyroidism on FGF23 levels, as well as the potential protective role of vitamin D_3 and calcium, remains insufficiently investigated. Understanding the nature of this relationship may also contribute to the development of strategies to prevent bone loss and metabolic disorders associated with hyperthyroidism.This study aimed to investigate the relationship between thyroid hormones and FGF23 in a levothyroxine-induced hyperthyroidism model, and to determine whether vitamin D_3 and calcium supplementation can modulate this regulatory axis. The study objectives are as follows: To measure serum T3, TSH, and FGF23 levels in rats treated with levothyroxine. In addition to evaluate the effect of high doses of the LT4 treatment on calcium and phosphorus metabolism. Furthermore to investigate the protective effects of vitamin D_3 and calcium

supplementation on FGF23 levels and mineral balance. Finally, to assess the correlation between thyroid hormones and FGF23.

2. Materials and Methods

2.1 Study Design:

This study was designed with 30 adult male Wistar

rats (weighing 200–250 g, aged 8–10 weeks) from an accredited animal center. The rats were housed under standard environmental conditions (temperature 22 ± 2 °C, humidity 55 ± 5%, 12-hour light/dark cycle) with continuous access to water and food. All experimental procedures were conducted in accordance with institutional guidelines for the care of laboratory animals and were approved by the local ethics committee. Only males were used to avoid hormonal fluctuations during the estrous cycle.

After a one-week acclimatization period, the rats were randomly assigned to six groups (n=5 per group):

1. Control group: Administered an oral carrier solution (distilled water).

2. LT4 Therapy Group: Levothyroxine 50 mcg/kg.

3. LT4 High-Dose Group: Levothyroxine 200 mcg/kg.

4. LT4 High-Dose Group + Calcium: Levothyroxine 200 mcg/kg + Calcium Carbonate 500 mg/kg.

5. LT4 High-Dose Group + Vitamin D_3: Levothyroxine 200 mcg/kg + Vitamin D_3 1000 IU/kg.

6. LT4 High-Dose Group + Vitamin D_3 and K_2: Levothyroxine 200 mcg/kg + a combination of Vitamin D_3 1000 IU/kg and Vitamin K_2 30 mcg/kg. The LT4 therapeutic dose represents the physiological replacement dose, while the higher dose represents a model for TSH-suppressive therapy used in differentiated thyroid cancer. The supplementation doses were selected based on previous rodent studies investigating bone metabolism (2, 25).

2.2 Treatment Protocol:

Experimental hyperthyroidism was induced using levothyroxine sodium tablets (EU-Thyroxin®, Merck KGaA, Darmstadt, Germany). The tablets were dissolved in physiological saline before administration and then administered orally via gastric tube (gavage) once daily for 30 days. Calcium carbonate, vitamin D_3, and a vitamin D_3/K_2 combination were prepared as suspensions before administration. All treatments were administered in the morning under fasting conditions to minimize daily variability in hormone levels and ensure optimal absorption of levothyroxine. Weights were measured weekly, but no significant differences were observed in average body weight or feed intake between the experimental groups during the study period.

2.3 Sample Collection:

Thirty days after administration of the treatments, the rats were fasted overnight for 12 hours, then anesthetized with isoflurane. Blood samples were collected by cardiac puncture into serum separation tubes and allowed to coagulate at room temperature for 30 minutes. The serum was then centrifuged at 3000 rpm for 15 minutes at 4°C and stored at −80°C until analysis. Femur bone samples were also rapidly excised, cleaned of soft tissue, and immediately frozen in liquid nitrogen the samples were then stored at −20°C.

2.4 Biochemical Tests:

2.4.1 Thyroid Hormone Tests

The concentration of triiodothyronine (T3) and thyroid-stimulating hormone (TSH) in blood serum was measured using an enzyme-linked immunosorbent assay (ELISA) kit specifically designed for rat samples (SUNLONG BIOTECH, Hangzhou, China). All analyses were performed according to the manufacturer's instructions.

2.4.2 Bone Turnover Markers:

Fibroblast growth factor 23 (FGF23), a phosphorylated hormone from bone, was measured using an ELISA kit specifically designed for rat samples (SUNLONG BIOTECH) with a detection range of 10–500 pg/mL and a sensitivity of 5.0 ng/mL.

2.4.3 Vitamin D3 Measurement

Serum 25-hydroxyvitamin D_3 concentration was determined using a rat ELISA kit (SUNLONG BIOTECH) with a detection range of 5–200 ng/mL and a sensitivity of 2.0 ng/mL.

2.4.4 Mineral Measurement

Serum calcium and phosphorus concentrations were measured using a spectrophotometer method based on spectroscopy, using commercially available test kits and in accordance with the manufacturers' instructions. Calcium was estimated using the Arsenazo III method (BioResearch, Jordan), while phosphorus concentration was determined using the phosphomolipid method (Agappe Diagnostics, Switzerland). Absorbance values were recorded using a UV-Vis spectrometer. Calcium was measured at 650 nm, while phosphorus was measured at

340 nm. All measurements were performed in pairs to ensure accuracy, and final values are expressed in mg/dL.

2.5 Statistical Analysis:

Statistical analysis was performed using GraphPad Prism software (version 10.6.1). Statistical relationships between treatments were assessed using one-way ANOVA for quantitative data, followed by Tukey's post-hoc test. Pearson correlation analysis was used to evaluate the relationship between thyroid hormones and FGF23. In all statistical analyses, a p-value less than 0.05 was considered statistically significant.

3. Results:

3.1 Effect of Levothyroxine on thyroid hormones and FGF23:

Serum T3, TSH, and FGF23 levels are summarized in Table (1). Administration of a high dose of LT4 (200 µg/kg) resulted in hyperthyroidism, represented by a significant increase in T3 levels (3.103 ± 0.2053 ng/mL vs. 1.626 ± 0.0894 ng/mL in the control group, $P < 0.001$), with a significant decrease in TSH levels (1.840 ± 0.2320 ng/mL vs. 3.864 ± 0.293 ng/mL, $P = 0.036$). FGF23 levels also increased significantly in the high-dose group (164.6 ± 7.273 pg/mL vs. 114.3 ± 9.450 pg/mL in the control group, $P < 0.001$), representing a 44% increase. The therapeutic dose of levothyroxine (50 µg/kg) did not cause any significant changes in T3, TSH, or FGF23 levels, with FGF23 levels reaching 97.57 ± 4.894 pg/mL. Furthermore, calcium supplementation partially reduced the hormonal changes caused by LT4, as T3 levels decreased to 2.589 ± 0.1983 ng/mL, while TSH levels recovered to (4.768 ± 0.6013 ng/mL). FGF23 levels also decreased to (140.2 ± 4.052 pg/mL), but remained higher than the control group ($P = 0.047$). Vitamin D_3 supplementation showed a greater effect on restoring hormonal balance, with T3 levels decreasing to (2.030 ± 0.06104 ng/mL) and TSH levels increasing to (4.904 ± 0.6084 ng/mL).

FGF23 levels also decreased significantly to (135.6 ± 4.081 pg/mL, P = 0.001 compared to the high-dose group). The vitamin D_3 and K_2 combination group showed the greatest decrease in FGF23 levels (127.9 ± 1.981 pg/mL), with T3 and TSH values approaching those of the control group.

Table 1. Effect of Levothyroxine and Supplementation on Thyroid Hormones and FGF23

Group	T3 (ng/mL)	TSH (ng/mL)	FGF23 (pg/mL)	Vitamin D_3 (ng/mL)
Control	1.626 ± 0.0894	3.864 ± 0.293	114.3 ± 9.450	21.93 ± 5.094
Therapeutic Dose	1.910 ± 0.06872	4.468 ± 0.2965	97.57 ± 4.894	67.18 ± 10.61***
High Dose	3.103 ± 0.2053***	1.840 ± 0.2320*	164.6 ± 7.273***	18.70 ± 2.124
High Dose+ Ca	2.589 ± 0.1983***	4.768 ± 0.6013	140.2 ± 4.052*	36.89 ± 5.283
High Dose + D_3	2.030 ± 0.06104	4.904 ± 0.6084	135.6 ± 4.081##	52.60 ± 10.31***
High Dose + D_3/K_2	2.004 ± 0.06265	4.816 ± 0.3166	127.9 ± 1.981#	76.24 ± 16.35***

Values are expressed as mean ± SEM (n=5 per group).

*p<0.05, **p<0.001 vs. Control group

#p<0.05, ##p<0. 01 vs. High Dose group

Statistical analysis: One-way ANOVA followed by Tukey's post-hoc test.

3.2 Effect on Mineral Metabolism:

Table (2) shows the effect of the different treatments on mineral metabolism. The high LT4 dose led to an increase in serum calcium (9.654 ± 0.06306 mg/dL vs. 8.474 ± 0.388 mg/dL in the control group) and a significant increase in phosphorus (12.53 ± 1.003 mg/dL vs. 6.694 ± 0.3052 mg/dL, $P < 0.001$), indicating hyperphosphatemia. Calcium supplementation resulted in the highest serum calcium levels (10.41 ± 0.3725 mg/dL, $P < 0.001$, vs. control group), while phosphorus levels decreased to (9.204 ± 0.4194 mg/dL), although these values remained elevated compared to the control group. On the other hand, vitamin D_3 supplementation contributed to restoring mineral balance, with phosphorus levels returning to near-normal values (6.786 ± 0.3210 mg/dL) and calcium levels stabilizing (9.864 ± 0.2363 mg/dL). Similar results were observed in the vitamin D_3 and K_2 combination group (calcium: 9.514 ± 0.1667 mg/dL; phosphorus: 7.640 ± 0.3645 mg/dL). Furthermore, vitamin D_3 levels were significantly affected by the different treatments. The therapeutic dose of levothyroxine led to an increase in its level (67.18 ± 10.61 ng/ml), while the high dose caused a decrease in its levels (18.70 ± 2.124 ng/ml). This indicates that supplementation resulted in a dose-dependent increase, with the high-dose group receiving LT4 supplementation with D_3/K_2 showing the highest level (76.24 ± 16.53 ng/ml, $P < 0.001$).

Table 2. Effect of Levothyroxine and Supplementation on Mineral Metabolism

Group	Calcium (mg/dL)	Phosphorous(mg/dL)	Ca:P Ratio
Control	8.474 ± 0.388	6.694 ± 0.3052	1.27

Therapeutic Dose	8.410 ± 0.4227	6.570 ± 0.2264	1.28
High Dose	9.654 ± 0.06306	12.53 ± 1.003***	0.77
High Dose+ Ca	10.41 ± 0.3725***	9.204 ± 0.4194*	1.13
High Dose + D_3	9.864 ± 0.2363*	6.786 ± 0.3210	1.45
High Dose + D_3/K_2	9.514 ± 0.1667	7.640 ± 0.3645	1.24

Values are expressed as mean ± SEM (n=5 per group).

*p<0.05, **p<0.001 vs. Control group

Statistical analysis: One-way ANOVA followed by Tukey's post-hoc test.

Ca:P ratio calculated as Calcium/Phosphorus.

3.3 Correlation between Thyroid Hormones and FGF23:

Correlation analysis using Pearson's correlation coefficient showed a moderate positive correlation between T3 and FGF23 (r = 0.61), while a negative correlation was found between TSH and FGF23 (r = −0.45). FGF23 also showed a negative correlation with vitamin D_3 levels (r = −0.44), indicating a relationship between elevated FGF23 levels and decreased vitamin D_3 levels in the body.

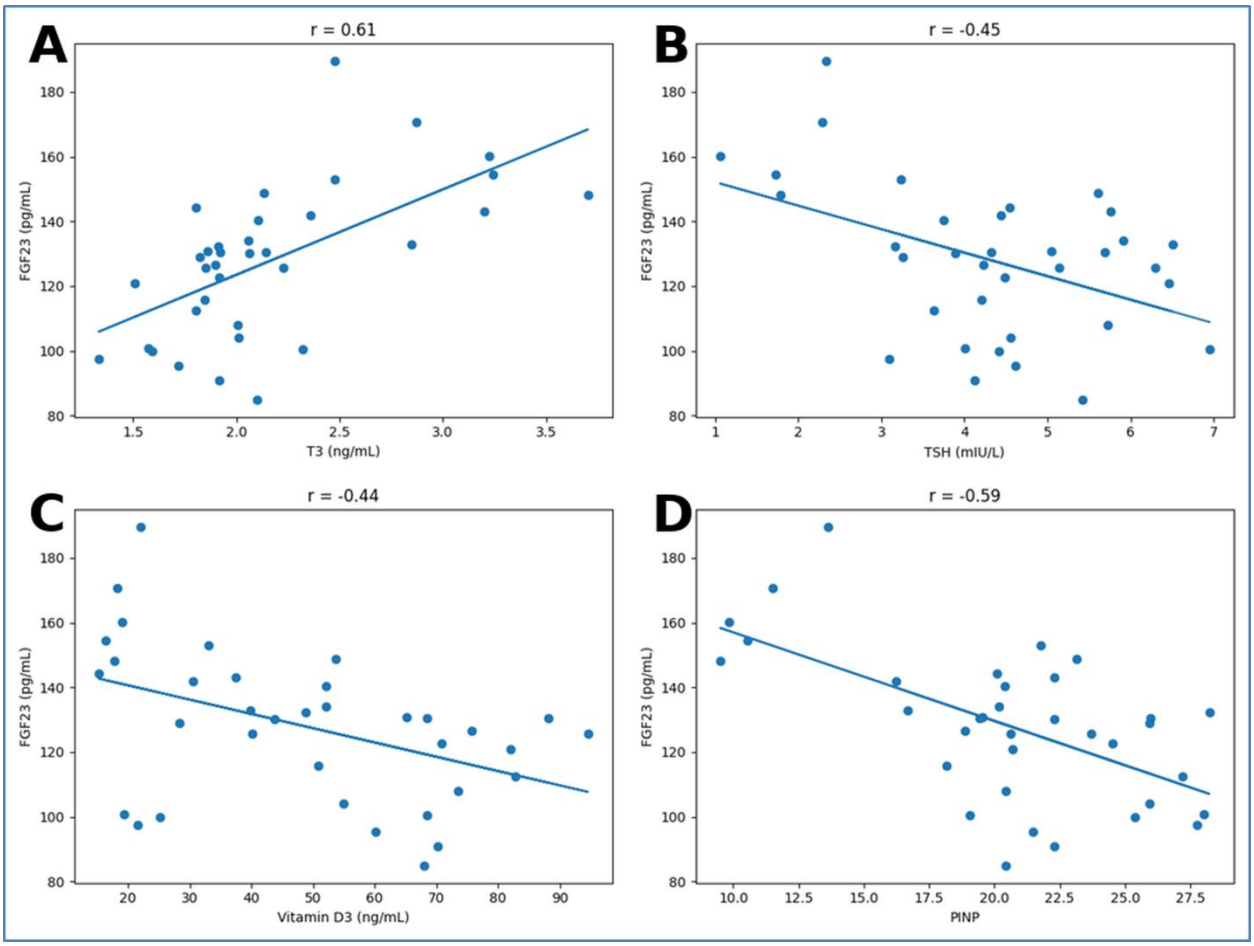

Fig. 1. Correlation analysis between FGF23 and biochemical parameters.

(A) T3 vs. FGF23.

(B) TSH vs. FGF23.

(C) Vitamin D_3 vs. FGF23.

(D) PINP vs. FGF23.

4. Discussion:

This study provides evidence supporting a regulatory interaction between thyroid hormones and FGF23. Levothyroxine-induced hyperthyroidism showed a significant increase in FGF23 secretion with a marked disturbance in mineral balance. Therefore, the results of this study indicate a regulatory axis between the thyroid gland and FGF23, and highlight the potential role of vitamin D_3

supplementation in modulating this regulatory pathway. The increase in T3 levels and the decrease in TSH levels in the high-dose levothyroxine group confirmed the successful induction of hyperthyroidism. The significant 44% increase in FGF23 levels represents an important metabolic response that has not been extensively studied in experimental hyperthyroidism models. These findings are consistent with the clinical observations reported by Lin et al. (2019), who documented changes in FGF23 levels in patients with Graves' disease (9). The mechanisms linking thyroid hormones to FGF23 production may be related to increased bone remodeling. Thyroid hormones stimulate osteoblast activity and accelerate bone turnover (14, 15), and since FGF23 is primarily produced by osteoblasts, increased bone metabolic activity may enhance its secretion. This interpretation supports the findings of Wang et al. (2024), who demonstrated a relationship between thyroid function and bone mineral density (4). The marked hyperphosphatemia observed in the high-dose LT4 group (12.53 mg/dL) may also contribute to the elevated FGF23 levels. Physiologically, FGF23 secretion is stimulated in response to elevated serum phosphate levels to promote its renal excretion (16, 17). However, chronically elevated thyroid hormones and FGF23 levels suggest that thyroid signaling may directly influence FGF23 production, independent of phosphate regulation.

Severe hyperphosphatemia and relative hypercalcemia in the high-dose group indicate a clear disruption of mineral metabolism.These changes in mineral metabolism are consistent with the increased bone resorption that occurs in hyperthyroidism, leading to the release of calcium and phosphate into the bloodstream (18, 17). Despite the elevated FGF23 levels, phosphate concentrations remained high, suggesting either partial resistance to the effects of FGF23 or that the amount of phosphate released from bone exceeded the kidneys' excretion capacity. Furthermore, the decrease in D_3 levels (18.70 ng/mL vs. 21.93 ng/mL in the control

group) may be related to the known effects of FGF23 on vitamin D_3 metabolism. This is because FGF23 inhibits 1α-hydroxylase and induces 24-hydroxylase, thereby reducing the synthesis of the active form of vitamin D_3 and increasing its breakdown (19, 20). The negative correlation between FGF23 and vitamin D_3 observed in this study supports this regulatory interaction.

Administering vitamin D_3 led to a significant improvement in hormonal and mineral indicators. In the high-dose group with vitamin D_3, T3 and TSH levels approached those of the control group, while FGF23 levels decreased significantly (135.6 pg/mL vs. 164.6 pg/mL in the high-dose group, $P = 0.001$). Additionally, mineral balance was restored, indicating a clear improvement in calcium-phosphate equilibrium. This result is consistent with Kamelian et al. (2018), who demonstrated that cholecalciferol treatment affects FGF23 levels in vitamin D3-deficient patients (12). Vitamin D_3 regulates FGF23 expression via a feedback mechanism through the vitamin D_3 receptor (VDR) in osteoblasts (21, 22). Furthermore, improved calcium absorption and reduced bone resorption may indirectly lead to decreased FGF23 secretion (23 , 24). Additionally, a study by Salem et al. (2023) demonstrated the protective effects of vitamin D_3 against hyperthyroid cardiomyopathy in rats (13). Our findings provide further evidence for the potential protective benefits of vitamin D_3 in improving mineral metabolism and regulating FGF23. The combination of vitamins D_3 and K_2 demonstrated a protective metabolic effect, with the lowest FGF23 level (127.9 pg/mL) recorded among the supplementation groups. Vitamin K_2 plays an important role in bone metabolism by activating proteins such as osteocalcin and matrix Gla protein, which regulate calcium deposition in bones and inhibit extraskeletal calcification (25, 26). The synergistic effects of vitamins D_3 and K_2 are likely due to the complementary regulation of calcium absorption and bone mineralization; vitamin D_3 enhances calcium availability and osteocalcin synthesis,

while vitamin K_2 activates osteocalcin to facilitate calcium incorporation into the bone matrix (27, 28). This coordinated interaction may contribute to reducing circulating blood mineral levels, thereby decreasing the stimulation of FGF23 secretion.

Identifying a regulatory axis between the thyroid gland and FGF23 may have significant clinical importance. Elevated FGF23 levels have been associated with adverse cardiovascular outcomes, including left ventricular hypertrophy and increased mortality in patients with chronic kidney disease (19,20). Saleh et al. (2025) also reported an association between FGF23 levels and left ventricular hypertrophy in children with kidney disease (17). Therefore, elevated FGF23 levels in hyperthyroidism may contribute to cardiovascular complications beyond the direct effects of thyroid hormones. Thus, measuring FGF23 may provide additional information about metabolic complications in hyperthyroid patients. In addition, the strong correlation between T3 ($p<0.001$) and FGF23 ($r = 0.782$) suggests that FGF23 may be a biomarker reflecting thyroid hormone activity at the tissue level.

This study had several limitations, including a 30-day trial period that may not be sufficient to demonstrate the long-term effects of hyperthyroidism on bone structure and mineral metabolism. Furthermore, bone turnover markers such as PINP and CTX-1, which could provide a deeper understanding of the underlying mechanisms, were not measured. Future studies should focus on the molecular mechanisms by which thyroid hormones regulate FGF23 transcription in osteoblasts and signaling pathways such as Wnt/β-catenin and MAPK. The FGF23-Klotho axis should also be investigated in hyperthyroidism, as Klotho acts as a co-receptor for FGF23 signaling in the kidney (19 , 20). Pasaoglu et al. (2021) reported interactions between FGF23, alpha-Klotho, and vitamin D_3 in the regulation of mineral metabolism (12), suggesting that alpha-Klotho regulation may also be involved in thyroid disorders.

5. Conclusion:

This study demonstrates a regulatory axis between the thyroid gland and FGF23. Levothyroxine-induced hyperthyroidism leads to a significant increase in FGF23 secretion and mineral imbalance. The strong positive correlation between T3 and FGF23 ($r = 0.782$, $p < 0.001$) supports a direct relationship between thyroid hormone activity and FGF23 regulation. High doses of T3 resulted in hyperphosphatemia, decreased vitamin D_3 levels, and increased FGF23 secretion, indicating a coordinated metabolic response to increased thyroid hormones was observed. Vitamin D_3 supplementation contributed to a 17.6% reduction in FGF23 levels and restored calcium and phosphate balance, while the combination of vitamin D_3 and K_2 resulted in the best metabolic outcome. These findings suggest that vitamin D_3 supplementation may be a useful preventative strategy for mitigating mineral imbalances and protecting bone health in hyperthyroidism. Furthermore, FGF23 may represent a potential biomarker reflecting thyroid hormone activity and metabolic complications associated with thyroid disorders. Further mechanistic clinical studies are needed to confirm these findings and explore their applications in the management of thyroid-related metabolic diseases.

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