BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

ARTICLE

Do Endocrinopathies Differ in Most Prevalent Hemoglobinopathy of Middle East: Beta-thalassemia?

Salma Ahi[1*] Mohsen Adelpour[1] Bahareh Haghdoost[2] Ali Jaberi[3]

1. Research Center for Noncommunicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran
2. Student Research Committee, Jahrom University of Medical Sciences, Jahrom, Iran
3. Student Research Committee, Bushehr University of Medical Science, Bushehr, Iran

ARTICLE INFO

Article history
Received: 13 July 2022
Revised: 1 August 2022
Accepted: 4 August 2022
Published Online: 8 August 2022

Keywords:
Thalassemia
Osteoporosis
Bone mineral densitometry
Endocrinopathies

ABSTRACT

Repeated blood transfusions in thalassemia patients is followed by endocrinopathies as diabetes, hypothyroidism, hypogonadism, hypoparathyroidism, and disorders in calcium and vitamin D homeostasis. The aim of this study was to evaluate the association of beta-thalassemia patients endocrinopathies and osteoporosis. Serum level of some factors related to the function of gonads, thyroid, adrenal, and pancreas along with serum levels of calcium, phosphate, albumin, vitamin D, and iron were measured. Bone marrow density was tested via dual-energy x-ray absorptiometry (DXA densitometry). In this study, 56 patients with major thalassemia were investigated. Paraclinical analysis indicated osteopenia in 17 (30.4%) and osteoporosis in 39 patients (69.6%) in addition to other types of endocrine disorders, such as hypogonadism in 29 (51.8%), hypothyroidism in 13 (23.2%), hypoparathyroidism in 1 (1.8%), hypocortisolism in 2 (3.6%), and diabetes in 9 (16.1%) patients. Endocrinopathies had no significant relationship with osteoporosis and osteopenia in men. However, hypogonadism had a significant relationship with osteoporosis and osteopenia in women with thalassemia. Estradiol level was lower in women with osteoporosis in comparison with women with osteopenia. Ferritin levels had neither association with osteoporosis nor with LH levels (P>0.05). Secondary hypogonadism disorders are the main causes of osteoporosis and osteopenia in female beta-thalassemia patients.

1. Introduction

Thalassemia is a genetic disorder resulting in disorders of hemoglobin synthesis which is diagnosed by a lack or shortage of human hemoglobin globin chains [1]. Patients with major beta thalassemia are in need of frequent blood transfusion. Frequent blood transfusion increases iron level of the body [2]. The human body has a limited capacity for controlling such kind of iron overload [3]. Liver, heart, and

*Corresponding Author:
Salma Ahi,
Research Center for Noncommunicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran;
Email: salmaahi.61@gmail.com

DOI: https://doi.org/10.30564/jer.v4i2.4888

endocrine glands have the highest sensitivity toward iron overload. However, iron deposits in most of the organs, such as the pancreas, pituitary gland, and parathyroid [4]. The most common disorder of endocrine glands in patients with major thalassemia is hypogonadism which is more commonly caused by iron deposit in pituitary gland [5]. Chelator agents as Deferoxamine (DFO) are used for the prevention of iron overload in major thalassemia patients [6]. However, inappropriate application of chelator agents reduces bone density and causes growth retardation in patients with major thalassemia [7]. Bielinsk et al. reported that all the patients with major thalassemia are exposed to reduced bone density [8]. Reduced bone density emerges as osteoporosis and osteopenia disorders which are the main underlies of disabilities in patients with major thalassemia and increase the risk of bone fracture [9]. Iron overload may cause calcium and vitamin D homeostasis disorders [10]. Vitamin D deficiency in patients with major thalassemia along with iron overload will intensify their bone disorders [11]. Due to the high prevalence of thalassemia in our country, we have decided to investigate the reasons causing osteoporosis in these patients.

2. Materials and Methods

This is an analytic-cross sectional study which investigates patients with major thalassemia who have referred to Motahari Hospital in Jahrom. This study was approved by Research Ethical Committee of Jahrom University of medical sciences (with registration code of IR.JUMS.REC.1395.108). Major thalassemia was diagnosed in the patients based on their number of blood transfusions (more than 8 blood transfusions) in the year before participating in the study and Hb electrophoresis. Excluding criteria is age below 10 or more than 50 years old, celiac and malabsorption and patients who were receiving treatments with growth hormone and glucocorticoids were excluded. Participants' at least have had ten to fifty years of disease duration based on their age and all of them were on chelation/blood transfusions more than 8 times in a year.

3. Evaluation

T-score based densitometry determines the osteoporosis (T-score lower than –2.5 indicates standard deviation in DXA densitometry) and osteopenia (T-score ranging from –1 to –2.5 indicates standard deviation in densitometry) in participants more than 45 years old and z score were used to determine secendary osteoprosis in younger participants, Z Score –2.5 or less is compatible with criteria for definition of secondary osteoporosis [12]. Densitometry in this study was carried out using Hollogic discovery WI DXA device, made in Germany. Cortisol and adrenocorticotropic hormone (ACTH) were investigated via Electrochemiluminescence (ECL) method (ACTH was only estimated in patients with hypocortisolism). T4 level was estimated via ECL method. TSH levels were estimated via ECL method. Thyroid peroxidase autoantibody (TPOAb) was only analyzed in patients with hypothyroidism.

Fasting blood sugar was analyzed by SELECTRA E. Hemoglobin A1c (HbA1C) was only analyzed in patients with diabetes via chemical machine.

Calcium and Phosphate were analyzed by the photometric method. Albumin, which is used for determining hypocalcemia, was analyzed via bromocresol green method. Vitamin D deficiency is lower than 15 ng/mL levels, vitamin D insufficiency is between 15 ng/dL ~ 20 ng/dL levels, and normal vitamin D is higher than 20 ng/mL levels [13].

4. Statistical Analysis

Data analysis was done via SPSS software version 21. The relationships between endocrine disorders were compared based on the Chi-square test. Nonparametric Mann–Whitney test was used to compare the levels of variables in patients with the osteoporosis. Moreover, the correlation between data was analyzed by Pearson test. Normal data were reported as mean ± standard deviation, and nonparametric data were reported as median (first and fourth quartiles). $P < 0.05$ was considered as the significance level.

5. Results

In this study, 56 patients with major thalassemia and the average age of 27.37 ± 7.93 were investigated. Demographic data of the participants are presented in Table 1. Paraclinical analysis indicated osteopenia in 17 (30.4%) and osteoporosis in 39 patients (69.6%) in addition to other types of endocrine disorders, such as hypogonadism in 29 (51.8%), hypothyroidism in 13 (23.2%), hypoparathyroidism in 1 (1.8%), hypocortisolism in 2 (3.6%), and diabetes in 9 (16.1%) patients.

The relationship between Hypogonadism and Osteoprosis has been described in Table 2. According to this table, although there was no significant relationship between hypothyroidism, hypocortisolism, type 1 diabetes, hypoparathyroidism, and hemochromatosis with osteoporosis or osteopenia disaggregated by gender, there was a significant relationship between osteoporosis and hypogonadism in women under investigation ($P < 0.05$). This kind of relationship was not observed in male patients. Hypogonadal women with major thalassemia were 7.55 times more exposed to the risks of osteoporosis in comparison with non-hypogonadal women (CI%95:1.49-

Table 1. Basal characteristics of study subjects.

Characteristic	Men	Women	P Value
Number, n (%)	22	34	-
Age, y	27.63±8.66	27.20±8.07	>0.05
Weight, cm	56.86±8.9	48.35±8.96	0.002
height, kg	163±8.22	153.70±6.85	<0.01
Education *	2(9.09)	8(23.52)	>0.05
Diabetes mellitus History, n (%)	3(13.63)	5(14.70)	>0.05
Fracture History, n (%)	0(0)	7(20.58)	0.023
Heart disease History†, n (%)	0(0)	2(5.88)	>0.05
Thyroid disease History, n (%)	1(4.54)	2(5.88)	>0.05
Dairy consumption**, n (%)	18(81.81)	32(94.11)	>0.05
Sunlight exposure***, n (%)	1(4.54)	14(14.17)	<0.01
Vitamin D****, n (%)	2(9.09)	10(29.41)	0.006

cm: centimeters. y: years of old. kg: kilograms. †: history of being admitted in hospital for cardiac disease**.** *: university educated patients. **: number of patients with lower than 5 unit dairy consumption per day. ***: number of patients with lower than 30 minutes sunlight exposure per day. ****: number of Vitamin D deficient patients.

Table 2. The relationship between Hypogonadism and Osteoporosis

No.		Osteoporosis		Osteopenia		Chi square test
		%	No.	%		
Women	Hypogonadal	17	50	17	50	OR=7.55(CI%95:1.49-38.20) p-value=0.010 chi-square value=6.68
	Non-Hypogonadal	6	17.64	6	17.64	

38.20). The results of paraclinical tests are presented in Table 3.

The results of the Mann-Whitney test in comparison of estradiol level in women with osteoporosis and women with osteopenia, indicated that women with osteoporosis had lower estradiol median (Mann-Whitney U = 37.00, p-value = 0.001). The results of paraclinical tests are presented in Table 3. These results indicate that patients with osteopenia had significantly higher Luteinizing hormone (LH) levels in comparison with patients with osteoporosis ($P < 0.01$). No significant difference was observed between vitamin D levels of patients with osteopenia and osteoporosis.

Correlation of different variables indicated that with an increase in age of osteoporosis patients, parathyroid hormone (PTH) level increases ($r = 0.324$, $p = 0.032$), however, albumin level decreases ($r = –0.384$, $p = 0.035$). With an increase in the weights of patients with osteoporosis, Bone Mineral Density (BMD) increases ($r = 0.322$, $p = 0.045$). Increased levels of follicle stimulating hormone (FSH) and LH in patients with osteoporosis are correlated with decreased levels of BMD ($r = 0.362$, $p = 0.024$ and $r = 0.392$, $p = 0.012$ respectively). Thyroid function tests indicated that T4 increases along with BMD and vitamin D in patients with osteopenia ($r = 0.528$ $p = 0.029$ and $r = 0.553$ $p = 0.021$ respectively).

Table 3. Para clinical Results

	BMD		
	Osteoporosis	Osteopenia	p-value
n	17	39	-
Age	29(21-33)	26(22-27)	0.090
LH	4.2(1.1-7.6)	7.2(4.95-13.25)	0.010
FSH	2.4(0.6-5.5)	2.5(1.84-4.25)	0.817
Testosterone	2.13(0.777-5.61)	4.965(1.92-7.22)	0.269
Estradiol	8.37(5-59)	103.3(33.9-21)	0.001
Cortisol	19(11.9-23)	18.7(14.4-28)	0.340
T4	7.7(6.6-8.9)	8.7(7.3-10)	0.064
TSH	2.8(1.8-4)	3.4(1.715-4.235)	0.568
FBS	95(87-109)	90(81-120.5)	0.318
HBA1c	7.1(4.875-7.8)	8.1(6-8.5)	0.432
Ca	9.7(9.4-10)	9.5(9.35-10)	0.754
p	4.8(4.2-5.4)	4.6(4-5.15)	0.492
Alb	4.5(4.3-4.7)	4.5(4.15-4.8)	0.893
PTH	21.4(9.1-30.5)	13.9(7.05-23.15)	0.222
Vitamin D	18.7(10.5-26)	22.1(10.65-25.85)	0.957
Ferritin	895(677-1004)	951(711.5-1439)	0.206
TPOAb	3.75(1.725-7)	1.8(0.95-3.05)	0.142

TSH: thyroid-stimulating hormone, FBS: Fasting blood sugar, LH: Luteinizing Hormone, FSH: follicle stimulating hormone, HbA1C: Hemoglobin A1C, PTH: parathyroid Hormone, TPOAb: thyroid peroxidase antibody, Alb: Albumin, Ca: Calcium, P: phosphorus

6. Discussion

Bone changes in patients with major thalassemia, and their expansive effects on physiology of endocrine system, have transformed thalassemia into a great dilemma [14]. Osteopenia was observed in 17 (30.4%) and osteoporosis in 39 patients (69.6%) and no healthy person underwent BMD analysis. These results were consistent with the reported results of Bielinski et al. on patients with thalassemia who were exposed to osteopenia and osteoporosis [8]. Anapliotou et al. claimed that all the patients with thalassemia experience decreased the level of BMD [15]. The most common disorders in patients with thalassemia are bone disorders which emerge as rickets, scoliosis, severe bone pains, deformation of spinal cord, severe osteopenia and osteoporosis, and multiple fractures. Pathogens of bone disorders are caused by the endocrine disorders, nutrition disorders, iron overload, reduced trabecular bone, thinning of cortex, and inefficient hematopoiesis [16]. Patients with major thalassemia have low levels of BMD. Most of them suffer from severe bone fractures and pains [17]. The results of this study indicated that, unlike men, there was a significant relationship between osteoporosis and hypogonadism in women. Moreover, there was no significant relationship between other types of endocrine disorders, such as diabetes, hemochromatosis, hypoparathyroidism, hypocortisolism, hypothyroidism, and osteoporosis in both men and women. Hypogonadism in women refers to weak or abnormal axis of hypothalamus- pituitary gland-ovary which may be observed as estradiol deficiency and increased levels of LH and FSH [18]. Primary hypogonadism or hypergonadotropic hypogonadism due to iron overload and iron deposits in gonads, is a possible mechanism of secondary osteoporosis in thalassemia also other mechanism is, hypogonadotropic hypogonadism or secondary hypogonadism due to iron deposits in pituitary and its dysfunction [19]. Estradiol protects the bones and prevents osteoporosis by decreasing apoptosis of osteoblasts and increasing apoptosis of osteoclasts [20]. Our study revealed that lower levels of estradiol are connected to osteoporosis, and patients with hypogonadism have lower levels of estradiol. These findings are consistent with the reposted findings of Anapllotou et al. who indicated that an increase in the level of estrogen of female major thalassemia patients will improve the BMD status [15]. Therefore, Hypogonadal women with major thalassemia were 7.55 times more exposed to the risks of osteoporosis in comparison with non-hypogonadal women (CI%95:1.49-38.20). These findings are consistent with the results of previous researches. Iron overload causes hypogonadism in gonadotropic cells of the pituitary gland of patients with

major thalassemia [21]. In the present study higher levels of ferritin was correlated with reduced serum level of calcium in men ($p = 0.06$, $r = 508$). These results are consistent with the reported results of Li Wang et al. They claimed that extracellular iron overload reduces absorption of calcium [22]. The role of calcium deficiency in development of osteoporosis is well documented [23,24]. Furthermore, our study indicated that high levels of FSH and LH in patients with osteoporosis will reduce BMD. However, women with osteopenia had significantly higher levels of LH than patients with osteoporosis. The exact role of LH in skeletal hemostasis is an area of uncertainty [25]. Bone protection is caused by strong effect of FSH hormone on bones and gender differences. Jie Wang also has referred to destructive role of FSH on bones [26]. But our subjects were patients with thalassemia which may reduce the value of this comparison. Berge et al. stated that ferritin has not a direct relationship with the level of female sex hormones [27], however, it has a direct relationship with male sex hormones [28]. Xu ZR et al.'s study, which was carried out on the society of Chinese women, indicated that increased LH decreases BMD [29]. These results are consistent with our findings. It seems that the relationship between LH level and osteoporosis or osteopenia is not dependent on the number of blood transfusions in patients with thalassemia. In fact, iron overload and its deposit in gonads may be followed by a simultaneous increase of LH and FSH levels, while this was not the case with our subjects. Therefore, primary ovarian failure was not observed in our subjects and we should look after other factors for hypo-gonadotropic hypogonadism. Thyrotoxicosis or excessive increase in thyroid hormones is associated with osteoporosis. Hypothyroidism can also reduce BMD [30]. But our study showed that T4 increase is positively correlated with an increase in BMD scores. However, the increase in T4 of our patients occurred in the normal range. So the appropriate increase in T4 levels can reduce the risk of osteoporosis in thalassemia patients. T4 accelerates bone remodeling. High levels of thyroid hormones in hyperthyroidism, due to excessive increase in the velocity of the bone remodeling cycle, can lead to incomplete cycles and osteoporosis [31]. In a cohort study in patients undergoing thyroidectomy, it was shown that thyroidectomy increases the chance of osteoporosis [32]. While several researches revealed that in the absence of endogenous thyroid hormone production after total thyroidectomy, replacement therapy with exogenous T4 does not affect BMD [33], it seems that thyroid hormones at normal concentrations tend to regulate bone metabolism and reduce the risk of BMD. Increased T4 was also correlated with increased vitamin D in osteoporosis patients. According to studies, thyroid hormones in hyperthyroid patients reduce the level of vitamin D by suppressing the transcription of the 25-Hydroxyvitamin D3 1α-Hydroxylase gene that is responsible for the production of vitamin D in the kidney [34]. It seems that these results are not consistent with our study, but changes in the T4 concentration of our subjects are occurring in normal range and vary with changes due to abnormal levels. However, there was no relationship between vitamin D levels of our participants and osteoporosis.

7. Conclusions

Hypogonadotropic hypogonadism is the most common endocrine disorder which was observed in our subjects (51.8%). Moreover, there was a significant relationship between osteoporosis and hypogonadism in our female subjects. It can be deducted that secondary hypogonadism disorders in women may lead in osteoporosis and osteopenia. However, there was no significant relationship between hypogonadism, hypothyroidism, hypocortisolism, type-1 diabetes, and hypoparathyroidism with osteoporosis or osteopenia in men.

Acknowledgment

We have to appreciate department of Internal Medicine and Endocrinology of Jahrom University of medical sciences.

Statement of Ethics

This manuscript was approved by Ethics committee of Jahrom University of medical sciences.

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Dr. Salma Ahi has designed the whole study. Bahareh Haghdoost, has collected the samples of thalassemia patients and followed the preclinical tests. Study has been analyzed and written by Ali Jaberi and Mohsen Adelpour.

References

[1] Galanello, R., Origa, R., 2010. Beta-thalassemia. Orphanet Journal of Rare Diseases. 5(1), 11.

[2] Mishra, A.K., Tiwari, A., 2013. Iron overload in beta thalassaemia major and intermedia patients. Maedica. 8(4), 328.

[3] Porter, J.B., 2005. Monitoring and treatment of iron overload: state of the art and new approaches. Semi-

nars in Hematology. 42(2 Suppl 1), S14-18.

[4] Andrews, N.C., 1999. Disorders of iron metabolism. New England Journal of Medicine. 341(26), 1986-1995.

[5] Chern, J.P., Lin, K.H., Tsai, W.Y., et al., 2003. Hypogonadotropic hypogonadism and hematologic phenotype in patients with transfusion-dependent beta-thalassemia. Journal of Pediatric Hematology /Oncology. 25(11), 880-884.

[6] Giardina, P.J., Grady, R.W., 1995. Chelation therapy in beta-thalassemia: the benefits and limitations of desferrioxamine. Seminars in hematology. 32(4), 304-312.

[7] De Virgillis, S., Congia, M., Frau, F., et al., 1988. Deferoxamine-induced growth retardation in patients with thalassemia major. The Journal of Pediatrics. 113(4), 661-669.

[8] Bielinski, B.K., Darbyshire, P., Mathers, L., et al., 2001. Bone density in the Asian thalassaemic population: a cross-sectional review. Acta Paediatrica. 90(11), 1262-1266.

[9] Haidar, R., Musallam, K.M., Taher, A.T., 2011. Bone disease and skeletal complications in patients with β thalassemia major. Bone. 48(3), 425-432.

[10] Root, A.W., Diamond, F.B., 2002. Calcium metabolism, normal homeostasis and disorders of calcium metabolism in the child and adolescent. Sperling MA, editor. Pediatric endocrinology. 2nd ed. Philadelphia: Saunders. pp. 65-110.

[11] Soliman, A., De Sanctis, V., Yassin, M., 2013. Vitamin D status in thalassemia major: an update. Mediterranean Journal of Hematology and Infectious Diseases. 5(1).

[12] Blake, G.M., Fogelman, I., 2007. The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. Postgraduate Medical Journal. 83(982), 509-517.

[13] Altrichter, S., Boodstein, N., Maurer, M., 2009. Matrix metalloproteinase-9: a novel biomarker for monitoring disease activity in patients with chronic urticaria patients? Allergy. 64(4), 652-656.

[14] Vogiatzi, M.G., Macklin, E.A., Fung, E.B., et al., 2009. Bone disease in thalassemia: a frequent and still unresolved problem. Journal of Bone and Mineral Research. 24(3), 543-557.

[15] Anapliotou, M.L., Kastanias, I.T., Psara, P., et al., 1995. The contribution of hypogonadism to the development of osteoporosis in thalassaemia major: new therapeutic approaches. Clinical Endocrinology. 42(3), 279-287.

[16] Benigno, V., Bertelloni, S., Baroncelli, G.I., et al., 2003. Effects of thalassemia major on bone mineral density in late adolescence. Journal of Pediatric Endocrinology & Metabolism. 16(Suppl 2), 337-342.

[17] Voskaridou, E., Terpos, E., 2008. Pathogenesis and management of osteoporosis in thalassemia. Pediatric Endocrinology Reviews: PER. 6, 86-93.

[18] Rothman, M.S., Wierman, M.E., 2008. Female hypogonadism: evaluation of the hypothalamic–pituitary–ovarian axis. Pituitary. 11(2), 163.

[19] Emerit, J., Beaumont, C., Trivin, F., 2001. Iron metabolism, free radicals, and oxidative injury. Biomedicine & Pharmacotherapy. 55(6), 333-339.

[20] Okman-Kilic, T., 2015. Conference proceedings. Estrogen Deficiency and Osteoporosis.

[21] Srisukh, S., Ongphiphadhanakul, B., Bunnag, P., 2016. Hypogonadism in thalassemia major patients. Journal of Clinical & Translational Endocrinology. 5, 42-45.

[22] Wang, L., Li, Q., Duan, X.L., et al., 2005. Effects of extracellular iron concentration on calcium absorption and relationship between Ca^{2+} and cell apoptosis in Caco-2 cells. World Journal of Gastroenterology: WJG. 11(19), 2916.

[23] Sahota, O., 2000. Osteoporosis and the role of vitamin D and calcium-vitamin D deficiency, vitamin D insufficiency and vitamin D sufficiency. Age and Ageing. 29(4), 301-304.

[24] Rodrıguez-Martınez, M.A., Garcıa-Cohen, E.C., 2002. Role of Ca^{2+} and vitamin D in the prevention and treatment of osteoporosis. Pharmacology & therapeutics. 93(1), 37-49.

[25] Mills, E.G., Yang, L., Nielsen, M.F., et al., 2021. The Relationship between Bone and Reproductive Hormones beyond Estrogens and Androgens. Endocrine Review. 42(6), 691-719.

[26] Wang, J., Zhang, W., Yu, C., et al., 2015. Follicle-stimulating hormone increases the risk of postmenopausal osteoporosis by stimulating osteoclast differentiation. PLoS One. 10(8), e0134986.

[27] Liu, Z., Ye, F., Zhang, H., et al., 2013. The association between the levels of serum ferritin and sex hormones in a large scale of Chinese male population. PloS one. 8(10), e75908.

[28] Berge, L.N., Bønaa, K.H., Nordøy, A., 1994. Serum ferritin, sex hormones, and cardiovascular risk factors in healthy women. Arteriosclerosis and Thrombosis: A Journal of Vascular Biology. 14(6), 857-861.

[29] Xu, Z.R., Wang, A.H., Wu, X.P., et al., 2009. Relationship of age-related concentrations of serum FSH and LH with bone mineral density, prevalence of osteoporosis in native Chinese women. Clinica Chimi-

ca Acta. 400(1-2).

[30] Dhanwal, D.K., 2011. Thyroid disorders and bone mineral metabolism. Indian Journal of Endocrinology and Metabolism. 15(Suppl2), S107.

[31] Ahn, H.Y., 2018. Effects of Abnormal Thyroid Function Status to Bone Metabolism. International Journal of Thyroidology. 11(1), 21-25.

[32] Hung, C.L., Yeh, C.C., Sung, P.S., et al., 2018. Is Partial or Total Thyroidectomy Associated with Risk of Long-Term Osteoporosis: A Nationwide Population-Based Study. World Journal of Surgery. 14, 1-8.

[33] Kim, C.W., Hong, S., Oh, S.H., et al., 2015. Change of bone mineral density and biochemical markers of bone turnover in patients on suppressive levothyroxine therapy for differentiated thyroid carcinoma. Journal of Bone Metabolism. 22, 135–141.

[34] Kozai, M., Yamamoto, H., Ishiguro, M., et al., 2013. Thyroid hormones decrease plasma 1α, 25-dihydroxyvitamin D levels through transcriptional repression of the renal 25-hydroxyvitamin D3 1α-hydroxylase gene (CYP27B1). Endocrinology. 154(2), 609-622.