ORIGINAL PAPER

Submitted: 17.10.2022
Accepted: 27.12.2022
Early publication date: 20.06.2023

Endokrynologia Polska
DOI: 10.5603/EP.a2023.0043
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 74; Number/Numer 4/2023

Association between TSH suppression therapy and type 2 deiodinase gene polymorphism in differentiated thyroid carcinoma

Xiaoke Zheng[1], Lichang Zhong[2], Tianjiao Zhou[1], Feng Zhao[1], Bin Chen[1]

[1]*Department of Otolaryngology Head and Neck Surgery, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China*
[2]*Department of Ultrasound in Medicine, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Abstract

Introduction: Oral levothyroxine (L-T4) suppression of thyroid-stimulating hormone (TSH) levels is the most commonly used clinical approach to manage and treat patients after thyroid cancer surgery. This study aimed to investigate the association between TSH suppression therapy and type 2 deiodinase gene (DIO2) polymorphism in differentiated thyroid carcinoma (DTC).

Material and methods: A total of 240 patients with DTC who received total thyroidectomy (TT; 120) and hemithyroidectomy (HT; 120) were enrolled in this study. The serum TSH, free triiodothyronine (FT3), and free thyroxine (FT4) levels were detected using an automatic serum immune analyser and electrochemiluminescence immunoassay. Based on the results of DIO2 gene detection, 3 genotypes of Thr92Ala were detected.

Results: The serum TSH levels were inhibited after oral L-T4 treatment, but the proportion of patients who reached the TSH suppression standard in the hemithyroidectomy group was higher than in the total thyroidectomy group. After TSH suppression treatment, serum FT4 levels were increased in both total thyroidectomy and hemithyroidectomy. The difference in serum TSH, FT3, and FT4 levels was associated with different genotypes, and patients with high cytosine cytosine (CC) genotypes may have difficulty meeting the TSH suppression criteria.

Conclusions: Patients who underwent total thyroidectomy exhibited higher postoperative serum FT4 levels than patients in the hemithyroidectomy group after TSH suppression therapy. The Thr92Ala polymorphism of type 2 deiodinase (D2) was associated with TSH suppression therapy. **(Endokrynol Pol 2023; 74 (4): 408–413)**

Key words: *differentiated thyroid carcinoma; TSH; DIO2; Thr92Ala; genotypes*

Introduction

According to the cancer statistics released by China in 2020, the incidence of thyroid cancer has increased in recent decades [1]. Differentiated thyroid cancer (DTC) is the most common malignant thyroid cancer. Surgery is still the first choice in the treatment of DTC, such as total thyroidectomy (TT) and hemithyroidectomy (HT) [2]. Oral levothyroxine (L-T4) inhibition of thyroid stimulating hormone (TSH) level is the most commonly used method in the clinical management and treatment of patients with DTC after surgery [3]. However, about 20% of patients with an adequate dose of L-T4 drugs still do not achieve effective inhibition of TSH levels, but the blood-free thyroxine (FT4) levels are increased, which affects the effect of postoperative management and treatment of thyroid cancer patients [4].

Thyroid hormones mainly include 3,3′,5′-triiodothyronine (T3) and 3,5,3′,5′-thyroxine (T4), which are produced by the thyroid gland under normal conditions. 80% of T3 is transformed from T4 through deiodinase [5]. However, triiodothyronine (T3) is the hormone that plays the function of thyroxine [6]. Thyroxine deiodinase can be divided into type 1 deiodinase (D1), type 2 deiodinase (D2), and type 3 deiodinase (D3), which have different sites of action on thyroid hormone [7]. In addition, the distribution of each deiodinase in the body tissue is different, among which, D2 is mainly distributed in the pituitary gland, hypothalamus, and thyroid gland; hence, D2 plays a crucial role in TSH suppression therapy [8]. D2 is the most important enzyme in thyroid hormone metabolism, which mainly acts on the transformation from T4 to T3 [9]. The D2 gene is polymorphic, which

Bin Chen, Department of Otolaryngology Head and Neck Surgery, Shanghai Sixth People's Hospital Affiliated, Shanghai Jiao Tong University School of Medicine, 600 Yishan Road, Shanghai 200233, China, tel: +86-021-38297000; e-mail: binchendoc@163.com

can affect thyroid hormone metabolism and lead to abnormal hormone levels [10, 11]. This phenomenon indicates that D2 gene polymorphism may be associated with TSH failure in patients with thyroid cancer after the operation. D2 is mostly located in the endoplasmic reticulum, and the gene encoding D2 (DIO2) is located on chromosome 14q24.3 [12, 13]. DIO2 has gene polymorphisms, and it is more common to change alanine to threonine due to the mutation of codon 92 acid, thus producing the Thr92Ala gene polymorphism of DIO2 [14]. Studies have shown that D2 Thr92Ala (rs225014) may affect the response rate of D2, and more L-T4 is required to achieve TSH suppression for thyroidectomy patients [15]. Exploring the D2 gene polymorphism is of great significance for the effective inhibition of TSH after thyroid cancer surgery.

This study tried to investigate the relationship between thyroid hormone changes and D2 genotype in DTC patients after different surgical methods, to further understand the influence of different D2 gene polymorphisms and the thyroid residual amount on thyroid hormone metabolism, and to seek breakthroughs for better management, diagnosis, and treatment of DTC patients after surgery.

Material and methods

Study population

A total of 240 patients who underwent thyroidectomy in the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, from January 2019 to December 2021, were enrolled in this study. The inclusion criteria included the following: (1) first-time surgery; (2) patients with complete thyroid function examination in our hospital within one month before surgery; (3) postoperative paraffin pathology was DTC; (4) the patient agreed to blood testing and signed an informed consent form; and (5) the surgical methods were TT and HT. The groups were as follows: HT group (A group, n = 120) — hemithyroidectomy plus central lymph node dissection (with or without cervical lymph node dissection); TT group (B group; n = 120) — total thyroidectomy + unilateral/bilateral central lymph node dissection (with or without unilateral/bilateral cervical lymph node dissection). The institutional Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine approved this study.

Postoperative follow-up and TSH levels

All patients were given oral L-T4 after surgery (50 μg levothyroxine sodium tablets, 100 tablets, Merck, Germany). The initial dose of L-T4 for patients who underwent HT after surgery was 50 μg/day, while the initial dose for TT patients was 100 μg/day, and the initial dose of L-T4 for HT patients with contralateral partial resection was 50 μg/day or 75 μg/day. The average dose of L-T4 for the HT surgery group (A group) was 106.875 μg/day, and for the TT surgery group it was 125.625 μg/day. The TSH concentration of thyroid cancer patients was maintained at ≤ 0.1–0.3 mU/L in stage I, 0.05–0.1 mU/L in stage II and stage III, and < 0.05 mU/L in stage IV.

If the TSH level of postoperative patients did not reach the standard, the dose of the drug was adjusted appropriately, and the dose of each adjustment was 12.5 μg or 25 μg. After the TSH of the enrolled patients reached and stabilized after the operation, the value of the first TSH reached the standard, and the FT3 and FT4 values of the same detection were taken using an automatic serum immune analyser and electrochemiluminescence immunoassay. The enrolled patients were treated with L-T4 for one year and those whose serum TSH level did not reach the standards were given T3+L-T4 combined therapy. The dose ratios of T3:T4 were 1:10, 1:15, and 1:20, respectively.

Deiodinase 2 (DIO2) genotype analysis

Blood samples were collected from the patients before surgery and stored in collection tubes with ethylenediaminetetraacetic acid (EDTA) for genetic testing. Deoxyribonucleic acid (DNA) was extracted from peripheral blood using a DNA extraction kit (HiJiLi Biotechnology Co., Wuhan, China). The absorbance at 260 nm and 280 nm was measured by an ultaviolet (UV) spectrophotometer, and the optical density (OD) ratio (260/280 nm) and DNA concentration were calculated. Then the target fragment was amplified by polymerase chain reaction (PCR). The primer sequences for PCR were as follows: DIO2 rs225014, forward, 5′-TGGCTCGTGAAAGGAGGTCAAGT-3′, reverse, 5′-CGTCAGGTGAAATTGGGTGAGGAT-3′. The DIO2 gene genotyping was performed by an ABI Prism 3700 DNA automated sequencing system.

Statistical analysis

The statistical analysis of the experimental data was completed by SPSS 20.0 statistical software. The data were presented as mean ± standard deviation (SD). Allele frequencies and genotype frequencies were counted, and Hardy-Weinberg equilibrium was performed for the HT and TT surgery groups. The difference in distribution frequency of single single nucleotide polymorphism (SNP) between HT and TT groups was analysed by the χ^2 test. The t-test or one-way ANOVA was performed for the difference comparison. A p-value lower than 0.05 was considered statistically significant.

Results

Comparison of thyroid hormone levels before and after treatment

The general data of the patients were not significantly different between the HT (A) group (age range: 25–65 years, mean age: 44 years, and sex: 36 males and 84 females) and the TT (B) surgery group (age range: 23–67 years, mean age: 45 years and sex: 33 males and 87 females). Also, the HT (A) group included 18 patients in stage I, 37 patients in stage II, 50 patients in stage III, and 15 patients in stage IV, while the TT (B) surgery group included 20 patients in stage I, 38 patients in stage II, 46 patients in stage III, and 16 patients in stage IV. There was no statistical difference between the A and B groups. As shown in Table 1, there was no significant difference in thyroid hormone levels between groups A and B before treatment. Serum TSH levels were inhibited after oral L-T4 treatment, and the levels were lower in group A than in group B ($p < 0.001$). After TSH suppression treatment, FT4 significantly increased in group A, and there was no significant difference in serum triiodothyronine (FT3) levels before and after the operation. Although serum FT4 levels were increased in most patients in group B after surgery, serum FT3 decreased after surgery. All the thyroid hormone levels had a statistical difference between groups A and B after treatment ($p < 0.001$, Tab. 1).

Table 1. *Comparison of serum thyroid indicators between groups before and after treatment*

Indicators	Time	A group (n = 120)	B group (n =120)	p-value
TSH [mU/L]				
	Before treatment	2.436 ± 0.559	2.488 ± 0.704	
	After treatment	0.341 ± 0.118	0.455 ± 0.144	< 0.001
FT3 [pmol/L]				
	Before treatment	5.086 ± 1.194	5.197 ± 1.011	
	After treatment	4.928 ± 0.961	4.188 ± 0.533	< 0.001
FT4 [pmol/L]				
	Before treatment	16.93 ± 0.689	17.01 ± 0.733	
	After treatment	20.00 ± 0.454	22.18 ± 0.694	< 0.001

A group — hemithyroidectomy (HT); B group — total thyroidectomy (TT); TSH — thyroid-stimulating hormone; FT3 — free triiodothyronine; FT4 — free thyroxine

Table 2. *Allele and genotype analysis in the differentiated thyroid carcinoma (DTC) patients with different surgery methods*

Surgery methods	DIO2 Thr92Ala (rs225014)				
	Genotype			Allele	
	CC	CT	TT	C	T
A group (frequency)	23 (0.192)	67 (0.558)	30 (0.250)	113 (0.471)	127 (0.529)
B group (frequency)	25 (0.208)	64 (0.533)	31 (0.258)	114 (0.475)	126 (0.525)
χ^2		0.146	0.007		0.008
p-value		0.702	0.932		0.927

A group — hemithyroidectomy (HT); B group — total thyroidectomy (TT); DIO2 — deiodinase 2; CC — cytosine cytosine; CT — cytosine thymine; TT — thymine thymine; C — cytosine; T — thymine

Allele frequency and genotype distribution in groups with different surgery methods

In 240 DTC patients, 3 DIO2 Thr92Ala (rs225014) genotypes were detected, including thymine thymine (TT) genotype, thymine cytosine (TC) genotype, and cytosine cytosine (CC) genotype. There were 23 cases (0.192) of DIO2 Thr92Ala CC genotype, 67 cases (0.558) of DIO2 Thr92Ala CT genotype, and 30 cases (0.250) of DIO2 Thr92Ala TT genotype in group A. The allele frequencies of C and T were 0.471 and 0.529, respectively. In group B, there were 25 cases (0.208) of DIO2 Thr92Ala CC genotype, 64 cases (0.533) of DIO2 Thr92Ala CT genotype, and 31 cases (0.258) of DIO2 Thr92Ala TT genotype. There was no statistical difference between the groups ($p > 0.05$, Tab. 2).

Allele frequency and genotype distribution analysis in groups achieving or not achieving the TSH suppression standard

After TSH suppression treatment, the serum TSH levels of some patients did not reach the TSH suppression standard during the follow-up period. There were 107 patients (89.17%) who achieved the TSH suppression standard in group A, but only 77 patients (64.17%) reached the standard in group B. Thus, we further analysed the allele frequency and genotype distribution in patients who reached the TSH suppression standard (184) and those who failed to reach the TSH suppression standard (56) (Tab. 3). There were 28 cases (0.152) of DIO2 Thr92Ala CC genotype, 98 cases (0.533) of DIO2 Thr92Ala CT genotype, and 58 cases (0.315) of DIO2 Thr92Ala TT genotype reaching the TSH suppression standard. The allele frequencies for C and T were 0.418 and 0.582, respectively. In the group failing to reach the TSH suppression standard there were 20 cases (0.357) of DIO2 Thr92Ala CC genotype, 33 cases (0.589) of DIO2 Thr92Ala CT genotype, and 3 cases (0.054) of DIO2 Thr92Ala TT genotype. The allele frequencies for C and T were 0.652 and 0.348, respectively. The proportion of CC genotypes in the group who failed to reach the TSH suppression standard was higher, while CT and TT genotypes were higher in the group who reached the TSH suppression standard ($p < 0.001$, Tab. 3).

Thyroid hormone levels in different genotypes

Considering the allele frequency difference in patients with different responses to TSH suppression treatment, the thyroid hormone levels were further analysed. The TSH levels (0.479 ± 0.150 mU/L) and FT4 levels

Table 3. *Allele and genotype analysis in the differentiated thyroid carcinoma (DTC) patients after thyroid-stimulating hormone (TSH) inhibition therapy*

	DIO2 Thr92Ala (rs225014)				
	Genotype			Allele	
	CC	CT	TT	C	T
Reaching TSH standard (frequency)	28 (0.152)	98 (0.533)	58 (0.315)	154 (0.418)	214 (0.582)
Below TSH standard (frequency)	20 (0.357)	33 (0.589)	3 (0.054)	73 (0.652)	39 (0.348)
χ^2		4.575	21.790		18.751
p-value		0.032	< 0.001		< 0.001

Table 4. *Comparison of serum thyroid indicators between different genotype groups after treatment*

Indicators	Genotype			p-value
	CC (n = 48)	CT (n = 131)	TT (n = 61)	
TSH [mU/L]	0.479 ± 0.150	0.389 ± 0.135	0.353 ± 0.131	< 0.001
FT3 [pmol/L]	4.126 ± 0.539	4.635 ± 0.897	4.733 ± 0.884	< 0.01
FT4 [pmol/L]	22.26 ± 0.689	20.82 ± 1.213	20.76 ± 1.087	< 0.001

TSH — thyroid-stimulating hormone; FT3 — free triiodothyronine; FT4 — free thyroxine

(22.26 ± 0.689 pmol/L) were highest while FT3 levels (4.126 ± 0.539 pmol/L) were lowest in the CC genotype group among the 3 genotypes ($p < 0.001$, Tab. 4).

Discussion

The present study analysed the thyroid hormone levels in DTC patients who received total thyroidectomy and hemithyroidectomy as well as TSH suppression therapy. The serum TSH levels were inhibited after oral L-T4 treatment, but the proportion of patients who reached the TSH suppression standard in the hemithyroidectomy group was higher than in the total thyroidectomy group. Most patients showed increased FT4 levels, while decreased FT3 levels were seen in the total thyroidectomy group. The serum FT4 levels were also increased in hemithyroidectomy while the serum FT3 levels showed no significant changes. After analysing the genotypes of the patients, we observed that the CC genotype has difficulty attaining the TSH suppression standard.

At present, surgery is a common treatment for DTC patients [16]. TSH suppression therapy is used in the management of patients thyroidectomized for DTC [17, 18]. The thyroid hormone levels were measured after surgery and TSH suppression therapy in the current study. The serum TSH levels were suppressed in patients who underwent total thyroidectomy and hemithyroidectomy. Although the serum FT4 levels were increased in both surgery method groups, the serum FT3 levels were decreased in the total thyroidectomy group, and no significant changes were found in the hemithyroidectomy group. These data reveal that patients with different surgery methods may need different management after surgery. A previous study revealed that the FT4/FT3 quotient increased the possibility that a thyroid nodule was malignant [19]. Elevated serum FT4 levels and depressed FT3 levels were also reported in thyroid-deficient patients post-surgery [20]. The phenomenon of increased levels of serum FT4 and decreased FT3 levels may influence the effect of postoperative management and treatment of thyroid cancer patients.

The DIO2 Thr92Ala polymorphism is associated with an increased risk for several diseases [14, 21–23]. For instance, homozygosity for the DIO2 Thr92Ala polymorphism is related to glycaemic control in type 2 diabetes mellitus [14]. A systematic review and meta-analysis showed that euthyroid Ala92-DIO2 carriers have increased body mass index (BMI) levels and higher fasting plasma glucose levels [24]. To explore the association between thyroid hormone levels and DIO2 Thr92Ala polymorphism of DTC patients, the genotype distribution and allele frequencies of patients were analysed. The genotype distribution and allele frequencies have no statistical difference between total thyroidectomy and hemithyroidectomy groups. A previous study in a subset of the Chinese population showed that the Thr92Ala distribution was 96 (0.338) TT genotype, 145 (0.511) TC genotype,

and 43 (0.151) CC genotype [25]. In the current study, the DTC patients seemed to have higher Thr92Ala CC genotype distribution (0.192/0.208) and lower TT genotype distribution (0.250/0.258). These findings show that the genotype distribution and allele frequencies in DTC patients may have differences in healthy individuals.

The TSH suppression rate of reaching the standard in the total thyroidectomy group was significantly lower than that of the hemithyroidectomy group patients. To reach the TSH suppression standard, the patients in the total thyroidectomy group may need more time than the hemithyroidectomy group patients. The patients were further divided into those who reached the TSH suppression standard and those who failed to reach the TSH suppression standard. The patients who failed to reach the TSH suppression standard exhibited higher rs225014 CC genotype distribution (0.357) and lower TT genotype distribution (0.054). Moreover, the difference in serum TSH, FT3, and FT4 levels was associated with different genotypes, which suggests that patients with high CC genotypes may have difficulty reaching the TSH suppression standard. A large population-based Western European cohort study showed that the Thr92Ala polymorphism of D2 was not associated with the difference in TSH, FT4, and FT3 in participants on thyroid hormone replacement therapy [26]. This finding was inconsistent with our results, which might be due to different treatment methods and populations. The association between TSH suppression therapy and DIO2 Thr92Ala polymorphism remains to be confirmed in large cohorts in the future. Also, the percentage of co-occurrence of autoimmune thyroiditis in thyroid cancer patients undergoing TT or HT surgery may have differences in achieving adequate postoperative TSH levels. The present study did not take this case into account, which may be a limitation and an interesting research field.

Conclusions

In conclusion, patients who underwent total thyroidectomy exhibited higher postoperative serum FT4 levels than patients in the hemithyroidectomy group after TSH suppression therapy. The Thr92Ala polymorphism of D2 was associated with TSH suppression therapy. These findings may provide a basis for effective screening of low-risk DTC patients for whom total thyroidectomy before surgery is not recommended and who should seek better T3+LT4 combination therapy.

Acknowledgements
None.

Conflicts of interest
The authors declare that they have no conflicts of interest.

Funding
This study was funded by a hospital-level project of Shanghai Sixth People's Hospital (Grant Number: DY2019001).

References

1. Cao W, Chen HD, Yu YW, et al. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. Chin Med J (Engl). 2021; 134(7): 783–791, doi: 10.1097/CM9.0000000000001474, indexed in Pubmed: 33734139.
2. Xu Y, Huang K, Huang P, et al. Benefits and harms of hemithyroidectomy, total or near-total thyroidectomy in 1-4 cm differentiated thyroid cancer. Clin Endocrinol (Oxf). 2021; 95(4): 668–676, doi: 10.1111/cen.14495, indexed in Pubmed: 33948971.
3. Zheng W, Rui Z, Wang X, et al. The Influences of TSH Stimulation Level, Stimulated Tg Level and Tg/TSH Ratio on the Therapeutic Effect of I Treatment in DTC Patients. Front Endocrinol (Lausanne). 2021; 12: 601960, doi: 10.3389/fendo.2021.601960, indexed in Pubmed: 34177793.
4. Gullo D, Latina A, Frasca F, et al. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. PLoS One. 2011; 6(8): e22552, doi: 10.1371/journal.pone.0022552, indexed in Pubmed: 21829633.
5. Kim JD, Leyva S, Diano S. Hormonal regulation of the hypothalamic melanocortin system. Front Physiol. 2014; 5: 480, doi: 10.3389/fphys.2014.00480, indexed in Pubmed: 25538630.
6. Gondou A, Toyoda N, Nishikawa M, et al. Effect of nicotine on type 2 deiodinase activity in cultured rat glial cells. Endocr J. 1999; 46(1): 107–112, doi: 10.1507/endocrj.46.107, indexed in Pubmed: 10426574.
7. Cicatiello AG, Di Girolamo D, Dentice M. Metabolic Effects of the Intracellular Regulation of Thyroid Hormone: Old Players, New Concepts. Front Endocrinol (Lausanne). 2018; 9: 474, doi: 10.3389/fendo.2018.00474, indexed in Pubmed: 30254607.
8. St Germain DL, Galton VA, Hernandez A. Minireview: Defining the roles of the iodothyronine deiodinases: current concepts and challenges. Endocrinology. 2009; 150(3): 1097–1107, doi: 10.1210/en.2008-1588, indexed in Pubmed: 19179439.
9. von Hafe M, Neves JS, Vale C, et al. The impact of thyroid hormone dysfunction on ischemic heart disease. Endocr Connect. 2019; 8(5): R76–R90, doi: 10.1530/EC-19-0096, indexed in Pubmed: 30959486.
10. Guerra A, Sapio MR, Carrano M, et al. Prevalence of Dio2(T92A) polymorphism and its association with thyroid autoimmunity. J Endocrinol Invest. 2013; 36(5): 303–306, doi: 10.3275/8618, indexed in Pubmed: 23013882.
11. Maino F, Cantara S, Forleo R, et al. Clinical significance of type 2 iodothyronine deiodinase polymorphism. Expert Rev Endocrinol Metab. 2018; 13(5): 273–277, doi: 10.1080/17446651.2018.1523714, indexed in Pubmed: 30257587.
12. Janowska M, Potocka N, Paszek S, et al. Evaluation of the association between angiotensin converting enzyme insertion/deletion polymorphism and the risk of endometrial cancer in and characteristics of Polish women. Adv Clin Exp Med. 2020; 29(5): 581–585, doi: 10.17219/acem/118843, indexed in Pubmed: 32442362.
13. Baksi S, Pradhan A. Thyroid hormone: sex-dependent role in nervous system regulation and disease. Biol Sex Differ. 2021; 12(1): 25, doi: 10.1186/s13293-021-00367-2, indexed in Pubmed: 33685490.
14. Zhang X, Sun J, Han W, et al. The Type 2 Deiodinase Thr92Ala Polymorphism Is Associated with Worse Glycemic Control in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Diabetes Res. 2016; 2016: 5928726, doi: 10.1155/2016/5928726, indexed in Pubmed: 27777960.
15. Torlontano M, Durante C, Torrente I, et al. Type 2 deiodinase polymorphism (threonine 92 alanine) predicts L-thyroxine dose to achieve target thyrotropin levels in thyroidectomized patients. J Clin Endocrinol Metab. 2008; 93(3): 910–913, doi: 10.1210/jc.2007-1067, indexed in Pubmed: 18073314.
16. Wang TS, Sosa JA. Thyroid surgery for differentiated thyroid cancer - recent advances and future directions. Nat Rev Endocrinol. 2018; 14(11): 670–683, doi: 10.1038/s41574-018-0080-7, indexed in Pubmed: 30131586.
17. Heemstra KA, Hamdy NAT, Romijn JA, et al. The effects of thyrotropin-suppressive therapy on bone metabolism in patients with well-differentiated thyroid carcinoma. Thyroid. 2006; 16(6): 583–591, doi: 10.1089/thy.2006.16.583, indexed in Pubmed: 16839260.
18. Grani G, Ramundo V, Verrienti A, et al. Thyroid hormone therapy in differentiated thyroid cancer. Endocrine. 2019; 66(1): 43–50, doi: 10.1007/s12020-019-02051-3, indexed in Pubmed: 31617165.

19. Sasson M, Kay-Rivest E, Shoukrun R, et al. The T4/T3 quotient as a risk factor for differentiated thyroid cancer: a case control study. J Otolaryngol Head Neck Surg. 2017; 46(1): 28, doi: 10.1186/s40463-017-0208-0, indexed in Pubmed: 28376913.
20. Castagna MG, Dentice M, Cantara S, et al. DIO2 Thr92Ala Reduces Deiodinase-2 Activity and Serum-T3 Levels in Thyroid-Deficient Patients. J Clin Endocrinol Metab. 2017; 102(5): 1623–1630, doi: 10.1210/jc.2016-2587, indexed in Pubmed: 28324063.
21. Marcondes AA, Gomez TGB, Ravache TT, et al. Assessment of children in the autistic spectrum disorder that carry the Thr92Ala-DIO2 polymorphism. J Endocrinol Invest. 2021; 44(8): 1775–82, doi: 10.1007/s40618-020-01497-x, indexed in Pubmed: 33449341.
22. Kang YE, Kang YMi, Park B, et al. Type 2 deiodinase Thr92Ala polymorphism is associated with a reduction in bone mineral density: A community-based korean genome and epidemiology study. Clin Endocrinol (Oxf). 2020; 93(3): 238–247, doi: 10.1111/cen.14206, indexed in Pubmed: 32324283.
23. Wang X, Chen K, Zhang C, et al. The Type 2 Deiodinase Thr92Ala Polymorphism Is Associated with Higher Body Mass Index and Fasting Glucose Levels: A Systematic Review and Meta-Analysis. Biomed Res Int. 2021; 2021: 9914009, doi: 10.1155/2021/9914009, indexed in Pubmed: 34660805.
24. He B, Li J, Wang G, et al. Association of genetic polymorphisms in the type II deiodinase gene with bipolar disorder in a subset of Chinese population. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33(6): 986–990, doi: 10.1016/j.pnpbp.2009.05.003, indexed in Pubmed: 19427350.
25. Wouters HJ, van Loon HCM, van der Klauw MM, et al. No Effect of the Thr92Ala Polymorphism of Deiodinase-2 on Thyroid Hormone Parameters, Health-Related Quality of Life, and Cognitive Functioning in a Large Population-Based Cohort Study. Thyroid. 2017; 27(2): 147–155, doi: 10.1089/thy.2016.0199, indexed in Pubmed: 27786042.