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Research Article

Investigating the Effect of Genetic Polymorphisms of Deiodinase Type 2 on Levothyroxine Dose Requirements in Patients with Hypothyroidism

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ABSTRACT

Background: Hypothyroidism is the most abundant thyroid disorder worldwide. For decades, levothyroxine was the main effective pharmacological treatment for hypothyroidism. A variety of factors can influence levothyroxine dose, such as genetic variations. Studying the impact of genetic polymorphisms on the administration of medications was risen remarkably. Different genetic variations were investigated that might affect levothyroxine dose requirements, especially the deiodinase enzymes. Deiodinase type 2 genetic polymorphisms' impact on levothyroxine dose was studied in different populations.

Objective: To examine the association of the two single nucleotide polymorphism (SNP)s of deiodinase type 2 (rs225013 and rs225014) and levothyroxine dose requirements.

Subjects and Methods: A cross-sectional study was conducted at Baghdad Center for Nuclear Medicine and Radiation Therapy located in Baghdad/ Iraq, from March to June 2022. Based on levothyroxine dose, the enrolled patients were divided into two groups: low dose group < 1.7 µg/kg/day and high dose group ≥ 1.7 µg/kg. Then genotyping analysis was done for both groups of the study.

Results: The mean age of the participants was 40.35 ± 9.5 years with a mean body mass index of 30.61 ± 5.72 kg/m2. The mean levothyroxine doses in the low- and high-dose groups were 81.67 ± 30.74 µg/day and 161.67 ± 35.19 µg/day, respectively. Significant differences existed in the levels of TSH and TT4 between the study's groups.

Conclusion: This study indicated that the differences in levothyroxine dose, TSH, TT4 and TT3 levels were not associated with the DIO2 rs225013. Similarly, the differences in TSH, TT3 and TT4 levels revealed a non-significant association with DIO2 rs225014 except for levothyroxine dose which was higher in the patients who carried the wild type allele (TT).

Introduction

Hypothyroidism was represented as a chronic illness of the endocrine system that is associated with insufficient production of thyroid hormones, thyroxine (T4) and triiodothyronine (T3) (1,2). The prevalence of hypothyroidism has been studied in different provinces of Iraq (3- 6). In Baghdad and Basrah (the two biggest provenances in center and south of Iraq), the distribution of hypothyroidism was found to be 3.2% and 12.5% respectively (3, 4). While in Duhok (the provenance in the north of Iraq),

hypothyroidism was found to be 1.20% of the studied population and in Kirkuk, there were 22.7 % had hypothyroidism of the study participants (5,6).

The standard pharmacological management for hypothyroidism is the replacement of thyroid hormones with oral administration of levothyroxine (7). The usual daily dose of levothyroxine is 1.6 - 1.8 mcg/kg/day (8). Multiple factors can affect levothyroxine dose requirement; among which are concomitant medications that interfere with levothyroxine absorption such as proton pump inhibitors, calcium and iron supplements (9, 10). Other factors included: physiological , comorbid conditions and adherence (11). Furthermore, several genetic variations were investigated and found to have a possible influence on the response to levothyroxine treatment like genetic polymorphisms in P-glycoprotein that controls the efflux of levothyroxine drug (12). Likewise, the hepatic enzymes UGT1A1 and UGT1A3 of UDP-the glucuronosyltransferases (UGTs) family which are responsible for the metabolism of thyroxine and their genetic variations had been studied (13). Besides, the effect of genetic polymorphisms in the thyroid stimulating hormone receptors (TSHR) and thyroid hormone receptors (THRα) on levothyroxine dose was investigated (14). Furthermore, there is a growing concern about the possibility of deiodinases (DIO) genetic polymorphisms in the determination of levothyroxine dose requirement. There are three types of deiodinase enzymes (encoded by DIO genes DIO1, DIO2, and DIO3); deiodinase 1 (D1), deiodinase 2 (D2) and deiodinase 3 (D3) that have an integral part in activation and deactivation of thyroid hormones (15). Multiple (SNPs) of DIO1, DIO2 and DIO3 were examined and studied for their effects on the thyroid hormones profile (16,17). Deiodinase type 2 is the major contributor to generating T3 from T4 (18). Various studies had investigated the effect of deiodinase type 2 genetics polymorphism on levothyroxine therapy, especially the single nucleotide polymorphism (rs225014). Conflicting outcomes of these studies were found regarding the influence of rs225014 on thyroid hormones. A study in Italy which included thyroidectomized patients stated that patients with the homozygous variant type (CC) for DIO2 rs225014 needed a higher dose of levothyroxine to provide favorable TSH levels (19). Likewise, a study in Turkey found a significant correlation between DIO2 (rs225014) and TSH levels in hypothyroid patients who have had thyroidectomy (20). Conversely, researchers of a cohort study in the Netherlands observed no association of DIO2 (rs225014) polymorphism with thyroid hormone levels (21).

In Iraq, hypothyroidism was studied widely and in different aspects including genetic variations effect on thyroid hormones (22-25).

The aim of this study was to investigate the association of single nucleotide polymorphisms (SNPs) of DIO2 (rs225013) and (rs225014) with levothyroxine dose requirements in patients with hypothyroidism from Iraqi hospital.

Subjects and Methods:

A cross-sectional study was conducted at Baghdad Center for Nuclear Medicine and Radiation Therapy in Baghdad/ Iraq, between March and June 2022. The study population included patients diagnosed with hypothyroidism who were receiving levothyroxine treatment and consented voluntarily to participate in the study. The participants were enrolled consecutively (according to their attendance at the study center) and allocated into two groups depending on the daily dose of levothyroxine: low dose group < 1.7 µg/kg/day and high dose group ≥ 1.7 µg/kg (20). The inclusion criteria were patients of both genders, aged 18-65 years, who were receiving levothyroxine therapy and had attained a euthyroid state for at least 2 months. While the excluded volunteers participants were pregnant or lactating women, patients having cardiovascular disease, congenital hypothyroidism and hepatic and renal impairment, patients who were receiving medications that impair levothyroxine bioavailability (proton pump inhibitors, histamine H2-blockers, aluminum hydroxide, calcium supplements, iron supplements, orlistat, carbamazepine, amiodarone, nevirapine, rifampin, ciprofloxacin, tamoxifen), those having medical conditions that cause a reduction in the absorption of levothyroxine (gastroesophageal reflux disease, lactose intolerance, gastric bypass, H. pylori infection, gastroparesis, coeliac disease, ulcerative colitis, Crohn's disease, atrophic gastritis) and those who were not consistent with using one particular brand of levothyroxine tablet. Socio-demographic and clinical data were obtained directly from the patients during face-to-face interviews. The information was prepared in a data collection sheet which included socio-demographic characteristics (age, gender, body mass index, educational level, marital status, occupational status, smoking habit and alcohol consumption), and disease-related characteristics (levothyroxine dose, duration of disease, concurrent medical conditions and medications, thyroid function tests (TSH, T4, T3), levothyroxine strength and brand). A venous blood sample was obtained from each patient to perform thyroid function tests and genotyping analysis.

Thyroid function tests

Thyroid function tests (TSH, TT4 and TT3 levels were performed using an automated enzyme immunoassay analyzer, AIA-900, by TOSOH BIOSCIENCE,USA. The principle of this analyzer is based on fluorescence enzyme immunoassay. The reference ranges of thyroid function tests were according to the manufacturer reference ranges that were used at the laboratory of Baghdad Center for Nuclear Medicine and Radiation Therapy which were (TSH = 0.38 – 4.31µIU/ml ,TT4 = 4.9 – 11.0 µg/dl and TT3 = 0.79 – 1.58 ng/ml).

Genotyping Analysis

Genomic DNA was isolated from blood samples according to the protocol ReliaPrep™ Blood gDNA Miniprep System, by Promega, USA. The amplification of extracted DNA was performed using the conventional polymerase chain reaction (PCR) technique. The sequencing of the used primers was as follows: DIO2 forward (5'-TGTAAAACGACGGCCAGTGACAACACACACCCATAGAG-3') and reverse (5'-CAGGAAACAGCTATGACCAATGTAGACCAGCAGGAAG-3'). PCR products were sent for Sanger sequencing using ABI3730XL, an automated DNA sequencer, by Macrogen Corporation – Korea. Then, the results were analyzed using Geneious Prime software, (V 2021.1.1) (Biomatters Ltd., Auckland, New Zealand; www.geneious.com).

Ethical Approval

The study was approved by the scientific committee of the College of Pharmacy/University of Baghdad and Medical City Directorate/ Ministry of Health/ Iraq. Verbal consent was obtained from each patient before their enrolment in the study.

Statistical analysis

Statistical analysis was accomplished via IBM SPSS Statistics for Windows version 25. Continuous variables were presented as mean ± standard deviation (SD) while categorical variables were presented as numbers and percentages. Analysis of variance (ANOVA) was used to estimate the differences in levothyroxine dose, TSH, TT4 and TT3 between three groups according to genotypes; GG, TG and TT for rs225013 and CC, TC and TT for rs225014. P-value of less than 0.05 was considered to be significant.

Results

Sixty hypothyroid patients participated in this study. They were categorized into two groups of 30 patients each: low-dose and high-dose groups. The socio-demographic features of the patients are presented in Table 1. The mean age of the participants was 40.35 ± 9.5 years with a mean body mass index (BMI) of 30.61 ± 5.72 kg/m2. The majority of patients were females (85%), married (90%) and unemployed (40%). Regarding the education level, results have shown that 50% of the patients had completed secondary school, and (33.3%) had a bachelor degree. About 93% of the patients were nonsmokers. None of the study participants was alcoholic.

Table 1: Socio-demographic characteristics of the study participants (n=30)

Variables	Low dose group Mean ± SD	High dose group Mean ± SD	Total n (60) Mean ± SD
Age (years)	43.37 ± 10.19	37.33 ± 7.81	40.35 ± 9.5
BMI (Kg/m2)	32.15 ± 5.47	29.07 ± 5.64	30.61 ± 5.72
Gender	n (%)	n (%)	n (%)
Male	7(23.3)	2(6.7)	9 (15.0)
Female	23(76.7)	28(93.3)	51 (85.0)
Education level			
Primary	6 (20)	4 (13.3)	10 (16.7)
Secondary	16 (53.3)	14 (46.7)	30 (50.0)
College	8 (26.7)	12 (40.0)	20 (33.3)
Occupational Status			
Employed	9 (30)	11 (36.7)	20 (33.3)
Unemployed	21 (70)	19 (63.3)	40 (66.7)
Marital Status			
Married	28 (93.3)	26 (86.7)	54 (90.0)
Unmarried	2 (6.7)	4 (13.3)	6 (10.0)
Smoking			
Yes	2 (6.7)	2 (6.7)	4 (6.7)
No	28 (93.3)	28 (93.3)	56 (93.3)

BMI = body mass index

Table 2 shows the clinical characteristics of hypothyroidism for patients in both study groups. The mean levothyroxine doses in the low- and high-dose groups were 81.67 ± 30.74 µg/day and 161.67 ± 35.19 µg/day, respectively. TSH, TT4 and TT3 means values were 2.08 ± 1.25 µIU/ml, 8.94 ± 1.61 µg/dl and 1.06 ± 0.17 ng/ml respectively. The median of levothyroxine treatment period was 4 years in low-dose group and 3 years in the high- dose group. Regarding hypothyroidism causes, the distribution of the patients showed that the primary hypothyroidism was the most frequent cause of hypothyroidism in the low-dose group (46.7%), whereas thyroidectomy and radioactive iodine were the most frequent cause in the high-dose group (53.3%). The most commonly used medications were vitamin D and metformin tablets. Only five hypothyroid patients suffered from diabetes mellitus.

Table 2: Clinical characteristics of the study participants (n=30)

Variables	Low dose group mean ± SD	High dose group mean ± SD	Total n(60) mean ± SD
TSH (µIU/ml)	2.5 ±1.05	1.65 ± 1.30	2.08 ± 1.25
TT4 (µg/dl)	8.16 ±1.25	9.720 ± 1.57	8.94 ± 1.61
TT3 (ng/ml)	1.06 ± 0.17	1.06 ± 0.17	1.06 ± 0.17
Levothyroxine Dose (µg)	81.67 ± 30.74	161.67 ± 35.19	121.67 ± 51.96
Duration of levothyroxine (years)	median 4	median 2	median 3
Etiology of Hypothyroidism	n (%)	n (%)	n (%)
Primary	14 (46.7)	2 (6.7)	16 (26.7)
Thyroidectomy	7 (23.3)	12 (40.0)	19 (31.7)
RAI	5 (16.7)	0 (0)	5 (8.3)
Thyroidectomy & RAI	4 (13.3)	16 (53.3)	20 (33.3)
Concomitant medications			
Vitamin D3 tab	5 (16.7)	5 (16.7)	10 (16.7)
Vitamin C tab	1 (3.3)	0 (0)	1 (1.7)
Metformine tab	2 (6.7)	2 (6.7)	4 (6.7)
Glibenclamide tab	1 (3.3)	0 (0)	1 (1.7)
Glimpride tab	2 (6.7)	1 (3.3)	3 (5.0)
Oral contraceptive tab	0 (0)	1 (3.3)	1 (1.7)
Comorbid conditions			
Diabetes mellitus	3 (10.0)	2 (6.7)	5 (8.3)

TSH, thyroid stimulating hormone; TT4, total thyroxin; TT3, total triiodothyronine; RAI, radioactive iodine

The differences in clinical characteristics of hypothyroidism are illustrated in Table 3. There were significant differences in the levels of TSH and TT4, where the participants in the high dose group had significantly lower TSH and higher TT4 than those in low dose group. Similarly, the levothyroxine dose in the high dose group was greater than the low-dose group.

Table 3: Differences of hypothyroidism characteristics and treatment between the groups (n=30)

Variables	Low dose group	High dose group	P-value
	Mean ± SD	Mean ± SD	
TSH (µIU/ml)□	2.5 ±1.05	1.65 ±1.30	0.007*
TT4 (µg/dl)□	8.16 ±1.25	9.720 ±1.57	0.000 *
TT3 (ng/ml)□	1.06 ± 0.17	1.06 ±0.17	0.988
Levothyroxine Dose (µg)□	81.67± 30.75	161.67 ±35.19	0.000*
Duration of levothyroxine (years) ‡	Mean rank 34.88	Mean rank 26.12	0.049

TSH= thyroid stimulating hormone, TT4= total thyroxin, TT3= total tri-iodothyronine, □ = Independent sample t-test, ‡ = Mann-Whitney U test, *= P-value < 0.05 is significant

The frequency of the studied SNPs (DIO2 rs225013, DIO2 rs225014) in both study groups is presented in Table 3.4. For DIO2 rs225013, 50% of the participants were heterozygous to the variant allele (TG) in the low-dose group and 43% of the patients had the wild type allele (TT). Only 6% of the patients in this group were homozygous for the variant allele (GG). On the other hand, the genotype distribution in the high dose group was as follows: the wild type allele (TT) was found in, 36% of the patients; the variant allele (TG) was found in 33% of the patients and the variant allele (GG), 30%. The distribution of the second studied DIO2 rs225014 was as the following: the variant allele (TC) represents the higher frequency in the two groups; furthermore the number of patients who carried the wild type allele (TT) and variant allele (CC) in the high dose group were higher than those in low-dose group.

Table 4: The frequencies of DIO2 genotypes of the study participants (n=30)

Gene SNP ID	Low dose group n (%)	High dose group n (%)	Total n (60) n (%)
DIO2 rs 225013			
T>G			
Genotype	2 (6.7)	9 (30.0)	11 (18.3)
GG	15 (50.0)	10 (33.3)	25 (41.7)
TG	13 (43.3)	11 (36.7)	24 (40.0)
TT			
DIO2 rs 225014			
T>C			6 (10.0)
Genotype	2 (6.7)	4 (13.3)	37 (61.7)
CC	22 (73.3)	15 (50.0)	17 (28.3)
TC	6 (20.0)	11 (36.7)	
TT			

There were non-significant differences in the thyroid function biomarkers (TSH, TT4 and TT3) and levothyroxine dose between DIO2 (rs225013) genotype groups (TT, TG and GG) (Table 5). In addition, there were non-significant differences in the thyroid function biomarkers (TSH, TT4 and TT3 levels) based on DIO2 rs225014 genotype groups (TT, TC and CC) (Table 3.6). In contrast, there was a significant difference in levothyroxine dose based on DIO2 rs225014 genotypes where patients with TT genotype had significantly higher doses when compared to patients carrying the TC genotype (Table 6).

Table 5: The differences in thyroid hormones levels and levothyroxine dose among DIO2 (rs225013) genotypes in hypothyroid patients

Variables	TT n (24) Mean ± SD	TG n (25) Mean ± SD	GG n (11) Mean ± SD	p-value
Levothyroxine dose (µg/day)	123.96 ± 51.330	117.00 ± 58.05	127.27 ± 41.01	0.833
TSH (µIU/ml)	2.04 ± 1.25	2.18 ±1.23	1.93± 1.36	0.849
TT4 (µg/dl)	9.20 ±1.57	8.74 ± 1.63	8.82 ±1.73	0.602
TT3 (ng/ml)	1.04±0.17	1.09 ±0.16	1.03 ± 0.19	0.490

P-value > 0.05 is non-significant according to ANOVA one-way test

Table 6: the differences in thyroid hormones levels among DIO2 (rs225014) genotypes in hypothyroid patients

Variables		TT n (17) Mean ± SD	TC n (37) Mean ± SD	CC n (6) Mean ± SD	p- value
Levothyroxine (µg/day)	**Dose**	151.47 ± 45.47	108.78 ± 49.37	116.67 ± 58.45	0.016*
TSH (µIU/ml)		1.80 ± 1.45	2.24 ±1.14	1.84 ± 1.32	0.436
TT4 (µg/dl)		9.11 ± 1.35	8.91 ± 1.79	8.58 ± 1.26	0.784
TT3 (ng/ml)		1.02 ± 0.16	1.09 ±0.179	1.02 ± 0.14	0.376

*= p-value <0.05 is significant according to ANOVA one-way test

Discussion

This study was evaluated the possible association of the DIO2 SNPs (rs225013 and rs225014) with the thyroid hormones parameters and the levothyroxine dose requirement. Based on the study's findings; hypothyroidism was more common in women than in men (85% versus 15%). This finding was also proved by other results of numerous previous studies both in Iraq and worldwide (3, 4, 26, 27). In a cross-sectional study in Baghdad, women with hypothyroidism represent the majority of the studied sample (77.6%) (3). Similarly, in Basrah, women were 83% of hypothyroid patients (4).

The results of the current study showed significant differences in TSH and TT4 levels between the studied groups; low-dose and high-dose groups. In normal physiological conditions the synthesis and secretion of thyroid hormone is regulated via the feedback mechanism of the hypothalamus-pituitary-thyroid (HPT) axis. Furthermore, the thyroid hormones decrease the release of TSH through negative feedback mechanism. Since levothyroxine is a synthetic form of human thyroid hormone (thyroxin T4), thus levothyroxine mimics the human's endogenous T4 (28,29). This could explain the significant difference in TSH and TT4 levels between the study groups.

With regards to the studied SNPs; according to rs225013 genotypes groups (GG, TG and TT), there were non-significant differences between these groups in levothyroxine dose, TSH, TT4 and TT3 levels. This finding is consistent with a previous study in the Saudi population that included patients with differentiated thyroid cancer who have had a total thyroidectomy and observed a non-significant relationship between the requirements of levothyroxine dose with rs225013 genotypes (30).

While for the rs225014 genotypes groups (CC, TC and TT), the current study's results showed that only patients with the wild type allele (TT) required significantly higher levothyroxine dose than those with the variant allele (TC). On the contrary, patients with the variant allele (CC) showed non-significant differences in levothyroxine dose when compared with patients who carried (TT) or (TC) alleles. For the TSH, TT4 and TT3 levels, the results showed no differences between these groups. Similar findings were achieved by a previous study which was conducted in the Netherlands which found that levothyroxine dose and thyroid hormones levels were not affected by the DIO2 rs225014 genotypes in patients with hypothyroidism (21). Additionally, a study was established in Iraq, Karbala city in which the participants were women who had primary hypothyroidism showed that there were no relations of DIO2 rs225014 with levothyroxine treatment requirement and thyroid hormones levels except total T4 level in women with primary

hypothyroidism (31). Another explanation for this result is that only six patients had the variant allele (CC) in this study.

While there was findings of different studies which disagree with this study's result (19,20,32). A study conducted in Italy established that the presence of rs225014 would lower the deiodinase type 2 activity and T3 serum level (32).

The most important limitation of this study was the relatively small sample size which could affect the results. In addition, the high cost of genotyping analysis limited the investigation of more genetic polymorphisms of deiodinase enzymes for a larger sample size.

Conclusion

The current study showed that the differences in levothyroxine dose, TSH, TT4 and TT3 levels were not associated with the DIO2 rs225013. Similarly, the differences in TSH, TT3 and TT4 levels showed a non-significant association with DIO2 rs225014 except for levothyroxine dose which was higher in the patients who carried the wild type allele (TT). Therefore, the patients who have the wild type allele (TT) of rs225014 required higher dose of levothyroxine to achieve euthyroid state. Further studies are required, necessity to larger sample size to study the frequency of genetic polymorphisms and its association with levothyroxine therapy to obtain conclusive results.

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Conflict of Interest

Authors declare no conflict of interest

Data availability

Data are available upon reasonable request

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References

[1] Guglielmi R, Grimaldi F, Negro R, Frasplda‌ti A, Misischi I, Graziano F, Cipri C, Guastamacchia E, Triggiani V, Papini E. Shift from levothyroxine tablets to liquid formulation at breakfast improves quality of life of hypothyroid patients. Endocrine, Metabolic & Immune Disorders Drug Targets. 2018;18:235–240.

[2] Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. The Lancet. 2017;390:1550–62.

[3] Tahir NT, Najim HD, Nsaif AS. Prevalence of overt and subclinical thyroid dysfunction among Iraqi population in Baghdad city. Iraqi Journal of Community Medicine. 2020;33(1):20-24.

[4] Mansour AA, Ali Alhamza AH, Abdullah Almomin AMS, Zaboon IA, Alibrahim NTY, Hussein RN, Kadhim MB, Mohammed AG, Jabbar Al-Waeli DK, Nwayyir HA, Alidrisi HAY, Hussein IH, Odhaib SA, Altemimi MTJ, Imran HJ. SUN-418 Patterns of Thyroid Disease in Basrah, Iraq. Retrospective Study. Journal of Endocrine Society. 2020;8(4):A391.

[5] Zaman, B, Rasool SO, Sabri SM, Raouf GA, Balatay AA, Abdulhamid MA, Hussein DS, Odisho SK, George ST, Hassan SM, Salman RF, Benyamin M. Prevalence of thyroid dysfunctions in a large, unselected population in Duhok city, Iraqi Kurdistan: A cross-sectional study. Journal of Biological Research - Bollettino Della Società Italiana Di Biologia Sperimentale. 2021;94(2):10067.

[6] Salih SM, Kamel WA, Abbas MT, Abass KS. Prevalence of hyperthyroidism and hypothyroidism and its correlation with serum antithyroglobulin among patients in Kirkuk-Iraq. Journal of Advanced Pharmacy Education and Research. 2021;11(2):57-60.

[7] Elmor R, Sandulli W, Carter CA. The economic impact of changing levothyroxine formulations in difficult-to-treat hypothyroid patients: an evidence-based model. Pharmacoeconomics. 2017;2:1–10.

[8] Chisholm-Burns MA, Schwinghammer TL, Malone PM, Kolesar JM, Bookstaver PB, Lee KC. Pharmacotherapy Principles & Practice. 5th edition, 2019; McGraw-Hill Education, pp 685-701.

[9] Okosieme OE, Thyroid hormone replacement: current status and challenges, Expert Opinion Pharmacotherapy. 2011;12:2315–28.

[10] Al-Shimmran BA, Anwer ZM, Al-Jarrah BH. Levothyroxine Therapy Adequacy, Dose Estimation and Vitamin D Effect Assessment in a Sample of Iraqi Female Patients with Different Causes of Hypothyroidism. Iraqi Journal of Pharmaceutical Science 2020;29(2):245-252.

[11] Biondi B, Wartofsky L, Treatment with thyroid hormone. Endocrine Reviews. 2014;35(3):433–512.

[12] Öztaş E, Garcia-Saavedra AP, Yanar F, Özçinar B, Aksakal N, Purisa S, Özhan G. P-glycoprotein polymorphism and levothyroxine bioavailability in hypothyroid patients. Saudi Pharmaceutical Journal. 2018;26(2):274-278.

[13] Santoro AB, Vargens DD, Barros Filho Mde C, Bulzico DA, Kowalski LP, et al. Effect of UGT1A1, UGT1A3, DIO1 and DIO2 polymorphisms on L- thyroxine doses required for TSH suppression in patients with differentiated thyroid cancer. British Journal of Clinical Pharmacology. 2014;78:1067–75.

[14] Al-Azzam SI, Alzoubi KH, Khabour O et al. The associations of polymorphisms of TSH receptor and thyroid hormone receptor genes with L-thyroxine treatment in hypothyroid patients. Hormones. 2014;13:389–397.

[15] Gereben B, McAninch EA, Ribeiro MO, Bianco AC. Scope and limitations of iodothyronine deiodinases in hypothyroidism. Nature Reviews Endocrinology. 2015;11:642–652.

[16] Panicker V, Saravanan P, Vaidya B, Evans J, Hattersley AT, Frayling TM, Dayan CM. Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. Journal of Clinical Endocrinology & Metabolism. 2009;94(5):1623–9.

[17] Verloop H, Dekkers OM, Peeters RP, Schoones JW, Smit JW. Genetics in endocrinology: genetic variation in deiodinases: a systematic review of potential clinical

effects in humans. European Journal of Endocrinology. 2014;171(3):R123-35 .

[18] Abdalla M, Bianco AC: Defending plasma T3 is a biological priority. Clinical Endocrinology (Oxf), 2014;81(5):633-41.

[19] Torlontano M, Durante C, Torrente I. Type 2 deiodinase polymorphism (threonine 92 alanine) predicts l-thyroxine dose to achieve target thyrotropin levels in thyroidectomized patients. Journal of Clinical Endocrinology & Metabolism. 2008;93(3):910–13.

[20] Arici M, Oztas E, Yanar F, Aksakal N, Ozcinar B, Ozhan G. Association between genetic polymorphism andlevothyroxine bioavailability in hypothyroid patients, Endocrine. 2018;65(3):317-23 .

[21] Wouters HJCM, van Loon HCM, van der Klauw MMet 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.

[22] Yassin AH, Al-Kazaz A-KA, Rahmah AM, Ibrahim TY. Association of CTLA-4 Single Nucleotide Polymorphisms with Autoimmune Hypothyroidism in Iraqi Patients. Iraqi Journal of Science. 2022;63(7):2891–99.

[23] Ameen IA, Saleh ES, Taha KN. Serum Ferritin Levels for Iraqi Patients with Hashimoto's Thyroiditis. Indian Journal of Public Health Research & Development. 2019;10(10):667-71.

[24] Naji RI, Turki KM, Al-Osami MH. Frequency of Hypothyroidism in Patients with Fibromyalgia Syndrome. Journal of Faculty of Medicine Baghdad. 2013;55(1):56-9.

[25] Jawad EH, Hoshi B, Jubair S. The role of deiodinase type 1 polymorphism, rs11206244 (C785T), in clinical management of a sample of Iraqi hypothyroidism patients treated with levothyroxine. Human Gene. 2022;34:201110.

[26] Garmendia MA, Santos PS, Guillen-Grima F, Galofre JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. Journal of Clinical Endocrinology & Metabolism. 2014;99:923-31.

[27] Strikić Đula I, Pleić N, Babić Leko M, Gunjača I, Torlak V, Brdar D, Punda A, Polašek O, Hayward C, Zemunik T. Epidemiology of Hypothyroidism, Hyperthyroidism and Positive Thyroid Antibodies in the Croatian Population. Biology (Basel). 2022;11(3):394.

[28] Crook MA, Clinical Biochemistry & Metabolic Medicine, 8th edition; 2012;164-174.

[29] Sarfaraz NK, In: Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Product, Boca Raton: CRC Press LLC, 2004;151–2.

[30] AlRasheed M, AlAnzi A, AlShalhoub R, Abanmy N, Bakheet D. A study of the role of DIO1 and DIO2 polymorphism in thyroid cancer and drug response to therapy in the Saudi population, Saudi Pharmaceutical Journal. 2019;(27):841-45.

[31] Zyara M, Hoshi B, Jubair S, The impact of deiodinase type II gene on the therapeutic response to levothyroxine in a sample of Iraqi hypothyroidism patients, Gene Reports. 2022;(28):101661.

[32] Castagna MG, Dentice M, Cantara S, Ambrosio R, Maino F, Porcelli T et al. DIO2 Thr92Ala reduces deiodinase-2 activity and serum-T3 levels in thyroid-deficient patients. Journal of Clinical of Endocrinology & Metabolism. 2017;102 (5):1623–30.

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