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# Association between genetic polymorphism and levothyroxine bioavailability in hypothyroid patients

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**Abstract.** Thyroid hormones play a vital role in the human body for growth and differentiation, regulation of energy metabolism, and physiological function. Hypothyroidism is a common endocrine disorder, which generally results from diminished normal circulating concentrations of serum thyroxine (fT4) and triiodothyronine (fT3). The primary choice in hypothyroidism treatment is oral administration of levothyroxine (L-T4), a synthetic T4 hormone, as approximately 100–125 μg/day. Generally, dose adjustment is made by trial and error approach. However, there are several factors which might influence bioavailability of L-T4 treatment. Genetic background could be an important factor in hypothyroid patients as well as age, gender, concurrent medications and patient compliance. The concentration of thyroid hormones in tissue is regulated by both deiodinases enzyme and thyroid hormone transporters. In the present study, it was aimed to evaluate the effects of genetic differences in the proteins and enzymes (DIO1, DIO2, TSHR, THR and UGT) which are efficient in thyroid hormone metabolism and bioavailability of L-T4 in Turkish population. According to our findings, rs225014 and rs225015 variants in *DIO2*, which catalyses the conversion of thyroxine (pro-hormone) to the active thyroid hormone, were associated with TSH levels. It should be given lower dose to the patients with rs225014 *TT* and rs225015 *GG* genotypes in order to provide proper treatment with higher effectivity and lower toxicity.

*Key words*: Levothyroxine, Hypothyroid, Genetic polymorphism

**THYROID HORMONE-RELATED CLINICAL SYMPTOMS AND LONG-TERM COMPLICATIONS** are mainly skin manifestations, atherosclerosis, bone mineral density, heart rate, obesity, hyperlipidaemia, bradycardia, fatigue and depression, which all have serious impact on life quality [1, 2]. Hypothyroidism, one of the most common endocrine disorders, is caused by lack of action of thyroid hormones that play a vital role in the human body for growth and differentiation, and regulation of energy metabolism, and physiological function. Hypothyroidism generally results from diminished normal circulating concentrations of fT3 and fT4 [3, 4]. The production of thyroid hormones is regulated by hypothalamus-pituitary-thyroid axis through a negative feedback system. The secretion of T3 and T4 is controlled by both hypothalamic thyrotropin-releasing hormone, which its action exerts by binding to thyroid hormone receptors (THR α and β) and thyroid stimulating hormone (TSH). TSH exerts its role through binding to TSH receptor (TSHR) [4, 5].

L-T4 is a synthetic T4 hormone in the treatment of hypothyroidism. In adults, L-T4 is administered orally as average 1.7 μg/kg body weight/day, being equivalent to approximately 100–125 μg per day. It is needed to higher doses than 1.7 μg/kg/day for new-borns, infants and adolescents. Age, gender, concurrent medications, patient compliance, genetic background *etc.* can influence proper L-T4 treatment [1, 6].

In recent years, it is clinically important approach the personalised medicine instead of empirical treatment to enhancing responses among patients [7]. The concentration of thyroid hormones in tissues is regulated by deiodinases and thyroid hormone transporters. Deiodinase enzyme isoforms (*DIO1*, *DIO2*, and *DIO3*) mainly control intracellular thyroid hormone concentrations. DIO enzymes convert biologically active hormone (T3) from

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L-T4. DIO1 and DIO2 catalyze activation of thyroid hormone secretion in contrast to DIO3 playing role inactivation of the secretion. Activities of DIO1 and DIO2 play pivotal role in the negative feedback regulation of pituitary TSH secretion [8, 9]. UDP-glucuronosyltransferases (UGTs) are responsible for T4 metabolism in human liver as thyroxine glucuronide. Two common UGT1A subfamily enzymes, UGT1A1 and UGT1A3, provide T4 glucuronidation in humans [10]. It was determined different responses dependently of genetic factors in the L-T4 treatment. The previously studies reported the genetic variations on proteins and enzymes have been played role in thyroid hormones metabolism, serum thyroid hormone concentrations, and bioavailability of L-T4 [8, 11]. Therefore, we aimed to comprehensively evaluate the effect of genetic differences in the proteins and enzymes (DIO1, DIO2, TSHR, THRα and UGT) which are efficient in thyroid hormones metabolism on bioavailability of L-T4.

## Material and Methods

Sample collection: This is a cross-sectional study approved by ethical committee of Istanbul University Istanbul Medical Faculty (2015/740), and was carried out in accordance with the Helsinki Declaration of 1975, with all amendments and revisions. A total of 94 unrelated patients with secondary hypothyroidism due to total thyroidectomy were recruited from Endocrine Surgery Clinic of General Surgery Department, Istanbul Medical Faculty, Istanbul University between March 2015 and October 2016. Patients included in this study are all those who completed puberty, aged with 18–75, underwent total thyroidectomy for different causes (multi nodular goitre, suspicion of cancer, pressure effect of large goitre and susbternal goitre) and on two types of doses of L-T4 as high and low doses (<1.7 μg/kg/day and ≥1.7 μg/kg/day). In the studied group, L-T4 was administered as a single dose daily. Neoplasm, liver dysfunction, renal failure, and psychiatric condition not related to hypothyroidism symptoms. Also, pregnancy and alcohol abuse patients on L-T4 treatment were accepted as the excluded criteria. TSH, fT3 and fT4 levels were measured by GenWay Biotach Inc. (San Diego, CA, USA) colorimetric ELISA kits according to manufacturer's instructions by specialists in biochemistry laboratories of Istanbul Medical Faculty.

Genotyping: DNA was isolated from venous blood samples by High Pure PCR Template Preparation Kit (Roche, Germany). The single nucleotide polymorphisms (SNPs) analysis was performed on real-time PCR platform (LightCycler 480, Roche, Germany) using LightCycler FastStart DNA Master HybProbe and Roche LightSNP assay probes (Roche, Germany). The studied SNPs were rs11206244, rs2235544 in *DIO1*; rs225014, rs225015, rs12885300 in *DIO2*; *rs939348* in *THR*α; rs4903957, rs1991517, rs2239610, rs2268458 in *TSHR*; rs1983023, rs3806596 in *UGT1A3* and rs8175347 in *UGT1A1*28*.

Statistical analysis: All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software (Version 20, Chicago, USA). The Hardy-Weinberg Equilibrium (HWE) analysis was performed to compare the observed and expected genotype frequencies of subject by using the chi-square ($\chi^2$) test. It was confirmed that the studied population was randomized by the results obtained from HWE analysis. Sample size was calculated with 95% confidence, and a margin of error 5% for an assuming population proportion of 0.5, and unlimited population size. Continuous variables were expressed as mean ± standard deviation (SD) whereas discrete variables were expressed as frequencies. The differences were accomplished by comparison with one way ANOVA. Post Hoc Tukey test and Independent *t* Test was applied to evaluate for the association between the clinical and biochemical characteristics and the studied genes. A significant difference is considered at $p < 0.05$.

## Results

It was evaluated the effects of 13 SNPs of *DIO1*, *DIO2*, *THR*α, *TSHR* and *UGT1A* on thyroid hormones metabolism and bioavailability of L-T4. The mean age of patients was 51.35 (±1.53) years, the mean body mass index (BMI, kg/m$^2$) was 29.16 (±0.65) and of the all participants 82.61% were female and 48.89% have familial background of thyroid disorders. Of the all participants, 22.83% were dyslipidemic, 23.92% were diabetic, and 20.41% were hypertensive. The patients were also evaluated by dividing into two groups based on current replacement L-T4 dose: low dose group (<1.7 μg/kg/day) and high dose group (≥1.7 μg/kg/day). Age distribution between two groups did not show any difference. As it is expected, the hypothyroid patients who received high dose of LT-4 had a slightly lower BMI. Also, it was found that high dose of LT-4 treatment was associated with lower levels of TSH, and higher levels of fT3 and

**Table 1** Characteristics of hypothyroid patients based on the dose of LT-4 replacement

| Variable | Low dose <1.7 μg/kg/day ($n$ = 66) | High dose ≥1.7 μg/kg/day ($n$ = 28) | $p$ value |
|---|---|---|---|
| Age | 52.00 ± 4.06 | 45.08 ± 2.03 | 0.101 |
| BMI (kg/m$^2$) | 29.82 ± 0.81 | 26.99 ± 1.41 | 0.079 |
| TSH (mIU/L) | 1.93 ± 0.37 | 0.51 ± 0.29 | **0.029** |
| fT3 (pmol/L) | 4.71 ± 0.16 | 5.39 ± 0.27 | **0.048** |
| fT4 (pmol/L) | 19.73 ± 0.66 | 22.09 ± 0.75 | **0.045** |

*Bold values mean* $p < 0.05$

fT4 ($p < 0.05$) (Table 1). The typical reference ranges for thyroid function parameters are between 0.4–4 mIU/L for TSH, 3.5–7.8 pmol/L for fT3, and 9–25 pmol/L for fT4 [12]. Similarly, the mean values of the parameters were 1.54 ± 0.44 μg/kg/day for L-T4 daily dose, 1.79 ± 2.33 mIU/L for TSH, 4.69 ± 1.02 pmol/L for fT3, and 19.75 ± 4.22 pmol/L for fT4 in the studied group.

Genotype distributions of studied SNPs are shown in Table 2. All genotypes were found to be consistent with the HWE ($p > 0.05$). Heterozygous type [*AT*/–] for *UGT1A1*28* (rs8175347) was not observed. Interestingly, we observed that *DIO2* rs225015 *G* and *TSHR* rs1991517 *C* alleles were wild types with the 66.1% and 88.9% frequencies, respectively. However, the ancestral alleles were indicated as *A* and *G* according to NCBI SNP database [https://www.ncbi.nlm.nih.gov/projects/SNP].

There was no significant correlation among genotypes and L-T4 dose ($p > 0.05$), the biochemical parameters including thyroid function test (TSH, fT3 and fT4), and body mass index. A statistical significance was found between *DIO2* rs225014 and TSH levels. Homozygous wild type (*TT*, *Thr/Thr*) for *DIO2* rs225014 was associated with higher levels of TSH ($p < 0.05$). Besides, *DIO2* rs225015 *GG* genotype was found to be associated with higher levels of TSH compared with the *AA* genotype ($p < 0.05$). Homozygous mutant types of *TSHR* rs4903957 (*AA*), rs1991517 (*CC*), rs2239610 (*CC*) and rs2268458 (*CC*) were related with higher levels of TSH. Although obtained significant differences in the values, the association did not reach statistical significance. Probably the reason is their excessive SDs. Additionally, homozygous variant types of *THR*α rs939348 (*TT*) and *UGT1A3* rs1983023 (*CC*) were related with lower levels of TSH (Table 3).

## Discussion

The present study is a comprehensive cross-sectional study, and first study to evaluation the genetic profiles of Turkish people in the genes related to thyroid metabolism (Table 3). There are limited publications about the relationship between the gene variants and drug-response in hypothyroidism treatment [1, 2, 8, 10, 13-20].

Panicker *et al.* [14] suggested that *DIO1* rs2235544 has a correlation with circulating fT3/fT4 levels both in the population with thyroid hormone replacement and in the general population. Rs2235544 *C* allele was associated with increased fT3 and decreased fT4 levels, however not associated with serum TSH levels. They also reported no association between *DIO1* rs11206244, which increase enzyme activity, and the levels of mentioned serum parameters. In the previous studies, it was suggested that the patient with carrying *C* allele of rs2235544 should be treated higher doses of L-T4 because *C* allele increases the function of *DIO1* [17, 18]. However, Santoro *et al.* [10] stated no association between dose and these genes. Similar to Santoro *et al.* [10], in the present study, we observed that the values of TSH, fT3 and fT4 were in normal range in patients with variant and wild alleles of *DIO1* rs11206244 and rs2233544. There was no association between *DIO1* (rs2233544) genotype and the TSH, fT3 and fT4 levels.

Heemestra *et al.* [19] observed no differences between *DIO2* rs225014 and thyroid hormone levels and L-T4 doses adjusted for age, gender, BMI and serum TSH levels. Similar results were observed by Panicker *et al.* [14] and Al-Azzam *et al.* [8]. However, Torlontano *et al.* [15] stated that the patient with homozygous variant type (*CC*, *Ala/Ala*) for *DIO2* rs225014 needed the higher dose of L-T4 to provide favourable TSH levels. They reported that an approximate 20% higher dose was needed in patient with homozygous variant type for target TSH levels to be reached. And, they suggested a reduced pituitary feedback due to abnormal DIO2 hypothalamic/pituitary activity. As it is known, DIO2 activity plays an important role in the negative feedback regulation of

**Table 2** The frequencies of 13 gene variants in the patients with hypothyroidism

| SNP | | Genotype *n* (%) | | |
|---|---|---|---|---|
| *DIO1* | rs11206244 | CC | CT | TT |
| | | 47 (52.2) | 35 (38.9) | 8 (8.9) |
| | rs2235544 | CC | CA | AA |
| | | 33 (36.7) | 44 (48.9) | 13 (14.4) |
| *DIO2* | rs225014 | TT | TC | CC |
| | | 38 (45.2) | 34 (40.5) | 12 (14.3) |
| | rs225015 | AA | AG | GG |
| | | 13 (14.4) | 35 (38.9) | 42 (46.7) |
| | rs12885300 | CC | CT | TT |
| | | 39 (43.8) | 43 (48.3) | 7 (7.9) |
| *THR*α | rs939348 | CC | CT | TT |
| | | 49 (54.4) | 35 (38.9) | 6 (6.7) |
| *TSHR* | rs4903957 | GG | GA | AA |
| | | 50 (55.6) | 36 (40) | 4 (4.4) |
| | rs1991517 | GG | GC | CC |
| | | 3 (3.3) | 14 (15.6) | 73 (81.1) |
| | rs2239610 | GG | GC | CC |
| | | 56 (62.2) | 32 (35.6) | 2 (2.2) |
| | rs2268458 | TT | TC | CC |
| | | 56 (62.2) | 32 (35.6) | 2 (2.2) |
| *UGT1A3* | rs1983023 | TT | TC | CC |
| | | 41 (45.6) | 37 (41.1) | 12 (13.3) |
| | rs3806596 | AA | AG | GG |
| | | 28 (31.1) | 41 (45.6) | 21 (23.3) |
| *UGT1A1*28* | rs8175347 | [AT] | [AT/–] | [–] |
| | | 24 (26.7) | 0 (0) | 66 (73.3) |

pituitary TSH secretion [15]. Similarly, in the present study, a statistical significance was found between *DIO2* rs225014 and TSH levels; homozygous wild type (*TT*, *Thr/Thr*) was associated with higher levels of TSH ($p < 0.05$). Also, *DIO2* rs225015 *GG* genotype was found to be associated with higher levels of TSH compared with the *AA* genotype ($p < 0.05$). For *DIO2* rs225014 and rs225015, their effected genotypes were observed in different frequencies. The common homozygous type for *DIO2* rs225014 (*TT*) and the mutant homozygous types for rs225015 (*GG*) were associated with higher levels of TSH compared with their other types. Therefore, the patients with for *DIO2* rs225014 (*TT*) and rs225015 (*GG*) variants have higher TSH levels, and should take higher L-T4 dose.

*THR*α rs939348 was associated with L-T4 replacement doses [1]. It was suggested that T allele carrying patients should be taken more doses of L-T4 because of the increased enzyme function. Similarly, we observed that the TSH level was lower in the patient with *THR*α rs939348 *TT* genotype in same dose L-T4 treatment.

The previous studies stated there was no association between *TSHR* and L-T4 dose [20, 21]. In the present study, it was found that homozygous mutant type of

**Table 3** The biochemical characteristics of the *DIO1*, *DIO2*, *THR*α, *TSHR*, *UGT1A3* and *UGT1A1*28* genotypes of the hypothyroid patients

| Genotype | | BMI (kg/m$^2$) | L-T4 daily dose | | TSH (mIU/L) | fT3 (pmol/L) | fT4 (pmol/L) |
|---|---|---|---|---|---|---|---|
| | | | (μg/day) | (μg/kg) | | | |
| *DIO1* | | | | | | | |
| rs11206244 | *CC* | 28.48 ± 0.99 | 111.1 ± 4.6 | 1.45 ± 0.06 | 1.91 ± 0.38 | 4.70 ± 0.21 | 19.85 ± 0.65 |
| | *CT* | 30.08 ±1.09 | 133.4 ± 10.4 | 1.67 ± 0.13 | 1.60 ± 0.39 | 4.72 ± 0.15 | 19.53 ± 0.72 |
| | *TT* | 28.42 ± 1.14 | 116.4 ± 11.9 | 1.56 ± 0.16 | 1.82 ± 0.56 | 4.36 ± 0.28 | 20.19 ± 1.08 |
| rs2235544 | *CC* | 27.26 ± 1.32 | 111.3 ± 5.5 | 1.50 ± 0.74 | 1.91 ± 0.62 | 4.97 ± 0.28 | 20.72 ± 1.15 |
| | *CA* | 30.12 ±1.04 | 135.3 ± 8.9 | 1.67 ± 0.11 | 1.18 ± 0.39 | 4.84 ± 0.22 | 20.22 ± 0.60 |
| | *AA* | 29.49 ±1.24 | 112.1 ± 10.2 | 1.43 ± 0.13 | 1.65 ± 0.47 | 4.64 ± 0.13 | 20.32 ± 1.36 |
| *DIO2* | | | | | | | |
| rs225014 | *TT* | 28.69 ± 1.09 | 117.8 ± 5.9 | 1.49 ± 0.75 | **2.33 ± 0.51*** | 4.63 ± 0.24 | 20.07 ± 0.78 |
| | *TC* | 29.39 ± 1.36 | 117.3 ± 8.3 | 1.75 ± 0.12 | 0.31 ± 0.09 | 5.06 ± 0.18 | 21.66 ± 0.91 |
| | *CC* | 30.09 ± 1.13 | 111.7 ± 16.9 | 1.45 ± 0.22 | 0.17 ± 0.06 | 4.71 ± 0.22 | 18.67 ± 0.93 |
| rs225015 | *AA* | 31.59 ± 1.27 | 144.5 ± 19.2 | 1.66 ± 0.22 | 0.16 ± 0.05 | 4.74 ± 0.16 | 20.07 ± 1.47 |
| | *AG* | 29.34 ± 1.28 | 136.7 ± 9.8 | 1.67 ± 0.12 | 0.95 ± 0.31 | 5.04 ± 0.15 | 21.37 ± 0.96 |
| | *GG* | 28.32 ± 1.01 | 112.7 ± 5.3 | 1.48 ± 0.07 | **2.44 ± 0.51*** | 4.78 ± 0.24 | 20.01 ± 0.72 |
| rs12885300 | *CC* | 29.32 ± 1.07 | 119.2 ± 8.6 | 1.53 ± 0.11 | 1.22 ± 0.52 | 4.81 ± 0.26 | 20.75 ± 0.79 |
| | *CT* | 28.87 ± 1.06 | 121.8 ± 7.1 | 1.55 ± 0.09 | 1.74 ± 0.43 | 4.84 ± 0.19 | 19.63 ± 0.81 |
| | *TT* | 29.16 ± 2.02 | 132.6 ± 8.8 | 1.65 ± 0.11 | 1.27 ± 0.54 | 5.09 ± 0.66 | 22.58 ± 0.99 |
| *THR*α | | | | | | | |
| rs939348 | *CC* | 28.93 ± 0.98 | 126.1 ± 7.1 | 1.60 ± 0.09 | 1.63 ± 0.42 | 4.71 ± 0.15 | 19.93 ± 0.69 |
| | *CT* | 29.55 ± 1.13 | 118.5 ± 6.4 | 1.49 ± 0.08 | 1.54 ± 0.45 | 4.91 ± 0.29 | 20.74 ± 0.96 |
| | *TT* | 27.27 ± 3.25 | 116.7 ± 16.0 | 1.61 ± 0.22 | **0.23 ± 0.16**$^{\dagger}$ | 5.88 ± 0.61 | 23.05 ± 1.26 |
| *TSHR* | | | | | | | |
| rs4903957 | *GG* | 29.09 ± 1.02 | 125.1 ± 6.3 | 1.58 ± 0.08 | 1.73 ± 0.43 | 5.07 ± 0.23 | 20.31 ± 0.87 |
| | *GA* | 29.52 ± 1.01 | 125.2 ± 8.1 | 1.54 ± 0.10 | 1.07 ± 0.35 | 4.66 ± 0.19 | 20.54 ± 0.60 |
| | *AA* | 33.91 ± 2.48 | 136.1 ± 5.4 | 1.51 ± 0.06 | **2.53 ± 2.23** | 4.93 ± 0.49 | 20.38 ± 2.90 |
| rs1991517 | *GG* | 27.34 ± 0.01 | 152.9 ± 2.9 | 2.13 ± 0.04 | 0.08 ± 0.01 | 4.91 ± 0.02 | 20.61 ± 0.05 |
| | *GC* | 31.13 ± 1.83 | 124.3 ± 8.9 | 1.54 ± 0.11 | 0.53 ± 0.29 | 5.41 ± 0.31 | 22.92 ± 1.28 |
| | *CC* | 28.66 ± 0.78 | 125.4 ± 5.7 | 1.55 ± 0.07 | **1.78 ± 0.35**$^{\dagger}$ | 4.71 ± 0.16 | 19.82 ± 0.57 |
| rs2239610 | *GG* | 29.94 ± 0.91 | 119.9 ± 5.6 | 1.49 ± 0.07 | 1.55 ± 0.38 | 4.78 ± 0.17 | 20.29 ± 0.81 |
| | *GC* | 28.46 ± 1.17 | 130.2 ± 9.3 | 1.68 ± 0.12 | 1.21 ± 0.41 | 5.02 ± 0.27 | 20.63 ± 0.61 |
| | *CC* | 35.82 ± 2.76 | 141.9 ± 0.9 | 1.51 ± 0.01 | **3.77 ± 3.21**$^{\dagger}$ | 4.62 ± 0.66 | 20.07 ± 5.01 |
| rs2268458 | *TT* | 28.74 ± 0.93 | 115.4 ± 5.3 | 1.53 ± 0.07 | 1.48 ± 0.39 | 4.86 ± 0.18 | 20.40 ± 0.82 |
| | *TC* | 28.76 ± 1.12 | 129.9 ± 8.8 | 1.62 ± 0.11 | 1.31 ± 0.41 | 4.88 ± 0.26 | 20.46 ± 0.61 |
| | *CC* | 35.82 ± 2.76 | 145.4 ± 3.9 | 1.51 ± 0.04 | **3.77 ± 3.22**$^{\dagger}$ | 4.61 ± 0.65 | 20.07 ± 5.01 |
| *UGT1A3* | | | | | | | |
| rs1983023 | *TT* | 28.37 ± 1.07 | 118.1 ± 8.6 | 1.51 ± 0.11 | 1.65 ± 0.45 | 4.52 ± 0.24 | 20.72 ± 0.83 |
| | *TC* | 29.73 ± 1.18 | 130.1 ± 6.7 | 1.55 ± 0.08 | 1.77 ± 0.49 | 5.11 ± 0.19 | 19.92 ± 0.85 |
| | *CC* | 28.74 ± 1.46 | 139.6 ± 10.4 | 1.74 ± 0.13 | **0.31 ± 0.09**$^{\dagger}$ | 4.84 ± 0.26 | 21.22 ± 1.18 |

**Table 3** Continued

| Genotype | | BMI (kg/m$^2$) | L-T4 daily dose | | TSH (mIU/L) | fT3 (pmol/L) | fT4 (pmol/L) |
|---|---|---|---|---|---|---|---|
| | | | (μg/day) | (μg/kg) | | | |
| rs3806596 | *AA* | 29.22 ± 1.15 | 103.8 ± 4.7 | 1.32 ± 0.06 | 1.82 ± 0.57 | 4.58 ± 0.37 | 20.47 ± 0.88 |
| | *AG* | 28.84 ± 1.14 | 128.0 ± 8.6 | 1.63 ± 0.11 | 1.63 ± 0.51 | 5.02 ± 0.19 | 20.41 ± 0.90 |
| | *GG* | 29.25 ± 1.41 | 126.0 ± 8.5 | 1.64 ± 0.11 | 1.06 ± 0.41 | 4.81 ± 0.22 | 20.37 ± 0.92 |
| | | | | *UGT1A1*28* | | | |
| rs8175347 | *[AT]* | 30.11 ± 1.31 | 126.3 ± 9.0 | 1.54 ± 0.11 | 1.07 ± 0.31 | 4.85 ± 0.15 | 19.41 ± 0.98 |
| | *[AT/–]* | — | — | — | — | — | — |
| | *[–]* | 28.46 ± 0.83 | 120.3 ± 6.1 | 1.57 ± 0.08 | 1.75 ± 0.41 | 4.85 ± 0.19 | 20.91 ± 0.63 |

* Indicates the statistically significant difference ($p < 0.05$).

† Indicates the association that did not reach statistical significance.

The biochemical characteristics for the patients with the *DIO1*, *DIO2*, *THR*α, *TSHR* and *UGT1A3* genotypes were analysed with Post Hoc Tukey test. Only, *UGT1A1*28* was analysed with independent-*t* test because of the absence of heterozygous type.

*TSHR* rs4903957 (*AA*), rs1991517 (*CC*), rs2239610 (*CC*) and rs2268458 (*CC*) were related with higher levels of TSH. However, the association did not reach statistical significance probably due to their excessive SDs.

The previous studies have showed a direct or indirect correlation between L-T4 dose and *UGT1A*. It was also indicated the importance of glucuronidation in T4 homeostasis and *UGT1A1* and *UGT1A3*. *UGT1A1* had a higher affinity than *UGT1A3* for T4 in T4 glucuronication while *UGT1A3* had higher capacity for T4 glucuronidation. It was stated a significant correlation between *UGT1A1*28* and T4 glucuronidation [13]. Graber *et al.* [13] pointed out hypothyroid patients with homozygous *UGT1A1*28* variant should receive a lower L-T4 dose. Santoro *et al.* [10] and Vargens *et al.* [16] reported that polymorphic individuals of *UGT1A* should be received lower doses of L-T4 to reach appropriate levels of TSH due to lower expressions of related SNPs of *UGT1A*. In our findings, homozygous variant type (*CC*) of *UGT1A3 rs1983023* were related with lower levels of TSH; however, the association did not reach statistical significance.

In conclusion; there was a significant correlation between rs225014 and rs225015 in *DIO2* and TSH levels. However, *DIO1*, *DIO3*, *UGT1A*, *THR*α and *TSHR* were not associated L-T4 treatment. It should be lower dose in the individuals with *DIO2* rs225014 (*TT*) and rs225015 (*GG*) in order to provide the more effectively treatment with lower toxicity. The observed significant correlations should be sensitive and precious biomarkers of thyroid function and treatment among patients. Therefore, personalised medicine should be tendered optimal treatment according to patients' genetic background.

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