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Original article

P-glycoprotein polymorphism and levothyroxine bioavailability in hypothyroid patients

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ABSTRACT

Objectives: P-glycoprotein (P-gp) contributes to the disposition of a wide variety of drugs; therefore, single nucleotide polymorphisms (SNPs) in the P-gp coding gene might affect its activity. It is well known that personalized medicine, instead of empirical treatment, is a clinically important approach for enhancing responses among patients. Indeed, there is a need to evaluate the association between SNPs of P-gp encoded multidrug resistance genes (*MDR1*, *ABCB1*), and the dosage requirements of these drugs. In the present study, we evaluated the association between the dosage of Levothyroxine (L-T4) and three common SNPs (C1236T, G2677T/A and C3435T).
Methods: Genotyping was done using a real-time PCR platform with DNA samples isolated from the venous blood of ninety post thyroidectomy hypothyroid patients. Thyroid hormone levels were measured as routine biochemistry laboratories in the Medical School of Istanbul University.
Results: In the genotype analysis, the minor allele frequencies were 0.48 for C1236T, 0.51 for G2677T/A, and 0.51 for C3435T. In the haplotype-based analysis, $T_{1236}T_{2677}T_{3435}$ and $C_{1236}G_{2677}C_{3435}$ were observed as major haplotypes (50.2 and 32.6%, respectively), in agreement with previous studies. The administered dose of L-T4 to achieve physiological thyroid hormone levels was found to be similar in all genotypes and haplotypes, indicating that there is no significant association between *MDR1* polymorphisms and L-T4 doses.
Conclusion: Because of conflicted previous reports about the genetic contribution of *MDR1* polymorphisms to drug disposition, further studies with large numbers of participants are required to clarify this influence.

1. Introduction

The desire for better individualized treatment for hypothyroid patients has led to research to clarify the role of genetic polymorphisms on L-T4 bioavailability. P-gp is a well-known transport protein found mostly in the cellular membrane of different cell types in the intestine, kidney, blood-brain barrier and parathyroid glands (Thiebaut et al., 1987; Borst and Schinkel, 1997). P-gp, an ATP-dependent efflux transporter, acts as a physiological barrier by extruding a wide range of substances, from xenobiotics to endogenous compounds such as pesticides, anticancer drugs, antibiotics, cardiac glycosides, small proteins and hormones (Schinkel, 1997). P-gp is encoded by the *MDR1* gene, which is located in the region 7q21.12 of chromosome 7 in humans (Wolking et al., 2015).

MDR1 has a crucial role in drug disposition, and genetic polymorphisms in this gene might alter the pharmacokinetics and bioavailability of a diverse range of P-gp substrates (Kurose et al., 2008). Although many variations in the coding region of *MDR1* have been found, there is no consensus on their implications at the clinical level (Kurata et al., 2002; Morita et al., 2003; Leschziner et al., 2007). So far, approximately one hundred single

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nucleotide polymorphisms (SNPs) in *MDR1* have been identified (Marzolini et al., 2004). Among all variations, C1236T (rs1128503, Gly412Gly), G2677T/A (rs2032582, Ser893Ala/Thr) and C3435T (rs1045642, Ile1145Ile) are common and have a different prevalence in different groups of the population (Hodges et al., 2011).

L-T4, a synthetic T4 hormone, is the first choice for the treatment of hypothyroidism, which is characterized by decreased levels of the circulating thyroid hormones triiodothyronine (T3) and its prohormone thyroxine (T4), which are secreted from the thyroid gland by stimulation from thyroid stimulating hormone (TSH) (Vanderpump, 2011; Mondal et al., 2016). L-T4 is usually administered 100–150 mcg/day for men and 75–100 mcg/day for women (Mandel et al., 1993); dose adjustment is made by a trial and error approach. However, besides age, gender, concurrent diseases and polypharmacy, genetic background may have a significant effect on the bioavailability of L-T4 treatment as well (Garber et al., 2012; Al-Azzam et al., 2014).

Since drug efflux is mediated by P-gp, *MDR1* polymorphisms play an important role in cell homeostasis by altering bioavailability of L-T4 and regulating the thyroid hormone levels. In the present study, we aimed to investigate the association between *MDR1* variants and thyroid function parameters in patients with L-T4 treatment. This study is the first that evaluates the effects of *MDR1* polymorphisms on L-T4 dose adjustment.

2. Material and methods

2.1. Subjects

The study was conducted as a cross-sectional study with Turkish participants recruited from endocrine surgery clinics of Istanbul University Istanbul Medical Faulty between March 2015 and October 2016. Ninety patients with secondary hypothyroidism caused by total thyroidectomy were included. All patients received various doses of L-T4, adjusted by the practitioners with regard to the patient's body mass index and level of thyroid function parameters. The study was approved by the ethical committee of Istanbul University (2015/740) and carried out in accordance with the Helsinki Declaration of 1975. All participants were provided informed consent.

2.2. Biochemical analysis

TSH, fT3 and fT4 levels were measured in biochemistry laboratories of the Medical School of Istanbul University by performing GenWay Biotech Inc. (San Diego, CA, USA) ELISA kits according to manufacturer's instructions.

2.3. Genotyping

DNA was isolated from venous blood samples using the High Pure PCR Template Preparation Kit (Roche, Germany) and kept at 4 °C. Genotyping was done by the LightCycler FastStart DNA Master HybProbe and Roche LightSNP assay probes (Roche, Germany) according to the manufacturer's instructions. In a final volume of 20 μL reaction mix per sample, the following mixtures was added: 1X FastStart DNA Master Mix, 2 mM $MgCl_2$, 0.2 μM LightSNP HybProbe, appropriate amount of PCR grade water and 500 ng DNA sample. The plates were sealed and centrifuged at 3000 rpm for a minute. Melting curve analyses were performed on a real-time PCR platform (LightCycler 480, Roche, Germany) by the Carousel-Based System PCR program (Table 1). In each plate, sterile water and a known genotyped sample were used as controls to achieve 100% concordance.

2.4. Statistical analysis

All statistical analyses were carried out by using Statistical Package for Social Sciences (SPSS) software (Version 21, Chicago, USA). Hardy-Weinberg equilibrium was tested using the chi-square. Data were expressed as median, minimum, maximum, frequencies and percentages. Genotypes were evaluated with the Mann-Whitney *U* test. The association between genotypes and L-T4 dose were assessed using binary logistic regression while TSH, fT3, fT4, age and BMI were covariates. Haplotypes were identified by a Bayesian approach using the PHASE algorithm (Version 2, Chicago, USA). A two-tailed value of $p < .05$ was considered a statistically significant difference.

3. Results

MDR1 C1236T, G2677T/A, and C3435T variants were evaluated in Turkish patients with secondary hypothyroidism. All samples (n = 90) were genotyped with at least a 96.7% success rate and 100% concordance. Genotype distribution was found to be consistent with the Hardy-Weinberg equilibrium model ($p > .05$), suggesting that the studied population was unbiased. Features of the studied SNPs are summarized in Table 2. Allele frequencies were found notably similar to Caucasians as stated in the NCBI SNP database (dbSNP, https://www.ncbi.nlm.nih.gov/snp).

The clinical and biochemical characteristics of the patients are summarized in Table 3. The median age was 51.35 (21–76) years, the median body mass index (BMI, kg/m^2) was 29.06 (19.72–38.58), and females represented 83.3% of the participants. The median values of thyroid hormones were 0.96 mIU/L for TSH (reference range: 0.4–4 mIU/L), 4.95 pmoL/L for fT3 (reference range: 3.5–7.8 pmol/L) and 19.54 pmoL/L for fT4 (reference range: 9–25 pmol/L) (Den Hollander et al., 2005).

The L-T4 dose distribution among genotypes, based on a dominant model comparing wild-type homozygous versus others, is illustrated in Fig. 1. The median L-T4 dose was observed much the same among the genotypes in each SNP. Additionally, binary logistic regression analysis showed that the selected SNPs had no influence on the L-T4 dose adjustment while TSH, fT3, fT4, BMI and age were covariates (Table 4).

Table 1
Carousel-Based System PCR program setup.

Program name	Cycles	Analysis mode	Target (°C)	Acquisition mode	Hold (sec)
Pre-Incubation	1	None	95	None	600
Amplification	45	Quantification	95	None	10
			60	Single	10
			72	None	15
Melting Curve	1	Melting Curve	95	None	30
			40	None	120
			75	Continuous	–
Cooling	1	None	40	None	30

Table 2
Genotype distribution and features of studied SNPs.

SNP	Amino acid change	Variant allele	Genotype	n (%)	MAF	HWE
C1236T	Gly412Gly	T	CC	25 (27.8)	0.48	0.04
			CT	41 (45.6)		
			TT	22 (24.4)		
G2677T/A	Ser893Ala/Thr	T/A	GG	10 (11.1)	0.51	<0.01
			AG	13 (14.4)		
			TG	40 (44.4)		
			TT	24 (26.7)		
C3435T	Ile1145Ile	T	CC	22 (24.4)	0.51	0.02
			CT	45 (50.0)		
			TT	23 (25.6)		

MAF, Minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Table 3
Clinical and biochemical characteristics of the patients.

Variable	Median (Range)
Age	51.35 (21–76)
BMI (kg/m^2)	29.06 (19.72–38.58)
Gender	
Female (n, %)	75 (83.3%)
Male (n, %)	15 (16.7%)
L-T4 (mcg/day)	118.02 (50–250)
TSH (mIU/L)	0.96 (0.01–12.20)
fT3 (pmol/L)	4.95 (0.80–22.07)
fT4 (pmol/L)	19.54 (2.20–29.11)

Seven haplotypes were observed and two major haplotypes, $T_{1236}T_{2677}T_{3435}$ and $C_{1236}G_{2677}C_{3435}$, were identified that accounted for 82.8% of all patients (Fig. 2). The remaining haplotypes were observed in up to 7 patients; hence, association between two major haplotypes and L-T4 dose was examined. Binary logistic regression showed that $T_{1236}T_{2677}T_{3435}$ (n = 33; OR [95% CI] = 1.010 [0.983–1.038]; p = .479) and $C_{1236}G_{2677}C_{3435}$ (n = 29; OR [95% CI] = 0.993 [0.969–1.017]; p = .542) haplotypes had no influence on the L-T4 dose adjustment while TSH, fT3, fT4, age and BMI were covariates.

4. Discussion

In the complex balance of body homeostasis, thyroid hormones play crucial roles in several metabolic pathways, such as protein, carbohydrate and fat metabolism, through regulation of the endocrine system. Thyroid hormones exert their action on nuclear receptors; thus, the equilibrium of thyroid hormones in cells is a major component for proper body development (Mondal et al., 2016). For patients with hypothyroidism, L-T4 is a commonly prescribed drug for hormone replacement therapy which aims to normalize serum TSH level. The success of the treatment depends on L-T4 bioavailability, which is affected by several factors such as timing of administration (Bach-Huynh et al., 2009), body mass (Santini et al., 2005), gender (Devdhar et al., 2011), age and concurrent diseases (Garber et al., 2012), pregnancy, cytochrome P450 enzyme inducers (Park and Lee, 2012), and genetic polymorphisms (Al-Azzam et al., 2013).

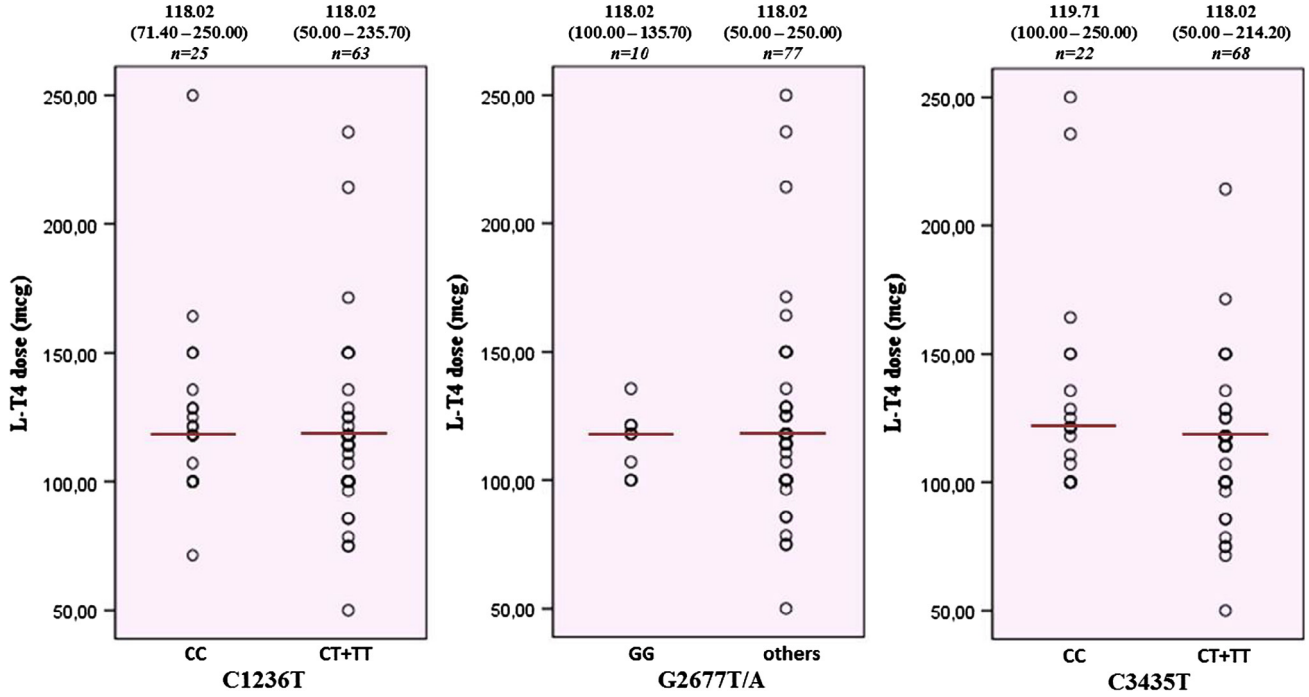

Fig. 1. L-T4 dose distribution among genotypes. Red lines represent median L-T4 doses (μg/day) and values were shown as median (range) above the related columns. n, number of patients.

Table 4
Effects of genotypes on L-T4 doses.

SNP	Genotype	B	SE	OR (95% CI)	*p*
C1236T	CC vs. CT + TT	−0.011	0.009	0.989 (0.972–1.006)	0.21
G2677T/A	GG vs. others	0.010	0.015	1.01 (0.982–1.039)	0.49
C3435T	CC vs. CT + TT	−0.016	0.009	0.984 (0.967–1.002)	0.08

B, Coefficient for the constant; SE, Standard error; OR, Odds ratio; CI, Confidence interval.

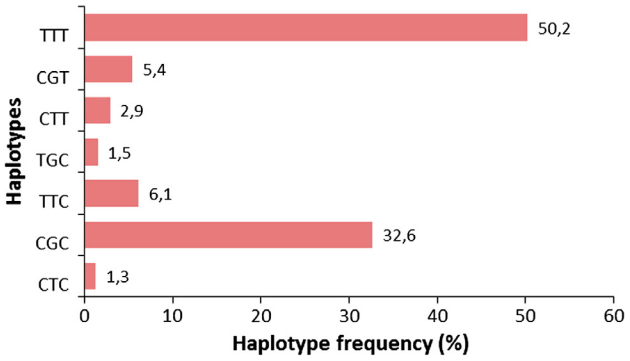

Fig. 2. *MDR1* haplotypes and frequencies based on C1236T/G2677T/C3435T genotypes identified by PHASE algorithm.

It is well established that *MDR1* encodes the membrane transporter P-glycoprotein (P-gp) which alters the disposition of a great variety of structurally unrelated substances and therefore has a great impact on drug bioavailability (Borst et al., 2000; Fromm, 2000; Aller et al., 2009). *MDR1* has been found to be highly polymorphic in various populations (Hoffmeyer et al., 2000; Cascorbi et al., 2001; Balram et al., 2003), yet the clinical implications remain uncertain. C1236T, G2677T/A and C3435T variants are the most studied SNPs due to their high frequencies in Caucasians and Asians (Fromm, 2002). C1236T and C3435T are silent SNPs, whereas G2677T/A results in an amino acid change (Pauli-Magnus and Kroetz, 2004). An interesting fact about these SNPs is that they are in linkage disequilibrium (Hodges et al., 2011), meaning that they occur together and it is difficult to study them separately.

Mathijssen et al. (2003) observed increased exposure to irinotecan in patients diagnosed with malignant solid tumors with the 1236 TT genotype. Zhang et al. (2008) reported that cyclosporine concentrations were greater in myasthenia gravis patients with 1236 TT or 2677 TT genotypes, whereas Schaich et al. (2009) found increased response of temozolomide treatment in glioblastoma patients with the 1236 CC genotype. Kim et al. (2001) reported that the 2677 TT and 3435 TT genotypes were associated with decreased plasma concentration of fexofenadine in healthy subjects; however, Yamauchi et al. (2002) reported that 2677 TT genotype was associated with increased tacrolimus neurotoxicity in liver transplantation patients. Hoffmeyer et al. (2000) reported that the 3435 TT genotype was associated with higher plasma concentrations of digoxin. In contrast, Nóvoa et al. (2006) reported lower plasma concentrations of atazanavir. Additionally, Zhu et al. (2004) and Haas et al. (2005) found that the 3435 TT genotype was associated with increased levels of nelfinavir in HIV-positive patients.

Although many researchers reported controversial associations with numerous drugs, there is a substantial opinion that suggests these SNPs have no effect on drug pharmacokinetics. C3435T is not associated with digoxin and fexofenadine concentrations in healthy subjects (Becquemont et al., 2001; Drescher et al., 2002), or with changes in cyclosporine and tacrolimus concentrations in renal transplant patients (Hesselink et al., 2003). Moreover, De Cassia Estrela et al. (2009) reported that the C1236T, G2677T/A and C3435T variants had no effect on lopinavir and ritonavir concentrations in HIV-infected men. Similarly, Lakhan et al. (2009) found that these SNPs are not associated with phenytoin, carbamazepine, phenobarbital, and valproate response in North Indian epileptic patients.

There are limited studies evaluating the relationship between *MDR1* polymorphisms and L-T4 administration. Mitin et al. (2004) and Jin et al. (2005) reported that P-gp is induced by long-term L-T4 administration in human colon carcinoma cell lines and Wistar rats, respectively. Siegmund et al. (2002) conducted a study with a limited number of human subjects who had normal thyroid functions and found that L-T4 administration caused *MDR1* upregulation. In the same study, no modulation by the C3435T polymorphism was observed, in contrast to the study by Hoffmeyer et al. (2000) who reported that the C3435T polymorphism does impact *MDR1* upregulation. However, the G2677T/A polymorphism was found to be associated with lower levels of L-T4. There are no previous studies regarding the effects of *MDR1* polymorphisms on L-T4 dose adjustment in patients with hypothyroidism. In the present study, no association was observed between the C1236T, G2677T/A or C3435T genotypes and the L-T4 dose that was required to achieve favorable thyroid hormone levels.

Haplotype analysis was conducted due to previous reports indicating that these three SNPs are closely linked in many populations. In the present study, two major haplotypes, $T_{1236}T_{2677}T_{3435}$ and $C_{1236}G_{2677}C_{3435}$in agreement with Kim et al. (2001), Tang et al. (2002) and Kroetz et al. (2003). Finally, the clinical outcomes of *MDR1* haplotypes are controversial regarding a wide range of drugs in different populations. Sai et al. (2003) reported that the $T_{1236}T_{2677}T_{3435}$ haplotype was associated with an increased concentration of irinotecan in Japanese cancer patients. Chowbay et al. (2003) reported that Asian heart transplantation patients with the $T_{1236}T_{2677}T_{3435}$haplotype had a higher concentration of cyclosporine. Additionally, Aarnoudse et al. (2008) and Xu et al. (2008) found that the $T_{1236}T_{2677}T_{3435}$haplotype, but not the CGC haplotype, was associated with increased digoxin exposure in Europeans and Chinese, respectively. However, Lakhan et al. (2009) and Xuan et al. (2014) observed that none of the *MDR1* haplotypes were associated with drug concentrations. Similarly, in the present study, neither the $T_{1236}T_{2677}T_{3435}$nor the $C_{1236}G_{2677}C_{3435}$ haplotype was found to be associated with L-T4 dose adjustment in hypothyroid patients.

5. Conclusion

In this first cross-sectional study conducted with secondary hypothyroidism patients, no association was found between L-T4 dose administration and the C1236T, G2677T/A, C3435T genotypes and haplotypes. In consideration of conflicted previous reports regarding the genetic contribution of *MDR1* to drug disposition, further studies are required to clarify the influence.

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Author disclosure statement

The authors declare that there are no conflicts of interest.

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