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Microwave ablation of symptomatic benign thyroid nodules: Short- and long-term effects on thyroid function tests, thyroglobulin and thyroid autoantibodies

Short title: Microwave ablation effects on thyroid tests

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Background: Microwave ablation therapy has been attracting great attention due to its advantages such as low complication rate, good cosmetic results, and effective nodule shrinking. Although the effect of thermal ablation therapy on the nodule volume reduction rate has been shown several studies, a limited number of papers has been reported for the effects of microwave ablation (MWA) on thyroid function tests.

Aim: The aim of this study was to investigate the short- and long-term effects of MWA therapy on thyroid function tests (TFTs), thyroglobulin (Tg) and thyroid autoantibodies in euthyroid patients.

Methods: Demographic data of the patients, TFTs, Tg, thyroid autoantibodies, and thyroid volume of the nodules were recorded before the procedure and follow-up. Any differences in serum thyroid hormone levels were investigated in pre-, post-, and 6-month follow-up periods before and after MWA.

Results: The difference between all thyroid hormone levels at pre MWA and 24 h after MWA were statistically significant (*P* <0.001). FT3 (4.62) pmol/L and FT4 (10.81) pmol/L median levels increased significantly (*P* <0.001) while TSH levels decreased at 24 h after MWA (*P* <0.001). Thyroid antibodies levels were not statistically different at 6-month (*P* >0.05) whereas Tg levels decreased (*P* <0.001) compared to pre MWA.

Conclusions:
While no significant effect was observed at 6-month, the effect of MWA on thyroid function tests was prominent at 24 h.

Key Words: Thyroid nodule, microwave ablation, thyroid function tests, thyroid hormones

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1. Introduction

Management of thyroid nodules (TNs) is a common problem in clinical endocrinology practice. Most TNs are asymptomatic and do not cause thyroid dysfunction.[1] Clinical follow-up is recommended for benign non-functioning asymptomatic TNs.[2] Symptoms attributable to compression of adjacent structures by TNs include dysphagia, globus sensation, dysphonia, and dyspnea.[3,4] Medical treatments have limited value in the treatment of compression symptoms and cosmetic concerns. Surgery in nodular thyroid diseases is usually preferred in patients with compression symptoms, in the presence of thyroid cancer, and in the selected cases with hyperthyroidism.[5] One of the most important priorities in the follow-up and treatment of TNs is to protect the patients from unnecessary surgery.

In the field of minimally invasive therapies, several ultrasound-guided techniques involving percutaneous ethanol injection, percutaneous thermal radiofrequency (RF) and laser ablation (LA) have revealed promising results over the last decade.[6] Recently, microwave ablation (MWA) has been emerging as a new image-guided thermal ablation therapy that helps to relieve compression symptoms and/or cosmetic problems of the nodule.[7]

Acute and excessive discharge of thyroid hormones into the blood may cause thyroid crisis.[8] This is particularly important in patients with comorbidities such as coronary artery disease and arrhythmia. To date, the effect of thermal ablation treatments on nodule shrinkage has been shown in many studies,[9] but there are a limited number of studies evaluating the effects of MWA on thyroid function tests. Heck et al.[10] reported in their recent study, in which all patients were evaluated with thyroid scintigraphy and cold nodules were included, that thyroid function tests (TFTs) were not significantly affected. However, function evaluation of TNs with thyroid scintigraphy is not recommended in euthyroid patients. Thus, the purpose of this study is to investigate the short and long-term effects of MWA therapy on TFTs, thyroglobulin and thyroid autoantibodies in patients with euthyroid nodules where functional evaluation has not been required by management guidelines.

2. Materials and Methods

2.1. Ethics statement

This study was approved by University of Health Sciences Antalya Training and Research Hospital Ethics Committee (Ethics Committee approval number and date: 27/10-26/12/2019) and

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written informed consent was obtained all patients before procedure.

2.2. Patients

A total of 46 TNs in 46 consecutive patients who underwent ultrasound-guided microwave ablation for TNs at our interventional radiology unit from June 2018 to November 2019 were included in this retrospective chart review study. Inclusion criteria of this study were as follows: 1) euthyroid symptomatic patients with solid or predominantly solid nodules; 2) ineligibility or unwilling to go surgery; 3) benign nodules (Bethesda Ⅱ) (Fine needle aspiration biopsy results based on Bethesda categories[11]). The exclusion criteria of this study were as follows: 1) suspicious or cytologically proven malignancy (Bethesda Ⅴ, Ⅵ); 2) suspicious ultrasound features for malignancy (i.e, irregular margins, a non-oval shape, marked hypoechogenicity or microcalcifications); 3) calcitonin levels that exceed normal limits; 4) retrosternal goiter. Preablative demographic data of the study population were summarized in Table 1.

2.3. Laboratory assessment

Serum levels of free triiodothyronine (FT3), free thyroxine (FT4), thyrotropin (TSH), thyroglobulin (Tg), thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb) were measured at the University of Health Sciences Antalya Education and Research Hospital Biochemistry Laboratory on the day of the procedure, and 24 h, 3, and 6 months after the procedure. After 12 h fasting, venous blood samples were drawn at 08:00-09:00 am and analyzed within 3 h using Unicel ™ Dxl 800 Access Immunoassay System (Beckman Coulter Inc., Brea, CA, USA). TSH and FT4 were measured by a specific two-site immunometric assay and FT3 was measured by a competitive binding immunoenzymatic assay. The reference ranges of TSH, FT4, and FT3 were 0.34-5.86 uIU/ml, 7.86-14.4 pmol/L, and 3.8-6.0 pmol/L, respectively. Tg, TgAb, and TPOAb were measured by a sequential two-step immunoenzymatic (“sandwich”) assay. The reference ranges of serum Tg, TgAb, TPOAb were 0.58-625.1 ug/L, 0-4 IU/ml and <10 IU/ml, respectively. If a sample contains more Tg than the stated value of the S5 calibrator, one volume of sample was diluted with appropriate volumes of Access Thyroglobulin Sample Diluent. To see whether there was a significant association between serum Tg% rise on day 1 and nodule shrinkage, the Tg% rise was correlated with the volume reductions rate at 3-and 6-month. Serum Tg% rise on day 1 was calculated based on the Formula: [Serum Tg on day 1-serum Tg before

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ablation]/[Serum Tg before ablation]. Complete blood count and coagulation tests were checked before procedure.

2.4. Microwave ablation procedure

All patients underwent a single MWA session on an outpatient basis in our interventional radiologic unit. A microwave generator (ECO-100AI3; Nanjing ECO Medical Instrument Co., Ltd. Nanjing, China) that capable of producing 1-100 W of power at 2450 MHz either continuously or in a pulse and a flexible internally cooled 16-gauge thyroid antenna (3 mm exposed tip and 10 cm shaft length) were used. The MWA was performed as an outpatient treatment under local anesthesia without sedation. Vascular access was obtained to all patients before the procedure via antecubital vein. The patient was placed in a supine position with the neck mildly hyperextended. After determination of best puncture side, local anesthesia with 30/70 mixture of 2% lidocaine (Osel Pharmaceuticals, Istanbul, Turkey) and saline was performed along the puncture pathway from the skin to thyroid capsule. The hydrodissection technique proposed by Yue et al.[12] was performed, and a mixture of 0.9% lidocaine and physiological saline was infused into the surrounding thyroid capsule to protect vital structures adjacent to the thyroid nodule. Thyroid antenna was positioned under ultrasound guidance via trans-isthmic approach or lateral cervical approach. The moving shot technique was used to ablate TNs.[13] The procedure was stopped when most of the nodule was covered with bubbles (hyperechoic echos). During the procedure, vital signs were monitored and phonation was assessed intermittently by talking to a patient. After the procedure, all patients were followed up for 1 h with cold compression to the neck to prevent hematoma. Before discharging patients, the ultrasound examination was performed to evaluate the changes of MWA-induced focal complication.

2.5. Treatment efficacy and follow-up

The US examination, 5-14 Mhz linear probe with a real time ultrasound system (Aplio 500, Toshiba Medical Systems, Tokyo, Japan) was used to evaluate volume and composition of the nodules before procedure and 1, 3, 6 months after procedure. Three orthogonal diameters (the largest and two other perpendicular diameters) of nodules were measured before ablation. The volume of nodule was calculated with the following equations: $V = \pi abc/6$ (V: volume, π; 3.14159 a: the largest diameter; b and c: the other two perpendicular diameters). The volume reduction

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ratio (VRR) was determined by the following equation: [Baseline volume-volume at visit]/[Baseline volume] × 100. The solid component of nodule was assessed by an US examiner and was classified as solid (≤10% of fluid component), predominantly solid (11-50% of fluid component), predominantly cystic (51-90% of fluid component), or cystic (>90% of fluid component). The success of the therapy was accepted as ≥50% volume reduction at a 6-month follow-up.[14] Cosmetic score (1 = no palpable mass; 2 = palpable mass with no cosmotic score; 3 = mass visible on swallowing and/or neck extension; 4 = easily visible mass) were objectively evaluated.[15]

2.6. Statistical analysis

All the statistical tests were carried out by SPSS® 20.0 (Statistical Packages for Social Sciences; SPSS Inc, Chicago, Illinois, USA). The Shapiro-Wilk test was used to evaluate the normality of the data. Because of the non-normal distribution, pre-, post-, and 6 months follow-up thyroid function variables and volume reduction rate percentages (VRR%) were compared by use of Friedman and Wilcoxon's signed rank tests. A possible correlation between volume reduction and the difference in thyroglobulin parameters was tested using Spearman's correlation analysis. Cosmetic scores were compared with Wilcoxon Signed-Rank test. A Mann-Whitney U test was used to compare the solid and predominantly solid nodules VRR% values. Qualitative variables were expressed as frequencies and percentages while quantitative as mean ± SD and median (IQR). The significance level was based on a *P* value of less than 0.05.

3. Results

A total of 46 TNs in 46 euthyroid patients was analyzed. Of those, 20 patients (43.5%) were male and 26 (56.5%) were female, and the mean age was 47.54 ± 11.07. Fourteen of the nodules were solid (≤10% of fluid component), and 32 of the nodules were predominantly solid (11-50% of fluid component). The median (IQR) cosmetic score was reduced significantly from 3.00 (3.00-4.00) to 2.00 (1.00–2.00) after MWA ($P < 0.001$). Volume reduction rate percentages (VRR%) were 37.84 (29.71-48.33), 63.09 (55.38-73.41), and 68.28 (61.57-79.44) for 1 month, 3 months and 6 months, respectively ($P < 0.001$).

The investigated laboratory parameters were assessed in terms of their normal distribution (Shapiro-Wilk's test of normality) and the presence of any outliers. The results were demonstrated

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in Figure 1. Due to the presence of nonparametric distribution and the moderate outliers in case of FT3 (Pre, 24h, 3 months, 6 months) and TSH (Pre, 24 h) parameters and some extreme outliers in FT4 (24 h), a Friedman test was conducted to determine if there were any differences in the examined thyroid serum levels during pre, post, and 6-month follow-up duration. Afterwards pairwise comparisons were performed with a Bonferroni correction for multiple comparisons by taking the baseline (pre-) as reference. Table 2 presents the summary of the Friedman test and followed-up pairwise comparisons. Serum levels of thyroid hormones were statistically significantly different at the different time points during 6-month follow-up period compared to baseline (P <0.001). In addition, post-hoc analysis revealed statistically significant differences between the all thyroid hormone levels at pre- and 24 h periods (P <0.001). To summarize, levels of FT4 (12.29) (11.33-12.81) pmol/L and FT3 (5.64) (5.20-6.67) pmol/L at 24 h increased significantly compared with baseline FT4 (10.81) (9.88-11.74) pmol/L and FT3 (4.62) (4.30-4.73) pmol/L levels while TSH level decreased from 0.72 (0.45-1.49) (μIU/L) to 0.49 (0.25-1.11) (μIU/L) in 24 h after ablation.

TgAb (P =0.318) and TPOAb (P = 0.256) did not change significantly at the 3- and 6-month follow-up (Table 2). None of the patients were found to develop thyroid antibodies during the follow-up period.

Cases 1, 5, 25, 35, 36, 41 were asymptomatic clinically so that no further follow-up were performed. On the other hand, cases 43, 44, 45 and 46 had tachycardia requiring treatment with β-blockers and biochemically hyperthyroid (FIGURE 1). FT3 (P = 0.922), FT4 (P = 0.197) and TSH (P = 0.063) levels of these patients before MWA therapy were not significantly different than others who did not demonstrate elevations in FT4 and FT3 after 24 h MWA. In short, pre TFTs did not predict clinical and biochemical hyperthyroidism. Individual data points of the symptomatic patients exhibiting marked elevations at 24 h after MWA was summarized in Table 3 based on Figure 1.

Most patients experienced a slight tingling and pain sensation in the neck, but this was well tolerated without causing interruption or termination of the procedure. Six (13.9%) patients complained of transient voice change lasting 4-6 h. Vocal cord examinations performed with flexible fiberoptic laryngoscopy were normal in all patients.

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4. Discussion

The outstanding advantages of image-guided minimal invasive therapy compared with conventional open thyroidectomy are low recurrent laryngeal nerve injury, good cosmetic result, and comfortable ablation in an outpatient setting without general anesthesia.[16] Due to these advantages, minimally invasive thermal ablation techniques such as LA, RF ablation, and recently, MWA is rapidly gaining acceptance as treatment options for patients with symptomatic non-functioning TNs.[17] In particular, the effectiveness of the MWA for nodule shrinkage has been shown between 60% and 80% as VRR% in many studies for 6-month follow-up.[7,12] Previous studies reported that mixed/mainly cystic smaller nodules showed a better VRR% than the mainly solid nodules.[7,12] In this study, no statistically significant difference was observed between the median VRR% values of solid (67.19%) and predominantly solid (70.57%) nodules at 6 months ($P > 0.05$). In addition, VRR% increased significantly over a short (1 month: 37.84%) and long (6 months: 73.57%) time of periods after the MWA procedure ($P < 0.001$) even if our study was conducted on large solid TNs. Overall, a treatment success was observed in 95% of nodules.

Several complications have been reported (i.e., voice change, vocal cord paralysis, skin burn, fever, bleeding etc.) related to MWA of TNs.[18] According to the Society of Interventional Radiology Clinical Practice Guidelines,[19] voice change lasting over one-month, permanent voice change, nodule rupture requiring drainage, horner syndrome, spinal accessory nerve injury are the major complications while voice change less than one month, nodule rupture with conservative treatment, mild transient confusion probably due to lidocaine complication, haematoma are the minor complications. In our study, no major complications occurred. However, six (13.9%) patients complained of transient voice change lasting 4-6 h as a minor complication. Vocal cord examinations performed with flexible fiberoptic laryngoscopy were normal in all patients. This transient minor complication could be associated with the short-term paralytic effect of lidocaine used for hydrodissection on the superior laryngeal nerve.

Thyroglobulin (Tg) is a 660 kDa dimeric protein with a half-life of 65 h. Follicular cells in the thyroid gland produce Tg.[20] Thermal ablation induces necrosis of follicular thyroid cells and causes the release of Tg into the circulation. Heck et al.[10] stated that Tg significantly increased in serum 24 h after MWA treatment and returns to previous levels at 3 months. Due to the properties of Tg mentioned before, we hoped to define Tg was expected to be a novel serum marker that predict nodule shrinkage more accurately in anti-Tg negative patients.[21] However, we did not find

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any correlations between the increase in serum percent Tg at 24 h and the nodule volume reduction rate at 1-, 3-, and 6- month. In the present study, serum Tg level increased approximately 30-fold after procedure. The present study revealed that thyroid autoimmunity did not develop during 6-month follow-up in anti-Tg negative patients, although the increase in Tg was more pronounced.

Antithyroid antibody development after MWA has been rarely described.[10] Çakır et al. [22] hypothesized that thyroid autoantibodies after thermal ablation was related to release of Tg into the bloodstream after procedure. In their study, anti-Tg level increased throughout the 3 months and reached a normal level at the end of one-year follow-up. Although the increase in Tg was more pronounced compared to previous study, we found that thyroid autoimmunity was not triggered by the exposure to MWA during the 6-month follow-up in anti-Tg negative patients.

In the case of MWA, electromagnetic microwaves irradiate and heat the water molecules in the target tissue so that the resulting heat leads to the cellular death due to coagulation necrosis.[23] However, after the thermal ablation of TNs, the normal tissue around the ablated region may be affected. This exposure is more pronounced in the RF compared to the MWA.[24,25] Destruction of surrounding thyroid parenchyma and autonomous functioning thyroid nodules may affect TFTs. The first study exhaustively investigating this topic by Heck et al.[10] stated that MWA does not affect TFTs significantly in short and long term follow up. In contrast, our study was carried out entirely in euthyroid patients and showed that FT4 and FT3 levels increased, and TSH levels decreased significantly 24 h after the procedure.

The comparison of the pre FT3, pre FT4 and pre TSH levels of the patients displaying elevations in FT4 and FT3 at 24 h after MWA with those of patients who did not demonstrate elevations in FT4 and FT3 after 24 h MWA was not statistically significant. These results can be explained by the challenges of clinical diagnosis of the autonomously functioning thyroid nodule (ATFN).[26] Treglia et al. [26] showed in their meta-analysis conducted on 2761 AFTN patients that pooled prevalence of AFTN with normal TSH detected by thyroid scintigraphy was 50% (95% CI: 32%-68%). In our study, it is likely that non-toxic AFTN might have been ablated. In the Current European and American clinical guidelines, functional evaluation of TNs in euthyroid state are not recommend.[2] Moreover, The Korean Society of Thyroid Ablation guideline recommends that functional evaluation with radionuclide scan should be performed only for AFTN before the procedure.[27] In line with these recommendations, we did not perform functional evaluation tests in our euthyroid patients.

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In this study, a significant short-term effect of MWA on TFTs was observed. According to this finding, it could be suggested that thyroid scintigraphy should be performed before thermal ablative treatments in patients with not only functioning nodules but also euthyroid nodules. On the other hand, TFTs and thyroid autoantibodies were not affected during the 6-month follow-up. Considering these results, MWA of benign large solid TNs under percutaneous is a safe and effective technique for the selected patients because of some advantages such as low complication rates, good cosmetic results, nodule shrinking rate, etc. Further studies are necessary to show the effects of MWA on the TFTs.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

The study conception and design were contributed by M.S.E. M.S.E, B.C, M.C, and H.U performed the material preparation, data collection and analysis. MSE wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Table 1. Demographic data of the study population

Characteristic	All patients (n = 46)
Age (years)	47.54 ± 11.07 (43-56)
Female	26 (56.5)
Nodule volume (cc)	19.00 (12.48-31.63)
Cosmetic score	
Grade 2	10 (21.7)
Grade 3	14 (30.4)
Grade 4	22 (47.8)
Nodule morphology	
Solid	14 (30.4)
Predominantly solid	32 (69.6)
Nodule location	
Left thyroid lobe	15 (32.6)
Right thyroid lobe	31 (67.4)
Tg (μg/L)	44.75 (35.42-68.13)
FT4 (pmol/L)	10.81 (9.88-11.74)
FT3 (pmol/L)	4.62 (4.30-4.73)
TSH (μIU/L)	0.72 (0.45-1.49)

Values are reported as mean ± SD or percentage for categorical variables and median (IQR) for numeric variables. FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; Thyroglobulin.

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Table 2. Baseline (pre) and changes of the thyroid function parameters after MW ablation at different dates of examination

	Pre	24 h	3 months	6 months
FT4 (pmol/L)	10.81 (9.88-11.74)	12.29 (11.33-12.81)**	11.07 (10.04-12.03)	11.14 (10.27-12.16)
FT3 (pmol/L)	4.62 (4.30-4.73)	5.64 (5.20-6.67)**	4.65 (4.25-4.92)	4.67 (4.27-4.85)
TSH (μIU/L)	0.72 (0.45-1.49)	0.49 (0.25-1.11)**	0.94 (0.52-1.48)	0.90 (0.59-1.40)*
Tg (μg/L)	44.75 (35.42-68.13)	1205.32 (777.90-1922.00)**	-	36.50 (30.00-56.00)**
TgAb (IU/mL)	0.2 (0.10-0.40)	-	0.2 (0.10-0.40)	0.2 (0.1-0.32
TPOAb (IU/mL)	0.6 (0.40-0.80)	-	0.6 (0.50-0.72)	0.6 (0.48-0.70)

Data are presented as median (IQR) for numeric variables. *P <0.05, **P <0.001

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Table 3. Individual data points of the patients exhibiting marked elevations[a] in FT4 and FT3 at 24 h after MWA

Case no.	Age (years)	Nodule volume (cc)	FT4 (pmol/L)		FT3 (pmol/L)		TSH (μIU/L)	
			Baseline	24h	Baseline	24h	Baseline	24 h
43	47	19.00	13.00	49.42	5.04	10.41	0.45	0.01
44	57	28.00	12.61	57.27	4.62	10.37	0.39	0.01
45	43	21.80	12.61	64.48	4.96	10.60	0.35	0.25
46	28	17.40	12.23	61.26	4.25	8.91	0.51	0.05

[a]Data for marked elevations was driven from Figure 1.

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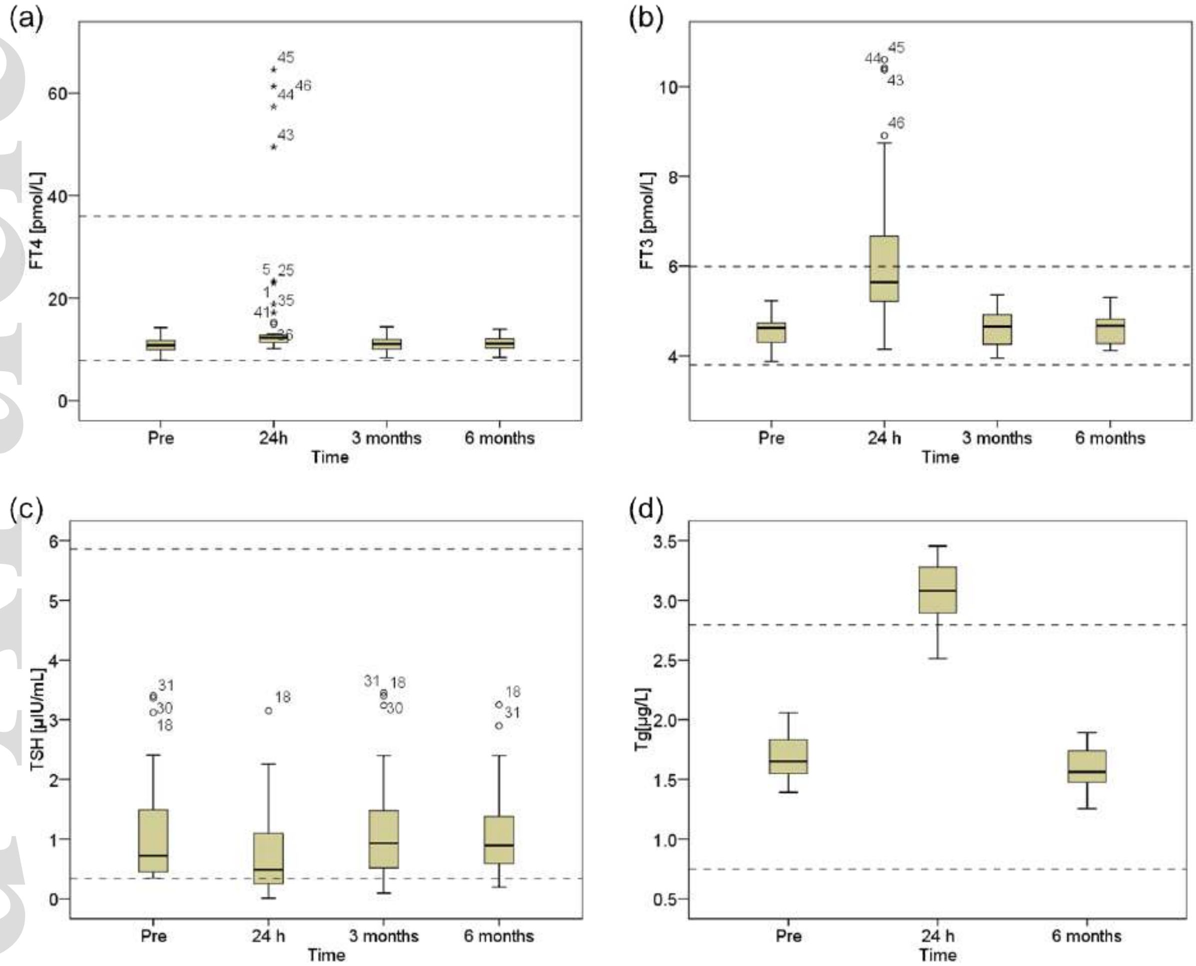

Figure 1. Thyroid hormone levels of (a) FT3, (b) FT4, (c) TSH and (d) Tg in the 6 months follow-up period. Tg values were logarithmised for better illustration. The areas between the dashed lines indicate normal ranges for each parameter. Data are presented as median (IQR).

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