Does radioactive iodine treatment have an effect on serum TWEAK and other cardio-metabolic parameters in hyperthyroid patients?

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Abstract

Purpose: Hyperthyroidism is a condition in which excess thyroid hormone is produced and released. It is not clear whether radioactive iodine (RAI), one of the treatment methods, increases cardiovascular risk in these patients. We investigated whether RAI increases cardio-metabolic risk by looking at serum soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) and other parameters.

Method: The study included 21 patients who underwent RAI and 21 patients followed up with anti-thyroid drugs. At the beginning and at the 3rd month, thyroid stimulating hormone, free T_3 ($fT_{3)}$, free T_4 (fT_4), fasting plasma glucose (FPG), triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL), C-reactive protein (CRP) and sTWEAK levels were measured. According to baseline and 3rd month data, both groups were compared with each other and within themselves.

Results: sTWEAK levels were higher in the RAI group at baseline and at the 3rd month than in the medical group (baseline sTWEAK 78.80 vs 49.90, p=0.004; 3rd month sTWEAK 76.60 vs 40.63, p=0.001, respectively). CRP level was higher in the RAI group at the 3rd month than in the medical group (2.70 vs 1.49, respectively, p=0.024).

Conclusion: Low-dose RAI does not lead to a change in cardio-metabolic risk in the early period.

Introduction

Hyperthyroidism is the clinical picture caused by the production and release of excess hormone from the thyroid gland. The most common causes are Graves' disease (GD), toxic adenoma and toxic multinodular goiter (TMNG). Treatment is medical with antithyroid drugs, radioactive iodine (RAI) or total thyroidectomy. All three methods are used frequently. The aim of RAI is to reduce the hormone level by destroying the follicle cells of the thyroid gland. RAI is easy to apply and easy to access and it is an effective treatment method. The most common side effects are sialedenitis, gastrointestinal complaints, and infertility, especially when high doses are given [1]. In addition to these, studies investigating the effect of RAI on the cardiovascular system attract attention in recent years. While an increase in risk was mentioned in some of these studies, a clear risk increase was not demonstrated in some [2, 3].

The tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is a transmembrane protein belonging to the tumor necrosis factor (TNF) family. In case of inflammation, it undergoes proteolysis and becomes soluable (sTWEAK). sTWEAK binds to the receptor named Fn14, the repair pathway of inflammation damage is initiated and there is a decrease in sTWEAK levels in the serum [4]. This system seems beneficial for the recovery of the organism in the acute situation, but it predisposes to diseases such as coronary artery disease, heart failure, and diabetes mellitus if chronically active. sTWEAK levels in the serum of these patients are found to be lower than in the healthy population [5].

Although there are studies showing that RAI treatment increases cardiovascular risk, it is not clear whether this is mainly due to RAI or hyperthyroidism itself. As is known, hyperthyroidism itself has

adverse cardiovascular effects. It is even recommended that subclinical hyperthyroidism should be treated at certain levels, since it increases cardiac risk [1].

The hypothesis of this study is whether RAI increases cardiometabolic risk in the early period. The sTWEAK level was also examined specifically for the study. sTWEAK was chosen because it is a marker showing chronic inflammation and chronic inflammation causes morbidity and mortality [5]. There is no study investigating the relationship between RAI and sTWEAK in the literature. In this respect, it is aimed to contribute to the literature.

Method

This is a prospective, follow-up study. It consists of patients who were given RAI for hyperthyroidism between October 2016 and June 2017 and the control group patients followed up with medical treatment.

Exclusion criteria

Pregnant women, < 18 years of age, patients who received RAI treatment or radiotherapy to the head and neck region, received antihyperlipidemic therapy, had alcohol or substance abuse, and had a mental illness that would affect compliance with the study (Figure).

The diagnosis of hyperthyroidism was confirmed by anamnesis, laboratory and imaging methods. There are 21 patients in the RAI group; 11 had toxic multinodular goiter (TMNG), 5 had toxic adenoma (TA), 5 had Graves' Disease (GD). 17 of 21 patients in the medical group had GH and 4 had TMNG. Patients who received RAI were followed up without medication after RAI.

Laboratory

FPG, TSH, fT_4, fT_3, LDL, HDL, TG and CRP levels were measured in all patients at the beginning and after the 3rd month. Normal laboratory ranges are 0.55–4.7 mU/L for TSH, 3.99–6.7 ng/L for fT_3, and 11.5–22.7 ng/dL for fT_4. FT_3, fT_4 and TSH measurements were studied with the “Siemens ADVIA centour XP” device using the chemiluminescent method.

The sTWEAK serums taken from the patients were frozen and stored at -20^0C. sTWEAK concentrations were measured using a commercial ELISA kit (Cloud Clone, USA). The limit of detection was 15.6 pg/ml. Intra and inter-assay precisions were < 10% and < 12%, respectively.

Data analysis

Statistical analyses were performed using the IBM SPSS for Windows Version 25.0 software. Numerical variables are summarized as mean ± standard deviation (SD) and median (minimum-maximum). Categorical variables were represented as numbers and percentages. The differences between the groups in terms of categorical variables were investigated using the Chi-square test or Fisher's exact test. Skewness and curtosis were used to determine whether the numerical variables showed normal

distribution. Homogeneity of variance was examined using the Levene test. The t-test was used for normally distributed parameters, and the Mann-Whitney U was used for non-normally distributed parameters. Spearman's correlation analysis was used to determine relationships between parameters. The significance level was accepted as $p < 0.05$.

Results

There were 21 patients in the RAI group and 21 patients in the medical treatment group. Gender distributions were similar. The RAI group was older (61.04 vs 43.90, p = 0.001). Thyroid tests were higher in the medical group in the direction of hyperthyroidism. sTWEAK was found to be higher in the RAI group (78.80 vs 49.40, p = 0.004) (Table 1). In the correlation analysis, no correlation was found between sTWEAK and age, TSH, fT3, fT4, CRP, ALT and creatinine. Further analysis (partial correlation) could not be performed because sTWEAK did not fit the normal distribution.

Table 1
Baseline characteristics of the group

Parameter	RAI group (n = 21)	medical group (n = 21)	P
Gender, n, %	14 (66.7)	18 (85.7)	0.277
Female	7 (33.3)	3 (14.3)	
Male			
Age	61.04 ± 12.455	43.90 ± 16.582	0.001*
BMI (kg/m^2)	28.0(17.5–40.0)	28.0 (21.0–40.0)	0.560
DM	2	4	0.700
HT	3	7	0.200
TSH	**0.04 (0.01–3.70)**	**0.01 (0.01–0.40)**	**0.003***
fT_3	**6.35 (4.6–31)**	**8.65 (4–30)**	**0.003***
fT_4	**15 (3.9–82)**	**31.5 (16–75)**	**< 0.0001***
FPG	95.14 ± 14.36	88.10 ± 17.70	0.174
LDL	116.61 ± 36.71	104.36 ± 29.72	0.257
TG	124.23 ± 58.84	110.63 ± 52.21	0.446
HDL	54.52 ± 12.85	52.21 ± 14.29	0.593
CRP	3.77 ± 2.80	2.11 ± 2.60	0.071
sTWEAK	**78.80 (22.64-567.65)**	**49.40 (32-108.60)**	**0.004***

RAI: radioactive iodine, BMI: body mass index, DM: diabetes mellitus, HT: hypertension, TSH: thyroid stimulating hormone, fT_3: free triiodotronine, fT_4: free thyroxine, FPG: fasting plasma glucose, LDL: low density lipoprotein, TG: triglyceride, HDL: high density lipoprotein, CRP: C-reactive protein, sTWEAK: soluable tumour necrosis factor-like weak inducer of apoptosis

The same parameters were checked again after 3 months. CRP and sTWEAK levels were higher in the RAI group (Table 2). Thereupon, Mann Whitney-U test was performed to compare in terms of ΔsTWEAK; While the median ΔsTWEAK = 14.04 (-376.16-197.43) in the RAI group, the median ΔsTWEAK = 6.80 (-21.06-44.72) in the medical treatment group, no statistically significant difference was found (p = 0.85). Both groups were analyzed according to ΔCRP change; no statistically significant difference was found (mean ΔCRP:0.35 in the RAI group, 0.78 in the medical group, p:0.60).

Table 2
Comparison of the groups according to 3.month parameters

Parameter	RAI group (n = 21)	medical group (n = 21)	P
TSH	1.50 (0.1–8.50)	1.74 (0.20–12)	0.85
fT_3	4.40 (3.30–12.60)	5 (3.58-6)	0.23
fT_4	14 (3.60–19)	13.50 (9.80–20)	0.43
FPG	94.80 ± 12.18	88.21 ± 13.55	0.11
LDL	118.60 ± 29.73	111.70 ± 24.86	0.62
TG	121.70 ± 58.73	104.35 ± 60.33	0.383
HDL	57.65 ± 12.71	55 ± 12.40	0.52
CRP	**2.70 ± 2.23**	**1.49 ± 1.87**	**0.024***
sTWEAK	**76.60 (26.15–454.80)**	**40.63 (16–75)**	**0.001***

RAI: radioactive iodine, TSH: thyroid stimulating hormone, fT_3: free triiodotronine, fT_4: free thyroxine, FPG: fasting plasma glucose, LDL: low density lipoprotein, TG: triglyceride, HDL: high density lipoprotein, CRP: C-reactive protein, sTWEAK: soluable tumour necrosis factor-like weak inducer of apoptosis

Comparisons were made within the RAI group with respect to the baseline and after the 3rd month. Thyroid functions had recovered compared to baseline. No significant difference was observed in other parameters (Table 3).

Table 3
Comparison of basal and 3.month parameters of RAI group

Parameter	Pre-RAI	Post-RAI	P
TSH	**0.04 (0.01–3.70)**	**1.50 (0.10–8.50)**	**< 0.0001***
fT_3	**6.35 (4,6–31)**	**4.40 (3.30–12.60)**	**< 0.0001***
fT_4	15 (3.90–82)	14 (3.60–19)	0.08
FPG	95.14 ± 14.36	94.80 ± 12.18	0.93
LDL	116.61 ± 36.71	116.28 ± 30.86	0.97
TG	124.23 ± 58.84	121.70 ± 58.73	0.89
HDL	54.52 ± 12.85	57.65 ± 12.71	0.43
CRP	3.77 ± 2.80	2.70 ± 2.23	0.20
sTWEAK	82.53 (27.25-567.65)	76.60 (26.15–454.80)	0.97

RAI: radioactive iodine, TSH: thyroid stimulating hormone, fT_3: free triiodotronine, fT_4: free thyroxine, FPG: fasting plasma glucose, LDL: low density lipoprotein, TG: triglyceride, HDL: high density lipoprotein, CRP: C-reactive protein, sTWEAK: soluable tumour necrosis factor-like weak inducer of apoptosis

At the end of the third month, improvement was observed in thyroid functions in the medical treatment group, but no significant difference was observed in other parameters (Table 4).

Table 4
Comparison of basal and 3.month parameters of medical group

Parameter	Başlangıç	3.ay	P
TSH	**0.01 (0.01–0.40)**	**1.74 (0.2–12)**	**< 0.0001***
fT_3	**8.65 (4–30)**	**5 (3.58-6)**	**< 0.0001***
fT_4	**31.5 (16–75)**	**13.50 (9.80–20)**	**< 0.0001***
FPG	88.10 ± 17.70	88.21 ± 13.55	0.98
LDL	104.36 ± 29.72	111.70 ± 24.86	0.43
TG	110.63 ± 52.51	104.35 ± 60.33	0.74
HDL	52.21 ± 14.29	55 ± 12.40	0.53
CRP	2.11 ± 2.60	1.49 ± 1.87	0.57
sTWEAK	49.40 (32-108.60)	40.63 (16–75)	0.40

TSH: thyroid stimulating hormone, fT_3: free triiodotronine, fT_4: free thyroxine, FPG: fasting plasma glucose, LDL: low density lipoprotein, TG: triglyceride, HDL: high density lipoprotein, CRP: C-reactive protein, sTWEAK: soluable tumour necrosis factor-like weak inducer of apoptosis

Discussion

In this study, patients who received RAI and medical treatment were compared in terms of risk factors. Patient data were analyzed at the start of the study and at the end of the 3rd month. Initially, the RAI group was older and the medical group was more thyrotoxic (Table 1). Although sTWEAK levels were higher in the RAI group at the beginning and at the end of the 3rd month (Tables 1 and 2), no significant difference was found in ΔsTWEAK levels. Again, while there was a significant improvement in thyrotoxicosis in both groups, no difference was observed in terms of other parameters (Table 3). No correlation was observed between sTWEAK and other parameters, including age. At the end of the 3rd month, CRP decreased in both groups and was still higher in the RAI group (Tables 1 and 2). However, there was no difference in ΔCRP. When the groups were compared within themselves, no significant change was found in other parameters except the improvement in thyroid function tests. Based on these results, it was determined that in the early period (first 3 months), RAI treatment did not cause positive or negative changes in cardio-metabolic parameters.

RAI is a frequently preferred treatment modality by both physicians and patients because it is easy, inexpensive and effective. It has few side effects. It has been used safely in clinical practice for a long time. Its use is contraindicated in certain clinical entities (pregnancy, moderate-severe Graves' ophthalmopathy) [6]. On the other hand, there are studies suggesting that RAI poses a risk in terms of cardiovascular and metabolic aspects [7–9]. It has been reported that the dose of radioactive iodine in the carotid artery is high enough to cause atherosclerosis [9]. In another study, hypothyroidism after RAI

was shown to cause this increased risk [10]. However, these studies are heterogeneous and there are differences such as the number of patients, the dose administered, and the duration of the study. In addition, hyperthyroidism itself has cardio-metabolic adverse effects such as arrhythmia, hypertension, hyperglycemia, and heart failure. These complications are observed more frequently, especially if they are left untreated for a long time [11–13]. Therefore, effective treatment is important to prevent the occurrence or exacerbation of these morbidities.

In our study, the patients in the RAI group were found to be older. However, RAI is mostly applied to patients with TMNG and TA. TMNG and TA are also observed mostly in middle-advanced ages. Most of the patients in the medical group also consist of GH, GH is seen in younger patients, and the effectiveness of medical treatment in GH is better than other causes, therefore drug treatment is more preferred in GH treatment. It was thought that the age difference stemmed from this [14]. There is also a significant difference in terms of basal thyroid function tests, toxicosis was found to be lower in RAI patients (Table 1). The reason for this can be explained as follows: RAI is mostly administered to TMNG and TA patients when there is hyperthyroidism at a level that does not require antithyroid medication.

Among the cardiovascular and metabolic diseases, the most common and most important ones are atherosclerotic heart disease (ASCD) and cerebrovascular disease (SVD), DM, and hyperlipidemia. DM and hyperlipidemia lead to endothelial dysfunction and inflammation, leading to cardiovascular morbidity and mortality. There are many routine and experimental tests used to predict cardiovascular and metabolic risk. FPG, lipoproteins (LDL, HDL, triglyceride) and CRP are routine tests. These are used both in the follow-up of related diseases and as markers in academic studies [15–17]. These parameters are also included in this study. There was no significant difference between these parameters in both groups, except for CRP, but ΔCRP was not different. In addition, sTWEAK was examined. While the sTWEAK pathway is beneficial for recovery in acute inflammation, chronic activation of this pathway increases systemic inflammation, thus increasing cardiovascular morbidity and mortality, and metabolic risk. Low sTWEAk level has been shown in many diseases such as carotid stenosis, type 1 DM, type 2 DM, bipolar disorder, and depression [5, 18–20]. For this reason, in patients with hyperthyroidism, it was examined whether the treatment affected the sTWEAK level in the early period. Although baseline and 3rd month sTWEAK levels were higher in the RAI group than in the medical group (Table 1–2), no significant increase or decrease in ΔsTWEAK was detected.

Our study has limitations. These are the number of patients, the duration of the study (3 months). Another limitation is the presence of diseases that increase cardiovascular risk, such as DM and hypertension. The number of patients and the duration of the study were determined according to the number of sTWEAK kits obtained. However, the most important advantage of our study is that; This is the first study investigating the relationship between sTWEAK and low-dose RAI. There is no doubt that larger number of patients and longer-term studies will contribute to this field.

Conclusion

Low-dose RAI has no effect on cardio-metabolic risk in the early phase of treatment.

Declarations

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Conflict of Interest

The authorshave no relevant financial or non-financial interests to disclose.

Ethical approval: The study was approved by the local clinical research ethics committee with the decision dated October 27, 2016 and numbered 16-839-16. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all the individual participants.

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Figures

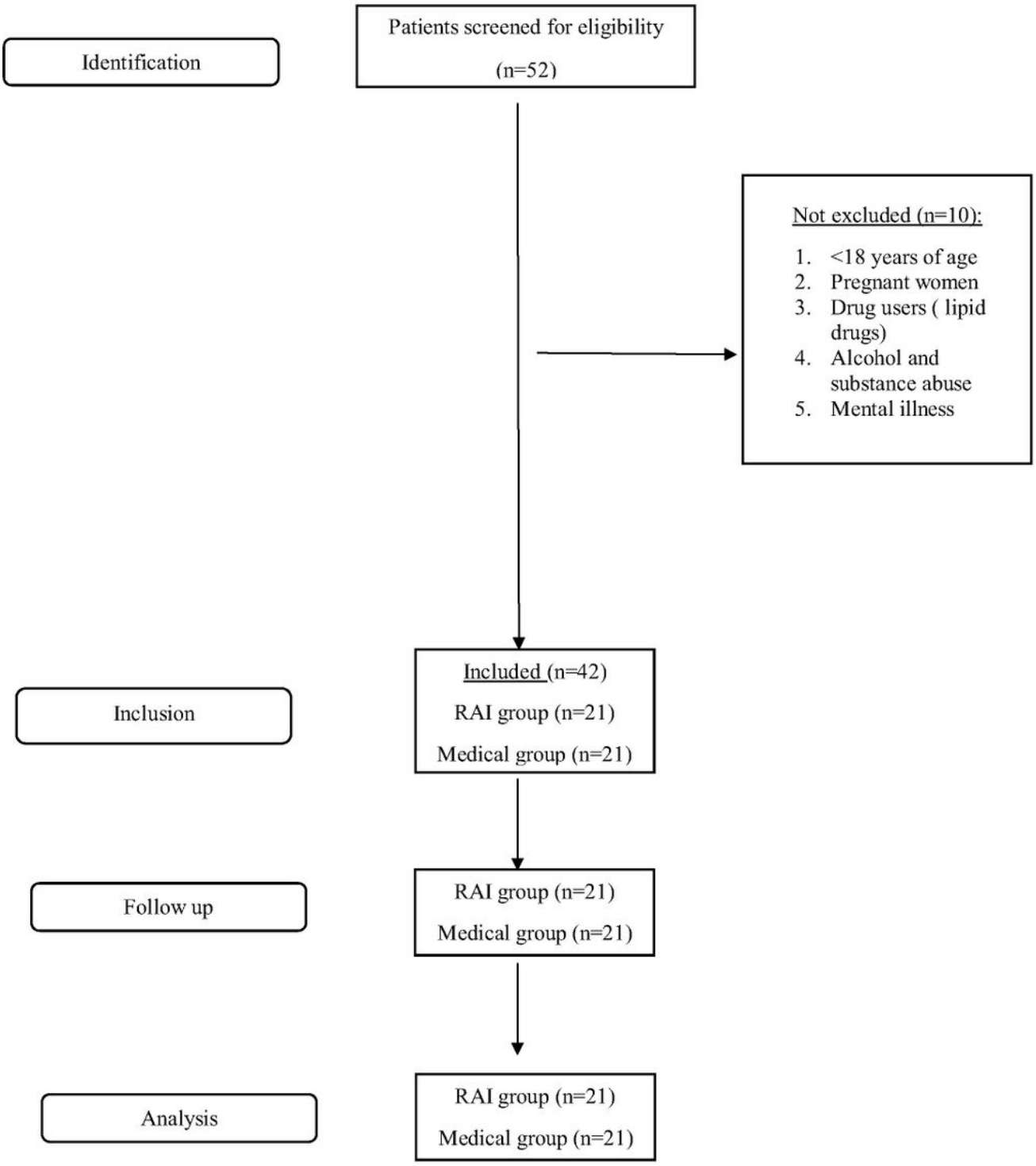

Figure 1

Patient flow diagram.