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Obesity is Associated with Increased Thyroid Volume and Heterogeneity in Ultrasonography

Obezite Tiroid Ultrasonografisinde Artmış Tiroid Volümü ve Heterojeniteyle İlişkilidir

Abbas Ali TAM, Didem ÖZDEMİR, Berna EVRANOS ÖĞMEN, Fatma Dilek DELLAL, Afra ALKAN*, Oya TOPALOĞLU, Reyhan ERSOY, Bekir ÇAKIR

Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey
*Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Biostatistics, Ankara, Turkey

Abstract

Objective: The aim of the present study was to investigate the possible association between obesity and thyroid functions and thyroid morphology. **Material and Methods:** A total of 674 subjects-121 obese and 553 nonobese-were included in the study. Body mass index, serum thyrotrophic, free triiodothyronine (fT3), free thyroxine (fT4), antithyroid peroxidase antibody, and antithyroglobulin antibody (antiTg) were evaluated in each subject. The subjects with thyroid nodules in ultrasonography (USG) were excluded. The thyroid volume of each subject was calculated and analyzed. **Results:** Obesity was significantly associated with increased age and low fT4 in univariate analysis (p<0.05). With multivariate analysis, the odds of obesity was found to increase by 21.8% (95% CI: 12.4-31.9%) for each 5-year increase in age anddecrease by 53.1% (95% CI: 0.4-77.9%) for each 1 ng/dL increase in fT4. The odds of obesity in patients with positive antiTg was 1.603 (95% 1.047-2.454) times higher than the odds of obesity in patients with negative antiTg. The median total thyroid volume was significantly higher in obese as compared to nonobese subjects (12.11 mL vs. 10.77 mL, p<0.001). Heterogeneous gland with negative thyroid antibodies was observed in 17 (14%) obese and 40 (7.2%) nonobese subjects (p=0.024). **Conclusion:** Obesity was positively associated with antiTg and age, whereas negatively associated with fT4. Approximately, in every seven obese subjects, one showed heterogeneity in US despite negative thyroid autoantibodies. This suggests that the value of US in the diagnosis of autoimmune thyroiditis might decrease in obese patients.

Keywords: Obesity; thyroid functions; thyroid volume; heterogeneity; thyroid morphology

Özet

Amaç: Obezite ile tiroid fonksiyonları ve tiroid morfolojisi arasındaki muhtemel ilişkiyi araştırmaktır. **Gereç ve Yöntemler:** Çalışmaya toplam 121'i obez 553'ü nonobez olmak üzere 674 birey alındı. Her bireyde beden kitle indeksi, serum tirotiropin, serbest triodotironin (sT3), serbest tiroksin (sT4), antitiroid peroksidaz antikoru ve antitiroglobulin antikoru (antiTg) değerlendirildi. Ultrasonografi (USG) de tiroid nodülü olanlar çalışma dışında bırakıldı. Her bireyde tiroid volümü hesaplandı ve analiz edildi. **Bulgular:** Univariate analizde obezite anlamlı olarak artan yaş ve düşük sT4 ile ilişkiliydi (p<0,05). Multivariate analizde obezite riski yaşta artan her 5 yıl için %21,8 (%95 güven aralığı (GA): %12,4-31,9) ve sT4'teki her bir ng/dL azalışta %53,1 (%95 GA: %0,4-77,9) artmaktaydı. AntiTg negatif hastalara göre antiTg pozitif olan hastalarda obezite riski 1,603 (%95 1,047-2,454) kat daha fazlaydı. Obezlerde nonobezlere göre median total tiroid volümü anlamlı olarak daha fazlaydı (12,11 mL'ye karşı 10,77 mL, p<0,001). Heterojen glandıyla birlikte tiroid antikorlarının negatifliği 17 (%14) obez ve 40 (%7,2) nonobez bireyde tespit edildi (p=0,024). **Sonuç:** Obezite antiTg ve yaş ile pozitif ve sT4 ile negatif olarak ilişkiliydi. Obezitesi olan yaklaşık olarak her 7 bireyin birinde tiroid antikorları negatif olmasına rağmen USG'de heterojenite vardı. Bu bize, obez hastalarda otoimmün tiroidit tanısında USG'nin değerinin azalabileceğini göstermektedir.

Anahtar kelimeler: Obezite; tiroid fonksiyonları; tiroid volümü; heterojenite; tiroid morfolojisi

Address for Correspondence: Abbas Ali TAM, Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey
Phone: :+90 312 2912525 **E-mail:** endoali@hotmail.com

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Introduction

Obesity is a major public health problem with increasing prevalence all over the world. Excess body weight is a predisposing factor for several diseases including diabetes, hypertension, cardiovascular disease, and various cancers (1). Although the complex pathophysiology of obesity could not be elucidated completely, many factors including genetic, environmental, behavioral, and psychological are known to play a significant role. Identification of thyroid hormone targets might provide insight for optimal management of the obese patients (2,3).

Thyroid hormones play a key role in the regulation of body metabolism at hunger and fed state. These hormones are also found to regulate the basal metabolic rate and thermogenesis. They significantly affect energy expenditure and body weight. While thyrotoxicosis is associated with increased energy expenditure, proteolysis, lipolysis, and weight loss, hypothyroidism affects these processes in the opposite direction (4,5). The literature reveals controversial results about thyrotropin (TSH) and thyroid hormone levels in obese patients. However, changes in thyroid functions are generally accepted as reversible, since they mostly return to normal ranges after weight loss obtained through diet or surgical intervention (4,6).

Although the current data provide evidence for an association between thyroid hormones and obesity, the mechanism is not explained clearly (4). A limited number of studies are availableregarding thyroid morphology in obesity. Preliminary studies reported a correlation between thyroid volume and body weight and body mass index (BMI) (6-8). Radetti et al. evaluated thyroid ultrasonography (US) in obese children and revealed that obesity was associated with structural changes in thyroid morphology which was not related to autoimmunity (6). In this study, we aimed to investigate the possible association between obesity and thyroid functions and thyroid morphology.

Material and Methods

This retrospective study was conducted in a single center and 674 subjects between the ages of 18-75 were included. Patients using thyroid hormone preparations, antithyroid drugs or drugs that can affect thyroid hormones (steroids, amiodarone, etc.), patients with a history of thyroid surgery or radiotherapy to head and neck region, and pregnant or lactating women were excluded from the study. Patients with thyroid nodules were also excluded owing to possible effects on thyroid volume. Demographical features, BMI, serum TSH, free triiodothyronine (fT3), free thyroxine (fT4), anti-thyroid peroxidase antibody (antiTPO), antithyroglobulin antibody (antiTg), and thyroid US findings were recorded in each subject. Weight and height were measured with light clothes and after taking off shoes. BMI was calculated as weight (kg) divided by the square of height (m^2). The classification of the World Health Organization was used to define obesity (BMI ≥30 kg/m^2).

Serum TSH, fT3, and fT4 and thyroid autoantibodies were measured by chemiluminescence methods (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA, USA and UniCel DXI 800, Beckman Coulter, Brea, CA). The normal levels for TSH, fT3, fT4, antiTPO, and antiTg were 0.4-4 μIU/mL, 1.57-4.71 pg/mL, 0.85-1.78 ng/dL, 0-35 IU/mL, and 0-40 IU/mL, respectively. Serum TSH lower than 0.4 μIU/mL was defined as low, serum TSH in normal ranges was defined as normal and serum TSH higher than 4 μIU/mL was defined as high TSH. The thyroid antibody levels over the upper range were accepted as positive.

Thyroid US was performed by two experienced endocrinologists using an Esaote color Doppler US (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) and a superficial probe (Model LA523 13-4, 5.5-12.5 MHz). The echogenicity of the thyroid parenchyma was evaluated in a longitudinal position and classified as normal and hypoechoic after comparison with the echogenicity of the adjacent sternohyoideus, sternothyroideus, and sternocleidomastoideus muscles (9). The thyroid gland that is not uniform in echogenicity with hypoechoic areas was defined as heterogeneous. The volume of each lobe was calculated with the formula (maximal length x width x depth x π/6). Thyroid volume was determined by the sum of the volume of two lobes. The isthmus was not taken into account in volume calculation. Written informed con-

sent was acquired from all the patients, included in the study. An approval from the local ethics committee was obtained in accordance with the ethical standards of the Helsinki Declaration.

Statistical Analysis

The distributions of the continuous variables were examined by Shapiro-Wilk's test and normality graphs. All continuous and categorical variables were summarized by median (min-max) and frequency (%), respectively. Mann-Whitney U test and Chi-square tests were used to compare obese and non-obese groups with respect to the continuous and categorical variables, respectively. All possible risk factors for obesity, having a p-value <0.250 in the univariate analysis, were investigated by multiple logistic regression analysis with backward likelihood ratio procedure. Odds ratio (OR) and 95% confidence interval (CI) of the estimates were reported. Simple and multiple linear regression analyses were performed for thyroid total volume in the same manner with automatic linear modeling using best subset variable selection method and automatic data preparation for outliers and influential data points. Regression coefficients of the predictors were provided with their standard errors (SE).
A p-value<0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Results

The obese group comprised of 22 (18.2%) male and 99 (81.8%) female subjects, whereas, there were 105 (19.0%) male and 448 (81.0%) female subjects in nonobese group (p=0.939). The median ages were 32 years (min-max:18-68) in obese and 41years (min-max:18-68) in nonobese groups (p<0.001). Differences in the levels of TSH, fT3, and fT4 among the two groups were statistically insignificant. AntiTPO and antiTg positivities were also similar in the obese and nonobese subjects. However, total thyroid volume was significantly higher in obese compared to nonobese subjects [median:12.11 mL (min-max: 3.65-25.88) *vs*. median:10.77 mL (min-max: 2.39-71.15), p<0.001]. Ultrasonographically, the thyroid parenchyma was heterogeneous in 70 (57.9%) of the obese and 305 (55.2%) of the nonobese subjects (p=0.589). There were 71 (58.7%), 2 (1.6%), and 48 (39.7%) obese patients with normal, low, and high TSH, respectively. In the nonobese group, 319 (57.7%) patients had normal, 14 (2.5%) had low and 220 (39.8%) were diagnosed with high serum TSH. The proportion of the patients with heterogeneous gland and negative antibodies was higher in the obese group than that in the nonobese group (14.0% *vs.* 7.2%, p=0.024). 16 (13.2%) obese and 55 (9.9%) nonobese patients had high TSH despite negative antibodies (p=0.368) (Table 1).
Univariate analyses revealed that age and fT4 were significantly related to obesity (p<0.05, Table 2). The effects of age, fT4, and antiTg positivity on obesity were significant in multivariate analyses. Although the effect of total thyroid volume was nonsignificant (p=0.056), the contribution of it to the model was significant. The odds of obesity was increased by 21.8% (95% CI: 12.4-31.9%) for each 5-years increase in age, adjusting for fT4, antiTG positivity and total volume. The odds of obesity was decreased by 53.1% (95% CI: 0.4-77.9%) for each one-unit increase in fT4. The odds of obesity in patients with positive antiTg was 1.603 times (95%CI: 1.047-2.454) higher than the odds of obesity in patients with negative antiTg (Table 2).
The factors that might affect thyroid volume were also analyzed. In univariate analyses, age, male sex, BMI, fT4, fT3, AntiTPO, and antiTg positivities had an increasing effect on total thyroid volume (Table 3). The multivariate analysis resulted in a model with the best subset of these variables as predictors; gender, antiTg positivity, BMI, and fT3, each having an increasing effect on total volume ($F=24.359$, $p<0.001$, $R^2=12.2\%$).
Based on the model, male patients had a larger volume with a mean of 3.855 mL (95% CI:2.693-5.018) than females.The total volume was 2.323 mL (95% CI:1.434-3.212) higher in patients with positive as compared to negative antiTg. The per unit increase in BMI and fT3 was associated with 0.186 mL (95% CI:0.097-0.276) and 1.098 mL (95% CI:0.239-1.957) increase in the total volume, respectively (Table 3).

Table 1. Demographic and clinical characteristics of obese and non-obese patients.

	Non-obese [n=553] Median (min-max) n (%)	Obese [n=121] Median (min-max) n (%)	Test Statistics	p
Age [years]	32 (18–68)	41 (18–68)	5.462	<0.001
Gender (Male)	105 (19.0)	22 (18.2)	0.006	0.939
TSH [μIU/mL]	3.24 (0.01–100.00)	3.22 (0.01–100.0)	0.348	0.728
fT3 [pg/mL]	3.27 (0.93–22.67)	3.15 (0.384.78)	1.262	0.207
fT4 [ng/dL]	1.18 (0.19–7.77)	1.15 (0.21–2.03)	1.908	0.056
AntiTg positivity	259 (46.8)	49 (40.5)	1.608	0.205
AntiTPO positivity	250 (45.2)	51 (42.1)	0.376	0.540
Total volume of thyroid [mL]	10.77 (2.39-71.15)	12.11 (3.65-25.88)	3.481	<0.001
Heterogenous US	305 (55.2)	70 (57.9)	0.293	0.589
TSH			0.340	0.844
High	220 (39.8)	48 (39.7)		
Normal	319 (57.7)	71 (58.7)		
Low	14 (2.5)	2 (1.6)		
Heterogeneous USG & negative antibodies	40 (7.2)	17 (14.0)	5.110	0.024
High TSH level & negative antibodies	55 (9.9)	16 (13.2)	0.810	0.368

TSH: Thyrotropin; fT3: Free triiodothyronine; fT4: Free thyroxine; Anti TPOAb: Anti-thyroid peroxidase antibody; Anti TgAb: Anti-thyroglobulin antibody; US: Thyroid ultrasonography.

Discussion

The association between obesity and thyroid hormones and the possible mechanisms of this association have yet to be elucidated. One of the hypotheses is the increased deiodinase activity as a defense mechanism. This stimulates the conversion of T4 to T3 in obesity. This causes increased energy expenditure which might counteract the accumulation of fat (4,10,11). It was also suggested that high serum levels of leptin in obese patients stimulate thyrotropin-releasing hormone (TRH) production in the hypothalamus, which in turn might affect thyroid hormones and thermogenesis (12). Some inflammatory cytokines secreted from the adipose tissue such as TNF-alpha, IL-1, and IL-6 might inhibit the expression of sodium/iodine symporter mRNA and iodine uptake activity which results in an increase in TSH levels. Tissue resistance to TSH that returns to normal after weight loss can partly be explained by this mechanism (6). There are contradictory results in thyroid functions in obesity. In many studies, high TSH, low fT4, and high fT3 were reported, while some others found normal or reduced TSH and fT3 and normal or increased fT4 (13). The variationsin results reported in different studies might be related to the differences in patient selection, BMI, presence of insulin resistance, and timing of samplings

Table 2. The possible risk factors of obesity.

Independent variables	OR (95% CI)	p
Univariate		
Age [per five years]	1.226 (1.133-1.325)	<0.001
Gender (F vs. M)	1.055 (0.634-1.754)	0.837
TSH [per μIU/mL]	1.009 (0.991-1.028)	0.310
fT3 [per pg/mL]	0.810 (0.607-1.083)	0.155
fT4 [per ng/dL]	0.451 (0.211-0.964)	0.040
AntiTg positivity	1.294 (0.868-1.930)	0.206
AntiTPO positivity	1.132 (0.761-1.686)	0.540
Total volume [per ml]	1.025 (0.996-1.054)	0.093
Multivariate		
Age [per five years]	1.218 (1.124-1.319)	<0.001
fT4 [per ng/dL]	0.469 (0.221-0.996)	0.049
AntiTg positivity	1.603 (1.047-2.454)	0.030
Total volume [per mL, increase]	1.032 (0.999-1.066)	0.056

OR: Odds ratio, CI: Confidence interval.
TSH: Thyrotropin; fT3: Free triiodothyronine; fT4: Free thyroxine; Anti TPOAb: Anti-thyroid peroxidase antibody; Anti TgAb: Anti-thyroglobulin antibody; US: Thyroid ultrasonography.

Table 3. The possible related factors of thyroid volume.

Independent variables	b±se (95% CI)	p
Univariate		
Age [per year]	0.040±0.019 (0.003-0.078)	0.034
Gender (M vs. F)	4.193±0.589 (3.035-5.350)	<0.001
BMI [per kg/m^2]	0.185±0.048 (0.091-0.279)	<0.001
TSH [per µIU/mL]	-0.080±0.083 (-0.242-0.082)	0.335
fT3 [per pg/mL]	1.410±0.446 (0.535-2.285)	0.002
fT4 [per ng/dL]	2.278±1.047 (0.222-4.334)	0.030
AntiTg positivity	1.982±0.474 (1.052-2.913)	<0.001
AntiTPO positivity	1.552±0.477 (0.615-2.489)	0.001
Multivariate		
Constant	8.672±2.078 (4.591-12.752)	<0.001
Gender (M vs. F)	3.855±0.592 (2.693-5.018)	<0.001
AntiTg positivity	2.323±0.453 (1.434-3.212)	<0.001
BMI [per kg/m^2]	0.186±0.046 (0.097-0.276)	<0.001
fT3 [per pg/mL]	1.098±0.437 (0.239-1.957)	0.012

b:Regression coefficient, se: Standard error, CI: Confidence interval. BMI: Body mass index; TSH: Thyrotropin; fT3: Free triiodothyronine; fT4: Free thyroxine; Anti TPOAb: Anti-thyroid peroxidase antibody; Anti TgAb: Anti-thyroglobulin antibody

such as without any intervention or when the patient was on a weight loss program including diet or strenuous exercise (14). In the present study, obesity was negatively associated with the level of fT4; however, there was not any association between obesity and TSH and fT3. In a frequently cited study about this subject -The Dan Thyr Study- BMI was also negatively correlated with fT4 and there was no correlation with fT3. This result was in accordance with ourstudy. However, a positive correlation observed between BMI and serum TSH in The Dan Thyr Study was in contradiction with the present finding (15).

Autoimmune thyroid dysfunctions and morphological changes in the thyroid gland in obesity are less studied subjects. In a study on morbidly obese patients, autoimmunity was observed in a minority of patients with hypoechoic thyroid glands in US. Hypoechoic appearance in the absence of any thyroid abnormality was observed in 1.9% of nonobese patients, while it was noted in 64.8% of morbidly obese patients (16). Radetti et al. also reported differences in thyroid structure and functions that cannot be explained by autoimmune involvement in obese children (6). Although thyroid US was suggestive for Hashimoto thyroiditis, thyroid autoantibodies were negative in 37.6% of obese children. Some of these children were evaluated by thyroid fine-needle aspiration biopsy and results indicated normal thyrocytes without evidence of autoimmune thyroid disease. It is difficult to explain the hypoechogenic appearance in obese subjects, but there arefew hypotheses. A possible mechanism behind this might be fat accumulation in the thyroid (6,16). However, this would result in hyperechoic instead of hypoechoic appearance in US (17). Another hypothesis predicts that secretion of cytokines and inflammatory cells from adipose tissue induce vasodilatation and increased permeability of thyroid vessels, which in turn result in plasma exudation to the thyroid parenchyma (13,14). In our study, the frequency of patients diagnosed with heterogeneous thyroid parenchyma in US which was suggestive for chronic thyroiditis and negative thyroid autoantibodies, comprised of 14% in the obese group, whereas, 7.2% in nonobese group. In a recent study with 10 morbidly obese and euthyroid patients, a 25% increase in the echogenicity of thyroid US was reported after >5% weight loss achieved by bariatric surgery (17). The authors, therefore, concluded that morphological changes in the thyroid in case of obesity were reversible with weight loss. Whatever the cause is, it seems that obesity affects thyroid morphology and the value of US in the diagnosis of autoimmune thyroiditis might decrease in obese patients.

A significant association between obesity and antiTg antibody was also demonstrated in our study. However,the relationship between thyroid autoimmunity and obesity is a controversial issue. Marzullo et al. suggested an attractive hypothesis about the link between obesity, leptin, and autoimmunity. They showed that leptin was higher in obese patients when compared to those without autoimmune thyroid disease (AITD). This association between AITD and leptin was irrespective of body fat mass or BMI. Multiple logistic regression analysis indicated female sex and leptin to be significant predictors of AITD. The mechanism underneath was explained by possible induction of autoimmune thyroid injury by high leptin levels in subjects, genetically or environmentally prone to Th-1 immune response (18).

In the study by Rotondi et al., although the prevalence of high TSH was higher in morbidly obese patients, thyroid autoantibodies were negative in most of them. They underlined that the diagnosis of subclinical hypothyroidism should be questioned in morbidly obese patients with negative thyroid autoantibodies since high TSH might not always indicate true hypothyroidism in these patients (2). In our study, though the frequency of patients with high TSH and negative autoantibodies was higher in the obese than the nonobese group, the difference was not significant statistically. However, the small sample size in these subgroups might be a limitation in this case.

The published reports have documented increasing thyroid volume with increasing BMI (7,8,19). Changes in body composition might affect thyroid volume. Sarı et al. reported that thyroid volume and TSH decreased in obese women who had lost more than 10% weight in six months (8). The thyroid volume was also found to be positively correlated with BMI, leptin, and TSH in obese women in the study undertaken by Eray et al. (7). Eray et al. also showed the change in thyroid volume with weight loss was affected only by BMI and leptin. In another study including 268 patients, there was a positive correlation between leptin and thyroid volume (20). These were in line with the present study where we observed a significant correlation between thyroid volume and BMI. These findings suggest a possible role of leptin in the relation between weight loss and decreased thyroid volume.

Cellular dysfunction induced by steatosis in nonadipose tissue of patients with obesity was shown in previous studies (21). Increased thyroid volume in obesity might also be a consequence of increased adipocyte in the thyroid gland. Lee et al. did not find any difference in TSH and fT4 between obese and nonobese patients. However, TSH was reported to be higher in those with interfollicular adipose depot or steatosis in thyroid follicular cells (22). Paracrine factors secreted from these adipocytes and thyroid steatosis due to interfollicular fat accumulation might cause changes in thyroid hormone levels (23).

The main limitation of our study was its retrospective design. Moreover, the serum leptin levels in patients were not evaluated. It is known that thyroid functions and volume might be influenced by some other factors such as TSH receptor antibody levels, iodine status of the patient which can be assessed by urinary iodine content, glucose metabolism disorders, and insulin resistance. Unfortunately, we did not have data about these parameters. As another limitation, thyroid US was performed by two clinicians. The smoking status of the patients was also not taken into consideration. Thiocyanate, which is a potential goitrogen and 2,3-hydroxypyridine, which inhibits thyroxine deiodination, might affect thyroid functions (24).

In conclusion, obesity was negatively associated with fT4 and positively associated with antiTg positivity and age in our study. Additionally, there was a significant association between obesity and morphological changes in the thyroid gland. Approximately, in every seven obese patients, one had heterogeneous thyroid gland despite negative thyroid autoantibodies. This suggests that the diagnostic value of US in autoimmune thyroiditis might reduce in obesity. These patients should be evaluated with clinical and biochemical findings and thyroid autoantibody results. Obesity also affects thyroid volume, possibly through changes in leptin levels. Further prospective studies might exhibit whether there is a causal relationship between obesity and changes in the thyroid gland.

Ethics

Ethics Committee Approval and Informed Consent: Ethical review board of Yıldırım Beyazıt University Ataturk Training and Research Hospital approved the study protocol.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Abbas Ali Tam, Bekir Çakır; Design: Didem Özdemir, Reyhan Ersoy; Data Collection and/or Processing: Berna Evranos Öğmen, Fatma Dilek Dellal; Analysis and/or Interpretation: Abbas Ali Tam, Afra Alkan; Literature Review: Abbas Ali Tam, Didem Özdemir; Writing the Article: Abbas Ali Tam, Didem Özdemir, Oya Topaloğlu.

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