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Are nonfunctioning adrenal incidentalomas really nonfunctioning? A retrospective single-center study

E. GÜNEŞ[1], M. GÜNEŞ[2]

[1]Department of Endocrinology, Health Sciences University, Bursa State Hospital, Metabolism and Diabetes, Bursa, Turkey
[2]Department of Endocrinology, Health Sciences University, Bursa Yuksek Ihtisas Training and Research Hospital, Metabolism and Diabetes, Bursa, Turkey

Abstract. – OBJECTIVE: In patients with adrenal incidentaloma (AI), cortisol levels <1.8 µg/dL after a dexamethasone suppression test (DST) are considered nonfunctioning in terms of autonomic cortisol hypersecretion (ACH). We aimed to investigate the frequency of hypertension (HT) in patients with nonfunctioning AI.

PATIENTS AND METHODS: Individuals with AI who were admitted to the endocrinology clinic between September 2020 and May 2023 were included as the patient group, and age- and gender-matched individuals admitted with thyroid nodules between the same dates were included as the control group.

RESULTS: The participants included 123 AI patients who fulfilled the study criteria and 114 age- and sex-matched patients with thyroid nodules (age: 53.0±10.9 years and 52.9±7.4 years, respectively, *p*=0.98; female/male distribution: 90/33 and 91/23, respectively, *p*=0.28). The frequency of HT was higher in the AI group than in the control group (50.4% and 31.6%, respectively, *p*=0.004). The frequency of HT was significantly lower in patients with a DST result <0.87 µg/dL compared to those with a DST result ≥0.87 µg/dL (42.6% and 66.1%, respectively, *p*=0.009). The factors affecting HT were analyzed using binary logistic regression analysis; it was found that age [β=0.068, odds ratio (OR); 1.07 (95% confidence interval (CI); 1.02-1.12), *p*=0.004] and DST [β=1.18, OR; 3.24 (95% CI); 1.02-10.34, *p*=0.047] were independent factors.

CONCLUSIONS: The frequency of HT increases in patients with nonfunctioning AI. The reason for this increase may possibly be the presence of ACH, which is not detected by the cut-off values we currently use to exclude ACH.

Key Words:
Adrenal incidentaloma, Nonfunctioning adrenal adenoma, Hypertension, Autonomic cortisol hypersecretion, Cushing's syndrome, Dexamethasone suppression test.

Introduction

In recent years, there has been a significant increase in the frequency of use of imaging modalities[1], which has led to more frequent detection of certain silent diseases, of which adrenal incidentaloma (AI) is one[2]. AI is defined as the discovery of lesions larger than 1 cm in the adrenal gland on imaging performed for another purpose[3]. The prevalence of AI varies between 3.4% and 6.9%[4,5]. Two conditions need to be clarified in individuals with AI. The first is the distinction between adenoma and non-adenoma, and the second is whether the AI is functional[2]. For functional evaluation, a 1 mg dexamethasone suppression test (1 mg DST) should be performed overnight to exclude Cushing's syndrome (CS)[3]. Autonomic cortisol hypersecretion (ACH) is excluded in patients with AI with a 1 mg DST result <1.8 µg/dL[3]. Subclinical CS (sCS) or possible ACH may be considered in patients with a test result between 1.8 and 5.0 µg/dL[3], whereas CS or ACH is diagnosed in patients with a test result >5.0 µg/dL[3]. Another diagnostic approach for functional AI is the analysis of metanephrine in 24-hour urine (24 uMN) or plasma metanephrine levels (pMN)[3]. Finally, in patients with hypertension (HT) or unexplained hypokalaemia, the aldosterone-to-renin ratio should be evaluated, and possible primary hyperaldosteronism (PHA) should be excluded[3]. AI in which no hormone production is detected in function tests is considered to be nonfunctioning, and follow-up of patients with an adenoma <4 cm is recommended[3,6].

Terzolo et al[7] found that both the systolic and diastolic blood pressures of patients with nonfunctioning AI were higher compared with healthy controls[7]. In another study, Chiodini et al[8] found that the bone mineral density of patients

Corresponding Author: Mutlu Güneş, MD; e-mail: mutlu.gunes@saglik.gov.tr

with nonfunctioning AI was lower in both males and females compared to age-matched healthy controls and that these patients had an increased risk of fracture[8]. These findings have led to the question: are AIs that appear to be nonfunctional really nonfunctional? Although this question has been asked for 20 years, it has not been sufficiently addressed in the literature. Therefore, the aim of this study was to investigate the frequency of HT in patients with nonfunctioning AI.

Patients and Methods

Patient Selection

The study is a retrospective data review that was conducted between September 2020 and May 2023 in the Endocrinology, Diabetes, and Metabolic Diseases Clinic at the Health Sciences University Bursa State Hospital. Written informed consent has been obtained from the patient(s) to publish this paper.

Inclusion Criteria

Patients with nonfunctioning AI who were 18 years of age or older were included in the patient group. Age- and gender-matched patients presenting with thyroid nodules were selected as the control group.

Exclusion Criteria

Patients with functional AI, chronic renal failure, renal parenchymal diseases, systemic rheumatic disease, and conditions affecting the gastrointestinal, respiratory, or other systems and requiring steroid treatment, and pregnant women were excluded.

Study Design and Obtaining Patient Information

The following information was obtained from patient files: fasting plasma glucose (FPG), creatinine (Cr), glomerular filtration rate (GFR), thyroid stimulating hormone (TSH), total cholesterol, low-density lipoprotein (LDL), 1 mg DST, high-density lipoprotein (HDL) and triglyceride (TG) levels, height, weight, age, diabetes mellitus (DM), HT and hyperlipidemia (HL). Body mass index (BMI) was calculated as kilogram/m^2.

After differentiating between adenoma and non-adenoma and conducting functional evaluations as per the current guidelines, patients with nonfunctioning AI and adrenal lesions smaller than 4 cm were included in the study and followed up[3,6]. The distinction between ACH and possible ACH was made according to the current guidelines[3,6].

Statistical Analysis

After the normal distribution was determined, an independent samples *t*-test was applied with a normal distribution, and the Mann-Whitney U test was applied to compare the data that did not have a normal distribution. Pearson's Chi-squared test was used to compare ratios and determine the correlation between the data Pearson and Spearman tests were used, and binary logistic regression analyses were applied to determine whether the correlated data were independent factors. To determine the best value associated with the disease receiver operating characteristic (ROC) analysis was used. A *p*-value lower than 0.05 was considered statistically significant. IBM® Statistical Package for the Social Sciences (SPSS) statistics 20 (IBM Corp., Armonk, NY, USA) was used to compare the data.

Results

A total of 123 individuals with nonfunctioning AI were included in the study and 114 age- and sex-matched thyroid nodule patients were selected as the control group. The demographic, clinical, and laboratory characteristics of the participants are provided in Table I.

HT

The frequency of HT was higher in the AI group than in the control group (Table I). The effect of age on HT was demonstrated in correlation and regression analyses (Tables II and III). ROC analysis was used to determine the best age value associated with HT. The cut-off value for age-associated with HT was 49.5 years. When the effect of AI on the frequency of HT was analyzed by dividing the patients into those under and over 50 years of age, it was observed that HT was more frequent in individuals with AI (Figure 1). The frequency of HT increased with age in both groups (Figure 1).

An analysis of gender showed that HT was more prevalent in both men and women in the AI group (Figure 2).

The effect of BMI on the frequency of HT in the AI and control groups is shown in Figure 3. When the patients were divided into those with a BMI <30 and those with a BMI ≥30, the frequency of HT was higher in individuals with AI in both groups.

ROC analysis was used to find the best 1 mg DST level associated with HT, which was found to be 0.87 µg/dL. When the patients were divided into 1 mg DST level below and 1 mg

Table I. Demographic and laboratory characteristics of the participants.

	Control group (n=114)	AI group (n=123)	*p*
Age (years)	52.9±7.4	53.0±10.9	0.98
Female/male (n)	91/23	90/33	0.28
Body mass index (kg/m^2)	30.0 (IQR:10.3)*	29.1 (IQR: 8.3)*	0.60
Fasting plasma glucose (mg/dL)	136.0 (IQR: 46.0)*	96.0 (IQR: 15.0)*	0.3
HbA$_{1c}$ (%)	7.5 (IQR: 2.5)*	5.65 (IQR: 2.8)*	*0.009*
TSH (uIU/mL)	1.90 (IQR: 2.9)*	1.26 (IQR: 8.28)*	0.071
Creatinine (mg/dL)	0.60 (IQR: 0.55)*	0.60 (IQR: 0.30)*	0.92
Total Cholesterol (mg/dL)	213.0 (IQR: 39.0)*	213.0 (IQR: 60.8)*	0.78
LDL (mg/dL)	91.0 (IQR: 39.5)*	131.5 (IQR: 57.5)*	0.18
TG (mg/dL)	280.0 (IQR: 290.0)*	142.0 (IQR: 65.0)*	0.09
HDL (mg/dL)	45.0 (IQR: 21.5)*	46.0 (IQR: 13.5)*	0.043
Hypertension (%)	31.6%	50.4%	0.004
Diabetes mellitus (%)	17.5%	17.1%	1.0
Hyperlipidemia (%)	27.2%	43.1%	*0.014*

*Since it does not show normal distribution, it is given as a median and interquartile range of 25-75 percentiles (IQR). AI: adrenal incidentaloma, Hb A$_{1c}$: hemoglobin A$_{1c}$, TSH: thyroid stimulating hormone, LDL: low-density lipoprotein, TG: triglyceride, HDL: high-density lipoprotein.

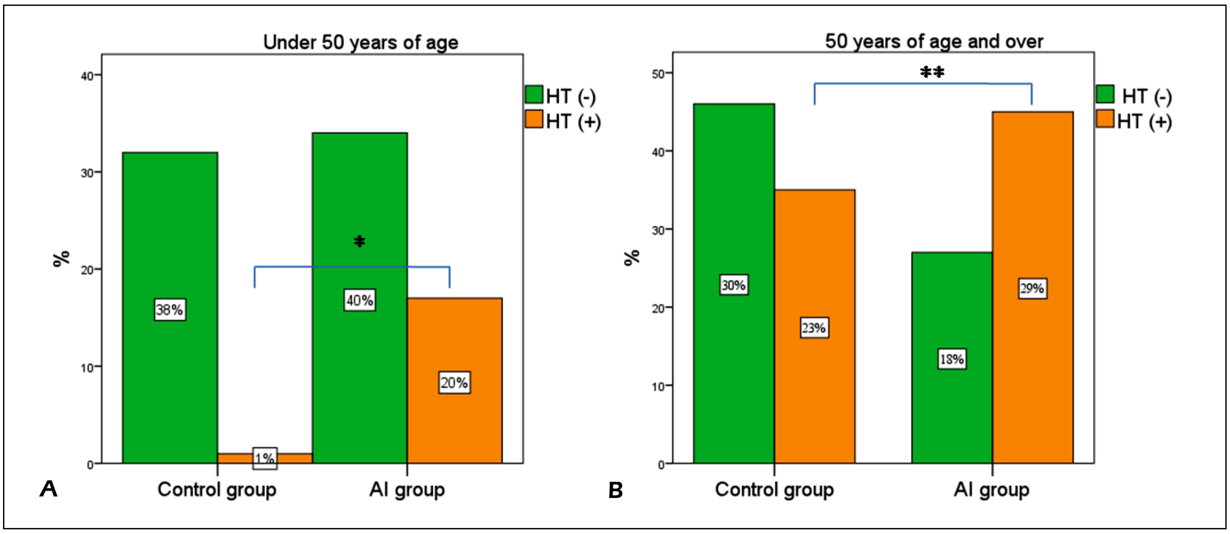

Figure 1. The hypertension (HT) frequencies of individuals under 50 years of age and over 50 years of age in the adrenal incidentaloma (AI) and control groups show that although there is an increase in the frequency of HT with age, the increase in the frequency of HT in the AI group compared to the control group did not change with age (*p=0.001, **p=0.023).

DST level above 0.87 µg/dL, the prevalence of HT was significantly lower in patients with the former (42.6%, 26/61) than in those with the latter (66.1%, 41/62, p=0.009).

Bivariate Correlation Analysis

The parameters correlated with HT and DM are provided in Table II. Our study group consisted of individuals with AI in whom ACH had been excluded, and, despite this, the results of our study showed that HT was correlated with 1 mg DST. This is a finding that should be emphasized (Table II).

Regression Analysis

The binary logistic analysis examining the effects of the parameters correlated with HT is provided in Table III. It is a very striking finding that the 1 mg DST was found to be an independent factor that affected HT in the nonfunctioning AI patient group (Table III).

Discussion

Our study has yielded two noteworthy findings. First, the frequency of HT was higher in

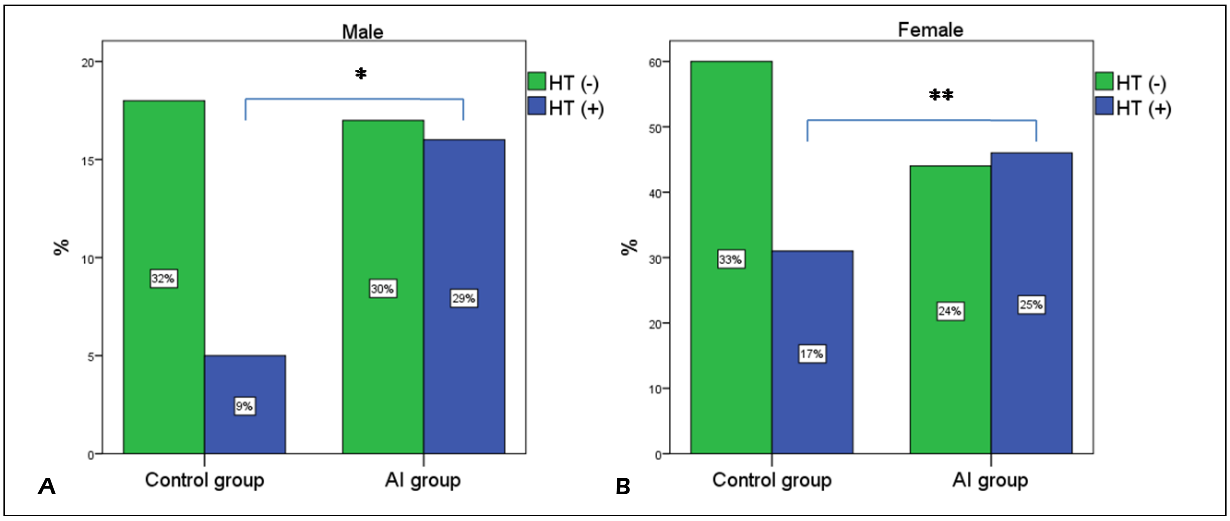

Figure 2. The hypertension (HT) prevalence in men and women in the AI and control groups. HT prevalence was higher in both men and women in the adrenal incidentaloma (AI) group compared to the control group (*p=0.042, **p=0.020).

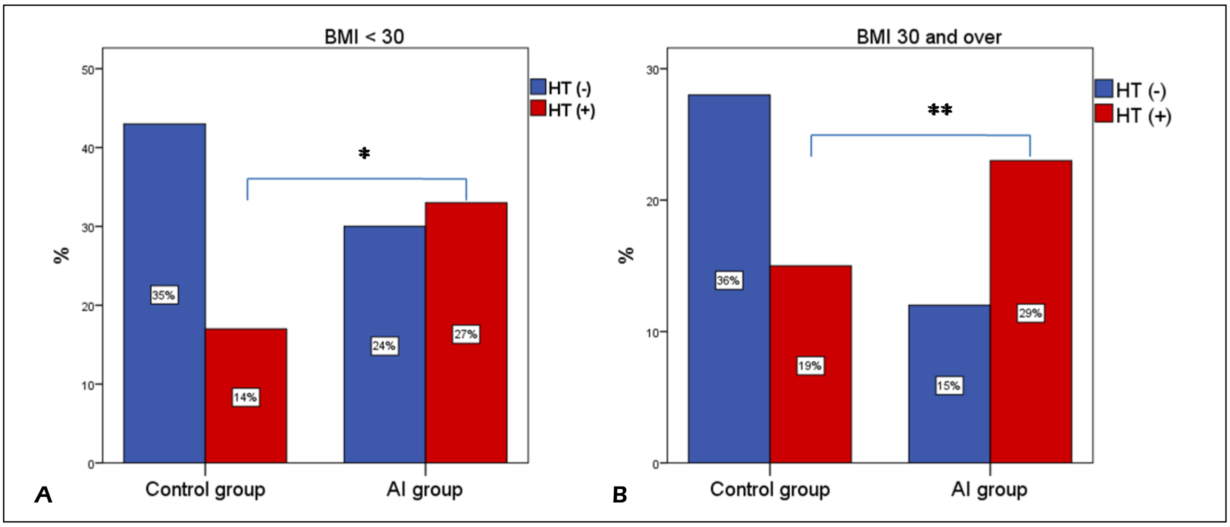

Figure 3. The hypertension (HT) frequencies in the adrenal incidentaloma (AI) and control groups according to BMI. BMI <30 and body mass index (BMI) ≥30 (*p=0.01, **p=0.012).

individuals with nonfunctioning AI than in individuals in the control group, and second, cortisol levels after the 1 mg DST were an independent factor affecting the frequency of HT.

In a study by Satman et al[9], the frequency of HT was found to be 31.4% in the general population[9]. In our study, the frequency of HT was found to be 31.6% in the thyroid nodule control group, which is compatible with the frequency in the general population[9]. On the other hand, the prevalence of HT in the nonfunctioning AI group in our study was higher than the frequency in the general population and the thyroid nodule control group, which is a remarkable finding. The frequency of HT increases with advancing age9. AI is rarely encountered in individuals below the age of 30 years[10], and its frequency increases with age11. The fact that both the frequency of AI and the frequency of HT increase with age suggests that there is a common factor affecting both. In our study, when the patients were divided into those under and those over 50 years, although the frequency of HT was significantly lower in those under the age of 50 years in the thyroid nodule control group, the frequency of HT was higher in individuals with AI compared

Table II. Parameters that correlate with DM and HT.

		Age	Gender	BMI	1 mg DST	DM	HT	Group
Age	*r*	1.00	-0.06	0.06	*0.25***	*0.30***	*0.34***	0.01
	p	.	0.40	0.43	*0.005*	*<0.001*	*<0.001*	0.87
Gender	*r*		1.00	0.125	0.072	-0.01	0.04	-0.08
	p		.	0.08	0.43	0.90	0.51	0.23
BMI	*r*			1.00	0.01	*0.19***	0.10	0.04
	p			.	0.92	*0.006*	0.17	0.60
1 mg DST	*r*				1.00	0.12	*0.23**	.
	p				.	0.20	*0.012*	.
DM	*r*					1.00	*0.34***	-0.01
	p					.	*<0.001*	0.92
HT	*r*						1.00	*0.19***
	p						.	*0.003*
Group	*r*							1.00
	p							.

BMI: body mass index, 1 mg DST: one-milligram dexamethasone suppression test, DM: diabetes mellitus, HT: hypertension, *=significance at $p<0.05$; **=significance at $p<0.01$.

Table III. Logistic regression analysis of factors affecting HT.

Dependent variable	Independent variables	β	Wald Chi-square	OR	OR 95% CI Lower	Upper	*p*
	Age	0.068	8.42	1.07	1.02	1.12	0.004
	Gender	-0.08	0.025	0.93	0.32	0.35	2.45
Model 1	BMI	0.03	0.40	1.03	0.94	1.13	0.53
HT	1 mg DST	1.18	3.94	3.24	1.02	10.34	0.047
	Constant	-5.48	11.0	0.004	1.05	1.14	0.001

HT: hypertension, OR: odds ratio, CI: confidence interval, BMI: body mass index, 1 mg DST: one-milligram dexamethasone suppression test.

to the thyroid nodule control group. On the other hand, the frequency of HT increased with age above 50 years, but the increase in the frequency of HT in the AI group compared to the thyroid nodule control group did not change with age. This discovery suggests that AI may trigger HT independently of age, but the triggering factor is unknown and requires further research.

Whether or not gender affects the frequency of AI is controversial. Ambrosi et al[12] found that AI was more frequent in women[12], whereas in the Co-work of Adrenal Research (COAR) study[11] conducted in Korea, AI was found to be more frequent in men. When the frequency of HT according to gender is analyzed, it has been observed that HT is more frequent in female individuals with DM compared to male individuals[9], whereas there is no difference in the frequency of HT between men and women in the normal population[9]. In our study, females with AI were predominant. Since the gender distribution of both the thyroid nodule control and AI groups was the same in our study, and HT was more frequent in both females and males with AI compared to the thyroid nodule control group, it would not be incorrect to say that the increase in the frequency of HT in individuals with AI is independent of gender. However, since the majority of the patients in our study were women, it cannot be concluded that AI is completely independent of gender, and this issue needs to be investigated in further studies.

Community-based studies[9,13] have prospectively demonstrated that BMI affects the frequency of HT. The TURDEP I study found that the rate of BMI >30 was 31.2% and the frequency of HT was 25.6%, whereas in the TURDEP II study conducted 12 years after the first study, the rate of BMI >30 was 36.0 and the frequency of HT was 31.4%[9,13]. Thus, it is clear that an increase in BMI is accompanied by an increase in the frequency of HT. In our study, the BMIs of the thyroid nodule control group and the AI group were similar, and when the frequency of HT according to BMI was analyzed, it was observed that the frequency of HT was higher in patients with AI both in the BMI <30 BMI group and in the BMI ≥30 BMI group. Again, based on this finding, it seems likely that an increase in the frequency of HT in patients with AI is independent of BMI.

In our study, when the factors affecting HT in individuals with non-functioning AI were analyzed, one of the prominent findings was that cortisol levels after the 1 mg DST were an independent factor. This finding means that the cut-off value of 1.8 µg/dL after the 1 mg DST, which is thought to exclude ACH, should be reviewed. In a recent multicenter study[14] in which 593 individuals with nonfunctioning AI were retrospectively analyzed, when the cut-off value for cortisol levels after the 1 mg DST was 0.9 µg/dL, it was found that the frequency of cardiovascular disease was higher in those with >0.9 µg/dL. In the same study, when the cut-off value for cortisol levels after the 1 mg DST was 1.4 µg/dL, it was found that the risk of developing ACH was higher in those with cortisol levels >1.4 µg/dL after the 1 mg DST14. In another study[15] published by the same author in 2019, the 1 mg DST cut-off value predicting the development of cardiovascular disease in individuals with nonfunctioning AI was found to be 1.8 µg/dL, while the 1 mg DST cut-off value predicting the development of DM was found to be 3.0 µg/dL[15]. A study published by Araujo-Castro et al[16] in 2022 found that the blood pressure of individuals with nonfunctioning AI improved after adrenalectomy[16]. The literature raises the question of whether the cut-off value of 1.8 µg/dL for the 1 mg DST really excludes ACH. In our study, patients whose 1 mg DST was below and those whose 1 mg DST was above 0.87 µg/dL showed different frequencies of HT. The frequency of HT in the group below 0.87 µg/dL was closer to that of the normal population. In addition, it should be emphasized that the fact that the 1 mg DST was correlated with the frequency of HT suggests that the threshold value of 1.8 µg/dL does not exclude ACH. Multicenter-controlled prospective studies are needed to clarify this issue.

Our study has some limitations. First, our study was retrospective in design. It is unclear whether the patients had controlled blood pressure since their blood pressure levels were not obtained. Therefore, the information about the presence or absence of blood pressure control was not available. Multicenter prospective studies in this field will contribute to a better understanding of the subject.

Conclusions

The presence of another age-independent factor that triggers HT in individuals with nonfunctioning AI is significant. In light of the findings of our study, it can be said that ACH cannot be completely excluded with the 1 mg DST cut-off values recommended by the current guidelines, that the factor sought may be possible ACH, and that a new cut-off value for 1 mg DST should be determined.

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Ethics Approval

The present study was approved by the Ethics Committee of the Health Sciences University, Bursa State Hospital, “07.12.2022, 2022-17/5, E-13012450-514.99”. In light of the retrospective nature of the study, all procedures were performed as part of routine care. The researchers affirm that they adhered to the Declaration of Helsinki.

Authors’ Contributions

Conceptualization, E.G. and M.G.; Methodology, E.G.; Software, M.G.; Validation, M.G.; Formal Analysis, E.G and M.G.; Investigation, E.G.; Resources, E.G.; Data Curation, E.G.; Writing – Original Draft Preparation, E.G and M.G.; Writing – Review and Editing, E.G and M.G.; Visualization, E.G.; Supervision, M.G.; Project Administration, M.G.; Funding Acquisition, E.G.”.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability

The data used for this manuscript will be made available upon reasonable request to the corresponding author.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

ORCID ID

Mutlu Güneş: 0000-0001-9756-2285
Elif Güneş: 0000-0002-5441-2604.

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