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Evaluation of iron deficiency anemia during acute infection in children

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ABSTRACT

Aims: The purpose of this study was to assess changes in infection and iron parameters during infection and at least 4-6 weeks after recovery in children diagnosed with infections, to investigate the impact of infection on iron metabolism and to determine the prevalence of iron deficiency anemia (IDA).

Methods: In this study, 151 patients who presented with fever, were diagnosed with an infection as the source of the fever, had no prior anemia investigations or antianemic treatment, and had no history of recurrent infections or chronic diseases, between September 2005 and October 2005 were included. In addition to specific tests focused on the site of infection, complete blood count, serum iron, serum total iron-binding capacity (TIBC), ferritin, C-reactive protein (CRP), transferrin saturation, and peripheral smear levels were measured at the time of admission and 4-6 weeks after follow-up.

Results: The mean age of the patients was 4.5±3.2 years, and 57.6% (n=87) of them were male. During the infection, 12% of the cases (n=18) showed iron deficiency, and 53% (n=80) were diagnosed with IDA. After infection, iron deficiency was identified in 5% of the cases (n=7), while IDA was present in 37.1% of the cases (n=50). A significant decrease in both iron deficiency (12% vs. 5%, p=0.001) and IDA (53.0% vs. 37.1%, p=0.001) ratios was observed after the infection. The group with IDA showed a larger decrease in leukocyte and CRP levels compared to the group without IDA, alongside a more marked increase in TIBC levels.

Conclusion: The reduction in iron deficiency and IDA rates following infection suggests that infection may lead to substantial changes in iron metabolism. Monitoring iron parameters during the infection phase in pediatric patients may play a crucial role in distinguishing anemia of inflammation from IDA.

Keywords: Anemia, ferritin, infection, iron deficiency anemia, total iron-binding capacity

INTRODUCTION

Iron deficiency anemia (IDA) remains one of the most common in developing countries.[1] It is characterized by a decrease in hemoglobin concentration due to insufficient iron, leading to impaired oxygen transport.[2] The pediatric population is particularly vulnerable to the effects of iron deficiency, which can have long-term consequences on cognitive development, growth, and overall health.[3]

Acute infections, frequently encountered in pediatric care, may complicate the diagnosis and management of IDA.[4] During an infection, inflammatory processes can alter iron metabolism, leading to a reduction in serum iron levels and changes in the hematological profile.[5,6] This phenomenon, known as anemia of inflammation (AI), shares several overlapping features with IDA, complicating the differentiation between these two conditions.[7,8]

Understanding the interaction between acute infections and iron deficiency in children is crucial for timely and effective management. Acute infections can mask or exacerbate pre-existing iron deficiency, leading to delayed treatment or inappropriate interventions.[9-11] Furthermore, anemia may worsen the course of infection, potentially prolonging recovery time and increasing susceptibility to further health complications.[12,13]

The purpose of this study was to assess changes in infection and iron parameters during infection and at least 4-6 weeks after recovery in children diagnosed with infections, to investigate the impact of infection on iron metabolism and to determine the prevalence of IDA.

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METHODS

Following the principles set forth in the Declaration of Helsinki, this prospective study was conducted at the Zeynep Kamil Women and Children's Diseases Training and Researches Hospital Child Health and Diseases Polyclinic from September 2005-October 2005. This study was produced in the thesis study conducted in 2006. Informed consent was obtained from all participants.

The study included 151 patients, aged 6 months to 13 years, who presented with fever, were diagnosed with an infection as the cause of the fever, had not been previously investigated for anemia or received any antianemic treatment, and had no history of frequent infections or chronic disease. At the initial evaluation, all patients underwent a Direct Coombs test and reticulocyte count to rule out hemolytic disease. In addition to specific tests focused on the site of infection, complete blood count, serum iron, serum total iron-binding capacity (TIBC), ferritin, C-reactive protein (CRP), transferrin saturation, and peripheral smear levels were measured at the time of admission and 4-6 weeks after follow-up.

The complete blood count and reticulocyte count were automatically measured within 90 minutes using the Beckman Coulter Gen-S device, after drawing 2 cc of blood into a K3 EDTA tube. The direct Coombs test was conducted with the Diamed-ID Micro Typing System kit (DiaMed AG, Morat, Switzerland). For the peripheral smear, a blood smear prepared from the fingertip was air-dried and stained with May Grünwald stain for 3 minutes. After removing excess stain with distilled water, it was stained with Giemsa for 8 minutes. The remaining stain was rinsed off with water, and the smear was air-dried again. The prepared smear was examined at 100x magnification with an immersion objective, and anisocytosis, hypochromia, and microcytosis were assessed. CRP values were determined by the immunonephelometric method on the BN Pro Spec device (Dade Behring, Derfield, IL, USA) using the Dade Behring kit. Ferritin levels were analyzed with the chemiluminescent immunometric method on the IMMULITE 2000 device (Diagnostic Products Corporation, LA, USA). Transferrin saturation was determined by the following formula using serum iron and total iron-binding capacity =(Serum iron / Serum TIBC)×100.

Iron deficiency was characterized by the presence of at least two of these criteria: serum iron levels below 50 µg/dl, serum ferritin below 15 ng/ml, or transferrin saturation below 12%. In addition to these criteria, patients with hemoglobin levels ≤11.5 g/dl were classified as having IDA.[14,15]

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean and standard deviation (SD) values while non-normally distributed variables are given as median (min-max). Paired sample T test, Wilcoxon signed-rank test, and mixed model for repeated measures (MMRM) analysis was performed for comparison of the post- infections laboratory findings; $p<0.05$ was considered statistically significant.

RESULTS

The study included 151 cases, comprising 87 boys (57.6%) and 64 girls, with a mean age of 4.5±3.2 years. All cases showed normal reticulocyte counts and negative direct Coombs tests. The distribution of infections was as follows: 31.1% of cases involved upper respiratory tract infections (URTIs), 18.5% involved lower respiratory tract infections (LRTIs), 17.9% involved cryptic tonsillitis, 16.6% involved acute gastroenteritis, and 15.9% involved urinary tract infections (UTIs). During the infection, 12% of the cases (n=18) showed iron deficiency, and 53% (n=80) were diagnosed with IDA. After infection, iron deficiency was identified in 5% of the cases (n=7), while IDA was present in 37.1% of the cases (n=50). A significant decrease in both iron deficiency (12% vs. 5%, p=0.001) and IDA (53.0% vs. 37.1%, p=0.001) ratios was observed after the infection. The changes in laboratory findings during and after infection are detailed in Table 1.

Table 1. Variations in laboratory findings before and after infection

Variables	During infection n=151	After infection n=151	p
Hemoglobin, g/dl	11.2±1.9	11.6±1.7	0.043*
Hematocrit, %	32.9±4.6	34.4±4	0.001*
RBC, %	4.6±0.5	4.6±0.4	0.001*
MCV, fL	72.0±9.0	73.8±8.6	0.001*
MCH, pq	24.5±3.7	24.6±3.7	0.245
MCHC, g/dl	33.9±1.7	34±1.6	0.204
RDW, %	15.7±3.9	15.7±3.7	0.398
Leukocytes, mm^3	10300 (4500-27500)	8600 (4900-13800)	0.001*
CRP, mg/L	8.1 (3.1-197)	3.2 (3.1-3.5)	0.001*
Serum iron, µg/dl	37 (3-99)	58 (11-99)	0.001*
TIBC, µg/dl	387.8±77.9	417.3±68.9	0.001*
Ferritin, ng/ml	30 (1.3-226)	17.3 (0.5-439)	0.001*
Transferrin saturation, %	10 (1-32)	14 (3-29)	0.001*
Iron deficiency, n (%)	18 (12.0)	7 (5.0)	0.001*
IDA, n (%)	80 (53.0)	56 (37.1)	0.001*

Numerical variables were shown as mean ± standard deviation or median (min-max). For numerical data showing normal distribution, the paired sample t-test was performed, while the Wilcoxon signed-rank test was used for those without a normal distribution. * p-value < 0.05 indicates statistical significance. Abbreviations: CRP: C-reactive protein, IDA: Iron deficiency anemia, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, TIBC: Total iron-binding capacity.

Table 2 presents the changes in laboratory findings for those with and without IDA after the infection. Hemoglobin, hematocrit, erythrocytes, serum iron, TIBC, ferritin, and transferrin saturation levels increased in both groups, whereas significant decreases were observed in leukocyte and CRP levels. The group with IDA showed a larger decrease in leukocyte and CRP levels compared to the group without IDA, alongside a more marked increase in TIBC levels.

DISCUSSION

In this study, we investigated the impact of acute infections on iron metabolism in pediatric patients, focusing specifically on iron deficiency and IDA. Our results show significant changes in iron parameters post-infection compared to during the infection, highlighting the dynamic relationship between infection and iron status. After infection, serum iron, TIBC, and transferrin saturation increased, while ferritin levels decreased. These observations are crucial, as they reflect the dynamic nature of iron homeostasis during the recovery phase of infection.

Table 2. The changes in laboratory findings during and after infection by presence of iron deficiency anemia after infection

Variables	IDA (-)			IDA (+)			
	During infection n=95	After infection n=95	p	During infection n=56	After infection n=56	p	Δp
Hemoglobin, g/dl	12.3±0.9	12.6±0.8	<0.001*	9.3±1.5	9.8±1.4	<0.001*	0.207
Hematocrit, %	35.5±2.5	36.7±2.1	<0.001*	28.5±4	30.6±3.5	<0.001*	0.094
RBC, %	4.6±0.4	4.7±0.4	<0.001*	4.4±0.6	4.5±0.5	<0.001*	0.305
MCV, fL	76.7±5.3	78.4±4.8	<0.001*	64±8.3	65.9±7.8	<0.001*	0.614
MCH, pq	26.4±2.1	26.5±2.2	0.542	21.4±3.8	21.5±3.6	0.168	0.705
MCHC, g/dl	34.5±0.8	34.6±0.8	0.102	32.9±2.3	33±2	0.779	0.487
RDW, %	13.9±1.3	14.0±1.1	0.136	18.7±4.9	18.6±4.7	0.531	0.097
Leukocytes, mm^3	9800 (4700-21000)	8600 (4900-13200)	<0.001*	11400 (4500-27500)	8750 (4900-13800)	<0.001*	0.037*
CRP, mg/L	6.1 (3.1-167)	3.3 (3.1-3.8)	<0.001*	10.1 (3.1-197)	3.2(3.1-3.5)	<0.001*	0.025*
Serum iron, µg/dl	50.8±26.9	64.8±17.7	<0.001*	22.5±16.4	33.7±14.5	<0.001*	0.216
TIBC, µg/dL	382.2±70.5	402.3±65.1	<0.001*	397.4±88.9	442.8±68.3	<0.001*	<0.001*
Ferritin, ng/ml	32.5(1.3-123)	21.3 (9-439)	<0.001*	22.1 (1.5-226)	9.8 (0.5-65.2)	<0.001*	0.077
Transferrin saturation, %	14 (1-32)	17 (10-29)	<0.001*	4 (1-22)	7 (3-20)	<0.001*	0.097

Numerical variables were shown as mean±standard deviation or median (min-max). For within-group temporal comparisons, paired sample t-tests were performed for numerical data with normal distribution, while the Wilcoxon signed-rank test was used for non-normally distributed data. Temporal changes between groups (Δ) were analyzed using a mixed model for repeated measures. * p-value <0.05 indicates statistical significance. Δp=Comparison of the changes of follow-ups between the groups with and without IDA. Abbreviations: CRP: C-reactive protein, IDA: Iron deficiency anemia, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, TIBC: Total iron-binding capacity.

Iron plays a dual role during infections. On one hand, it is essential for immune cell proliferation and function, particularly for T cells and macrophages. On the other hand, many pathogens, such as *Escherichia coli* and *Salmonella*, require iron for growth, making excess iron potentially harmful by fostering bacterial proliferation.[16,17] This dual role underscores the body's tight regulation of iron during infections, where limiting iron availability helps to control pathogen growth. The reduction in ferritin levels post-infection reflects the body's shift away from this defensive iron-sequestration strategy. Ferritin, an acute-phase reactant, tends to rise during infection as part of the body's defense mechanism to limit iron availability to pathogens. This phenomenon is driven by the action of hepcidin, which restricts iron release from storage sites by inducing the internalization of ferroportin, the main iron-exporting protein.[18-20] Consequently, serum iron levels drop during infection, contributing to what is known as AI. Once the infection resolves, hepcidin levels decrease, allowing iron to be mobilized from storage, which explains the observed drop in ferritin and the rise in serum iron and transferrin saturation.[21,22]

A marked reduction in the ratios of patients with iron deficiency and IDA post-infection was noted. While we could not find any studies in the literature reporting the frequency of IDA before and after infection, several studies have shown that during infection, elevated hepcidin levels are positively correlated with ferritin levels and negatively correlated with serum iron levels.[23-25] This findings indicates that inflammation-induced iron sequestration might temporarily raise IDA rates during infection, with the true incidence of IDA becoming clear after the infection resolves.[18] This points to the importance of differentiating AI from true IDA, particularly in pediatric patients, as misdiagnosis could lead to inappropriate treatment strategies. One of the challenges in clinical practice is distinguishing between AI, commonly associated with infections, and true IDA. The mechanisms described above cause changes in iron metabolism during acute inflammation.[18-20] This results in a temporary, infection-related anemia that mimics IDA. Once the infection resolves, ferritin levels normalize and iron is released back into circulation, which may cause the previously exaggerated frequency of IDA due to the inflammatory response to return to its true values. Given this, clinicians must be cautious in diagnosing IDA during active infection. Serum ferritin, a marker for iron storage, can be misleading as it is elevated during inflammation. Instead, combining serum iron, transferrin saturation, and other markers like soluble transferrin receptor (sTfR) can provide a clearer picture of iron status.[26,27] In order to prevent misdiagnosis, it may be essential to reassess iron indicators once the infection has resolved.

The increase in hemoglobin, hematocrit, and erythrocytes in groups with and without IDA following infection suggests a recovery in erythropoiesis. After infection resolves, the release of iron from stores supports enhanced erythropoiesis, particularly in the bone marrow.[28] The increase in iron indicators in both groups is indicative of improved iron availability after the infection resolves. Among these indicators, only TIBC levels exhibited a more pronounced rise in the IDA group post-infection. As the inflammation resolves and iron becomes available again, the body increases TIBC to facilitate iron transport. Unlike in patients without IDA, where iron stores are relatively intact, IDA patients may rely more on circulating iron for erythropoiesis, leading to increased TIBC levels post-infection. On the other hand, studies have shown that transferrin, reflected by elevated TIBC, plays an immunoregulatory role by scavenging free iron and preventing it from facilitating the production of reactive oxygen species, thus influencing the inflammatory response.[29-31] Elevated CRP and leukocyte levels typically correlate with high hepcidin levels during infection, which leads to iron sequestration.[32] The more pronounced reduction in hepcidin levels after infection in IDA patients may have contributed to the greater decrease in inflammatory parameters and the more substantial rise in TIBC. These findings are in line with the possible role of hepcidin in the inflammatory response.[20,33]

Limitations

This study, despite providing useful insights into iron metabolism post-infection, is limited by its small sample size, which reduces the statistical strength and generalizability of the findings. Conducted at a single center, the results may not apply to broader populations, particularly given variations in healthcare and nutrition across regions. The study's reliance on only CRP and leukocyte levels as inflammatory markers, without considering key regulators like hepcidin or IL-6, limits the understanding of the mechanisms at play. Additionally, the lack of long-term follow-up restricts conclusions about recovery, and potential confounders such as diet or socioeconomic status were not accounted for. Finally, the type of infection was not stratified, though different pathogens may influence iron regulation in distinct ways.

CONCLUSION

This study underscores the complex interplay between iron metabolism and inflammation in pediatric infections, with notable shifts in iron parameters post-recovery. A significant reduction in both iron deficiency and IDA was observed after the infection, highlighting the body's capacity to restore iron balance once inflammation subsides. The marked improvements in hemoglobin, serum iron, and transferrin saturation, especially in IDA patients, emphasize the importance of addressing iron deficiency during recovery. These findings suggest that monitoring and managing iron levels post-infection is crucial to optimize recovery and prevent long-term iron depletion in children prone to infections.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was produced in the thesis study conducted in 2006.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Is the peripapillary area completely healthy in Stargardt disease?

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ABSTRACT

Aims: To evaluate the peripapillary retinal nerve fiber layer (pRNFL) thickness measured using spectral domain optical coherence tomography (SD-OCT) in patients with Stargardt disease (STGD).

Methods: This was a single-center, cross-sectional case-control study. Twenty eyes with STGD were staged according to Fishman STGD classification. Peripapillary RNFL thickness was measured using Heidelberg Spectralis SD-OCT. The mean pRNFL thickness of the four quadrants (temporal, superior, nasal, and inferior) and all quadrants were compared with the mean pRNFL thickness from 20 eyes of age-matched healthy subjects.

Results: The mean age of Stargardt patients was 40.9 years (range, 18–59 years) and that of the control group was 40.6 years (range, 19–59 years). Twenty eyes (70%) had thinner pRNFL thickness in the temporal quadrant (mean: -7.55 µm, 95%CI -3 to -12 µm, 10% thinner than the control group), whereas in the nasal quadrant, 13 of 20 eyes (65%) had thicker pRNFL (mean: 6.85 µm, 95% CI, 1–13 µm; 9% thicker compared to the control group). There was no statistically significant difference in the thickness of the superior and inferior quadrants and the global pRNFL compared to the control group.

Conclusion: STGD is considered pathognomonic for the preservation of the peripapillary retina and retinal pigment epithelium (RPE), and is mainly characterized by RPE and photoreceptor cell loss in the macula. STGD was associated with thinning of the temporal quadrant, corresponding to the macular area in the pRNFL analysis. It is not yet known whether the RNFL loss is due to transneuronal degeneration or direct damage to ganglion cells resulting from degeneration of the outer retinal layers.

Keywords: ABCA4, retinal nerve fiber layer, spectral-domain optical coherence tomography, Stargardt disease, transneuronal degeneration

INTRODUCTION

Stargardt disease (STGD) is the most common inherited macular dystrophy, with a prevalence of approximately 1 in 10,000.[1] In most patients, the inheritance pattern is autosomal recessive (AR), with the most commonly reported mutation occurring in the ABCA4 gene located on the short arm of chromosome 1 (1p22.1).[2] The ABCA4 gene encodes a transmembrane protein, a retina-specific adenosine triphosphate (ATP)-binding cassette transporter, which is localized to the rims of disc membranes in the outer segments of rod and cone photoreceptor cells and plays a critical role in retinoid recycling within the visual cycle. It functions as a retinoid translocase responsible for the active transport of N-retinylidene-phosphatidylethanolamine in the retinoid cycle, which facilitates the reduction of all-trans-retinal to all-trans-retinol by retinol dehydrogenase, thereby preventing side reactions that lead to the formation of toxic bisretinoid compounds.[1,3] The loss of functional activity of the transporter leads to the accumulation of the retinoid intermediate N-retinylidene-phosphatidylethanolamine in the photoreceptor disc membranes, where it reacts with all-trans-retinal to form phosphatidyl-pyridinium bisretinoid A2PE, the precursor of A2E, which abnormally accumulates in the retinal pigment epithelium (RPE).[2,3] The accumulation of A2E, a major component of lipofuscin, in the RPE is toxic and leads to RPE dysfunction through complement activation, which subsequently causes photoreceptor degeneration.[3,4]

In STGD, while the age of onset and progression varies among individuals, most patients typically experience significant bilateral loss of visual acuity, central scotoma, delayed dark adaptation, abnormal color vision during the early part of the first or second decade of life, and progressive central vision loss throughout their lives.[1,4] Yellow-white flecks within the RPE around the macula and mid-peripheral retina, along with macular degeneration showing a beaten-bronze or bull's-eye appearance due to progressive RPE atrophy, are characteristic of STGD. The end-stage fundus appearance is characterized by extensive RPE and choriocapillaris atrophy, with resorbed flecks and sparse pigmentation.[5] Peripapillary retina and RPE sparing is a diagnostic feature of STGD, even in advanced stages.[6]

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Peripapillary retina sparing (absence of flecks around the optic disc) is a well-known characteristic of STGD. However, Newman et al.[7] reported that significant defects in the peripapillary retinal nerve fiber layer (RNFL) are observed during fundus examinations of hereditary retinal dystrophy patients including STGD, which primarily affect photoreceptors and/or the RPE. Accurate detection of wedge-shaped RNFL defects on fundus examination is challenging in the presence of widespread RPE atrophy. With the clinical use of spectral-domain optical coherence tomography (SD-OCT), it is possible to evaluate the structural integrity of the RNFL, RPE, and photoreceptor layer in vivo. Recent studies have reported peripapillary retinal nerve fiber layer (pRNFL) loss measured by SD-OCT in hereditary retinal dystrophies, including X-linked juvenile retinoschisis, as well as autosomal recessive cone-rod dystrophy and autosomal recessive retinitis pigmentosa, both associated with ABCA4 gene mutations.[8-10]

The aim of this study is to evaluate pRNFL thickness in Stargardt disease using SD-OCT and to analyze its consistency with previously reported pRNFL defects in Stargardt patients.

METHODS

Between 2014 and 2022, 20 eyes from 10 patients diagnosed with STGD at our clinic, either through referral or during their initial examination, were included in this single-center, cross-sectional, case-control study along with 20 eyes from 10 age-matched healthy individuals. The study was conducted with the permission of the Ethics Committee of Health Sciences University, Dışkapı Yıldırım Beyazıt Training and Researches Hospital (Date: 22.06.2020, Decision No: 90/14). The study was performed in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants. The stage of disease was graded according to the Fishman STGD classification.[11] Stage (S) 1 is characterized by macular pigmentary changes (ranging from faint/irregular pigment mottling to beaten-bronze appearance to atrophy) and irregular pigmented lesions (flecks) within one disc diameter of the fovea. These yellowish pigmented lesions can merge to form pisiform (fishtail-shaped), reticular, or branching structure. S2 is defined by yellow-white flecks that extend beyond the vascular arcades temporally and often extend nasally to the optic disc but are always confined posterior to the equator. S3 is identified by the resorption of previously observed flecks, resulting in focal atrophy of the choriocapillaris and RPE in the macula. Lastly, in S4, diffusely resorbed flecks and extensive atrophy of the choriocapillaris and RPE are observed throughout the fundus. None of the patients had evidence of acquired or hereditary systemic disease in their medical records or ophthalmological examinations. To quantify RNFL changes independent of potentially concurrent ocular diseases, patients with a history of glaucoma, increased intraocular pressure (IOP) ≥21 mmHg, optic neuropathy, congenital optic nerve anomalies, uveitis, any retinal diseases other than STGD, or a history of intraocular surgery (except for uncomplicated cataract extraction) were excluded from the study. Patients with a refractive error exceeding ±5 diopters (D) sphere or ±2 D cylinder, as well as eyes with poor OCT image quality, were also excluded.

All patients underwent a complete ocular examination, including best-corrected visual acuity (BCVA) measurement using a Snellen chart (converted to logMAR during data analysis), intraocular pressure (IOP) measurement with Goldmann applanation tonometry, slit-lamp biomicroscopy, and dilated fundus examination using a 90 D lens. Additionally, color fundus photography, fundus autofluorescence (FAF) imaging, fundus fluorescein angiography (FFA), and macular SD-OCT (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany) were performed.

The Spectralis SD-OCT has an axial resolution of 3.9 micrometers (μm) and scans 40,000 A-scans per second. For pRNFL measurements, an RNFL examination protocol was used for scan acquisition. The software automatically measures the RNFL by detecting Bruch's membrane opening (BMO) to determine the optic disc (OD) center and creates a calculation circle with a diameter of 3.45 mm around the OD center, following pupil dilation with 1% cycloplegia.[12] Various studies highlight the importance of fovea-disc (FoDi) alignment in pRNFL thickness measurements.[13] Measurements based on the axis between the fovea and the center of the optic disc, as determined by the BMO, provide more accurate assessments of optic nerve head and pRNFL thickness.[14] In this study, detection of the fovea using SD-OCT and performing measurements based on the anatomical axis connecting the fovea to the optic disc center were emphasized. Patients who did not meet these criteria were excluded. The RNFL thickness for each 90° quadrant (temporal, superior, nasal, and inferior) and the average thickness of all quadrants (global) were recorded in micrometers (μm) for both the case and the control groups. Then, the data were analyzed by matching individuals based on age.

The pRNFL thickness was measured at least three times in each eye on the same day and data were used only if measurements were reproducible in at least two-thirds of the acquisitions. For patients with inconsistencies in all three initial measurements, the scan was repeated three additional times, and their data were included in the study if at least two-thirds of the new measurements were consistent. Since only eyes with high-quality imaging were included in the study, there were no segmentation errors, and no manual corrections needed to be made.

Statistical Analysis

All statistical analyses were performed using SPSS software. For descriptive data analysis, the mean, standard deviation (SD), and 95% confidence interval (95%CI) were calculated. Spearman's correlation coefficient (rho) was used to analyze the correlation between the stage of the disease and disease duration (the time from the diagnosis of STGD to the age at which the patient was included in the study).

RESULTS

A total of 20 eyes from 10 STGD patients (6 females and 4 males) with an average age of 40.9 years (range, 18–59 years) were analyzed. The control group included 20 eyes from 10 healthy individuals (6 females and 4 males), with an average age of 40.6 years (range, 19–59 years). Among these patients, the earliest age of initial diagnosis was 14 years, the latest was 47 years, and the average age of initial diagnosis was 30 years. Table 1 presents detailed information about the patients with STGD. The IOP for all patients at the time of the study was between 12-20 mmHg (mean 16.1 mmHg). In the control group, the IOP ranged from 10 to 18 mmHg (mean 15.9 mmHg). According to the Fishman STGD classification, 10

eyes from five patients were classified as S1, eight eyes from four patients as S2, and two eyes from one patient as S3. Figure 1 shows multimodal imaging of a Stargardt patient classified as S2. None of the patients were classified as S4 in the study. Disease stage and duration were also correlated. (rho= 0.66, p=0.037) Figure 2 shows an example of pRNFL thickness analysis for the right eye of a STGD patient included in the study.

Table 1. Clinical data of the STGD patients in the study group

Patient no	Age (years)	Onset (years)	Gender	BCVA OD logMAR	BCVA OS logMAR	Fishman STGD classification
1	18	14	M	0,5	1	1
2	34	31	F	0,5	0,5	1
3	42	32	F	1.1	1	1
4	52	47	F	0,7	1	1
5	59	45	M	1	1	1
6	25	20	M	0,4	0,5	2
7	30	18	F	1	1	2
8	43	23	F	0,7	1,1	2
9	51	34	F	0,7	0,7	2
10	55	36	M	0,9	1	3

STGD: Stargardt disease, F/M: Female/male, BCVA: Best-corrected visual acuity, OD/OS: Right eye/left eye

The pRNFL thickness of each patient was compared to an age-matched healthy individual. Differences in pRNFL thickness for each quadrant are shown in Figure 3. In the temporal quadrant, 14 of 20 eyes showed thinner pRNFL (T: mean −7.55 µm, 95% CI −3 to −12 µm, 10% thinner compared to the control group), while in the nasal quadrant, pRNFL was thicker in 13 of 20 eyes (N: mean 6.85 µm, 95% CI 1–13 µm, 9% thicker than the control group). There were no statistically significant differences in global pRNFL thickness (G: mean −0.75 µm, 95% CI −6 to 5 µm), superior quadrant thickness (S: mean 3.65 µm, 95% CI −8 to 15 µm) or inferior quadrant thickness (I: mean −6 µm, 95% CI −16 to 4 µm) when compared with the control group.

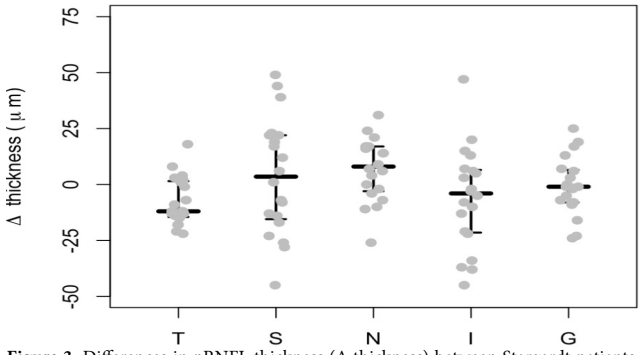

Figure 3. Differences in pRNFL thickness (Δ thickness) between Stargardt patients and the control group are shown for each quadrant (temporal, superior, nasal, and inferior) and the global (the average thickness of all quadrants). Each patient was compared with an age-matched healthy individual.

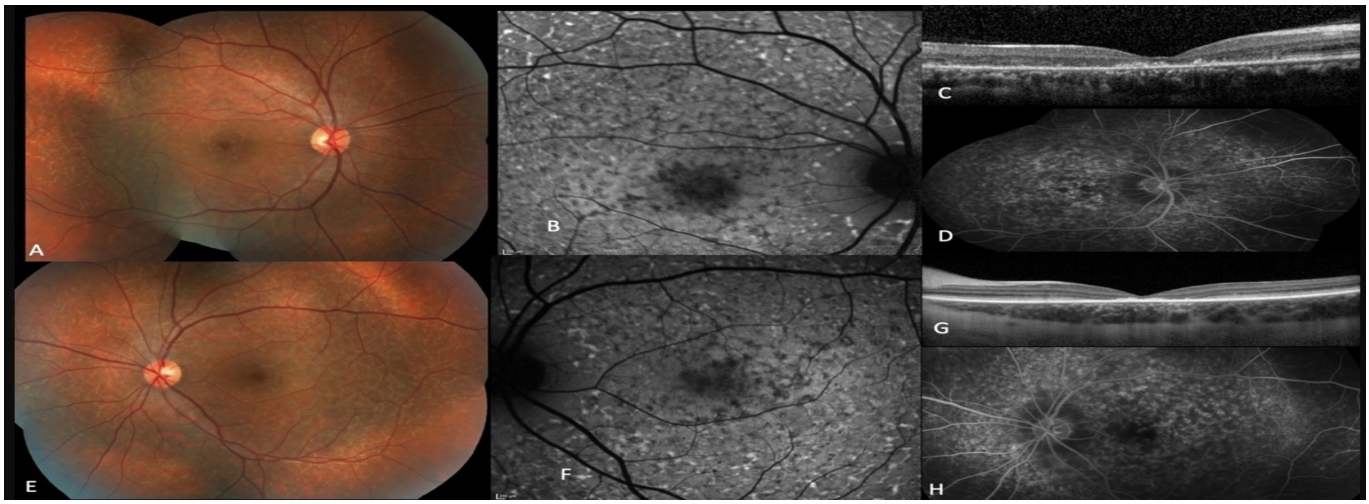

Figure 1. Multimodal imaging of a Stargardt patient classified as E2
Color fundus photographs of the right and left eyes reveal widespread yellow flecks extending beyond the vascular arcades temporally and nasally towards the optic disc, along with irregular pigment epithelial changes in the macula (A, E). In the FAF images, while the peripapillary area is spared bilaterally, flecks scattered across the posterior pole show hyperautofluorescence, whereas areas with localized RPE atrophy appear hypoautofluorescent (B, F). Horizontal line scans from SD-OCT of both eyes show lipofuscin accumulation in the RPE and disorganization in the photoreceptor layer (C, G). FFA demonstrates choroidal hypofluorescence due to lipofuscin accumulation in the RPE, along with a 'dark choroid' that allows better visualization of the retinal circulation and highlights hyperfluorescent flecks in both eyes (D, H).

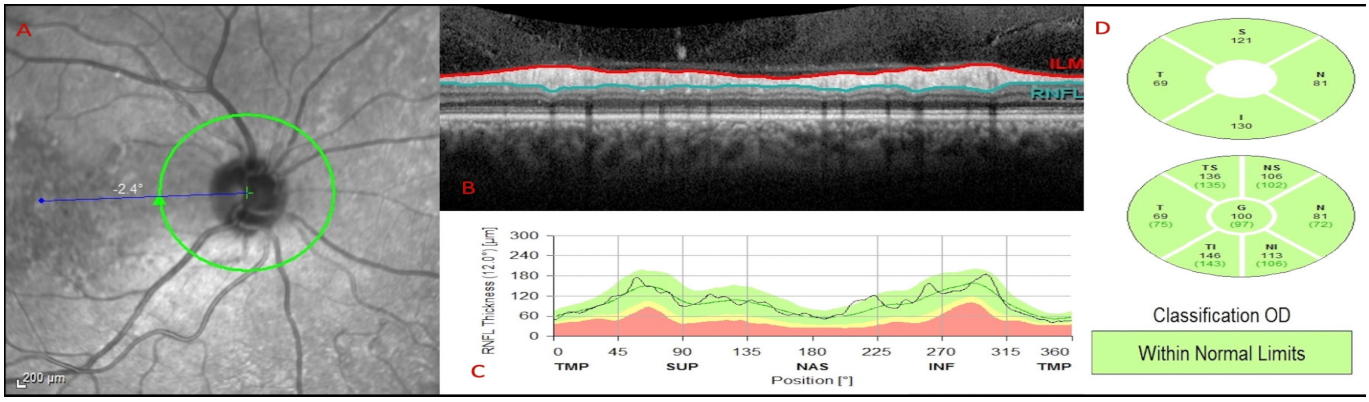

Figure 2. Measurement of pRNFL thickness using OCT in a Stargardt patient
A) Infrared fundus image showing the calculation circle with a diameter of 3.45 mm around the optic disc center (green circle) and the anatomical axis connecting the fovea to the optic disc center (blue line). The FoDi angle is observed as -2.4. B) Circumferential OCT scan of the peripapillary retina along the calculation circle shows no segmentation errors. C) The quantification of RNFL thickness, plotted against the position along the peripapillary OCT scan (in degrees) is presented. D) The quantification of pRNFL thickness by quadrant and clock-hour sectors is shown in the pie chart with black numbers.

Table 2. Peripapillary RNFL thickness in Stargardt patients and the control group

	All Eyes n=20 (mean±SD)		Stage 1 n=10 (mean±SD)		Stage 2 n=8 (mean±SD)		Stage 3 n=2 (mean±SD)	
	Patient Group	Control Group	Patient Group	Control Group	Patient Group	Control Group	Patient Group	Control Group
Temporal, µm	67,6±9	75,2±5	64,5±9	76,7±6	67,6±7	74,5±4	83,5±5	70,5±2
Superior, µm	132,4±23	128,8±12	122,7±14	131,2±16	136,1±26	124±6	166±6	135,5±6
Nasal, µm	79,6±10	72,7±9	77,6±9	71,6±11	79,1±9	70,8±4	91,5±15	86±7
Inferior, µm	121,4±17	127,6±15	115,9±15	131,8±19	119,8±11	123,6±11	155,5±13	122±6
Global, µm	100,2±11	101±8	95,2±3	102,8±10	100,6±12	98,2±4	124±4	103±1

n: Number of eyes in the patient group, SD: Standard deviation, RNFL: Retinal nerve fiber layer

The mean pRNFL thickness of each quadrant and the global for both STGD patients at different stages and the control group, is listed in Table 2. Figure 4 illustrates the distribution of pRNFL thickness between the STGD and control groups.

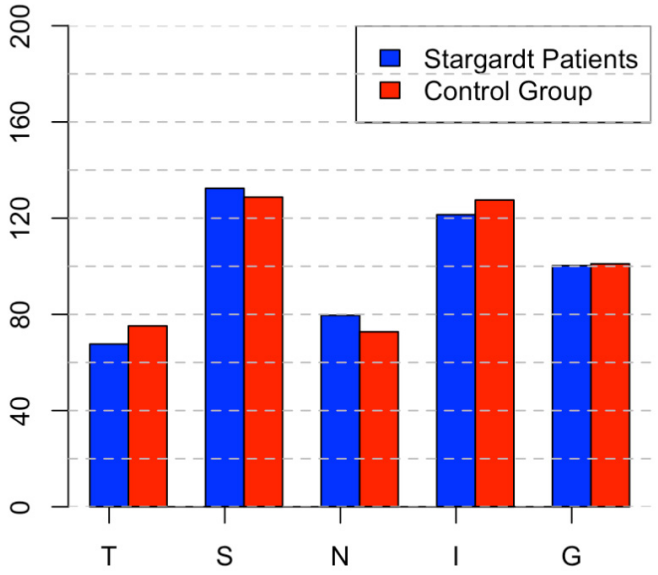

Figure 4. Distribution of pRNFL thickness (in micrometers) between Stargardt patients and the control group

DISCUSSION

Axonal loss in the peripapillary RNFL can be observed in progressive neurodegenerative optic neuropathies such as glaucoma, which is characterized by damage to retinal ganglion cells (RGCs) and their axons. It can also occur in ischemic, inflammatory, and compressive optic neuropathies.[15-17] While pRNFL thickness analysis is important for diagnosing and monitoring the progression of these pathologies, studies have also reported that axonal damage in the RNFL can occur in macular diseases that accompany optic nerve pathologies, potentially affecting pRNFL analysis. Law et al.[18] reported that advanced stages of age-related macular degeneration (AMD) are associated with thinner peripapillary RSLT, and that defects, particularly in the inferior quadrant, complicate glaucoma evaluation. In another study that included 76 eyes with dry AMD, the thickness of the macular ganglion cell-inner plexiform layer and pRNFL was thinner compared to 76 healthy eyes, with the most prominent difference observed in the temporal quadrant of the pRNFL. This preferential thinning of the papillomacular fiber bundle is explained by the fact that the axons of RGCs within the macular region are assumed to be located mainly in the temporal sectors of the optic nerve head, and the temporal pRNFL is less susceptible to glaucomatous damage than the superior and inferior quadrants. Although the outer retinal layers are primarily affected in AMD, it has been suggested that inner retinal neurons may be affected secondarily due to photoreceptor degeneration.[19] Additionally, in rat models of retinal degeneration, histochemical changes in both the inner plexiform layer and the RGC layer have been attributed to photoreceptor cell damage.[20] To quantify pRNFL changes resulting from macular diseases independently of potentially coexisting optic nerve pathologies, it is reasonable to focus on hereditary macular dystrophies, which are typically seen in younger individuals.Pasadhika et al.[9] reported that in a study of 11 patients with cone-rod dystrophy, thinning of the pRNFL was observed in 8 patients, most prominently in the temporal quadrant. They suggested that, the inner retinal layers can also be affected in degenerative retinal diseases that primarily affect the outer retinal layers. Their study proposed that this might result from either transsynaptic degeneration or, as yet unidentified mechanisms by which photoreceptor cell degeneration directly affects the inner retinal layers.[9] In retinitis pigmentosa (RP), characterized by progressive degeneration of photoreceptor cells and the RPE, it has been proposed that damage to the outer retinal layers leads to transneuronal changes resulting in RGC loss.[7] Stone et al.[21] have shown a relationship between the loss of photoreceptor cells and transneuronal ganglion cell death. Another study performed on the retinas of human retinitis pigmentosa donors with intermediate and advanced stages of RP showed a loss of the inner nuclear layer and retinal ganglion cell layer, as well as a reduction in the number of RGCs.[22]Reports in the literature indicate that hereditary retinal dystrophies, including Stargardt disease, are primarily characterized by photoreceptor and/or RPE dysfunction, thinning of the inner retinal layers, and defects in the pRNFL.[7,23] However, pRNFL thickness analysis specifically in STGD has been reported in only two studies to date. Genead et al.[24] reported that, among 27 patients with STGD, thinning of the pRNFL was observed in one or more quadrants in 24 eyes (46.2%) from 14 patients (51.9%). The distribution of abnormal thinning was noted as follows: 33.3% in the superior quadrant, 33.3% in the inferior quadrant, 16.7% in the nasal quadrant, and 16.7% in the temporal quadrant.[24] This distribution is noteworthy considering that STGD primarily affects the macula with the papillomacular bundle corresponding to the temporal quadrant, especially when compared to studies related to hereditary retinal dystrophies mentioned above. Reich et al.[25] reported that in their study of 20 Stargardt patients (39 eyes), thinning of the pRNFL in the temporal quadrant was detected in 36 of 39 eyes, with the mean pRNFL thickness in the temporal quadrant being 16% thinner than the control group. This study highlighted the importance of manually correcting the fovea-optic disc (FoDi) angle when evaluating pRNFL thickness using OCT. In cases where automatic software detection of the fovea failed due to macular

atrophy, Reich et al.[25] manually corrected the fovea-optic disc (FoDi) axis in 11 patients (15 eyes) and presented the results before correction. Before correcting the FoDi axis, thinning of the pRNFL was detected in one or more quadrants in 17 eyes (43.6%) of 11 patients (55%), with thinning observed in 54% of the inferior quadrant, 33.5% of the temporal quadrant, and 12.5% of the superior quadrant. This distribution was consistent with the findings reported by Genead et al.[24] Since Genead et al. did not describe corrections for misalignments in RNFL measurements relative to the fovea, Reich et al. suggested that the observed thinning in the inferior quadrant might be due to errors in fovea detection, emphasizing the importance of the FoDi angle in improving the reliability of pRNFL thickness analysis. In previous studies, mean FoDi angle values range between -5.6° and -7.7° and the FoDi distribution is between -17° (the fovea is 17° below the disc) and +7° (the fovea is 7° above the disc).[15] To remain consistent with the literature, our study ensured that measurements adhered to these FoDi angle values. Patients in whom the fovea was not correctly detected or whose measurements were not aligned with the anatomical axis connecting the fovea and the optic disc center were excluded from the analysis. In 70% of the eyes, thinning of the pRNFL was observed in the temporal quadrant, which was 10% thinner than that in the control group, supporting the findings of Reich et al.Since the correct alignment of the FoDi axis has no influence on the global RNFL, no significant differences were observed in our study, similar to the results reported in Reich et al.[25] and Genead et al.[24]

Primary neuronal injury affects distal neurons, a process known as transsynaptic or transneuronal degeneration, which can be divided into anterograde and retrograde based on the site of origin and direction of spread.[26] Reich et al.[25] proposed that RGC loss resulting from photoreceptor cell damage may be due to anterograde transsynaptic axonal degeneration. This degeneration is described as 'dying-forward,' where the postsynaptic neuron is affected by damage to the presynaptic neuron. This process is believed to be caused by defective afferent innervation, reduced transmission of growth and survival factors from the supplying cell.[25,27] Furthermore, it has been reported that in glaucoma, damage starting in the RGCs initiates a transneuronal degeneration chain, which affects both the outer retinal layers and the visual cortex.[26,28]Although the confidence interval is wider compared to the results of Reich et al.[25] we also detected increased RNFL thickness in the nasal quadrant, where the photoreceptor cells are still functional. Given that STGD primarily affects the macula, but in advanced stages, RPE and photoreceptor loss extend beyond the macula toward the nasal side of the optic disc, thinning of the pRNFL in the temporal quadrant is expected, whereas the nasal quadrant might not show RSLT loss. RPE plays a key role in RGC neurogenesis through the Wnt and Numb/Notch signaling pathways. Therefore, it is possible that impaired signaling early in development due to dysfunctional RPE may lead to a prolonged period of ganglion cell neurogenesis, potentially resulting in increased RNFL thickness.[29] In Stargardt disease, where sparing of the peripapillary retina and RPE is considered pathognomonic, recent studies have shown that flecks and RPE atrophy can also be observed in the peripapillary retina.[30,31] These findings were not detected in the imaging of our patient group.Although our study included a sex- and age-matched control group, one of its limitations is the relatively small number of patients. In advanced stages of STGD, further RNFL loss is expected as atrophy extends beyond the macula.

Limitations

Among the patients, only one was classified as S3 according to the Fishman classification, and no patient was classified as S4. As a result, the extent of pRNFL loss in advanced stages and the correlation between the stage and the extent of pRNFL loss could not be investigated. In addition, our study lacked longitudinal follow-up data. Given these limitations, further multicenter studies with larger patient cohorts, including those in advanced stages and with long-term follow-up are needed for comprehensive analysis of pRNFL in STGD.

CONCLUSION

STGD, characterized by RPE atrophy and photoreceptor cell loss in the macula, shows thinning in the temporal quadrant of the pRNFL, corresponding to the papillomacular nerve fiber bundle, which consists of axons of the RGCs from the fovea and nasal macula. It is not yet clear whether the loss of RNFL is due to transneuronal degeneration or an as-yet-undefined mechanism where the degeneration of outer retinal layers directly affects the inner retinal layers, potentially involving retinal remodeling.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Ethics Committee of Health Sciences University, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 22.06.2020, Decision No: 90/14).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Evaluation of the relationship between gastroesophageal reflux disease and glycogenic acanthosis

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ABSTRACT

Aims: This study aims to evaluate the possible etiologic factors, espacially gastroesophageal reflux disease (GERD), in the presence of glycogenic acanthosis (GA).

Methods: A total of 387 patients who underwent upper gastrointestinal endoscopy between November 2023 and April 2024 were enrolled for the study. Participants were divided into two groups on the basis of the presence of GA. Groups were compared in terms of factors such as age, smoking, GERD, hiatal hernia, and *Helicobacter pylori*.

Results: Group comparasion revealed no significant difference except the presence of hiatus hernia, and GERD which was observed higher in the GA (+) group (p<0.001, for both parameters). In terms of the identification of the predictors of GA positivity, univariate and multiple variate analysis were performed. Only GERD (OR: 7.628, 95% CI: 3.202-18.169, p<0.001) and hiatus hernia (OR: 3.449, 95% CI: 1.387-8.579, p=0.008) were demonstrated as independent predictors of GA positivity in the multiple variate analysis.

Conclusion: In this study, we demonstrated that GA may be associated with GERD and hiatal hernia.

Keywords: Gastroesophageal reflux disease, glycogenic acanthosis, hiatal hernia

INTRODUCTION

Glycogenic acanthosis (GA) of the esophagus is a frequent incidental endoscopic observation characterized by a plaque-like appearance resulting from the accumulation of glycogen deposits in squamous epithelial cells over time.[1-3] Despite its benign nature, clinical significance and etiology of GA remains unclear.[4]

Gastroesophageal reflux disease (GERD) is a disorder which is common in the society and can occur in all age groups, characterized by regurgitation of gastric acid content into the esophagus, thay may progress with symptoms such as burning sensation and pain behind the chest, and reduces the quality of life to a certain extent.[5,6] GERD can be associated with esophagitis and hiatus hernia.[7,8] Previous studies suggest a pathophysiological link between GA and gastro-esophageal reflux.[9,10] However, there is limited consensus regarding their predictive value for GA positivity. In addition, the majority of existing studies are not up-to-date and vary in design, and limited factors that may be associated with GA have been evaluated. Therefore, the data in the literature on GA is insufficient and further studies are warranted in this field.

In the presented prospective observational study, we aimed to assess the association between the presence of GA, and GERD, and related conditions such as esophagitis and hiatus hernia.

METHODS

Ethics

This prospective observational study was conducted at Yenimahalle Training and Research Hospital and approved by Scientific Researches Assessment and Ethics Committee of the same medical institution (Date: 08.11.2023, Decision No: E-2023-59). A written informed consent was obtained from the participants for study inclusion. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

All consecutive eligible patients who applied to outpatient gastroenterology clinic of Yenimahalle Training and Research Hospital with dyspeptic complaints and underwent upper gastrointestinal endoscopy between November 2023 and April 2024 were involved in the study, prospectively. Subjects under 18 years of age, having previous history of gastrointestinal surgery, pregnancy, chronic diseases, anti-acid medication use, unwilling to participate in the study, suboptimal endoscopic evaluation due to patient intolerance or device-related problems, emergency endoscopy and candida esophagitis were excluded from the present research. Study participants were categorized into two separate groups and analyzed accordingly:

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those with glycogenic acanthosis (GA+ group) and those without (GA- group).

Data Collection and Definitions

Demographic data including age, sex, smoking status, history of chronic diseases and surgery, body-mass index (BMI) were collected prospectively. The GERD diagnosis was made by Gastro-esophageal Reflux Questionnaire, by evaluating the clinical reflux findings. Esophageal pH monitoring or impedance testing cannot be performed due to their unavailability. Data regarding the presence of glycogenic achantosis, hiatus hernia and esophagitis on endoscopic evaluation along with the presence of *Helicobacter pylori* (HP) on pathological examination were collected prospectively.

Detection and identification of GA was based on gastroscopic examination findings. On gastroscopy, glycogenic acanthosis manifests as multiple slightly elevated whitish plaques that are usually less than 1cm in diameter. Within the scope of the study, lesions conforming to this description have been regarded as glycogenic acanthosis, and histological confirmation has not been deemed necessary.

Esophagitis was defined as mucosal damage observed on gastro-esophageal junction during upper gastrointestinal endoscopy. Hiatal hernia was defined as the measurement of the distance greater than 3 cm between the gastroesophageal junction and the diaphragmatic hiatus during endoscopy. Diagnosis of HP infection of the gastric mucosa was performed via pathological examination.

Statistical Analysis

The normality distribution of continuous variables was analyzed by using the Kolmogorov-Smirnov test. As all continuous variables were distributed non-normally, they were given as median (interquartile range) and Mann-Whitney U test was performed for the comparison. categorical parameters were presented as frequencies (percentages) and Chi-square method was performed for analysis. Univariate binary logistic regression analyses were carried out for variables that may predict GA. After, multiple variate binary logistic regression analyses were conducted for variables that had a p-value ≤0,1 in univariate analyses. The results were presented as Odds ratio (OR), 95% confidence interval (CI), and p-value. A p-value <0,05 was considered statistically significant. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for analyses.

RESULTS

Baseline demographic data and clinical properties of the participants are presented in Table 1. The study groups does not revelaed any differences, between the GA (-) and GA (+) groups, in terms of age (median [IQR]: 58 [46.5-68.0] vs. 59.5 [53.0-66.3], p=0.341), gender distribution (female, n [%]: 178 [66.2] vs. 86 [72.9], p=0.192), smoking status (n [%]: 15 [5.6] vs. 6 [5.1], p=0.844), or BMI (median [IQR]: 25.4 [24.0-27.5] vs. 25.1 [23.9-26.7], p=0.059). Yet, significant differences were noted in the prevalence of GERD, esophagitis, and hiatus hernia (all p<0.001). Specifically, the GA (+) group showed a higher prevalence of GERD (37.3% vs. 7.1%), esophagitis (17.8% vs. 4.1%), and hiatus hernia (20.3% vs. 3.3%) compared to the GA (-) group. Detection of HP infection was observed in 129 (48.0%) and 59 (50.0%) patients in GA (-) and GA (+), respectively (p=0.711).

Table 1. Demographic, clinical characteristics and endoscopic findings of the study group

	GA (-) group (n=269)	GA (+) group (n=118)	p value
Age, years, median (IQR)	58 (46.5-68)	59.5 (53-66.25)	0.341
Gender, female, n (%)	178 (66.2)	86 (72.9)	0.192
Smoking, n (%)	15 (5.6)	6 (5.1)	0.844
BMI, kg/m², median (IQR)	25.4 (24-27.45)	25.05 (23.93-26.7)	0.059
GERD, n (%)	19 (7.1)	44 (37.3)	**<0.001**
Esophagitis present, n (%)	11 (4.1)	21 (17.8)	**<0.001**
Hiatus hernia, n (%)	9 (3.3)	24 (20.3)	**<0.001**
HP, n (%)	129 (48)	59 (50)	0.711

Significant p values are bold. GA: Glycogenic acanthosis, BMI: Body-mass index, GERD: Gastroesophageal reflux disease, HP: *Helicobacter pylori*

Table 2 presents the data of univariate and multivariate assessment for the identification of the predictors of GA positivity. In univariate analysis, BMI (OR: 0.886, 95% CI: 0.796-0.987, p=0.028), GERD (OR: 7.824, 95% CI: 4.305-14.217, p<0.001), esophagitis (OR: 5.078, 95% CI: 2.361-10.922, p<0.001), and hiatus hernia (OR: 7.376, 95% CI: 3.309-16.441, p<0.001) were revealed to be statistically significant predictors of GA positivity. However, in the multivariate analysis, only GERD (OR: 7.628, 95% CI: 3.202-18.169, p<0.001) and hiatus hernia (OR: 3.449, 95% CI: 1.387-8.579, p = 0.008) remained as independent predictors of GA positivity.

DISCUSSION

GA is an asymptomatic benign lesion of the esophagus which is often detected incidentally during endoscopic examination.[11-14] Due to its asymptomatic and benign nature, it does not require an enodoscopic follow-up program.[4] In the current literature, a definite etiology of GA has not been identified and there are insufficient studies on this subject. In previous studies, the incidence of GA was observed to increase with older age.[10,15] In the present study, no significant relationship was demonstrated between the presence of GA and age. This difference in these results can be attributed to sample size thus, multicenter studies examining the increase in the incidence of advanced age and GA are required. Smoking was also evaluated in our study and no relationship was observed in terms of GA positivity. In a previous study by Ikeda et al.[16] smoking was found to be predictor of GA presence in male subjects. In our study, smoking was not found to be a predictor of GA positivity. However, we did not evaluate the effect of smoking in gender subgroups, which may explain the different outcomes. Therefore, further studies on gender subgroups are needed to examine the association of cigarette smoking with GA, since the smoking rate is lower in the female gender subgroups. In addition, we evaluated whether HP infection is involved as a risk factor in the presence of GA. However, a significant association of HP infection with an increase in the presence of GA has not been demonstrated. Similarly, a study carried out by Emiroglu et al.[17] in a pediatric patient group showed similar results to our findings, which demonstrated no relationship between HP positivity and GA positivity. Our findings are consistent with the current literature.

Whether reflux disease has an effect on the development of GA has also been the subject of research in previous studies. Data in the literature have revealed that GERD may be involved as

Table 2. Univariate and multiple variate logistic regression analysis of predictors for GA positivity

	Univariate analysis				Multiple variate analysis			
		95% CI				95% CI		
	OR	Lower	Upper	p	OR	Lower	Upper	p
Age	1.013	0.996	1.030	0.135	-	-	-	-
Gender, male	0.728	0.451	1.174	0.193	-	-	-	-
Smoking	0.844	0.343	2.399	0.907	-	-	-	-
BMI	0.886	0.796	0.987	**0.028**	0.908	0.807	1.022	0.111
GERD	7.824	4.305	14.217	**<0.001**	7.628	3.202	18.169	**<0.001**
Esophagitis	5.078	2.361	10.922	**<0.001**	0.509	0.163	1.588	0.245
Hiatus hernia	7.376	3.309	16.441	**<0.001**	3.449	1.387	8.579	**0.008**
HP	1.085	0.704	1.673	0.711	-	-	-	-

Significant p values are bold. GA: Glycogenic acanthosis, CI: Confidence interval, BMI: Body-mass index, GERD: Gastroesophageal reflux disease, HP: *Helicobacter pylori*

a pathophysiologic factor in the process of GA development. In this concept, a researched conducted by Yılmaz et al.[10] GERD was demonstrated to be associated with GA positivity. In addition, in a study carried out by Nazlıgül et al.[15] it was similarly demonstrated that GERD and hiatal hernia were associated with the detection rate of GA. Moreover, the findings of the study by Asaoka[18] revealed a positive correlation between the GERD and GA. Consistent with the literature, our data also demonstrated a association between the GERD and GA. On the basis of these findings, it can be hypothesized that the presence of GA may be a manifestation of GERD. Therefore, clinicians may consider GERD in patients in whom GA is detected during endoscopic examination. However, prospective studies with multicenter and larger numbers of subjects are needed to support this hypothesis in order to reach a more definitive conclusion. In addition, studies examining the effect of GERD treatment on the course of GA are also warranted. Lastly, esophagitis was significantly higher in the GA (+) group, but in multivariate analyses, esophagitis could not be shown to be a predictor of GA positivity. Considering that esophagitis is not the only factor determining the severity of GERD in literature, the relationship between GERD severity and the presence of GA cannot be established based on these findings alone.[19,20] Therefore, further studies are needed to examine the relationship between the factors determining the severity of GERD and the presence of GA.

Limitations

The main limitation of our presented study is that the diagnosis of GERD cannot be confirmed by ambulatory 24h esophageal pH monitoring, since their unavailability. In addition, the long-term effects of GERD on GA could not be presented. Moreover, since the study was a single center study, it has a relatively small sample size. Lastly, histological confirmation for the diagnosis of GA could not be provided.

CONCLUSION

In conclusion, the fingings of the present study revealed an association between the presence of GA and GERD, therefore, GA may be a manifestation of GERD. Further studies are warranted on this issue.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Scientific Researches Evaluation and Ethics Committee of Yenimahalle Training and Researches Hospital (Date: 08.11.2023, Decision No: E-2023-59).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Clinical presentation, diagnosis, complications and treatment of obstructive sleep apnea syndrome

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ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by recurrent obstruction of the upper airway during sleep. The most common nocturnal symptom is snoring, and the most common daytime symptom is excessive sleepiness. OSAS causes serious morbidity and mortality due to its cardiovascular, social and neuropsychological consequences. Early diagnosis and treatment are needed at all ages.

Keywords: Sleep, obstructive sleep apnea, diagnosis, treatment

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by recurrent complete or partial upper airway obstruction during sleep and frequently decreased blood oxygen saturation.[1] It is a respiratory-related sleep disorder with a high prevalence and often overlooked. It is characterized by frequent awakenings during the night, hypoxemia, sleep disruption and decreased sleep quality.[2] Apneas are classified into 3 groups according to the presence of respiratory effort: obstructive, central and mixed. Obstructive apnea is the presence of respiratory effort despite the absence of airflow in the mouth and nose; central apnea is the absence of both airflow and respiratory effort; and mixed apnea is the continuation of apnea, which is initially of the central type, despite the onset of respiratory effort.[2,3] In adults, apnea is the complete cessation of airflow in the mouth and nose for at least 10 seconds. Hypopnea is a decrease in airflow of at least 30% for 10 seconds or longer and a 3% decrease in oxygen saturation or arousal.[2-4]

PHYSIOPATHOLOGY IN OSAS

Since 2023, the new scoring rules revised by the American Academy of Sleep Medicine (AASM) have been applied.[5] The most important feature of sleep apnea is the repetitive inhibition of respiration by collapse of the upper airway (URTI) during sleep.[6,7] OSAS is a pathologic condition in which recurrent narrowing or closure of the upper airway during sleep causes complete cessation of airflow (apnea) and/or partial (>50%) reduction of airflow (hypopnea) for at least 10 seconds, leading to a minimum 4% decrease in blood oxygen saturation level (SAO_2).[2,6-8] OSAS was described by Guilleminault et al.[9] in 1976.

In the physiopathology of OSAS, narrowing of the lateral diameter of the upper airway and decrease in muscle activity play an important role. The development of upper airway obstruction depends on three main factors. These are the tone of the pharyngeal muscles, the negative pressure during inspiration and the anatomy of the upper airway.[7] The patency of the upper airway is maintained by the activity of the upper airway dilator muscles against the collapsing effect of the negative intraluminal pressure during inspiration. The pressure reaching the upper airways during breathing is counteracted by the muscles and no collapse of the upper airway occurs. If there is a pathology in the activity of these muscles, apnea develops as a result of collapse.[10,11] Pathologies that narrow the upper airway extending from the tip of the nose and mouth to the trachea (large uvula, tonsillar hypertrophy, retrognathia, hypertrophy of the tongue root, plicae forming stenosis in the pharyngeal mucosa), anteroposteror disharmony cause more negative pressure for inspiration. Thus, obstructive apnea occurs.[11] After deep sleep and a further decrease in muscle tone, the accelerated inspiratory air in the narrowed upper airway creates more negative pressure and suction force on the airway wall. When the suction force exceeds the muscle tone trying to keep the airway open, the airway in that area collapses and apnea develops. In patients with OSAS, negative pressure is countered by the activities of the m.genioglossus and m.tensor

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palatini muscles during wakefulness. In sleep, compensation is lost, and symptoms appear.[11]

In addition, orexin, also known as hypocretin, is a neurotransmitter that maintains alertness and stimulates feeding. Orexin by glucose and leptin. Leptin is an anorexigenic hormone that gives a feeling of fullness in normal people. It has been shown that patients with OSAS have leptin resistance. The inhibitory effect of leptin on orexin and the function of orexin in maintaining wakefulness are thought to play a role in the development of sleep in OSAS.[12]

PHYSICAL EXAMINATION IN PATIENTS WITH OSAS

Detailed physical examination is of great importance in the selection of patients for PSG to identify individuals at risk for OSAS. In determining the severity of OSAS, neck circumference measurement and body-mass index (BMI) calculation, which are highly correlated with apnea hypopnea index (AHI), should be included in routine physical examination.[13] A neck circumference above 43 cm in men and above 40 cm in women constitutes a significant risk for OSAS. In most studies, waist/hip ratio has been shown to be a better predictor in individuals diagnosed with OSAS. Maxiofacial and cephalometric measurements can also be performed.[8]

RADIOLOGY IN PATIENTS WITH OSAS

Radiology is not routinely required in patients with OSAS. In these patients, radiology is used to evaluate and decide on some treatment approaches such as intraoral appliances or skeletal surgery.[9]

RISK FACTORS IN PATIENTS WITH OSAS

Gender

Although male gender is considered to be an important risk factor, recent studies have reported that OSAS can be seen at a high rate especially in premenopausal and obese women and the female/male ratio is approximately 1/3 for each age group. Pharyngeal anatomical structures, fat distribution, craniofacial dimensions and male hormones of men are more prone to obstruction formation.[2,7,14]

Age

It is usually seen in children between 2-6 years of age. It is less common in children who have undergone tonsillectomy. The risk increases between the ages of 10-60 and with increasing age. There is a two-fold increase in incidence every ten years. After the age of 60, the incidence continues to increase but the severity of the clinic decreases.[4,7]

Obesity there is a definite relationship between obesity and apnea formation. Obesity increases the risk of OSAS 10-fold in the middle-aged population.[15] The most commonly used parameter to assess the degree of obesity is body-mass index (BMI). In studies, it is known that high BMI leads to some sleep problems.[2,7,14,16]

Anatomical Risk Factors

Craniofacial anomalies such as retrognathia or micrognathia and nasal septum deviation narrow the upper airway passage and cause sleep apnea. Airway length, neck diameter (>43 cm in men, >38 cm in women, head-neck position, dynamic upper respiratory tract (URT) collapse. Abnormal soft tissue mass in the upper airway due to fat deposition or large tonsils is another cause of obstruction. In addition, sleeping in the supine position may increase the severity of sleep apnea by causing the tongue root to obstruct the URT.[17]

Genetics

OSAS is more common in relatives of patients than in normal people. There are studies showing that it is associated with many congenital diseases (Fragile x, Trisomy 21, Marfan syndrome). Sleep disorders are associated with many genes and show complex inheritance characteristics in which environmental interaction is more frequent. Genetic association is common in obstructive sleep apnea syndrome, narcolepsy and restless legs syndrome.[18]

Alcohol

Decreases pharyngeal dilator muscle activity by suppressing neurological stimulation. Thus, pharyngeal collapse is facilitated. In addition, alcohol increases pharyngeal and nasal resistance with its irritant and vasodilator effect on mucous membranes. This leads to an increase in pleural and pharyngeal negative pressure, again facilitating upper airway collapse. Individuals with apnea should stop drinking alcohol 4-6 hours before going to sleep. It has been reported that the number and frequency of apneas are more severe in the first hour of sleep after alcohol intake.[4,7] While Wisconsin found an independent association between OSAS and smoking, Stardling and Crosby found no association between smoking and OSAS.[4]

Individuals with OSAS should also avoid the use of sedative and hypnotic drugs. Sedatives selectively decrease the activity of the nervus hypoglossus and nervus recurrens. These nerves innervate the genioglossus and posteror cricoarytenoid muscles, muscles that play an important role in maintaining rigidity of the oropharynx and larynx. This facilitates upper airway collapse.[11]

Race

It is more common in Asians and African-Americans.[4]

Neuromuscular and Mechanical Factors

URS dilator muscles, dilator muscle-diaphragm relationship, upper airway reflexes lead to OSAS. Airway diameter and shape, lying position, URI resistance, URI compliance, intraluminal pressure, extraluminal pressure, mucosal adhesive effects and vascular factors play a role.[9]

Central Factors

Hypocapneic threshold, periodic breathing, arousal, cytokines are important.[19]

CLINICAL DIAGNOSIS

The three major symptomatic manifestations of the disease are snoring, diagnosed apnea and excessive daytime sleepiness (Table 1).[3]

Snoring

It is the sound caused by noisy vibration in the oropharynx upper airways during inspiration during sleep. It is one of the most common symptoms in the diagnosis of OSAS and is present in 70-95% of cases.[20] Snoring is prominent in two

Table 1. Daytime and nocturnal findings associated with OSAS

Findings associated with OSAS*	
Day	**Night**
• Witnessed apnea • Snoring • Waking up without rest • Night sweats • Don't be thirsty at night • Nokturi • Insomnia**	• Excessive daytime sleepiness • Traffic, home, work accident • Fatigue • Morning headache • Impaired concentration • Irritability • Mood disorders • Decreased libido • Impotence

*OSAS: Obstructive sleep apnea syndrome, **Inability to stay asleep or wake up and go back to sleep

disease groups such as upper airway resistance syndrome (UARS) and OSAS. Most patients with OSAS snore at least 5 nights a week and sleep are interrupted by frequent recurrent apneas.[21]

Witnessed Apnea

It can often be recognized by a relative or intimate partner.[12] Excessive Daytime Sleepiness (EDS).[15] The American Academy of Sleep Medicine (AASM) defines ODSS as the inability to maintain wakefulness during certain waking periods of the day, with sleep occurring involuntarily or at inappropriate times for at least 3 months.[5] The common daytime symptoms of OSAS are GASD (feeling very sleepy at times or completely) and fatigue (feeling low energy and unmotivated).[15] The pathogenesis of EDS is still controversial. It has been reported that nocturnal hypoxemia and autonomic arousal may play an important role in the development of GAUH. There is evidence that chronic intermittent hypoxia and oxidative stress lead to neuronal brain damage resulting in EDS.[12] Apnea duration, decreases in nocturnal 02 saturation, cardiac autonomic dysregulation, and increased sleep fragmentation level are factors that affect EDS.[12] The prevalence of EDS is around 18%, with 13% in men and 6% in women. EDS has been found to be higher especially in patients with severe OSAS compared to the normal population.[22,23] It has been reported that the AHI index is the strongest predictor of the ELS score.[4,22] However, EDS in OSAS is not always correlated with AHI.[12] EDS is a symptom with low specificity because it can be seen in many acute and chronic diseases other than OSAS. OSAS-related EDS can be improved in more than 90% of patients receiving continuous positive airway pressure (CPAP) therapy.[22]

Several scales and questionnaires have been developed to help select patients for polysomnography (PSG) to predict the diagnosis of OSAS. These include the Epworth Sleepiness Scale (ESS), a subjective test in OSAS, or the Maintenance of Wakefulness test (MWT) and Multiple Sleep Latency Test (MSLT), objective tests. The EDS is the most commonly used scale for the determination of excessive daytime sleepiness.[6] Although the EDS is the most widely used questionnaire, the STOP-BANG questionnaire is the most comprehensive. The STOP-BANG questionnaire is a questionnaire frequently used by anesthesiologists to investigate OSAS in preoperative evaluation.[8] The Berlin sleep questionnaire is a questionnaire designed for community screening of OSAS.[24] In cases where OSAS persists despite CPAP treatment and if OSAS that disappears with CPAP treatment develops again, the adequacy of sleep duration should be ensured. There may be different conditions such as misdiagnosis of OSAS, incorrect CPAP titration, inadequate CPAP compliance, inadequate sleep hygiene, depression, narcolepsy, idiopathic hypersomnia, other sleep disorders, secondary acquisition. Other conditions associated with residual sleepiness despite CPAP therapy include depression, narcolepsy with cataplexy, narcolepsy without cataplexy, idiopathic hypersomnia, behaviorally induced insufficient sleep syndrome, Kleine-Levin syndrome, hypersomnia associated with menstruation, hypersomnia due to drug or substance use, circadian rhythm sleep disorder (shift work disorder, delayed sleep phase disorder, early sleep phase disorder, irregular sleep-wake rhythm.[12]

POLYSOMNOGRAPHY

PSG is the gold standard in the diagnosis of OSAS. PSG is the process of simultaneous and continuous recording of respiratory, cardiovascular, neurophysiologic and other physiologic parameters during sleep, usually throughout the night. With these channels, the presence of apnea, apnea duration, apnea type (obstructive/central) and the stage of sleep are evaluated. It is a very expensive, time-consuming study that requires trained personnel and specialized equipment.[3,6,12] When analyzing the PSG recording, the patient's sleep, respiratory and arousal scoring, leg movements during sleep and other pathologies are scored. In addition to normal parameters, snoring sounds, intrapleural pressure, pulmonary artery pressure, and arterial blood gas values can be measured optionally.[3,4,25] Anterior tibial muscle EMG is important in determining restless leg syndrome by examining periodic leg movements.[7,25] As a result of many developments in recent years, automatic diagnosis of OSAS patients is made using polysomnography data, signal processing and artificial intelligence methods.[3,9]

As a result of polysomnographic study, the value obtained by dividing the sum of the number of apneas and hypopneas in sleep by the duration of sleep in hours is called the apnea hypopnea index AHI. The grading of OSAS is based on the AHI value determined as a result of PSG.[4,7] The AHI value is measured by the number of apnea episodes that occur due to oxygen desaturation in a certain period of sleep. According to this index, AHI<5 is considered as non-OSAS, 5< AHI< mild, 15< AHI <30 moderate, AHI >30 severe OSAS (Table 2).[6-8]

Table 2. Characteristic PSG* findings for OSAS

- Frequent recurrent apneas, hypoppneas and waking reactions
- Increase in superficial sleep duration, decrease in deep sleep and REM** sleep duration
- Frequent recurrent episodes of oxygen desaturation
- Increase in frequency and duration of apneas and degree/duration of oxygen desaturation
- Typically, paradoxical chest and abdominal movements during apnea
- Bradycardia during apnea, tachycardia and arrhythmias afterwards
- Loud and irregular snoring interrupted by frequent recurrent episodes of apnea

*PSG: Polysomnography, **REM: Rapid eye movement, OSAS: Obstructive sleep apnea syndrome

AUXILIARY DIAGNOSTIC METHODS

Although PSG is the gold standard method for the diagnosis of OSAS, auxiliary diagnostic methods are utilized because they are time consuming and expensive.[9,12] These methods include chest radiography, thoracic tomography, magnetic resonance, nasopharyngolaryngoscopy, blood and urine tests, pulmonary function tests and arterial blood gas examinations.[3,4]

TREATMENT

There are various alternatives in treatment. These include weight loss, avoidance of alcohol and sedatives, exercise, changing the lying position, intraoral device (IOD), nasal

positive airway pressure (CPAP-Continuous positive airway pressure) and surgical treatment (Table 3).

Table 3. OSAS treatment

General precautions	
• Treatment for risk factors • Treatment of concomitant diseases* • Warning about traffic and work accidents • Weight loss	• Medical • IOD** • CPAP *** • Surgical • Combination

OSAS: Obstructive sleep apnea syndrome, *Hypotroism, acromegaly,diabetes mellitus, excessive androgen release, respiratory diseases, neurological and cardiovascular diseases, **IOD: Intraoral device, ***CPAP: Continuous positive airway pressure

The gold standard treatment method in OSAS is CPAP application. The aim of CPAP treatment is to achieve an AHI <5 and to eliminate the most common symptoms (snoring, apnea with apnea EDS). It is mainly applied to patients with moderate and severe OSAS with AHI >15. However, CPAP treatment is recommended in patients with mild OSAS with AHI between 5 and 15 who have significant symptoms and/or cardiovascular and cerebrovascular risk factors. The mechanism of action of CPAP, which has been the most important treatment of OSAS for the last 20 years, is the view that it prevents URS collapse like a kind of stent and prevents apneas by maintaining patency.[12,26] This theory was first proposed in 1981 by Sullivan et al.[4] Although some studies have shown that CPAP leads to an increase in lung volume, which increases the stabilizing effect of the upper airway, it has been shown that inflammation and cytokines in OSAS can be reduced by CPAP treatment.[12] In CPAP treatment, EDS may persist despite an AHI <5. The persistence of EDS despite optimal CPAP treatment is called residual sleepiness.[12] Modafinil and armodafinil are effective in the treatment of residual sleepiness in OSAS patients using CPAP. Long-term CPAP therapy significantly reduces diurnal sympathetic tone in OSAS patients. With CPAP treatment, 5% OSAS patients may experience persistent sleepiness.[26] With weight loss, patients with OSAS experience a decrease in AHI and improvement in sleep quality. Prevention of supine sleeping has been shown to improve sleep-disordered breathing in mild position-dependent OSAS patients. There is no specific pharmacologic agent used. Although partial responses have been obtained to the most studied drugs such as proptilin, medroxyprogesterone and acetazolamide, the current accepted opinion is that drugs are ineffective in the treatment of OSAS. OID treatment is generally applied in patients with simple snoring or mild OSAS, in moderate and severe OSAS in whom CPAP cannot be applied, in patients who are candidates for tonsilloctomy, adenoidectomy, tracheostomy but refuse this attempt, in upper URS resistance syndrome, after failed uvulopalatopharyngoplasty (UPPP) operation. Polysomnography should be performed before starting and during the follow-up of OID treatment. OID are known as devices that keep the tongue in front and advance the mandible forward.[11,26]

The surgical method of treatment is UPPP, which includes the elimination of nasal problems, soft palate and tonsils. The success rate of UPPP operation is around 90% for snoring and 50% for apnea. For simple snoring and mild apnea, a method called somnoplasty, which works with radiofrequency waves, is also used.[9]

Regarding driving safety, it has been stated that people without excessive sleepiness and with an AHI of less than 20 per hour are eligible for a commercial license without treatment for OSAS. It has been found that untreated OSAS patients cause 2-7 times more traffic accidents than the normal population. According to the revised Turkish legislation dated 29.12.2015, applicants with a BMI >33 kg/m^2 at the time of driver's license renewal or new application must undergo a full night PSG test regardless of their symptoms. Rigorous assessment of driver's license applicants with a BMI above 33 kg/m^2 can play an important role in improving safety on the road.[27]

COMPLICATIONS

OSAS triggers neurophysiologic reactivations including an increase in systemic inflammatory response, plasma adrenocorticotropic hormone, plasma norepinephrine and a decrease in growth hormone concentrations (Table 4).[28]

Table 4. Complications in OSAS

Cardiovascular system	Systemic hypertension Cardiac arrhythmias Left heart failure Ischemic heart disease Pulmonary hypertension Right heart failure
Pulmonary system	Overlap syndrome Bronchial reactivity
Neurological system	Cerebrovascular disease Excessive daytime sleepiness Morning headache Nocturnal epilepsy Restlessness
Cognitive impairment	Depression Anxiete
Endocrine system	Decreased libido Impotence
Nephrological	Nokturi Nocturnal enuresis
Gastrointestinal system	Gastroesophageal reflux
Hematologic system	Secondary polycythemia
Socioeconomic	Traffic and work accidents Economic losses Decreased quality of life Glaucoma Hearing loss Sudden death

OSAS: Obstructive sleep apnea syndrome

With the increase in negative intrathoracic pressure during OSAS, right ventricular return increases, the right ventricle is distended, the interventricular septum is displaced to the left and left ventricular filling is prevented, thus decreasing the stroke volume. In addition, left ventricular afterload increases with overstimulation of the sympathetic nervous system and cardiac output decreases. The risk of congestive heart failure more than doubles in OSAS. Recurrent hypoxemia during sleep, systemic hypertension and increased sympathetic activity facilitate the development of atherosclerosis.[19] Systemic hypertension is seen in 30-50% of OSAS patients. Pulmonary hypertension may develop as a result of hypoxic pulmonary vasoconstriction and remodeling. The incidence is 20-41.[8]

It has been found that there is a progressive increase in systemic blood pressure during the day and during sleep in patients with OSAS.[14] Sleep apnea and hypopnea episodes cause transient blood pressure changes including an increase of 30 mmHg or more in arterial blood pressure. Changes in renin-angiotensin and vasoactive paptides and insulin resistance syndrome, especially in overweight sleep apnea patients, may also increase the occurrence of hypertension.[29] Patients with a history of coronary angioplasty, coronary artery bypass, cerebrovascular

events or acute coronary syndrome have been found to have a positive association with OSAS.[30]

OSAS is more common in COPD patients with high BMI.[16,31] The association of respiratory system diseases (COPD, asthma, cystic fibrosis and interstitial lung disease) with OSAS is known as overlap syndrome. CPAP therapy controls nocturnal attacks in asthma and reduces bronchial hyperresponsiveness.[32] The presence of inflammatory cytokines in the peripheral circulation of patients with OSAS and the effects of superoxide radicals activate immune and inflammatory pathways, leading to asthma and COPD.[8,21]

Tissue hypoxia and associated oxidative stress and inflammation products that occur during OSAS lead to endothelial damage and metabolic irregularities.[33] Studies have found a relationship between OSAS and snoring and DM (diabetes mellitus). Sleep quality is impaired in most patients with type 2 DM. This is usually related to DM type 2 and cardiovascular diseases.[34]

As a result of tissue hypoxia, cerebral blood flow changes and stress mechanisms are stimulated. Neurohumoral and autonomic activation leads to disturbances in glucose metabolism and the release of proinflammatory cytokines such as TNF-alpha, IL-1 and IL-6. Insulin resistance is around 20% in OSAS. The metabolic disorder is expected to improve 3 months after the start of CPAP use.

Sleep interruptions have been shown to increase blood cortisol levels. Growth hormone, which is normally released in slow wave sleep, is suppressed in OSAS patients due to a decrease in deep sleep. Due to less and inefficient sleep, leptin level decreases, ghrelin level and appetite increase and obesity increases. A strong association has been found between OSAS and some psychiatric disorders such as post-traumatic stress disorder, anxiety, anxyiete and depression. OSAS impairs cognitive stages such as memory, thinking and perception.[15,35] Accelerated tumor angiogenesis and high oxidative stress observed in nocturnal hypoxia have been reported to promote possible tumor formation by damaging DNA and RNA, and severe OSAS has been reported to cause an increase in cancer-related mortality.[8]

Decreased REM sleep duration was found to be statistically significant in patients with severe OSAS.[7] It was found that the percentage of sleep efficiency and the percentage of REM sleep decreased and sleep duration increased in these patients. Periodic leg movements (PBMs) are involuntary, repetitive, sterotypic, short-term, segmental and often affecting the lower extremities during sleep. High AHI values are associated with PBD.[7,12] Lying in supine position during rapid eye movement (REM) and non-REM sleep causes sleep-disordered breathing in most cases. In OSAS, changing from a ninety-degree sitting to a lying position narrows the pharyngeal opening in both apneic and normal individuals due to the effect of gravity. A decrease of at least 50% in AHI occurs in the transition from supine to lateral position.[25] The currently accepted view is that patients should be advised to lie in the lateral position and no additional measures should be taken. Placing a tennis ball, backpack or sandbag on the patient's back so that the patient is uncomfortable when turning over is no longer on the agenda.[11]

Since erythropoietin does not decrease during sleep in OSAS patients, secondary polycythemia is seen in 10%.[36]

In OSAS patients, atrial natriuretic paptide (ANP) release increases due to stretching of the right atrial wall caused by fluctuations in intrapleural negative pressure. ANP increases urinary and sodium excretion by suppressing the renin-angiotensin-aldeserone system. Nocturia is very common in this group with a rate of 28%.[37]

Increased respiratory effort and increased gastric pressure with abdominal pressure cause gastroesophageal reflux. Intermittent hypoxemia may lead to hyperlipidemia and hepetosteatosis.[38]

Many neuropsychiatric complications such as depression, anxiety, cognitive impairments, memory impairment, forgetfulness, personality changes, amnesia, and difficulty in concentration may be observed. The incidence of morning headache, nocturnal epilepsy and cerebrovascular disease may increase.[35]

OSAS is one of the causes of sudden death during sleep. Malignant arrhythmias, ischemic heart diseases, heart rate changes and acute myocardial infarction may cause sudden death.[39]

PROGNOSIS

The risk of morbidity and mortality increases when OSAS is severe. It is generally thought that this is a consequence of asphyxia and wakefulness reactions during apnea-hypopnea formation. Patients are lost due to cardiac arrhythmias, transient pulmonary artery pressure changes and post-apnea hypoxemia, especially during the REM period of sleep. Sudden deaths may also occur due to cardiac and cerebral causes related to hypertension. Traffic and occupational accidents in OSAS patients are another reason that increases mortality.[7,27]

CONCLUSION

OSAS is a common but understudied disorder in the population. It is characterized by recurrent complete or partial upper airway obstruction during sleep, leading to recurrent oxygen desaturations, cyclic adverse changes in heart rate, blood pressure and sympathetic activity, and disruption of sleep structure. Dentists evaluating the anamnesis and clinical examination findings can serve as the first line of care. Considering that this disease is at the root of serious cardiovascular and cerebrovascular diseases such as hypertension and cardiac arrhythmias, early diagnosis and treatment are crucial in improving the quality of life of patients and reducing morbidity and mortality. Supportive studies are needed to find new biomarkers, genetic risk assessment, and to determine the specific pathology of the patient.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The effect of sodium-glucose linked transporter 2 inhibitor and glucagon-like peptide-1 receptor agonist on weight and blood pressure control in an obese diabetic patient: a case report

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ABSTRACT

Obesity and diabetes are two closely related and often co-occurring clinical conditions that are difficult to treat and full of uncertainties. Moreover, they are often accompanied by another disease that is just as difficult to treat: hypertension. Although the picture may seem complex, pessimistic, and requiring a lot of medication, it is possible to develop a holistic strategy. With the case we have presented, we would like to share our treatment plan focused on the treatment of diabetes and its results and draw attention to the effects of sodium-glucose linked transporter 2 inhibitor, and glucagon-like peptide-1 receptor agonist therapies on weight loss and blood pressure control.

Keywords: Sodium-glucose linked transporter 2 inhibitor, SGLT2-i, glucagon-like peptide-1 receptor agonist, GLP-1RA, type 2 diabetes, hypertension

INTRODUCTION

Obesity, hypertension, and diabetes mellitus are commonly seen in society, and the frequency of coexistence of these conditions is increasing.[1] Considering the coexistence of these conditions and their effects on each other, considering their comorbidities as a whole in the management of patients will be beneficial in terms of treatment response. As is well known, obese patients can benefit from the use of sodium-glucose linked transporter 2 inhibitor (SGLT2-i), and glucagon-like peptide-1 receptor agonist (GLP-1 RA) group drugs in the treatment of type 2 diabetes mellitus due to their ability to aid in weight loss.[2] Weight loss in these patients is also effective in terms of effective control of blood pressure.

We aimed to emphasize the versatility of hypertension treatment by talking about the effect of blood glucose and weight control on blood pressure regulation in our morbidly obese and diabetic hypertension patients.

CASE

A 51-year-old woman was admitted to our clinic with irregular blood glucose and blood pressure monitoring despite medication use and hypoglycemia attacks. Her medical history included type 2 diabetes mellitus, hypertension, hyperlipidemia, and chronic kidney disease. He was regularly taking metformin 2x1000 mg/day, insulin glargine 1x60 U/day, insulin aspart 3x30 U/day, atorvastatin 20 mg/day, irbesartan/amlodipine/hydrochlorothiazide 300/10/12.5 mg/day, and metoprolol 50 mg/day as antihypertensive treatment. The patient was 130 kilograms and 162 centimeters at admission. Body-mass index (BMI) was calculated as 49.5 kg/m^2. Blood pressure was measured as 160/90 mmHg. Physical examination revealed no abnormal findings except anthropometric measurements consistent with morbid obesity. Laboratory tests revealed HbA1c 9.4%, eGFR 57 ml/min, fasting blood glucose 295 mg/dl. Other laboratory test results were within the normal range. When the patient's home blood glucose monitoring form was examined, hypoglycemic values of 50–60 mg/dl and extreme values of 400–500 mg/dl were observed. In blood pressure monitoring, systolic arterial blood pressure was measured at values as high as 180 mmHg.

The patient's medication was reorganized by targeting weight loss, blood glucose regulation, blood pressure regulation, and nephroprotection. It was also learned that the patient, who had been using quadruple insulin therapy for many years, was non-compliant with his treatment because he was fatigued of multiple injections during the day, skipped meals, and had irregular insulin doses. Insulin treatment was planned to be reduced to two injections per day. Pancreatic lipase inhibitors SGLT2-i and dipeptidyl peptidaz-4 inhibitor (DPP-4i)were

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added to the drug treatment, and the treatment was changed to metformin/sitagliptin 2x1000/50 mg/day, dapagliflozin 10 mg/day, insulin degludec+aspart 2x40 U/day, orlistat 2x120 mg/day. Diet and insulin use training was given to the patient. The diet recommended to the patient was a Mediterranean diet based on salt and carbohydrate restriction, targeting negative energy metabolism at 500 kcal per day. The diet also aimed to avoid skipping meals and to place them at certain times. Lifestyle change recommendations were made. Antihypertensive and antilipidemic treatment was continued with the same drugs, and the patient was followed up.

At the end of the 1st week, the patient had a weight loss of 6 kg; fasting and postprandial blood sugars were between 120-170 and 140-230 mg/dl, respectively. Insulin degludec+aspart was reduced to 2x35 U/day. At the end of the 1st month, there was a total weight loss of 11 kg, and blood glucose measurements were lower than the 1st week. In addition, arterial blood pressure was measured as 150-160 mmHg at most, which had previously been 180 mmHg intermittently. Insulin degludec+aspart 2x30 U/day was administered. At the end of the 2nd month, the patient had a total weight loss of 17 kg, and fasting blood glucose values decreased to around 100-110 mg/dl. Insulin degludec+aspart was reduced to 2x25 U/day. At the end of the 3rd month, total weight loss was 19 kg compared to baseline. Final BMI was calculated as 42.2 kg/m^2. HbA1c was 8.2%. No adverse changes in laboratory parameters were observed during this whole period. A new treatment modification was planned for the patient whose weight loss slowed down despite diet, lifestyle change, and the new treatment arrangement. GLP-1 RA was added to the patient's treatment, DPP-4i was stopped, and the insulin dose of the patient whose blood sugars were regulated was reduced to once a day, and the patient was switched to basal insulin. Metformin 2x1000 mg/day, dapagliflozin 10 mg/day, U300 insulin glargine 40 U/day, orlistat 2x120 mg/day, and exenatide 2x5 mcg/day were prescribed. At the end of the 4th month, the patient lost 7 kg compared to the 3rd month, and the U300 insulin glargine dose was decreased to 30 U/day after blood glucose levels were regulated. The patient's arterial blood pressure was found to be regulated in blood pressure follow-up, and the patient's 4th antihypertensive drug, beta blocker, was discontinued.

At the end of the 6th month, the patient lost 9 kg compared to the 4th month, and HbA1c was measured as 7.8%. No negative change was observed in other laboratory parameters. U300 insulin glargine was reduced to 10 U. The maximum systolic arterial pressure was measured as 140 mmHg in blood pressure monitoring. At the end of the 8th month, the patient weighed 90 kg. BMI was 34.3 kg/m^2. No hypo-hyperglycemia or other adverse side effects were observed, and insulin treatment was discontinued after blood glucose monitoring. As the highest systolic blood pressure values of 120-130 mmHg were observed in blood pressure follow-up, the thiazide treatment of the patient, who was currently using irbesartan/amlodipine/hydrochlorothiazide 300/10/12.5 mg/day as antihypertensive, was discontinued. In the following months, as the patient's blood pressure follow-ups remained stable, the dose of amlodipine was halved, and the patient was continued to be followed up with dual antihypertensive treatment. During follow-up, arterial blood pressure and blood glucose levels were regulated, there was no hypo-hyperglycemia, and no abnormal changes were observed in laboratory parameters.

DISCUSSION

It is noteworthy that weight loss, blood pressure, and blood sugar regulation were achieved in connection with the change in treatment in our patient. While blood pressure control and blood sugar regulation were achieved, the need for antihypertensive drugs and insulin decreased. Therefore, evaluating the comorbidities of the patients together will be beneficial in treatment response, and such treatment approaches may reduce the need for bariatric surgery in patients, especially in the morbidly obese patient group.[3]

Although SGLT2-i and GLP-1 RA group drugs are antidiabetic, they are also effective on hypertension.[4] SGLT2-i causes glucosuria by inhibiting the reabsorption of glucose in the kidney.[5] Glucose passing into the urine provides diuresis and natriuresis with an osmotic effect and enables SGLT2-i to exert diuretic effect.[6,7] In terms of GLP-1 RA, improvement in endothelial function with receptor activation, provision of natriuresis, and increase in vasodilation may explain this activity.[8] Independently, suppression of sympathetic nervous system activity may also play a role in blood pressure reduction.[9] This group of drugs has been a new research topic in the literature in terms of antihypertensive efficacy. Studies and some meta-analyses suggest that the combined use of these drugs may be effective in some patients.[10]

CONCUSION

As in our case, control of diseases other than hypertension is an important part of antihypertensive treatment in patients with comorbidities. Treatment management should be patient-specific, and the patient should be considered as a whole. Each drug class has its own additional properties other than lowering blood pressure, and if these properties are used effectively, it is possible to see extraordinary responses. If obesity is also present in patients with type 2 diabetes mellitus, SGLT2-i and GLP-1 RA group drugs may be considered in the foreground. In addition, more studies are needed to evaluate the antihypertensive effects of these drugs in both diabetic and non-diabetic patients.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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An obstructive retrosternal thyroid mass mimicking asthma

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ABSTRACT

The term retrosternal/intrathoracic goiter was first defined by Haller in 1749. It is usually located in the anterior mediastinum. When it reaches large sizes, it can cause various pressure symptoms. Respiratory distress may occur due to tracheal compression, difficulty swallowing due to esophageal compression, and venous fullness findings may occur as a result of pressure on vascular structures. Although rare, it can be life-threatening; it may also cause respiratory failure, which may develop as a result of sudden growth that may occur secondary to intrathyroidal hemorrhage or cystic degeneration. In this case, we aimed to present a patient who experienced respiratory distress due to a thyroid mass extending retrosternally and causing tracheal compression, and whose symptoms persisted despite optimal asthma treatment.

Keywords: Asthma, retrosternal thyroid mass, plonjon goitre

INTRODUCTION

Asthma is a chronic inflammatory disease affecting more than 300 million people worldwide. While most asthma patients respond well to current treatments, approximately 5-10% of asthma patients do not respond adequately to treatment despite optimum treatment. When evaluating patients with symptoms suggestive of difficult asthma, the differential diagnosis of difficult asthma should be made first and conditions mimicking asthma should be revealed, then comorbidities and conditions that make asthma control difficult, triggering factors should be identified and controlled, then the drug compliance of the patients should be evaluated and finally the most appropriate treatment option should be applied for the patients, taking into account the asthma phenotypes.

The term retrosternal/intrathoracic goiter was first defined by Haller in 1749.[1] It is usually located in the anterior mediastinum. When it reaches large sizes, it can cause various pressure symptoms.[2] Respiratory distress may occur due to tracheal compression, difficulty swallowing due to esophageal compression, and venous fullness findings may occur as a result of pressure on vascular structures. Although rare, it can be life-threatening; It may also cause respiratory failure, which may develop as a result of sudden growth that may occur secondary to intrathyroidal hemorrhage or cystic degeneration. In this case, we aimed to present a patient who experienced respiratory distress due to a thyroid mass extending retrosternally and causing tracheal compression, and whose complaints did not go away despite optimum asthma treatment.

CASE

A 76-year-old female patient, who had been receiving asthma treatment for 20 years, applied to our outpatient clinic with the complaint of increased shortness of breath.

In her detailed anamnesis, it was learned that she had a known history of hypertension, vertigo, osteoporosis and a previous cerebral transient ischemic attack. The patient, who is a housewife, has not worked in any job before. It was learned that the patient was sensitive to odors and did not use cigarettes or alcohol. The patient was receiving inhaled corticosteroid, long-acting beta agonist, leukotriene receptor antagonist and short acting beta agonist treatment for asthma, but her symptoms still continued. There was no other respiratory symptoms like stridor and wheezing and also there was no esophageal compression symptoms like dysphagia, odynophagia, regurgitation or chest pain. There was no involuntary weight loss or night sweats.

On physical examination, breathing sounds were evaluated as rough. There were no rales or rhonchi. There was no use of accessory respiratory muscles or cyanosis. The saturation value was measured as 96% with a fingertip pulse oximeter.

Expansion of the upper mediastinum was observed on chest radiography. The trachea was observed deviated to the left (Figure 1). A restrictive and obstructive pattern was observed in the pulmonary function test (PFT). FEV1: 0.8 (47%) FVC:1.31 (59%) FEV1/FVC:61% was measured (Figure 2).

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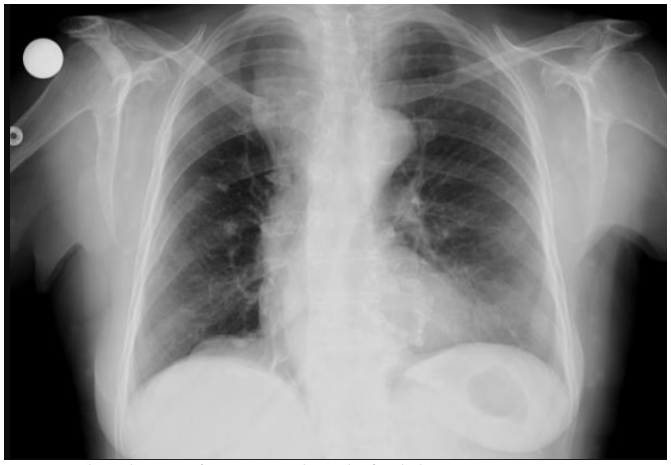
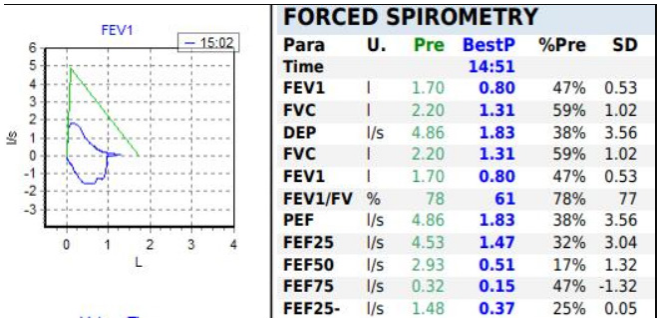


Figure 1. The pulmonary function test showed a fixed obstruction



FORCED SPIROMETRY

Para	U.	Pre	BestP	%Pre	SD
Time			14:51		
FEV1	l	1.70	0.80	47%	0.53
FVC	l	2.20	1.31	59%	1.02
DEP	l/s	4.86	1.83	38%	3.56
FVC	l	2.20	1.31	59%	1.02
FEV1	l	1.70	0.80	47%	0.53
FEV1/FV	%	78	61	78%	77
PEF	l/s	4.86	1.83	38%	3.56
FEF25	l/s	4.53	1.47	32%	3.04
FEF50	l/s	2.93	0.51	17%	1.32
FEF75	l/s	0.32	0.15	47%	-1.32
FEF25-	l/s	1.48	0.37	25%	0.05

Figure 2. The PTS's showed a fixed obstruction

Contrast-enhanced thorax computerized tomografy was planned due to upper mediastinum widening detected on chest radiography. In the thorax CT; it was reported that the size of the right lobe of the thyroid gland had increased significantly, and coarse calcifications and hypodense nodular appearances were observed in the right lobe of the thyroid gland. The lower contours of the right lobe of the thyroid extend to the neighborhood of the arcus aorta and occasionally contact the main vascular structures in the upper mediastinal area, and it was observed that the trachea secondary to retrosternal goiter was deviated to the left and narrowed the tracheal lumen. Additionally, a few pure calcific subpleural nodules measuring 13x6 mm in size were also seen in the anterior upper lobe of the right lung (Figure 3).

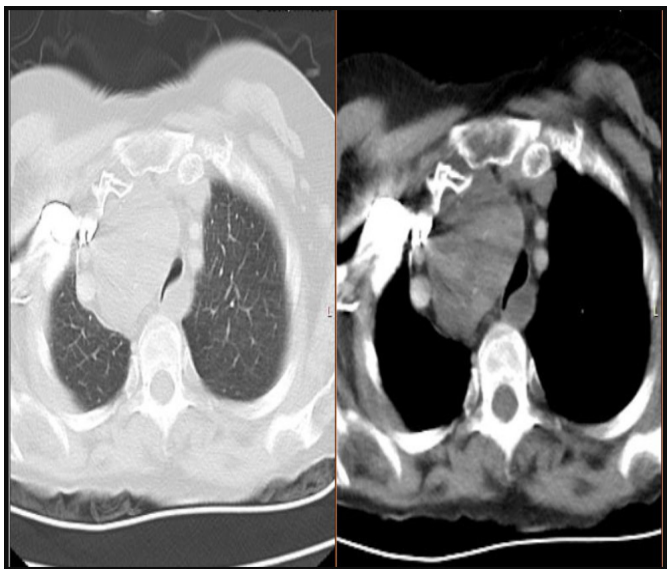


Figure 3. Chest computed tomography revealed a giant mass lesion pressured on the trachea from the right side

PET-CT was planned due to the suspicion of malignancy of the nodular lesions. In the PET-CT report, a hypodense mass lesion of 8 cm in size was seen in the right lobe of the thyroid gland, extending to the retrosternal area and creating significant pressure on the trachea from the right side, narrowing the airway significantly.

It was thought that the patient's respiratory symptoms unresponsive to bronchodilator treatment were the result of the retrosternally extending giant thyroid mass compressing the trachea, and the patient was referred to general surgery for surgical treatment. The patient did not come for follow-up later.

DISCUSSION

Asymptomatic patients with retrosternal goiter account for about 15-30% of all such patients.[3] Retrosternal goiter should be considered in cases such as tracheal deviation and mediastinal expansion, which are detected incidentally on a chest radiograph taken for any reason in asymptomatic patients.[4,5] In cases with retrosternal goiter, it usually occurs due to pressure on vital organs between the sternum and vertebral column.

While retrosternal goiter causes stridor, shortness of breath or cough due to the compression of the trachea, in some cases, difficulty in swallowing occurs due to esophageal compression. In our case, there was a complaint of shortness of breath despite the use of inhaler therapy, and there were no pathological findings on physical examination. In cases like ours, alternative diagnoses should be considered in situations where there is no response to optimum treatment. Hoarseness due to recurrent laryngeal nerve compression or invasion, or rarely, vena cava superior (VCS) syndrome, pulmonary hypertension or ischemic attacks due to superior vena cava, pulmonary artery or carotid artery compression.

By looking at the flow-volume curve, it can be interpreted whether the lesion is intrathoracic or extrathoracic. In fixed obstruction, the airway diameter does not change throughout the respiratory cycle. The clinical symptoms and changes in PFT of fixed type of obstruction in the upper respiratory tract and large airways are well known.

During the evaluation of our patient, who was diagnosed with asthma and applied to the outpatient clinic with complaints of shortness of breath, goiter causing tracheal stenosis was detected in the chest X-ray and thorax CT. PFT showed fixed obstruction. The patient was referred to surgery.

As a result, monitoring fixed obstruction in PFT in patients presenting with shortness of breath should be a warning about possible upper airway stenosis.

CONCLUSION

Upper airway stenosis is one of the pathologies that should be considered in patients with severe and progressive shortness of breath during follow-up. Plungant goiter is one of the causes of obstruction, and both intrathoracic and extrathoracic PFT findings can be detected depending on the goiter compression. In conclusion, imaging and surgical evaluation are crucial for early diagnosis and intervention, as they significantly improve quality of life and survival. Therefore, as in our case a multidisciplinary approach is essential.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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