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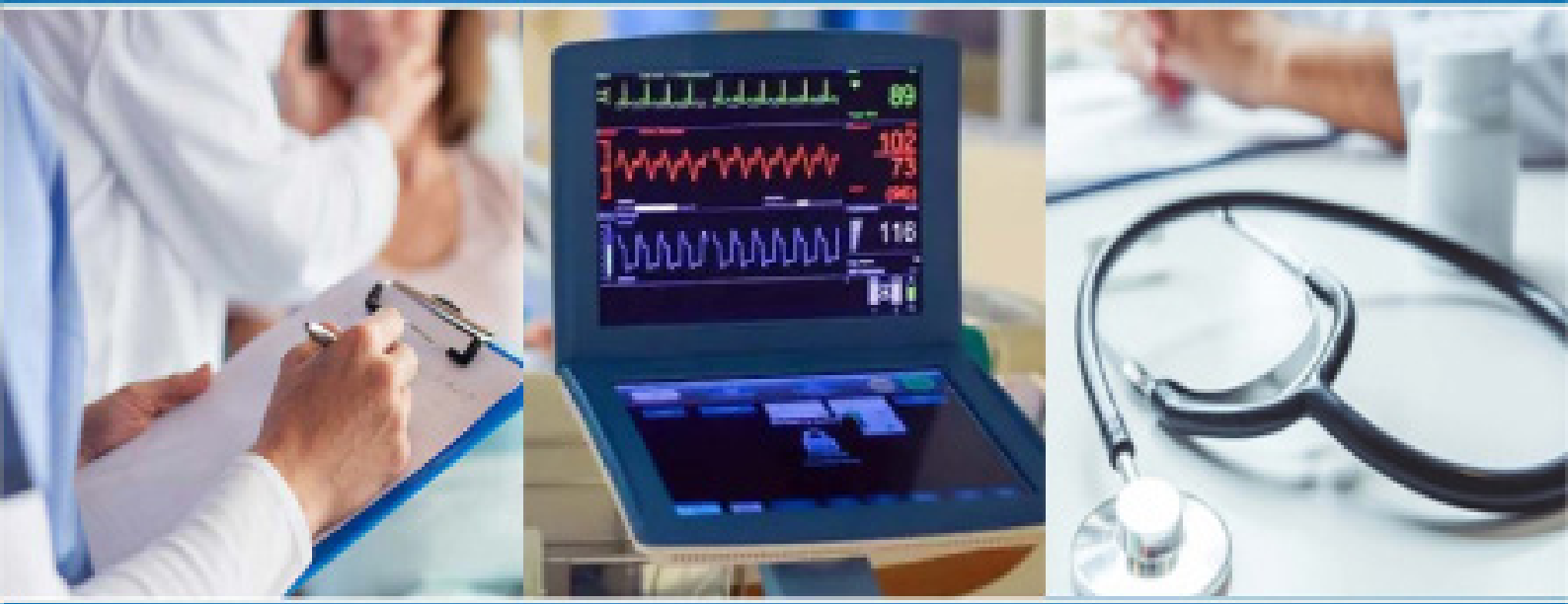

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CONTENTS

Volume: 3 Issue: 3 Year: 2025

ORIGINAL ARTICLES

REVIEW

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Original Article

Can long-term treatment of hashimoto's thyroiditis effectively improve sexual dysfunction in women?

Tunç Ozan[1], Ahmet Karakeçi[1], Kader Uğur[2], İrfan Orhan[1]

[1]Department of Urology, Faculty of Medicine, Fırat University, Elazığ, Turkiye
[2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Fırat University, Elazığ, Turkiye

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ABSTRACT

Aims: Numerous studies have identified thyroid diseases as a significant risk factor for women's sexual health. This study aimed to evaluate how treatment of women diagnosed with Hashimoto's thyroiditis affected their sexual function and psychological well-being, comparing them with a control group.

Methods: In this study, 61 sexually active women with permanent primary hypothyroidism, diagnosed for at least one year and treated for at least 6 months between January 2022 and December 2023, were included. The inclusion criteria for group 1 were as follows: participants had to have overt hypothyroidism with a thyroid stimulating hormone level >10 IU/ml and a serum free T4 level <0.86 ng/dl. The control group comprised 31 sexually active, age-matched, healthy women.

Results: Response to treatment was assessed using the Female Sexual Function Index questionnaire and the Beck Depression Inventory by interview. No significant difference was found between the two groups in terms of Female sexual function index parameters and Beck depression scores (p: 0.198 and p:0.353 respectively) except in TSH levels (p: 0.016).

Conclusion: Long-term (at least 6 months) treatment of hypothyroidism may be able to improve sexual dysfunction in women. Further studies of larger series and longer treatment follow-up are needed to confirm the present findings.

Keywords: Hashimoto's thyroiditis, female sexual dysfunction, hypothyroidism

INTRODUCTION

The interaction between the neurological, endocrine, and circulatory systems plays a critical role in human sexuality, as it is a complex physiological process. Additionally, diverse sexual orientations and behaviors may have associations with mental health.[1] Due to the less defined parameters of female sexual dysfunction (FSD) compared to those of male sexual dysfunction, accurately determining the prevalence of sexual dysfunction in women poses a significant challenge. Sexual dysfunction refers to a condition that occurs during the sexual response cycle, hindering an individual from obtaining satisfaction from their sexual activities.[2]

In recent years, there has been increased awareness of FSD. This condition includes a range of issues and can significantly affect a woman's quality of life. Therefore, it is important to conduct thorough patient screening and diagnosis before starting appropriate treatment.[3]

Arousal, desire, orgasm, lubrication, pain/discomfort, and satisfaction are the key categories used to define FSD.[4] Studies have revealed that FSD affects a substantial proportion of women, with estimates ranging from 40% to 60%.[5] Importantly, sexual dysfunction can be associated with endocrine pathologies and may serve as an indicator of more severe endocrine disorders.[6]

Hashimoto's thyroiditis is a leading cause of hypothyroidism in regions with sufficient iodine intake. It is an autoimmune disorder initiated by environmental triggers in individuals with a genetic predisposition.[7] The condition predominantly affects young and middle-aged women, with its prevalence increasing with age. The annual incidence is estimated at 0.3 to 1.5 cases per 1,000 individuals, with a female-to-male ratio of approximately 7:1.

Patients with Hashimoto's thyroiditis typically present with lymphocytic infiltration of the thyroid gland and elevated serum levels of thyroid autoantibodies, including anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO).[8] Although irregular menstruation and infertility are frequently associated with hyperthyroidism, female sexual dysfunction, menstrual irregularities, anovulation, and impaired fertility can also occur in both overt and subclinical hypothyroidism.[9,10]

While thyroid gland hyperactivity and hypoactivity are more prevalent in women of all ages than in men, there have been limited studies utilizing the Female Sexual Function Index (FSFI) to assess the impact of thyroid disorders on women's sexual function. Most of these studies have been based on small, randomized, population-based samples and selected

Corresponding Author: Tunç Ozan, drtuncozan@yahoo.com

patient populations. However, many of them have indicated a connection between thyroid disease and sexual dysfunction, particularly in women.[11] The incidence of sexual dysfunction (SD) in women with hypothyroidism ranges from 22% to 46%. Numerous studies indicate a significant correlation between hypothyroidism and SD, demonstrating a notable decrease in FSFI scores among women with hypothyroidism compared to control groups.[6,10,12-14] Nevertheless, some studies in the literature have reported contradictory results.[15,16]

To date, no studies have specifically evaluated the effects of long-term treatment on changes in thyroid function among women with permanent hypothyroidism secondary to Hashimoto's thyroiditis. The present study aimed to investigate the impact of long-term treatment on sexual function and psychological well-being in female patients diagnosed with Hashimoto's thyroiditis, by comparing outcomes with those of a matched control group.

METHODS

The study received approval from the Fırat University Non-interventional Researches Ethics Committee (Date: 18.02.2022, Decision No: 2022/02-10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Before the study, we obtained informed consent from all patients and women in the control group. In this study, 61 sexually active women with permanent primary hypothyroidism, diagnosed for at least one year and treated for at least 6 months between January 2022 and December 2023 were included (group 1). The inclusion criteria for group 1 were as follows; participants had to have overt hypothyroidism with a thyroid stimulating hormone (TSH) level >10 IU/ml and a serum free T4 level <0.86 ng/dl. Additionally, they needed to exhibit diffuse fibrous bands and/or a lobular appearance and/or pseudonodule appearance on thyroid ultrasonography, have anti thyroid peroxidase (TPO) and anti thyroglobulin (TG) antibodies before treatment, and have received levothyroxine treatment at a dose of 1.2-1.8 µg/kg/day for at least 6 months. The target posttreatment TSH level was considered to be 0.4-4.5 mU/L on average.[8] The control group comprised 31 sexually active, age-matched, healthy women (group 2). All patients in group 1 were monitored and treated at the endocrinology outpatient clinic of Fırat University Hospital. We assessed demographic characteristics such as age, education level (primary, high school, or university graduate), smoking, alcohol use, income status, number of births, and occupational status (whether they had an occupation or not) for all women. Participants with neurological disease, cardiovascular disease, a history of previous pelvic surgery, major psychiatric illness, premature ovarian failure, diabetes and those who have not engaged in sexual activity in the last month, as well as individuals diagnosed with secondary or subclinical hypothyroidism with abnormal TSH levels outside of the post-treatment target, pregnant or breastfeeding women, and participants using any medication other than levothyroxine that may affect thyroid function or sexual response were excluded from the study. The study included women who were in stable heterosexual relationships and were sexually active.

The Female Sexual Function Index questionnaire was completed using a mutual interview method. This questionnaire is comprised of 19 questions, validated in Turkish, and assesses 6 parameters including arousal, orgasm, sexual desire, lubrication, pain, and satisfaction. It aims to evaluate sexual functioning and any associated issues within the past 4 weeks. The questionnaire includes 19 questions, each with a specific scoring range. 1. Questions 1 and 2 focus on sexual desire and are scored between 1 and 5 points. 2. Questions 3, 4, 5, and 6 assess sexual arousal, with a scoring range of 0-5 points. 3. Questions 7, 8, 9, and 10 pertain to vaginal lubrication and are also scored on a scale of 0-5 points. 4. Questions 11, 12, and 13 are about orgasm and carry a scoring range of 0-5 points. 5. Questions 14, 15, and 16 analyze sexual satisfaction and are rated between 1 and 5 points. 6. The last three questions, 17, 18, and 19, evaluate pain during intercourse and are scored between 0-5. The following coefficients are used to assess female sexual function: 0.6 for desire, 0.3 for arousal and lubrication, and 0.4 for orgasm, satisfaction, and pain. If the total score is less than 26.55, it is considered indicative of female sexual dysfunction.[17]

The Beck Depression Inventory (BDI) is a self-reported inventory consisting of 21 items, previously adapted for the Turkish population.[18,19] Each of the 21 questions is rated on a scale of 0 to 3 (none to severe), with the highest possible total score being 63. Psychiatric evaluation was conducted using the BDI, and a diagnosis of depression was made when the BDI score was 17 or higher.

Statistical Analysis

We conducted statistical analysis using the SPSS (Statistical Package for Social Sciences for Windows 22) software package (IBM Corp. Armonk, NY). Mean values were reported as median (minimum-maximum) for descriptive continuous variables. Categorical variables were presented as frequency and percentage. We used the Pearson chi-square test to compare categorical variables between groups and the non-parametric Mann-Whitney U test to compare continuous variables between two independent groups. A significance level of $\alpha=0.05$ was set for all statistical tests conducted.

RESULTS

Post Hoc power analysis was performed for our study. The calculated power (1-beta) based on this test is 0.852, considering type I error (alfa) of 0.05, sample size of 30, effect size of 0.79 and two-sided alternative hypothesis (H1). The average age of the 61 hypothyroid patients participating in the study was 39.25 (±8.04) years, while it was 35.73 (±6.17) years in the control group. The average duration of treatment was 263.8 days (181-328). The two groups did not differ significantly in terms of age (p: 0.106). Demographic details for both groups can be found in **Table 1**.

Apart from TSH levels, there were no other significant differences between the two groups in terms of variables (**Table 2, Figure a, b**).

In the control and hypothyroidism groups, there was no correlation between the parameters within the groups (**Table 3**).

DISCUSSION

Numerous studies have identified thyroid diseases as a significant risk factor for women's sexual health. Despite considerable research, the precise mechanisms through which thyroid diseases trigger FSD remain incompletely understood. Notably, investigations in women have highlighted the crucial

Table 1. Demographic characteristics of the groups

Categories	Group 1 (n: 61, %)	Group 2 (n: 31, %)
Education level		
No literacy	1 (1.63%)	0 (0%)
Primary school	1 (1.63%)	0 (0%)
Middle school	25 (40.98%)	0 (23.3%)
High school	20 (32.78%)	4 (12.90%)
University	14 (22.98%)	27 (37.20%)
Economic status		
Low	24 (39.34%)	0 (0%)
Middle	16 (26.23%)	0 (0%)
High	21 (34.43%)	31 (100%)
Occupation		
Housewife	47 (77.09%)	0 (0%)
Retired	1 (1.63%)	0 (0%)
Worker	1 (1.63%)	7 (22.58%)
Officer	12 (19.68%)	23 (74.19%)
Self-employed	0 (0%)	1 (3.23%)
Other	0 (0%)	0 (0%)
Smoking status		
Yes	9 (14.75%)	9 (29.03%)
No	52 (85.25%)	22 (70.97%)
Alcohol use		
Yes	0 (0%)	2 (6.45%)
No	61 (100%)	29 (93.55%)
Number of children		
None	8 (13.12%)	2 (6.45%)
1	9 (14.75%)	11 (35.50%)
2	28 (45.90%)	10 (32.25%)
3 or more	16 (26.23%)	8 (25.80%)

Table 2. The median values of the hypothyroid and control groups, respectively, and the p-values in the comparison between the groups

	Group 1 (hypothyroid)	Group 2 (control)	p
BMI	27.42 (±5.77)	25.50 (±3.35)	0.094
Waist circumference	89.52 (±12.92)	85.00 (±10.74)	0.157
Total cholesterol	180.14 (±43.28)	165.72 (±49.64)	0.164
LDL	120.58 (±36.96)	108.32 (±42.21)	0.161
Triglyceride	130.97 (±67.32)	120.05 (±60.76)	0.455
HDL	53.02 (±12.34)	53.96 (±14.61)	0.752
FSH	10.95 (±13.44)	8.92 (±9.72)	0.970
LH	9.16 (±9.68)	6.74 (±7.22)	0.242
Prolactin	12.47 (±9.93)	14.07 (±20.03)	0.882
Fasting blood glucose	90.51 (±13.29)	86.35 (±10.98)	0.138
fT3	2.96 (±0.47)	3.09 (±0.50)	0.187
fT4	1.20 (±0.25)	1.12 (±0.13)	0.112
TSH	4.49 (±4.88)	2.30 (±1.09)	0.016
Desire	3.18 (±1.06)	3.01 (±1.30)	0.546
Arousal	2.90 (±1.16)	2.28 (±1.44)	0.052
Satisfaction	3.52 (±1.32)	3.52 (±1.13)	0.995
Lubrication	2.55 (±1.05)	2.29 (±1.19)	0.668
Orgasm	2.56 (±1.20)	2.48 (±0.93)	0.365
Pain	2.19 (±2.01)	2.03 (±1.72)	0.827
Total FSFI	17.51 (±5.00)	16.00 (±5.36)	0.198
Beck depression score	15.77 (±9.43)	14.01 (±6.34)	0.353

BMI: Body-mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, fT3: Free triiodothyronine, fT4: Free thyroxine, TSH: Thyroid stimulating hormone, FSFI: Female Sexual Function Index

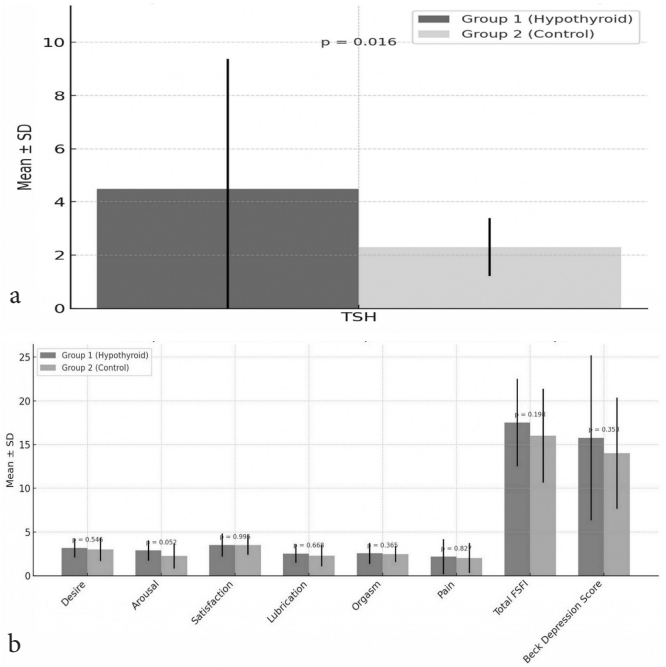

Figure. a) Comparison of TSH levels between groups, b) Comparison of sexual function and depression scores between groups

TSH: Thyroid stimulating hormone

Table 3. p and r values in comparison of parameters within the control and hypothyroidism groups

Group 1 (hypothyroid)	FSFI	Beck score
Beck score	0.232 (0.158)	
T3	0.135 (-0.254)	0.713 (-0.063)
T4	0.325 (-0.130)	0.411 (-0.108)
TSH	0.955 (-0.008)	0.614 (-0.067)
Group 2 (control)		
Beck score	0.260 (-0.216)	
T3	0.596 (-0.103)	0.401 (0.156)
T4	0.728 (-0.067)	0.638 (-0.088)
TSH	0.555 (0.114)	0.110 (0.293)

FSFI: Female Sexual Function Index, T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone

role of low circulating levels of thyroid hormone as one of the primary factors influencing the development of FSD. This suggests a complex interplay between thyroid function and sexual health that warrants further investigation. The study conducted by Oppo et al.[14] revealed a compelling link between the circulating levels of TSH, free thyroxine (fT4) and the degree of FSD in women with hypothyroidism. Changes in the functioning of the hypothalamic thyroid axis can lead to disruptions in prolactin levels, while variations in circulating thyroid hormone levels can impact the genitals due to the presence of thyroid hormone receptors. These physiological conditions are particularly important to consider. The increased levels of prolactin due to hyperprolactinemia have inhibitory effects on the pulsatile release of gonadotropin-releasing hormone. This, in turn, leads to a decrease in the production of dehydroepiandrosterone (DHEA), estrogen and testosterone. It has been claimed that symptoms such as mood disorders, fatigue and depression may also indirectly lead to FSD.[14,20]

In studies conducted in women with hypothyroidism undergoing FSFI, statistically significant decrease was found in the subdomain scores of FSFI in a way inversely

proportional to TSH towards fT4 when comparing women with clinical hypothyroidism with healthy controls.[14]

In their study, Atis et al.[7] demonstrated that the FSD levels were notably elevated in women diagnosed with subclinical hypothyroidism and clinical hypothyroidism, particularly when their TSH levels exceeded 10 mU/L, in comparison to women in the healthy control group. In a recent study including 104 women diagnosed with clinical hypothyroidism (Hashimoto's thyroiditis, nodular goiter, idiopathic hypothyroidism,), significant decreases in parameters such as, arousal, lubrication and desire were observed compared to the control group. However, no significant differences were found in subdomains such as overall FSFI score, satisfaction, sexual pain or orgasmic function.[6] Veronelli et al.[21] indicated that there was a negative correlation between the presence of antithyroid antibodies and the FSFI score. The results of the study by Krysiak et al.[12] involving 50 women with hypothyroidism indicated that women with hypothyroidism caused by inflammatory infiltration of the thyroid gland had lower rates of FSD compared to those with hypothyroidism caused by other factors such as radiotherapy, iodine deficiency, radioiodine therapy, thyroid hypoplasia or thyroid surgery. In a comparative study involving 16 euthyroid women with Hashimoto's thyroiditis and 18 controls, it was observed that the rate of FSD, as determined by the FSFI score, was notably lower in patients with subclinical autoimmune hypothyroidism, yet comparatively higher than in the control group. The authors suggested that this situation could potentially result in thyroid dysfunction due to the combined impact of autoantibodies and hormonal dysregulation. They found an inverse relationship between TPO antibody levels and total FSFI scores, lubrication, sexual satisfaction and sexual desire in individuals with euthyroid Hashimoto's thyroiditis and autoimmune subclinical hypothyroidism.

Thyroid autoimmunity was found to be significantly linked to hypoactive sexual desire disorder (HSDD) regardless of thyroid function. No significant differences were observed in other parameters compared to the control group, and there was no discernible relationship between FSFI scores and TSH or T4 levels ($p>0.05$).[14]

Pasquali et al.[6] discovered that women with Hashimoto's thyroiditis had a lower total FSFI score than the established cut-off value. However, there was no significant difference compared to the control group. The existing data regarding the impact of euthyroid hormone therapy on sexual function in women is conflicting. Nevertheless, similar to hypothyroidism in women, it is believed that the existence of autoantibodies may contribute to the development of sexual dysfunction in this specific patient population. In studies conducted in women with hypothyroidism undergoing FSFI, statistically significant reductions were found in the subdomain scores of FSFI inversely proportional to TSH and propotional to fT4.[14]

Contradictory results have been found in studies on subclinical hypothyroidism. One study involved 25 untreated women with subclinical hypothyroidism, 20 women with clinical hypothyroidism, and 25 age-matched healthy women. The findings indicated that 56% of the women with clinical hypothyroidism, 54.6% of those with subclinical hypothyroidism, and only 14.6% of the control group experienced FSD.[10] In a comprehensive study by Luo et al.,[15] 1,119 Chinese women were surveyed, with 168 diagnosed with subclinical hypothyroidism and 951 healthy controls. The results revealed no significant variance in FSD rates between the two groups. Furthermore, detailed subgroup analysis showed no noteworthy differences in the occurrence of low arousal, low desire, decreased orgasm, poor lubrication, sexual pain and low satisfaction between the two groups. A similar conclusion has been speculated by Hong et al.[16]

Correction of hypothyroidism in women has been associated with improvements in sexual function. Administration of L-thyroxine is known to normalize prolactin levels in the majority of patients with hypothyroidism. This reduction in prolactin levels has been proposed as a potential mechanism for decreasing the incidence of female sexual dysfunction (FSD) in this population.[22] As a matter of fact, Oppo et al.[14] showed that after 3 months of treatment, the desire, satisfaction and pain areas of FSFI were completely normalized, while the arousal and orgasm areas were largely unchanged in hypothyroid patients, and that this partial response was probably due to the short period of time, and that full normalization of the sexual function was possible after a longer treatment. The strong connection found between serum fT4 and TSH and FSFI in both treated and untreated hypothyroid women suggests that reduced levels of circulating thyroid hormones play a significant role in FSD associated with hypothyroidism.

In another study, Pasqueli et al.[6] found that 33% of women with hypothyroidism who were receiving treatment for Hashimoto's thyroiditis showed no significant difference in FSD or FSFI scores compared to the control group.

Gomez et al.[23] definitively established that hypothyroid women experience a significantly higher prevalence of desire, penetration pain, and sexual dysfunction during intercourse, even when effectively treated with levothyroxine. They confidently asserted that this phenomenon is a result of hypothyroidism causing dysfunction in sexual response.

These studies suggest that some aspects of sexual dysfunction in women with thyroid disorders are reversible. In our study, improvement was found in all aspects of FSFI scores of Hypothyroid patients. We may conclude the improvement of all parameters to the longer duration of treatment and long-term regulation of the circulating thyroid hormone level.

In our study, only TSH values showed a significant difference between the groups, and this can be explained by the fact that despite the improvement in free T3 and T4 in the treatment groups, fluctuations in TSH levels are quite frequent and this may be considered as a clinically expected result.

Non-thyroid factors (cardiovascular, endothelial, neurological (somatic/autonomic) and mood changes) have been reported to contribute to the development of FSD in association with hypothyroidism. It has been well known that marked thyroid dysfunction may be associated with reversible mental dysfunctions that may mimic almost every psychiatric symptom profile.[14] As a matter of fact, it has been suggested that thyroid autoimmunity may also be associated with mood disorders, which are mainly represented by refractory depression and anxiety, independent of thyroid function.[24] The fact that the patients we treated also had positive Beck depression scores suggests the positive effects of medical treatment on mood. Therefore, we think that the normal mood of our patients due to the improved active thyroid hormone level also contributes to the improvement of the FSFI results.

Limitations

This study has several limitations, including the low number of cases and the absence of baseline FSFI and BDI data in the hypothyroidism group before treatment. To address this, we implemented a control group to mitigate these limitations.

CONCLUSION

As a result, long-term treatment of hypothyroidism (defined as a minimum duration of six months) may contribute to improvements in sexual dysfunction among women. However, further studies involving larger cohorts and extended follow-up periods are necessary to validate these findings and establish definitive clinical recommendations.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Fırat University Non-interventional Researches Ethics Committee (Date: 18.02.2022, Decision No: 2022/02-10).

Informed Consent

Before the study, we obtained informed consent from all patients and women in the control group.

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.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Original Article

Efficiency of ledipasvir/sofosbuvir treatment in hepatitis C virus infection

Elif Bilgiç[1], Yasir Furkan Çağın[2], Oral Menteş[3], Murat Aladağ[2]

[1]Department of Internal Medicine, Gülhane Training and Research Hospital, University of Health Sciences, Ankara, Turkiye
[2]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Turgut Özal Medical Center, İnönü University, Malatya, Turkiye
[3]Department of Chest Diseases, Gülhane Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

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ABSTRACT

Aims: This study analyzes the efficiency of a combination of ledipasvir/sofosbuvir (LED/SOF), a newly developed direct-acting antiviral agent, in patients infected with hepatitis C virus (HCV) with or without a treatment history [pegile-interferon±ribavirin (PEG-IFN±RBV)] who subsequently developed recurrence.

Methods: Files of hepatitis C-infected patients who received LED/SOF treatment for 3-6 months with recurrence or without a treatment history (PEG-IFN±RBV) before admission to Gülhane Training and Research Hospital between 06.06.2016 and 23.05.2018 were taken into account.

Results: This study included 45 patients, 20 of whom were female (44.4%) and 25 of whom were male (55.6%). Among those patients, 22 were administered PEG-IFN±RBV treatment and experienced recurrence, whereas 23 had no previous treatment history. Age; sex; 6-month aspartate aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, and albumin, international normalized ratio (INR), hemoglobin (HGB) and thrombocyte (PLT) values; and 1-, 2- and 6-month-old HCV-RNA levels were evaluated in this study. When the pretreatment HCV-RNA levels and the 1st, 2nd and 6th month HCV-RNA levels were compared, the decrease in the values was statistically significant ($p<0.05$, $p<0.05$, $p<0.05$, $p<0.05$). The initial and 6-month AST, ALT, GGT, and ALB levels and the PLT were statistically significant ($p<0.05$, $p<0.05$, $p<0.05$, $p<0.05$, $p<0.05$, $p<0.05$, respectively).

Conclusion: LED/SOF treatment in patients with or without HCV infection treatment experience was found to be reliable and successful.

Keywords: RBV, PEG-IFN, HCV-RNA, LED/SOF

INTRODUCTION

Hepatitis C virus (HCV) infection is a well-known cause of chronic liver disease. The estimated number of people infected with HCV is 71 million globally.[1] Epidemiological studies performed in Turkiye have shown that its prevalence is approximately 1%.[2]

The purpose of HCV treatment is to achieve a sustained virologic response (SVR). The SVR defines the occurrence of aviremia in the 12th and 24th months after the commencement of treatment (SVR12-SVR24). SVR is associated with normalization of liver enzymes and suppression of necroinflammation in patients who have not yet developed cirrhosis. The possibility of relapse in patients who have achieved a SVR has decreased considerably. In patients with advanced liver deficiency (METAVIR score F3-F4), the SVR is associated with a reduction in hepatic deficiency and portal hypertension risk. In patients with advanced liver deficiency, SVR has been shown to reduce the risk of hepatocellular carcinoma (HCC) development and liver-related fatalities.[3-9]

Over the years, as the HCV lifecycle, genomic construction and pathogenesis have been clarified, studies on direct-acting treatments for the virus have been conducted.[10] By employing newly developed direct-acting antivirals (DAAs), regimens without interferon (IFN) and RBV have been developed. Through such treatment regimens, nearly total SVR has developed, with a definite increase in patient quality of life.[11] Compared with formerly used medicines, newly developed DAAs can be used reliably in patients with comorbid disorders, resulting in a greater response to treatment. Given these data, the use of DAAs has revolutionized HCV infection, demonstrating that the condition could be acceptable as a curative.[12,13]

The purpose of our study was to analyze the efficiency of LED/SOF treatment, a directly acting antiviral agent, in HCV patients with no treatment history or recurrence.

METHODS

Selection of Cases and Compiling the Data

The files of the HCV patients who applied to Gülhane Training and Research Hospital between 06.06.2016 and 23.05.2018

Corresponding Author: Elif Bilgiç, elifbilgic@gmail.com

and who received LED/SOF treatment for 3-6 months, either nonexperienced or experienced to treatment later developing a recurrence, were retrospectively evaluated as per the Helsinki Declaration Resolutions, Patient Rights Regulations and ethical rules, subject to İnönü University Health Sciences Non-interventional Clinical Researches Ethics Committee (Date: 26.11.2019, Decision No:2019/414).

Age, gender, AST, ALT, ALP, GGT, total bilirubin, albumin, INR, HGB and PLT values at the beginning and 6th month of treatment, and HCV-RNA levels at the beginning and 1st, 2nd and 6th month were analyzed (HCV-RNA level and genotyping evaluated by Abbott real-time HCV assay).

HCV genotypes are classified based on phylogenetic analysis of nucleotide sequence variability, primarily within the NS5B and Core/E1 regions of the viral genome. This classification delineates HCV into seven major genotypes,[1-7] each comprising multiple subtypes (e.g., 1a, 1b, 3a), with inter-genotypic sequence divergence of approximately 30% and intra-genotypic divergence of around 15%. Genotyping is typically performed using reverse transcription polymerase chain reaction (RT-PCR) followed by sequence analysis or line probe assays. The distribution of HCV genotypes varies geographically and has significant implications for disease progression, epidemiology, and treatment response, making accurate genotypic determination a critical component of clinical management.

The treatment start and 6-month values of the patients were compared to evaluate the response to treatment. While pediatric patients were not included, those aged 18 years or older were included. Twentysix patients were not covered because they had previously undergone a liver transplant, 10 were not covered because they failed to attend follow-up regularly, and 1 patient was not covered because of receiving RBV treatment along with LED/SOF. A total of 23 patients who did not previously receive treatment and 22 patients who underwent PEG-IFN±RBV treatment with recurrence, totaling 45 patients, were included. Among those, 44.4% were female, and 55.6% were male. The average age of the patients was 66.16 years. Our study was retrospective and did not involve any invasive procedures. İnonu University Turgut Özal Medical Center Biochemistry and Microbiology laboratory data were used.

Statistical Analysis

For the purposes of comparing the pre- and posttreatment HCV-RNA values of HCV patients at a reliability level of 95% (α=0.05) and 80% strength (β=0.20), the minimum number of patients to be covered by the study, considering an efficiency of 0.79, was estimated to be 15. The data are presented as the average±standard deviation and number (%). Compliance with the normal distribution was carried out via the Shapiro-Wilk test. For the statistical analyses, the Fridman test, Wilcoxon test, and Spearman correlation coefficient were employed as necessary, and a p-value <0.05 was considered statistically significant.

RESULTS

A total of 45 patients, 20 women (44.4%) and 24 men (55.6%) were included in our study. Of these patients, 22 had previously received PEG-IFN±RBV treatment and relapsed; and 23 were inexperienced patients. The age of the patients ranged between 25-90 years with a mean age of 66.16 years old. Treatment duration of the patients: 5 (22.5%) patients for 3 months and 40 (77.5%) patients for 6 months. When the patients included in study were categorized according to their genotypes: 37 (82.2%) patients were GT1b, 5 (11.1%) patients were GT1, 2 (4.4%) patients were GT4, 1 (2.2%) patient was GT1a (**Figure 1**).

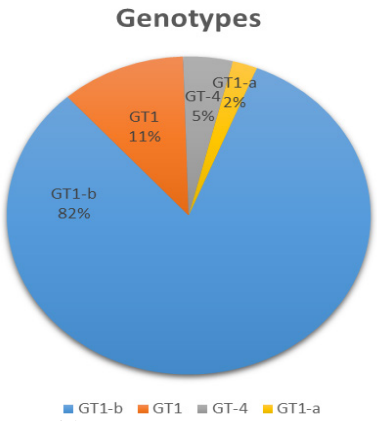

Figure 1. Genotypes of the patients

The pretreatment HCV-RNA level of the patients was 9.79±17.22 million/copy, while the posttreatment 1st month HCV-RNA level was 0.12±0.71 million/copy, and the 2nd and 6th month HCV-RNA levels were calculated to be 0 (zero). The decrease in the posttreatment HCV-RNA level was statistically significant (p<0.001).

When the pretreatment HCV-RNA levels and the posttreatment 1st, 2nd and 6th month HCV-RNA levels were compared, the decrease in the values was statistically significant (p<0.05, p<0.05, p<0.05 and p<0.05, respectively) (**Figure 2**).

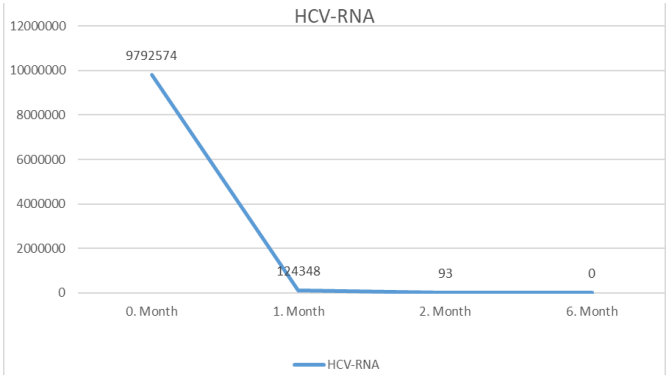

Figure 2. HCV-RNA (copy) levels according to the months of treatment
HCV: Hepatitis C virus, RNA: Ribonucleic acid

The AST, ALT, ALP, GGT, total bilirubin, albumin, INR, HGB, and PLT values were compared with the pretreatment and posttreatment 6th month values. The AST, ALT, GGT, and ALB levels and the PLT were significantly different between the starting and 6th months (p<0.05, p<0.05, p<0.05, p<0.05, p<0.05, p<0.05, respectively). Similarly, when the ALP, total bilirubin, INR and HGB results were evaluated separately, no statistically significant differences were detected (p>0.05, p>0.05, p>0.05, p>0.05) (**Table 1, 2**) (laboratory values reference intervals AST: 5-34 U/L, ALT: 0-55 U/L, ALP: 40-150 U/L, GGT: 9-64 U/L, total bilirubin: 0.2-1.2 mg/dl, albumin: 3.5-5 g/dl, INR: 0.8-1.2).

Table 1. HCV-RNA, AST, ALT, ALP, and GGT values at the start and 6th months of treatment (O±SD) and p-values

Parameters	HCV-RNA (million/copy)	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)
Start (O±SD)	9.79±17.22	110.42±278.59	148.87±419.48	104.66±38.77	86.24±84.20
6th month (O±SD)	0	26.26±10.11	23.03±15.12	87.30±31.15	31.75±17.64
p-value	<0.001	<0.001	<0.001	0.330	<0.001

O: Average, SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase

Table 2. Total bilirubin, albumin, INR, HGB and PLT values at the start and 6th months of treatment (O±SD) and p-values

Parameters	Total bilirubin (mg/dl)	Albumin (g/dl)	INR	HGB	PLT
Start (O±SD)	1.12±0.66	3.42±0.50	1.15±0.23	13.52±2.22	158.09±73.17
6th month (O±SD)	1.15±0.79	3.66±0.51	1.10±0.16	13.73±2.45	154.45±78.72
p-value	0.829	0.003	0.132	0.151	0.046

INR: International normalization ratio, HGB: Hemoglobin, PLT: Thrombocyte, O: Average, SD: Standard deviation

DISCUSSION

HCV infection has become one of the foremost causes of chronic liver disease.[14] Over the years, as the life cycle, genomic construction and pathogenesis of HCV have clarified, treatments directly acting on the virus have been developed.[10] DAAs represent a revolution in HCV infection treatment, showing that the disease could be considered curative.[12,13] The most common HCV subtype encountered worldwide is genotype 1.[15] In a previous study, the genotype frequency worldwide was as follows: GT1, 46%; GT3, 22%; GT2, 13%; and GT4, 13%.[16] HCV-related studies in Turkiye revealed that, as is the case globally, the most frequently observed type was GT1b, with a frequency of 60-100%.[17] In our study, GT1b (82.2%) was the most frequently observed group.

In this study, in patients with HCV infection, with or without a history of treatment (PEG-IFN±RBV), LED/SOF (NS5A/NS5B inhibitor) treatment efficiency and its impact on liver function test (LFT) values were investigated. The treatment starts and posttreatment 1st, 2nd and 6th month values were compared. In addition, the AST, ALT, ALP, GGT, total bilirubin, albumin, INR, HGB and PLT values were compared between the first and second months of treatment. Since 11 patients failed to attend their follow-up visits regularly, SVR24 was not evaluated. Since the posttreatment 1st and 2nd month HCV-RNA values of those patients were zero and treatment efficiency was monitored, the values in those months were included.

In Chen et al.[18] administered LED/SOF treatment to 127 chronic HCV patients for 12 weeks with RBV (8.7%) or without RBV (91.3%). Among patients who received LED/SOF treatment without RBV, in the non-cirrhosis and cirrhosis patient groups, the SVR12 rates were 100% (39/39) and 97.3% (73/75), respectively. Compared with the pretreatment values, the reductions in the serum ALB and GGT levels were statistically significant ($p<0.001$). However, total bilirubin and the international normalized ratio (INR) were not significantly different ($p>0.05$). In our study, data supporting these findings were also obtained, and the reductions in the serum ALB and GGT levels were found to be statistically significant ($p<0.05$). The total bilirubin and INR values were not significantly different ($p>0.05$). The SVR ratio was found to be 100%.

ION studies are very important since they are first evaluations aimed at chronic HCV patients using treatment without RBV or INF. In the ION-1 study, in GT1 patients without a treatment history, 12 weeks of LED/SOF treatment was administered and found to be effective. Adding RBV did not contribute to SVR. The failure ratio of the virological response was 0.3%.[19] In our study, the SVR was 100%, which was in compliance with the literature.

In a study by Juan et al.,[20] 122 patients were administered LDP/SOF treatment, whereas an SVR was obtained in 112 patients. With respect to their genotypes, 98.82% (84/85) of GT1 patients, 43.75% (7/16) of GT3 patients and 100% (21/21) of GT4 patients achieved SVR. In our study, GT1 (95%) and GT4(5%) infected patients were evaluated, revealing results in compliance with the literature (SVR 100%).

In a study by Gane et al.[21] that analyzed the efficiency of LDP/SOF treatment in GT2 patients, the SVR was 96% in patients receiving 12 weeks of treatment (25/26), whereas in patients receiving 8 weeks of treatment, the SVR was 74% (20/27). Although the difference in response rates was not statistically significant, a shorter treatment period was found to reduce the treatment response. In our study, GT1 and GT4 patients were also evaluated, with LDP/SOF treatment being applied for 12 (5/45) and 24 (40/45) weeks, resulting in an SVR of 100%.

Zeng et al.[22] evaluated 187 GT1b-infected patients; in the 1st group, cirrhosis patients were administered LDP/SOF+RBV treatment for 12 weeks; in the 2nd group, non-cirrhosis patients were administered LDP/SOF+RBV for 8 weeks; and in the 3rd group, non-cirrhosis patients were given LDP/SOF treatment for 8 weeks. The SVR ratios of groups 1, 2 and 3 were 96.8% (61/63), 96.9% (63/65) and 96.9% (62/64), respectively. Among the patients in group 3, 1 patient experienced relapse at the 4th week after treatment. Overall, this study revealed that, with or without the addition of RBV, LDP/SOF treatment is efficient and reliable in GT1b patients. In our study, 82% (36/45) of the patients were infected with GT1b, whereas 29 reached SVR24, with a 100% SVR consistent with the literature.

Gane et al.,[23] in their study, administered LDP/SOF+RBV and LDP/SOF treatments to GT3 and GT6 patients. Among the GT3 patients without a treatment history, 64% (16/25) achieved SVR in the LDP/SOF treatment group, whereas 100% (26/26) achieved SVR in 26 patients subjected to LDP/SOF+RBV treatment. LDP/SOF+RBV treatment was applied to GT3 patients with a treatment history, resulting in an SVR of 82% (41/50). LDP/SOF treatment was given to GT6 patients with or without a treatment history, with an SVR of

96% (24/25). In our study, there were no GT3 or GT6 group patients, while our treatment success rates were higher. In conclusion, the treatment response of GT3 and GT6 patients was lower than that of patients with other GTSs, and a better response was obtained with trio combination treatment.

Corma-Gomez et al.[24] compared a patient group with HIV+HCV coinfection and only with HCV infection and compared the efficiency of 8-week and 12-week LDP/SOF treatment. In 322 patients with HIV+HCV coinfection who received 8 weeks (102) and 12 weeks (220) of treatment, the SVR ratios were 92.2% and 97.3%, respectively. The relapse rates were 4.9% and 0.5%, respectively. When the patient groups subjected to 8 weeks of treatment with HCV monoinfection (51%, 107) and with HIV+HCV coinfection (49%, 102) were compared, the SVR rates were 96.3% and 92.2%, respectively. The relapse rates were 0.9% and 4.9%, respectively. In our study, patients without HIV coinfection were also evaluated, and in line with the literature, SVR rates were higher than those in HIV+HCV-coinfected patients.

In a study carried out by Akin et al.[25] in Turkiye, 11 liver transplant patients and 12 kidney transplant patients with HCV infection were administered LDP/SOF±RBV treatment. All kidney transplant patients and 91% of the liver transplant patients were infected with GT1. While 9 kidney transplant patients used tacrolimus as the main immunosuppressive agent, 2 used cyclosporine. All liver transplant patients used tacrolimus. Four weeks after treatment, 75% of the kidney transplant patients and 91% of the liver transplant patients achieved SVR. Twelve weeks after treatment, all patients who received either liver or kidney transplants achieved an SVR.

In this study, 45 patients infected with GT1 (95%) or GT4 (5%) were analyzed, while 24-month control data from 9 patients were inaccessible. Among those patients, the 1st or 2nd month HCV-RNA values were zero, so they were included. All patients who visited for 24-month controls[26] achieved SVR24. In this context, our study results are in accordance with the literature.

Limitations

The limitation of this study was the lower number of patients. In our study, patients who did not undergo liver transplantation were also evaluated, and the results were similar to those reported in the literature.

CONCLUSION

The treatment starts and posttreatment 6th month HCV-RNA levels, AST, ALT, GGT, albumin and PLT results were analyzed, and a statistically significant difference was detected in relation to the ALP, total bilirubin, INR and HGB results. These findings demonstrate that medicinal use suppressed viral replication and decreased LFT levels. With scientific developments, understanding the HCV-RNA structure and new treatments are promising. In the future, the notion of providing a cure against HCV is encouraging.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İnönü University Health Sciences Non-interventional Clinical Researches Ethics Committee (Date: 26.11.2019, Decision No:2019/414).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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.

Aknowledgement

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Original Article

Monitoring antibiotic resistance with a cumulative antibiogram in a university hospital

Yeliz Tanrıverdi Çaycı[1], Canberk Çınar[1], Sreylis Nay[2], Demet Gür Vural[1], Kemal Bilgin[1], Asuman Birinci[1]

[1]Department of Medical Microbiology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkiye
[2]Department of Emergency Medicine, Faculty of Medicine, Uludağ University, Bursa, Turkiye

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ABSTRACT

Aims: Treatment of infectious diseases is empirically regulated in many centers. It is very important to follow the antimicrobial resistance rates and resistance profile. For this, sharing the cumulative antimicrobial susceptibility results of each institution will contribute to clinicians in choosing antibiotics. This study aimed to contribute to clinicians' empirical treatment selection by determining the resistance rates of *Enterobacteriaceae* and nonfermentative gram-negative bacilli isolated from various clinical samples in hospitalized patients to some antibiotics.

Methods: A retrospective study of 23118 *Enterobacteriaceae* and 6864 non-fermentative gram-negative bacilli was performed over a 5-year period (2015-2019) at Ondokuz Mayıs University Faculty of Medicine Hospital. Isolates were identified and their antibiotic susceptibilities were determined using the Vitek MS (bioMérieux, France) system. Results were interpreted according to the EUCAST criteria of that year.

Results: The sensitivity rates of some of the investigated antibiotics have decreased over the years. Carbapenems are the most sensitive group for *Enterobacteriaceae* isolates, and aminoglycoside antibiotics remain important for non-fermentative bacteria.

Conclusion: To determine empirical treatment for microorganisms frequently isolated in the clinic and to reduce mortality and morbidity, many clinical microbiology laboratories should regularly publish cumulative antimicrobial susceptibility testing data. There is widespread agreement that cumulative antibiogram reports should be prepared and incorporated into hospital infection control policies.

Keywords: *Enterobacteriaceae*, non-fermentative bacteria, cumulative antibiogram, resistance

INTRODUCTION

Antibiotic resistance rates may vary over time and regionally. Clinical microbiology laboratories regularly share cumulative antimicrobial susceptibility testing data to determine empirical treatment for microorganisms frequently isolated in hospitals and to reduce mortality and morbidity.[1] Today, multidrug-resistant *Enterobacteriaceae* and non-fermentative gram-negative bacilli are prominent in hospital infections due to their limited treatment options and negative effects on patient survival rates.[2] Gram-negative bacilli of clinical importance in healthcare-associated infections are *Enterobacteriaceae* [especially *Klebsiella* species and *Escherichia coli (E. coli)*], *Pseudomonas aeruginosa (P. aeruginosa)* and *Acinetobacter baumannii (A. baumannii)*. Resistant strains of these bacteria are detected at high rates all over the world.[3] Antimicrobial susceptibility testing is used in hospitals to detect widespread antimicrobial resistance, monitor local trends, and guide targeted empirical treatment by determining antibiotic policy.[4] Cumulative antimicrobial susceptibility test reports are guiding in investigating resistance trends that develop over time in a region and in regulating antibiotic use. It is reported that each hospital's regular evaluation of its own data plays an important role in regulating treatment with culture and antibiogram results and preventing antibiotic resistance.[5] The aim of this study is to evaluate the cumulative antimicrobial susceptibility data of bacteria isolated from various clinical samples sent to the microbiology laboratory and to contribute to the antibiotic management policies of our hospital.

METHODS

The ethics committee approval for this study was obtained from the Ondokuz Mayıs University Faculty of Medicine Ethics Committee (Date: 27.11.2020, Decision No: 2020/657). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A cumulative antibiogram is a cumulative report of the in vitro susceptibility percentage of clinically significant primary bacterial isolates to various antibiotics over a specific period (usually one year) in a healthcare facility. Bacterial species with >30 isolates are evaluated according to cumulative antibiogram guidelines.[6] Isolates were identified using an automated mass spectrometry microbial identification system (bioMérieux, France) employing VITEK MS, matrix-

Corresponding Author: Canberk Çınar, cinarcanberk57@gmail.com

assisted laser desorption ionization time-of-flight (MALDI-TOF) technology, and antimicrobial susceptibility testing was performed using the VITEK® 2 COMPACT automated microbial identification system. The results were interpreted according to the criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2020) for that year. Cumulative antibiogram reports of isolates were prepared according to the criteria in the CLSI M39-A4 2014 guideline for the analysis and presentation of antimicrobial susceptibility data and the 2019 guideline of the Association of Clinical Microbiologists (KLIMUD).[6] Bacterial species with 30 or more isolates during the study period were included in the study. Patients' first isolates were evaluated. Routinely tested antibiotics were included in the study, and susceptibility rates to these antibiotics were reported. Isolates were divided into two groups: *Enterobacteriaceae* and non-fermentative gram-negative bacilli. Descriptive statistics such as numbers and percentages were used for the samples included in the study. Routinely tested antibiotics were those tested for *Enterobacteriaceae* and non-fermentative gram-negative bacilli according to the EUCAST criteria for that year. These antibiotics are listed in the tables within the study. Antibiotics for which sensitivity rates could not be determined are left blank in the table.

RESULTS

The susceptibility rates of 23118 *Enterobacteriaceae* and 6864 non-fermentative gram-negative bacilli were retrospectively analyzed over a 5-year period (2015-2019) at Ondokuz Mayıs University Faculty of Medicine Hospital. Seven *Enterobacterales* and two non-fermentative gram-negative bacilli species were included in the study. The species distribution of the samples is shown in **Figure 1, 2**.

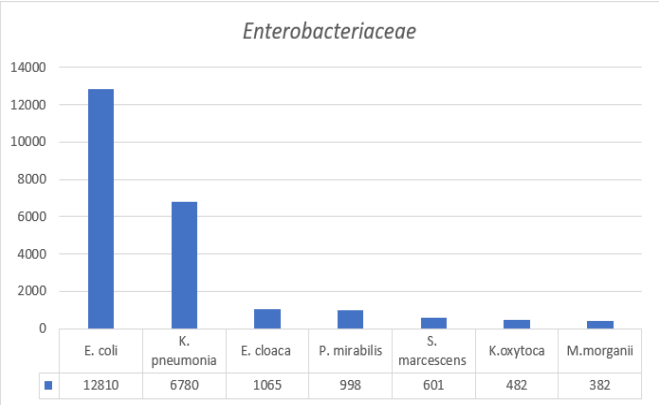

Figure 1. Types of *Enterobacteriaceae* isolates

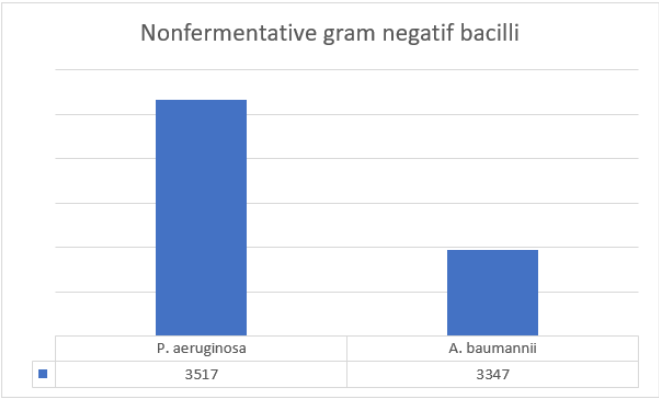

Figure 2. Types of nonfermentative gram-negative bacilli

Table 1. Antibiotic susceptibility rates of *E. coli* isolates

E. coli	2015	2016	2017	2018	2019
Ampicillin	28%	32%	32%	33%	32%
AMC	51%	47%	51%	35%	32%
Piperacillin	64.7%	63.2%	74.9%	75%	74%
Cefepim	73.6%	71.3%	49.6%	46%	40.8%
Cefixime	-	44.2%	%61.3	%52.6	%51.5
Ceftazidime	66.5%	60.6%	58.7%	52.1%	50.5%
Ceftriaxone	62.5%	60.6%	59.1%	52.2%	50.2%
Cefuroxime	54.3%	54.4%	53.7%	46.1%	43.3%
Imipenem	99.4%	99.1%	99%	94.7%	94.2%
Meropenem	99.4%	99.2%	98.8%	95.4%	93.8%
Ertapenem	97%	97%	98%	88%	92%
Ciprofloxacin	64.3%	60.2%	59.4%	51.1%	49.1%
Amikasin	86%	84%	89%	88%	90%
Gentamicin	82.8%	84.2%	83.5%	80.8%	84.3%
Tigecycline	98%	95%	94%	88%	92%

E. coli: Escherichia coli, AMC: Amoxicillin-clavulonic acid

Table 2. Antibiotic susceptibility rates of *K. pneumonia* isolates

K. pneumonia	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	33%	36%	35%	26%	23%
Piperacillin	40%	40.2%	42.9%	37.5%	39.7%
Cefepim	41.4%	37.8%	34%	29.3%	23.4%
Cefixime	-	32.6%	42.7%	36.8%	34.8%
Ceftazidime	39%	36%	38.3%	32.5%	27.5%
Ceftriaxone	38%	36.1%	38.6%	33%	28%
Cefuroxime	34%	33.3%	35.2%	29.7%	26.4%
Imipenem	70.8%	74.5%	85.2%	73.6%	69.1%
Meropenem	72.8%	74.5%	81.4%	71.9%	67%
Ertapenem	59%	63%	65%	61%	59%
Ciprofloxacin	51.2%	52.6%	53.3%	43.3%	37.7%
Amikasin	73%	76%	83%	76%	70%
Gentamicin	74.2%	70.4%	68.2%	65.5%	62%
Tigecycline	80%	71%	75%	53%	53%

K. pneumonia: Klebsiella pneumonia, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

The most frequently detected isolate among *Enterobacteriaceae* was *E. coli*, with *K. pneumoniae* coming in second. Among non-fermentative gram-negative bacilli, *P. aeruginosa* and *A. baumannii* isolates were also included in the study. When the antibiotic susceptibilities of *E. coli* isolates were compared over the years, it was observed that the susceptibilities of some antibiotics [amoxicillin-clavulonic acid (AMC), ceftazidime, ceftriaxone, imipenem, meropenem, ertapenem, ciprofloxacin] decreased. When *K. pneumoniae* isolates were examined over a five-year period, a decrease in the susceptibility rates of some antibiotics (AMC, piperacillin, cefepime, gentamicin) was observed. The highest susceptibility rates were seen with carbapenems in both groups. Antimicrobial susceptibility rates for *E. coli* and *K. pneumoniae* are given in **Table 1, 2**.

When *K. oxytoca* isolates were examined over a five-year period, AMC sensitivity decreased. No decrease in sensitivity

to other antibiotics was observed. The highest sensitivity rates were again observed in carbapenems. A decrease in cephalosporin susceptibility has been observed for *Enterobacter cloacae (E. cloacae)* isolates in the last two years. The highest susceptibility rates in both groups were observed for carbapenems and aminoglycosides. Susceptibility rates for *K. oxytoca* and *E. cloacae* are given in **Table 3, 4**.

Table 3. Antibiotic susceptibility rates *of K. oxytoca isolates*

K. oxytoca	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	60.9%	74.8%	62.5%	54.9%	57%
Piperacillin	66%	79%	76%	80%	85%
Cefepim	71.6%	83.8%	72.4%	84.1%	94.3%
Cefixime	-	54.5%	80.4%	89%	75.7%
Ceftazidime	72.8%	84.8%	79%	87.6%	86.5%
Ceftriaxone	65.2%	68.5%	73.1%	83.1%	83.1%
Cefuroxime	63%	75%	72%	78%	83%
Imipenem	92.4%	96.7%	95.9%	95%	96.5%
Meropenem	96.7%	97.8%	96.6%	95.5%	96.6%
Ertapenem	77%	86%	92%	91%	97%
Ciprofloxacin	75%	93%	83%	87%	86%
Amikasin	95.6%	90%	95.8%	96.6%	96.6%
Gentamicin	76%	96%	88%	93%	97%
Tigecycline	93.75%	94.3%	92%	88.1%	96%

K. oxytoca: Klebsiella oxytoca, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

Table 4. Antibiotic susceptibility rates of *E. cloacae* isolates

E. cloacae	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	NR	NR	NR	NR	NR
Piperacillin	64%	57%	82%	58%	74%
Cefepim	80.5%	82.7%	80%	71%	72%
Cefixime	-	-	-	-	-
Ceftazidime	67%	84.8%	70.6%	59.7%	61.8%
Ceftriaxone	71.7%	68.5%	71.1%	59.7%	62%
Cefuroxime	24%	75%	6%	1%	2%
Imipenem	94%	97.6%	96.9%	93.5%	97.2%
Meropenem	95.4%	97.7%	98%	96%	97%
Ertapenem	87%	88%	92%	84%	89%
Ciprofloxacin	95%	96%	91%	80%	90%
Amikasin	97.4%	93%	96%	53.4%	98.5%
Gentamicin	95.4%	96.7%	90.5%	84%	95.8%
Tigecycline	71.7%	76.3%	89%	75.8%	84.7%

E. cloacae: Enterobacter cloacae, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

Decreased susceptibility to ampicillin, AMC, ceftazidime, and ceftriaxone was observed in *Proteus mirabilis* isolates. Susceptibility rates for *Morganella morganii*, *Serratia marcescens* and *Proteus mirabilis* are shown in **Table 5-7**.

P. aeruginosa and *A. baumannii*, which are frequently isolated from non-fermentation bacteria, were analyzed, and their antimicrobial susceptibility rates are shown in **Table 8, 9**.

Table 5. Antibiotic susceptibility rates of *M. morganii* isolates

M. morgagni	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	NR	NR	NR	NR	NR
Piperacillin	59%	76%	90%	92%	67%
Cefepim	66%	76%	92%	81%	60%
Cefixime	-	30	54.5%	46.5%	30.7%
Ceftazidime	45%	63%	73%	65%	49%
Ceftriaxone	48.5%	63.7%	75.3%	67%	52.3%
Cefuroxime	0%	3%	1%	0%	2%
Imipenem	95.2%	92.4%	93.7%	100%	88.5%
Meropenem	100%	99%	99%	100%	100%
Ertapenem	100%	97%	99%	100%	99%
Ciprofloxacin	45.4%	69%	75.3%	49.4%	52.3%
Amikasin	77%	90%	92%	99%	94%
Gentamicin	69.7%	81.3%	78%	73%	69.2%
Tigecycline	5.9%	12.8%	12%	7.9%	17.5%

M. morganii: Morganella morganii, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

Table 6. Antibiotic susceptibility rates of *P. mirabilis* isolates

P. mirabilis	2015	2016	2017	2018	2019
Ampicillin	56.6%	52.2%	53.2%	42%	40%
AMC	86.6%	74.7%	75.3%	59.3%	69.4%
Piperacillin	94.2%	85.6%	90.2%	89.6%	96.7%
Cefepim	86.8%	79.6%	91.7%	68.6%	74.2%
Cefixime	-	69.6%	54.5%	71.7%	69.6%
Ceftazidime	84%	81%	81%	81%	79%
Ceftriaxone	89.7%	81.5%	82%	82.5%	77.5%
Cefuroxime	85.4%	80.5%	79.3%	78.1%	70.3%
Imipenem	96.7%	86%	90.8%	88.6%	93.8%
Meropenem	99.4%	92.6%	97.3%	95.7%	97.6%
Ertapenem	90.1%	86.6%	91.3%	80.7%	88.5%
Ciprofloxacin	77.7%	68.7%	77.4%	59%	60.5%
Amikasin	96%	89%	91%	88%	88%
Gentamicin	81%	73%	76%	74%	75%
Tigecycline	NR	NR	NR	NR	NR

P. mirabilis: Proteus mirabilis, AMC: Amoxicillin-clavulonic acid, NR: Naturally resistant

Table 7. Antibiotic susceptibility rates of *S. marcescens* isolates

S. marcescens	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	NR	NR	NR	NR	NR
Piperacillin	73.4%	88.9%	75.2%	86.6%	90.3%
Cefepim	88.9%	95.2%	85.5%	88.1%	85%
Cefixime	-	18.2%	35.5%	-	23.8%
Ceftazidime	77.9%	90.7%	82.4%	85.9%	84.1%
Ceftriaxone	81.6%	88.1%	80.8%	82.8%	80.9%
Cefuroxime	NR	NR	NR	NR	NR
Imipenem	92.5%	99.1%	89.1%	98.2%	97.4%
Meropenem	100%	99%	93%	98%	99%
Ertapenem	88%	99%	83%	93%	95%
Ciprofloxacin	94%	94%	92%	90%	93%
Amikasin	87.7%	94.9%	85.6%	97.6%	98.4%
Gentamicin	86.7%	95.7%	84%	93.7%	97.6%
Tigecycline	22.6%	-	76%	68.4%	79.8%

S. marcescens: Serratia marcescens, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

Table 8. Antibiotic susceptibility rates of *P. aeruginosa* isolates

P. aeruginosa	2015	2016	2017	2018	2019
Piperacillin	51.8%	56.3%	62.5%	57.3%	50.5%
Piperacillin-tazobactam	61%	56%	64.7%	61.4%	66.6%
Cefepim	72.8%	71.5%	79%	66.5%	68.8%
Ceftazidime	74.2%	76.1%	80.2%	76.9%	79.7%
Imipenem	75.5%	73%	70.8%	63.2%	64.3%
Meropenem	75.5%	73.5%	70.3%	62.5%	63.7%
Ciprofloxacin	82%	75.3%	72.6%	63.7%	63.4%
Levofloxacin	78.3%	69%	65.9%	58%	59.1%
Amikasin	90.8%	90.2%	88.2%	81.1%	79%
Gentamicin	88.8%	87.6%	87.8%	74.4%	81.9%

P. aeruginosa: Pseudomonas aeruginosa

Table 9. *Antibiotic susceptibility* rates of *A. baumannii* isolates

A. baumannii	2015	2016	2017	2018	2019
Imipenem	16.3%	13.7%	14.8%	15.4%	9.7%
Meropenem	16.5%	13.8%	14.8%	15.1%	9.6%
Ciprofloxacin	15%	92.1%	13.3%	14.1%	5.9%
Levofloxacin	15.4%	13.4%	13.4%	13.7%	9.2%
Amikasin	25%	47%	64%	73.6%	47.3%
Gentamicin	22.3%	28.2%	41.3%	38%	17.3%
Trimethoprim sulfamethoxazole	48.8%	29%	27%	25.9%	14.8%

A. baumannii: Acinetobacter baumannii

Imipenem and meropenem susceptibility were higher in *P. aeruginosa* than in *A. baumannii* isolates. Carbapenem susceptibility decreased over time in both species.

DISCUSSION

Preparation of cumulative antibiogram reports is crucial for antimicrobial stewardship.[7] Antibiotic resistance rates in *Enterobacteriaceae* and non-fermentative gram-negative bacilli vary over time. Therefore, regular reporting of antimicrobial susceptibility profiles and their characteristics is necessary for each site.[8] Because the incidence of antibiotic resistance varies geographically, clinicians need to understand regional resistance rates to best manage empiric treatment.[4] Monitoring the sensitivity rates of antibiotics used with cumulative antibiogram is an important part of antibiotic stewardship programs.[9] Choosing the right antimicrobial is possible by knowing the bacteria that are frequently identified as pathogens in the hospital and their antimicrobial susceptibility results.[6] Studies suggest that routine microbiology laboratories can contribute to the clinician's empirical treatment and to use antibiotics rationally by preparing annual cumulative antibiogram reports using data from antibiotic tests, thus achieving success in the treatment of resistant infections.[10] When we look at the studies on antimicrobial susceptibility of *Enterobacteriaceae* and non-fermentative gram-negative bacilli conducted in our country, it is observed that there has been an increase in multidrug-resistant *Acinetobacter* spp. and multidrug-resistant *P. aeruginosa* isolates, including carbapenems, and in extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* strains over the years.[11] In our study, a five-year retrospective analysis of data showed that carbapenems are still effective against *Enterobacteriaceae* but susceptibility to some antibiotics has decreased over time. Among non-fermentative bacteria, *P. aeruginosa* was found to have higher susceptibility rates to aminoglycosides, while *A. baumannii* isolates were found to have lower susceptibility rates to aminoglycosides and other antibiotics.[7] Evaluation of *E. coli* isolates revealed that the most effective antibiotics were amikacin, ertapenem, meropenem, cefotetan, fosfomycin, and piperacillin-tazobactam. Based on these results, carbapenems are the preferred antibiotic group for empirical treatment of *Enterobacteriaceae* until antibiogram results are available.[2] In a study conducted with *Enterobacteriaceae* and non-fermentative gram-negative bacilli from blood cultures, the antibiotics with the lowest resistance rates for *E. coli* and *K. pneumoniae* were found to be carbapenems, as in our study. For *P. aeruginosa* and *A. baumannii* the most effective group was found to be aminoglycosides, as in our study.[12] Various studies conducted on this subject in our country and other countries have revealed that resistance rates in *Enterobacteriaceae* and non-fermentative gram-negative bacilli have increased.[13] In a six-year study presenting antibiogram data of gram-negative bacteria, carbapenems were found to perform well for gram-negatives, but susceptibility to cephalosporins and fluoroquinolones was reduced.[14] In another study, similar to our study, it was found that susceptibility to cefepime, fluoroquinolones, aminoglycosides decreased in *Enterobacteriaceae* and non-fermentatives, and it was reported that limited prescription of carbapenems may be beneficial.[15] In a study conducted in our country on this subject, carbapenem resistance rates were found to be lower for *E. coli*, as in our study. However, carbapenem resistance rates for *Klebsiella, Pseudomonas*, and *Acinetobacter* were significantly increased.[16] A study examining data between 2014 and 2023 found a gradual increase in *E. coli* with the extended-spectrum beta-lactamase phenotype. Small but statistically significant decreases in *E. coli* susceptibility to ceftriaxone and meropenem were detected over the past decade. These data reveal a concerning trend.[17] In a study evaluating *E. coli* and *Klebsiella* spp. isolates, high susceptibility levels were observed for carbapenems, piperacillin/tazobactam, amikacin, and nitrofurantoin. It has been reported that they can be used in appropriate empirical treatment.[18] In our study, we examined the antimicrobial susceptibility profiles of the most frequently isolated bacteria by year. We sought to identify increasing resistance rates over a five-year period and the antibiotics to which the isolates were most susceptible. A disadvantage of our study is that the isolates were not discriminated against at the material level and their statistical analysis was not performed.

CONCLUSION

As a result, the resistance problem of *Enterobacteriaceae* and non-fermentative gram-negative bacilli is increasing in our region. More measures should be taken on infection control at hospital and sub-hospital level. It is thought that regular cumulative data collection may contribute to the prevention of antibiotic resistance. The cumulative antibiogram data presented in this study are expected to provide a scientific basis for updating our institution's empirical antibiotic treatment protocols and to contribute to the development of a more effective and targeted antimicrobial management strategy in the fight against antimicrobial resistance.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the the Ondokuz Mayıs University Faculty of Medicine Ethics Committee (Date: 27.11.2020, Decision No: 2020/657).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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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Original Article

Analysis of patients diagnosed with acute pancreatitis: a retrospective single-centre study

Ramazan İpek[1], Mehmet Erdem[2], Ozan Aydemir[2], Orhan Sezgin[3]

[1]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye
[2]Department of Internal Medicine, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkiye
[3]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Mersin University, Mersin, Turkiye

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ABSTRACT

Aims: Acute pancreatitis is an inflammatory disease of the pancreas and may be limited to the pancreas or may affect many organs and result in death. Different theories have been proposed in its pathogenesis. The aim of this study was to discuss the demographic characteristics, etiological causes and clinical features of patients with acute pancreatitis, whose frequency is not known in our country but which we see frequently in our daily practice.

Methods: The files of patients admitted to the gastroenterology clinic between May 2005 and May 2014 and diagnosed with acute pancreatitis were retrospectively reviewed. Age, gender, mode of presentation, cause of acute pancreatitis, clinical features and prognosis were analysed.

Results: A total of 630 patients were retrospectively analysed. Of the 630 patients diagnosed with acute pancreatitis, 289 (45.9%) were male and 341 (54.1%) were female. The mean age was 55.58±17.4 years. The most common etiological cause was biliary causes in 420 (66.7%) patients. The most common reason for presentation was abdominal pain and nausea and vomiting in 415 (65.9%) patients. The most common presentation (28%) was in the spring season. 614 (97.4%) patients were discharged with recovery and 16 (2.6%) patients died. It was found that 3 methods (Ranson, APACHE, Atlanta) used in prognosis determination gave similar results.

Conclusion: Acute pancreatitis, which can be a mortal disease, has different etiological factors and the most common etiological factor is biliary origin. Abdominal ultrasonography is a valuable method in the detection of biliary pathologies. The most common presentation is abdominal pain accompanied by nausea and vomiting. It was observed that different scoring systems did not differ from each other.

Keywords: Acute pancreatitis, demographic characteristics, Ranson criteria

INTRODUCTION

Pancreas is an organ that provides synthesis, storage and secretion of large amounts of proteins consisting of digestive enzymes. Acute pancreatitis is a complex disease in which inactive digestive enzymes of the pancreas become active due to any etiological cause and may lead to pancreatic tissue damage, multiple organ failure and pancreatic necrosis.[1] This clinical condition may manifest itself in a wide range including mild abdominal pain, hypotension, fluid sequestration, metabolic disorders, sepsis and severe complications including death.[2] Approximately 25-30% of pancreatitis-related deaths occur in the first week of the disease and develop due to systemic causes related to progressive organ failure. Deaths observed in patients after the second week of hospitalisation are usually due to local complications including infected pancreatitis and necrosis.[3]

The most commonly used scoring system to determine the severity of acute pancreatitis today is the Ranson, Acute Physiology and Chronic Health Evaluation (APACHE) II and Atlanta criteria.[4]

The disease improves with conservative treatment to a great extent. Methods such as early intensive care follow-up, enteral feeding, ERCP, sphincterotomy, broad-spectrum antibiotherapy are used in the treatment of severe acute pancreatitis. The mortality rate of severe acute pancreatitis with mortality <1% is very high. This rate reaches 25% in patients with infected pancreatic necrosis or multiorgan failure. Diabetes mellitus may develop in 1/3-5 of recovered cases.[5]

METHODS

Study Design

The study was carried out with the permission of the Mersin University Ethics Committee (Date: 05.06.2014, Decision No: 2014/117). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study included 630 patients hospitalised with the diagnosis of acute pancreatitis in the Gastroenterology

Corresponding Author: Mehmet Erdem, dr.mehmet_erdem@hotmail.com

Clinic of Mersin University Medical Faculty Hospital between May 2005 and May 2014. The study data were collected retrospectively from files and system records. Demographic characteristics, clinical conditions, laboratory tests and imaging results were recorded.

Inclusion Criteria

Patients aged 17 years and older, patients diagnosed with acute pancreatitis.

Exclusion Criteria

Patients under 17 years of age, patients who refused treatment, patients who developed pancreatitis after ERCP.

Statistical Analysis

SPSS 11.5 statistical package programme was used for statistical analysis of the data. For categorical variables, numbers and percentages were used as descriptive statistics. Chi-square analysis was performed to determine the relationship between two categorical variables. MedCalc 10.3.0 statistical package programme was used to determine the categorical variables with ratio difference between them. Median, minimum and maximum values were given as descriptive statistics for continuous variables that did not meet the assumption of normal distribution. Mann Whitney test, one of the nonparametric tests, was performed to examine the difference between two groups. Pearson correlation coefficient was used to determine the relationship between length of hospitalisation and wbc, crp ast. Logistic regression analysis was used to determine the independent markers that increase ranson 48 using the predetermined possible factors. Statistical significance level was taken as 0.05.

RESULTS

630 patients were included in the study. Gender, age below/above 55 years, body mass index, aetiology, initial presentation complaint and laboratory results at initial presentation are shown in **Table 1**. Of the patients, 289 (45.9%) were male, 341 (54.1%) were female, and the mean age was 55.58±17.4 years. Body mass index of 260 patients was calculated. Body-mass index was classified as underweight, normal, overweight, obese and morbidly obese. According to body-mass index, underweight 5 (1.9%), normal 73 (28.1%), overweight 116 (44.6%), obese 60 (23.1%) and morbidly obese 6 (2.3%) patients were observed. The most common aetiology was due to biliary causes (66.7%). When other causes were analysed, 8.6% were alcohol, 5.4% hyperlipidaemia and 19.4% other causes. Etiological classification was also made according to gender. The etiology of acute pancreatitis in women was 76.2% biliary causes, 1.1% alcohol, 4.7% hyperlipidaemia and 18.8% other causes, while in men it was 55.4% biliary causes, 17.3% alcohol, 6.2% hyperlipidaemia and 20.1% other causes. There was a significant relationship between etiology and gender ($p<0.05$). This relationship was thought to be due to the difference in the rates of biliary and alcoholism between men and women ($p<0.0001$). The most common reason for presentation was abdominal pain and nausea and vomiting (65.9%).

Ultrasonography was performed in 551 patients (87.5%) during hospitalisation. The most common ultrasonographic finding was gallbladder calculi (33%) and other findings are shown in **Table 2**.

When the seasons during admission to the hospital were analysed, the least admission was in winter (22%) and the most admission was in spring (28%). This difference was statistically significant ($p=0.03$). However, there was no difference according to other seasons (**Figure**).

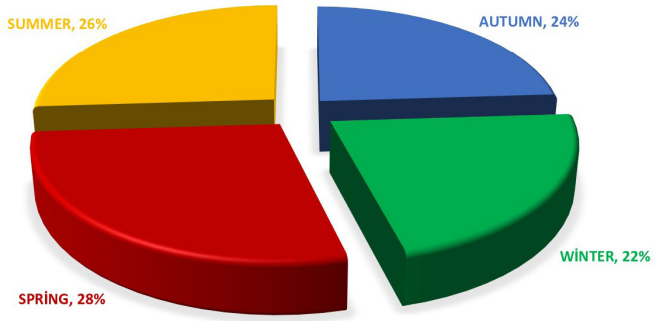

Figure. Frequency of acute pankreatitis according to seasons

The antibiotics taken by the patients during hospitalisation, complications and discharge status are shown in **Table 3**. It was observed that 66.7% of the patients did not receive antibiotics, 16.5% received imipenem and 14% received ceftriaxone. It was observed that 94.1% of the patients did not develop any local complications and 73% did not develop systemic complications. Local complications were necrosis in 4.3%, pseudocyst in 1%, abscess in 0.7% and other complications in 0.5%. The number of patients discharged was 614 (97.4%) and the number of patients who died was 16 (2.6%).

The demographic characteristics of the patients and the relationship of clinical and imaging results with the severity of acute pancreatitis according to Ranson, Atlanta and APACHE scoring are shown in **Table 4**.

Chest radiography was performed in all patients. Acute pancreatitis severity was divided into mild and severe according to Ranson, APACHE and Atlanta scoring. Patients with findings in favour of pneumonia and pleural fluid on chest radiography were identified. According to the Ranson scoring, pneumonia was seen in 1 (0.2%) and pleural fluid was seen in 12 (2.3%) patients who were considered mild; pneumonia was seen in 2 (1.8%) and pleural fluid was seen in 11 (9.6%) patients who were considered severe. According to APACHE scoring, pneumonia was seen in 2 (0.4%) and pleural fluid in 13 (2.6%) patients who were considered mild; pneumonia was seen in 1 (0.8%) and pleural fluid in 10 (7.9%) patients who were considered severe. According to the Atlanta scoring, no pneumonia was observed in any of the patients who were considered mild, while pleural fluid was seen in 8 (1.6%) patients; pneumonia was seen in 3 (2.2%) and pleural fluid in 15 (10.9%) patients who were considered severe. A significant difference was found between mild and severe groups in all three scoring systems in patients with chest radiographs ($p<0.05$).

Computerised tomography was performed in 169 patients. 555 of the patients had a first episode of pancreatitis. No significant difference was observed in the severity of pancreatitis in the three scoring systems among patients who underwent computed tomography, those who had one or more episodes of pancreatitis and between genders ($p>0.05$).

In patients under and over 55 years of age, the severity of acute pancreatitis was evaluated according to Ranson, APACHE and

Table 1. Demographic, clinical characteristics and laboratory results of patients with acute pancreatitis				
			n (%)	
Gender	Female		341 (54.1)	
	Male		289 (45.9)	
Age (years)	Under 55 years		321 (51)	
	Over 55 years		309 (49)	
Body-mass index	Underweight		5 (1.9)	
	Normal		73 (28.1)	
	Overweight		116 (44.6)	
	Obese		60 (23.1)	
	Morbid obese		6 (2.3)	
Etiology	Biliary causes	Female	260 (76.2)	420 (66.7)
		Male	160 (55.4)	
	Alcohol	Female	4 (1.1)	54 (8.6)
		Male	50 (17.3)	
	Hyperlipidemia	Female	16 (4.7)	34 (5.4)
		Male	18 (6.2)	
	Other causes	Female	64 (18.8)	122 (19.4)
		Male	58 (20.1)	
Clinical presentation	Abdominal pain		196 (31.1)	
	Nausea-vomiting		1 (0.2)	
	Fever		1 (0.2)	
	Abdominal pain+nausea-vomiting		415 (65.9)	
	Abdominal pain+fever		7 (1.1)	
	Abdominal pain+nausea-vomiting+fever		10 (1.6)	
Laboratory values at initial admission				
Parameter		**Median**	**Minimum**	**Maximum**
Leukocytosis (cells/mm^3)		11550	2100	66650
Fasting blood glucose (mg/dl)		120	11	570
AST (IU/L)		20	10	579
LDH (IU/L)		314	29	2822
LDL (mg/dl)		104	15	262
Triglyceride (mg/dl)		110	28	13750
Total cholesterol (mg/dl)		170	44	1355
Amylase (IU/L)		1167	24	9590
Lipase (IU/L)		2249	21	51460
ALP (IU/L)		113	25	1175
GGT (IU/L)		144	3.6	5825
Total bilirubin (mg/dl)		1.1	0.03	68
Direct bilirubin (mg/dl)		0.4	0	60

AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, LDL: Low-density lipoprotein, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase

Atlanta scoring. Statistically, there was a significant difference between patients under and over 55 years of age according to all three severity scores ($p<0.0001$).

DISCUSSION

Female gender (54.1%) was more common in the patients admitted to our study. According to body mass index, overweight patients (44.6%) were more common. Although biliary causes (66.7%) were the most common in both males and females, there was a significant difference between etiology and gender. The main reason for this difference was that alcohol use was less in women and more in men. The most common presenting complaint was abdominal pain with nausea and vomiting (65.9%), and all patients had abdominal pain (99%). Patients presented most frequently in spring and least frequently in winter. A significant difference was observed between these two seasons. Most of the patients did not develop any local or systemic complications and 16 patients died while 614 patients were discharged. There was a statistically significant difference between the patients who had chest radiographs and who were over and under 55 years of age according to Ranson, APACHE and Atlanta scoring.

The pancreas is an organ of the gastrointestinal tract with both endocrine and exocrine functions. In acute pancreatitis,

Table 2. Ultrasonographic findings of the patients

Findings	n	%
Normal	82	13
Enlarged pancreas	30	4.8
Peripancreatic fluid	5	0.8
Heterogeneous pancreas	33	5.2
Cyst-pseudocyst	3	0.5
Gallbladder stones-sludge	208	33
Stone in common bile duct-dilated duct	28	4.4
Dilated intrahepatic bile ducts	7	1.1
Other (pancreatic duct dilation/mass)	7	1.1
Enlarged pancreas/cyst-pseudocyst	22	3.5
Enlarged pancreas/stone in common bile duct-dilated duct	30	4.8
Cyst-pseudocyst/stone in common bile duct-dilated duct	19	3
Stone in common bile duct-dilated duct/dilated intrahepatic bile ducts	39	6.2
Stone in common bile duct-dilated duct/other (pancreatic duct dilation/mass	13	2.2
Enlarged pancreas/cyst-pseudocyst/stone in common bile duct-dilated duct	14	2.2
Stone in common bile duct-dilated duct/dilated intrahepatic bile ducts/other	11	1.7
Total	551	87.5

digestive enzymes in the pancreatic tissue damage the pancreas for any reason. While mild pancreatitis causes only local effects, severe pancreatitis may cause systemic effects and lead to multiple organ failure.[6]

In a recent study including 104 patients, 59.6% were male and 40.4% were female. The mean age was 71.5 years. Etiologically, 58.7% were idiopathic, 37.5% biliary causes and 3.8% malignancies. While 98 of the patients were discharged, 6 of them died.[7]

Table 3. Antibiotic use and clinical course during hospitalization of patients with acute pancreatitis

		n	%
Antibiotic	None	420	66.7
	Ceftriaxone	88	14
	Imipenem	104	16.5
	Other (ciprofloxacin, sulperazone)	14	2.1
	Ceftriaxone+imipenem	3	0.5
	Ceftriaxone+imipenem+other	1	0.2
Local complications	None	594	94.1
	Abscess	2	0.3
	Pseudocyst	4	0.6
	Necrosis	25	4.1
	Other	3	0.5
	Pseudocyst+abscess	1	0.2
	Abscess+pseudocyst+necrosis	1	0.2
Systemic complications	None	460	73
	Circulatory	8	1.3
	Respiratory	8	1.3
	Renal	2	0.3
	Other	132	21.1
	Involvement of multiple systems	19	3
Discharge	Non-operated	600	95.2
	Operated	14	2.2
Death	Non-operated	13	2.1
	Operated	3	0.5

In the study by Gümüş et al.[8] 163 (40.6%) of the patients were male and 238 (58.4%) were female and the mean age was 58.6 years. According to the APACHE scoring system, the mean age was 67.5 years in severe pancreatitis and 52.8 years in mild pancreatitis. Of the patients with acute pancreatitis, 304 (75.8%) were due to gallstones. While 385 (96%) of the

Table 4. Relationship of patients' demographic characteristics, clinical and imaging results with the severity of acute pancreatitis based on Ranson, APACHE, and Atlanta scoring systems

		Ranson		APACHE		Atlanta	
		Mild (%)	Severe (%)	Mild (%)	Severe (%)	Mild (%)	Severe (%)
Chest X-Ray (n: 630)		515 (81.9)	115 (18.1)	504 (80)	126 (20)	491 (78.1)	139 (21.9)
Pneumonia		1 (0.2)	2 (1.8)	2 (0.4)	1 (0.8)	0	3 (2.2)
Plevral effusion		12 (2.3)	11 (9.6)	13 (2.6)	10 (7.9)	8 (1.6)	15 (10.9)
p		0.001		0.028		<0.0001	
Computed tomography (n: 169)		112 (66.3)	57 (33.7)	112 (66.3)	57 (33.7)	99 (58.5)	70 (41.5)
p		>0.05					
Number of pancreatitis attacks	First attack (n: 555)	450 (81.1)	105 (18.9)	438 (78.9)	117 (21.1)	427 (76.9)	127 (23.1)
	Attack >1 (n: 75)	66 (88)	9 (12)	66 (88)	9 (12)	64 (85.3)	11 (14.7)
p		>0.05					
Gender	Female (n: 341)	270 (52.4)	70 (61.4)	275 (54.6)	66 (52.4)	265 (54)	75 (54.3)
	Male (n: 289)	245 (47.6)	44 (38.6)	229 (45.4)	60 (47.6)	226 (46)	63 (45.7)
p		>0.05					
Gender	<55 (n: 321)	300 (58.3)	21 (18.4)	289 (57.3)	32 (25.4)	287 (58.5)	33 (23.9)
	>55 (n: 309)	215 (41.7)	93 (81.6)	215 (42.7)	94 (74.6)	204 (41.5)	105 (76.1)
p		<0.0001					

APACHE: Acute Physiology and Chronic Health Evaluation

patients presented at the first attack, 16 (4%) presented with recurrent attacks. While no gender difference was observed in acute pancreatitis cases not due to gallstones, a statistically significant difference was found in female gender (M/F: 1/1.7) in acute pancreatitis due to gallstones ($p<0.05$). According to Atlanta scoring, 244 (61.8%) patients were evaluated as mild and 157 (39.2%) as severe acute pancreatitis. Twenty-seven of the patients underwent emergency surgery and the other patients received medical treatment. Mortality was observed in 7 (25.9%) patients who underwent surgery and mortality was observed in 18 (4.5%) of all patients.

In another study, 86 patients were included. The mean age of the patients was 52.33 years, 48 (55.8%) were female and 38 (44.2%) were male. All patients complained of abdominal pain at presentation, nausea and vomiting were found in 48 (55.81%) patients and dyspnoea in 2 (2.32%) patients. In the evaluation of the severity of acute pancreatitis according to Atlanta scoring, mild acute pancreatitis was found in 58 (67.4%) patients and severe acute pancreatitis was found in 28 (32.6%) patients. The mean duration of hospitalisation was 6.96 days. As a result of the treatment of the patients, 85 patients were discharged, 1 patient died and mortality was found to be 1.16%.[9]

In a study investigating the relationship between the severity of acute pancreatitis and platelet lymphocyte ratio, 418 patients were included and 370 (65.4%) of these patients were female and 197 (34.6%) were male. The mean age of the patients was 45.44±36.94 years. The mean duration of hospitalisation was 6.61±3.15 days. Etiologically, 301 (72%) patients had biliary origin and 117 (28%) patients had non-biliary origin. According to Ranson scoring, pancreatitis was mild in 394 (94.25%) patients and severe in 24 (5.75%) patients.[10]

The results of our study were similar to those found in the literature. However, it is remarkable that gallstones are approximately 8 times more common in the etiology of acute pancreatitis than alcohol consumption. This difference may be explained by the difference in alcohol consumption habits in our society compared to western societies.

Abdominal ultrasonography is useful in the detection of pancreatic enlargement and inflammatory changes and etiological pathology of the gallbladder and biliary tract. The disadvantage of the method is that it is user dependent and the evaluation is not adequate in the presence of intra-abdominal gas. The visualisation rate of the pancreas varies between 62% and 90%.[11] In our study, 551 (87.5%) of 630 patients were evaluated by ultrasonography and 469 (85.1%) of these patients had pathological findings in the pancreas, gallbladder or biliary tract. This gave us speed and time in making the diagnosis and then organising the treatment.

In our study, it was revealed that patients with acute pancreatitis were seen more frequently especially in the spring months and there was a statistically significant difference compared to the number of patients presenting in the winter months. Considering its relation with nutrition, foods rich in fat content significantly increase cholecystitis attacks in the presence of gallstones.[12] In pancreatitis of biliary origin, it may be expected to increase in relation with fatty diet. Therefore, patients with acute pancreatitis were expected to be more frequent in winter seasons when fatty food consumption is high. This may be explained by the lack of records and recording errors in our retrospective study.

In a meta-analysis published by Villatora et al.[13] 7 studies and 414 patients were evaluated and it was observed that other antibiotics such as ciprofloxacin and cephalosporin except imipenem had no benefit in preventing pancreatic necrosis or mortal complications and imipenem significantly prevented pancreatic necrosis. In our study, 210 (33.3%) patients received antibiotic treatment, 104 (49.5%) of which were imipenem group antibiotics.

In the literature, 80-85% of acute pancreatitis is mild pancreatitis and 15-20% is severe pancreatitis.[14] In our study, it was found that the APACHE, Ranson and Atlanta score systems of the patients were similar and 80% of the patients had mild pancreatitis and 20% had severe pancreatitis.

The patients were divided into two groups as below 55 years of age and above 55 years of age and it was found that the severity of pancreatitis increased with increasing age. It was also observed that patients who presented with acute pancreatitis attacks had mild severity of the first attacks. There was no difference in severity between patients who had more than one acute pancreatitis attack and patients who had their first attack.

Limitations

One of the most important limitations was that our study was single center. Another limitation was that our study was retrospective. We believe that prospective and multicenter studies on acute pancreatitis will contribute more to the literature.

CONCLUSION

Patients diagnosed with acute pancreatitis should be evaluated with a multidisciplinary approach. Scoring systems should be used during initial hospitalization. Although different scoring systems were used, the 3 systems we analysed were found to be similar. Depending on the severity of the disease, most patients with acute pancreatitis are discharged with cure, while the prognosis of the patient groups, especially those accompanied by complications, may result in death.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Mersin University Ethics Committee (Date: 05.06.2014, Decision No: 2014/117).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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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Review

Obstructive sleep apnea and comorbidities: a current perspective from diagnosis to treatment

Ümmühan Tuğba Tümüklü, Zehra Seyfikli
Department of Pulmonology, Faculty of Medicine, Yozgat Bozok University, Yozgat, Turkiye

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ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is a significant health condition characterized by recurrent upper airway obstructions during sleep, with widespread systemic consequences. This review aims to present a comprehensive overview of OSAS, encompassing its pathophysiological foundations, risk factors, clinical manifestations, associated comorbidities, and contemporary diagnostic and therapeutic strategies. OSAS not only impairs sleep quality but also adversely affects cardiovascular, metabolic, neurocognitive, and psychological health, thereby reducing both lifespan and quality of life. While polysomnography remains the gold standard for diagnosis, home sleep tests and subjective assessment tools are increasingly utilized in clinical practice. Treatment approaches vary depending on disease severity and individual characteristics, ranging from lifestyle modifications and positive airway pressure devices to oral appliances and surgical interventions. In recent years, promising innovations such as neurostimulation and pharmacotherapy have emerged in OSAS management. This review highlights the multidimensional impact of OSAS at both individual and societal levels, emphasizing the need for early diagnosis and integrated treatment strategies.

Keywords: Obstructive sleep apnea, OSAS, comorbidities, diagnosis and treatment

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a prevalent sleep disorder characterized by recurrent complete (apnea) or partial (hypopnea) obstruction of the upper airway during sleep. Despite ongoing respiratory effort during these episodes, airflow is reduced or completely interrupted, leading to oxygen desaturation, sleep fragmentation, and non-restorative sleep.[1] OSAS is not limited to snoring and excessive daytime sleepiness; it exerts broad adverse effects on cardiovascular, metabolic, and neurocognitive systems, significantly reducing both quality of life and survival.[2] In pediatric populations, the condition is particularly important due to its association with growth retardation and behavioral problems.[3]

Epidemiological data indicate that the prevalence of OSAS is increasing globally. A comprehensive meta-analysis in the elderly population reported a global prevalence exceeding 35% in this age group.[4] The rates are similarly high among adults. A recent study conducted in the United States revealed that approximately one in four adults meets diagnostic criteria for OSAS, yet 80% of these individuals remain undiagnosed.[5] In a large-scale cohort study among middle-aged individuals, the prevalence was found to be 57.7% in men and 41.7% in women, with a significant association with cardiometabolic comorbidities.[6] Importantly, not only prevalence but also access to and adherence with treatment constitute critical aspects of OSAS epidemiology. A recent meta-analysis in elderly individuals demonstrated that continuous positive airway pressure (CPAP) therapy significantly reduces both mortality and morbidity.[7]

Moreover, OSAS is not merely an individual concern but a major public health issue directly impacting population health. When left undiagnosed and untreated, it contributes to an increased burden of cardiovascular diseases, diabetes, obesity, depression, and cognitive impairments.[10] Current literature underscores the importance of prioritizing OSAS in public health policies and enhancing access to diagnostic and therapeutic services.[8] Additionally, global warming due to climate change has been proposed to exacerbate OSAS prevalence and severity by impairing sleep quality, potentially intensifying its health burden in the coming years.[9,10] Collectively, these findings highlight that OSAS should be addressed as a critical public health concern, with attention to its clinical, societal, environmental, and economic dimensions.

PATHOPHYSIOLOGY

The pathophysiology of OSAS arises from the interplay between anatomical and neurophysiological factors. Structural characteristics of the upper airway are among the most critical determinants of the disorder. A narrow pharyngeal airway, hypertrophy of the soft palate and uvula, macroglossia (enlarged tongue), or retrognathia (posteriorly

Corresponding Author: Ümmühan Tuğba Tümüklü, tugba.tumuklu@bozok.edu.tr

positioned mandible), are craniofacial anomalies that increase the risk of upper airway collapse during sleep.[11-13] In children, adenotonsillar hypertrophy is one of the most common anatomical substrates for OSAS.[3] These structural narrowings, when combined with the reduction of muscle tone during sleep, lead to repeated airway obstructions.[14]

The decrease in muscle tone is particularly pronounced during REM sleep due to pharyngeal muscle relaxation. Under normal circumstances, these muscles maintain airway patency through tonic activity; however, reduced activation during sleep, together with anatomical narrowing, facilitates apneic and hypopneic episodes. Therefore, OSAS is not only an anatomical problem but also a disorder associated with impaired neuromuscular control.[11-13]

This process not only diminishes sleep quality but also initiates systemic biological effects. Recurrent hypoxic episodes lead to oxygen desaturation and carbon dioxide retention, triggering oxidative stress and inflammatory responses. Endothelial dysfunction, heightened sympathetic nervous system activity, and hormonal imbalances result in the development of multifactorial outcomes such as hypertension, atherosclerosis, and insulin resistance.[11,13] Thus, OSAS transcends being merely a sleep disorder characterized by snoring, evolving into a disease with multisystemic consequences.

One of the most powerful determinants in the pathophysiology of OSAS is obesity and increased neck circumference. Fat accumulation in the neck exerts external pressure, narrowing the upper airway, while visceral adiposity adversely affects respiratory mechanics. This mechanical narrowing, when combined with metabolic disturbances such as leptin resistance, insulin resistance, and chronic inflammation, exacerbates the progression of OSAS.[1,11,16,23] Indeed, clinical studies have demonstrated a strong correlation between weight gain and OSAS severity in obese individuals, with neck circumference serving as an important prognostic indicator.[6,23]

Recent studies have shown that OSAS cannot be explained by anatomical factors alone; non-anatomical mechanisms, such as impaired central respiratory control, alterations in sleep architecture, and differences in arousal threshold, also play a critical role in disease phenotypes.[14] Therefore, understanding and managing OSAS requires a comprehensive approach that considers not only anatomical features but also neurophysiological and metabolic mechanisms.

In conclusion, the pathophysiology of OSAS is the result of a complex interaction involving anatomical airway narrowing, reduced muscle tone, obesity-related compression, recurrent hypoxia, and inflammatory-oxidative processes. Accordingly, the disorder should be regarded as a comprehensive clinical entity that significantly affects not only sleep but also long-term health.[11-14,16,23]

RISK FACTORS

OSAS is a complex disorder that does not arise from a single cause, but rather results from the convergence of multiple interrelated risk factors (**Figure 1**). While each of these factors is significant on its own, they often act synergistically, collectively increasing the overall burden of disease.

One of the strongest determinants of OSAS is obesity. Particularly, the accumulation of adipose tissue in the neck region leads to narrowing of the upper airway and significantly increases the risk of apnea development.[23] Notably, weight gain not only creates mechanical pressure but also facilitates the development of OSAS through metabolic and hormonal pathways. Therefore, obesity is considered a multifaceted factor that aggravates the risk profile via both direct and indirect mechanisms.[11,13]

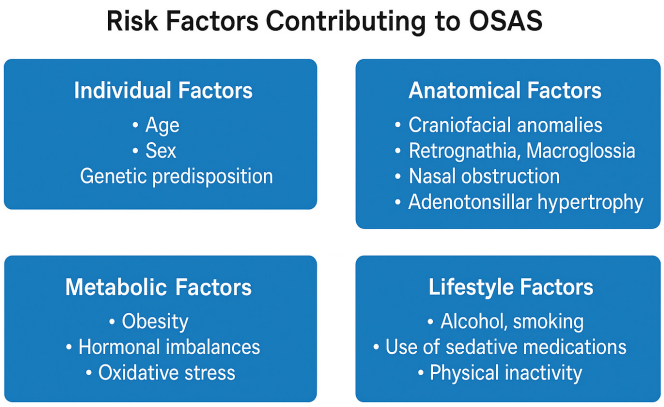

Figure 1. Factors contributing to the development of obstructive sleep apnea syndrome

Age and sex also play a significant role in determining OSAS risk. The prevalence of the disorder increases notably in middle age and beyond, with men being at higher risk compared to women.[4,6] However, after menopause, the risk in women also rises significantly due to hormonal changes. This phenomenon can be explained not only by biological differences but also by structural variations in upper airway anatomy.[2,3]

In recent years, genetic predisposition has increasingly gained attention. For example, polymorphisms in matrix metalloproteinase (MMP-1, MMP-3, MMP-9) genes may affect tissue elasticity and inflammatory processes, contributing to the development of OSAS.[22] Similarly, SIRT1 gene variants are thought to facilitate disease onset via oxidative stress and metabolic regulation mechanisms.[21] These findings demonstrate that OSAS is a reflection not only of environmental conditions but also of a significant genetic foundation.

Additionally, craniofacial anatomical anomalies play a crucial role in shaping the risk profile. Conditions such as retrognathia, macroglossia, or nasal obstruction lead to upper airway narrowing, which facilitates apnea formation.[12,14] In pediatric populations, adenotonsillar hypertrophy stands out as one of the most frequently encountered risk factors.[3] These findings suggest that OSAS should be considered a significant health concern not only in adults but also in children.

Lifestyle-related factors must also be acknowledged. For instance, alcohol consumption and the use of sedative medications reduce muscle tone during sleep, thereby promoting airway collapse.[1] Cigarette smoking may exacerbate upper airway narrowing by increasing mucosal inflammation.[8] As such, lifestyle modifications are not only important during treatment but are also critical in preventive strategies.

Another emerging aspect in recent years is the influence of environmental factors. Evidence suggests that global warming may contribute to increased OSAS prevalence, indicating that the condition should be addressed not only from an individual

risk perspective but also at societal and environmental levels.[9] Indeed, rising temperatures may impair sleep quality and intensify symptoms.

In light of all these findings, it is clear that the risk factors for OSAS are not isolated but interrelated and often overlapping. Therefore, risk assessment must be comprehensive for each individual, and personalized prevention and treatment strategies should be developed. This approach may help prevent the onset of the disorder and improve the clinical course of existing cases.

CLINICAL FEATURES AND SYMPTOMS

OSAS is a significant sleep disorder characterized by a wide spectrum of symptoms and clinical manifestations that negatively impact an individual's quality of life. The most commonly reported complaints include loud and intermittent snoring, witnessed breathing pauses during sleep (witnessed apnea), and excessive daytime sleepiness. These symptoms not only prevent individuals from achieving restorative sleep but also lead to serious societal consequences such as reduced attention, impaired cognitive performance, and increased risk of occupational accidents (**Table 1**).[15]

In a recent large-scale study, the clinical features of OSAS were categorized into three main groups:

- Patients experiencing excessive daytime sleepiness and attention deficits
- Cases with significantly impaired sleep quality
- Individuals who present with cardiometabolic comorbidities despite the absence of prominent symptoms

Furthermore, treatment preferences among patients may vary, underscoring the importance of personalized approaches in clinical management.[16]

OSAS is a complex condition characterized by a broad range of clinical manifestations that extend beyond snoring, witnessed apnea, and excessive daytime sleepiness. Common neurocognitive complaints in patients include morning headaches, difficulties in attention and concentration, forgetfulness, and irritability.[15] Additionally, nocturia (frequent nighttime urination), excessive night sweating, sudden awakenings with a feeling of choking, and dry mouth in the morning are among the typical symptoms.[17] Gender-specific differences are also noteworthy; women often report psychiatric symptoms such as depression, anxiety, and insomnia, whereas men are more likely to present with cardiometabolic complications.[16]

Recent studies have shown that the presence of OSAS in the perioperative period increases sensitivity to anesthesia and raises the risk of respiratory and cardiovascular complications.[18] These findings highlight the clinical heterogeneity of OSAS and emphasize the need for a multidisciplinary approach in both diagnostic and therapeutic processes.[19]

OSAS AND ASSOCIATED COMORBID CONDITIONS

OSAS is not limited to episodes of apnea and hypopnea during sleep but is also closely associated with the development and progression of various systemic diseases. Therefore, OSAS should not be considered merely a sleep disorder, but rather a clinical condition with multifaceted effects (**Figure 2**).[6,8]

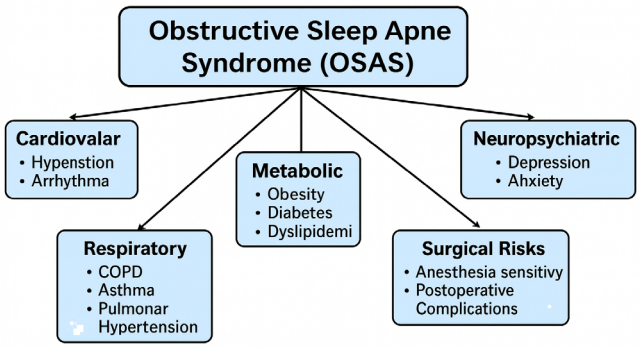

Figure 2. Relational flowchart of obstructive sleep apnea syndrome and its associated comorbid conditions

Cardiovascular Comorbidities

One of the most prominent and well-studied associations of OSAS is with the cardiovascular system. Repeated episodes of hypoxemia continuously activate the sympathetic nervous system and lead to vascular dysfunction. As a result, OSAS emerges as a major risk factor for the development of resistant hypertension.[20] Clinical observations show not only difficulty in controlling blood pressure in these patients, but also an increased susceptibility to cardiovascular diseases. Research has revealed that severe cardiac problems such as coronary artery disease, arrhythmias, and heart failure occur more frequently in individuals with OSAS.[6,16] This suggests that the respiratory disturbances experienced during sleep become a sustained cardiovascular burden throughout the day.

Metabolic and Endocrine Comorbidities

In addition to cardiovascular effects, OSAS also has profound impacts on metabolism. Fragmented sleep and hypoxemia-induced oxidative stress contribute to insulin resistance, laying the groundwork for the development of type 2 diabetes.[23] Many patients experience both conditions simultaneously, complicating the treatment process. Obesity lies at the center of this relationship-it is both the most significant risk factor for OSAS and a condition that OSAS itself may worsen through hormonal and metabolic mechanisms.[23] Moreover, hormonal imbalances are noteworthy. Elevated aldosterone levels have been found to correlate with the severity of OSAS, which is clinically important, particularly in hypertensive patients.[17] Thus, OSAS evolves beyond being merely a sleep disorder, becoming a multifaceted endocrine-metabolic dysregulation syndrome.

Table 1. Symptoms of obstructive sleep apnea syndrome and their clinical significance

Symptom	Definition	Clinical significance
Snoring	A loud and disturbing sound caused by turbulent airflow due to narrowing of the upper airway.	Commonly observed in the general population, disrupts sleep quality, and negatively affects social life.[11]
Witnessed apnea	Periods during sleep when breathing completely stops or significantly decreases, observed by a bed partner.	A direct indicator of apnea, plays a critical role in the diagnostic process.[11]
Excessive daytime sleepiness	Recurrent sleep episodes, lack of attention, and persistent fatigue during the day due to non-restorative sleep.	Leads to occupational and traffic accidents and significantly impairs quality of life.[11]

Respiratory and Inflammatory Comorbidities

OSAS also significantly affects the respiratory system. When combined with obesity and inflammatory processes, it can play a key role in the development of acute respiratory distress syndrome (ARDS).[16] Additionally, when coexisting with chronic obstructive pulmonary disease (COPD), the clinical picture worsens-a condition referred to in the literature as "overlap syndrome." This syndrome is associated with deeper hypoxemic episodes and a poorer prognosis.[6] For this reason, the presence of OSAS should always be evaluated in individuals with respiratory diseases.

Neuropsychiatric and Neurocognitive Comorbidities

Another critical but often overlooked dimension of OSAS is its neuropsychiatric and cognitive consequences. Chronic sleep fragmentation and recurring nocturnal hypoxemia directly impact brain function, leading to symptoms such as forgetfulness, difficulty concentrating, and reduced attention span.[15] Emotional aspects are equally important. Depression and anxiety are more prevalent in individuals with OSAS than in the general population. Interestingly, while depressive symptoms and insomnia are more pronounced in women, men are more frequently affected by cardiometabolic problems.[19] These differences suggest the influence of both gender-based biological mechanisms and sociocultural factors.

Perioperative Risks

The comorbidities associated with OSAS are not limited to chronic diseases; they also pose significant risks during surgical procedures. These patients have increased sensitivity to anesthesia, as well as higher rates of airway complications and cardiovascular instability.[18] Therefore, diagnosing OSAS prior to surgery is crucial for preventing perioperative complications.

Public Health Perspective

Considering all these associations, it becomes clear that OSAS transcends being a merely individual health issue. When coupled with cardiometabolic, respiratory, and psychiatric conditions, it contributes substantially to the overall burden of disease in the population.[4,8] Furthermore, rising obesity rates and global environmental changes indicate that the prevalence of OSAS may continue to grow in the coming years.[9] Consequently, OSAS should not only be a priority for clinicians but also for public health professionals.

DIAGNOSTIC METHODS

The diagnostic methods used for OSAS aim to evaluate both the clinical symptoms and objective sleep data.

Polysomnography

Polysomnography is considered the gold standard diagnostic method for OSAS. It is a comprehensive sleep study that simultaneously records brain electrical activity (EEG), eye movements (EOG), muscle tone (EMG), heart rhythm (ECG), respiratory airflow, thoracoabdominal effort, and oxygen saturation during sleep.[1,2] This allows for the objective identification of sleep stages as well as the number, duration, and severity of apneic and hypopneic episodes. From a clinical perspective, polysomnography not only determines disease severity based on the Apnea-Hypopnea Index (AHI), but also reveals the patient's sleep architecture, arousal responses, and cardiorespiratory effects.[3,11] Because of these features, in-lab polysomnography remains an indispensable tool for differential diagnosis, treatment planning, and long-term follow-up of OSAS.

During polysomnography, electroencephalography (EEG) plays a central role in assessing sleep stages. The brain's activity across various frequency bands reflects transitions between wakefulness and sleep cycles (**Table 2**).

- Alpha waves (8-13 Hz) typically emerge when the eyes are closed and the person is awake but relaxed. They diminish during sleep onset.[1]
- Beta waves (13-30 Hz) are higher in frequency and are prominent during active mental processing and REM sleep.[2]
- Theta waves (4-7 Hz) are a hallmark of the N1 sleep stage and become dominant during light sleep.[3]
- Delta waves (0.5-4 Hz) are characteristic of deep slow-wave sleep (N3) and play a critical role in physiological restoration, memory consolidation, and metabolic repair processes.[4]

The regular recording of these brain waveforms enables detailed analysis of sleep architecture and allows for the objective detection of micro-arousals and disruptions in sleep continuity in disorders such as sleep apnea.[1,11,24] Thus, polysomnography not only evaluates respiratory parameters but also reveals the neurophysiological dynamics of the brain during sleep.

In the diagnosis of OSAS, polysomnography makes it possible to differentiate between apnea types by recording not only changes in airflow but also thoracoabdominal effort. Different types of sleep apnea can be identified based on patterns of airflow and thoracoabdominal effort:

In obstructive sleep apnea, airflow ceases due to upper airway collapse, while thoracic and abdominal muscles continue to exert effort. This pattern is characterized by visible respiratory effort without effective air passage into the lungs.[25]

In central sleep apnea, the issue is not mechanical obstruction of the airway but a cessation of respiratory drive from the brainstem. As a result, both airflow and thoracoabdominal effort are absent simultaneously.[26]

Table 2. Frequency ranges and clinical significance of EEG waves

Wave type	Frequency range	Associated sleep stage and function
Alpha waves	8-13 Hz	Occur during relaxed wakefulness with closed eyes; diminish during sleep onset.[1]
Beta waves	13-30 Hz	High frequency; prominent during active mental processing and REM sleep.[2]
Theta waves	4-7 Hz	Characteristic of N1 stage; dominant during light sleep.[3]
Delta waves	0.5-4 Hz	Associated with deep slow-wave sleep (N3); essential for physiological restoration, memory consolidation, and metabolic repair.[4]

EEG: Electroencephalography

Mixed apnea involves both mechanisms; it typically begins with the lack of effort seen in central apnea, followed by obstructive respiratory effort.

Hypopnea is defined by a significant reduction in airflow without complete cessation, accompanied by oxygen desaturation.

Recognizing these patterns is crucial for accurate classification of sleep disorders and for guiding clinical management.

Home Sleep Apnea Testing (HSAT)

HSAT has emerged as a more accessible and practical alternative, especially for high-risk individuals. While polysomnography remains the gold standard, HSAT devices are increasingly used due to their ease of use, home-based application, and lower cost to healthcare systems.[25] These tests typically record parameters such as airflow, oxygen saturation, heart rate, and thoracoabdominal effort to evaluate the presence and severity of sleep apnea.

Importantly, home testing allows for assessment in a natural sleep environment, which may yield more clinically relevant insights.[26] However, HSAT may not be suitable for patients with comorbidities or suspected complex sleep disorders. Selecting the appropriate patient population for HSAT is essential to prevent false negatives and to ensure diagnostic reliability.[25,26]

Screening Tests

Screening tools are essential for supporting clinical assessment in the diagnosis of OSAS. One of the most widely used tools is the Epworth Sleepiness Scale (ESS), which allows patients to subjectively evaluate their daytime sleepiness. The scale assesses the tendency to fall asleep during routine daily activities such as sitting, reading, watching TV, or being a passenger in traffic. The resulting score provides valuable clues about the severity of sleep disorders.[25] In individuals suspected of having OSAS, high ESS scores often prompt further diagnostic testing such as polysomnography.[26] Although ESS is entirely subjective and not diagnostic on its own, its ease of use and rapid assessment capability make it a valuable screening tool to clarify a patient's clinical disorders.[25,26]

CLASSIFICATION OF OSAS

OSAS is classified during the diagnostic process based on the AHI, following international standards. According to the guidelines of the American Academy of Sleep Medicine (AASM), an AHI value between 5 and 14 is defined as mild OSAS, between 15 and 29 as moderate OSAS, and 30 or above as severe OSAS (**Table 3**).[27]

This classification not only indicates the frequency of apneic and hypopneic events but also helps guide the clinical course, treatment necessity, and evaluation of associated comorbid conditions.

Moreover, the international classification of sleep disorders (ICSD-3) considers OSAS as a distinct clinical category, emphasizing that diagnostic criteria should include not only objective measurements but also symptomatic features-such as excessive daytime sleepiness, snoring, and witnessed apneas.[27] This approach highlights that the condition should not be evaluated solely through numerical parameters but must also consider its impact on quality of life and functional capacity. In doing so, international classification systems provide clinicians with diagnostic clarity while also enhancing the comparability of data across different populations.

TREATMENT APPROACHES

Lifestyle Modifications

The first-line approach in the management of OSAS often begins with lifestyle modifications. This is because the condition is not only influenced by medical devices or surgical interventions but also significantly shaped by an individual's daily habits. As such, lifestyle changes are considered a fundamental therapeutic strategy that directly impacts both the onset and progression of the disease.

Weight control is one of the most critical components in OSAS management. Excess body weight-particularly the accumulation of fat tissue around the neck-narrows the upper airway and increases the risk of apnea. Clinical observations have shown that weight loss not only provides mechanical relief but also improves metabolic processes, leading to a significant reduction in the AHI.[25] Therefore, adjusting dietary habits and achieving an ideal body weight are essential not only for OSAS but also for overall health.

Another important factor is alcohol consumption. Alcohol intake, especially at night, reduces pharyngeal muscle tone, making the airway more susceptible to collapse. This results in prolonged apnea episodes and more pronounced oxygen desaturation.[26] Thus, patients are advised to limit or completely avoid alcohol.

Similarly, smoking is a detrimental lifestyle factor in OSAS. Cigarette smoke increases inflammation in the upper respiratory tract, causing mucosal edema and narrowing of the airways. This can exacerbate both the frequency and severity of apnea events.[25] Smoking cessation is therefore a crucial step not only for pulmonary health but also for improving sleep quality.

Sleep hygiene should also not be overlooked. Regular sleep schedules, sufficient sleep duration, and a proper sleep environment help alleviate symptoms in OSAS patients. Moreover, adapting to a lateral sleeping position is particularly effective in mild cases. Sleeping on the back can cause the tongue base to fall backward due to gravity, whereas side-sleeping reduces this effect and supports better airflow.[26]

Finally, regular physical activity is a powerful preventive component among lifestyle modifications. Exercise not only

Table 3. OSAS within the framework of the ICSD-3

AHI	Severity	Description
5-14 events/hour	Mild OSAS	Associated with light symptoms; may affect sleep quality and daytime function.
15-29 events/hour	Moderate OSAS	More frequent events; often causes noticeable daytime sleepiness and reduced quality of life.
≥30 events/hour	Severe OSAS	High frequency of events; linked to significant health risks, including cardiovascular and metabolic disorders.

OSAS: Obstructive sleep apnea syndrome, ICSD-3: International classification of sleep disorders, AHI: Apnea-Hypopnea Index

facilitates weight loss but also strengthens respiratory muscles, supports respiratory function, and reduces cardiometabolic risks.[25] Therefore, lifestyle interventions play a pivotal role not only in symptom control but also in improving the long-term health outcomes of OSAS.

Medical Treatment

In the management of OSAS, medical approaches aim to alleviate symptoms and prevent complications by targeting the underlying pathophysiology of the condition. Within this context, oral appliances and positive airway pressure (PAP) devices stand out as effective and customizable therapeutic alternatives.

Role and limitations of oral appliances: Oral appliances are a non-surgical treatment option primarily recommended for patients with mild to moderate OSAS. These devices typically function by repositioning the mandible anteriorly, thereby mechanically maintaining patency of the pharyngeal airway and reducing the risk of upper airway collapse.[28] They serve as a viable alternative for patients who cannot tolerate or do not adhere to CPAP or BiPAP therapy. However, their effectiveness may be limited in severe cases of OSAS and they are not recommended for individuals with temporomandibular joint disorders.[28] Long-term use may be associated with side effects such as jaw pain and alterations in dental alignment. Therefore, careful patient selection and a multidisciplinary approach to monitoring the treatment process are essential.

PAP therapy: This is considered the first-line treatment for OSAS. Continuous CPAP devices deliver a constant and positive pressure throughout the night to keep the airway open.[29] Due to its simplicity and efficacy, this method is widely used. Regular use of the device and close patient monitoring are essential to ensure adherence to therapy. Tracking the adaptation process and integrating digital monitoring systems can directly influence the success of CPAP therapy.[30]

Some patients may struggle to adapt to a fixed pressure. In such cases, Bilevel Positive Airway Pressure (BiPAP) devices can be used as an alternative. BiPAP delivers different pressure levels during inhalation and exhalation, which allows for a more comfortable sleep experience.[30] This modality may be particularly effective in patients with advanced OSAS or those suffering from hypoventilation syndrome.

Surgical Treatment Options

OSAS is a condition with highly variable responses to treatment. A one-size-fits-all approach may not be effective for every patient; therefore, an individualized treatment strategy is essential. While PAP therapy is the first-line recommendation, some patients may not adapt to this method, or they may not achieve sufficient symptom relief despite regular use of the device. In such cases, particularly in patients with prominent anatomical narrowing, surgical interventions come into consideration.[26]

The main goal in evaluating surgical options is to determine the location and degree of anatomical obstruction in the upper airway and to develop a structured intervention plan for these areas. For this purpose, diagnostic tools such as imaging methods, flexible endoscopy, and, when necessary, drug-induced sleep endoscopy (DISE) are used. The surgical approach not only offers a mechanical solution but can also enhance the success of PAP therapy.[26]

One of the most commonly performed procedures is uvulopalatopharyngoplasty (UPPP), which aims to enlarge the airway by removing excess tissue from the soft palate, uvula, and posterior pharyngeal wall. This method is particularly effective in patients with oropharyngeal-level obstruction.[26] However, because this surgery addresses only a limited anatomical region, it may not be sufficient on its own in some cases.

In more extensive and deeper airway obstructions, advanced surgical procedures such as maxillomandibular advancement (MMA) are employed. MMA involves advancing both the maxilla and mandible forward to create a permanent expansion of all segments of the upper airway and has a high success rate in cases with multilevel obstruction.[27]

Additionally, in patients with significant tongue base obstruction, targeted interventions such as glossectomy, genioglossus advancement, or hypoglossal nerve stimulation may be utilized. Nasal surgeries such as septoplasty and turbinate reduction, although not direct treatments for OSAS, can support treatment success by improving PAP compliance or correcting nasal obstruction.[27]

The success of surgical interventions is closely related to proper patient selection, appropriate surgical techniques, and postoperative follow-up processes. However, it should be remembered that surgery is always an invasive option, and the decision-making process should be shaped within the framework of patient education and multidisciplinary evaluation. Since each individual's anatomical structure and clinical needs differ, surgical treatment must also be equally personalized.

Emerging Developments and Future Treatment Options in OSAS

In recent years, remarkable innovations have emerged in the treatment of OSAS, driven by scientific and technological advancements. These innovations are designed both to enhance treatment response and to improve patient comfort. Considering the multifaceted nature of the disease, future treatment options are becoming increasingly diverse.

Neurostimulation and Electrical Modulation

Hypoglossal nerve stimulation (HNS) has emerged as an effective alternative, particularly for patients who cannot tolerate CPAP or require surgical intervention due to anatomical factors. Experimental studies on animal models have demonstrated that this method reduces the number of apneic episodes and improves oxygen levels.[33] These findings suggest that the physiological effects of HNS contribute not only to muscle activation but also to systemic oxygenation.

Moreover, engineering-based research on the energy efficiency and volumetric performance of implantable neurostimulator systems indicates that future generations of these devices will be longer-lasting and more user-friendly.[34] These developments may offer significant clinical advantages in terms of mobility and quality of life.

Pharmacological Approaches

While pharmacotherapy has not yet become a routine clinical practice in OSAS treatment, drug development targeting the underlying pathophysiological mechanisms has gained momentum. Recent studies have shown promising results

from drug combinations aimed at parameters such as reduced upper airway muscle tone, ventilatory instability, and arousal threshold.[35] These novel pharmacological strategies may play a complementary role, particularly in multidisciplinary treatment plans.

Advanced Diagnostic and Monitoring Technologies

Low-contact systems designed to reduce patient burden during the diagnostic process and increase accessibility are also gaining attention. Notably, ongoing studies are exploring cost-effective and efficient home-based diagnostic systems that combine millimeter-wave radar technology with pulse oximetry data.[36] These technologies have the potential to improve both accuracy and accessibility in the diagnosis of OSAS.

TREATMENT APPROACHES ACCORDING TO CLINICAL STAGES OF OSAS

Determining treatment strategies based on the stage of OSAS is crucial for ensuring effective and sustainable interventions tailored to individual disease progression. Each stage of OSAS presents different clinical needs in terms of symptom severity and complication risk. Addressing these differences not only improves patient quality of life but also yields meaningful improvements in long-term health outcomes.

Treatment Approach in Mild OSAS

Mild OSAS is defined as having an AHI between 5 and 15 and is typically characterized by less severe symptoms. At this stage, the primary approach is based on lifestyle modifications and conservative interventions. Behavioral measures such as weight loss, avoiding alcohol and sedatives that reduce upper airway tone, quitting smoking, and refraining from sleeping in the supine position are recommended as the first-line strategies.[29]

If symptoms are not adequately controlled through these measures, or if the patient experiences persistent complaints such as excessive daytime sleepiness or morning headaches that impair quality of life, alternative medical treatments should be considered.

At this point, the use of oral appliances emerges as an effective option. These devices aim to increase upper airway patency by repositioning the mandible forward and can significantly reduce the frequency of apneas and hypopneas during the night.[28] Being portable, quiet, and non-invasive, oral appliances enhance patient comfort, though they should be used cautiously in patients with temporomandibular joint disorders. In mild OSAS, they may offer better patient adherence compared to more intensive treatments such as CPAP.[28]

Although PAP devices are not usually the first choice for mild OSAS, in some clinical situations, their use may become medically necessary. For instance, if significant daytime sleepiness is detected through standardized tests like the Epworth Sleepiness Scale and it negatively affects the patient's functionality and quality of life, PAP therapy may be initiated.[29] Similarly, in patients with treatment-resistant hypertension, PAP can be beneficial in suppressing increased sympathetic tone associated with OSAS.[29]

PAP therapy is also recommended in patients with cardiac comorbidities-particularly those with congestive heart failure or atrial fibrillation-due to its beneficial effects in reducing cardiac workload. Moreover, for patients who have experienced cerebrovascular events such as stroke, PAP treatment may support neurological recovery during the post-ischemic phase.[29]

Lastly, for individuals in occupations requiring high alertness-such as pilots and commercial drivers-initiating PAP therapy may be necessary even in the presence of mild OSAS to prevent potential work-related accidents.[29] These examples clearly demonstrate that treatment planning should be guided not only by the AHI score but also by the broader clinical context.

Treatment Approach in Moderate OSAS

Moderate OSAS refers to clinical cases where the AHI falls between 15 and 30. Treatment at this stage should be more structured and individualized. According to the clinical guidelines recommended by the AASM, PAP therapy is suggested as the first-line treatment for patients in this group.[29]

The most commonly used form of PAP is the CPAP (Continuous Positive Airway Pressure) device, which delivers a constant and steady positive pressure to the patient's upper airway throughout the night. This mechanism prevents airway collapse, thereby reducing the frequency of apneas and hypopneas, and significantly improving both sleep quality and daytime alertness.[29] CPAP therapy is a standard approach in moderate OSAS, aiming to relieve symptoms and reduce long-term cardiometabolic risks.[31]

However, not all patients can easily adapt to CPAP therapy. Discomfort with the mask, noise, or psychological unease may cause some to discontinue treatment. In such cases, BiPAP (Bilevel PAP) devices, which allow separate adjustments for inspiratory and expiratory pressures, may provide a more comfortable experience. Alternatively, for individuals with suitable anatomical structures and milder symptoms, oral appliances can be considered.[31]

Another important factor influencing treatment decisions in moderate OSAS is the presence of comorbidities. Systemic conditions such as hypertension, type 2 diabetes, and obesity should be considered during treatment planning, and the potential benefits of PAP therapy evaluated within this context.[29] Moreover, enhancing treatment adherence through patient education and regular follow-ups should be a priority to improve clinical outcomes.

Treatment Approach in Severe OSAS

A diagnosis of severe OSAS is made when the AHI exceeds 30. In this patient group, not only sleep quality but also cardiovascular, metabolic, and neurological systems can be significantly affected. Therefore, treatment at this stage requires a more aggressive and multidisciplinary approach.[29]

In severe OSAS, CPAP therapy is the first-line and most strongly evidence-supported treatment option. CPAP applies constant positive pressure to the upper airway during sleep, preventing airway collapse and ensuring continuous breathing. This mechanism reduces the frequency of apnea-hypopnea episodes and provides significant improvement in symptoms such as daytime sleepiness, cognitive impairment, and hypertension.[29]

However, the success of CPAP therapy depends not only on prescription but also on patient adherence and consistent use of the device. Therefore, telemetric monitoring systems

developed to track treatment adherence play a crucial role in increasing its effectiveness and sustainability. Today, many CPAP devices transmit cloud-based data, allowing both healthcare professionals and patients to regularly monitor usage duration and pressure parameters.[30]

Some patients may not tolerate CPAP for various reasons. In such cases, alternative positive pressure systems such as BiPAP (Bilevel Positive Airway Pressure) may be used. BiPAP delivers different pressure levels during inhalation and exhalation and is often better tolerated in patients with hypoventilation or coexisting respiratory disorders. In cases where CPAP or BiPAP fails to control symptoms and in patients with prominent anatomical obstructions, surgical interventions (e.g., uvulopalatopharyngoplasty) may be considered.[29]

In conclusion, treatment planning for severe OSAS should be based not only on the AHI score but also on the patient's symptom profile, lifestyle, comorbidities, and adherence potential. Patient education, device usage guidance, and regular follow-up are key components of successful treatment.

The management of OSAS is most effective when approached through multidisciplinary and holistic strategies. Although treatment options vary according to disease severity, lifestyle modifications remain a cornerstone of care at all levels. These include weight control, reduction of alcohol and tobacco use, and adjustments in sleep position.

Beyond lifestyle measures, medical therapies such as PAP devices, oral appliances, and pharmacological interventions can be applied. When indicated, surgical approaches may also be considered. Importantly, treatment should not only be guided by severity classification but also tailored to the individual's anatomical features, physiological characteristics, and lifestyle factors. Such personalized care ensures both efficacy and long-term adherence, supporting better clinical outcomes and improved quality of life.

CONCLUSION

Although OSAS often presents with seemingly "simple" symptoms such as snoring or pauses in breathing during sleep, it hides a complex condition that can lead to serious health issues. These silent obstructions during sleep not only disrupt sleep quality but also negatively impact many areas-from cardiovascular health and metabolic balance to mood and daily performance. Therefore, OSAS should be approached as a systemic disorder that affects not just nighttime rest but an individual's overall quality of life. In this context, early diagnosis is of vital importance. A timely evaluation can prevent numerous serious complications such as hypertension, heart disease, stroke, or depression. The earlier treatment begins, the greater the improvement in the patient's quality of life and overall health. However, effective treatment is not limited to a device or surgical intervention. Managing OSAS is a multidisciplinary process that requires collaboration among various fields, including otolaryngology, pulmonology, cardiology, nutrition, and psychology. This teamwork not only accelerates diagnosis but also enhances treatment adherence and helps patients feel understood and supported. In conclusion, managing OSAS should aim not only to treat a disorder but also to holistically improve a person's sleep, health, and quality of life. Through awareness, early action, and interdisciplinary collaboration, a breath that stops during sleep can be transformed into a life renewed with health.

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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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