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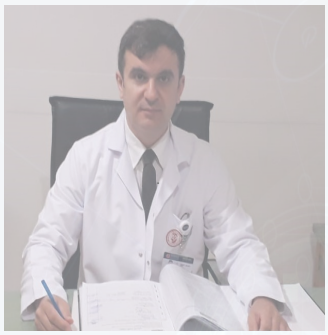

Editorial services in AI-powered publishing

I am delighted to introduce a new member of our editorial team who has played a significant role in crafting this issue of our journal. Alongside our dedicated human editors, we have been fortunate to collaborate with artificial intelligence (AI) language models. This advanced AI Technologies have been trained on a vast amount of information, providing a wealth of knowledge and linguistic capabilities that have greatly assisted in the creation of this editorial introduction.

The integration of AI into the editorial process has allowed us to enhance the efficiency and accuracy of our work. ChatGPT, as a language model, has been instrumental in generating coherent and contextually appropriate text, making it a valuable resource for refining the content and structure of our journal. It has been trained on an extensive corpus of scientific literature and general knowledge, allowing it to provide relevant information and insights on a wide range of topics within the field of human health sciences.

However, it's important to note that while AI has been a valuable tool in our editorial endeavors, the final decisions, editorial oversight, and ethical considerations are the responsibility of our human editors. The collaboration between AI and human expertise enables us to leverage the strengths of both, ultimately ensuring the highest quality of content for our readers.

We believe that incorporating AI technology into our editorial process not only streamlines our operations but also opens up new possibilities for exploration and discovery within the field of human health sciences. As AI continues to advance and evolve, we are excited to harness its potential to further enrich our journal and contribute to the advancement of scientific knowledge.

Thank you for your continued support, and we hope you find this issue of our journal both informative and thought-provoking.

The following texts belong to AI, who wrote an introductory article using some abstract and keywords of the articles in the new issue of our journal. Enjoy!

Editor-in-Chief

Assoc. Prof. Mehmet Emin Demir

Issue Editors

Prof. Dr. Ebru Gök Oğuz

Assoc. Prof. Dr. Kadir Gökhan Atılgan

AI Journal Editor

Welcome to the latest issue of our journal, dedicated to exploring the latest advancements and discoveries in the field of human health sciences. In this issue, we have curated a collection of articles and reviews that delve into various aspects of medical research, ranging from the identification of predictive markers for liver diseases to the evaluation of thyroid functions in patients with obstructive sleep apnea syndrome. Additionally, we present insightful case reports

and comprehensive reviews on topics such as organ transplantation, endoscopy, and the impact of innovative therapeutic approaches.

Our first article, titled "Can the Monocyte/HDL Ratio be used as A Marker to Predict Fatty Liver and Its Stages?", addresses the growing concern of fatty liver diseases and investigates the potential of a novel marker in predicting their stages. This study holds promise for early detection and management of this prevalent condition, contributing to improved patient outcomes.

The second article, "Evaluation of Thyroid Functions and Correlation of Body Mass Index with Apnea-Hypopnea Index in Patients with Obstructive Sleep Apnea Syndrome," sheds light on the complex interplay between thyroid function, body mass index, and sleep-related disorders. Understanding these correlations can guide clinicians in developing targeted interventions for patients with obstructive sleep apnea syndrome.

Another notable contribution in this issue is the article titled "The Assessment of Stroke Patients Using the Functional Independence Measurement Scale." This research focuses on enhancing the assessment of stroke patients' functional abilities, which is crucial for determining appropriate rehabilitation strategies and optimizing their recovery process.

Furthermore, we present an enlightening study titled "Knowledge, Attitudes, and Behaviors of Patients Diagnosed with End-Stage Kidney Disease Registered on the Kidney Transplant Waiting List Regarding Organ Transplantation and Donation." By examining patients' perspectives and behaviors towards organ transplantation and donation, this research aims to improve education and communication strategies to address the existing knowledge gaps and promote positive attitudes towards this life-saving procedure.

In addition to these insightful articles, we present three comprehensive reviews. The first review, "The Synergistic Role of Endoscopy and Cytology in the Diagnosis of Aspergillosis: A Comprehensive Review of Human and Avian Medicine," explores the combined use of endoscopy and cytology techniques in diagnosing this fungal infection, highlighting the shared learnings across human and avian medicine.

The second review, titled "Gestational Diabetes Mellitus" provides a comprehensive overview of this prevalent condition, examining its risk factors, diagnostic methods, and management strategies. This review will serve as a valuable resource for healthcare professionals involved in the care of pregnant women.

Lastly, we present the review, "The Impact of Sodium-Glucose Co-Transporter-2 Inhibitors on Weight Loss in Obesity," which investigates the role of these inhibitors in achieving weight loss among individuals with obesity. The findings of this review contribute to our understanding of potential therapeutic avenues in combating obesity and its associated health complications.

Lastly, we feature a compelling case report titled "Canakinumab For The Treatment of Amyloidosis Secondary to Lung Cancer," showcasing the successful utilization of a targeted therapeutic approach in managing a rare complication of lung cancer. This case report highlights the importance of personalized treatment strategies and the potential of novel therapies in improving patient outcomes.

We hope that this diverse collection of articles and reviews provides our readers with valuable insights, stimulates further research, and sparks meaningful discussions within the realm of human health sciences. We extend our gratitude to the authors, reviewers, and editorial team for their dedication and contribution in making this issue possible. Together, let us continue to advance the frontiers of medical knowledge and promote better health for all.

Enjoy reading this issue!

[Artificial Intelligence Editor on Behalf of Editorial Team]

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Original Article

Can the Monocyte/HDL Ratio be used as A Marker to Predict Fatty Liver and Its Stages?

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ABSTRACT

Background: Our study aims to determine whether the monocyte/HDL ratio is a marker that can be used to predict the presence and stage of non-alcoholic fatty liver.

Material and Method: Patients aged 18-65 years without known chronic diseases and medication use who applied to our hospital for a check-up were included in the study. Patients were divided into 4 groups based on ultrasonography findings: those without hepatosteatosis, those with stage 1, stage 2, and stage 3 hepatosteatosis. Groups were compared in terms of fasting glucose, insulin resistance, lipid profile, liver function tests, monocyte/HDL ratios.

Results: Fasting glucose, insulin resistance, total cholesterol, LDL cholesterol, triglycerides, alanine aminotransferase, monocytes, and monocyte/HDL ratio were significantly higher in the group with hepatosteatosis than in the group without hepatosteatosis, and this increase was directly proportional to the stage. HDL was significantly lower in the hepatosteatosis group than in the group without hepatosteatosis, and HDL decreased further as the stage of hepatosteatosis increased. No difference was found between the groups in terms of aspartate aminotransferase. Multivariate regression analyses revealed that hepatosteatosis was independently associated with alanine aminotransferase, insulin resistance, and monocyte/HDL ratio.

Conclusion: Monocyte/HDL ratio can be considered a simple, easily accessible, and inexpensive marker to predict the presence and stages of hepatosteatosis.

Keywords: Hepatosteatosis, inflammation, insulin resistance, monocyte/HDL ratio, non-alcoholic fatty liver disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a condition marked by abnormal fat accumulation in the liver that is unrelated to alcohol consumption (1). Fat accumulation in hepatocytes can cause inflammation and hepatocyte damage, and if it progresses further, it can cause fibrosis, cirrhosis, and even hepatocellular carcinoma (2). NAFLD affects more than a quarter of the adult population worldwide, and its prevalence is expected to rise to 56% in the next decade (3). NAFLD is closely linked to sedentary lifestyle, high-calorie diet, and obesity, as well as insulin resistance, type 2 diabetes mellitus, and metabolic syndrome, and is thus the most common liver disease seen in developed countries (4). The fact that it is very common and has serious life-threatening consequences makes NAFLD important. Most patients with hepatosteatosis (HS) are asymptomatic. Patients are usually detected incidentally with elevated liver function tests and ultrasonography findings. Hepatic transaminases are normal in two-thirds of patients but increased in one-third of patients, typically dominated by alanine aminotransferase (ALT). On ultrasonography, hepatomegaly and increased liver echogenicity are in favor of the presence of HS (5). Although biopsy is the definitive diagnostic method, it is performed in selected cases considering the cost and risk. Chronic low-grade inflammation has been identified as an essential component of NAFLD pathophysiology, implying that markers of chronic inflammation may predict the presence and stage of NAFLD (6). C-reactive protein (CRP), tumor necrosis factor- α (TNF-α), interleukin (IL)-1, IL-6, IL-8, and monocyte chemoattractant protein 1 (MKP-1) are chronic inflammation markers that have been linked to NAFLD (7,8). In recent years, monocyte/

HDL ratio (MHR) has come to the forefront as a new marker of systemic inflammation (9). Monocytes are natural inflammatory cells responsible for the increase in proinflammatory cytokines (10). HDL is a cholesterol subtype with antioxidant and anti-inflammatory effects (11). Considering the proinflammatory properties of monocytes and the anti-inflammatory properties of HDL, it was thought that the MHR may be a noninvasive, easily accessible, and low-cost marker that can be used to predict the presence and stage of an inflammatory disease such as NAFLD. This study aims to determine the association of MHR with the presence and stages of HS.

MATERIAL AND METHODS

Our study is a retrospective study in which we included patients aged 18-65 years who had a check-up at Istanbul Medipol University Hospital between January 2020 and January 2023. Demographic data of patients including age, sex and comorbidities, laboratory parameters including fasting blood glucose, insulin resistance, lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides), liver enzymes (ALT and aspartate aminotransferase (AST)) and complete blood count, abdominal ultrasonography (USG) findings indicating HS status were obtained and recorded on our patient management information system. Patients were divided into four groups based on USG findings: those without HS, those with stage 1 HS, those with stage 2 HS, and those with stage 3 HS and compared in terms of demographic data and laboratory parameters. Monocyte counts from the patients' complete blood counts were divided by HDL cholesterol, and MHR were calculated to determine whether this parameter differed in the group with HS compared to the group without HS, as well as whether it differed between the stages in the group with HS, and whether it was a marker that could be used to predict the presence and stages of HS.

Studying Laboratory Parameters

Blood samples were obtained after 12 hours of fasting. Whole blood counts were analyzed by Sysmex XN-1000 (USA) device. Fasting blood glucose, total cholesterol, LDL, HDL, triglycerides, ALT, AST were analyzed by Roche Hitachi Cobas C501 (Switzerland), fasting insulin levels were analyzed by Roche Hitachi Cobas e601 (Switzerland), HOMA-IR was calculated as follows: fasting insulin (mIU/ml) x fasting blood glucose (mg/dl) / 405. The presence of one or more of total cholesterol > 200, LDL > 130, triglycerides > 150, HDL < 40 for men and HDL < 50 for women was considered dyslipidemia. Fasting blood glucose ≥126 was considered diabetes mellitus and HOMA-IR > 2.4 was considered insulin resistance. The normal range of ALT is 0-33 U/L in women, 0-41 U/L in men, and the normal range of AST is 0-32 U/L in women and 0-40 U/L in men. Values above these were considered as liver enzyme elevation. Monocyte normal range is 0.16-0.90 10*3/µL. Values above this were accepted as monocytosis. Results above these values were considered elevated liver enzymes. Normal values for monocytes; results above this were considered monocytosis.

Diagnosis of Hepatosteatosis Based on USG Findings

Ultrasound imaging was performed on all patients by a single radiologist with the abdominal probe of the GE logiq 9 pro ultrasound device in B mode.

The severity of echogenicity was graded (12,13);

Grade 1: Mild diffuse echogenicity increase

Grade 2: Moderate increase in echogenicity

Grade 3: Portal vein wall with increased echogenicity; inability to visualize the diaphragm and posterior part of the liver

Inclusion Criteria

Male and female patients between the ages of 18-65 who did not have a diagnosed chronic disease and did not regularly use medication/food supplement were included in our study.

Exclusion Criteria

Patients under 18 and over 65 years old, patients with hypertension, hyperlipidemia, diabetes mellitus, malignancy, anemia, thyroid dysfunction, renal dysfunction, chronic liver disease coronary artery disease, heart failure, acute/chronic inflammatory disease, acute/chronic infection, patients using alcohol (female > 20 g/day - male > 30 g/day), antibiotics, oral antidiabetic, antihypertensive, statin, fenofibrate and/or any drug/food supplement for the treatment of obesity, patients with HbsAg+ / Anti HCV+ and smokers were not included in our study.

STATISTICAL ANALYSIS

All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). For the normality check, histogram and Q-Q plots were used. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Normally distributed continuous variables were analyzed with the independent samples t test or one way analysis of variance (ANOVA) depending on count of groups. Non-normally distributed continuous variables were analyzed with the Mann Whitney U test or Kruskal Wallis test depending on count of groups. Categorical variables were analyzed with the chi-square tests. Pairwise comparisons were adjusted by the Bonferroni correction method. Prediction performance of the monocyte to HDL ratio was assessed by using Receiver Operating Characteristic (ROC) curve analysis. Optimal cut-off points were determined by using Youden

index. Logistic regression analyses were performed to determine significant factors independently associated with the hepatic steatosis. Variables were analyzed with the univariable regression analysis and statistically significant variables were included into the multivariable analysis. Pearson or Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

We included 106 patients with HS and 85 healthy controls into our study. Age was significantly higher in the patients than in the controls (p<0.001). We found no significant difference between groups in terms of sex. Fifty eight (54.72%) patients had grade 1, 28 (26.42%) patients had grade 2 and 20 (18.87%) patients had grade 3 HS.

ALT (p<0.001), elevated liver function test percentage (p<0.001), fasting blood glucose (p<0.001), impaired fasting glucose percentage (p<0.001), HOMA-IR (p<0.001), insulin resistance percentage (p<0.001), total cholesterol (p<0.001), triglyceride (p<0.001), LDL (p<0.001), dyslipidemia percentage (p<0.001), monocyte count (p<0.001) and MHR (p<0.001) was significantly higher in the hepatic steatosis group than in the control group. HDL (p<0.001) was significantly lower in the HS group than in the control group. There were no significant difference between groups in terms of AST (Table 1).

MHR had 81.13% sensitivity, 72.94% specificity, 77.49% accuracy, 78.90% positive predictive value and 75.60% negative predictive value to predict hepatic steatosis for the cut-off point of 12.4 (values higher than this indicate hepatic steatosis). Area under ROC curve was 0.823 (95% CI: 0.763 - 0.882, p<0.001).

Multivariable logistic regression analysis had revealed that elevated liver function tests, insulin resistance and high MHR (>12.4) were independently associated with the hepatic steatosis. Individuals with elevated liver function tests had 3.195-fold higher risk to had hepatic steatosis than other individuals had (OR: 3.195, 95% CI: 1.291 - 7.909, p=0.012). Individuals with insulin resistance had 8.498-fold higher risk to had HS than other individuals had (OR: 8.498, 95% CI: 3.435 - 21.021, p<0.001). Individuals with high MHR (>12.4) had 9.973-fold higher risk to had HS than other

Table 1. Summary of variables with regard to hepatic steatosis

	Hepatic steatosis		
	No (n=85)	Yes (n=106)	p
Age	45 (39 - 57)	55 (46 - 62)	<0.001
Sex			
Male	43 (50.59%)	51 (48.11%)	0.734
Female	42 (49.41%)	55 (51.89%)	
Hepatic steatosis grade			
Grade 1	-	58 (54.72%)	-
Grade 2	-	28 (26.42%)	
Grade 3	-	20 (18.87%)	
ALT	26.81 ± 7.06	36.46 ± 15.63	<0.001
AST	25.40 ± 6.31	27.13 ± 10.03	0.147
Elevated liver function test	29 (34.12%)	67 (63.21%)	<0.001
Fasting blood glucose	91.27 ± 12.88	102.75 ± 13.01	<0.001
Impaired fasting glucose	22 (25.88%)	62 (58.49%)	<0.001
HOMA-IR	1.8 (1.6 - 2.2)	3.35 (2.2 - 5.6)	<0.001
Insulin resistance	11 (12.94%)	69 (65.09%)	<0.001
Total cholesterol	154.91 ± 29.19	189.26 ± 40.71	<0.001
Triglyceride	107 (64 - 136)	154.5 (110 - 189)	<0.001
LDL	94 (84 - 107)	112.5 (96 - 136)	<0.001
HDL	51.25 ± 13.11	43.46 ± 9.62	<0.001
Dyslipidemia	47 (55.29%)	85 (80.19%)	<0.001
Monocyte	496.59 ± 186.42	768.68 ± 267.20	<0.001
Monocyte to HDL ratio	10.24 ± 4.67	18.80 ± 8.70	<0.001

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

individuals had (OR: 9.973, 95% CI: 4.187 - 23.757, p<0.001) (Table 2).

Age was significantly higher in the grade 1, grade 2 and grade 3 than in the grade 0 (p<0.001). We found no significant differences between grades in terms of sex. ALT was significantly higher in the grade 2 than in the grade 0, also was significantly higher in the grade 3 than in the other grades (p<0.001). Elevated liver function tests percentage was significantly higher in the grade 2 than in the grade 0, also was significantly higher in the grade 3 than in the grade 0 and grade 1 (p<0.001). Fasting blood glucose was significantly higher in the grade 1, grade 2 and grade 3 than in the grade 0, also was significantly higher in the grade 3 than in the grade 1 (p<0.001). Impaired fasting glucose percentage was significantly higher in the grade 2 and grade 3 than in the grade 0 (p<0.001). HOMA-IR was significantly higher in the grade 1, grade 2 and grade 3 than in the grade 0, also was significantly higher in the grade 2 and grade 3 than in the grade 1 (p<0.001). Insulin resistance percentage was significantly higher in the grade 1, grade 2 and grade 3 than in the grade 0, also was significantly higher in the grade 2 and grade 3 than in the grade 1 (p<0.001). Total cholesterol was significantly higher in the grade 1, grade 2 and grade 3 than in the grade 0, also was significantly higher in the grade 2 and grade 3 than in the grade 1 (p<0.001). Triglyceride was significantly higher in the grade 2 and grade 3 than in the grade 0 and grade 1 (p<0.001). LDL was significantly higher in the grade 1 and grade 2 than in the grade 0, also was significantly higher in the grade 3 than in the other grades (p<0.001). HDL was significantly lower in the grade 2 and grade 3 than in the grade 0, also was significantly lower in the grade 3 than in the grade 1 (p<0.001). Dyslipidemia percentage was significantly higher in the grade 2 and grade 3 than in the grade 0, also was significantly higher in the grade 3 than in the grade 1 (p<0.001). Monocyte count was significantly higher in the grade 1, grade 2 and grade 3 than in the grade 0, also was significantly higher in the grade 3 than in the grade 1 (p<0.001). MHR was significantly higher in the grade 1, grade 2 and grade 3 than in the grade 0, also was significantly higher in the grade 2 and grade 3 than in the grade 1 (p<0.001) (Figure 1). There were no significant difference between grades in terms of AST (Table 3).

MHR had 81.25% sensitivity, 80.42% specificity, 80.63% accuracy, 58.21% positive predictive value and 92.70% negative predictive value to predict grade 2&3 HS for the cut-off point of 16.1 (values higher than this indicate grade 2 or grade 3 hepatic steatosis). Area under ROC curve was 0.821 (95% CI: 0.744 - 0.899, p<0.001) (Figure 2).

Multivariable logistic regression analysis had revealed that elevated liver function tests, insulin resistance and high MHR (>16.1) were independently associated with the grade 2&3 hepatic steatosis. Individuals with elevated liver function tests had 5.015-fold higher risk to had grade 2&3 HS than other individuals had (OR: 5.015, 95% CI: 1.498 - 16.792, p=0.009). Individuals with insulin resistance had 25.112-fold higher risk to had grade 2&3 HS than other individuals had (OR: 25.112, 95% CI: 6.404 - 98.475, p<0.001). Individuals with high MHR (>16.1) had 8.905-fold higher risk to had grade 2&3 HS than other individuals had (OR: 8.905, 95% CI: 2.863 - 27.694, p<0.001) (Table 4).

MHR was positively correlated with age (r=0.248, p=0.001), ALT (r=0.312, p<0.001), fasting blood glucose (r=0.297, p<0.001), HOMA-IR (r=0.436, p<0.001), total cholesterol (r=0.388, p<0.001), triglyceride (r=0.328, p<0.001) and LDL (r=0.413, p<0.001). We found no correlation between MHR and AST (Table 5).

DISCUSSION

Our study, in which we evaluated whether the MHR is a marker that can be used to predict the presence and stages of HS, found that the MHR was much higher in patients with HS compared to those without HS and this elevation increased in direct proportion to the stage.

Various markers are used in the diagnosis of inflammatory

Table 2. Odds ratios for hepatic steatosis, logistic regression analysis results

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.066 (1.035 - 1.098)	<0.001	1.040 (0.998 - 1.084)	0.060
Sex, Female	1.104 (0.624 - 1.954)	0.734		
Elevated liver function test	3.317 (1.825 - 6.029)	<0.001	3.195 (1.291 - 7.909)	0.012
Impaired fasting glucose	4.035 (2.170 - 7.504)	<0.001	1.666 (0.694 - 4.000)	0.254
Insulin resistance	12.545 (5.933 - 26.526)	<0.001	8.498 (3.435 - 21.021)	<0.001
Dyslipidemia	3.273 (1.724 - 6.213)	<0.001	0.998 (0.412 - 2.418)	0.996
Monocyte to HDL ratio, >12.4	11.591 (5.858 - 22.936)	<0.001	9.973 (4.187 - 23.757)	<0.001
Nagelkerke R^2	-		0.594	

OR: Odds ratio, CI: Confidence interval

Table 3. Summary of variables with regard to hepatic steatosis grade

	Hepatic steatosis grade				
	Grade 0 (n=85)	**Grade 1 (n=58)**	**Grade 2 (n=28)**	**Grade 3 (n=20)**	**p**
Age	45 (39 - 57)	55 (46 - 62) *	52.5 (46 - 62) *	58 (48 - 63) *	<0.001
Sex					
Male	43 (50.59%)	27 (46.55%)	12 (42.86%)	12 (60.00%)	0.657
Female	42 (49.41%)	31 (53.45%)	16 (57.14%)	8 (40.00%)	
ALT	26.81 ± 7.06	30.16 ± 12.97	36.43 ± 9.03 *	54.80 ± 15.94 *#§	<0.001
AST	25.40 ± 6.31	26.97 ± 11.49	27.79 ± 7.42	26.70 ± 8.97	0.424
Elevated liver function test	29 (34.12%)	28 (48.28%)	20 (71.43%) *	19 (95.00%) *#	<0.001
Fasting blood glucose	91.27 ± 12.88	98.84 ± 12.84 *	104.68 ± 10.37 *	111.40 ± 12.57 *#	<0.001
Impaired fasting glucose	22 (25.88%)	27 (46.55%)	20 (71.43%) *	15 (75.00%) *	<0.001
HOMA-IR	1.8 (1.6 - 2.2)	2.35 (1.8 - 3.2) *	5.0 (3.95 - 7.2) *#	8.65 (4.1 - 10.2) *#	<0.001
Insulin resistance	11 (12.94%)	24 (41.38%) *	26 (92.86%) *#	19 (95.00%) *#	<0.001
Total cholesterol	154.91 ± 29.19	176.60 ± 25.50 *	199.39 ± 40.40 *#	211.80 ± 60.96 *#	<0.001
Triglyceride	107 (64 - 136)	131.5 (79 - 158)	167 (120 - 203) *#	215 (178.5 - 262) *#	<0.001
LDL	94 (84 - 107)	104 (95 - 120) *	117.5 (96.5 - 145) *	155.5 (139 - 166) *#§	<0.001
HDL	51.25 ± 13.11	46.98 ± 9.55	40.71 ± 8.15 *	37.10 ± 7.17 *#	<0.001
Dyslipidemia	47 (55.29%)	39 (67.24%)	26 (92.86%) *	20 (100.00%) *#	<0.001
Monocyte	496.59 ± 186.42	710.00 ± 229.72 *	810.36 ± 326.05 *	880.50 ± 242.76 *#	<0.001
Monocyte to HDL ratio	10.24 ± 4.67	15.72 ± 6.00 *	20.75 ± 9.38 *#	25.02 ± 10.46 *#	<0.001

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. *: Significant difference from Grade 0, #: significant difference from Grade 1, §: Significant difference from Grade 2

diseases and the evaluation of treatment response, but the majority of these markers are not used in daily practice due to high costs and difficulty in access. Therefore, simple, easily accessible, and low-cost markers are required for the detection of the presence and severity of inflammation (14). Monocyte/HDL ratio is one of the new markers being tested for this purpose.

Monocytes, which account for approximately 3-8% of leukocytes in peripheral blood, play an important role in the regulation of inflammatory processes. HDL inhibits the transmigration of monocytes and the expression of endothelial adhesion molecules. This prevents macrophages from transferring lipid loads to the arterial wall (11). Recent research has also shown that HDL regulates the proliferation of monocyte progenitor cells (15). All of these findings indicate that monocytes have pro-inflammatory effects, and HDL cholesterol acts as a factor that reverses this process. Given the anti-inflammatory effects of monocytes and HDL, the ratio of these two values to each other has emerged as a good indicator of inflammation.

The effectiveness of the MHR in predicting the diagnosis and prognosis of many diseases with inflammation in their etiology has been studied since the idea that it

Table 4. Odds ratios for grade 2&3 hepatic steatosis, logistic regression analysis results

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.045 (1.011 - 1.081)	0.010	0.985 (0.930 - 1.044)	0.613
Sex, Female	0.959 (0.499 - 1.844)	0.900		
Elevated liver function test	6.538 (2.943 - 14.527)	<0.001	5.015 (1.498 - 16.792)	0.009
Impaired fasting glucose	5.165 (2.503 - 10.656)	<0.001	2.538 (0.783 - 8.229)	0.121
Insulin resistance	46.286 (13.538 - 158.243)	<0.001	25.112 (6.404 - 98.475)	<0.001
Dyslipidemia	15.244 (3.559 - 65.297)	<0.001	5.524 (0.950 - 32.113)	0.057
Monocyte to HDL ratio, >16.1	17.798 (7.728 - 40.988)	<0.001	8.905 (2.863 - 27.694)	<0.001
Nagelkerke R^2	-		0.710	

OR: Odds ratio, CI: Confidence interval

may be a marker of inflammation and oxidative stress emerged. There is even evidence that it may indicate low-grade systemic inflammation in the absence of overt disease manifestation. For example, obesity causes low-grade chronic systemic inflammation. In a recent study conducted in Turkey, the status of the MHR in obese and non-obese individuals was investigated, and it was discovered that MHR was higher in obese individuals, and this increase was directly proportional to the degree of obesity (16). These studies led to the conclusion that MHR is a marker that can reflect even the pre-inflammatory state and correlates with the severity of inflammation.

Table 5. Correlations between monocyte to HDL ratio and other variables

	Monocyte to HDL ratio	
	r	p
Age, years	0.248	0.001
ALT	0.312	<0.001
AST	0.062	0.394
Fasting blood glucose, mg/dl	0.297	<0.001
HOMA-IR	0.436	<0.001
Total cholesterol, mg/dl	0.388	<0.001
Triglyceride, mg/dl	0.328	<0.001
LDL, mg/dl	0.413	<0.001

r: Correlation coefficient

Our study showed that MHR was much higher in the group with HS than in the group without HS. Furthermore, as the HS stage increased, the MHR also increased. The reason for this is that inflammation becomes more severe as fat accumulation increases in hepatocytes (17).

Since NAFLD is so common and has such serious consequences, it must be diagnosed early and closely monitored. Due to the mechanisms involved in pathogenesis, it is important to remember that NAFLD is linked not only to liver-related mortality but also to cardiovascular mortality (18). The MHR is also used to predict the prognosis of cardiovascular disease (19,20). According to the World Health Organization's 2020 report, 30 million people aged 30 to 69 die each year as a result of non-communicable diseases. The most common cause of noncommunicable diseases is metabolic abnormalities. HS is common in societies with obesity, hyperlipidemia, insulin resistance, type 2 Diabetes Mellitus, and metabolic syndrome (21). As a result, high-risk individuals with these diseases should be thoroughly examined for the presence of NAFLD. Similarly, the presence of these diseases must be investigated in a patient in whom HS is detected for any reason (22).

The prevalence of all these predisposing diseases, and thus the prevalence of NAFLD increases with age (23). Consistent with this data, our study showed that age was significantly higher in the group with HS compared to the group without HS. Hospital visits for these patients increase after diagnosis, and this situation causes a serious economic burden. There was no difference in the sex distribution between the HS and non-HS groups in our study. This was thought to be due to the similar prevalence of predisposing diseases in men and women. In the study of Yozgat et al. investigating the MHR in NAFLD, similar to our study, age was found to be higher in the group with HS, but no difference was observed in terms of sex distribution (10).

Insulin resistance is widely regarded as the primary cause of metabolic syndrome and NAFLD. The metabolic

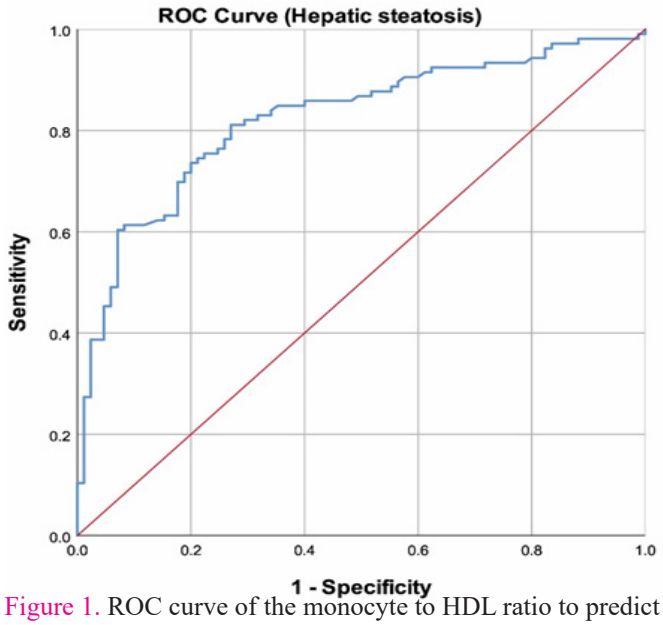

Figure 1. ROC curve of the monocyte to HDL ratio to predict hepatic steatosis

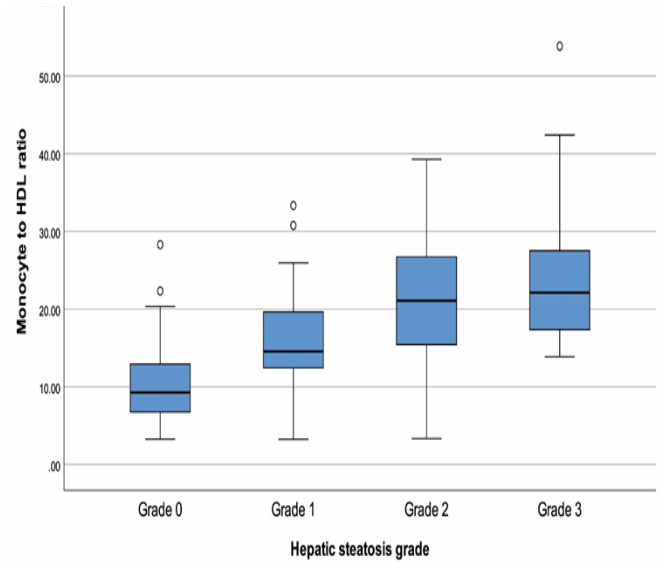

Figure 2. Box-plot of the monocyte to HDL ratio with regard to hepatic steatosis grade

syndrome is characterized by low HDL and increased triglycerides levels. Insulin resistance promotes lipolysis in adipose tissue, which results in the release of free fatty acids and their storage in the liver, and thus the development of HS. Dyslipidemia has a direct impact on the onset and progression of HS (24). Non-HDL cholesterol is a value that indicates the total level of harmful fats in the blood and can be calculated simply by subtracting HDL cholesterol from total cholesterol. IR causes a decrease in HDL cholesterol levels and an increase in NON-HDL cholesterol levels. In a study conducted in China in which 2717 individuals were followed up for an average of 1.6 years, a significant correlation was found between newly developing NAFLD and non-HDL/HDL cholesterol levels (25). In the presence of HS, trigliseride increase is also observed in addition to low HDL. In a recent study of 18061 patients, trigliseride /HDL ratio was found to be directly associated with NAFLD and this was also associated with insulin resistance (26).

AST and ALT are markers of hepatocellular damage. AST is found in the liver, heart muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes. It is not as sensitive and specific for the liver as ALT. ALT is a liver-specific enzyme and ALT increase is more prominent than AST increase in laboratory findings reflecting HS (27).

However, in our study, fasting blood glucose, insulin resistance, total cholesterol, LDL, triglyceride, and ALT were significantly higher in the group with HS compared to those without HS and these values increased as the stage of HS increased and when correlation analysis was performed, MHR was positively correlated with these values. HDL was significantly lower in the group with HS compared to the group without HS and decreased as the stage of HS increased. There was no significant difference in terms of AST between the HS and non-HS groups.

Regression analyses show that the MHR is an important predictor of HS. Only ALT, insulin resistance, and the MHR are found to be independently associated with HS. A patient with increased ALT, the liver function test that best reflects HS, is 3.1 times more likely to have HS, and a patient with insulin resistance, the most important risk factor for HS, is 8.4 times more likely to have HS. The possibility of HS is 9.9 times higher in patients with an increased MHR. The study's findings indicate that, just as we investigate the presence of HS in a patient with increased ALT and insulin resistance, we need to be equally careful in a patient with a high MHR and risk factors for HS.

LIMITATIONS OF THE STUDY

Ours is a single-center study involving 191 patients. We don't have the patients' height, weight, or Body Mass Index parameters because the study was done retrospectively. Multicenter prospective studies with a larger number of patients that include these parameters are required. Furthermore, a recent infection may have affected the patients' monocyte values, but there is no information about this in the patient files. Another limitation is that the diagnosis of HS is made using USG. USG has the disadvantages of being a subjective evaluation, the difficulty of use in obese patients, and low sensitivity in histologic liposis below 30%.

CONCLUSION

MHR is closely associated with the presence and stages of NAFLD. It can be used as a marker to predict the presence and stages of HS in high-risk groups and may also be useful in evaluating the treatment response.

DECLARATIONS

Ethics Committee Approval: Approval of the the study was obtained from the Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee for the study. (Date: 30.01.2023 / Number: E-10840098-772.02-739)

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Author contributions: The idea, method and planning of the study, data collection and statistical analysis were made by Ece Yiğit, the evaluation and interpretation of the findings, literature review and article drafting were made by İlknur Sayar. All authors read and approved the final manuscript.

Conflict of interest: None

Informed consent form: Since the study is a retrospective study based on the examination of patient files, informed consent form was not obtained.

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Original Article

Evaluation of Thyroid Functions and Correlation of Body Mass Index with Apnea-Hypopnea Index in Patients with Obstructive Sleep Apnea Syndrome

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ABSTRACT

Background: Thyroid hormone deficiency and excessive weight, which are considered endocrine disorders, can be easily detected, have low cost, and guide treatment planning in obstructive sleep apnea syndrome (OSAS). We examined thyroid hormone levels in patients diagnosed with OSAS using polysomnography and conducted a study to investigate the correlation between body mass index (BMI) values and apnea-hypopnea index (AHI).

Material and Methods: This study included patients who presented to the Ear, Nose, and Throat Clinic and Sleep Disorders Center of Dicle University Faculty of Medicine Hospital between July 2008 and November 2010, and were diagnosed with OSAS based on polysomnography (PSG) results. The study group consisted of a heterogeneous group in terms of presenting complaints, with most patients reporting complaints of snoring, while others had a history of witnessed apneas by their partners, excessive daytime sleepiness, fatigue, and headaches. From the group diagnosed with OSAS (AHI>5) based on PSG results, the first 100 randomly selected patients were included in the study.

Results: The mean age of the cases diagnosed with OSAS based on PSG results was 48.79±10.70. The age of women ranged from 24 to 76, with a mean age of 55.44±19.25. The age of men ranged from 24 to 77, with a mean age of 46.33±15.48. Among the 100 patients, 33 had mild, 19 had moderate, and 48 had severe OSAS. Among these 100 cases, hypothyroidism was detected in 5 patients (2 with mild OSAS and 3 with severe OSAS) based on serum thyroid hormone levels. Among the patients with hypothyroidism, 2 were female and 3 were male. In all cases, a positive correlation was found between BMI and AHI, with a significance level of 45.9% and a statistically significant correlation.

Conclusion: Based on these findings, it can be concluded that screening for hypothyroidism and measuring BMI should be necessary for all patients presenting to sleep laboratories with suspected OSAS.

Keywords: OSAS, thyroid, BMI, hypothyroidism

INTRODUCTION

Despite sleep being an essential aspect of our lives, occupying approximately one-third of our time and being crucial for a healthy life, the physiology of sleep could only be explained in the 20th century with the application of EEG (1). The effects of sleep on respiration were demonstrated in 1965 by Gastaut through polysomnography, which is now considered the "gold standard" for diagnosing sleep apnea syndrome (2). Initially, sleep apnea syndrome was not recognized as a significant public health issue, but its prevalence, ranging from 1% to 5%, has been shown to be quite high, and it is commonly associated with diseases such as diabetes mellitus and bronchial asthma (3-5). Thus, it has rightfully gained its deserved recognition.

Although there are many diseases that can cause respiratory disorders during sleep, the most significant group is constituted by "sleep apnea syndrome," with "obstructive sleep apnea syndrome" (OSAS) practically being understood when referring to sleep apnea syndrome due to its prevalence, accounting for 90-95% of all cases (6).

The detection of respiratory disorders during sleep is crucial for both the prognosis of the disease and the implementation of appropriate treatment. However, the gold standard for diagnosing this condition, polysomnography, is a costly, time-consuming, and resource-intensive procedure that requires specialized equipment (7). Moreover, the number of laboratories capable of conducting this study at a sufficient level is limited both globally and in our country. Therefore, selective criteria need to be applied when determining who should undergo polysomnographic testing.

The spectrum of symptoms in OSAS is quite broad. These symptoms provide indications of OSAS, but not all of them have diagnostic significance. Among the etiological factors, thyroid hormone deficiency and excessive weight, which are considered endocrine disorders, can be easily detected, have low cost, and provide guidance in treatment planning (8,9).

Based on this premise, we examined thyroid hormone levels in patients diagnosed with OSAS using polysomnography and conducted a study to investigate the correlation between body mass index (BMI) values and the Apnea Hypopnea Index (AHI).

MATERIAL and METHODS

This study included patients who presented to the Ear, Nose, and Throat Clinic (ENT) and Sleep Disorders Center of Dicle University Medical Faculty Hospital between July 2008 and November 2010 and were diagnosed with OSAS based on polysomnography (PSG) results. The study group consisted of a heterogeneous group of patients with diverse complaints. Most of them complained of snoring, while others presented with a history of breathing pauses during sleep reported by their partners, excessive daytime sleepiness, fatigue, and headaches. From the group of patients diagnosed with OSAS (AHI>5) based on PSG results, the first 100 patients were randomly selected. No gender distinction was made among the patients.

The study excluded the following cases: Secondary cases who had previously received a diagnosis of OSAS and undergone any surgical intervention in any clinic due to sleep disorders. Cases who presented with other complaints received a diagnosis of thyroid dysfunction and underwent replacement therapy.

Age, body weight, and height measurements were recorded to calculate their BMI, and its correlation with the AHI was evaluated. Thyroid-stimulating hormone (TSH), Free T3 (FT3), and Free T4 (FT4) hormone levels were examined. The prevalence of existing thyroid dysfunction associated with OSAS was determined as a percentage. Changes in symptoms in patients receiving replacement therapy or undergoing surgical treatment were recorded and compared with the reevaluation of thyroid function in subsequent follow-ups.

A detailed medical history was obtained from the patients included in the study, as well as from their spouses. The patients were asked to answer the following questions:

- Frequency, intensity, and association with sleep position of snoring.
- Presence or absence of respiratory irregularities and feelings of suffocation during sleep.
- Frequency of nighttime awakenings.
- Ease or difficulty of waking up in the morning.
- Changes in intellectual functions such as learning, comprehension, management, and memory.
- Sexual problems such as decreased libido or impotence.

These questions aimed to gather information about the patients' symptoms and experiences related to sleep and to assess potential associations with OSAS.

After obtaining the medical history, a routine ENT examination was performed on each patient. The examination included evaluating nasal structure and nasal passage patency, the condition of the soft palate, length of the uvula, epiglottis position, mandibular structure, size of the tongue, presence of craniofacial anomalies, and the size and movement of lymphoid tissues such as tonsils and adenoids.

In this study, PSG recordings were conducted at the Sleep Laboratory of Dicle University Hospital's Chest Diseases Clinic under the supervision of a technician, and during the patients' spontaneous sleep. A video camera system was used to record audio and visual data throughout the night. Patients were admitted to their designated rooms two hours before their usual bedtime and were encouraged to settle into the sleeping environment. After the process of attaching electrodes to the patients, the computer-controlled the status of all electrodes, and then the patients were left alone to sleep. PSG recordings included EEG, mentalis and submental EMG, EMG from the right anterior tibial muscle, airflow measurement from the mouth and nose, chest and abdominal respiratory movements, and pulse oximetry throughout the night. Respiratory monitoring was achieved by integrating a pulse oximeter and oronasal airflow measurement (oronasal cannula) into the main device. Respiratory sounds were recorded using a microphone placed on the neck, and thoracic and abdominal movements were assessed using piezoelectric bands to examine respiratory effort. Body position sensors (back, front, right, left) were used to record patients' sleeping positions. Additionally, heart rhythm was monitored throughout the night using EKG electrodes. All procedures and recordings were conducted under the supervision of a technician.

PSG recordings were scored according to the international sleep disorder criteria (AASM 2007) using the Twin polysomnographic analysis program. The PSG results obtained in the study were compared with anthropometric measurements. The device used in the study was the Compumedics e-series with 44 channels. The recordings were initially scored using computer software and later manually evaluated by the physician for further analysis. The reports were then explained by the responsible physician.

BMI is calculated as Body Weight (kg) divided by Height squared (m^2).

This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subject

STATISTICAL ANALYSIS

SPSS (Statistical Package for Social Sciences) for Windows 15.0 software was used for data analysis. Descriptive statistical methods (mean, standard deviation, frequency) were employed to evaluate the study data. Student's t-test was used for comparing normally distributed quantitative variables between groups, and a one-way ANOVA test was used for comparing means among more than two groups. The Chi-square test was utilized for evaluating categorical variables, and a two-way ANOVA test was applied when assessing two categorical variables. The Chi-square test was used for comparing qualitative variables. The Pearson correlation test was employed to examine the relationships between variables. The results were presented as mean, standard deviation, and 95% confidence intervals for each variable. Statistical significance was evaluated at $p<0.05$ level.

RESULTS

A total of 100 cases with ages ranging from 24 to 77 years who applied to the ENT Clinic and Sleep Disorders Center of xxxx University Faculty of Medicine were included. Of the cases, 27 (27%) were female and 73 (73%) were male. The characteristics of the participants were given in **Table 1**.

Table 1. The characteristics of patients (n=100)

	Mean (±SD)
Age, year	48.79±10.70
Weight, kg	85.63±12.65
Height, cm	171.0±7.94
BMI, kg/m2	29.09±4.41
AHI	37.66±29.21

BMI; body mass index, AHI; Apnea-Hypopnea Index

All cases underwent routine ENT examinations. Specifically, the nasal passage patency, nasopharynx, soft palate, uvula, palatine tonsils, tonsillar pillars, and posterior pharyngeal wall mucosa were evaluated. Secondary cases who had previously received a diagnosis of OSAS and undergone any surgical intervention, as well as cases with other complaints who had been diagnosed with thyroid dysfunction and received replacement therapy, were not included in the study.

Patients who presented with complaints of snoring underwent polysomnographic examination based on the anamnesis and physical examination findings, leading to a preliminary diagnosis of sleep apnea. The average age of patients diagnosed with OSAS was 48.79 years. The ages of female patients ranged from 24 to 76, with an average of 55.44 years. The ages of male patients ranged from 24 to 77, with an average age of 46.33 years. Serum-free T3, T4, and TSH levels were measured, and body weight and height were recorded to calculate BMI. The apnea-hypopnea indices of the patients were calculated based on the polysomnographic examination. Among the 100 patients, 33 had mild, 19 had moderate, and 48 had severe OSAS. Among these 100 patients, hypothyroidism was found in 5 patients (2 with mild OSAS and 3 with severe OSAS) based on the measured serum thyroid hormone levels. Of the patients with hypothyroidism, 2 were female and 3 were male.

When calculating the average ages of patients according to gender, there was a statistically significant difference between male patients (46.33±8.866) and female patients (55.44±12.473) ($p<0.0001$). According to this result, the average age of females is approximately 9 years higher than that of males. There is no statistically significant difference in the distribution of cases by gender based on the AHİ ($p>0.05$, **Table 2**).

Table 2. The frequency of AHI between genders

	Male	Female	Total
Mild	34.2%	29.6%	33.0%
Moderate	17.8%	22.2%	19.0%
Severe	47.9%	48.1%	48.0%
Total	100%	100%	100%

$x^2=0.33$ and $p>0.05$. No significant difference

The heights of the individuals range between 150 cm and 194 cm, with an average of 171 cm. The weights of the individuals range between 55 kg and 120 kg, with an average of 85.63 kg. The BMI levels of the individuals range between 22.30 and 44.10, with an average of 29.09. When the BMI averages are calculated according to gender, there is no statistically significant difference between the two groups ($p>0.05$). The average BMI for males (n=73) is 28.79±3.95 and for females, the average BMI is 29.92±5.46 ($p>0.05$).

According to the AHI, there is a statistically significant difference in BMI averages among female cases. The BMI levels of female cases with severe AHI are significantly higher than those with mild and moderate AHI. However, there is no statistically significant difference in BMI levels among cases with mild and moderate AHI .

According to the AHI, there is a statistically significant difference in BMI averages among male cases. The BMI levels of male cases with severe AHI are significantly higher than those with mild and moderate AHI. However, there is no statistically significant difference in BMI levels among cases with mild and moderate AHI (**Table 3**).

According to the AHI, there is a statistically significant difference in BMI averages among all cases. The BMI levels of cases with severe AHI are significantly higher than those with mild and moderate AHI. However, there is no statistically significant difference in BMI levels among cases with mild and moderate AHI (**Table 4**).

DISCUSSION

There are some risk factors for obstructive sleep apnea syndrome (OSAS) including male gender, advanced age, and family history. Diabetes mellitus, hypothyroidism, acromegaly, and obesity are endocrine disorders believed to be associated with OSAS. Various cellular-level changes in hypothyroidism contribute to an increased susceptibility to OSAS. Although this relationship has been clearly established, the exact prevalence of hypothyroidism in OSAS patients is not fully known.

According to the literature, the coexistence of OSAS and hypothyroidism is reported to be between 1.2% and 11% (8,10,11). In investigations exploring the connection between thyroid dysfunction and OSAS, Mickelson et al. conducted a study involving 842 cases and found that the prevalence of clinical hypothyroidism was 1.2%. Among these cases, 5 out of 10 patients exhibited simple snoring (2 with a previous history, 3 diagnosed through PSG). The frequency of hypothyroidism among OSAS patients did not differ significantly from the general population (12). Similarly, Winkelman et al. reported a prevalence of 2.9% for hypothyroidism among 255 cases diagnosed with OSAS using PSG (13). Skjodt et al. conducted a study on 200 patients diagnosed with OSAS and observed a prevalence of 1.5% for hypothyroidism among individuals tested via PSG, while suspects of OSAS showed a prevalence of 2.4%. They emphasized the importance of screening for hypothyroidism to prevent misdiagnosis of primary sleep apnea and unnecessary expenses on sleep studies (14). Furthermore, Popovici et al. observed a high coexistence rate of 11% between the two diseases in a group of 95 patients diagnosed with OSAS (15). Another crucial aspect to consider regarding the association between OSAS and hypothyroidism is the similarity in symptoms shared by both conditions. Symptoms and findings such as daytime sleepiness, fatigue, apathy, lethargy, decreased libido, depressive mood, headache, obesity, and snoring, which are commonly seen in hypothyroidism, are frequently encountered in patients with OSAS as well (16). Orr et al. emphasize the importance of recognizing myxedema and obstructive sleep apnea syndrome as potential life-threatening complications in hypothyroid patients experiencing excessive daytime sleepiness (17).

Looking at studies conducted in Turkey, Guven et al. diagnosed OSAS in 111 out of 134 cases (82%) who presented to the sleep center with suspicion of OSAS and underwent overnight PSG. Among these patients, hypothyroidism was detected in 5 cases (4.5%). This finding is similar to our study (18).

In our study of 100 cases, 33 had mild OSAS, 19 had moderate OSAS, and 48 had severe OSAS. Among these 100 patients, hypothyroidism was detected in 5 cases (2 with mild OSAS, 3 with severe OSAS) based on their serum thyroid hormone levels. Of the patients with hypothyroidism, 2 were female and 3 were male. After hormone replacement therapy, there was an improvement in the symptoms of patients with mild OSAS, while no changes were observed in the symptoms of the 3 patients with severe OSAS. The co-occurrence rate of OSAS and hypothyroidism in our study was found to be 5%, which is consistent with the literature.

Table 4. Mean BMI according to OSAS severity levels in all cases.

Mild	27.50±0.85
Moderate	28.06±1.03
Severe	31.08±0.68

There are three important physiological factors involved in the development of upper airway obstruction and collapse. These are the anatomy of the upper airway, the

Table 3. Descriptive statistics of the BMI variable according to Gender and OSAS groups

OSAS	BMI, Male, n=77	BMI, Female, n=23
Mild	27.67 ± 1.83, CI 95% 26.009 - 29.343	27.32 ± 1.48, CI 95% 24.379 - 30.271
Moderate	27.19 ± 1.16, CI 95% 24.881 - 29.503	28.93 ± 1.71, CI 95% 25.532 - 32.335
Severe	30.18 ± 1.70, CI 95% 28.774 - 31.591	31.98 ± 1.16, CI 95% 29.674 - 34.296

OSAS; obstructive sleep apnea syndrome, BMI; body-mass index

negative pressure generated during inspiration, and the loss of muscle activity that dilates the pharyngeal airway (19,20). Various risk factors for OSAS facilitate these physiological conditions and increase the susceptibility to OSAS. Age, gender, obesity, neck circumference, smoking, alcohol, and sedative use, and certain accompanying diseases are among the major proposed risk factors (19).

Age, gender, and obesity are the most significant risk factors. Aging is associated with changes in body fat distribution, tissue elasticity, and control of ventilation, which increase the tendency for OSAS (21). It has been reported that OSAS is most commonly observed in the 40-65 age group and its prevalence decreases after the age of 65 (22).

Comparisons conducted on the elderly show a higher rate of detection of disorders based on the AHI, but the clear relationship between this and the development of morbidity and mortality due to daytime sleepiness is not known. In a study conducted in a nursing home, the prevalence of OSAS in individuals aged 65 and above was reported to be 62% (23). However, whether age alone increases the risk of OSAS has not been fully clarified. The increase in the disease with age is not as significant in individuals over the age of 65 as it is in those under the age of 65 (24). This can be explained by the possibility of more deaths in OSAS or a decrease in the disease with age. However, there is no definitive evidence to suggest that OSAS causes death or declines with age. It has been observed that reports of snoring decrease in the elderly compared to the middle-aged group, and this has been attributed to a decrease in the survival of bed partners who can witness the snoring in elderly patients and an increase in the frequency of central apnea in the elderly (25). The complexity of the relationship between age and OSAS prevalence can be explained by cohort effects and difficulties in detecting OSAS in the elderly. The lack of sufficient information on OSAS incidence and mortality rates specific to age groups makes it difficult to make definitive conclusions on the subject.

Male gender is also an important risk factor for OSAS. The frequency of OSAS has been reported to be higher in men than in women during middle age. The accumulation of fat, particularly in the neck area, due to androgenic fat distribution in men increases the risk of OSAS. Epidemiological studies in the 1980s found high male-to-female ratios of 10/1 to 7/1 (26,27). However, recent studies have reported that the gender difference is not as high, with a female-to-male ratio of 1/3 for every age group (27). The gender-related difference may be attributed to women reporting OSAS symptoms such as apnea, snoring, and waking up choking less frequently, seeking medical help less often for these symptoms, and doctors considering the diagnosis of OSAS less frequently in female patients presenting with the same complaints compared to male patients. Bed partners may also report less snoring and choking-like symptoms in women. The lower prevalence of OSAS in premenopausal women compared to men has been attributed to differences in fat distribution due to sex hormones (28). However, administration of sex hormones (estrogen and progesterone) did not lead to a decrease in AHI in male and postmenopausal female OSAS patients (29). Occupational and environmental factors, upper airway structure, and differences in fat distribution have been proposed to explain the gender-related differences in OSAS prevalence, but there is no definitive evidence regarding these factors.

In a screening study conducted by Nieto et al. (30) with 6,132 individuals, it was reported that approximately 37% of diagnosed OSAS cases were women. In our study, 73% of our OSAS patients were male and 27% were female. Our findings are consistent with the literature.

Obesity plays an important role in the pathophysiology of OSAS (31,32). In fact, improvement in the OSAS clinic can be observed with weight loss (31,32). When defining obesity as an increase in body fats, the most important determinant factor of the health risks posed by obesity is the distribution of fat in the body. Male-type obesity is generally characterized by central fat deposition, particularly in the abdomen and neck regions. Female-type obesity, on the other hand, is characterized by fat deposition around the hips. Numerous studies have shown that android fat distribution, which is centered around the neck and abdominal organs, leads to more complications. Güven et al. found that 69% of mild OSAS patients and 77% of moderate and severe OSAS patients were obese (BMI >29) among 67 OSAS cases (18).

In the past, OSAS used to be associated with obesity as a prevalent condition. However, recent studies have revealed that approximately 40% of OSAS patients are not classified as obese (33,34). When considering AHI, there is a noteworthy difference in average BMI among female cases. Specifically, females with severe AHI (48.1%) exhibited significantly higher BMI levels (31.9) compared to those with mild (29.6%) and moderate (22.2%) AHI levels (27.3-28.9). No statistically significant difference was found in BMI levels between cases with mild and moderate AHI. Similarly, among male cases, a statistically significant variance in average BMI was observed. Males with severe AHI (47.9%) had significantly higher BMI levels (30.1) than those with mild (34.2%) and moderate (17.8%) AHI levels

(27.6-27.1). Again, no statistically significant difference was detected in BMI levels between cases with mild and moderate AHI. Moreover, there is a statistically significant discrepancy in the average BMI across all cases. Cases with severe AHI demonstrated higher BMI levels (31.0) compared to those with mild and moderate AHI levels (27.5-28.0). No statistically significant difference was found in BMI levels between cases with mild and moderate AHI. Notably, a significantly positive correlation exists between BMI levels and AHI in females, with a correlation coefficient of 57.2% and statistical significance (r(AHI, BMI)=0.572, p= 0.002). Similarly, a positive and statistically significant correlation was observed between BMI levels and AHI in males, with a correlation coefficient of 38.3% (r(AHI, BMI)=0.383, p=0.001). Overall, there is a positive correlation between BMI and AHI across all cases, with a correlation coefficient of 45.9% and statistical significance (r(BMI, AHI) = 0.459, p<0.001).

When calculating the average BMI according to gender, there was no statistically significant difference between the two groups. İbrahim et al. observed that OSAS females had significantly higher BMI values compared to males and there was no significant difference in average BMI values among different OSAS categories (35).

It is known that PSG is the gold standard test for diagnosing OSAS, but it is expensive, time-consuming, requires a specialized team and the number of laboratories capable of conducting sufficient studies is limited. Therefore, although they do not provide a definitive diagnosis, it is important to interpret obesity, which plays an important role in the etiology of OSAS, in determining cases to be referred for polysomnographic examination. However, it should not be concluded that every obese patient needs to be referred for PSG. Because patients with obesity constitute a large population, and not all obese patients have OSAS. We believe that the Epworth Sleepiness Scale should be evaluated before referring to PSG. According to our results, showing that BMI is an important determinant of AHI, there is a relationship between obesity and OSAS.

CONCLUSION

The association between Obstructive Sleep Apnea Syndrome (OSAS) and hypothyroidism has been established in the literature, although the exact prevalence of hypothyroidism in OSAS patients remains uncertain. The reported coexistence rate of OSAS and hypothyroidism ranges from 1.2% to 11% in various studies. Both conditions share similar symptoms, such as daytime sleepiness, fatigue, apathy, and obesity, making it crucial to consider the possibility of hypothyroidism in OSAS patients. Screening for hypothyroidism in individuals suspected of having OSAS can prevent misdiagnosis and unnecessary expenses for sleep studies. Thyroid replacement therapy has been shown to improve OSAS symptoms in patients with hypothyroidism.

Several risk factors contribute to the development of OSAS, including male gender, advanced age, and obesity. Aging is associated with changes in body fat distribution and ventilation control, increasing the susceptibility to OSAS. The male gender has a higher prevalence of OSAS, possibly due to androgenic fat distribution, while women may underreport symptoms and seek medical help less often. Obesity, particularly with android fat distribution around the neck and abdomen, plays a significant role in OSAS pathophysiology. BMI is commonly used to evaluate obesity and higher BMI levels are associated with more severe OSAS.

While PSG is the gold standard for diagnosing OSAS, it is expensive and requires specialized facilities. Considering the relationship between obesity and OSAS, BMI can be used as a screening tool to determine which patients should be referred for PSG. However, not all obese individuals have OSAS, so careful assessment, including the Epworth Sleepiness Scale, is necessary to determine the need for PSG.

Overall, understanding the relationship between OSAS and hypothyroidism, as well as the impact of risk factors like gender and obesity, can contribute to more accurate diagnoses and effective treatment strategies for patients with OSAS.

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Original Article

The Assessment of Stroke Patients Using the Functional Independence Measurement Scale

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ABSTRACT

Background: The objectives of this study are; evaluating hemiplegic patients using the "Functional Independence Measurement Scale (FIM)", assessing the long-term daily life activities of patients receiving and not receiving rehabilitation based on FIM scale, emphasizing the prognostic importance of functional status assessment, and establishing the routine use of this scale in our clinic.

Material and Methods: The study conducted at Şişli Etfal Hospital used the Functional Independence Measurement Scale (FIM) to assess the functional independence of patients with cerebrovascular hemorrhage or ischemia. The patients were evaluated at different time points, including admission, discharge, and six months after the event. The FIM scale consists of 18 items in six categories, and each item is evaluated based on specific criteria. The study aimed to assess the effectiveness of a conventional rehabilitation program on the functional independence of the patients. $p<0.05$ was assumed statistically significant at 95% CI.

Results: The study suggests that patients who received rehabilitation showed significant motor function improvement over time compared to those who did not receive rehabilitation. There was a strong correlation between the motor function status achieved after 6 months and the rehabilitation program. In the non-rehabilitation group, significant gains in motor function were observed during the initial period of the disease and the subsequent home control, but no significant change was seen between discharge and the 6-month home control ($p>0.05$).

Conclusion: The results indicated that patients who received rehabilitation showed significant improvements in motor function over time, and these improvements were greater compared to the non-rehabilitation group. The age, gender, and etiological cause of the stroke did not significantly affect the functional outcomes.

Keywords: OSAS, thyroid, BMI, hypothyroidism

INTRODUCTION

The prevalence of chronic diseases with long-term consequences presents significant medical and socio-economic challenges in today's society. Among these conditions, cerebrovascular events (CVEs) stand out as one of the most severe globally, ranking as the third leading cause of death after cardiovascular diseases and cancer (1). As a result, there is a growing body of research aimed at optimizing the functional outcomes for patients who have experienced cerebrovascular events.

In the United States, CVEs hold the utmost urgency and frequency among all neurological disorders in adults and rank as the third most common cause of death (2). Surprisingly, nearly 29.6% of these patients fall below the age of 65, with 25.9% belonging to the 45-65 age group (3, 4).

Functional assessment plays a crucial role in measuring the extent to which individuals utilize their skills in various aspects of daily life, including work, leisure activities, social relationships, and other essential situations. By employing functional performance assessment measures, healthcare professionals can determine the patient's level of functioning upon admission and discharge. These measures also allow for the analysis of rehabilitation program effectiveness, goal attainment, and goal setting. Furthermore, they facilitate the identification of the patient's developmental process, evaluation of the rehabilitation program, as well as the identification of the patient's needs, goals, and achieved level of functioning.

In light of the aforementioned factors, the objectives of this study are as follows:

- To assess hemiplegic patients admitted to our neurology department between November 1993 and March 1994, following cerebrovascular events,

using the "Functional Independence Scale."
- To mathematically express and monitor the long-term daily life activities of patients receiving rehabilitation and those not receiving rehabilitation based on this assessment.
- To underscore the prognostic significance of functional status assessment.
- To establish the routine utilization of this scale in our clinic.

This study aims to provide a clear research direction and contribute to the field of functional assessment in patients recovering from cerebrovascular events.

MATERIALS AND METHODS

This study was conducted between November Şişli Etfal Education and Training Hospital, Physical Therapy and Rehabilitation Clinic, Istnabul. A total of 25 patients presenting with cerebrovascular hemorrhage or ischemia were included in the study.

Patients were evaluated using the Functional Independence Measurement Scale (FIM-1) within the first 72 hours of admission to our neurology department. During this assessment, a brief medical history was taken, risk factors were identified, and a general physical examination was performed. In addition to hemiplegia, any existing systemic diseases, thrombophlebitis, gastrointestinal problems, cataracts, nephropathy, oncological history, benign prostatic hyperplasia, epilepsy, congenital hip dislocation, bronchitis, and decubitus ulcers were recorded, along with the medications they were currently taking, including cardiovascular regulators, antiplatelets, antihypertensives, anticonvulsants, antidiabetic drugs, diuretics, bronchodilators, and oral anticoagulants.

Patients continued to receive treatment in the Neurology Department until they were medically stable. Upon completion of treatment in this department, the patients were divided into two groups: some were transferred to the Physical Medicine and Rehabilitation Department of the same hospital, while others were discharged home. Patients discharged and sent home and those transferred to the physical therapy department were subjected to a second scoring on the same day (FIM-2).

Patients who underwent a conventional rehabilitation program for an average of 4.7 weeks, five days a week, were assessed for a third time on the day of discharge (FIM-3).

All included patients were individually visited and re-evaluated in their homes six months after the cerebrovascular event (FIM-4).

The study did not include patients with muscle strength of 2/5 or higher in their upper and lower extremities, those with a poor overall condition, and those residing outside Istanbul and unable to attend the six-month follow-up.

Inclusion Criteria:
- Patients presenting with cerebrovascular hemorrhage or ischemia.
- Patients evaluated using the Functional Independence Measurement Scale (FIM-1) within the first 72 hours of admission to the neurology department.
- Patients with hemiplegia and existing systemic diseases, except thrombophlebitis, gastrointestinal problems, cataracts, nephropathy, oncological history, benign prostatic hyperplasia, epilepsy, congenital hip dislocation, bronchitis, and decubitus ulcers.
- Patients taking medications, including cardiovascular regulators, antiplatelets, antihypertensives, anticonvulsants, antidiabetic drugs, diuretics, bronchodilators, and oral anticoagulants.
- Patients who receive treatment in the Neurology Department until medically stable.
- Patients who are either discharged home or transferred to the Physical Medicine and Rehabilitation Department of the same hospital.
- Patients who undergo a conventional rehabilitation program for an average of 4.7 weeks, five days a week.
- Patients who can attend the six-month follow-up evaluation.

Exclusion Criteria:
- Patients with muscle strength of 2/5 or higher in their upper and lower extremities.
- Patients with a poor overall condition
- Patients residing outside Istanbul and unable to attend the six-month follow-up.

Evaluation

All the patients included in the study were divided into two groups, and those undergoing rehabilitation programs were evaluated four times using the FIM, while the other group was evaluated three times.

Functional Independence Measure is a measurement tool used to assess limitations in functions using scales. It has been found to be quite useful in determining the type and amount of services needed by disabled individuals. Assessing the level of independence in basic activities of daily living for any disabled person is essential for designing an effective rehabilitation program. Such a criterion should be highly standardized. Previously, the Barthel Index was commonly used for this purpose. However, the FIM, proposed by the American Physical Therapy and Rehabilitation Academy and the Rehabilitation Congress of America in 1986, gained significant attention and started to be used in the field of medical rehabilitation. FIM has the advantage of evaluating not only physical disability but also cognitive functions. It can be considered as a comprehensive disability index. It consists of 18 items in six categories (Table 1).

Within these six categories, there are separate evaluations, resulting in 18 different item options. FIM is divided into two subgroups: motor and cognitive, and it provides a total score. The scoring ranges from 1 to 7, resulting in a total score ranging from 18 to 128.

Table 1. FIM indicates six functional status

1	Self-care activities	Eating, personal grooming, bathing, upper extremity dressing, lower extremity dressing, toileting, bladder and bowel control
2	Sphincter control	Bladder control, bowel control
3	Transfers	Bed, chair, and wheelchair transfers, toilet transfers, shower, tub bench transfers
4	Locomotion	Walking, wheelchair use, stair climbing
5	Communication	Understanding, expression,
6	Social cognition	Problem-solving, social interaction, memory

The motor group represents the sum of the first four items, which are self-care, sphincter control, transfers, and locomotion. As these four items have 13 sub-features, the maximum score for this group is 91, and the minimum score is 13. The cognitive group represents the sum of the last two items, which are communication and social cognition. It includes five different features. Its impact on the total score ranges from a maximum of 35 to a minimum of 5.

FIM Scale Evaluation

Eating: Evaluates the ability to bring properly prepared food to the mouth, chew, and swallow. Opening canned goods, cutting meat, spreading butter on bread, serving water, and similar actions are not included in the evaluation.

This evaluation assesses oral care, hair care, washing of hands and face, and shaving or applying makeup.
1.Independent - A) (**7 scores**) Eats from a regular plate and drinks from a regular cup or glass, can eat using a regular knife, fork, or spoon, B) (6 scores) can eat with modified utensils (e.g., adaptive cutlery) or takes longer than usual to complete the eating process, if the person is receiving parenteral nutrition, they can prepare it themselves.
2.Assisted- A) (5 scores) Requires assistance (e.g., standing by, giving verbal cues, praising for the task, preparing orthoses used during eating), B) (4 scores) can perform 75% or more of the task, C) (3 scores)can perform 50-74% of the task, D) (2 scores)can perform 25-49% of the task, or if the person cannot take food orally for any reason and is receiving nutrition through parenteral or gastrostomy route, they can prepare it themselves, E) (1 score)can perform 25% or less of the task, if the person receives nutrition through the parenteral or gastrostomy route.

Self-Care: This evaluation assesses oral care, hair care, washing of hands and face, and shaving or applying makeup.
1.Independent- A) (7 scores) Performs dental and gum care, brushes or combs hair, washes face and hands, shaves or applies makeup, and completes all preparations independently, B) (6 scores) can perform these tasks using special tools such as orthoses and prostheses or takes longer than usual to complete them.
2.Assisted- A) (5 scores) Requires assistance (e.g., standing by, giving verbal cues, praising for the task) or preparing orthoses used during self-care, using specially adapted self-care tools, or performing pre-task preparations such as applying toothpaste on a toothbrush or opening makeup containers, B) (4 scores) can perform 75% or more of the task, C) (3 scores) can perform 50-74% of the task, D) (2 scores) can perform 25-49% of the task, E) (1 score) can perform 25% or less of the task.

Bathing: Assesses washing of the entire body from the neck down, excluding the back. This function can be performed in a bathtub, shower, or by sponge bathing in bed.
1.Independent- A) (7 scores) Can bathe and dry off independently, B) (6 scores) can bathe using special tools or takes longer than usual, or requires extra caution.
2.Assisted- A) (5 scores) Requires assistance (e.g., standing by, giving verbal cues, praising for the task) or preparing orthoses used during bathing, preparing specialized self-care tools, or performing pre-task preparations such as preparing water or setting up bathing tools, B) (4 scores) can perform 75% or more of the task, C) (3 scores) can perform 50-74% of the task, D) (2 scores) can perform 25-49% of the task, E) (1 score) can perform 25% or less of the task.

Dressing (upper body): This refers to dressing the upper part of the body, including the act of dressing and, if applicable, removing and putting on orthoses and prostheses.
1.Independent- A) (7 scores) Can dress and undress, retrieve clothing from typical locations (such as a closet or drawer), put on a bra, use overhead or front-zip garments, handle zippers, buttons, and snaps, and put on and take off orthoses and prostheses if applicable, B) (6 scores) may require special tools such as Velcro or take longer than usual to dress.
2.Assisted- A) (5 scores) Requires assistance (e.g., standing by, giving verbal cues, praising for the task) or preparing orthoses, special dressing tools, or garments, B) (4 scores) can perform 75% or more of the task, C) (3 scores) can perform 50-74% of the task, D) (2 scores) can perform 25-49% of the task, E) (1 score) can perform 25% or less of the task.

Dressing (lower body): Scoring the same as upper body dressing

Going to the Toilet: This evaluation assesses the ability to perform perineal hygiene, and manage clothing before and after toilet use, or after using a bedpan.
1.Independent- A) (7 scores) Can clean themselves after urination and defecation, insert sanitary pads or tampons, and manage their clothing after toilet use, B) (6 scores) may require special devices, take longer than usual, or need to be very cautious.
2.Assisted- A) (5 scores) Requires assistance (e.g., standing by, giving verbal cues, praising for the task) or preparing orthoses, special dressing tools, or garments, B) (4 scores) can perform 75% or more of the task, C) (3 scores) can perform 50-74% of the task, D) (2 scores) can perform 25-49% of the task, E) (1 score) can perform 25% or less of the task.
COMMENT: If the person requires assistance in using sanitary pads for menstrual periods (3-5 days per menstruation), the evaluation level would be 5 (under supervision or assistance with preparation).

Bladder Control: This evaluation assesses independent control of the bladder or the use of agents and tools to maintain control.
1.Independent- A) (7 score) No urinary incontinence occurs, and there is complete control, B) (6 score) requires the use of a catheter, urinary bag, or medication for control. If the person uses a catheter, they can independently insert, remove, clean, sterilize, and prepare it for reuse. If the individual uses a device, such as a condom catheter or an ileal device, they can independently apply, remove, empty, clean, or empty their leg bag. There are no accidents during these procedures.
2.Assisted- A) (5 score) Requires assistance (e.g., standing by, giving verbal cues, praising for the task) or experiences occasional urinary leakage due to time constraints in achieving satisfactory emptying or reaching the toilet. However, this occurs less than once a month, B) (4 score) minimal assistance is needed from external support. The person can perform 75% or more of the tasks independently but may experience occasional urinary leakage, not exceeding more than once a week, C) (3 scores) moderate assistance is required. The patient can perform 50-74% of the process of urination independently. There may be instances of urinary leakage, but it should not exceed once a day, D) (2 score) significant assistance is required. Despite the assistance, the patient frequently wets themselves. Bed pads or diapers should be used to absorb the urine or provide the patient with pads. In such cases, perineal care or catheterization is recommended, with or without these measures. The person can achieve 25-49% control of urination, E) (1 score) full assistance is required. Despite

the assistance, the patient frequently wets themselves. Bed pads or diapers should be used to absorb the urine or provide the patient with pads. In such cases, perineal care or catheterization is recommended, with or without these measures. The person has 25% or less control over urination.

Rectal Control: This evaluation assesses independent control of the rectum or the use of agents and tools to maintain control.
1.Independent-A) (7 scores) Complete control without any accidents, B) (6 scores) uses digital stimulation, various softeners, suppositories, laxatives, or medications to facilitate bowel movements. If the person has a colostomy, this is continued. There are no accidents.
2.Assisted- A) (5 scores) To achieve sufficient and satisfactory bowel movements, the establishment of a preparation team or the recommendation of a colostomy is advised. The person may experience occasional fecal incontinence, but it should not occur more than once a month, B) (4 score) requires minimal assistance for adequate bowel movements using suppositories, enemas, or external support. The person can handle 75% or more of the process independently. However, accidents may occur, not exceeding more than once a week, C) (3 score) Requires moderate assistance for adequate bowel movements using suppositories, enemas, or external support. The person can handle 50-74% of the process independently. However, accidents may occur, not exceeding more than once a day, D) (2 score) significant assistance is required. Despite the assistance, the patient frequently soils themselves. Bed pads or diapers should be used to absorb the stool or provide the patient with pads. In such cases, colostomy or rectal catheterization is recommended, with or without these measures. The person can achieve 25-49% control of bowel movements, E) (1 score) full assistance is required. Despite the assistance, the patient frequently soils themselves. Bed pads or diapers should be used to absorb the stool or provide the patient with pads. In such cases, colostomy is recommended. Rectal control is 25% or less.

Bed, Chair, Wheelchair: This assessment includes transfers from bed to chair, chair to wheelchair, and other transfers from a wheelchair, as well as the ability to stand upright in the typical walking mode.
1.Independent- A) (7 scores) If the individual can walk: They can ambulate, sit, and transition from a regular chair to a standing position. They can also transfer from bed to chair. All these tasks are performed safely, B) (6 scores) if the individual is in a wheelchair: They approach the desired chair, lock the brakes, raise footrests, and, if necessary, armrests. They sit, slide to another location, and can return safely.
2.Assisted- A) (5 scores) Assistance is required (e.g., standing nearby, providing verbal commands, praising after the task) or preparations need to be made, such as placing a sliding board or lifting the footrest, B) (4 scores) can perform 75% or more of the task, C) (3 scores) can perform 50-74% of the task, D) (2 scores) can perform 25-49% of the task, E) (1 score) can perform 25% or less of the task.

Toilet: This assessment evaluates the individual's ability to independently perform their toilet needs and return to their normal state afterward.
1.Independent- A) (7 scores) If the individual is in a wheelchair: They approach the toilet, lock the brakes, raise footrests, and, if necessary, armrests. They sit upright, slide to another location, and can return safely, B) (6 scores) if the individual can walk: They can approach the toilet, sit down, and stand up from a standard-height toilet. They perform all these tasks safely.
2.Assisted- A) (5 scores) Assistance is required (e.g., standing nearby, providing verbal commands, praising after the task) or preparations need to be made, such as placing a sliding board or lifting the footrest, B) (4 scores) can perform 75% or more of the task, C) (3 scores) can perform 50-74% of the task, D) (2 scores) can perform 25-49% of the task, E) (1 score) can perform 25% or less of the task.

Shower, Shower Chair: This assessment evaluates the individual's ability to enter and exit a bathtub or shower tray.
1.Independent- A) (7 scores) If the individual can walk: They can approach the bathtub or shower tray, enter and exit safely, if the individual is in a wheelchair: They approach the bathtub or shower, lock the brakes, raise footrests, and, if necessary, armrests. They sit upright, slide to another location, and can return safely, B) (6 scores) The individual uses a sliding board, lever, safety belt, or a specially designed seat. They can perform the task over an extended period or with great caution.
2.Assisted- A) (B) (5 scores)) Assistance is required (e.g., standing nearby, providing verbal commands, praising after the task) or preparations need to be made, such as placing a sliding board or lifting the footrest, B) (4 scores) can perform 75% or more of the task, C) (3 scores) can perform 50-74% of the task, D) (2 scores) can perform 25-49% of the task, E) (1 score) can perform 25% or less of the task.

Locomotion (Walking, Wheelchair Use): This assessment evaluates the individual's ability to walk, stand upright, or use a wheelchair in an upright position within the home.
1.Independent- A) (7 scores) The individual walks at least 150 feet without any assistance. They do not use a wheelchair and it is safe, B) (6 scores) The individual walks up to 150 feet with the use of orthotics, a prosthetic leg, specially designed shoes, a cane, or a walker. They take longer than the normal time to complete the task and need to be very cautious, C) (5 scores) exceptional mobility within the home: The individual walks at least 50 feet without assistance, with or without an assistive device. They take longer than normal to complete the task or can use a powered wheelchair for at least 50 feet without assistance.
2.Assisted- A) (5 scores) If the individual is walking: They need continuous observation, verbal commands, and praise to walk up to 150 feet. If the individual is in a wheelchair: They need continuous observation, verbal commands, and praise to use the wheelchair to travel up to 150 feet, B) (4 scores) The individual independently accomplishes at least 75% of the task to travel a minimum of 150 feet, C) (3 scores) the individual independently accomplishes 50-74% of the task to travel a minimum of 150 feet, D) (2 scores) the individual independently accomplishes 25-49% of the task to travel a minimum of 50 feet. They require assistance from only one person, E) (1 score) The individual can perform 25% or less of the task, requiring assistance from two people. They cannot walk 50 feet or use a wheelchair.
COMMENT: There are various methods to evaluate the percentage of effort expended. For example, if the individual walks without assistance for the first 75 feet but requires assistance for the next 75 feet, they would be classified as Level 4. If they require continuous assistance throughout the remaining distance, they would be classified as Level 3.

Stairs: This assessment evaluates the individual's ability to go up and down a set of stairs consisting of 12 to 14 steps in a single attempt.
1.Independent- A) (7 scores) The individual goes up and down the stairs at least once without holding onto the railing or any support. They perform this task safely, B) (6 scores) The individual goes up the stairs at least

once while holding onto the railing, using a cane, or with portable support. It takes longer than usual and requires caution, C) (5 scores) exceptional mobility within the home: The individual can go up and down 4 to 6 steps independently with or without an assistive device. They take longer than normal to complete the task.
2.Assisted- A) (5 scores) Under supervision, with verbal commands and praise, the individual can go up and down the stairs in a single attempt, B) (4 scores) the individual can accomplish 75% or more of the stair climbing task independently, C) (3 scores) the individual can accomplish 50-74% of the stair climbing task independently, D) (2 scores) the individual can accomplish 25-49% of the stair climbing task independently. They require assistance from one person, E) (1 score) the individual can perform 25% or less of the stair climbing task and requires assistance from two people. They are unable to go up and down the stairs and need to be carried.

Comprehension: This assessment involves understanding through auditory and visual communication, which refers to comprehending what is being conveyed through spoken or written words.
1.Independent- A) (7 scores) The individual understands spoken and written instructions or complex and abstract conversations, B) (6 scores) The individual struggles to understand spoken and written instructions or complex and abstract concepts. They may require hearing, visual, and other assistive aids and may take a longer time to comprehend the given instructions.
2.Assisted- A) (5 scores) Reminder assistance: The individual understands what is written or spoken about daily events with more than 90% accuracy but may require reminders for less than 10% of the time, B) (4 scores) minimal reminder assistance: The individual understands what is written or spoken about daily events with 75% to 90% accuracy, C) (3 scores) moderate reminder assistance: The individual understands what is written or spoken about daily events with 50% to 75% accuracy, D) (2 scores) Maximal reminder assistance: The individual understands what is written or spoken about daily events with 25% to 49% accuracy. More than half of the time relies on reminders, E) (1 score) fully dependent: The individual understands what is written or spoken about daily events with 25% or less accuracy, or they do not understand or respond correctly even with assistance.

Expressing: This assessment involves expressing the language's clear expression either verbally or silently, which means conveying instructions in the spoken or graphical form appropriately and accurately with proper grammar.
1.Independent- A) (7 scores) The individual expresses complex and abstract ideas skillfully through continuous speech or nonverbal signs or in written form, B) (6 scores) the individual expresses complex and abstract ideas with some difficulty. This may require the use of augmentative communication tools or systems to enhance communication.
2.Assisted- A) (5 scores) This individual expresses basic needs and ideas about daily events with more than 90% accuracy and may require reminders for less than 10% of the time, B) (4 scores) This individual expresses basic needs and ideas about daily events with 75% to 90% accuracy, C) (3 scores) This individual expresses basic needs and ideas about daily events with 50% to 74% accuracy, C) (2 scores) This individual expresses basic needs and ideas about daily events with 25% to 49% accuracy. More than half of the time is spent relying on reminders, E) (1 score) This individual can express basic needs and ideas about daily events with 25% or less accuracy or cannot express them even with reminders.

Social Adaptation: This assessment evaluates the ability to interact with others in therapeutic or social relationships.
1.Independent- A) (7 scores)7- The individual establishes good relationships with staff, fellow patients, and family members (e.g., demonstrates self-control, accepts criticism, is aware of the impact of their words and actions on others), B) (6 scores) The individual establishes appropriate relationships with staff, fellow patients, and family members in certain structured situations or modified environments. They may require an extended period of time for social adaptation. Medication may be utilized to achieve this level.
2.Assisted- A) (5 scores) They require supervision only in tense or unfamiliar situations, such as monitoring through cameras, verbal control, giving commands, or providing various forms of praise. However, no more than 10% of the time should be spent on these interventions, B) (4 scores) The individual adapts to the environment appropriately for 75% to 90% of the time, C) (3 scores) The individual adapts to the environment appropriately for 50% to 75% of the time, D) (2 scores) The individual adapts to the environment appropriately for 25% to 49% of the time. They may require occasional intervention from others, E) (1 score) They can adapt to the environment for 25% or less of the time or may not be able to adapt at all.

Problem-Solving: This assessment measures the ability to solve daily life problems. It involves making logical, safe, and timely decisions considering the financial, social, and personal aspects of the problem, as well as the initiation, outcome, and self-correction processes and activities.
1.Independent- A) (7 scores) Consistently arrives at appropriate decisions. Begins the process and proceeds step by step to solve the problem until completion. If a mistake is made, they self-correct, B) (6 scores) Encounters some difficulty in decision-making and self-correction in unfamiliar situations. Takes longer than necessary for decision-making and problem-solving.
2.Assisted- A) (5 scores) Requires supervision. Only requires supervision for solving problems in tense or unfamiliar situations. However, no more than 10% of the time should be spent on supervision, B) (4 scores) Solves problems for 75% to 90% of the time, C) (3 scores) Solves problems for 50% to 75% of the time, D) (2 scores) 2- Solves problems for 25% to 49% of the time. Requires guidance for more than half of the time, E) (1 score) Solves problems for 25% or less of the time or may not be able to solve problems at all.

Memory: This assessment evaluates the individual's ability to store and utilize information, particularly in verbal and visual forms. It assesses the recognition of being a part of society. A memory error can hinder both the storage and retrieval of information.
1.Independent- A) (7 scores) Easily recognizes familiar people, remembers daily routines, and fulfills others' requests without the need for repetition, B) (6 scores) Encounters difficulty in recognizing people, remembering daily routines, and fulfilling others' requests. Requires commands or cues from oneself or the environment.
2.Assisted- A) (5 scores) Requires external commands or verbal support only in tense or unfamiliar situations. However, this assistance should not exceed 10% of the time, B) (4 scores) Recognizes and remembers for 75% to 90% of the time, C) (3 scores) Recognizes and remembers for 50% to 75% of the time, D) (2 scores) 2- Recognizes and remembers for 25% to 49% of the time. Requires reminders for more than half an hour, E) (1

score) Recognizes and remembers for 25% or less of the time, or may not recognize or remember at all.

RESULTS

A total of 25 patients who presented with cerebrovascular hemorrhage or ischemia were included in the study. The clinical and laboratory characteristics of the patients are provided in Table 1. Among these patients, 18 completed their medical treatment and were discharged home without undergoing any rehabilitation program, while 7 were transferred to the rehabilitation service and received an average of 4.7 weeks (33 sessions) of treatment. The classic hemiplegia rehabilitation program was applied to all patients as part of the rehabilitation process. Following their initial days of illness, all patients were visited at home 6 months later to evaluate their condition. The average age of patients included in the rehabilitation group was 59.85, while for patients discharged directly to the home, it was determined to be 63.88. The mean rehabilitation duration was 33 days and similar between males and females (p>0.05).

Table 1. Participants' characteristics

Age, years	62.76±14.08 (40-89)
Sex, male/female, n,%	13/12
Involvement, n **Cerebral ischemia** **Cerebral hemorrhagia**	 20 5
Involved body site • **Left** • **Right**	 11 14

The incidence of ischemic and hemorrhagic strokes in women was 10.4% and 2.6%, respectively, while in men it was 9.6% and 2.4%, respectively. There was no significant difference between genders (p>0.05). There was a higher prevalence of asthma bronchial in 12% of cases among the patients. Diabetes (%8), ischemic heart disease (%8), and hypertension (%4) are also observed. Among the patients, only one had a tracheostomy due to laryngeal cancer, which limited their ability to speak. There were 4 patients with a history of prior stroke (SVO) among them.

Table 2. FIM scores

		FIM 1 (Mean)	FIM 2 (Mean)	FIM 3 (Mean)	FIM 4 (Mean)
Eating	A	3.04	4.92	6.42	5.88
Self-care	B	3.04	5.16	6.14	5.2
Bathing	C	1.72	3.44	5.14	4.12
Dressing-upper body	D	2	3.28	5	4.36
Dressing-lower body	E	1.8	3	4.71	4.2
Toileting	F	1.64	2.6	5.14	4.48
Bladder	G	2.04	3.84	6.42	5.4
Rectum	H	3.56	5.16	7	5.72
Bed, chair	1	1.32	2.92 ..	6.42	4.88
Toilet	J	1.28	2.2	5.14	4.44
Shower	K	1.08	1.72	3.14	3.48
Walking	L	1.04	1.76	4.71	3.76
Stairs	M	1	1.32	4.71	3
Comprehension	N	5.72	6.72	7	6.72
Expressin	0	4.84	5.56	6.28	5.8
Social life	P	5.44	6.2	6.71	5.88
Problem solving	R	4.68	5.44	6.85	5.76
Memory	S	6.32	6.76	6.85	6.4
Total		51.12	71.96	103.78	89.48
Standard Deviation		16.41	18.06	14.23	29.15

Figure 1 displays the distribution of patients based on the risk factors associated with CVO (cerebrovascular occlusion). Hypertension and heart disease were found to be more prevalent in our group. However, no patients were identified who had a history of oral contraceptive use or polycythemia.

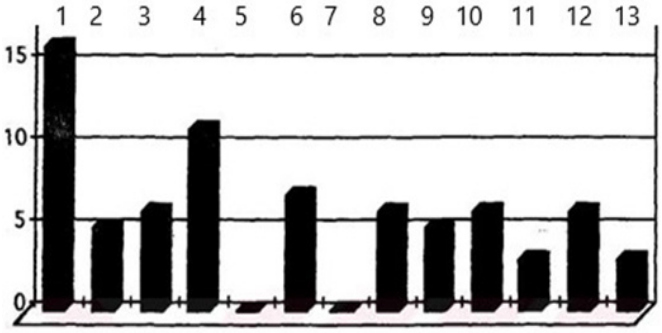

Figure 1. 1-Hypertension, 2-Diabet, 3-Dyslipidemia, 4-Heart disease, 5-Polcyctemia, 6-Smoking, 7-Oral contraceptive, 8-Alcohol, 9-TIA, 10-Migren, 11- Diet, 12-Obesity, 13-Hyperuricemia (n)

Table 2 presents the average values of FIM measurements in the 18 subgroups during four different periods. This allows for observing the changes in each specific characteristic during the course of the disease prognosis.

Table 3 shows the changes in total FIM averages depending on the etiological cause between the groups that received and did not receive a rehabilitation program.

Table 3. Etiology-related changes in FIM scores in each period

	Clinical	TFIM1	TFIM2	TFIM3	TFIM4
Reh (+)	Ischemia	60.2	79.8	103.6	108.6
	Hemorrhagia	41.5	60.5	104.5	121.5
	Total	54.85	74.28	103.78	112.28
Reh (-)	Ischemia	51.66	73.33	x	79
	Hemorrhagia	39.66	59.66	*	87.66
	Total	49.66	71.15	x	80.44
	General	51.12	71.96	103.78	89.48

Reh; Rehabilitation, TFIM; total FIM scores

In Figure 2, the difference in scores during the evaluation of total FIM between admission to the neurology service and discharge from the neurology service is shown for both the rehabilitation group and the non-rehabilitation group. While both groups show a similarity between TFIM-1 and TFIM-2, the notable difference lies in the differentiation during home control.

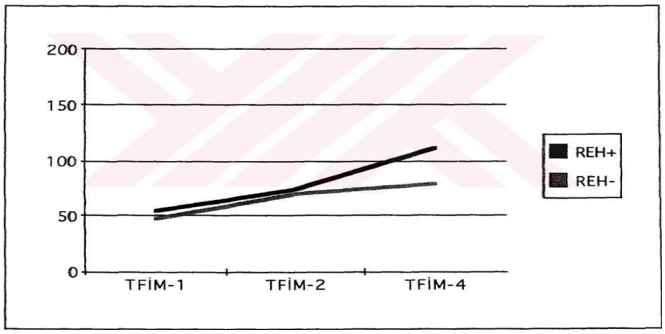

Figure 2. TFIM scores according to rehabilitation status.

Table 3 demonstrates motor gains over time in both groups ($p<0.05$). In the group that received rehabilitation, there was a consistently positive improvement in motor function over time, with significant progress in each period compared to the previous one.
The correlation ($r=0.75$) between the motor function status achieved by the patient 6 months after rehabilitation and the rehabilitation program is strong.
In the non-rehabilitation group, there were significant gains in motor function between the patient's admission to the neurology service and their discharge, as well as during the initial period of the disease and the subsequent home control after 6 months. However, there was no significant change between their discharge from neurology service and their condition during the home control after 6 months.

DISCUSSION

Stroke is the most common cause of disability and death in the elderly population (5,6). Treatment begins with the identification of cerebrovascular events and should initially focus on identifying acute medical problems and stabilizing the patient. Subsequently, a rehabilitation plan is developed to regain lost abilities and functions and achieve the highest possible quality of life. Generally, hemiplegia rehabilitation starts from the acute phase, continues during the hospital stay, encompasses the evaluation and correction efforts during the return to the community, and then transitions into the monitoring of the patient. The primary goal is not only to improve functions during the rehabilitation period but also to teach independence after the rehabilitation program. The success of the rehabilitation program is measured by the individual's functional level in maintaining daily life activities.

Hemiplegia rehabilitation is a costly and time-consuming process (7). Therefore, it is important to identify patients who will benefit from and recover through rehabilitation in advance. The functional level assessment of the patient is performed by the treatment team at the beginning of the rehabilitation program, and the treatment is based on this evaluation.

The determination of the expected discharge level is necessary at the beginning of rehabilitation. Factors such as age, accompanying systemic diseases with hemiplegia, functional ability level during admission and discharge periods, family support, and the patient's mental and psychological condition can influence the expected level of recovery, treatment intensity and type, and length of hospital stay. Age, gender, and disease severity can also influence the prognosis and functional outcomes of stroke patients (8,9).

In this study, the patients were evaluated with the FIM within the first 72 hours of admission to our hospital's neurology department (FIM-1). The patients continued to receive treatment in the neurology department until they became medically stable. After completing their treatment in this department, 7 patients were transferred to the Physical Medicine and Rehabilitation Department of the hospital, and 18 patients were discharged and sent home. The discharged patients and those transferred to the physical therapy department were re-evaluated on the same day (FIM-2). Patients who underwent a 4.7-week rehabilitation program, five days a week, using the conventional method were evaluated for the third time on the day of discharge (FIM-3). All included patients were individually followed up and evaluated at their homes six months after the cerebrovascular event (FIM-4).

In recent years, functional evaluation of patients has become crucial, with numerous benefits in terms of clinical practice, research, education, application, economy, quality assurance, and workload reduction. FIM has been widely used since 1986, particularly in countries such as the United States, Australia, Canada, France, Japan, Italy, Germany, and Sweden. It assesses 18 different items and scores range from 1 to 7, with a total score range of 18 to 126 (10). In our study, the results were consistent with the literature. There was a moderate inverse correlation between the total FIM4 score and the age of the patients, which was the same for both groups.

In many studies, the incidence of cerebrovascular events has been found to differ between genders (11,12). In our study, 52% of patients were male and 48% of patients were females, this similar ratio allowed us to make generalizations without any gender-related bias. The impact of gender on prognosis has not yet been definitively determined and remains a subject of debate. However, according to the literature, both genders have a positive effect on recovery individually.
Although there are authors who argue that gender does not affect prognosis, a study conducted on 736 hemiplegic cases at the Belfast City Hospital between 1948 and 1956 emphasized that women had a better recovery compared to men (13-15). In our study, however, there was no significant difference between genders in the total FIM scores obtained by patients on the first day of the illness and during the follow-up home visits.

In today's world, the incidence of stroke is increasing among individuals under the age of 55, while the prevalence of stroke is decreasing among those aged 55 and above (16). However, approximately 20% of men experienced a stroke of any kind during the follow-up period from 50 to 98 years of age, resulting in a cumulative incidence that approached 50% (17).

In our study, the average age was 62.76±14.08, and 36% of the patients were in the 40-55 age group. Among the two groups we divided the patients into, the average age of rehabilitated individuals was found to be 59.85, while for non-rehabilitated individuals, it was 63.88. This study demonstrates similar results to previous studies reported from data of the Turkish Population regarding age, cause of stroke, and gender (18). Boru et al. detected 50 stroke cases in their study. 80% of those were found to have had an ischemic stroke, 14% of those were hemorrhagic cases, and 6% of those had an unclassified stroke type. The overall prevalence rate in those $\geqslant$ 18 years was 1.7%. The male/female ratio was 0.92. Young (<45) stroke prevalence was found to be 0.6% (18).

Black-Schaffer R.M. and colleagues examined the relationship between age and return to work in 79 hemiplegic patients and found that younger individuals were more likely to return to work compared to older individuals (19,20). Age, cognitive independence, and pain can predict rehabilitation outcomes after stroke. Treatment of cognition and pain should be taken into account during rehabilitation (21).

Ischaemic stroke remains the most common type of stroke (22). In our study, 80% of the patients were admitted due to ischemia, while 20% were admitted due to hemorrhage. Despite having the same etiological causes, the course of the disease varied, which was entirely related to the size and location of the lesion. When we divided the patients in our study into rehabilitation

and non-rehabilitation groups based on their etiological causes, it was noteworthy that the total FIM scores of ischemic patients were higher in the early stages of the disease. In the later stages, it can be observed that both groups, especially the hemorrhagic patients, catch up with or even outperform the ischemic patients in terms of functional outcomes.

When examining the connection between the etiology of the disease and functional changes in our study, a strong correlation was found between cognitive changes and the etiology of the disease in patients undergoing rehabilitation.

Derickt and colleagues conducted a study on the effects of gender and the affected side on prognosis, concluding that the affected side only changed the type of handwriting and did not affect daily life activities (23). The affected side has also important clinical implications. Patients with right hemispheric strokes present later to an emergency department, have a lower chance to receive thrombolytic therapy and have worse clinical outcomes than patients with left hemispheric strokes (24). Except for one of our patients, all of them were right-dominant. When patients reached a neurologically stable condition, the mean FIM-2 score was found 69.86 for patients with right-sided (dominant) involvement and 75.1 for patients with left-sided involvement. The difference between the two groups was not statistically significant. We attributed this to the patient's psychological problems and lower educational levels during the acute phase, as well as their lack of effort.

Early rehabilitation can help prevent complications that may arise from prolonged immobility or inactivity, such as muscle atrophy, joint stiffness, and pressure sores. It also allows individuals to capitalize on their heightened potential for recovery during this period and maximize functional gains. The optimal time to begin rehabilitation after a stroke remains unsettled, though the evidence is mounting that for at least some deficits, initiation of rehabilitative strategies within the first 2 weeks of stroke is beneficial. Commencing intensive therapy in the first 24 h may be harmful (25,26).

Early rehabilitation significantly improves upper extremity movements, sensation, body image, mental state, aphasia, and lower extremities occurred after 14 weeks (27,28). The rate of improvement may reach up to 80% six weeks after the onset of the disease, and functional recovery closely follows neurological improvement. The reason for conducting this assessment at the end of the acute phase of the disease is that functional recovery is most rapid in the first two weeks. Various publications have reported a significant slowdown in recovery after six months (26-28). Galski and colleagues state that early initiation of rehabilitation leads to faster improvement in patients' cognitive abilities. The significant improvement in these functions that affect the patient's rehabilitation has shortened the length of stay in the rehabilitation service and positively affected the prognosis (29,30).

However, A variety of physiotherapy interventions improve functional outcomes, even when applied late after a stroke. The efficacy of the intervention was particularly evident when short- and long-distance walking were considered as separate outcomes and activities of daily living independence (31). The literature information regarding the length of stay in rehabilitation departments for patients from the end of acute neurological problems indicates an average of 1 month (32,33). In this study, the average duration of rehabilitation was 33 days, which includes the period in which patients could mobilize with the assistance of independent aids such as a cane. There was no significant difference in terms of hospital stay between genders.

The important thing here is to objectively evaluate the results of the applied rehabilitation in order to assess the success and suitability of the program by the treatment team and determine any necessary changes if needed. Patients who were admitted to the rehabilitation program and those who were directly sent home without being included in the program were evaluated based on FIM-2 scores. There was no statistically significant difference between the two groups. According to this result, there was a statistically significant difference in the FIM-4 scores during the 6-month follow-up home visits between the two groups with the same initial conditions. This result shows that the difference between the group that underwent rehabilitation and the group that did not undergo rehabilitation can be demonstrated through FIM scoring.

There are many studies in the literature that evaluate stroke outcomes using FIM scoring (34,35). In all of these studies, the changes in patients' activities of daily living before and after rehabilitation show a significant improvement in favor of the patient in a statistically significant manner, as in our studies. In our study, we examined the patients in two groups: those who underwent rehabilitation and those who did not. The changes in motor functions increased significantly for both patient groups during the period from the onset of the disease until they returned home. There was a strong correlation between functional gain during this period and rehabilitation. These results were consistent with previous studies (34,35). In patients who were not included in the rehabilitation program, the motor changes during the 6-month follow-up home visits were statistically insignificant. In fact, there were decreases in total scores, especially in motor functions, for some patients. Similarly, after the discharge of patients in the rehabilitation group in terms of daily life activities, their changes were significant. This change indicates that the patient is becoming increasingly independent.

When patients were evaluated in terms of cognitive functions, there was a strong correlation between the group admitted to the rehabilitation program and the cognitive scores gained during the program until the condition reached by the patients after 6 months. In a relevant source that supports our study, a secondary analysis of individuals receiving inpatient stroke rehabilitation care and examined the correlations between measures of cognitive impairments and participation in the rehabilitation program. The study found a strong correlation between the group admitted to the rehabilitation program and the cognitive scores gained during the program. This suggests that stroke patients who participated in the rehabilitation program showed improvements in cognitive functions over timethe researchers evaluated the cognitive functions of patients before and after participating in a rehabilitation program (36).

Considering that there are studies indicating the evaluation of cognitive functions with FIM and the impact of these scores on the total length of hospital stay for patients, it is necessary to provide such support to the patient during the rehabilitation period (37,38).

However, this view, which is valid for stroke patients, is not clear whether same for individuals with spinal cord injury (39,40).

These results indicate that our rehabilitation outcomes and the rate of benefiting from treatment are not significantly different from other countries, and in fact, our patients benefit even more from the treatment.
In our study, we examined the extent to which all the data obtained from the patient were effective in determining the prognosis of patients undergoing rehabilitation. According to our findings, in determining the patient's condition after 6 months, the dominant side involvement, educational status, total motor and total FIM scores during discharge from the neurology service, age, and etiological cause were found to be determinants with an 84% rate, as determined by multiple regression analysis. While the study provides valuable insights into the rehabilitation outcomes of stroke patients, it is important to acknowledge its limitations

1.The most important limitation is the data cover an old specialization thesis and consists of a small sample size considering the large sample-sized studies conducted following this thesis.

2.Sample size and generalizability: The study had a relatively small sample size, which may limit the generalizability of the findings. The results might not be representative of the broader population of stroke patients, and larger studies with diverse populations are needed to confirm the findings.

3.Single-center study: The study was conducted at a single center, which may limit the generalizability of the findings to other healthcare settings. Multicenter studies involving different geographic locations and healthcare systems would enhance the external validity of the results.

4.Lack of control group: The study did not include a control group of stroke patients who did not undergo rehabilitation. A comparison between the rehabilitation group and a control group would have allowed for a more comprehensive understanding of the impact of rehabilitation on functional outcomes.

5.Potential confounding variables: Although the study considered various factors that could influence rehabilitation outcomes, there may still be other unmeasured confounding variables that could have affected the results. Factors such as socioeconomic status, comorbidities, and access to post-discharge support were not fully explored but may have influenced the outcomes.

6.Follow-up period: The study's follow-up period was limited to six months after the cerebrovascular event. A longer-term follow-up would provide insights into the sustainability of the functional gains achieved through rehabilitation and any potential changes over time.

7.Assessment tools: While the study utilized the Functional Independence Measure (FIM) to assess functional outcomes, other outcome measures could provide additional perspectives on the rehabilitation process. Incorporating a broader range of assessment tools, such as quality-of-life measures or specific functional scales, could provide a more comprehensive evaluation of the patient's progress.

8.Absence of qualitative data: The study relied solely on quantitative measures and did not include qualitative data, such as patients' experiences and perspectives on rehabilitation. Including qualitative data could enrich the understanding of the rehabilitation process and offer valuable insights into patient-centered outcomes.

Addressing these limitations in future research would strengthen the evidence base and provide a more comprehensive understanding of the factors influencing rehabilitation outcomes in stroke patients.

CONCLUSION

Early rehabilitation initiation, tailored treatment plans, comprehensive functional assessments, and continuous evaluation play vital roles in optimizing outcomes and promoting independence in stroke patients. Understanding the factors influencing prognosis can guide healthcare professionals in providing individualized care and support to stroke survivors.

DECLARATIONS

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Original Article

Knowledge, Attitudes, and Behaviors of Patients Diagnosed with End-Stage Kidney Disease Registered on the Kidney Transplant Waiting List Regarding Organ Transplantation and Donation

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ABSTRACT

Background: The aim of this study is to determine the knowledge, attitudes, and behaviors of patients diagnosed with end-stage renal disease who are registered on the kidney transplant waiting list regarding organ donation and transplantation. Additionally, it will be examined whether these results vary according to sociodemographic characteristics.

Materials and Methods: The research was conducted with patients registered on the kidney transplant waiting list at Medicana International Ankara Hospital between April 15 and June 15, 2022. An attempt was made to reach the entire population, and the research was conducted with 120 participants (28.5%). A survey was used as the data collection method in this descriptive study, consisting of 30 questions that included sociodemographic characteristics as well as statements regarding organ donation and transplantation.

Results: It was found that 52.5% of the participants were female, 31.7% were in the 35-49 age range, 70.8% did not smoke, 37.5% had primary school education, and 70.8% were married. All patients were undergoing dialysis treatment, and 36.7% had been on the kidney transplant waiting list for less than 3 years. It was found that 53.3% of the participants had previously received education on organ transplantation or donation, 75% did not have an organ donation card, and 46.7% were not willing to donate organs. 74.2% of the patients found the studies conducted nationwide on organ donation to be inadequate, and 45% did not trust the organ distribution system.

Conclusion: The knowledge, attitudes, and behaviors of the participants regarding organ donation and transplantation are not at the desired level. There are statistically significant differences in the knowledge, attitudes, and behaviors of patients according to their age and education level. It is considered that the study results will assist decision-makers in identifying the situation related to patients, raising awareness among all stakeholders, and determining a roadmap for solution proposals.

Keywords: Organ donation, transplantation, ESRD, attitudes, behaviors

INTRODUCTION

Kidney transplantation is one of the most successful advancements in modern medicine (1). It improves patient survival and quality of life, while also reducing the socio-economic burden of organ failure in society (2).

Although hemodialysis is the most commonly chosen treatment method for end-stage renal diesease (ESRD) patients (3,4), kidney transplantation is the desired approach (5,6). Compared to hemodialysis, kidney transplantation offers significant advantages in terms of patient survival, quality of life, and cost-effectiveness (7-9).

In the United States, despite performing 40,000 transplants in 2021, 17 people on the waiting list lose their lives each day due to the inability to undergo organ transplantation. As of August 2022, approximately 106,000 patients, with around 91,000 of them waiting for kidney transplantation, are awaiting organ and tissue transplants (10). In the European Union, within the Eurotransplant program involving eight countries, around 14,000 patients are on the waiting list, with 10,000 of them awaiting kidney transplantation as of August 2022 (11). In Turkey, despite 3,375 kidney transplantations being performed in 2021, approximately 28,000 patients, including 24,000 kidney patients, are currently on the organ waiting list (12). Worldwide,

while approximately 100,000 solid organ transplants are performed each year, over 1 million people are waiting for organ transplants (13,14). Despite the increasing number of transplantations over the years due to advancements in technology, skilled personnel, and capacity, the number of patients on the waiting lists continues to rise, resulting in many patients losing their lives before receiving a transplant (15).

Although many patients continue to wait for kidney transplantation, there are significant limitations in organ procurement (9). The fundamental challenge in organ transplantation is the imbalance between organ demand and organ supply (16). Analyzing and effectively managing this situation is crucial (9). Organ and tissue transplant coordinators play an active role in brain death determination, family consultations, organ retrieval preparation, and the monitoring and preparation of transplant recipients in the transplant process. Therefore, presenting the coordinators' experiences, the problems they encounter in the field, and their recommendations will provide significant contributions to a more comprehensive analysis of organ procurement issues.

The aim of this study is to determine the knowledge, attitudes, and behaviors of patients diagnosed with ESRD who are registered on the kidney transplant waiting list regarding organ donation and transplantation. Additionally, the study will examine the impact of sociodemographic characteristics on donation perception.

MATERIALS AND METHODS

Study Design and Participants

This is a descriptive study. The research population consists of patients registered on the kidney transplant waiting list of the Turkish Ministry of Health (Transplantation, Dialysis, and Monitoring Systems/ TDIS) through Medicana International Ankara Hospital. The aim was to reach all registered patients without calculating the sample size. Upon investigation, it was determined that there were 421 registered patients, and efforts were made to reach out to these patients. However, due to reasons such as refusal to participate, inability to establish communication, and incomplete or erroneous completion of the survey form, the study was conducted with 120 patients. The participation rate in the study is 28.5%.

Data collection

Data collection in the study was conducted using a questionnaire as the data collection tool (**Supp1**). The questionnaire was created by the researcher based on the literature information (references 75-77) and included 30 multiple-choice questions regarding participants' socio-demographic characteristics such as age, gender, education level, marital status, smoking status, as well as their knowledge, attitudes, and behaviors towards organ donation and transplantation. Some of the statements in the questionnaire included: "Have you received any education on organ transplantation or organ donation?", "Have you registered as an organ donor to be used after your death?", "Do you find the efforts on organ donation adequate?", "In your opinion, what is the most effective method to increase organ donation rates?" The questionnaire form is presented in Table 1. The individual responses were did not shared with third persons or institute.

Implementation of The Study

After obtaining approval from the Hamidiye Health Sciences Institute of Health Sciences University and ethical permission from the Academic and Ethical Board of Medicana International Ankara Hospital, the study was conducted between April 15 and June 15, 2022, at Medicana International Ankara Hospital.

Participants were approached by the researcher when they visited the hospital for appointments, or attempts were made to reach them via email. The individual responses were did not shared with third persons or institute.

Inclusion criteria for participation in the study

•Being diagnosed with ESRD

•Being registered on the Ministry of Health kidney transplant waiting list and on the waiting list through Medicana International Ankara Hospital

•Volunteering to participate in the study

•Having the cognitive ability to understand and answer the questions

•Having communication skills

Exclusion criteria for the study

•Not being registered on the kidney transplant waiting list through Özel Medicana International Ankara Hospital

•Waiting for organ transplants other than kidney transplantation

•Not volunteering to participate in the study

•Not having the cognitive ability to understand and answer the questions

•Not having communication skills

This study was conducted at Medicana International Ankara Hospital Organ Transplantation Unit which has started performing kidney and liver transplants in October 2009, followed by bone marrow transplants in February 2012 (**Table 1**). In our hospital, 2 transplant nephrologists, 2 transplant surgeons, two coordinators, 1 transplant service, 3 transplant polyclinics provide support for recipients and donors in transplantation for more than 10 years.

Ethical approval

The ethical appropriateness of the research has been evaluated by the " Medicana International Ankara

Table 1. Kidney transplant performance of Medicana International Ankara Hospital (2017-2022)

Transplantation type	2017	2018	2019	2020	2021	2022	Total
Living	66	56	97	92	125	89	528
Deceased	5	7	10	7	-	1	30
Total	71	63	107	99	125	90	558

Hospital Academic and Ethical Committee," and it has been determined to be appropriate in the decision dated 30/03/2022, with IRB number 2022/08. The research was conducted in accordance with the ethical principles of the Helsinki Declaration.

STATISTICAL ANALYSIS

The data collected in the study were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22.0. Descriptive statistics were performed using frequency analysis, and the results were presented in numbers and percentages. The Chi-square test was used to determine the relationship between categorical variables. Regression analysis was used to demonstrate the impact of variables on organ donation willingness. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The study involved 120 participants, with a slightly higher proportion of females (52.5%) compared to males (47.5%). The mean age was approximately 54.24±14.25. The majority of participants were between 35-64 years old (31.67%), with smaller percentages in the younger and older age groups. The majority of participants (70.8%) did not smoke, while 23.3% were smokers and 5.8% occasionally smoked. In terms of educational background, primary school education was the most common (37.5%), followed by high school education and university graduates (both 20%). A significant portion of participants (70.8%) were married, while single and divorced individuals accounted for smaller percentages. The leading cause of ESRD was attributed to hypertension (38.3%), followed by diabetes (19.2%) and other conditions such as polycystic kidney disease and kidney stones (**Table 2**).

Given dialysis choices, the majority of hemodialysis (HD) patients preferred center hemodialysis (90%), while smaller proportions opted for peritoneal dialysis (5.8%) or home hemodialysis (4.2%). The duration of renal replacement therapy varied, with some patients on the waiting list for less than 3 years (33.3%) and others on HD for over 10 years (23.3%).

Participants' registration on the National Waiting List showed that a significant portion had been registered for less than 3 years (36.7%), with varying durations of 3-5 years, 6-10 years, and over 10 years. The primary sources of guidance to join the waiting list were the dialysis center (53.4%) and nephrologists (24.2%), while family members and personal decisions played smaller roles.

Table 3. The socio-demographic characteristics of the participants in our study are presented

Sex		Marital status	
male/female, n	57/63	Married	85
		Status	35
Age, year		The primary cause of ESRD, n	
• 18-34	13	HT	46
• 35-49	38	DM	23
• 50-64	36	PCKD	9
• >64	33	Urological problems	13
		GN	7
		Unknown	6
		Other	16
Literacy		Smoking, yes/no, n	35/85
University	24		
High-school	24		
Primary school	61		
No Literacy	11		

ESRD, end-stage renal disease, DM; diabetes mellitus, HT; hypertension, PCKD; polycystic kidney disease, GN; glomerulonephritis

A minority of participants (18.3%) had undergone a kidney transplant before, while the majority (81.7%) had not. Some participants (19.2%) reported being called for a transplant, suggesting a potential opportunity for transplantation. However, the majority (80.8%) had not received a call from the registered transplant center.

In terms of familial presence on the transplant waiting list, a small percentage (7.5%) mentioned having another family member waiting for an organ transplant, while the majority (91.7%) did not have any family members in the same situation.

Regarding knowledge about organ donation and transplantation, slightly over half of the participants (53.3%) reported receiving education on the topic, while a smaller percentage (44.2%) had not. Some participants (2.5%) were uncertain about whether they had received education on organ transplantation or donation. Additionally, the majority (67.5%) reported being knowledgeable about the concept of brain death, while a significant proportion (32.5%) stated being unfamiliar with it.

A significant proportion of participants in the study had knowledge about organ transplantation and donation, including awareness of brain death. However, their personal familiarity with individuals who have received organ transplants, either through deceased or living donation, was limited. Only a small percentage knew someone who had undergone a transplant (19.2% for deceased donation and 20.8% for living donation). This suggests that participants' awareness and education on transplantation might not be matched by personal experiences.

A minority of participants (12.5%) reported having family members who have donated organs and obtained a donation card, while the majority (84.2%) stated that no one in their families had done so. A few participants expressed uncertainty in this regard.

The majority of participants (80.8%) reported not being called for a kidney transplant by the registered transplant center. Additionally, a small percentage (7.5%) mentioned having another family member waiting for an organ transplant. More than half of the participants (53.3%) reported receiving education on the topic. Concerning awareness of brain death, a significant majority (67.5%) indicated being knowledgeable about it.

Regarding familiarity with organ transplant recipients, a minority of participants (19.2%) reported knowing someone who had received a transplant through a deceased organ donation, while a similar percentage (20.8%) knew someone who had received a transplant from a living donor.

A majority of the participants (74.2%) believed that the efforts regarding organ donation were insufficient, while 33.3% expressed trust in the organ distribution system and 45.0% did not trust it. Opinions on the right to change the decision after organ donation were divided, with 56.7% believing they had the right to change their decision and 20.8% believing they did not. Concerning the requirement of being completely healthy to become an organ donor, 57.5% believed it was necessary, while 25.8% did not.

When asked about the most effective method to increase organ donation rates, the majority (69.2%) selected

"All" as the most effective method. A notable proportion (23.3%) stated that their views and opinions regarding organ donation changed as a result of the survey.

The analysis found no significant association between gender and receiving education about organ donation and transplantation ($p>0.05$). There was no significant association between gender and awareness of brain death ($p > 0.05$).

A small percentage (21.7%) reported having a donation card, indicating their willingness to participate. Additionally, a considerable proportion (45.8%) expressed their willingness to engage in organ donation. Gender does not have a significant influence on awareness of brain death, possession of an organ donation card, willingness to donate organs, perception of the adequacy of organ transplant efforts, or trust in the Ministry of Health Organ Distribution System ($p>0.05$).

Age is associated with possession of an organ donation card and willingness to donate organs, with the highest percentages observed in the 35-49 age group ($p<0.05$). However, age is not significantly associated with the perception of organ transplant efforts being adequate or trust in the Ministry of Health Organ Distribution System.

Education level is significantly associated with the possession of an organ donation card, with higher education levels being more likely to possess a card ($p<0.05$). There is no significant association between education level and receiving education about organ donation and transplantation, knowledge about the concept of brain death, willingness to donate organs or trust in the Ministry of Health Organ Distribution System.

DISCUSSION

This study aimed to determine the knowledge, attitudes, and behaviors of patients diagnosed with chronic kidney failure who are registered on the kidney transplant waiting list regarding organ donation and transplantation.

In Turkey, the prevalence of ESRD in adults is 15.7%, and it is more common in the elderly population (17). In our study, when examining the causes of ESRD in patients, hypertension and diabetes were found to be prominent. A study conducted in the United States indicated that diabetes and hypertension were the main causes, while studies conducted in Turkey mentioned chronic glomerulonephritis, diabetes, and hypertension as the main causes (18-20). The findings of our research are consistent with the literature.

Hemodialysis is the most common type of treatment in Turkey (21,22). In this cohort, all participants were receiving hemodialysis treatment. The low number of patients in peritoneal dialysis may be attributed to the complications associated with peritoneal dialysis and its suitability, particularly for younger patients who are also more suitable for transplantation (22). The number of hemodialysis patients increased from approximately 56,000 in 2014 to over 70,000 in 2022. As a result, the number of hemodialysis centers also increased, from 849 in 2014 to 918 in 2022, in response to the growing number of patients (22,23). It is important to note that the high number of ESRD patients in Turkey constitutes approximately 5% of the health budget spent on dialysis.

In our study, more than half of the participants were informed about organ transplantation and donation, and 75% of the patients referred to transplant centers for registration on the waiting list by dialysis centers and nephrologists. Another study found that approximately 70% of patients were informed, and 75% were directed by their dialysis physician and nephrologist (9). Patients awaiting organ transplantation often experience fear, anger, hopelessness, uncertainty, fatigue, and anxiety. Many of these emotions result from inadequate information (24,25). Therefore, it is anticipated that providing patients with information about the organ transplantation system, its operation, kidney transplantation surgery, and complications by relevant healthcare professionals would contribute to their quality of life and psychological well-being.

In this cohort, 46.7% of the participants were willing to donate organs, but only 21.7% had an organ donation card. In a study conducted with kidney and liver transplant waiting patients in Spain, 91% of the patients expressed their willingness to donate their organs after brain death, 6% were undecided, and 3% were unwilling to donate (26). Examining studies conducted with other groups is also important to clarify the community's stance on the subject. In a study conducted with teachers in Bosnia and Herzegovina, none of the participants had an organ donation card, but the majority were willing to donate organs from both living and deceased donors (27). In previous studies, Uzuntarla found that 52.8% of healthcare workers in Turkey were willing to donate their organs, but only 16.7% had an organ donation card (9). In a study conducted in Germany by Radunz et al., 74% of the participants were willing, but only 55% had an organ donation card (28). Hobeika et al. conducted a study with surgeons and medical school students in the United States, where 64% were willing, and 49% had an organ donation card (29). In a study conducted by Lima et al. in Brazil, 78% of physicians were willing, and in a study conducted in Poland, 73% of nurses were willing (30). Vlaisavljević et al. conducted a study with nurses in Serbia, where 32.0% were willing, and 0.3% had an organ donation card (31). As seen from the results of these studies, organ donation rates are high in Spain and European countries, while they are low in developing or underdeveloped countries. Furthermore, it can be stated that healthcare professionals have a more positive attitude towards organ donation and transplantation due to their knowledge and experience compared to patients and other members of society.

We determined that 45% of the participants did not trust the organ distribution system of the Ministry of Health, and 21.7% were undecided. 74.2% of the participants considered organ transplantation efforts in the country to be inadequate. Another study conducted with ESRD patients in Turkey found that 64.4% of the participants believed that they could not receive a kidney transplant from a deceased donor due to the inadequacy of donation and transplantation efforts in the country (9). In a study conducted by Balwani et al. in India with ESRD patients, approximately 32% of the participants expressed concerns about the misuse, abuse, or unfair distribution of donated organs, indicating a lack of trust in the system (32). Therefore, it becomes necessary to assure people that no priority is given to wealthy or influential individuals in the organ distribution system. It is important to build trust in society by demonstrating the transparency of the process, where factors such as wealth, social status, race, and gender are never taken into account. To establish trust and address such concerns, it is necessary to provide education to the public. When examining the reasons for individuals' negative attitudes towards organ donation in research, it was found in the study by Özkan et al. that distrust in physicians, personal preferences, concerns about the disruption of bodily integrity, and religious reasons were the reasons for not donating organs (33). In Özkan's study with the relatives of ESRD patients, lack of sufficient knowledge, fear, and religious reasons stood out as prominent factors

(34). In a study conducted by Tarhan et al. with the relatives of patients, fear, unsuitable health conditions, and religious reasons were identified as the reasons why participants did not engage in organ donation (35). Studies conducted by Nadoushan et al. with physicians in Iran, Hu and Huang with healthcare personnel in China, and Hobeika et al. with surgeons and medical students in America revealed that a significant portion of the participants had concerns about the disruption of bodily integrity (29,36,37). It is observed that reluctance to donate organs due to religious reasons can be seen in all societies. However, all Abrahamic religions approve of organ donation. The Presidency of Religious Affairs of the Republic of Turkey issued a fatwa in 1980 stating that organ transplantation is permissible if there is a medical necessity, basing it on the verse (Surah Al-Ma'idah/32) in the Quran which says, "Whoever saves one life, it is as if he has saved all of humanity."

In our study, approximately 70% of the participants, who are considered to be individuals believe that all institutions such as healthcare organizations, media, religious institutions, and schools should actively contribute to increasing the organ donation rate. Similar studies have also indicated that lack of information is the biggest obstacle to organ donation and needs to be addressed. In this regard, it has been emphasized that increasing public awareness, using media, and providing education to the community are crucial (38,39). In a study by Smiths et al. with middle school students in the Netherlands, the control group was given a questionnaire on organ donation and transplantation. The experimental group, however, was provided with a 45-minute presentation where five former patients who had previously received kidney transplants through cadaver donation shared their knowledge and experiences. The study found that the experimental group, which received the educational program, had an increased willingness to fill out organ donation forms and an increased knowledge and awareness of organ donation (40). In a study by Uzuntarla with high school students in Ankara, a pre-test was conducted first, and then the students were given a 45-minute education session by an organ transplantation coordinator, followed by a post-test. The study found that the knowledge level, which was 11.5% in the pre-test, increased to 88.5% after the education session, and the voluntary organ donation rate increased from 15% to 53.1%. This study has demonstrated that the deficiency in organ donation can be significantly addressed through education (41).

Individuals aged 35-49 had significantly more positive knowledge and attitudes regarding brain death awareness, possession of an organ donation card, and willingness to donate organs compared to others. It is believed that the higher knowledge and experience, more active working life, and presumably higher health literacy levels of individuals in this age group influenced the results. While significant differences according to age were found in some previous studies, they were not found in others (16,42-44). Those with higher education levels had a more positive attitude compared to literate and primary school graduates. The findings of the study are consistent with previous research (16, 44).

Limitations of the study: The study's participants were only patients on the kidney transplant waiting list, which may not provide a comprehensive understanding of the broader population's knowledge, attitudes, and behaviors towards organ donation and transplantation. Including a more diverse sample, such as individuals from different age groups, educational backgrounds, and socioeconomic statuses, could enhance the study's validity and generalizability. The study touched upon certain factors, such as education level and age, but did not explore other potential influencers, such as cultural and religious beliefs, social norms, or personal experiences. Investigating a broader range of factors that may impact attitudes and behaviors towards organ donation could yield a more comprehensive understanding.

CONCLUSION

The knowledge, attitudes, and behaviors of patients on the kidney transplant waiting list regarding organ donation and transplantation require improvement. The study provides valuable insights for policymakers and stakeholders to evaluate the current situation, increase awareness, and develop strategies to address the identified issues. It underscores the need for comprehensive education programs, transparent organ allocation systems, and collaborative efforts to promote organ donation and transplantation in the population.

DECLARATIONS

Ethical approval: This study was carried out in accordance with the Declaration of Helsinki. The study was approved by the Medicana International Hospital Scientific Research Ethics Committee (Date:30.03.2022, Approval number: BŞH-2022/08).

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Supp 1

Questionnaire Form

Information, Attitudes and Behaviors of Patients with Chronic Kidney Failure Diagnosed in the Kidney Waiting List on Organ Transplantation and Donation

Dear participant; This questionnaire form has been prepared to evaluate the information, attitudes and behaviors of the patients who are registered to the Ministry of Health Organ Waiting List (TDIS) in the Medicana International Ankara Hospital Organ Transplantation Center, who are being treated for end-stage chronic renal failure or undergoing dialysis, and to increase the awareness of organ donation. If you agree to participate in the study, the results will be published in the research article and your personal information will be kept strictly confidential. Please read all the questions carefully and choose the option that suits you best. Thank you for your support, participation and help.

I was informed about the purpose of the survey, I voluntarily agree, participate in the research;

( ) I CONFIRM

( ) I DO NOT CONFIRM

1. Your gender

( ) Male female

2. Your Age Group

( ) 18-24 ( ) 25-34 ( ) 35-49 ( ) 50-64 ( ) Age 65 and over

3. Do you smoke?

( ) Yes ( ) No ( ) Occasionally

4. What is your Education Status?

( ) Literate ( ) Primary school ( ) Secondary school ( ) High school ( ) University

5. What is your marital status?

( ) Married ( ) Single ( ) Divorced

6. Which of the following is your cause of chronic kidney failure?

( ) Hypertension ( ) Diabetes ( ) Polycystic Kidney Disease
( ) Bladder Problems ( ) Kidney Stone ( ) Nephritis
( ) Cause Unknown ( ) Other …….

7. Are you on dialysis? If yes, what type of dialysis do you do?
( ) Yes No
( ) Hemodialysis ( ) Home Dialysis ( ) Peritoneal Dialysis
8. If you are on dialysis, how many years have you been receiving dialysis treatment?
( ) I do not enter ( ) 1-3 years ( ) 3-5 years ( ) 5-10 years ( ) More than 10 years
9. For how many years have you been registered on the Ministry of Health National Organ waiting list?
( ) 1-3 years ( ) 3-5 years ( ) 5-10 years ( ) More than 10 years
10. Who directed you to enroll in the Ministry of Health National Organ Waiting List?
( ) My family ( ) Dialysis Center ( ) My Nephrology Doctor ( ) My Friends
( ) Myself
11. Have you ever had a kidney transplant?
( ) Yes No
12. Have you been called for a kidney transplant by the transplant center you registered before?
( ) Yes No
13. Are there any patients in your family who are waiting for an organ besides you?
( ) Yes ( ) No ( ) Not sure
14. Have you ever received training on organ transplantation or organ donation?
( ) Yes ( ) No ( ) Not sure
15. Have you heard of the concept of brain death before? What do you think is brain death?
( )Yes ……..
( )No ……..
16. Do you know anyone who has had a transplant with organ donation as a result of death?
( ) Yes ( ) No ( ) Not sure
17. Do you have a relative or acquaintance who has a suitable donor and has had a transplant?
( ) Yes ( ) No ( ) Not sure
18. Is there anyone in your family who has donated organs and received a donation card?
( ) Yes ( ) No ( ) Not sure
19. Did you donate organs to be used after death?
( ) Yes ( ) No ( ) Not sure
20. If your answer to the previous question is ‘no’, would you like to donate an organ?
( ) Yes ( ) No ( ) Not sure
21. Do you know where and how organ donation is made?
( ) Yes ( ) No ( ) Not sure
22. Would you recommend organ donation to your family and friends?
( ) Yes ( ) No ( ) Not sure
23. If a relative of yours dies, would you donate their organs?
( ) Yes ( ) No ( ) Not sure
24. Do you want your relatives to donate your organs after you die?
( ) Yes ( ) No ( ) Not sure
25. Do you find the studies on organ donation sufficient?
( ) Yes ( ) No ( ) Not sure
26. Do you trust the organ distribution system of the Ministry of Health?
( ) Yes ( ) No ( ) Not sure
27. Do you think you have the right to cancel the decision after organ donation?
( ) Yes ( ) No ( ) Not sure
28. Is it necessary to be completely healthy to be an organ donor?
( ) Yes ( ) No ( ) Not sure
29. What do you think is the most effective method to increase the rate of organ donation?
( ) Media ( )School ( )Family ( )Religious Organizations
( ) Healthcare Institutions ( ) All
30. Have your views and ideas on organ donation changed with this survey?
( ) Yes ( ) No ( ) Not sure

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Original Article

Musculoskeletal and Neurological Examination Findings in Post-COVID-19

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ABSTRACT

Background: This study investigated the musculoskeletal and neurological examination findings in symptomatic patients who had previously experienced COVID-19.

Material and Methods: A prospective cohort of 101 patients who had been diagnosed with COVID-19 between January and April 2021 was included in this study. These patients received medication treatment and were followed up but did not require intensive care unit (ICU) admission. The patients' symptoms, dysfunctional segments identified through cervical and thoracic examinations, and visual analog scale (VAS) scores were analyzed.

Results: Myalgia (63%) was the most commonly reported symptom in the post-COVID-19 period. The T5 segment (23%) was the most frequently observed dysfunctional segment. Older individuals had a higher VAS score and a statistically significant correlation was found between age and VAS scores (p=0.013 and r2: 0.265).

Conclusion: This study highlights the prevalence of myalgia as a common symptom in patients who have previously had COVID-19 and emphasizes the importance of assessing the T5 segment for managing pain and facilitating pulmonary rehabilitation in such individuals. These findings can contribute to the development of more effective treatment strategies for post-COVID-19 patients experiencing musculoskeletal symptoms.

Keywords: Post COVID-19, pulmonary rehabilitation, dysfunctional segment, myalgia, pain

INTRODUCTION

The COVID-19 pandemic has affected millions of people worldwide, causing a range of health issues and complications. While the primary respiratory symptoms of COVID-19 are well-known, emerging evidence suggests that the virus can also have musculoskeletal manifestations (1-3). Many individuals who have recovered from COVID-19 report experiencing persistent musculoskeletal symptoms, such as muscle aches, joint pain, and generalized discomfort (3,4). These symptoms can significantly impact an individual's quality of life, physical functioning, and overall well-being. Therefore, it is crucial for healthcare providers and patients alike to recognize and manage these post-COVID-19 musculoskeletal symptoms effectively.

There are numerous studies in the literature regarding musculoskeletal involvements following COVID-19 (1-4). Muscles and joints (commonly affecting the shoulders, neck, back, and limbs), spine (the cervical and thoracic regions of the spine; with symptoms such as neck pain, stiffness, and discomfort in the upper back region), chest wall (chest wall pain or discomfort), extremities (affect the arms and legs, including symptoms such as limb weakness, muscle fatigue, and joint stiffness) (2,5,6). However, data regarding these involvements' segmental patterns and frequency are still limited.

This study aims to investigate the musculoskeletal and neurological examination findings of non-hospitalized symptomatic post-COVID-19 patients to determine

whether there is specific segmental involvement.

MATERIAL AND METHODS

Study Design and Participants

This descriptive study included 101 patients who had previously experienced COVID-19 and presented to the Physical Therapy and Rehabilitation (PTR) outpatient clinic of Medicana International Hospital Between January-April 2021 following a documented COVID-19 within recent 4-12 weeks. Patients who had been admitted to the intensive care unit (ICU) and required a prolonged hospitalization were excluded from the study. The study data included variables such as age, gender, patient complaints (a list of complaints was given, and participants were asked to select the options that described their discomfort), dysfunctional segments identified through cervical and thoracic examinations, and Visual Analog Scale (VAS) scores assessed by an experienced physician.

Inclusion and Exclusion Criteria

Patients who were referred to PTR due to post-COVID-19 persistent musculoskeletal discomfort were enrolled in the study. Participants with acute illness and known neuropathy, including dyscopathy, were excluded This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects.

STATISTICAL ANALYSIS

The study utilized descriptive statistics (mean and ± standard deviation), chi-square test, scatter plot with correlation analysis, regression analysis, and independent samples t-test (possibly) to analyze the data by using SPSS 13.0 for Windows. $p<0.05$ was assigned as significant

RESULTS

The demographical and clinical features of 101 patients were given in Table 1. Of the patients included in the study, 63% were male, while 37% were female. The average age of all patients with post-COVID-19 syndrome was 38.6±12.2. The average age for males was 41.9±11.3, and for females, it was 36.7±10.89. Myalgia was the most frequently reported symptom, accounting for 63% of cases. The frequency of symptoms between genders was similar (p=0.658). Age and sex have no impact on symptom development (p=0.329 and p=0.512, respectively).

Table 1. The characteristics of the participants

Age, years	38.6±12.2
Sex, male/female, n=	63/38
Mean postCOVID-19 duration	18 days
Symptoms, %	
• Myalgia	63
• Fatigue	53
• Shortness of Breath	24
• Chest Pain and Palpitations	25
• Sleep Disorders	22
• Loss of Smell and Taste	13
• Gastrointestinal Symptoms	23

The study examined the presence of dysfunction in specific segments of the cervical and thoracic regions in post-COVID-19 patients. It was found that 23% of the patients had dysfunction in the T5 segment. Following that, dysfunction was observed in 16% of patients in the C2 and T6 regions, 13% in the C4 region, and 11% in the T4 region (**Table 2**).

Younger patients were at lower and higher VAS scores, while older patients were at higher VAS scores, given the scatter plot between these two variables. A statistically significant relationship was found between age and VAS scores (p=0.013 and r2: 0.265).

These findings suggest that dysfunction in specific segments of the cervical and thoracic regions is common in post-COVID-19 patients, with the T5 segment being the most frequently affected.

Table 2. The affected segments of patients included in the study

T5: 23 cases (23%)
C2: 16 cases (16%)
T6: 16 cases (16%)
C4: 13 cases (13%)
T4: 11 cases (11%)
T9: 8 cases (8%)
T3: 6 cases (6%)
T8: 5 cases (5%)
T7: 2 cases (2%)
T10: 1 case (1%)
Total: 101 cases (100%)

DISCUSSION

This study aimed to investigate the musculoskeletal and neurological examination findings in symptomatic patients who had previously experienced COVID-19. The findings provide valuable insights into the prevalence of symptoms, dysfunctional segments, and their implications for pain management and pulmonary rehabilitation in post-COVID-19 patients.

In the literature, the prevalence of arthralgia or myalgia in patients with COVID-19 varies. In a retrospective cohort study conducted by Hoong et al, involving 294 hospitalized patients with COVID-19, it was observed that 30% of patients reported musculoskeletal complaints. Among those with musculoskeletal complaints, the study found that 37.5% experienced myalgia, 5.7% had

arthralgia, 6.8% reported new-onset backache and 50% had generalized body ache (7). However, myalgia can occur in a range of 15.5-68% in previous studies (7,8). It is difficult for many physicians to differentiate a specific involvement type when patients describe a generalized pain. The most commonly reported symptom in this study was myalgia, with a prevalence of 63%. This aligns with existing literature that suggests muscle pain is a common complaint among individuals recovering from COVID-19. The high prevalence of myalgia diagnosis in this cohort may be attributed to patients being referred to a physical therapy specialist based on their complaints.
In terms of dysfunctional segments identified through cervical and thoracic examinations, the T5 segment was the most frequently affected, observed in 23% of the patients. Dysfunctions in the C2 and T6 regions were also relatively common (16%), followed by the C4 (13%) and T4 (11%) regions. These findings indicate the potential involvement of specific spinal segments in post-COVID-19 musculoskeletal issues. Understanding the pattern of dysfunction can guide healthcare providers in developing individualized treatment plans, including manual therapy, exercise, and rehabilitation strategies, to address segment-specific impairments.

Pain assessment using the VAS scores revealed a statistically significant relationship between age and pain levels, indicating that older patients tended to report higher levels of pain or discomfort. This observation suggests that age may be a contributing factor to the severity of musculoskeletal symptoms experienced by post-COVID-19 patients. The impact of age on pain perception and functional outcomes should be taken into consideration when designing rehabilitation programs for this population. Cevei et al. highlighted the need for post-acute rehabilitation after COVID-19, especially in elderly people with underlying health problems (9). Previous studies have shown that during the post-COVID-19 period, many symptoms have adversely affected the quality of life and functional capacity over a 6-month period. The priority of treatment should be given to cardiopulmonary, psychiatric, and musculoskeletal rehabilitation (10).

The findings of this study have clinical implications for the management of post-COVID-19 musculoskeletal symptoms. Considering the high prevalence of myalgia, healthcare providers should prioritize pain management strategies tailored to individual patients. Addressing dysfunctional segments, particularly the commonly affected T5 segment, through targeted interventions such as manual therapy and specific exercises, may help improve functional outcomes and alleviate musculoskeletal discomfort.

Furthermore, incorporating pulmonary rehabilitation in the post-COVID-19 rehabilitation programs is warranted (9,10). Given the relationship between dysfunctional segments and pain, addressing these issues may positively impact respiratory function and overall rehabilitation outcomes. Pulmonary rehabilitation programs can help individuals recovering from COVID-19 regain their respiratory capacity, enhance physical endurance, and improve their quality of life (9-12).

It is important to note that this study had some limitations. The sample size was relatively small, and the data was collected from a single center, which may limit the generalizability of the findings. Additionally, the study focused on patients who did not require ICU admission, potentially excluding those with more severe cases of COVID-19. Future research with larger and more diverse cohorts is needed to validate and expand upon these findings.

In conclusion, this study provides valuable insights into the musculoskeletal and neurological examination findings in post-COVID-19 patients. Myalgia was the most commonly reported symptom, and dysfunction in specific cervical and thoracic segments, particularly the T5 segment, was frequently observed. Understanding these findings can guide the development of targeted rehabilitation strategies for managing musculoskeletal symptoms and improving overall functional outcomes in individuals recovering from COVID-19. Further research is warranted to explore the long-term effects of COVID-19 on the musculoskeletal system and optimize rehabilitation interventions for post-COVID-19 patients.

DECLARATIONS

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Review

The Synergistic Role of Endoscopy and Cytology in the Diagnosis of Aspergillosis: A Comprehensive Review of Human and Avian Medicine

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ABSTRACT

The use of endoscopy and cytology for the diagnosis of aspergillosis has gained significant attention in recent years due to its accuracy and reliability. The present literature review highlights the potential advantages of combining these two techniques in diagnosing aspergillosis, including the ability to visualize affected tissues and detect the presence of fungal elements. The use of endoscopy and cytology is applicable both in Human and Avian medicine which provides a rapid diagnosis, earlier treatment, and improved patient outcomes, making these techniques valuable to diagnose aspergillosis.

Keywords: Aspergillosis, endoscopy, isoflurane, ketamine, cyto-diagnosis

INTRODUCTION

The endoscopic diagnosis of aspergillosis allows for the visualization of the affected tissues, such as the lungs, sinuses, and gastrointestinal tract. It can help to identify the presence of fungal lesions or other characteristic changes in the tissue, such as granulomas or nodules. In a study by Vanita et al. (2021), endoscopic findings in patients with chronic rhinosinusitis with nasal polyps showed that the presence of fungal debris was highly suggestive of fungal sinusitis, including aspergillosis (1). Cytology, on the other hand, involves the microscopic examination of cells or tissues to detect the presence of Aspergillus spores in samples including bronchoalveolar lavage fluid, sputum, biopsy specimens, and aspirates. A study performed in 2019 found that the sensitivity and specificity of cytology in diagnosing pulmonary aspergillosis were 80% and 100%, respectively (2).

Advantages of Combined Endoscopy and Cytology procedures

Combining endoscopy and cytology can further improve the diagnostic accuracy of aspergillosis. Endoscopic examination and cytological analysis of bronchial brushing specimens showed a sensitivity of 94% and a specificity of 100% in diagnosing pulmonary aspergillosis (3,4). Various techniques have been developed to improve the detection of Aspergillus spores using endoscopy and cytology. For instance, immunohistochemistry can help identify the presence of Aspergillus antigens in tissues, while polymerase chain reaction (PCR) can detect Aspergillus DNA in samples. Recent studies showed that combining endoscopic biopsy, cytology, and PCR can increase the sensitivity and specificity of diagnosing aspergillosis (5,6). The major advantage of a combined procedure includes the following.

1.One of the advantages of using the combination of endoscopy and cytology procedures was the rapid and accurate diagnosis that allows for timely treatment and improved patient outcomes.

2.Endoscopy is a minimally invasive procedure that could be performed in an outpatient setting providing real-time visualization of the affected tissues. It allows the immediate identification of abnormalities or lesions and characteristic tissue changes. Additionally, endoscopy can be performed in multiple locations, including the sinuses, lungs, and gastrointestinal tract, allowing for identification of the site of infection.

3.Cytology involves the examination of cells or tissues in samples obtained non-invasively, such as through sputum or bronchoalveolar lavage.

Overall, the rapid diagnosis provided by the combination of endoscopy and cytology can lead to earlier treatment and improved patient outcomes, making these techniques

valuable in diagnosing aspergillosis.

A Comparative Study of Human and Avian Endoscopy

There are some differences in the techniques used in human and avian endoscopy due to the anatomical and physiological differences between the species. The difference in human and avian endoscopy procedures are the following.

1.One of the main differences is the species-specific anatomical differences in the respiratory system of avian species that differs from mammals, which can affect the type and location of lesions and the ability to obtain adequate samples for diagnosis (6).

2.Another difference is in the type of endoscopy equipment used in veterinary that is smaller in size and different shapes to accommodate the anatomical differences between species. In humans, a flexible fiberoptic endoscope has been used, while in avian species, a rigid endoscope is preferred due to the smaller size of the avian respiratory system (6). A rigid endoscope in birds allows for a better view of the affected areas and can also reduce the risk of trauma to the delicate tissues of the respiratory system.

3.Additionally, there may be differences in the clinical signs and symptoms exhibited by humans and animals with aspergillosis. For example, avian aspergillosis may present with respiratory distress, lethargy, and anorexia, while human pulmonary aspergillosis may present with coughing, fever, and shortness of breath (6).

4.Another difference is in the anesthetic management required for endoscopy. In humans, sedation or general anesthesia was used, while in birds, anesthesia is necessary to prevent stress and injury during the procedure (6-8). The choice of anesthetic agent and monitoring techniques may also differ between species.

In human endoscopy, sedation or general anesthesia is commonly used to provide comfort to the patient and minimize the risk of complications. Sedation is achieved by using intravenous medications such as midazolam and fentanyl, while general anesthesia may require the use of inhaled anesthetics or muscle relaxants (7,8). The choice of anesthetic technique will depend on the patient's age, medical history, and the type and duration of the procedure.

Sedation is one commonly used technique in human endoscopy, which involves the administration of intravenous medications to relax the patient and reduce their anxiety. The most used sedative medications include benzodiazepines such as midazolam and diazepam, and opioids such as fentanyl or propofol (7,8). General anesthesia might be used in endoscopic procedures, particularly for longer or more invasive ones. General anesthesia involves the administration of inhaled anesthetics, muscle relaxants, and other medications to induce and maintain a state of unconsciousness during the procedure (7,8).

Anesthesia is used for diagnostic and therapeutic procedures like endoscopy in avian medicine to minimize stress and prevent injury to the bird. However, the anesthesia management in avian medicine is different from that used in human endoscopy due to the unique physiology of birds. Injectable anesthesia is the most used technique in avian endoscopy that were ketamine, propofol, and tiletamine-zolazepam (6-8). These drugs are administered either intramuscularly or intravenously, and their effects are quickly reversible.

Isoflurane is a halogenated ether, the most used inhalant anesthetic agent widely used in avian medicine (9). It has a rapid onset and offset of action, allowing for rapid induction and recovery time. Isoflurane also has a low solubility in blood, which enables the adjustment of anesthesia depth during the procedure. Administration of isoflurane was typically vaporized in a carrier gas, such as oxygen or air, and delivered via a face mask or an endotracheal tube. The concentration of isoflurane in the carrier gas was adjusted according to the bird's response to the anesthetic and monitoring the bird's respiratory and cardiovascular parameters is essential during the procedure (9).

Despite these differences, the principles of endoscopy and cytology for the diagnosis of aspergillosis are similar between human and veterinary medicine. Both rely on the visualization of affected tissues and the detection of Aspergillus spores in samples obtained via endoscopy and cytology. Overall, the use of endoscopy and cytology has shown great potential for the diagnosis of aspergillosis in both human and veterinary medicine, with the potential to improve early detection and treatment outcomes (9-17).

Endoscopic Diagnosis of Aspergillosis

During an endoscopy, characteristic signs of aspergillosis may include the presence of nodules or growths on the lining of the respiratory tract. These growths can appear as whitish-yellow patches or raised, reddish bumps (**Figure 1**).

The tissue surrounding the growths may also appear inflamed or irritated. Aspergilloma, also known as a fungal ball, is a mass of Aspergillus fungus that grows within a pre-existing cavity in the lungs. The appearance of aspergilloma through endoscopy may vary depending on the size and location of the fungal ball (**Figure 2**). It can appear as a round, solid mass, white or yellow colored (14-17). The surrounding tissue may also

appear inflamed or irritated. In severe cases, sporulating colonies may be seen (**Figure 3**).

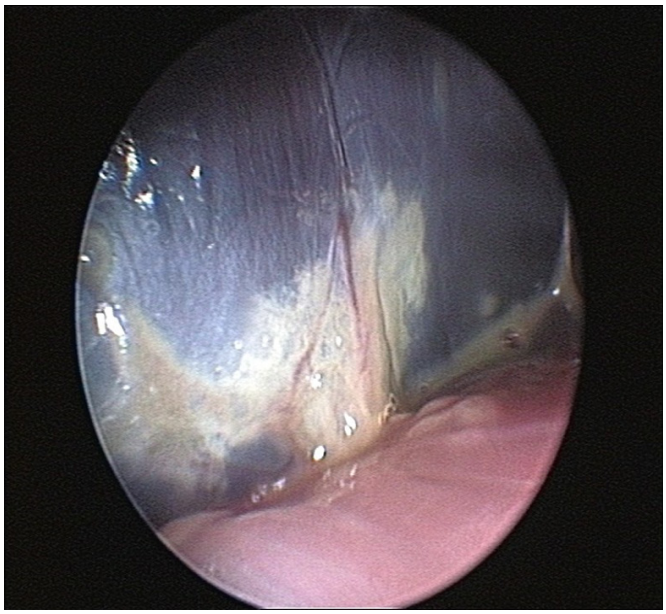

Figure 1. Endoscopic view of disseminated aspergillosis in the air sac of a Gyrfalcon (Falco rusticolus), the largest of the falcon species.

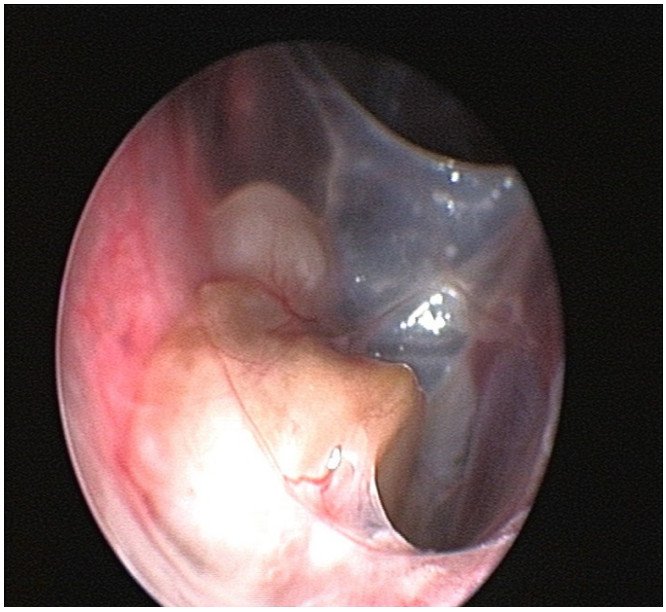

Figure 2. Aspergilloma in the air sac of a Gyr-Peregrine hybrid falcon.

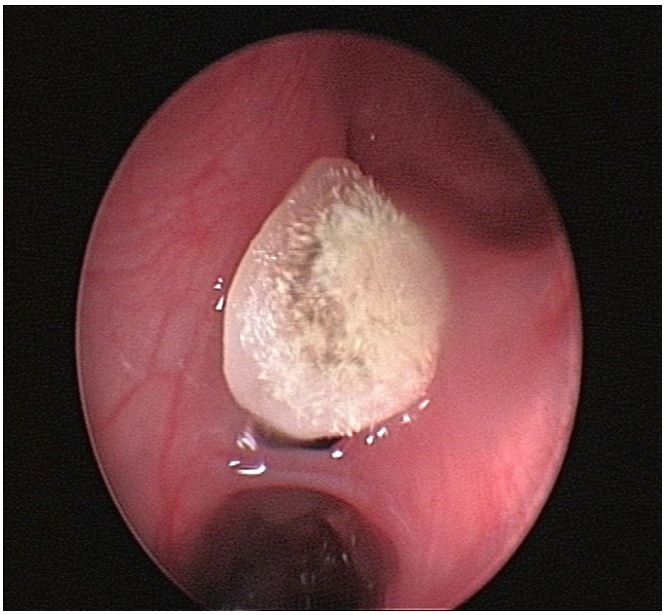

Figure 3. Sporulating aspergillosis in the air sac of a Gyrfalcon (Falco rusticolus).

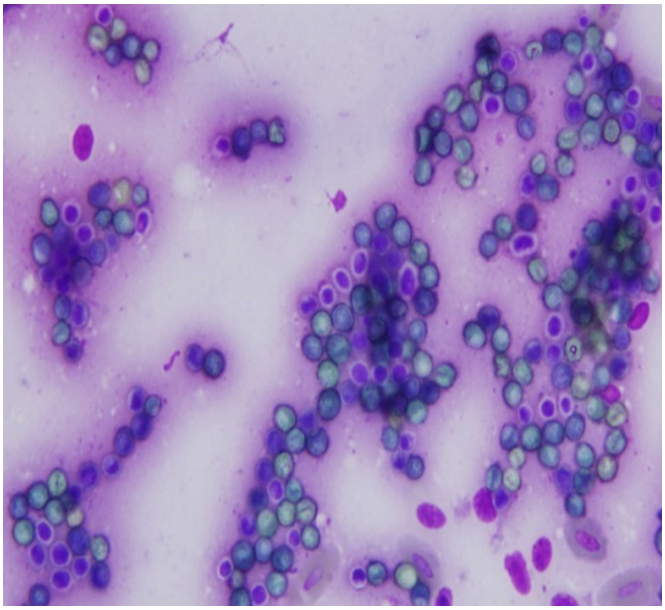

Figure 4. Cytology from the air sac of a Gyrfalcon (Falco rusticolus) with aspergillosis showing numerous fungal spores.

Diagnostic Cytology of Aspergillosis

The diagnosis of aspergillosis through cytology includes the appearance of fungal elements and cellular changes depending on the site of infection and the type of specimen obtained for analysis. Pulmonary aspergillosis is the most common form of aspergillosis, in which sputum or bronchoalveolar lavage (BAL) fluid is collected for cytological examination (10-13).

Microscopic examination of sputum or BAL fluid may reveal characteristic fungal elements, such as spores, conidiophores, and septate hyphae with acute-angle branching, which are typical of Aspergillus species (**Figure 4**). The cellular changes seen are necrotic tissue, inflammatory cells, multinucleated giant cells, and mucus. The presence of Aspergillus hyphae in tissue specimens, identified by histological examination or fungal cultures, is a hallmark of invasive Aspergillosis (**Figure 5**).

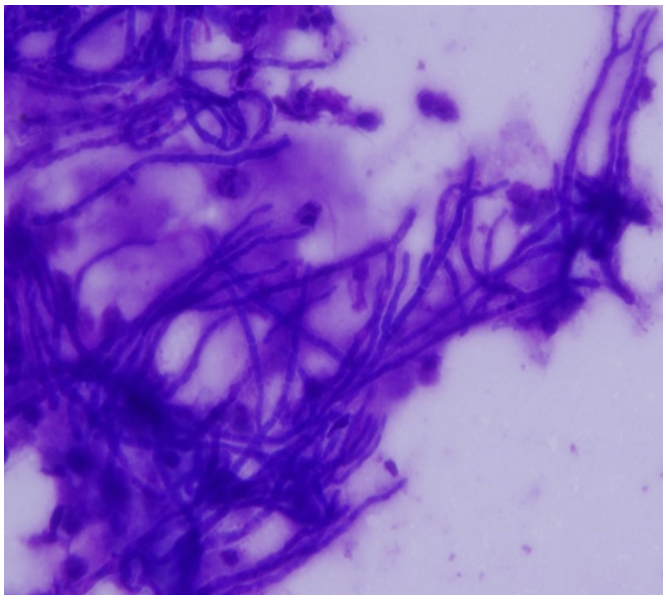

Figure 5. Cytology from the air sac of Gyrfalcon (Falco rusticolus) with aspergilloma showing fungal hyphae.

CONCLUSION

The use of endoscopy and cytology in the diagnosis of aspergillosis has gained significant attention in recent years due to its accuracy and reliability. The present literature review highlights the potential advantages of combining these two techniques in diagnosing aspergillosis, including the ability to visualize affected tissues and detect the presence of Aspergillus spores. It can be performed on a wide range of samples, including bronchoalveolar lavage fluid, sputum, biopsy specimens, and aspirates. Therefore, cytology can be a valuable tool in the diagnosis of aspergillosis, especially when combined with other diagnostic methods. Combining endoscopy and cytology can further improve the diagnostic accuracy of aspergillosis.

Various techniques have been developed to improve the detection of Aspergillus spores using endoscopy and cytology, immunohistochemistry, and PCR. These methods can increase the sensitivity and specificity of diagnosing aspergillosis, especially in cases with atypical presentations or immunocompromised patients. The use of endoscopy and cytology in the diagnosis of aspergillosis has shown promising results in recent studies, and combining these techniques can further improve the accuracy of diagnosis.

DECLARATIONS

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Review

Gestational Diabetes Mellitus

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ABSTRACT

Gestational diabetes mellitus (GDM) refers to the onset of diabetes occurring after the conclusion of the first trimester of pregnancy. GDM is currently one of the most common pregnancy-related medical complications and a cause of diabetes in young women. Maternal overweight and obesity, older age at birth, a history of GDM, a family history of type 2 diabetes mellitus, and ethnicity are important risk factors for GDM development during pregnancy. GDM increases the risk of long-term complications in both the mother and infant, including obesity, impaired glucose metabolism, and cardiovascular disease. It is also associated with adverse pregnancy outcomes such as macrosomia, shoulder dystocia or other birth injuries (also called birth trauma), hypertension, and preeclampsia, perinatal depression, preterm birth, and stillbirth. Managing the mother and infant optimally during long-term follow-up remains challenging. Dietary modification and increased physical activity are the primary treatments for GDM and can alleviate GDM-related complications. However, hypoglycemic agents, traditionally insulin, are used when normoglycemia is not achieved. This review focuses on the current knowledge of GDM and briefly discusses its updates.

Keywords: Gestational diabetes mellitus, risk factors, outcomes, diabetes mellitus, complications

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that occurs in the second or third trimester of pregnancy (1-4). GDM encompasses a range of hyperglycemia, from mild impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) to overt diabetes (5). It is an important risk factor for subsequent type 2 diabetes mellitus (DM) and is typically diagnosed during pregnancy without any symptoms. While GDM usually resolves after childbirth, there is a high risk of recurrence in future pregnancies (3). GDM poses various risks to the mother, fetus, and newborn, with potential long-term consequences such as obesity, glucose intolerance, and diabetes in childhood and adulthood (6). Screening, diagnosis, and effective treatment of GDM can improve maternal and perinatal outcomes and prevent future diabetes in both the mother and child (7).

The prevalence of GDM indirectly reflects the future prevalence of type 2 diabetes in a given population (1). The exact prevalence of GDM is unknown and can vary based on screening and diagnostic criteria, population region, data collection methods, and sample selection (8,9). Generally, the prevalence of GDM ranges from 2% to 6%, but certain studies have reported rates as high as 10% to 20% (10-13). In the Turkish population, it is estimated that the incidence of GDM falls between 4% and 10% (3). In a study conducted with a two-step diagnostic method involving 2,643 pregnant women from 51 centers across different regions, the prevalence of GDM in the Turkish population was found to be 16.2%, with no significant difference between urban and rural areas (9). GDM accounts for approximately 90% of diabetic pregnancies (14). In recent years, the increasing rates of advanced maternal age and obesity have contributed to the rising prevalence of GDM. According to the TURDEP II study, the prevalence of DM in Turkey was reported as 16.5% (15).

For women at risk of developing GDM, it is important to assess GDM or gestational glucose intolerance during the initial prenatal visit, with tests interpreted as if the woman were not pregnant (3,16). The American Diabetes Association (ADA) has outlined low and high-risk factors for GDM development, as shown in **Table 1** (3,5,7,16). Pre-conceptional overweight or obesity are major risk factors for GDM (5). Maternal age has a strong correlation with GDM. Although factors such as

Table 1. Risk assessment in pregnant for GDM development

Low-risk	High-risk	
Age <25	Overweight or obesity (BMI ≥25kg/m2)	Pre-pregnancy diet (rich in red/processed meat products)
Normal weight before pregnancy	Advanced age (>40)	Physical inactivity
An ethnic group with a low prevalence of DM	Ethnicity	Short individuals
No diabetes in first-degree relatives	Family history of type 2 DM	α-Thalassemia
No history of abnormal glucose tolerance	Previous history of prediabetes	Hypertension
No history of poor obstetric outcome	Previous history of GDM	Hyperlipidemia
	Presence of glycosuria	Corticosteroids or antipsychotic medication
	Parity (more than 20 weeks of pregnancies)	Macrosomia (birth ≥4.5kg)
	Multiple pregnancies	Low birth weight
	Genetic factors	History of poor obstetric outcome
	Polycystic ovary syndrome	Acanthosis nigricans
	Cigarette smoking	Male fetus

DM; diabetes mellitus

body mass index (BMI), previous history of GDM, and family history of diabetes are independent predictors for GDM development, GDM can still occur in 1 out of 20 low-risk pregnancies (9).

PATHOPHYSIOLOGY of GESTATIONAL DIABETES

GDM is a heterogeneous disease resulting from the interaction between genetic and environmental risk factors. In addition to diet and lifestyle factors, environmental and psychosocial factors are thought to be possible contributors to the risk of developing GDM (5).

In fact, it has been known for a long time that insulin resistance develops similarly to type 2 DM during pregnancy (17). Increased insulin resistance and pancreatic β-cell dysfunction constitute the main physiopathological mechanism in women with GDM (2,5,6,8,18). Insulin resistance during pregnancy occurs at varying rates. It may be the result of maternal obesity with adipocytokine production or increased diabetogenic placental hormone production (2,8,19). As insulin resistance increases during pregnancy, there is a compensatory increase in insulin secretion to induce euglycemia (1,2,5).

Pancreatic β-cell hyperplasia occurs in response to glycogenic hormones during pregnancy (PAPP-A; pregnancy-associated plasma protein A, PLGF; placental growth factor, SHBG; sex hormone binding globülin, etc.) (19). Physiological resistance to the effect of insulin becomes evident in the second trimester and insulin sensitivity gradually decreases (2,17). Impairment of glucose tolerance occurs especially in the third trimester. β-cell dysfunction often precedes pregnancy and is

Table 2. Biomarkers result in GDM and their mechanism of action was summarized

Biomarkers	Mechanism of action	Probable pathway in GDM
Adiponectin	Modulation of glucose and lipid metabolism. Involvement in inflammation, apoptosis, and angiogenesis.	Low levels associated with decreased insulin sensitivity and GDM
Leptin	Adjustment of energy balance and expenditure. Act on hormone regulation and immunity.	Increased leptin causes hyperinsulinemia and insulin resistance
PAPP-A	Increase the bioavailability of IGF-1 and promotes somatic growth. Role in wound healing and bone remodeling.	Decreased levels of PAPP-A contribute to an increase in insulin resistance
PLGF	Vascular endothelial growth factor-like protein. Role in angiogenesis and placentation.	High PLGF levels promote the abnormal vascular network in the placenta of GDM pregnancies
TNF-α	The regulation of immune cells, inflammation, and autoimmune diseases.	Increased levels of TNF-α impair insulin signaling and beta-cell function, leading to insulin resistance and GDM
CRP	Role in tissue injury, inflammation, and infection	High levels associated with insulin resistance and systemic inflammation
IL-6	Role in immune response regulation, inflammation, and hematopoiesis.	Increased secretion by adipocytes and placental cells, leading to a chronic inflammatory process and insulin resistance
SHBG	Glycoprotein that binds androgen and estrogen.	Decrease SHBG levels associated with hyperinsulinemia and GDM

GDM; gestational diabetes mellitus, PAPP-A; pregnancy-associated plasma protein A, IGF-1; insulin growth factor 1, PLGF; placental growth factor, TNF-α; tumor necrosis factor α, CRP–C; reactive protein, IL-6; interleukin 6, and SHBG; sex hormone-binding globulin. (Retrieved from reference 20)

clinically manifested by increased insulin resistance during pregnancy (5). The rapid decrease in insulin resistance after birth suggests that placental hormones play a major role in insulin resistance (2). There are numerous biomarkers have been described in GDM (Table 2) (20).

Basal endogenous glucose production, especially hepatic glucose production, is 30% higher in pregnant women with GDM compared to healthy pregnant women. Peripheral insulin sensitivity decreases by approximately 50% in late pregnancy. In late pregnancy, the skeletal muscle content of insulin receptor substrate 1 (IRS1), one of the signal molecules, is lower in pregnant women with GDM compared to non-pregnant women. Additionally, the autophosphorylation of the insulin receptor β-subunit (IRβ) is lower in women with GDM compared to pregnant women with normal glucose tolerance. Maternal amino acid and lipid metabolism are also affected by decreased insulin sensitivity during pregnancy, which is associated with increased fetal growth and adiposity (5). Glucose transfer across the placenta stimulates fetal insulin secretion, and insulin acts as an essential growth hormone (17). Fetal insulin stimulates triglyceride synthesis, leading to increased white adipose tissue in the fetus (5).

Current evidence suggests that pancreatic β-cell defects in GDM result from similar underlying causes of hyperglycemia in general, including autoimmune disease, monogenic causes, and insulin resistance (2). Although genetic inheritance is believed to play a role in the etiology of GDM, studies examining the relationship between specific genetic factors and GDM are limited. Only a small proportion (2-13%) of women with GDM have antibodies against specific β-cells. Approximately 5% of women with GDM also have monogenic diabetes variants that involve a glucokinase mutation, which is most commonly observed in Caucasians (5,12). As a result, 5% of cases may exhibit maturity-onset diabetes of the young (MODY), and 2% may have type 1 diabetes mellitus (DM).

DIAGNOSTIC AND SCREENING CRITERIA FOR GESTATIONAL DIABETES

According to standard diagnostic criteria, it is recommended to screen pregnant women with risk factors for the development of DM for undiagnosed prediabetes and diabetes during their initial prenatal visit (6). Early screening for GDM is particularly important for women in populations with a high prevalence of type 2 DM (8).

During the first prenatal visit, fasting plasma glucose (FPG), HbA1C, or random plasma glucose (PG) should be measured in all pregnant women or those at high risk (20). Selective screening for GDM may result in a missed diagnosis in over 40% of GDM cases. If the FPG falls within the prediabetic range (100-125 mg/dl) at the beginning of pregnancy, it should be interpreted as in non-pregnant women, preferably by conducting an oral glucose tolerance test (OGTT) or assessing HbA1c. Conversely, if the 2nd-hour PG in the OGTT is between 140-199 mg/dl (or HbA1c is between 5.7-6.4%), pregestational prediabetes should be considered, and the pregnant woman should be monitored as if she has diabetes. A fasting plasma glucose level of ≥126 mg/dL (≥7.0 mmol/l), random plasma glucose level of ≥200 mg/dL (≥11.1 mmol/l), or HbA1C level of ≥6.5%, confirmed by the same or a subsequent test, indicates overt diabetes (3,20). If the 2nd-hour PG in the OGTT is ≥200 mg/dL (or HbA1C is ≥6.5%), the diagnosis of "pregestational diabetes" is made (3). All women without diabetes who have normal test values at the beginning of pregnancy should be screened again between 24 and 28 weeks of pregnancy (1,6,13).

Screening for GDM between 24 and 28 weeks of pregnancy: The International Association of Diabetes and Pregnancy Working Groups (IADPSG) recommends a 75g OGTT for screening during this period (20). Some guidelines also recommend a single-step 75g OGTT using IADPSG criteria during gestational weeks 24-28 (21,22). A one-step approach may be preferred if the prevalence of GDM is high (16). It is believed that the rate of GDM diagnosis may be lower with a two-step approach compared to a single-step approach (17). It is estimated that approximately 25% of GDM cases could be missed with the two-step method (5).

There is no consensus regarding the use of diagnostic tests and glucose threshold values for GDM (3,7). As the adoption of the one-step diagnostic approach increases, evidence suggests that perinatal outcomes are favorable and there is actually a "cost-effective" improvement in pregnancy outcomes. However, the one-step approach may simplify the diagnosis of GDM and increase the number of pregnant women diagnosed with GDM, leading to potential economic and emotional challenges (3,7,8). While national guidelines in Turkey suggest either approach, most centers still prefer the two-step approach using the Carpenter-Coustan criteria (9).

GDM diagnosis can be made with one of two approaches (Table 3).

1. "One step" approach with 75 g OGTT according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria; OGTT is performed in the morning after at least 8 hours of night fasting. If any value of serum glucose exceeds the threshold, GDM is diagnosed (21).

2. Scanning by using 50 g of glucose followed by 100

g of glucose "two-step" approach (Carpenter-Coustan criteria) (24)

Table 3. Glucose threshold values of OGTT in the diagnosis of GDM

	One Step- 75 gr glucose	'Two Steps- 100 gr glucose
FPG	92 mg/dL (5.1 mmol/L)	95 mg/dL (5.3 mmol/L)
1 hour	180 mg/dL (10.0 mmol/L)	180 mg/dL (10.0 mmol/L)
2 hours	153 mg/dL (8.5 mmol/L)	155 mg/dL (8.6 mmol/L)
3 hours		140 mg/dl (7.8 mmol/L)

FPG; fasting glucose

Women who do have not pregestational DM should be screened by random plasma glucose following 50 g glucose ingestion within 24-28 weeks of pregnancy (fasting is not necessary). If the 1st hour PG ≥140 mg/dl a 100 g OGTT is performed in the morning after 8 hours of night fasting. GDM is diagnosed when at least two criteria are met or exceeded (6).

In a 50 g glucose loading test when 1st-hour glucose is ≥140 mg/dl (7.8 mmol/L), it is recommended to perform 100 g OGTT (6). With this approach, ~80% of women with GDM are identified, and when the threshold value is set to ≥130 mg/dL (7.2 mmol/L) sensitivity increases to ~90% (1,14,15). It is recommended that those with PG ≥180 mg/dl in the 1st hour should be considered as GDM without the need for OGTT and follow-up and treatment should be started. Those who pass only one cut-off point in the 100-gr OGTT test are considered 'Gestational Glucose Intolerance' and it is recommended that these pregnant women be followed closely like GDM (3).

In the single-step approach, when one or more glucose values exceed the threshold, the incidence of preeclampsia was doubled, and the incidence of preterm birth and primary cesarean section was 45% higher. It has been reported that high FPG levels (lower than the diagnosis of diabetes) in the first trimester are associated with a later diagnosis of GDM and risks of adverse pregnancy outcomes (20). The diagnosis of GDM is not possible with the OGTT after surgical procedures that affect absorption (dumping syndrome) (25).

HbA1c values are useful in the evaluation of pregestational diabetes; however, when normal, it is not useful for the management of GDM (1). HbA1C is slightly lower in pregnancy than in non-pregnant women with increased erythrocyte cell turnover (26). HbA1C was ≥5.9% in early pregnancy is associated with poor outcomes such as congenital malformation risk, preeclampsia, shoulder dystocia and perinatal death (27).

TREATMENT of GDM

In women with a history of GDM, the development of type 2 DM can be prevented or delayed by lifestyle modification and/or medical treatment (11,28). The incidence of hypertension and preeclampsia also decreases with GDM treatment (3). The main goal of GDM treatment is to prevent fetal overgrowth and pregnancy complications (5,24). If left untreated, perinatal morbidity and mortality may increase (17).

In the prenatal period, treatment of women with a history of GDM should consist of medical nutrition therapy (MNT) and weight management, exercise, blood glucose self-monitoring (SMBG), and pharmacological therapy if necessary (8). All pregnant women with GDM should be taught to measure blood glucose at home (3). They are encouraged to monitor their own blood sugar levels before main meals and 1-2 hours after meals. Diet modification and increased physical activity are first-line treatments for GDM; however, insulin is usually used when normoglycemia cannot be achieved with this approach (5).

Lifestyle Change

Mild GDM can be treated 80-90% with only lifestyle changes (5,6.10,26). It has been shown that the risk of GDM can be reduced by diet, exercise, and lifestyle changes, especially when it is initiated in the first or second trimester of pregnancy (26). In high-risk women, it is recommended to start to lifestyle modification in early pregnancy and continue throughout pregnancy. A moderately personalized lifestyle change reduced the incidence of GDM in high-risk pregnant women by 39%. Findings in lifestyle intervention studies that focused on preventing type 2 diabetes were also encouraging, showing a risk reduction of 58% (18). It shows that it can be prevented by maintaining (BMI) of < 25 kg/m2, exercising ≥ 30 minutes a day, and not smoking (5).

Following the diagnosis of GDM, treatment begins with medical nutrition therapy, physical activity, and weight management depending on pregestational weight (26). Expected weight gain in normal pregnancy varies with pre-pregnancy weight. Recommended weight gain rates during pregnancy are shown in **Table 4** (13,25).

Table 4. Recommended weight gain rates during pregnancy

BMI, kg/m^2	Total weight gain	2. ve 3. trimester weekly weight gain
≤18,5 kg/m2	12.5–18 kg	0.5–0.6 kg
18.5–24,9 kg/m2	11.5–16 kg	0.4–0.5 kg
25.0–29,9 kg/m2	7–11.5 kg	0.2–0.3 kg
≥30 kg/m2	5–9 kg	0.2-0.3 kg

BMI; body mass index

Exercise

Regular physical exercise, fitness programs, or sports reduce the risk of GDM and increase the capacity to cope with pregnancy and childbirth, especially in women

who had pregestational obesity. Short exercise programs are beneficial in the first hour after main meals (25). The simple unaided physical exercise should be brisk walking for at least 30 minutes, at least 3 times a week. Physical activity should begin before conception or in the first trimester (1,25). The optimal type of exercise is unknown, but walking is generally recommended (10). Moderate-intensity aerobic activity (walking, cycling, or swimming) helps control blood sugar (13). Exercise helps to control both fasting and postprandial glucose levels by increasing insulin sensitivity (8,10).

Medical Nutrition Therapy

Medical nutrition therapy is defined as "designing meals with controlled carbohydrate levels for normal nutrition, normal sugar levels, and prevention of ketosis and adequate nutrition" (10). A food plan is designed to improve fetal/neonatal and maternal health, achieve glycemic goals, and promote appropriate gestational weight gain should ensure adequate caloric intake (26). During pregnancy, diets with high fat and low fiber intake and high glycemic index increase the risk of developing GDM; therefore, it is thought that a low glycemic index and high fiber diet greatly reduces the need for insulin in diabetic patients (10).

Pregnant should be counseled by a dietitian following diagnosis of GDM to initiate MNT, which forms the basis of any management plan, and should be advised to eat a main meal and 3 snacks (8). The nutrition program should be prepared in accordance with the targeted weight and physical capacity of the pregnant woman, as well as taking into account the needs of the fetus; targeted normoglycemia should be regulated so that ketosis does not occur (1,13). Maternal ketonemia and/or ketonuria in pregnant women with diabetes have been associated with lower mental and/or motor function in offspring (5).

Recommended food content; carbohydrates should be 40-55%, protein 20%, fat 25-40%. The percentage of carbohydrates should not be less than 40% or 175 g/day. Carbohydrates with high fiber content (28 g fiber) and low glycemic index should be preferred, and at least 71 g protein should be taken (10,24,25). The number of carbohydrates should be lower at breakfast than at lunch and dinner (25).

There is no conclusive research that specifically defines optimal caloric intake for women with GDM or suggests that their caloric needs differ from pregnant women without diabetes (26). Calorie intake is calculated based on ideal body weight [25-35 kcal/kg/day (ideal weight)] (1). It is 30 kcal/kg/day for women with normal body mass index and 24 kcal/kg/day for overweight women. However, 12-15 kcal/kg/day can be recommended for obese pregnant. Average calorie restriction (33% reduction in calorie intake) does not lead to ketosis but controls weight gain and glucose levels in obese women (10). This calorie content will ensure that 75-80% of pregnant women are normoglycemic (1). Most pregnant should receive 350 calories more from the beginning of the 4th month of pregnancy (13).

Pharmacological Treatment

Pharmacological therapy should be initiated when hyperglycemia persists after a fortnight of lifestyle change (5,8). Ultrasonography-based assessment of fetal growth can also help adjust the intensity of glucose control needed. If the baby is growing appropriately, especially with fetal abdominal circumference <75 percentile, it may be safe to delay the initiation of pharmacological therapy. Conversely, excessive fetal growth may lead to the intensification of therapy to achieve low glycemic targets (5).

Oral Antidiabetics (OAD): OAD is not recommended during pregnancy. OAD has no long-term safety data (8,25). Insulin therapy should be initiated in women with type 2 DM who become pregnant unplanned (3). Metformin and glyburide (glibenclamide) are not recommended as first-line therapy because they cross the placenta and are lacking in fetal safety data (26).

Metformin may slightly increase the risk of prematurity (26). Metformin crosses the placenta but is not associated with teratogenesis (3). The most important advantage is that it does not cause hypoglycemia. There is increasing concern about the safety of glyburide in GDM (1). Following the widespread use of glyburide in the USA, it has been observed that there is a risk of large infants according to gestational age (LGA), neonatal hypoglycemia, birth injury, and respiratory distress in infants of treated women (1,5).

Insulin: Traditionally, insulin should be started if glycemic therapy goals are not achieved within one to two weeks with lifestyle changes (5). Since insulin does not measurably cross the placenta, it is preferred and recommended first-line agent in treatment (26). It should be arranged according to the SMBG and ketone monitoring to be performed by the patient (3). Although insulin is usually started when glycemic targets are exceeded, some studies suggest that insulin should be initiated solely on the basis of fetal ultrasonographic parameters such as increased fetal abdominal circumference (8).

Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable administration strategies and neither has been shown to be superior to the other during pregnancy. Insulin requirement typically rises during the early stages of the first trimester of pregnancy, but gradually decreases within the span of 9-16 weeks. Repeated and rapidly

increasing insulin resistance after 16 weeks requires an approximately 5% weekly increase in insulin dose to achieve glycemic targets. By the end of the third trimester, the insulin requirement roughly doubles (26).

Types of insulin that can be used during pregnancy include intermediate-acting insulin (neutral protamine Hagedorn-NPH), long-acting insulin (detemir), and rapid-acting insulin analogs (lispro and aspart). It has been shown that the safety and efficacy of insulin detemir are not inferior to NPH insülin (1,5,8). Insulin detemir has been associated with less hyperglycemia and hypoglycemia than NPH insulin. Although data in regard to insulin glargine use is not sufficient yet, published cohort studies have not raised concerns about its use in pregnancy (5). Hypoglycemia is a risk factor and can develop with aggressive management of glucose levels with insulin. Patients and family members should be informed about the monitoring and treatment of hypoglycemia (1).

The total insulin dose varies between 0.7-2 IU/kg (1). In general, a smaller proportion (<50%) of the total daily dose should be given as basal insulin and a larger proportion (>50%) as postprandial insulin. Intermediate/long-acting insulin (NPH/detemir) once or twice daily or multiple-dose insulin therapy (a basal-bolus regimen using rapid-acting insulin before main meals) may be preferred (3,5).

Insulin can be discontinued immediately after birth; however, glucose monitoring should be performed for several days to exclude ongoing hyperglycemia (5).

GLYCEMIC CONTROL GOALS in PREGNANCY

Ideally, the HbA1C target in pregnancy is 6% if achievable without significant hypoglycemia; however, the target can be stretched up to 7% to prevent hypoglycemia. In the second and third trimesters, the risk of large-growth baby development, preterm birth, and preeclampsia is lowest, with a target of HbA1C ≤ 6% (26) (**Table 5**).

Table 5. Glycemic targets in pregnants

FPG	<95 mg/dL (5.3 mmol/L)
Postprandial 1-hour	<140 mg/dL (7.8 mmol/L)
Postprandial 2-hour	<120 mg/dL (6.7 mmol/L)
HbA1C	6-6.5% (42-48 mmol/mol)

FPG; FPG; fasting glucose

MATERNAL and FETAL COMPLICATIONS in GDM

It is thought that there is a relationship between adverse pregnancy outcomes, even at maternal mildly elevated glucose levels (5,8,11,25). Short- and long-term complications for the mother and fetus are shown in **Table 6** (8,16,22,25,26).

Table 6. Maternal/fetal short- and long-term complications in GDM

Maternal Complications	Fetal Complications
Hypertensive disorders Preterm birth Cesarean delivery Shoulder dystocia Preeclampsia Polyhydramnios Birth canal lacerations Metabolic comorbidities (diabetes, metabolic syndrome, cardiovascular diseases)	Neonatal hypoglycemia Hyperbilirubinemia Macrosomia Polycythemia Neonatal hypocalcemia, hypomagnesemia Respiratory distress syndrome Metabolic comorbidities (obesity, diabetes, prediabetes, hypertension, metabolic syndrome) fetal death

In the Hyperglycemia and Adverse Outcomes in Pregnancy (HAPO) study, a multicenter, multinational study, 75-g 2-hour OGTT was administered to 23,316 pregnants on 24-28s of pregnancy week (average 28 weeks) and a relationship between maternal glucose, newborn adiposity, and increased fetal insulin has been demonstrated (29). Shoulder dystocia in GDM increases the risk of perinatal death and birth trauma and makes the need for cesarean section more likely. Insulin-sensitive tissue, such as adipose tissue around the chest, shoulders, and abdomen, especially in the fetus, is overgrowth (17).

GDM carries a high risk for pyelonephritis, asymptomatic bacteriuria, and preeclampsia and has a 10% risk of polyhydramnios. Fetal risks of poor glucose control include stillbirths and macrosomia. Since glucose intolerance develops in the later stages of pregnancy, there is no increased risk for congenital anomalies (1). Hyperglycemia in pregnancy, whether associated with high birth weight or not, is associated with obesity and glucose intolerance that develops in these infants later in life (29).

There is no common consensus on the time and mode of delivery in pregnant with GDM; however, when the estimated birth weight is ≥4.5 kg, the risk of shoulder dystocia is usually significantly increased and cesarean delivery is recommended for those (25).

POSTNATAL MANAGEMENT in GDM

In GDM, insulin resistance decreases rapidly, usually within six weeks after birth, and glucose tolerance returns to normal in approximately 95% of cases (1,17). In postnatal 4-12. weeks women with GDM should be screened for prediabetes or diabetes diagnoses according to standard criteria by performing 75 g OGTT. Those women should also be screened at least every 3

years for the development of diabetes or prediabetes (3,6,26). Intensive lifestyle changes and/or metformin are recommended for women found to be prediabetic to prevent or delay diabetes (3,6,8). While the risk of progression to diabetes decreased by 35% in these women after a follow-up period of about 10 years; when metformin is added to lifestyle changes, the risk of developing DM is reduced by 40-50% (3,5). However, since metformin passes into milk during lactation, the use of metformin is not preferred except for limited indications.

There is a 7-8 times increased risk of type 2 DM development in women following GDM (11,25,27). The risk of new-onset type 2 DM increases linearly by 9.6% with each year of follow-up in those women (30). The risk of developing DM in women is 35-60% within 10 years and 50-70% after 15-20 years (11,25-27). Even in the first year after conception, approximately 20% of European women have various forms of impaired glucose metabolism. Impaired glucose tolerance does not improve after pregnancy in approximately 13-40% of cases (25).

The risk of conversion to overt diabetes is increased in women who are obese before conception, Asian women, diagnosed with GDM before 24 weeks, receiving insulin therapy, OGTT ≥200 mg/dl at the 1st hour of pregnancy, and HbA1C ≥5.7% at the diagnosis of GDM (25). Weight gain during pregnancy or postpartum is associated with an increased risk of adverse pregnancy outcomes in subsequent pregnancies and earlier progression to type 2 DM (25). FPG levels during pregnancy are also thought to be an important predictor of conversion to postpartum DM (8). The incidence of type 1 DM in risk groups 5-10 years after GDM is 2,3-10% (25).

The recurrence rate of GDM depends on the following factors; (10,12,25)

- •Parity,
- •BMI (>30 kg/m2),
- •Early diagnosis of GDM (<24 weeks),
- •Insulin requirement,
- •Weight gain of more than 3 kg between pregnancies,
- •the interval between pregnancies (<24 months),
- •In ethnic groups at high risk of diabetes (Asia, Latin America), the risk rises to 50-84% with a high FPG two months after birth.

In different studies, it has been observed that the disease occurs at a rate of 30-70% in subsequent pregnancies (10).

Epidemiological studies show that maintaining physical activity, adopting healthy dietary patterns, avoiding post-pregnancy weight gain, and frequent, prolonged and more intense breastfeeding reduce the risk of overt progression to diabetes. Breastfeeding improves weight and glucose tolerance, so it should be encouraged (8).

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Review

The Impact of Sodium-Glucose Co-Transporter-2 Inhibitors on Weight Loss in Obesity

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ABSTRACT

Obesity is a chronic medical condition characterized by excessive body fat accumulation, posing health risks. Obesity is influenced by genetic, environmental, behavioral, and socioeconomic factors, emphasizing its complexity. It is associated with numerous comorbidities, including type 2 diabetes, cardiovascular diseases, respiratory disorders, and certain cancers. Obesity management involves a multidisciplinary approach, including lifestyle modifications, behavioral therapy, pharmacotherapy, and bariatric surgery in severe cases. Studies highlight the weight loss effects of various sodium-glucose co-transporter 2 inhibitors (SGLT-2i) such as canagliflozin, dapagliflozin, and empagliflozin, in diabetic and non-diabetic obese individuals. Modest reductions in body weight have been observed, supporting the use of SGLT-2i as a weight management option. SGLT-2i, initially used for diabetes, have demonstrated additional benefits for managing obesity and related metabolic conditions. Clinical trials and real-world evidence consistently show significant weight loss in individuals treated with SGLT-2i, independent of their glucose-lowering properties. The weight loss observed is smaller than expected due to adaptive mechanisms that increase energy intake to counterbalance the loss. Combining SGLT-2i with appetite-suppressing drugs, such as GLP-1 analogs, may enhance weight reduction. However, further research is needed to optimize the weight-reducing effects and explore combination therapies. Despite these limitations, SGLT-2i remains valuable in managing obesity and offers benefits beyond glycemic control.

Keywords: Obesity, SGLT-2 inhibitors, weight loss, diabetes

INTRODUCTION

Obesity is a complex and chronic medical condition characterized by an excessive accumulation of body fat to the extent that it poses a health risk (1). It is commonly defined based on an individual's body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of their height in meters (BMI = weight (kg) / height² (m²)).

The World Health Organization (WHO) and many health organizations worldwide use the following BMI classifications to define obesity:

- •BMI < 18.5: Underweight
- •BMI 18.5 - 24.9: Normal weight
- •BMI 25.0 - 29.9: Overweight
- •BMI ≥ 30.0: Obesity

Within the obesity category, there are further classifications based on BMI:

- •Class I Obesity: BMI 30.0 - 34.9
- •Class II Obesity: BMI 35.0 - 39.9
- •Class III Obesity (also known as severe or morbid obesity): BMI ≥ 40.0

It's important to note that while BMI is a useful screening tool, it has limitations and does not provide a complete picture of an individual's health. Other factors such as body composition, distribution of fat, and metabolic health should also be considered when assessing obesity.

Obesity is influenced by a combination of genetic, epigenetic, environmental, behavioral, and socioeconomic factors (2,3). Obesity is a complex condition influenced by various factors, and not solely a result of personal choices or lack of willpower.

Obesity has significant health implications and is associated with an increased risk of various comorbidities, including:

- •Type 2 diabetes
- •Cardiovascular diseases (e.g., hypertension, heart disease, stroke)
- •Respiratory disorders (e.g., sleep apnea, asthma)

•Musculoskeletal conditions (e.g., osteoarthritis)
•Certain cancers (e.g., breast, colorectal, prostate)
•Metabolic syndrome
•Non-alcoholic fatty liver disease
•Mental health issues (e.g., depression, anxiety)
•Reproductive disorders (e.g., polycystic ovary syndrome)

Obesity management involves a multidisciplinary approach that includes lifestyle modifications (such as adopting a healthy diet and increasing physical activity), behavioral therapy, pharmacotherapy, and, in severe cases, bariatric surgery. Successful management of obesity aims to improve overall health, reduce the risk of obesity-related complications, and enhance the quality of life for individuals affected by this condition. Moreover, clinicians must stay updated, especially regarding weight loss pharmacotherapies, before referring to an invasive intervention since bariatric interventions bear more complications compared to pharmacological interventions.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors (SGLT-2i) are a class of medications that inhibit sodium glucose co-transporter-2 protein localized in the brush border on S2 and S3 segments of proximal renal tubules and primarily used for the management of type 2 diabetes (4,5). SGLT-2i increase the excretion of glucose through urine, thereby lowering blood glucose levels (6). While initially developed for diabetes treatment, SGLT-2i have shown additional benefits beyond glycemic control. In recent years, they have gained attention for their potential use in managing obesity and related metabolic conditions (6,7).

Clinical trials and real-world evidence have consistently demonstrated significant weight loss in individuals treated with SGLT-2i (7,8). The weight loss is attributed to multiple factors, including calorie loss through glucosuria (glucose excretion in urine), reduction in fat mass, and decreased visceral adiposity. The weight loss effects are independent of the glucose-lowering properties of these medications, making them a valuable option for individuals with obesity, even in the absence of diabetes (8,9). Previous studies demonstrated some oral antidiabetics, as SGLT-2i can, result in weight loss.

•SGLT-2i: As mentioned earlier, SGLT-2i, such as canagliflozin, dapagliflozin, and empagliflozin, have been consistently associated with weight loss. These medications increase urinary glucose excretion, leading to calorie loss and reductions in fat mass (7-9).

•GLP-1 receptor agonists: While GLP-1 receptor agonists are usually administered via injection, there is an oral formulation available (semaglutide). GLP-1 receptor agonists, such as exenatide, liraglutide, and semaglutide, have been shown to promote weight loss. They work by slowing gastric emptying, increasing satiety, and reducing appetite (10-11).

•Metformin: Recent studies have provided emerging evidence supporting the notion that metformin-induced weight loss can be attributed to various mechanisms, including the modulation of hypothalamic appetite-regulatory centers, alterations in the gut microbiome, and the reversal of age-related effects. Furthermore, metformin is being investigated for its potential role in managing the complications associated with obesity, such as hepatic steatosis, obstructive sleep apnea, and osteoarthritis (12,13).

STUDIES ADDRESSING WEIGHT LOSS EFFECTS OF SGLT-2I IN DIABETIC AND NON-DIABETIC OBESE INDIVIDUALS

Weight Loss in SGLT-2i Studies

Weight loss effects of SGLT-2i were observed in many studies (14). The leading trials were listed below regarding this topic:

•The EMPA-REG OUTCOME trial: This landmark trial evaluated empagliflozin in patients with type 2 diabetes and established cardiovascular disease. It demonstrated significant weight loss in patients treated with empagliflozin compared to those receiving a placebo, with an average weight reduction of approximately 2 kg (15).

•The CANVAS Program: This study investigated the effects of canagliflozin in patients with type 2 diabetes and a high risk of cardiovascular events. It revealed that canagliflozin was associated with weight loss, with participants experiencing an average weight reduction of about 2-3 kg compared to the placebo group (16).

•Dapagliflozin trials: Various clinical trials, including the DECLARE-TIMI 58 trial, have shown that dapagliflozin leads to modest weight loss in patients with type 2 diabetes. The weight reduction observed in these trials ranged from approximately 1-2 kg (17,18).

•Real-world evidence: Several real-world studies have corroborated the findings from clinical trials, demonstrating weight loss in individuals using SGLT-2i. These studies have shown weight reductions ranging from 1-5 kg over varying durations of treatment (5,19).

Weight Loss With SGLT-2i in Patients with Obesity

The results of many studies demonstrated reductions in body weight compared to placebo for all SGLT-2i treatments of approximately 1.5–2 kg, and these effects are probably dose-dependent (20). Bays et al. reported that in overweight and obese subjects without diabetes mellitus, canagliflozin significantly

reduced body weight compared with placebo and was generally well tolerated (8). Bays et al., in a recent study, demonstrated that licogliflozin (a dual inhibitor of sodium/glucose co-transporter 1 and 2) produced significant reductions in body weight versus placebo in adults with overweight or obesity. However, the magnitude of weight reduction was modest (21). They suggested that the 50-mg once-daily dose had perhaps the best balance between efficacy and tolerability. He et al. reported similar results with licogliflozin use in obese patients with or without diabetes (22). Hollander et al. studied the coadministrations of canagliflozin and phentermine in phase 2a, a randomized, double-blind, placebo-controlled, multicenter, parallel-group study. Phentermine is a sympathomimetic amine anorectic that plays a role in stimulating the satiety centers in the brain through the upregulation of dopamine, noradrenaline, and serotonin. They highlighted that canagliflozin and phentermine produced meaningful reductions in body weight and were generally well tolerated in individuals who were overweight or obese without type 2 diabetes (23) (**Table 1**). Dapagliflozin/exenatide dual therapy reduced body weight (≥5% body weight loss) and frequency of prediabetes and was well tolerated in obese adults without diabetes (24). Dapagliflozin administration in patients with prediabetes with mild obesity (BMI; 30.3±3.5 kg/m2) decreased body weight, BMI, waist circumference, fasting glucose, and uric acid, with a tendency to increase insulin sensitivity without changes in insulin secretion (25).

There is an ongoing discussion and varying perspectives regarding the use of SGLT-2i for the purpose of weight reduction. Ferrannini et al. found that SGLT-2i used alone results in a disproportionate decrease in body weight due to their glucosuric effects. However, the weight loss observed with SGLT-2i is smaller than expected based solely on their ability to increase urinary glucose excretion. This may be due to the body's adaptive mechanism of increasing energy intake to counterbalance weight loss. According to Ferrannini et al., the human body may have developed an enhanced appetite as a way to stabilize body weight in response to the weight loss effects of SGLT-2i. This concept is supported by other researchers. As a result, there is growing interest in combining SGLT-2i with appetite-suppressing drugs that act on the hypothalamus, such as GLP-1 analogs (26,27). Additionally, a recent meta-analysis including 116 randomized-controlled trials reported that compared with SGLT-2i, SGLT-1/SGLT-2 inhibitors had a significantly larger reduction in weight (28). The summary of a few studies highlighting the outcomes of SGLT-2i use on weight change is given in **Table 1**.

CONCLUSION

The studies included in this review suggest that SGLT-2i are effective as a weight loss therapy in patients with obesity with or without diabetes mellitus. These

Table 1. Several studies are available for revealing favorable outcomes of SGLT-2 inhibitor use for weight reduction.

Study	Study Design	Participants	Outcomes
Licogliflozin, a Novel SGLT-1 and 2 Inhibitor: Body Weight Effects in a Randomized Trial in Adults with Overweight or Obesity (2020) (21)	RCT, 24 weeks, PBO vs licogliflozin (once daily or twice daily)	N=674, adults with overweight or obesity	≥5% weight loss at week 24 revealed significant differences versus placebo, which were most pronounced with highest doses of 50 mg twice daily.
Coadministration of Canagliflozin and Phentermine for Weight Management in Overweight and Obese Individuals Without Diabetes: A Randomized Clinical Trial (2017) (23)	RCT, 26 weeks, phase 2a PBO vs CANA 300 mg	N=335, obeses or overweight without type 2 diabetes	≥%5 weight loss and superior SBP reduction with CANA
Dapagliflozin once daily plus exenatide once weekly in obese adults without diabetes: Sustained reductions in body weight, glycaemia and blood pressure over 1 year (2017) (24)	RCT, 52 weeks, DAPA+Exenatide vs PBO	N=50, obese adults without diabetes	-5.7 kg weight change with treatment, -5.3 kg total body fat, -12 mmHg SBP
Effect of Dapagliflozin on Insulin Secretion and Insulin Sensitivity in Patients with Prediabetes (2018) (25)	RCT, 12 weeks, DAPA vs PBO	N=24, prediabetes with mean BMI 30.3 kg/m^2	BMI, WC, FG, UA reduction with DAPA
Sodium-Glucose Co-Transporter-2 Inhibitors in Non-Diabetic Adults With Overweight or Obesity: A Systematic Review and Meta-Analysis (2021) (29)	Systematic review and meta-analysis of 6 RCTs Various SGLT-2i types	N=872, adults with overweight or obesity without diabetes	-1.42 kg BW, -0.47 BMI with SGLT-2i

SGLT-2; Sodium-glucose co-transporter 2, RCT; randomized controlled trial, PBO; placebo, CANA; canagliflozin, SBP; systolic blood pressure, BMI; body mass index, WC; waist circumference, FG; fasting glucose, UA; uric acid, SGLT-2i; Sodium-glucose co-transporter 2 inhibitor, BW; body weight

medications promote weight loss by facilitating glucose excretion through urine which leads to a loss of about 300 calories per day. However, the body can adapt to this condition by increasing appetite and calorie intake, resulting in less weight loss than initially expected. Since this adaptive response may partially attenuate the weight-reducing effects of SGLT-2i, combining a GLP-1 agonist with SGLT-2i will improve the weight-reduction strategy. Nonetheless, SGLT-2i remains a valuable option for weight management in individuals with obesity, and its benefits extend beyond glycemic control.

DECLARATIONS

Ethics Committee Approval: Not necessary.

Informed Consent Form: Not necessary.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: Authors declare no conflict of interest.

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Case Report

Canakinumab For The Treatment of Amyloidosis Secondary to Lung Cancer

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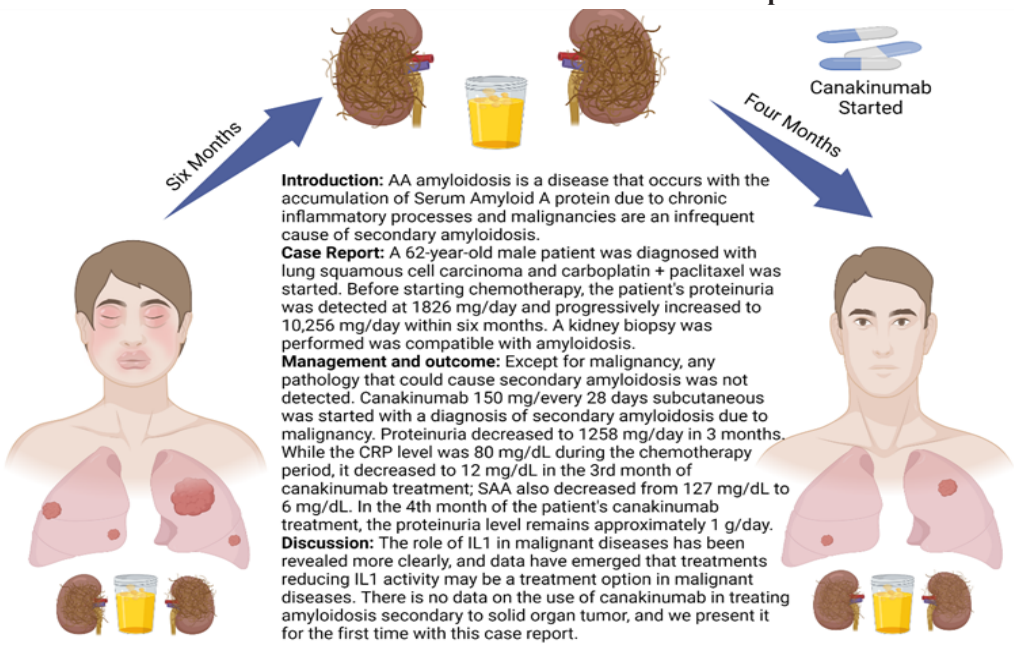

ABSTRACT

AA amyloidosis is a disease that occurs with the accumulation of Serum Amyloid A protein due to chronic inflammatory processes. Malignancies are an infrequent cause of secondary amyloidosis; therefore, there is not much data on the treatment of amyloidosis in these patients. We present a 62-year-old male patient was diagnosed with AA amyloidosis secondary to lung squamous cell carcinoma and successfully treated with canakinumab. Ramipril was started for the patient because of the 2 gram/day proteinuria at the time of lung cancer diagnosis. However, in the follow-ups, the proteinuria increased to 10 g/day, and the kidney biopsy was compatible with amyloidosis. Canakinumab (150 mg every 28 days) treatment was started, and proteinuria regressed below 1 g/day in 3 months. As the role of IL 1 in malignant diseases has become clear, data have emerged suggesting that treatments reducing IL 1 activity may be a treatment option in these diseases. There is no data on the use of canakinumab in treating amyloidosis secondary to solid organ tumor, and we present this usage for the first time with this case report.

Keywords: Amyloidosis, canakinumab, inflammation, lung cancer, proteinuria

INTRODUCTION

Amyloidoses are characterized by misfolded polypeptides in which proteins acquire an alternative and relatively misfolded state at subsequent aggregate. AA amyloidosis (secondary amyloidosis) is a disease characterized by deposition of serum amyloid A-derived fibrils as a result of chronic inflammation. The main goal of treatment is the treatment of the underlying chronic inflammatory disease (1).

The most prominent pro-inflammatory activities of A-SAA include the induction of the synthesis of IL-1α, pro-IL-1β and IL-6 (2). Canakinumab is a monoclonal

antibody to interleukin-1 (IL-1β) beta, often used to treat autoinflammatory diseases. Canakinumab has been used in treating secondary amyloidosis in various patient groups, such as colchicine-resistant familial Mediterranean fever or rheumatoid arthritis. It has been shown to provide effective control of the underlying inflammatory condition (3,4).

To our knowledge, this is the first case to demonstrate the success of the IL-1 antagonist canakinumab in reducing proteinuria in treating secondary amyloidosis in a patient with a solid organ tumor.

CASE

A 62-year-old male patient with no known comorbidity was diagnosed with lung squamous cell carcinoma ten months ago. Carboplatin + paclitaxel treatment was started in the patient with liver and bone metastases. The treatment was changed to nivolumab (200 mg/2 weeks) due to the progression of the disease in the fourth month of treatment. Before starting chemotherapy, the patient's kidney function tests were normal, but proteinuria was detected at 1826 mg/day, and ramipril 2.5 mg/day was started due to proteinuria. At that time, no further research was conducted on the etiology of proteinuria. Follow-up revealed that proteinuria progressively increased to 10,256 mg/day within six months. A kidney biopsy was performed for the etiology of nephrotic syndrome, and the biopsy result was compatible with amyloidosis. Positive expression was also detected in AA amyloid staining by immunohistochemical analysis. On physical examination, the patient's blood pressure was 90/50 mmHg, and there was no skin lesion or rash suggestive of vasculitis. Laboratory tests, including anti-nuclear antibodies (ANA), anti-dsDNA, anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF), and serum complement 3 and 4 (C3-C4) levels, were normal. Hepatitis serology was negative, and serum and urine protein electrophoresis did not reveal any pathology suggestive of plasma cell dyscrasias. Serum urea was 12 mg/dL, and creatinine was 0.68 mg/dL. Except for malignancy, no pathology that could cause secondary amyloidosis was detected. Canakinumab 150 mg/every 28 days subcutaneous therapy was started with a preliminary diagnosis of secondary amyloidosis due to malignancy. Nivolumab treatment continued with canakinumab for three months. During follow-up, proteinuria decreased to 1258 mg/day in 3 months. While the CRP level was 80 mg/dL during the chemotherapy period, it decreased to 12 mg/dL in the 3rd month of canakinumab treatment, while SAA decreased from 127 mg/dL to 6 mg/dL. During these three months, the patient required antibiotic treatment, once for a urinary tract infection and once for bacterial pneumonia. Both infections were not life-threatening. The computer tomography taken at the end of the treatment showed regression of the disease compared to before. At the 4th month of the patient's canakinumab treatment, the proteinuria level remains approximately 1 g/day.

DISCUSSION

IL-1 cytokines play critical roles in cancer development and progression, both in the tumor microenvironment and in systemic immune surveillance. It has been shown that IL1 inhibition, especially in the early stages of malignant development, provides a more potent suppressive effect on malignant cells (5). Inflammatory pathways play an essential role in tumor development and tumor progression (6). The development of amyloidosis due to chronic inflammatory conditions is also frequently encountered. Canakinumab is a monoclonal antibody to interleukin-1 (IL-1 β) beta, frequently used in secondary amyloidosis treatment (3,4). To our knowledge, no other patient in the literature canakinumab was used to treat amyloidosis secondary to solid organ tumor.

There is concern over the use of canakinumab in malignant patients, as it may cause both immunosuppressive effects and malignancy progression. However, the role of IL-1β in the development of malignancy has been revealed by numerous studies in recent years, so studies on its use in malignant patients in treatments targeting IL-1β have increased (6). The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) showed that canakinumab significantly reduced the incidence of lung cancer development in patients with high inflammatory condition (7,8).

The common point of the studies that tried the efficacy of canakinumab in patients with lung cancer is the role of IL-1β in developing malignant cells. For this reason, it is reasonable to use canakinumab, a frequently tried treatment option in malignant patients due to its anti-inflammatory properties, to treat amyloidosis secondary to malignancy. In our patient, inflammation markers (Hs-CRP and ESR) were persistently high during chemotherapy and immunotherapy periods, and decreased rapidly after canakinumab treatment. During the 3 months of canakinumab treatment, the patient encountered two opportunistic infections that could be treated with oral antibiotics, but a severe infective pathology was not encountered. The patient's malignant disease process also regressed.

Although studies investigating the use of canakinumab in malignant diseases have obtained contradictory results, the relationship between malignant diseases and canakinumab continues to attract attention (9,10). In addition to the fact that our case was the first case of amyloidosis secondary to malignancy that responded to canakinumab treatment, the significant improvement in the malignant disease process after the combined use of

nivolumab and canakinumab also gives an idea about the anti-tumor efficacy of canakinumab.

CONCLUSION

In recent years, the role of inflammatory processes in the development of solid and hematological tumors has attracted attention, and treatment agents targeting these inflammatory processes have been tried in many studies. We think that canakinumab should be kept in mind as a treatment agent that can be used if amyloidosis is detected secondary to increased chronic inflammation in patients with malignant tumors.

DECLARATIONS

Ethics Committee Approval Number: Not necessary

Informed Consent: Informed consent was taken from the patient.

Referee Evaluation Process: Externally peer-reviewed

Conflict of Interest Statement: The authors declare that they have no potential conflict of interest relevant to this article.

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