DAHUDER MEDICAL JOURNAL

e-ISSN: 2791-9250 Volume 4 Issue 4

29 EKİM 2024 CUMHURİYETİMİZİN 101. YILI

DAHUDER Medical Journal

https://dergipark.org.tr/tr/pub/dahudermj

e-ISSN:2791-9250

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The journal is published quarterly (January, April, July, and October).

No fee is required for publishing the manuscipt.

All articles are detected for similarity.

Abstracting & Indexing

The journal is abstracted and indexed with the following: Google Scholar, ResearchGate, CrossRef, DRJI, ResearchBib, Asos Index, ROAD, and OUCI.

Publisher

The Association of Internal Medicine Specialist (DAHUDER)

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DAHUDER
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Impact of obesity severity on hepatic steatosis and systemic inflammatory markers: a comparative analysis across obesity classes

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ABSTRACT

Objectives: Obesity has become a global health issue, with its prevalence steadily increasing. It is closely linked to several metabolic disorders, cardiovascular diseases, non-alcoholic fatty liver disease, and chronic low-grade inflammation and can progress to more severe liver conditions. This study evaluates the relationship between obesity and inflammatory markers in individuals with different obesity levels.

Methods: A cross-sectional study was conducted among 50 patients categorized into three obesity classes based on body mass index (BMI). Blood samples were taken to evaluate inflammatory and metabolic markers, including white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP). Results: There were no statistically significant differences in inflammatory markers such as WBC, NLR, or CRP; a trend toward higher CRP levels was observed in Class 3 obesity.

Conclusion: In our study, no statistically significant association was observed between inflammatory markers and the degree of obesity. Although the sample size was relatively small, it is essential to acknowledge that obesity is a multifaceted condition, and genetic variations may play a role in these results.

Keywords: Obesity, inflammation, the neutrophil-to-lymphocyte ratio, the C-reactive protein

Obesity is a global health concern, with its prevalence continuing to rise significantly over the past decades. Obesity is strongly associated with metabolic complications such as type 2 diabetes mellitus (T2DM), cardiovascular diseases, and hepatic steatosis, mainly non-alcoholic fatty liver disease (NAFLD). Hepatic steatosis, which refers to the excessive accumulation of fat in the liver, often manifests as part of the metabolic syndrome in obese individuals. The pathogenesis of NAFLD is multifactorial, mainly driven by insulin resistance, central obesity, and systemic inflammation, which contributes to the progression of simple steatosis to more severe liver conditions such as non-alcoholic steatohepatitis (NASH) and cirrhosis.[1, 2]

Chronic low-grade inflammation plays a crucial role in obesity-related metabolic dysfunction and the development of hepatic steatosis. Several inflammatory markers, including C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII), have been identified as critical indicators of metabolic dysregulation in obese individuals. Recent studies have demonstrated a strong association between elevated inflammatory

Received: *October 17, 2024;* ***Accepted:*** *October 25, 2024;* ***Published Online:*** *October 29, 2024*

How to cite this article: *Uyar S, N Koca, Oral A, Zorlu Görgülügil G. Impact of obesity severity on hepatic steatosis and systemic inflammatory markers: a comparative analysis across obesity classes. DAHUDER MJ 2024,4(4):77-82. DOI: 10.56016/dahudermj.1567959*

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Available at http://dergipark.org.tr/en/pub/dahudermj

markers and both hepatic steatosis and cardiovascular risk in obese populations.[1, 3]

The relationship between obesity, inflammation, and liver health is of increasing interest due to the rising incidence of NAFLD in parallel with the obesity epidemic. Emerging evidence suggests that central obesity and insulin resistance are primary drivers of both hepatic fat accumulation and systemic inflammation, contributing not only to liver disease but also to an increased risk of cardiovascular morbidity and mortality.[2, 4]

This study aims to explore the differences in demographic, metabolic, and inflammatory profiles among individuals with varying degrees of obesity and hepatic steatosis, providing further insights into the interplay between obesity-related inflammation and liver health.

METHODS

Study Design and Population

This cross-sectional study evaluated and compared demographic characteristics and laboratory parameters among 50 patients with Class 1, Class 2, and Class 3 obesity. The study population consisted of individuals who presented to the outpatient clinic for routine health examinations and were diagnosed with obesity based on their body mass index (BMI) values. The inclusion criteria were adults aged 18 and older with a BMI ≥30 kg/m². Patients with any history of chronic liver disease, active infection, autoimmune disorders, or malignancy were excluded from the study.

Obesity Classification

Obesity was classified according to BMI into three categories: Class 1 (BMI 30.0–34.9 kg/m²), Class 2 (BMI 35.0–39.9 kg/m²), and Class 3 (BMI ≥40.0 kg/m²). These classes are consistent with the World Health Organization (WHO) criteria for obesity stratification.[5]

Data Collection

Demographic data, including age, gender, height, weight, and waist circumference, were collected through patient interviews and physical examinations. BMI was calculated by dividing the patient's weight (in kilograms) by the square of their height (in meters). Hepatic steatosis was assessed by ultrasound and graded into three categories: Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe) steatosis.

Laboratory Measurements

Blood samples were collected after an overnight fast to assess various laboratory parameters. The following parameters were measured using standard automated techniques:

- **White blood cell (WBC) count, neutrophil (Neu) count**, and lymphocyte (Lymph) count were measured as indicators of systemic inflammation.
- **Hemoglobin (Hb) and platelet (Plt)** counts were assessed to evaluate hematologic status.
- **Fasting blood glucose (FBG), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)** were evaluated as markers of metabolic and liver function.
- **Thyroid-stimulating hormone (TSH)** levels were measured to assess thyroid function.
- **The neutrophil-to-lymphocyte ratio (NLR),** a marker of systemic inflammation, was calculated by dividing the neutrophil count by the lymphocyte count.
- **C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)** were measured as additional inflammatory markers.
- The **FIB-4 index,** an indicator of liver fibrosis, was calculated using the formula:

$$\text{FIB-4} = (\text{age} \times \text{AST}) / (\text{platelet count} \times \sqrt{\text{ALT}})$$

Ethical Consideration

This study followed the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Antalya Training & Research Hospital Institutional Review Board (IRB) before the initiation of the study (2024-15/21). The confidentiality and privacy of participants were strictly maintained, and all data were anonymized before analysis to ensure participant protection. Additionally, the study adhered to all local and national guidelines for human research ethics.

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation (SD) or median (range) for continuous variables and as frequencies (percentages) for categorical variables. The normality of distribution was assessed using the Shapiro-Wilk test. Comparisons between the three obesity classes were performed using one-way analysis of variance (ANOVA) for normally distributed continuous variables and the Kruskal-Wallis test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

A p-value <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS (version 26).

RESULTS

Demographic Comparison Among Obesity Classes

The comparison of demographic characteristics among patients with Class 1, Class 2, and Class 3 obesity is summarized in Table 1. There was no significant difference in age among the three obesity classes (47.42±9.94 vs. 52.47±12.52 vs. 48.09±8.43, p=0.331). Additionally, the gender distribution did not differ significantly between the groups, with a female predominance observed in all classes (62.5% vs. 46.7% vs. 63.6%, p=0.567).

Participants' height was also comparable across obesity classes (166.38±9.9 cm vs. 164.33±8.89 cm vs. 164.09±8.4 cm, p=0.718). However, there were notable differences in weight, with individuals in Class 3 obesity having significantly higher body weight compared to those in Class 1 and Class 2 obesity (93.42±29.33 kg vs. 98.47±12.55 kg vs. 115.73±15.74 kg, p<0.001).

Waist circumference showed a progressive increase with increasing obesity class, significantly more prominent in Class 3 compared to the other two groups (110.54±8.73 cm vs. 115.6±7.47 cm vs. 126.45±4.89 cm, p<0.001). Similarly, BMI increased significantly across the obesity classes (32.08±1.3 kg/m² vs. 36.33±1.33 kg/m² vs. 43.3±2.14 kg/m², p<0.001).

Regarding hepatic steatosis, there was a statistically significant difference among the classes, with higher grades of steatosis being more prevalent in Class 3 obesity (Grade 1: 50% vs. 40% vs. 9.1%; Grade 2: 37.5% vs. 46.7% vs. 27.3%; Grade 3: 12.5% vs. 13.3% vs. 63.6%, p=0.010).

Laboratory Parameter Comparison Among Obesity Classes

The comparison of laboratory parameters across the different obesity classes is summarized in Table 2. No statistically significant differences were observed in WBC count among the three classes (8.73±2.6 vs. 8.45±3.67 vs. 8.63±2.95 cells/µL, p=0.776). Similarly, the neutrophil count showed no significant variation (5.17±2.09 vs. 4.75±2.43 vs. 5.22±2.01 cells/µL, p=0.522), nor did the lymphocyte count (2.66±0.71 vs. 2.77±1.03 vs. 2.5±0.72 cells/µL, p=0.835).

Table 1. The comparison of demographics among the obesity classes

	Class 1 Obesity (n=24)		Class 2 Obesity (n=15)		Class 3 Obesity (n=11)		*p*
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
Age	47.42±9.94	47.5(30-68)	52.47±12.52	55(24-72)	48.09±8.43	48(31-62)	0.331*
Gender, n (%)							0.567
Female		15 (62.5)		7 (46.7)		7 (63.6)	
Male		9 (37.5)		8 (53.3)		4 (36.4)	
Height, cm	166.38±9.9	165(150-184)	164.33±8.89	164(150-182)	164.09±8.4	164(155-183)	0.718*
Weight, kg	93.42±29.33	91.5(70-220)	98.47±12.55	99(80-130)	115.73±15.74	109(102-156)	<0.001
Waist Circumference, cm	110.54±8.73	112.5(95-128)	115.6±7.47	114(104-131)	126.45±4.89	128(119-133)	<0.001*
BMI, kg/m^2	32.08±1.3	31.9(30.1-34.9)	36.33±1.33	35.8(35-39.2)	43.3±2.14	43,7(40,2-46,6)	<0.001
Steatosis, n (%)							0.010
Grade 1		12 (50)		6 (40)		1 (9.1)	
Grade 2		9 (37.5)		7 (46.7)		3 (27.3)	
Grade 3		3 (12.5)		2 (13.3)		7 (63.6)	

BMI: body mass index
*: one-way ANOVA

The levels of Hb were consistent across the obesity classes (13.46±2 vs. 13.85±1.69 vs. 13.85±1.05 g/dL, p=0.727), as were Plt counts (291.75±70.09 vs. 287.27±74.91 vs. 271.55±90.09 cells/µL, p=0.766).

While FBG values varied among the obesity classes, these differences were not statistically significant (124.75±64.32 vs. 93.93±20.36 vs. 104.28±46.44 mg/dL, p=0.577). The liver enzymes AST and ALT also did not show significant differences among the groups (AST: 20.63±8.28 vs. 21.2±12.11 vs. 25.82±16.89 IU/L, p=0.678; ALT: 25.71±16.2 vs. 26.33±24.58 vs. 26.55±9.36 IU/L, p=0.304).

Regarding thyroid function, no significant difference was noted in TSH levels between the obesity classes (3.04±2.34 vs. 2.03±1.29 vs. 11.42±32.04 mIU/L, p=0.422). The NLR, an important marker of inflammation, showed no significant variation across classes (2.02±0.82 vs. 1.78±0.65 vs. 2.17±0.8, p=0.481).

Although CRP levels tended to increase with higher obesity class, especially in Class 3 (5.83±4.22 vs. 6.73±4.49 vs. 11.76±9.65 mg/L), this trend did not reach statistical significance (p=0.218). Similarly, the ESR comparison across the classes did not reveal any significant differences (16.61±10.56 vs. 18.13±10.18 vs. 13.43±8.98 mm/h, p=0.505).

Lastly, the FIB-4 index, a marker of liver fibrosis, was not significantly different among the obesity classes (0.72±0.32 vs. 0.74±0.33 vs. 1.06±0.72, p=0.367).

Table 2. The comparison of laboratory parameters among the obesity classes

	Class 1 Obesity (n=24)		Class 2 Obesity (n=15)		Class 3 Obesity (n=11)		*p*
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
WBC, cells/mL	8.73±2.6	7.8(5.1-14.1)	8.45±3.67	7.6(5.7-20.5)	8.63±2.95	8.4(5.1-15.9)	0.776
Neu, cells/mL	5.17±2.09	4.52(2.66-9.8)	4.75±2.43	4.03(2.71-12.39)	5.22±2.01	5.12(2.95-10.46)	0.522
Lymph, cells/mL	2.66±0.71	2.56(1.24-3.85)	2.77±1.03	2.59(1.27-5.78)	2.5±0.72	2.5(1.05-3.61)	0.835
Hb, g/dL	13.46±2	13.2(9.4-17.2)	13.85±1.69	13.6(10.5-17.3)	13.85±1.05	14.1(12.1-15.9)	0.727*
Plt, cells/mL	291.75±70.09	279(188-436)	287.27±74.91	261(178-421)	271.55±90.09	235(181-475)	0.766*
FBG, mg/dL	124.75±64.32	97.5(70-323)	93.93±20.36	90(53-130)	104.28±46.44	102(3.1-191)	0.577
AST, IU/L	20.63±8.28	19(10-50)	21.2±12.11	19(12-64)	25.82±16.89	19(15-74)	0.678
ALT, IU/L	25.71±16.2	20(9-84)	26.33±24.58	21(9-113)	26.55±9.36	24(16-48)	0.304
TSH, mIU/L	3.04±2.34	2.95(0.62-11)	2.03±1.29	1.86(0.29-4.6)	11.42±32.04	1.6(0.8-108)	0.422
N/L Ratio	2.02±0.82	1.87(1.03-3.92)	1.78±0.65	1.61(0.81-3.23)	2.17±0.8	1.91(1.34-4.1)	0.481
CRP, mg/L	5.83±4.22	6.4(0.9-20.4)	6.73±4.49	7(1.2-16.9)	11.76±9.65	8.7(1.3-27.2)	0.218
ESR, mm/h	16.61±10.56	16.37(3-45)	18.13±10.18	19(2-35)	13.43±8.98	13(2-27)	0.505
FIB4 Score	0.72±0.32	0.65(0.31-1.45)	0.74±0.33	0.79(0.15-1.38)	1.06±0.72	0.89(0.38-2.89)	0.367

WBC: white blood cells, Neu: Neutrophils, Lymph: lymphocyte, Hb: hemoglobin, Plt: platelets, PBG: fasting blood glucose, AST: aspartate aminotransferase, ALT: alanine aminotransferase, N/L Ratio: neutrophils/Lymphocyte Ratio, CRP: c-reactive protein, ESR: erythrocyte sedimentation rate, FIB4: index for liver fibrosis
*: one-way ANOVA

DISCUSSION

In this study, we observed significant differences in both demographic and laboratory parameters among the three obesity classes. Specifically, higher obesity classes were associated with significantly increased body weight, waist circumference, and BMI, reflecting greater central adiposity. Notably, the prevalence of severe hepatic steatosis (Grade 3) increased significantly with higher obesity classes, indicating a strong relationship between adiposity and liver fat accumulation.

Obesity is strongly linked with heightened inflammatory activity, a relationship that can become detrimental over time. Chronic inflammation can trigger maladaptive immune responses, leading to tissue damage, including fibrosis and necrosis. This prolonged inflammatory state may ultimately result in organ dysfunction or failure.[6] A study conducted in the United States identified a positive association

between obesity and two specific inflammatory biomarkers: the systemic immune-inflammation index (SII) and the systemic inflammation response index (SIRI). These findings suggest that as obesity increases, so does the activity of these inflammatory markers, reinforcing the link between excess body weight and systemic inflammation.[1] Research has consistently demonstrated that as adipose tissue expands, it releases pro-inflammatory cytokines, contributing to chronic low-grade inflammation. This inflammatory state is linked to various metabolic disorders and contributes to the progression of obesity-related complications, such as insulin resistance and cardiovascular diseases. Another study demonstrated that as BMI increased, there was a corresponding rise in WBC, neutrophil, and lymphocyte counts. However, these elevated values decreased after weight loss, suggesting a link between obesity and heightened inflammatory activity, which can be mitigated by reducing body weight.[7]

However, many studies indicate that the correlation between obesity and inflammatory markers is inconsistent. In a survey conducted by Bahadır *et al*., a positive correlation was found between the degree of obesity and specific inflammatory markers, including WBC, lymphocyte, and CRP. However, the study did not observe any significant relationship between the levels of neutrophils and the NLR, suggesting that not all inflammatory markers increase consistently with obesity levels.[8] In a study conducted in Iran, a comparison was made between patients with metabolic syndrome and those without it. The results showed no significant difference in the NLR between the two groups, indicating that NLR may not be a distinguishing factor in the presence or absence of metabolic syndrome.[9]

In our study, while there were no significant differences in inflammatory markers such as WBC, NLR, or CRP levels, trends toward higher CRP levels in Class 3 obesity suggest a potential increase in systemic inflammation. The variation in findings between studies on the association between the degree of obesity and inflammatory markers suggest that the degree of obesity does not uniformly result in heightened levels of inflammation. In some cases, inflammatory markers remain stable or show minimal variation. This variability may be due to differences in individual metabolic responses, genetic predispositions, or varying degrees of adipose tissue activity across different populations.[10] Our study's limited number of patients may account for this discrepancy, and we recognize this as a potential limitation of our research. A larger sample size could have provided more robust data and increased the generalizability of our findings.

CONCLUSION

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Antalya Training & Research Hospital (IRB). (Decision number: 2024-15/21).

Authors' Contribution

Study Conception: SU, GZG; Study Design: NK; Supervision; AO; Materials: NK; Data Collection and/or Processing: GZG; Analysis and/or Data Interpretation: SU, GZG; Literature Review: SU; Critical Review: AO, NK; Manuscript preparing: SU.

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Original Article
Internal Medicine
DOI: 10.56016/dahudermj.1561401

DAHUDER
Medical Journal
e-ISSN: 2791-9250

Evaluation of patients with hepatic cirrhosis due to etiology for the complication

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ABSTRACT

Objectives: Hepatic cirrhosis is a disease with high mortality. The leading causes of morbidity and mortality in patients with hepatic cirrhosis are disease-associated complications. We aimed to describe the association between the difference in laboratory parameters, complications, and commonly known causes of cirrhosis, such as hepatitis B, hepatitis C, alcoholic liver disease (NASH), and autoimmune hepatitis.

Methods: We investigated 541 patients with different etiologies of cirrhosis who applied to a gastroenterology clinic from 2009 to 2018 in Florance Nightingale Hospital. All patients were divided into five groups according to the etiology of cirrhosis, such as hepatitis B, hepatitis C, alcoholic liver disease (ALD), NASH, and autoimmune hepatitis. Biochemical and metabolic parameters were evaluated between five groups.

Results: 83 patients with alcoholic liver disease, 242 patients with hepatitis B-associated cirrhosis, 112 patients with hepatitis C-associated cirrhosis, 77 patients with NASH, and 27 patients with autoimmune hepatitis were enrolled. Laboratory parameters due to the etiology of hepatic cirrhosis are shown in Table 2. Ascites and hepatic encephalopathy were statistically higher in alcoholic liver disease, hepatitis B, and NASH cirrhosis, while esophageal variceal bleeding was higher in NASH and autoimmune hepatitis. Spontaneous bacterial peritonitis was statistically higher only in cirrhosis due to autoimmune hepatitis.

Conclusion: It is very important to assign complications that may develop in liver cirrhosis and manage them by etiology.

Keywords: Cirrhosis, Mortality, Etiology

Cirrhosis is the late stage of progressive hepatic fibrosis caused by various liver diseases. It is the 11th most common cause of death and accounts for 3.5% of all-cause mortalities.[1] There are many causes of liver disease which can result in cirrhosis. The epidemiology of liver cirrhosis can be different with socioeconomic conditions. The significant causes of cirrhosis in European and American countries are chronic hepatitis C and alcoholic liver disease.[2-3] Chronic hepatitis B is the primary etiology of cirrhosis in Turkey.[4] Chronic hepatitis C, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), and autoimmune hepatitis are the other causes of cirrhosis in Turkey.

The clinical manifestations of cirrhosis include nonspecific symptoms such as weight loss, weakness, fatigue, and complications of hepatic decompensation such as esophageal varices bleeding, ascites, and confusion due to hepatic encephalopathy. Laboratory abnormalities can be elevated serum bilirubin, abnor-

Received: *October 4, 2024****; Accepted:*** *October 28, 2024****; Published Online:*** *October 29, 2024*

How to cite this article: *Çavuşoğlu Türker B, Şahin T, Türker F. Evaluation of patients with hepatic cirrhosis due to etiology for the complication. DAHUDER MJ 2024,4(4):83-88. DOI: 10.56016/dahudermj.1561401*

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mal aminotransferases, elevated alkaline phosphatase/gamma-glutamyl transpeptidase, a prolonged prothrombin time/elevated international normalized ratio (INR), hyponatremia, hypoalbuminemia, and thrombocytopenia.

Laboratory parameters and complications can be different depending on the etiology of cirrhosis. Therefore, we aimed to describe the association between the difference in laboratory parameters, complications, and commonly known causes of cirrhosis, such as hepatitis B, hepatitis C, alcoholic liver disease (ALD), and autoimmune hepatitis.

METHODS

Study Participants

The Haseki Training and Research Hospital Ethics Committee, University of Health Sciences, Istanbul, Turkey, approved the study. This retrospective cohort study was conducted following principles of good clinical practice and the declaration of Helsinki. We investigated 541 patients (409 men and 132 women) with different etiologies of cirrhosis who applied to the gastroenterology clinic from 2009 to 2018 in Florance Nightingale Hospital. Patients under 18 years, patients with cardiovascular disease (congenital heart disease, valvular heart disease, coronary heart disease), severe lung disease, thrombo-embolism, kidney disease, and active infection were excluded.

The current study was organized using a computerized database in Florance Nightingale Hospital. Data for the study analyses were derived from the electronic hospital management system dispensing records and Florance Nightingale Hospital profile databases. Standardized data collection includes patient demographic information, medical history, abdominal ultrasound, and laboratory examination. Demographic data, medical history, vital signs at admission, medication, and final diagnosis were obtained from patients' electronic medical records.

Laboratory Measurements

Routine blood samples were drawn between 6:00 am and 7:00 am, in the morning. After a 12-hour fasting period, blood samples were drawn and analyzed immediately afterward. Alanine transaminase (ALT), aspartate transaminase (AST), serum albumin (ALB), bilirubin, prothrombin time (PT), total cholesterol (TC), triglyceride, low-density lipoprotein (LDL), high-density lipoprotein, white blood cell (WBC) count, red blood cell (RBC) count, platelet count, blood glucose, hemogram were analyzed in the laboratory of Florance Nightingale Hospital, University of Bilim. The laboratory findings were obtained from the patient's electronic medical records at the hospital. Biochemical parameters were performed for all participants.

All patients were divided into five groups such as hepatitis B, hepatitis C, alcoholic liver disease ALD, NASH, and autoimmune hepatitis according to the etiology of cirrhosis. Viral hepatitis was diagnosed with positive hepatitis serology (positive hepatitis B surface antigen for more than six months or positive hepatitis C virus). ALD was diagnosed with a history of alcohol intake (more than 21 units of alcohol per week for males and 14 units per week for females). NASH was diagnosed in patients with the presence of hepatic steatosis on imaging or histology in the absence of significant alcohol consumption. Autoimmune hepatitis was diagnosed with positive autoimmune antibodies. Biochemical and metabolic parameters were evaluated between five groups.

Paracentesis was performed in patients with ascites, and serum ascites albumin gradient was measured. Neutrophil levels in ascites fluid were examined in the laboratory, and values above 250/mm3 were evaluated as peritonitis. A gastroenterologist performed endoscopy, and the presence of esophageal varices was examined. Endoscopic band ligation and medical treatment were applied to patients hospitalized due to variceal bleeding.

Statistical Analysis

Data are expressed as the mean ± standard deviation. A statistical analysis was performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Basic descriptive statistics, including the means, standard deviations, ranges, and percentages, were measured. The normality of the distribution was examined using the Kolmogorov–Smirnov test. The Mann compared

Table 1. Frequency of cirrhosis patients according to etiology

	Frequency	Percent (%)
Alcoholic Liver Disease	83	15
Hepatitis B Virus	242	44,7
Hepatitis C Virus	112	20,7
Nonalcoholic Steatohepatitis	77	14,2
Autoimmune Hepatitis	27	5,9

Table 2. Comparison of laboratory parameters related to the etiology of hepatic cirrhosis

	Alcoholic Liver Disease Group 1	Hepatitis B Virus Group 2	Hepatitis C Virus Group 3	Nonalcoholic Steatohepatitis Group 4	Autoimmune Hepatitis Group 5	P value
Age	54,7±7,9	53,2±7,6	55,9±7,4	59,1±7,1	45,6±13,9	IV, VI, VII, IX,X
Glucose	120,4±45,3	111,3±42,2	112,8±39,5	126,7±47,9	94,6±20,9	IV, VI, VII,IX,X
Body Mass Index	27,8±4,2	27,3±3,8	27,8±4,7	30,4±5,1	26,8±5,2	III, VI, VIII, X
MELD Score	17,1±4,7	14,9±5,9	15,2±5,3	15,8±4,8	18,7±4,9	VII
CHILD Score	9,2±1,9	8,2±2,5	8.6±2.2	8.3±1.9	9.5±1.8	NS
Hemoglobin	11.1±2.2	12.4±2.3	11.7±2.2	11.3±2.1	10.2±1.9	I, VI, VII
Platelet	121593±116491	96698±57580	89650±48927	96884±42746	139429±93565	NS
INR	1,6±0,3	1,6±0,5	1,6±0,5	1,6±0,3	1,6±0,4	NS
AST	59,8±37,7	78,1±69	84,9±55,7	48,6±25,1	118,5±88,4	IV, VI, VIII, X
ALT	39,6±24,9	55,9±52,8	56,3±38,9	32,1±24,9	74,8±56,1	VI. VIII, X
ALP	170,1±126	157,7±112,5	130,4±78,1	128,5±80,8	296,2±212,3	IV.VII.IX.X
GGT	99,5±90,1	107,9±158,2	80,3±79,8	117,1±246,8	214,6±290,2	IV.VII.IX
Albumin	3±0,5	3,2±0,7	3±0,6	2,9±0,6	2,8±0,5	NS
Total Bilirubin	4,4±4,6	3,8±5,2	3,8±4,2	3,1±3,6	8,9±8,9	IV.VII.IX.X
Creatinine	1±0,4	0,9±0,4	0,9±0,7	1±0,5	0,8±0,9	NS
Total cholesterol	141,7±54,5	138,1±50,1	122,9±46,6	127,9±41,1	140,1±69,7	NS
TSH	2,8±2,5	1,9±1,5	2,5±2,9	2,5±2,6	1,8±1,1	NS
AFP	25,3±116,3	54,9±144,9	42,7±89,8	6,9±12,3	9,9±34,3	NS

Statistical significance is shown in bold-faced type ($p < 0.05$). INR= International Normalized Ratio; AST = aspartate aminotransferase; ALT= alanine aminotransferase; ALP= alkaline phosphatase; GGT= gamma-glutamyl transferase ; TSH =thyroid stimulating hormone; AFP= alpha-fetoprotein I Group 1 versus 2, II Group 1 versus 3, III Group 1 versus 4, IV Group 1 versus 5, V Group 2 versus 3, VI Group 2 versus 4, VII Group 2 versus 5, VIII Group 3 versus 4, IX Group 3 versus 5, X Group 4 versus 5 NS not significant

mean values between two independent groups-the Whitney U test for continuous variables and the $\chi 2$ test for categorical parameters; comparisons between more than two subgroups were performed by ANOVA and Kruskal–Wallis h tests. Bivariate correlations were explored by Pearson's (continuous variables). Differences were considered statistically significant if the two-tailed P value was less than 0.05.

RESULTS

541 patients who had either hepatitis B, hepatitis C, alcoholic liver disease (ALD), NASH, or autoimmune hepatitis as the primary etiology of the cirrhosis were included in the study. 83 patients with alcoholic liver disease, 242 patients with hepatitis B-associated cirrhosis, 112 patients with hepatitis C-associated cirrhosis, 77 patients with NASH, and 27 patients with autoimmune hepatitis were enrolled. The patients were predominantly male except for the cirrhosis from the autoimmune hepatitis cohort, where the female patients were dominant. The mean age and age range of these patients were shown in Table 1 that NASH-associated cirrhosis was more often in the older age group, and autoimmune hepatitis-associated cirrhosis was in the younger age group. The autoimmune hepatitis-associated cirrhosis group decreased glucose levels compared to other groups. NASH had increased glucose levels rather than the hepatitis B-associated cirrhosis group. There was a significant difference in BMI levels between NASH and other groups. NASH had higher BMI levels. The autoimmune hepatitis-associated cirrhosis group had a significantly higher MELD score than hepatitis B-associated cirrhosis. The five groups had no significant difference in CHILD PUGH score, platelet, INR ratio, albumin, creatinine, total cholesterol, TSH, free T4, and free T3. The hepatitis B-associated cirrhosis group had elevated hemoglobin levels compared to ALD, NASH, or autoimmune hepatitis-associated cirrhosis. AST and ALT levels were lower in NASH-associated cirrhosis compared to hepatitis B, hepatitis C, and autoimmune hepatitis-associated cirrhosis patients. There was a significant difference in gamma-glutamyl transferase, alkaline phosphatase, and bilirubin levels between autoimmune hepatitis-associated cirrhosis and other groups (Table 2).

Ascites and hepatic encephalopathy were statistically higher in alcoholic liver disease, hepatitis B, and NASH cirrhosis, while esophageal variceal bleeding was higher in NASH and autoimmune hepatitis (Table 3). Spontaneous bacterial peritonitis was statistically higher only in cirrhosis due to autoimmune hepatitis.

DISCUSSION

We described the laboratory parameters and liver complications of the five most common causes of cirrhosis. We analyzed the liver features of hepatitis B, hepatitis C, alcoholic liver disease (ALD), NASH, and autoimmune hepatitis-associated cirrhosis to distinguish each other.

Autoimmune hepatitis is a chronic progressive liver disease. It is characterized by hyperglobulinemia and a mixed histological infiltrate of plasma cells and lymphocytes, leading to cirrhosis.[5, 6] According to the antibody profile, autoimmune hepatitis can be divided into two subgroups. Autoimmune hepatitis – 1 is characterized by the presence of ANA and/or anti-smooth muscle antibodies (SMA). Autoimmune hepatitis -2 is characterized by the positivity of anti-liver-kidney microsomal antibody type one (LKM1), anti-LKM3, and/or anti-liver cytosol type 1 antibody (LC1). Autoimmune hepatitis affects mainly women.[7] The peak incidence of the disease is in the adolescence of 30-45 years of age. Estrogen plays a vital role in immu-

Table 3. Comparison of etiology-related complication frequency with all cirrhosis cases.

	Alcoholic Liver Disease	Hepatitis B Virus	Hepatitis C Virus	Nonalcoholic Steatohepatitis	Autoimmune Hepatitis
Gender M/F	80/3**	208/34**	63/49**	54/23	4/23**
Ascites	77**	157**	81	61**	20
Esophageal varices bleeding	30	68	30	22*	3*
Hepatic encephalopathy	43*	78*	40	41**	12
Spontaneous bacterial peritonitis	8	19	9	4*	3

Statistical significance is shown *p≤0.05 **p<0.001

nology, and increased estrogen levels can inhibit the Th1 response and promote the Th2 response, causing antibody production. Prolactin, growth hormone, and progesterone can regulate the immune system by changing the cytokine secretion and the expression of the estrogen receptor.[8,9] In this study, autoimmune hepatitis-associated cirrhosis presented in the younger age group and was dominant in the female gender due to all these immune system alterations. There was a significant difference in gamma-glutamyl transferase, alkaline phosphatase, and bilirubin levels between autoimmune hepatitis-associated cirrhosis and other groups. Cholestasis in autoimmune hepatitis-associated cirrhosis is more prominent than in other cirrhosis. Autoimmune hepatitis-associated cirrhosis had decreased glucose levels compared to other groups.

Non-alcoholic fatty liver disease (NAFLD) is a chronic progressive liver disease characterized by dysregulated lipid metabolism and chronic inflammation, and it results in fibrosis. NAFLD can progress to NASH and cirrhosis. In this study, the patients who had NASH-associated cirrhosis had significantly higher BMI levels due to dysregulated lipid metabolism. AST and ALT levels were lower in NASH-associated cirrhosis compared to hepatitis B, hepatitis C, and autoimmune hepatitis-associated cirrhosis patients. The patients with NASH-related cirrhosis experienced more frequent hepatic encephalopathy than other patients.

Alcoholic hepatitis is a multisystem disease that occurs in patients who abuse large amounts of alcohol for many years. The development of alcoholic hepatitis is complex and depends on a variety of genetic and environmental factors.[10] Severe alcoholic hepatitis has a high mortality rate with fulminant hepatic failure without liver transplantation.[11] In our study, we observed that the development of ascites and hepatic encephalopathy was statistically higher in patients who developed cirrhosis due to alcoholic hepatitis.

Hepatitis B has an important place in the etiology of chronic hepatitis. It is thought that there are approximately 400 million people infected with HBV.[12] Despite vaccines and new antiviral therapies, HBV infection remains severely underdiagnosed. Few patients eligible for treatment receive antiviral therapy.[13,14] The study determined that viral factors play an essential role in the etiology of hepatic cirrhosis. In our study, 242 patients were diagnosed with hepatitis B-related cirrhosis, and 112 patients were diagnosed with hepatitis C-related cirrhosis. Hepatitis B and C-related cirrhosis were observed to be more common in male patients. Ascite development was higher in hepatitis B-associated cirrhosis.

The etiological causes and frequency of complications of the included patients were evaluated. In conclusion, hepatic cirrhosis is a disease with high mortality. The leading causes of morbidity and mortality in patients with hepatic cirrhosis are disease-associated complications. Therefore, managing complications properly when they develop is very important.

Conflict of Interest

The author(s) declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

Funding Sources

The author(s) received no financial support for this article's research, authorship, and/or publication.

Ethical Approval

This study was accepted by the local Ethics Committee of Haseki Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. This retrospective cohort study was managed according to principles of good clinical practice and the declaration of Helsinki. The ethics committee's approval was obtained from Haseki Training and Research Hospital. (No: 126-2021- 01.12.2021).

Authors' Contribution

Study Conception: TŞ; Study Design: FT; Supervision; FT; Funding: FT; Materials: FT; Data Collection and/or Processing: TŞ; Analysis and/or Data Interpretation: BÇT; Literature Review: BÇT; Critical Review: TŞ; Manuscript preparing: BÇT.

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Original Article
Internal Medicine
DOI: 10.56016/dahudermj.1445132

DAHUDER
Medical Journal
e-ISSN: 2791-9250

The relationship between erectile dysfunction and serum adropin level in male patients with type 2 diabetes mellitus

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ABSTRACT

Objectives: Diabetes Mellitus is a chronic, progressive disease with increasing worldwide prevalence and is a public health problem because of the high cost of treatment and complications. Adropin has been discovered in recent years, and it has been reported to be associated with glucose, lipid metabolism, and endothelial dysfunction. In this study, it was aimed to investigate the relationship between erectile dysfunction and Adropin level in Type 2 diabetic male patients.

Methods: Forty patients with type 2 DM with erectile dysfunction and 25 patients with type 2 DM without erectile dysfunction, aged between 40 and 60, who applied to the internal medicine outpatient clinic between November 2019 and March 2020, were included in the prospective study. In addition to routine blood tests in the study groups, Adropin levels were measured using the ELISA method.

Results: The study was conducted with 65 men aged 40 and 60 between November 2019 and February 2020. The mean age of the men was 52.71±6.04. The study used 40 (61.5%) Case groups and 25 (38.5%) Control groups. The case group consisted of 12 (18.5%) Mild ED, 20 (30.8%) Moderate ED, and 8 (12.8%) Severe ED, and the control group consisted of Type 2 Diabetes Mellitus Patients without erectile dysfunction.

Conclusion: According to our results, serum Adropin levels in Mild ED, Moderate ED, and Severe ED groups were found to be higher than those in Type 2 Diabetes Mellitus patients without erectile dysfunction.

Keywords: Diabetes mellitus, Adropin, Erectile Dysfunction

Diabetes mellitus (DM) constitutes a significant health problem. Every year, 8 to 14 million people die worldwide due to diabetes and other chronic diseases such as cardiovascular diseases and cancer. Type 2 diabetes is increasing rapidly in all developed and developing societies. The diabetes epidemic is mentioned in developing countries, especially in communities migrating from these countries to developed countries.[1, 2] The main reasons for this are the increase in obesity and physical inactivity due to population growth, aging, and lifestyle changes brought about by urbanization.[3] Diabetes ranks fifth among the diseases that cause death in many countries.[4,5] DM is the most common cause of end-stage renal disease, blindness under 65 years of age, and non-traumatic among the diseases that cause death in many countries.[4,5]

Adropin was first described in 2008 by Kumar *et al*. It is a peptide hormone discovered by.[6] It is coded over the gene related to energy balance (ENHO), and it is produced by the liver and brain tissue in the first studies.[7] It has an approximate molecular weight of

Received: *February 29, 2024;* ***Accepted:*** *October 25, 2024;* ***Published Online:*** *October 29, 2024*

How to cite this article: *Arslan G, Özdemir A. The relationship between erectile dysfunction and serum adropin levels in patients with type 2 diabetes mellitus.DAHUDER MJ 2024,4(4):89-96. DOI: 10.56016/dahudermj.1445132*

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7,927 kDa and comprises 76 amino acids. The release of Adropin in the body is regulated by hunger and nutrition.

Erectile dysfunction (ED) is defined as the inability to achieve and/or maintain an erection adequate for sexual activity.[8,9] ED has profound effects on psychosocial health and negatively affects patients' quality of life.[10,11] Penile erection is a complex psycho-neurovascular event characterized by increased arterial flow, relaxation of sinusoidal smooth muscles, and decreased venous return, resulting from the coordinated work of neuromediators, striated and smooth muscles, and tunica albuginea.[12] Increasing knowledge about ED increases the number of patients seeking treatment and searching for reliable, appropriate, and well-tolerated treatment.[13]

ED is a severe medical problem that affects more than 100 million men and their sexual partners worldwide. According to an optimistic estimate, the worldwide incidence is around 20 million men.[14]

In this study, we aim to determine the relationship between blood serum Adropin levels in male patients diagnosed with Type 2 DM, according to the presence of erectile dysfunction, between the patient groups and the control group.

METHODS

The Istanbul Fatih Sultan Mehmet Training and Research Hospital local ethical committee approved the study with the decision dated 02.08.2013 and numbered 0208. Forty patients with Type 2 DM with erectile dysfunction and 25 patients with Type 2 DM without erectile dysfunction, aged between 40 and 60 years, who applied to the Diabetes Polyclinic of Fatih Sultan Mehmet Training and Research Hospital between November 2019 and March 2020 were included in the study. The patients who agreed to participate in the study were informed, and a consent form was issued. Stories of all participants included in the study were taken, and systemic physical examinations were performed. The drugs the patients were taking were determined in the patient groups. BMI [BMI=Weight (kg)/Height $(m)^2$] of all participants was calculated. Individuals with atherosclerotic heart disease, kidney failure, smoking, urological evaluation of erectile dysfunction other than diabetes, diabetes for less than 1 year, and chronic diseases other than hyperlipidemia were not included in the study.

The name, surname, age, gender, date of diagnosis, waist circumference, medications used, and examination results of the patients included in the study were recorded in the study forms for analysis. Other clinical features and biochemical parameters of the patient groups (HbA1c, total cholesterol,

HDL-cholesterol, LDL-cholesterol, triglyceride), and drug treatments, if any, were recorded from the patient files simultaneously during their routine application and evaluated.

After 8-10 hours of fasting, 5 ml blood samples were taken from the antecubital vein to study the Adropin levels from the study groups. A straight biochemistry tube was used for blood samples. After the blood was taken into the biochemistry tube and was kept for 45 minutes, it was centrifuged at 3500- 4000 rpm for 5 minutes, and the serum was separated. The separated serums were stored in 2 ml Eppendorf tubes in a deep freezer at -80°C to study Adropin levels.

After the serums were brought to room temperature and melted on the working day, serum Adropin levels were studied with the appropriate ELISA kit (Bioassey technology laboratory catalog no: E3231Hu, Shanghai, China) following the working method in Fatih Sultan Mehmet Training and Research Hospital Biochemistry Department Laboratory.

Statistical Analysis

While evaluating the findings obtained in the study, the IBM SPSS Statistics 22.00 (IBM SPSS, Turkey) program was used for statistical analysis. While considering the study data, the conformity of the parameters to the normal distribution was evaluated with the Shapiro-Wilks test. While considering the study data, the One-way ANOVA test was used to compare normally distributed parameters in contrast to quantitative data and descriptive statistical methods (mean, standard deviation, frequency). The Kruskal-Wallis test was used to compare the parameters that did not show normal distribution, and Dunn's test was used to determine the group that caused the difference. Mann-Whitney U test was used to compare two parameters that did not show normal distribution. Fisher Freeman Halton test was used to compare qualitative data. Pearson correlation analysis was used to analyze the relationships between parameters conforming to the normal distribution. Spearman's rho correlation analysis examined the relationships between parameters that did not conform to the normal distribution. Significance was evaluated at the $p<0.05$ level

RESULTS

The study used 40 (61.5%) Case groups and 25 (38.5%) Control groups. The case group consisted of 12 (18.5%) Mild ED, 20 (30.8%) Moderate ED, and 8 (12.8%) Severe ED, and the control group consisted of Type 2 Diabetes Mellitus Patients without erectile dysfunction. The age of diabetes is below 10 years in 67,7 % of the cases and over 10 years in 32.3% of the cases. While 64.6% have hyperlipidemia, 35.4% do not. Statins are used in 36.9% and not used in 63.1%. While 95.4% use oral antidiabetics, 4.6% do not use it. While insulin is used at 38.5%, it is not at 61.5%. While ASA is used in 21.5%, it is not in 78.5%. Erectile dysfunction is mild in 30%, moderate in 50% and severe in 20%.

There was no statistically significant difference between the case and control groups in terms of age, BMI, diabetes age, waist circumference, HbA1c, total cholesterol, HDL, LDL, and triglyceride parameter values, statin use rates, oral antidiabetic use rates, insulin use rates and Acetylsalicylic acid (ASA) use rates (p>0.05) (Table 1).

The serum Adropin level values of the case group were statistically significantly higher than the Type 2 Diabetes Mellitus Patients without erectile dysfunction group (p:0.001; p<0.05, Table 2).

There was a statistically significant difference between the groups regarding serum Adropin level values (p:0.008; p<0.05). As a result of the pairwise comparisons made to determine the difference, The serum Adropin level values of the control group were found to be statistically significantly lower than those of the mild ED and moderate ED groups (p1:0.004; p2:0.006; p<0.05). There was no statistically significant difference between the other groups regarding serum Adropin level values (p>0.05, Table 3).

There was no statistically significant difference in serum Adropin levels between the diabetic age groups and between those with and without hyperlipidemia in the case and Type 2 Diabetes Mellitus Patients without erectile dysfunction groups (p>0.05).

In the mild ED group, moderate ED group, severe ED group, and the Type 2 Diabetes Mellitus Patients

Table 1. Evaluation of study parameters between groups

		Mild ED	Moderate ED	Severe ED	Type 2 Diabetes Mellitus Patients without erectile dysfunction	p
Age		51.75±6.22	52.5±5.72	57.25±2.66	51.88±6.6	**1 0.149**
BMI		28.5±3.97	29.45±4.84	27.88±5.11	27.04±3.4	**1 0.297**
Diabetes Age		8.67±4.33	6.45±3.85	9.5±5.13	8±5.24	**1 0.372**
Waist circumference		103.17±7.25	104.3±10.7	103.25±9.47	98.24±8.54	**1 0.139**
HgA1c(median)		9.21±2.47 (8.8)	7.53±1.37 (7.1)	7.46±1.49 (7)	8.01±1.91 (7.4)	**2 0.192**
Total cholesterol		186.42±35.51	192.55±41.08	157±27.76	186.36±40.15	**1 0.179**
HDL (median)		41.17±10.5 (37.5)	49.5±26.26 (46)	46.25±10.55 (42)	47.08±13.05 (47)	**2 0.579**
LDL		106.5±32.93	109.7±24.22	89±30.4	106.92±28.25	**1 0.363**
Triglyceride		190.5±151 (122.5)	204.05±164.6 (138)	113.13±73.39 (93.5)	159.32±110.71 (109)	**2 0.106**
		n (%)	**n (%)**	**n (%)**	**n (%)**	
Statin use	**Yes**	7 (%58.3)	6 (%30)	2 (%25)	9 (%36)	**3 0.382**
	No	5 (%41.7)	14 (%70)	6 (%75)	16 (%64)	
Oral antidiabetic use	**Yes**	11 (%91.7)	19 (%95)	7 (%87.5)	25 (%100)	**3 0.228**
	No	1 (%8.3)	1 (%5)	1 (%12.5)	0 (%0)	
İnsulin use	**Yes**	7 (%58.3)	5 (%25)	5 (%62.5)	8 (%32)	**3 0.123**
	No	5 (%41.7)	15 (%75)	3 (%37.5)	17 (%68)	
ASA use	**Yes**	3 (%25)	2 (%10)	2 (%25)	7 (%28)	**3 0.485**
	No	9 (%75)	18 (%90)	6 (%75)	18 (%72)	

[1]Oneway Anova Test *[2]Kruskal Wallis Test* *[3]Fisher Freeman Halton Test*

Table 2. Evaluation of serum Adropin level between Case and Control groups

	Serum Adropin level
Case group	167.08±177.5 (82.3)
Control group	131.22±196.38 (57.1)
p	**0.001***

Mann Whitney U Test **p<0.05*

Table 3. Evaluation of serum Adropin level between the groups

	Serum Adropin level
Mild ED	186.04±191.62 (88.7)
Moderate ED	168.25±189.99 (79.1)
Severe ED	135.71±134.62 (79.5)
Type 2 Diabetes Mellitus Patients without erectile dysfunction	131.22±196.38 (57.1)
p	**0.008***

Kruskal Wallis Test **p<0.05*

without erectile dysfunction group, there was no statistically significant relationship between serum Adropin level values and values of age, BMI, diabetes age, waist circumference, HgA1c, total cholesterol, HDL, LDL and triglyceride parameters (p>0.05, Table 4, Figure 1).

The case group has a positive, 34.5%, and statistically significant relationship between serum Adropin level and waist circumference values (p:0.029; p<0.05). No statistically significant relationship exists between serum Adropin level values and BMI, diabetes age, HgA1c, total cholesterol, HDL, LDL, and triglyceride parameters (p>0.05, Table 5, Figure 2).

Type 2 Diabetes Mellitus Patients without erectile dysfunction groups have no statistically significant relationship between serum Adropin level values and age, BMI, diabetes age, waist circumference, HgA1c, total cholesterol, HDL, LDL, and triglyceride parameter values (p>0.05, Table 5, Figure 2).

DISCUSSION

DM is a progressive disease with an increasing prevalence and complications all over the world. The main aim of diabetes is to improve the patient's quality of life and prevent and delay the complications that may develop.

It has been reported that the Adropin molecule, discovered in recent years, is associated with glucose and lipid metabolism. ED is the inability to achieve and/or maintain an erection sufficient for sexual activity.

This study aimed to examine the relationship between erectile dysfunction and Adropin levels in Type 2 diabetic male patients.

Penile erection is a neurovascular event that depends on neural integrity, functional circulatory system, and healthy cavernous tissue. Therefore, endothelial dysfunction causes erectile dysfunction. Atherosclerotic vascular disease is shown as a cause of ED in 40-50% of cases over the age of 50. Diabetic adult ED is associated with autonomic neuropathy and endothelial dysfunction.[15] Unlike other independent ED, diabetic ED begins at an earlier age.

Table 4. Evaluation of the correlation between serum Adropin level and demographic and laboratory values between the groups

	Serum Adropin level							
	Mild ED		Moderate ED		Severe ED		Type 2 Diabetes Mellitus Patients without erectile dysfunction	
	r	p	r	p	r	p	r	p
Age (years)	0.317	0.315	0.038	0.875	0.257	0.539	0.051	0.808
BMI (kg/m2)	-0.134	0.677	0.254	0.280	0.846	0.008	0.007	0.972
Diabetes age (years)	-0.082	0.799	-0.082	0.731	0.199	0.637	-0.205	0.326
Waist circumference(cm)	0.151	0.639	0.375	0.104	0.616	0.104	0.159	0.447
HgA1C⁺	-0.322	0.308	-0.257	0.274	-0.214	0.610	-0.034	0.874
Total cholesterol	0.47	0.123	-0.188	0.428	-0.289	0.488	-0.133	0.526
HDL⁺	0.231	0.471	-0.12	0.615	0.503	0.204	-0.042	0.841
LDL	0.179	0.578	-0.215	0.363	-0.215	0.608	-0.087	0.678
Triglyceride⁺	0.070	0.829	-0.100	0.675	-0.229	0.586	0.016	0.938

Pearson Correlation Analysis *⁺Spearman Rho Correlation Analysis*

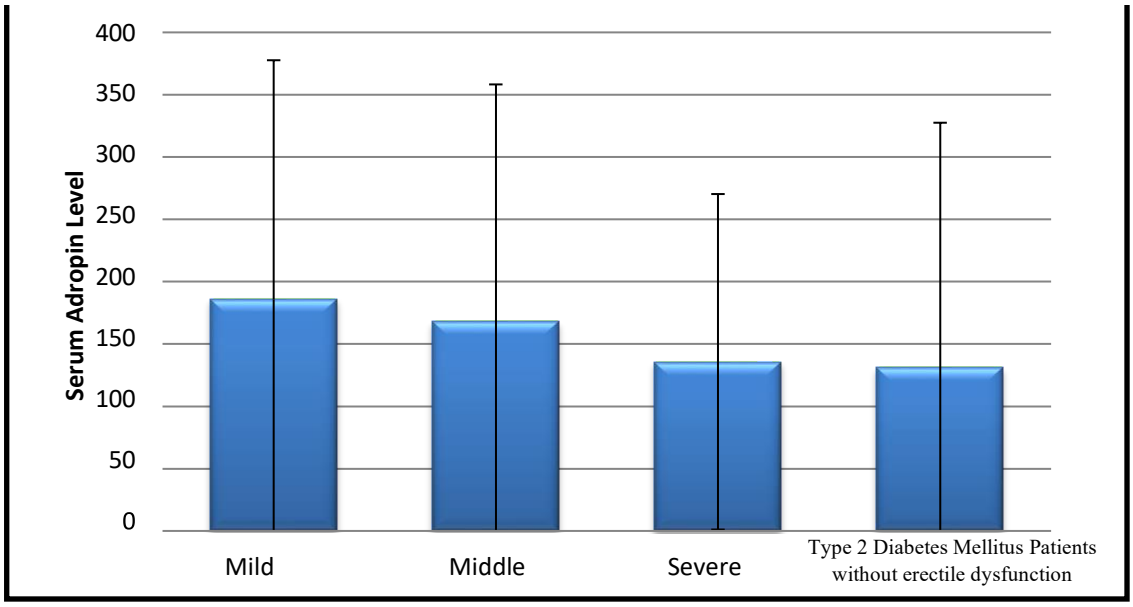

Figure 1. Evaluation of serum Adropin level between groups

This is the second study to determine the relationship between Adropin levels and ED. Adropin participates in Nitric oxide bioavailability and affects inducible nitrite oxide synthase expression. Adropin, encoded by the gene to provide energy homeostasis, is present in various organs such as pancreatic tissue, brain, kidney, endocardium, myocardium, epicardium, and endothelium.[7] Adropin-treated endothelial cells exhibit more significant proliferation, migration, capillary-like tube formation, less permeability, and tumor necrosis factor-α-induced apoptosis.[16]

In their study, Kumar *et al*.[6] showed that blood serum Adropin levels increased in high-fat diets. Another study revealed that excessive secretion of the Adropin hormone or systemic administration of the hormone for treatment in mice with diet-induced obesity decreased insulin resistance and improved glucose tolerance. Celik *et al*.[17], in another study conducted in this area, compared the serum Adropin levels of the patient group diagnosed with gestational DM and the healthy control female group. This study found that the blood serum Adropin level in the patient group with gesta-

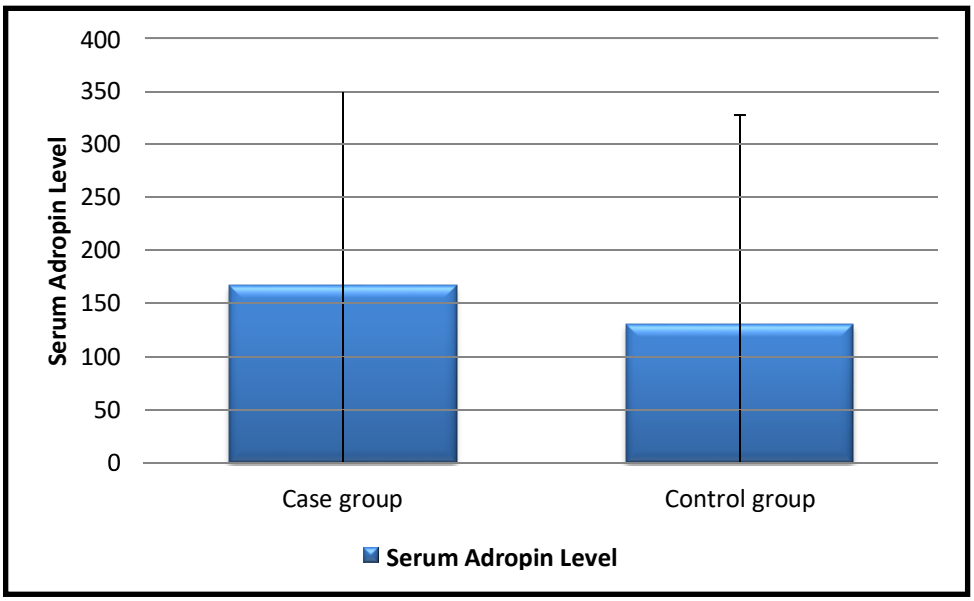

Figure 2. Evaluation of serum Adropin level between Case and Control groups

Table 5. Evaluation of the correlation between serum Adropin level and demographic and laboratory parameters between Case and Control groups

	Serum Adropin level			
	Case group		Control group	
	r	p	r	p
Age (years)	0.107	0.511	0.051	0.808
BMI (kg/m2)	0.239	0.138	0.007	0.972
Diabetes age (years)	-0.04	0.808	-0.205	0.326
Waist circumference (cm)	*0.345*	*0.029**	0.159	0.447
HgA1C⁺	-0.171	0.291	-0.034	0.874
Total cholesterol	0.027	0.867	-0.133	0.526
HDL⁺	0.05	0.759	-0.042	0.841
LDL	-0.041	0.803	-0.087	0.678
Triglyceride	-0.099	0.542	0.016	0.938

Pearson Correlation Analysis *⁺Spearman Rho Correlation Analysis* **p<0.05*

tional DM was statistically significantly lower than in the control group. This result may show us that high Adropin levels may have a role in the development of diabetes. On the other hand, it also suggests that the increase in Adropin levels secondary to high serum glucose levels may be increased to decrease the blood glucose level.

Topuz *et al*. evaluated endothelial dysfunction and flow-mediated dilatation in type 2 diabetes mellitus patients. They found a positive correlation between plasma Adropin levels and flow-mediated dilatation values, and the authors suggested that Adropin levels could be used to quantify endothelial dysfunction.[18]

In a study conducted on cardiac syndrome X (CSX) patients, serum Adropin levels were significantly lower than in healthy subjects. Therefore, it was assumed that lower serum Adropin levels were an independent risk factor for CSX.[26]

Wu *et al*.[19] reported that low serum Adropin levels were associated with coronary atherosclerosis in type 2 diabetic and non-diabetic patients. The authors asserted that lower Adropin levels might be a novel predictor of coronary atherosclerosis.

Celik *et al*.[20], in a study that aimed to determine the relationship between Adropin levels and ED, found that the average Adropin level was significantly lower in patients with ED. Study results show that Adropin levels are higher in the group with severe coronary artery disease, but the difference between the groups is not statistically significant. In light of this information, decreased serum Adropin levels in erectile dysfunction are the expected result.

However, in our study, Type 2 Diabetic patients with serum Adropin levels and erectile dysfunction were found to be significantly higher than those without erectile dysfunction. This is because the circulating pharmacokinetics of Adropin are virtually unknown. Therefore, a single measurement may not be sufficient to evaluate Adropin levels.

To our knowledge, there is no study on serum Adropin levels in patients with diabetic erectile dysfunction. Previously, Palizban *et al*.[21] found that serum Adropin levels were high in the following years as an adaptive response to pathogenic conditions such as endothelial dysfunction, insulin resistance, dyslipidemia, and glucose intolerance in Type 2 DM. Kuloğlu *et al*.[7] reported that high

Adropin levels may play a role in the development of diabetes, and Adropin levels increase secondary to high serum glucose levels to reduce the blood glucose level.

Limitations of the study

The most important limitation is that endothelial dysfunction and the presence of autonomic neuropathy were not tested in our study. A more comprehensive and multicenter study is needed to reveal the role of Adropin in the pathogenesis of ED and its effects on this molecule.

CONCLUSION

This is the first study in the literature investigating Adropin levels in diabetic ED patients. According to our results, serum Adropin levels in Mild ED, Moderate ED, and Severe ED groups were found to be higher than those in Type 2 Diabetes Mellitus patients without erectile dysfunction. If our results are supported by studies with a more significant number of patients,

a guiding role of Adropin may be disclosed in both the diagnosis and treatment of ED patients

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The Istanbul Fatih Sultan Mehmet Training and Research Hospital local ethical committee approved the study with the decision dated 02.08.2013 and numbered 0208.

Authors' Contribution

Study Conception: GA, AÖ; Study Design: GA; Supervision; GA, AÖ; Funding: GA; Materials: GA; Data Collection and/or Processing: GA; Analysis and/or Data Interpretation: GA; Literature Review: GA; Critical Review: GA; Manuscript preparing: GA.

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Case Report
Internal Medicine
DOI: 10.56016/dahudermj.1437116

DAHUDER
Medical Journal
e-ISSN: 2791-9250

Acute toxic hepatitis caused by inula viscosa (andız (yapıskan) herb): A case report

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ABSTRACT

Acute toxic hepatitis may progress with inflammation and necrosis. Herbal products may also be a reason for this situation. Many people use plants for healing, but sometimes, these products can be toxic to the liver. Here, we presented the first case in the literature that developed toxic hepatitis due to the use of Inula Viscosa (Andiz Herb).

Keywords: Toxic hepatitis, herbal drugs, Inula Viscosa

Acute toxic hepatitis usually develops acutely; it may progress with inflammation and necrosis. It can develop in autoimmune and ischemic conditions, as well as with viruses, some poisonous mushrooms, alcohol, and herbal products.[1] Many people have generally used officinal plants for healing since ancient times. Still, these products have side effects and toxic effects due to variables such as dosage and the way they are used on the liver sometimes.[2] In this article, we aimed to present the first case in the literature of acute toxic hepatitis due to the use of Inula Viscosa (IV).

CASE

An 80-year-old female patient applied with shortness of breath and cough for 1 week. She said that within the first week, she drank a plant called Oath herb for her cough 4-5 times. The patient had heart failure, chronic renal failure, and Chronic Obstructive Pulmonary Disease already. In the physical examination, crackles and rhonchi were heard in the lungs. There was no defense and rebound in the abdomen but tenderness in the right upper quadrant. Vital importance in the application: Blood pressure:120/70 mmHg, pulse: 74, SpO_2: 94, fever: 37,3 C. Laboratory examinations are in the table below (Table 1). Autoantibodies and inflammation markers were requested to exclude autoimmune and viral hepatitis. Although, we thought that ischemic and toxic hepatitis coexisted with heart failure and IV side effects. However, the patient had heart failure for a long time. For this reason and the history of herbal products, we focus on toxic hepatitis more than ischemic hepatitis. The Abdomen Ultrasonography report was only hepatomegaly. The patient had a severe increase in blood values due to IV. The alanine aminotransferase / alkaline phosphatase ratio was calculated and found to be compatible with the type of hepatocellular damage. After seeing the blood results, we ordered the patient's hepatotoxic medications to be immediately discontinued, and the N-acetylcysteine (NAC) protocol was started. (150mg/kg N-Acetylcysteine (NAC) 5% in 500cc

Received: *February 14, 2024****; Accepted:*** *April 3, 2024****; Published Online:*** *October 29, 2024*

How to cite this article: *Kılıç N, Oral A. Acute toxic hepatitis caused by inula viscosa (andız (yapıskan) herb): A case report.DAHUDER MJ 2024,4(4):97-98. DOI: 10.56016/dahudermj.1437116*

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Available at http://dergipark.org.tr/en/pub/dahudermj

dextrose iv inf >1 hour, 50mg/kg N-Acetylcysteine (NAC) 5% 500cc dextrose iv inf 4 hours, 100mg/kg N-Acetylcysteine (NAC) 5% in 1000 cc of dextrose in 16 hours). After the treatment, the patient's blood results started to get normal. Also, Hepatitis B Virus (HBV), Hepatitis C Virus(HCV), Cytomegalovirus (CMV), Human Immune deficiency Virus(HIV) serology, and autoantibodies like Antinuclear Antibody(ANA), Anti Smooth Muscle Antibody(ASMA), Anti Liver Kidney microsomal Antibody-1(LKM-1) results were negative. Our diagnosis was supported by the improvement in the blood results and the negative autoantibodies and serologies.

DISCUSSION

The liver is one of the very important organs in our body, and many chemical reactions occur and are metabolized there. Detoxifying toxic substances is also among its functions. With these features, it is one of the indispensable organs. As a result of its damage, significant disruptions occur in the body.[3] In our society, it is common to use plants as treatment and symptom relievers. Still, when factors that vary from person to person are added, these applications may produce different results for everyone.[2] Studies have shown that medicinal plants cause liver toxicity.[4] As in our case, in our patient who used IV upon recommendation, this plant had a toxic effect and caused deterioration in liver enzymes.

IV is a woody, hairy, glandular plant usually found on the Mediterranean coast. It reaches up to 150 cm in height, with abundant and upright branches. Its leaves are scattered, spiky flowers are 1-1,5 cm in diameter, golden yellow and showy.[5]

Although a study has shown that IV has an antioxidant effect on the liver[6], liver toxicity should be kept in mind in patients with a history of using such plants.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: NK, AO; Study Design: AO, NK; Supervision; NK, AO; Funding: AO, NK; Materials: AO; Data Collection and/or Processing: NK; Analysis and/or Data Interpretation: NK, AO; Literature Review: NK, AO; Critical Review: AO, NK; Manuscript preparing: NK, AO.

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Case Report
Internal Medicine
DOI: 10.56016/dahudermj.1442236

DAHUDER
Medical Journal
e-ISSN: 2791-9250

Amlodipine-induced gingival hyperplasia

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ABSTRACT

Calcium channel blockers (CCB) are the best-known, most widely used drugs in the treatment of hypertension in the world. Gingival hyperplasia is one of the uncommon side effects of CCB usage. Among CCBs, it's most commonly seen due to nifedipine. Gingival hyperplasia is rarely seen with the use of amlodipine. The mechanism of drug-induced gingival enlargement is not entirely understood, but it's clear that it is due to multifactorial influences. Although the pharmacologic effect of each drug is different, all of them are estimated to act similarly to the secondary target tissue, i.e., the gingival connective tissue, thus resulting in common histopathological findings. Both inflammatory and non-inflammatory mechanisms are involved. This case has been presented to emphasize that the development of gingival hyperplasia in patients with hypertension could be a side effect of amlodipine usage.

Keywords: Gingival hyperplasia; amlodipine; side effect

Gingival hyperplasia is an enlargement of the tissue in the shape of a pyramid located between the teeth. Gingival hyperplasia is rarely encountered in clinical practice. The common causes of gingival hyperplasia are drugs, heredity, non-Hodgkin's lymphoma, acute monocytic leukemia, granulomatous diseases, fibroma, lipoma, malign melanoma, and chronic periodontal infections. However, drug assumption is the most common.[1] The three main drugs inducing gingival overgrowth (DIGO) are anticonvulsants and immunosuppressive and antihypertensive agents. Although the pharmacologic effect of each drug is different, all of them are estimated to act similarly to the secondary target tissue, i.e., the gingival connective tissue, thus resulting in common histopathological findings. Both inflammatory and noninflammatory mechanisms are involved.[2] The incidence of gingival hypertrophy with CCB, especially nifedipine treatment, has been shown to be as high as 20%, and this rate is much higher than amlodipine-induced gingival hyperplasia. It has been hypothesized that these patients have abnormal sensible fibroblasts to the drug. It has been shown that fibroblasts from the overgrown gingiva of these patients are characterized by elevated levels of protein synthesis and decreased collagenase activity, and, finally, accumulation of protein in the gingiva, especially collagen. Amlodipine is a long-acting dihydropyridine calcium antagonist frequently used for the treatment of hypertension and angina. Its effect is inhibited by the transmembrane influx of calcium ions into the smooth and cardiac vascular muscles. Although various adverse effects of amlodipine, like headache, edema, dizziness, flushing, and palpitations, have been reported, gingival overgrowth is rarely seen.[3]

Received: *March 5, 2024****; Accepted:*** *May 8, 2024****; Published Online:*** *October 29, 2024*

How to cite this article: *Seyman Çetinkaya G. Amlodipine-induced gingival hyperplasia. DAHUDER MJ 2024,4(4):99-102. DOI: 10.56016/dahudermj.1442236*

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CASE

A 40-year-old woman presented in our outpatient clinic with a complaint of painless swollen gums. The patient was referred to our clinic by her dentist with the pre-diagnosis of a drug-induced adverse effect. Gingival overgrowth involved the interdental papilla and marginal gingiva localized on the anterolateral facial surface of the labial maxillary and mandibular gingiva. History revealed that the patient was diagnosed with hypertension nine months previously, and amlodipine (5 mg) was prescribed. She did not have any addictions, drug usage, allergies, or significant family history of any critical diseases. At three months, she noticed painless gingival enlargement. She previously applied to the dental clinic for this complaint and was referred to our clinic. There wasn't any specific physical finding except the gingival overgrowth (figure 1).

Poor oral hygiene was observed. Her vital signs were within the normal range. Complete hemogram, biochemical kidney, liver function tests, fasting glucose, lipid profile, serum electrolyte levels, and thyroid function test were done, and all the parameters were in the normal range. Her physical examination showed no peripheral and cervical lymphadenopathy, hepatosplenomegaly, or B symptoms. Herewith, we exclude malignant diseases. The medication was replaced with ramipril 10mg/day, and the patient followed for two months. A marked reduction of gingival overgrowth was evident two months after the withdrawal of amlodipine (figure 2).

Thus, the diagnosis of amlodipine-induced gingival overgrowth (AIGO) was confirmed. There is no more need for gingival biopsy, surgical intervention, and gingivectomy. The patient's dentist followed up with oral cleaning, scaling, and monitoring of gingival status. A patient has given us written permission to write this case report.

DISCUSSION

Especially three classes of drugs are accused of drug-induced gingival overgrowth. Among these drugs, the most ordinary cause of DIGO is diphenylhydantoin. Nifedipine is the most common CCB associated with gum enlargement, although other agents implicated include verapamil, felodipine, nitrendipine, diltiazem, and amlodipine.[2,4]

Amlodipine is a dihydropyridine CCB that is commonly prescribed as an antihypertensive drug. The prevalence of AIGO has been reported to be 1.7%-3.3%. The incidence of gingival hypertrophy with nifedipine treatment is as high as 20%, and a 2002 study reported that the prevalence with the use of CCBs could be nearly 38%.[5,6] In the United States of America, Jorgensen estimated the prevalence of gingival hyperplasia caused by amlodipine in 1997 to be 3.3% for patients. Also, a study conducted in India in 2014 by Tejnaniet al. found a similar number of 3.4%.[3,7] This suggests that the prevalence of AIGO is similar across populations of dissimilar races and geography and has stayed stable over time.

It was known that CCBs such as nifedipine could cause gingival hyperplasia. When amlodipine came into the market, there were also similar reports of amlodipine-induced gingival hyperplasia. This was first reported by Ellis et all in 1993.[8] This side effect is three times more common in males. AIGO is generally started at the dose of 10 mg/day within three months

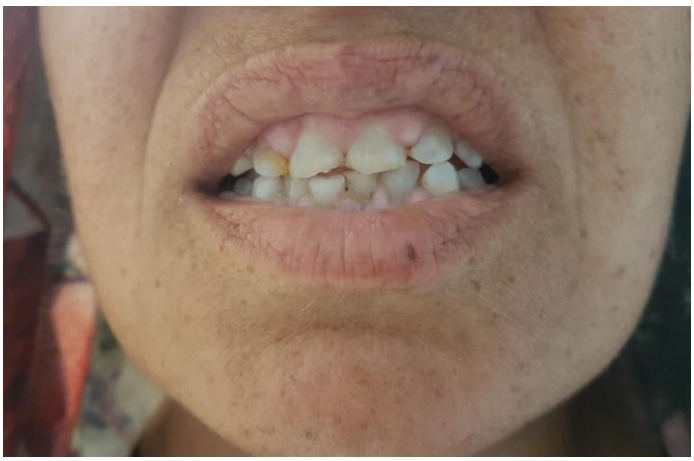

Figure 1. The patient's gingival view during amlodipine treatment

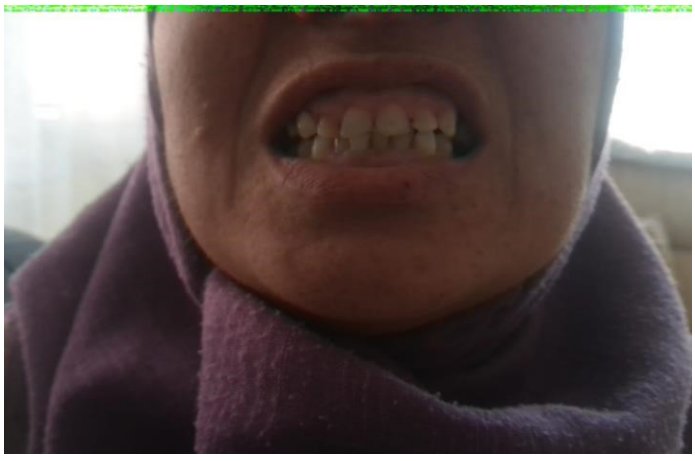

Figure 2. The patient's gingival view after withdrawal of amlodipine treatment

of drug initiation.[3] Although few cases of AIGO have been reported, our case is interesting as it occurred with a low dose of amlodipine (5 mg), and our case was female.

The etiology of DIGO is not entirely understood, but it is now known that a multifactorial role could be involved in its cause. With this, the effect of age, sex, duration, and dosage of the drug on the pathogenesis of gingival overgrowth is not clearly understood. Current studies have investigated the pathogenesis of these drugs' direct and indirect effects on the gingival fibroblast mechanism. It has been hypothesized that these individuals have abnormally sensible fibroblasts to the drug. It has been shown that fibroblasts from the overgrown gingiva of these patients are characterized by elevated levels of protein synthesis, especially collagen.[9] A unifying hypothesis states that anticonvulsants, immunosuppressive agents, and CCBs all cause cation of flux inhibition. Decreased cation influx of folic acid activate transfer within gingival fibroblasts causes diminished cellular folate uptake, which decreases the synthesis and activation of matrix metalloproteinases, a group of enzymes responsible for collagen breakdown. This reduces collagenase activity, causing decreased degradation and, thus, connective tissue accumulation, eventually presenting gingival overgrowth. Also, periodontal hygiene appears to play a significant role in gingival hyperplasia. Bacterial plaques allow the concentration of drugs in the build-up area and produce an inflammatory state, leading to increased fibroblast proliferation, which assists in DIGO formation.[9,10] Substituting the drug amlodipine with another antihypertensive remains the basis of management. Supplements of folic acid and ascorbic acid are also recommended. Reduction in the size of gingival overgrowth has been reported within a week of drug withdrawal and may lead to complete resolution.[2] Patients benefit from effective oral hygiene measures, professional tooth cleaning, scaling, and root planning. If gingival enlargement persists after carefully considering previously mentioned approaches, these cases must be treated by either gingivectomy or flap surgery. [2,5,6] In our patient, substituting the drug amlodipine with ramipril was enough. Gingivectomy or other surgical interventions were not performed. The patient's dentist followed up with oral cleaning, scaling, and monitoring of gingival status.

Finally, we emphasize that gingival overgrowth could be a side effect of amlodipine even with a very short-term, low-dose administration and in females. Physicians and dentists should be aware of the etiologic medications that can induce gingival hyperplasia and be able to identify changes in the oral cavity in such patients and to prevent, diagnose, and successfully manage them. Also, in this case, when CCB is started in patients with poor oral hygiene, informing the patient about these side effects will be beneficial in avoiding unnecessary examinations.

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Case Report
Internal Medicine
DOI: 10.56016/dahudermj.1442873

DAHUDER
Medical Journal
e-ISSN: 2791-9250

Adult celiac disease presented with celiac crisis: Report of two cases

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ABSTRACT

Two patients (case 1: 29 years old and case 2: 66 years old. female) with no known medical history of chronic diseases, including celiac disease, presented to the hospital with prolonged diarrhea, weight loss, and severe hypocalcemia at different times. They were admitted to the hospital for hemodynamic instability in the setting of severe dehydration and electrolyte disturbances. Physical examination revealed a positive trousseau sign in Case 1. The typical laboratory features of both cases were low magnesium, low potassium, low vitamin D, low ferritin, and prolonged coagulation tests. In addition to those labs, case 2 also has metabolic acidosis. In both cases, the titers of the tissue transglutaminase IgA and IgG and the anti-endomysium antibody were high, and the histopathology of the duodenal biopsy was consistent with villous atrophy, crypt hyperplasia, and an increase in intraepithelial lymphocytes, suggesting celiac disease. Both cases responded quickly to treatment with a gluten-free diet, fluid, electrolyte, vitamin D, and K replacements, and were discharged. Celiac crisis is a rare presentation of celiac disease characterized by acute, severe metabolic imbalances resulting in high mortality and morbidity, with severe diarrhea, hypoproteinemia, and metabolic and electrolyte disturbances. It is typically seen in children under 2 years of age but can also be encountered in adulthood. Most cases respond to gluten cessation, nutritional support, and rarely steroid treatment.

Keywords: Celiac crisis, Dehydration, Diarrhea, Electrolyte imbalance, Metabolic disturbance

Celiac disease (CD) is a systemic, immunologically mediated disease that occurs in genetically susceptible individuals due to consuming gluten-containing foods. The frequency is reported to be 1% in most populations. The common symptoms include chronic diarrhea, abdominal pain, bloating, and weight loss. The clinical range of cases can vary from asymptomatic to life-threatening, requiring hospitalization.[1] Standard diagnostic criteria for celiac are modified Marsh classification 3a or higher and positive tissue transglutaminase antibodies, endomysium antibody or deamidated gliadin peptide antibody serology, or positive HLA DQ2 or DQ8 and clinical response to treatment with a gluten-free diet.[2,3] The Celiac crisis was first described in a case series in 1953, characterized by a mortality rate of 9%, which can occur mostly in children under the age of 2 but can also be seen in adults. It has high morbidity and high mortality, characterized by acute, dramatic metabolic imbalances resulting from celiac disease, including severe diarrhea, hypoproteinemia, and metabolic and electrolyte imbalances.[4-6] Treatment for celiac crisis consists of a gluten-free diet, parenteral fluid replacement, nutritional support, and corticosteroids are used in some cases.[7]

Celiac crisis is a rare presentation of acute, dra-

Received: *February 26, 2024****; Accepted:*** *March 26, 2024****; Published Online:*** *October 29, 2024*

How to cite this article: *Uzunlulu M, Eken E, Pala E, İğneci E, Nehar Toprak Z. Adult celiac disease presented with celiac crisis: Report of two cases. DAHUDER MJ 2024,4(4):103-107. DOI: 10.56016/dahudermj.1442873*

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Available at http://dergipark.org.tr/en/pub/dahudermj

matic, metabolic imbalance of celiac disease, characterized by severe diarrhea, hypoproteinemia, and metabolic and electrolyte disturbances requiring hospitalization, with high mortality and morbidity.

Although celiac crisis is mainly seen in children under 2 years of age, it can also be diagnosed in adults. Precipitating factors such as surgery, pregnancy, immunosuppressive therapy, and infections may not always be identified.

Celiac crisis should be considered in the differential diagnosis of patients presenting with unexplained diarrhea and weight loss accompanied by hemodynamic disturbance and severe electrolyte deficiency, with or without a known diagnosis of Celiac disease. Early diagnosis of celiac crisis, gluten-free diet, parenteral fluid replacement, and nutritional support will reduce mortality and morbidity in these patients.

These cases reported female cases of different ages, with no medical history of celiac disease, who presented to the hospital with a similar clinic and were diagnosed with celiac crisis based on clinical, serological, and histopathological findings. Informed consent was obtained from all patients at the beginning of the study procedure.

CASE PRESENTATION

CASE 1

A 29-year-old female patient who is 2 months postpartum, without any chronic disease, presented to the emergency department with complaints of diarrhea and muscle cramps in her hands that have been ongoing for 1 month. The patient had yellow, watery, non-bloody, mucus-free, and odorless diarrhea that occurred 8 to 10 times a day for the past 1 month. The review of the systems showed positive results for fatigue, dizziness, and weight loss of approximately 15 kilograms in the last month.

Vitals were temperature of 36,7°C, blood pressure of 90/50 mmHg, pulse of 100 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% (in room air).

On physical examinations, the patient was not ill, appearing, alert, and oriented to person, place, and time. Mucous membranes were dry, and bowel sounds were hyperactive during the abdominal examination. The Trousseau sign was positive.

Laboratory results showed hypokalemia (2.7 mEq/L, standard: 3.5-5.1), hypocalcemia (corrected: 7,3 mg/dL, expected: 8.4-10.2), hypomagnesemia (0.9 mg/dL, expected: 1.6-2.6), vitamin D deficiency (3 µg/L, expected: 30-100), and prolonged coagulation test results (active partial thromboplastin time: 36.2 seconds, expected: 25.6-35.2, and INR: 2.04, normal range: 0.8-1.25). The EKG showed a normal sinus rhythm. Chest x-ray and urinalysis were normal. No blood cells were seen in the stool microscopy. No growth was seen in stool and blood cultures. Colonoscopies were normal. Gastroscopy showed blunting of the papilla in the second portion of the duodenum, nodular appearance, and scalloping in the mucosa. Biopsies were taken from the bulb and the second

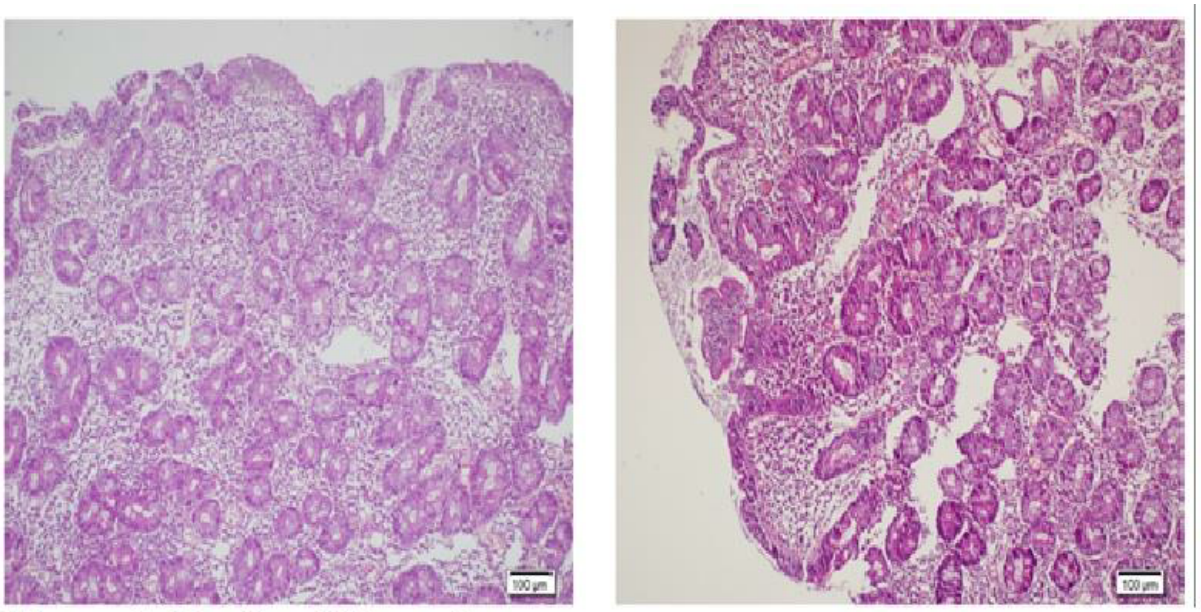

Figure 1. Duodenal biopsy image

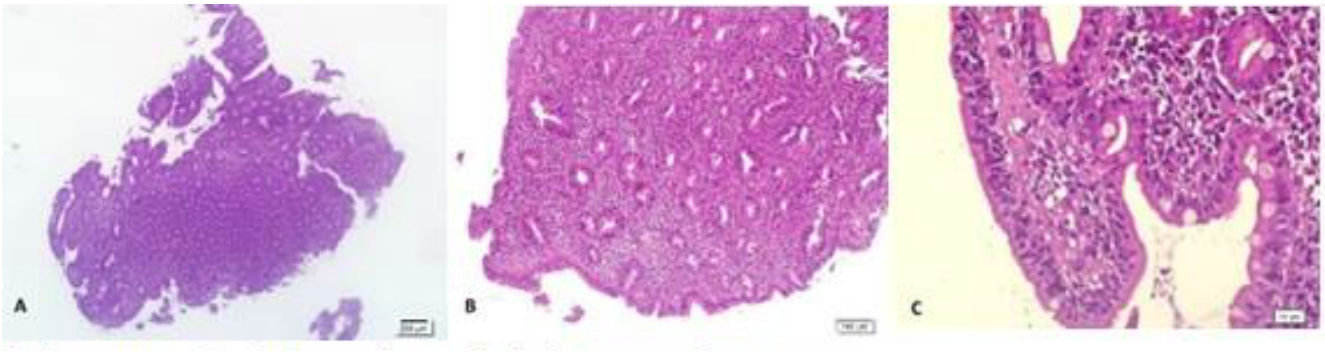

Figure 2. Duodenal biopsy image

portion. Histopathological analysis showed marked villous atrophy, blunting, and increased intraepithelial lymphocytes in the duodenum (see Figure 1). It was evaluated as Marsh type 3b. Serological tests showed high levels of tissue transglutaminase immunoglobulin A (>200, normal range: <20) and immunoglobulin G (1.63, normal range: <1), antigliadin immunoglobulin A (>200, normal range: <25), and immunoglobulin G (124.16, normal range: <25). Anti-endomysium antibody 4+ (titer: 1/320) was detected.

Clinical course: The patient's vitals were monitored. Electrolytes are replaced as needed with intravenous calcium, magnesium, and potassium. Vitamin D was also administered orally. Intravenous vitamin K was administered for abnormalities on coagulation tests, considering these imbalances and deficits caused by malabsorption. Based on all findings, the patient was diagnosed with a Celiac crisis and started a gluten-free diet. After replacement, the electrolyte values returned to normal, the coagulation tests improved, and the patient was discharged with stable vital signs. At 1-week follow-up, the patient's diarrhea had resolved.

CASE 2

A sixty-six-year-old female with no medical history of chronic disease and not on any medications presented to the emergency department with a complaint of diarrhea for the last 15-20 days. She has been experiencing diarrhea 3-4 times a day, without blood or mucus. The patient has taken probiotics a few times and lost 5-6 kilograms since the onset of diarrhea. Also, she has had shorter and intermittent diarrhea attacks in the past. Vitals were temperature of 36,5 °C, blood pressure of 100/55 mmHg, pulse of 112/min, breathing rate of 15 breaths per minute, and oxygen saturation in room air of 99%.

On physical examination, the patient was not ill-appearing, alert and oriented. She had dry mucous membranes and hyperactive bowel sounds on abdominal auscultation. Laboratory tests were significant for iron-deficiency anemia (hemoglobin: 10.3 g/dl normal: 12.5-16, MCV: 67.5 f normal: 80-100, iron: 18 µg/dL normal: 33-193, ferritin: 9 µg/L normal: 13-150), mild renal dysfunction (creatinine: 1.27 mg/dL normal: 0.5-0.9), hypokalemia (2.9 mmol/L normal: 3.5-5.1), hypocalcemia (corrected calcium: 7.74 mg/dL normal: 8.4-10.2), hypomagnesemia (1.53 mg/dL normal: 1.6-2.6), metabolic acidosis (pH: 7.15, HCO3: 10.4 mmol/L, PCO2: 27.5 mmHg), elevated C-reactive protein (3.05 mg/L normal range: 0-5), prolonged coagulation tests (aPTT: 29.1 sec (normal range: 25.6-33.6), INR: 2.93 (0.8-1.25), and low vitamin D: 10.2 µg/L (30-100). Urinalysis and chest radiograph were normal. The EKG showed a normal sinus rhythm. Stool tests showed liquid and mucus diarrhea, with no leukocytes or erythrocytes seen under the microscope. The stool and blood cultures showed no growth. The colonoscopy was normal. Gastroscopy showed erosion in the antrum, effacement, and nodularity in the duodenal folds. Biopsy of the second part of the duodenum showed histopathology of villous atrophy, crypt hyperplasia, increased intraepithelial lymphocytes, and widespread active inflammation (see Figure 2). It was evaluated as Marsh type 3c. Serological tests showed tissue transglutaminase IgA (>200 RU/ml normal range: <20), tissue transglutaminase IgG (0.91 normal range: <1), anti-gliadin IgA (126.9 RU/ml normal range: <25), and anti-endomysium antibody 4+ (titer: 1/3200).

Clinical course: The patient's vitals were monitored. Calcium, potassium, magnesium, and vitamin D were replaced. Bicarbonate was given for severe metabolic acidosis. Intravenous vitamin K was administered for abnormalities on coagulation tests.

Based on clinical, serological, and histopathological findings, the patient was diagnosed with a Celiac crisis and started a gluten-free diet. After electrolyte replacement, values returned to the normal range, coagulation tests and metabolic acidosis improved, and the patient was discharged with stable vitals. At 1 week of follow-up, the patient's diarrhea had been resolved.

DISCUSSION

The Celiac crisis is a rare and life-threatening acute malabsorptive condition that accounts for less than 1% of all cases of celiac disease. However, its prevalence has increased over the past ten years, probably due to improved diagnostic criteria.[8] Although most celiac patients experience mild symptoms, the cause of celiac crisis in some individuals remains unclear. It may be related to severe mucosal inflammation, immune activation, and disrupted standard motility patterns.[9]

Although there are no universally accepted, standardized diagnostic criteria for celiac crisis, it is considered a potentially life-threatening acute malabsorptive condition. It is characterized by hospitalization and/or the need for parenteral nutrition, as well as severe symptoms related to celiac disease. These symptoms include acute-onset or rapidly progressive gastrointestinal symptoms, along with at least two of the following criteria: severe dehydration symptoms, including hemodynamic instability and/or orthostatic changes, renal dysfunction (creatinine >;2.0 g/dL), metabolic acidosis (pH<;7.35), hypoproteinemia (albumin <;3 g/dL), electrolyte imbalances (hyponatremia/hypernatremia, hypocalcemia, hypokalemia, or hypomagnesemia), and weight loss (> 5 kg) are used to diagnose celiac crisis.[9]

In our cases, weight loss, electrolyte disturbances, and hemodynamic imbalance/ orthostatic hypotension were the standard diagnostic criteria in addition to the main criteria. In contrast, in Case 2, metabolic acidosis accompanied the picture. The common features of our cases included: both cases were female, there was no known history of celiac disease, severe diarrhea, and weight loss were the predominant symptoms, and the initial presentation was serious dehydration causing hemodynamic instability and severe electrolyte disturbances. In addition, both patients responded quickly to treatment. The differences between the cases included the age and the presence of mild renal dysfunction and iron deficiency anemia in case 2.

Although the pathophysiological mechanism responsible for the celiac crisis is not fully understood, surgery, pregnancy, immunosuppressive therapy, infections, and other causes are described as trigger factors.[6,7,10,11] In our cases, it was thought that giving birth 2 months ago might be a triggering factor in case 1, but no triggering factor was found in case 2.

It has been shown that clinical improvement is achieved in approximately 50% of the cases with a gluten-free diet, parenteral fluid replacement, and nutritional support.[9] In cases where rapid recovery cannot be achieved with standard treatment, short-term prednisone or budesonide treatment has been reported to be beneficial.[12] In our cases, rapid improvement was observed with a gluten-free diet, parenteral fluid replacement, and nutritional support without the corticosteroid treatment.

CONCLUSION

In patients with unexplained diarrhea and weight loss accompanied by hemodynamic instability and severe/multiple electrolyte disturbances, regardless of age, sex, or medical history of celiac disease, the possibility of a celiac crisis should be considered.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MU, EE, EP, Eİ, ZNT; Study Design: MU, EE, EP, Eİ, ZNT; Supervision; MU, EE, EP, Eİ, ZNT; Materials: EP, MU, Eİ; Data Collection and/or Processing: EP, Eİ, ZNT; Analysis and/or Data Interpretation: EE, MU, EP; Literature Review: MU, EE; Critical Review: EE, MU; Manuscript preparing: MU, EE.

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