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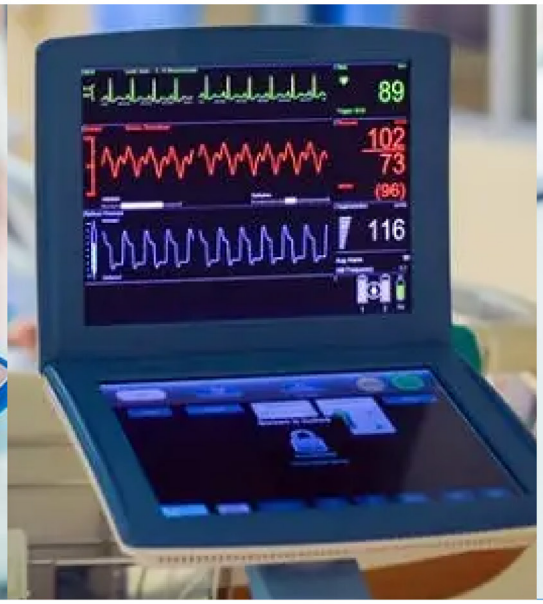

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Dear Colleagues,

In 2023 was the first year of our journal, the Intercontinental Journal of Internal Medicine, and we proudly shared first 4 issues with you. In 2024, we are proud to continue our way by presenting studies that will shed light on science and the future.

We are publishing our first issue this March, as we do last year. In this issue, current and interesting information in different medical fields is shared with original articles, case reports and reviews. We believe that this content, which shares recent and current topics from internal medicine ,will be useful for all physicians.

As we celebrate the 2nd publishing year of our journal, we would like to take this opportunity to thank the readers, for their continued interest throughout the year, the authors who submitted their articles to the journal, to reviewers who provided objective guidance in the evaluation of the articles, and all our editors who ensured that ICJIM continued its regular publication life, for their contributions.

Assoc. Prof. Bilgin Bahadır BAŞGÖZ
Associate Editor-in-Chief

The Intercontinental Journal of
Internal Medicine

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Original Article

Isolated first hour hyperglycemia in oral glucose tolerance test is associated with insulin resistance

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ABSTRACT

Aims: To investigate metabolic and hemogram derived inflammatory markers in patients with isolated hyperglycemia on 1st hour of oral glucose tolerance test.

Methods: The subjects undergone 75 g OGTT for any reason were enrolled to the present retrospective cross sectional study. Plasma glucose, insulin and hemogram derived inflammatory markers, including mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) of the subjects in isolated hyperglycemia group compared to those in healthy controls.

Results: Mean PLR of the isolated hyperglycemia and control groups were 106.4±28.8% and 121.4±38%, respectively (p=0.043). Mean HOMA–IR values of patients and controls were 4.09±2.84 and 3.02±2.2, respectively (p=0.027). Plasma glucose at 1st hour was significantly correlated with fasting insulin (r=0.286; p=0.018) and HOMA-IR (r=0.32; p=0.007).

Conclusion: We think that isolated 1st hour hyperglycemia in OGTT should not be classified as normal since it is associated with increased fasting insulin and HOMA-IR levels. However, studies with larger cohort are needed to confirm our results.

Keywords: Isolated hyperglycemia, oral glucose tolerance test, insulin, HOMA-IR, platelet to lymphocyte ratio

INTRODUCTION

Subjects were considered to have prediabetes when their glucose levels on fasting and at 2nd hour in oral glucose test do not meet the criteria to establish diabetes mellitus diagnosis but yet, too high to consider as normal. There is no international consensus on the definition of prediabetes. Impaired fasting glucose (IFG) is defined as fasting plasma glucose levels between 100-125 mg/dl, and 2-hour plasma glucose levels <140 mg/dl, while impaired glucose tolerance (IGT) is defined as fasting plasma glucose levels <100 mg/dl, and 2-hour plasma glucose levels between 140-199 mg/dL.[1]

Although international guidelines have changed over the years to reduce the threshold for the diagnosis of diabetes and prediabetes, according to the current definitions of prediabetes, the beta-cell function is greatly impaired at the time of diagnosis, thus it is recommended that attention should be focused on early identification of individuals with prediabetes. Since it is found that beta-cell function progressively decreases even at glucose levels below the threshold values for IFG or IGT, more sensitive diagnostic methods are needed to identify individuals at risk for Type 2 diabetes mellitus (DM). [2,3]

The relationships between prediabetes and increased risk of early forms of diabetic kidney disease, diabetic neuropathy, macrovascular disease, and diabetic retinopathy have been well established in data in literature.[4] Therefore, early diagnosis of prediabetes and prevention of its possible complications are essential.

No current international guidelines for prediabetes diagnostic criteria include plasma glucose one hour after oral glucose tolerance test (OGTT). However, recent studies have shown that individuals with elevated plasma glucose levels after standard OGTT are at high risk for diabetes development, micro-macrovascular complications, and mortality.[5,6]

High serum glucose levels at first hour in OGTT were also reported to be associated with obesity, hypertension, hypercholesterolemia, metabolic syndrome, diabetic retinopathy, left ventricular diastolic dysfunction, and an

increase in carotid artery intima thickness and, therefore, atherosclerosis.[7-9]

Platelets have many bodily functions and they have essential role in thrombosis, progression of atherosclerotic lesions and plaque destabilization. They contain many mediators of coagulation, inflammation, and atherosclerosis and they release these substances when necessary.[10] A hemogram marker, mean platelet volume (MPV) is considered as a marker of platelet activation and refers the size of circulating platelets.[11] Platelet volume is introduced as a marker of platelet function as well activation and may have other functions in inflammatory conditions.[12] MPV has been shown to be higher in prediabetic patients than in normoglycemic subjects. It has also been observed that among the patients with normal fasting glucose, those with more elevated glucose have higher MPV compared to those with lower glucose.[13,14]

Infections and inflammatory stimuli cause an increase in neutrophil count and a reduction in lymphocyte count, which constitutes neutrophil/lymphocyte ratio as a superior marker than its components in diagnosis of inflammatory conditions.[15] NLR is higher in patients with a previous diagnosis of uncomplicated diabetes and newly diagnosed with OGTT compared to subjects with impaired glucose tolerance. It is also higher in people with impaired glucose tolerance than those with normal glucose tolerance.[16]

PLR was found to be the lowest in the newly diagnosed diabetic group and lower in the impaired glucose tolerance group than in the normal glucose tolerance group; however, PLR was higher in the previously diagnosed diabetic group compared to the other groups.[16]

These markers have not been studied in Isolated hyperglycemia at 1-hour on OGTT. In this study, we compared MPV, NLR, and PLR values of patients with isolated 1-hour glucose elevation during OGTT with those with normal glucose tolerance. We also investigated whether early diagnosis of prediabetes and diabetes is possible by assessing this tool.

METHODS

Ethics

The approval of Ethics Committee of Kırıkkale University, dated 02.10.2018 and numbered 02.10.2018 was obtained before the study, and it was conducted in accordance with the Declaration of Helsinki.

Study Cohort

From January 1, 2016 to December 31, 2017, patients who underwent a 75-gram standard oral glucose tolerance test (OGTT) in the Internal Medicine/Endocrinology Clinic at the Kırıkkale University Faculty of Medicine Hospital were selected to participate in the study if they had an isolated 1-hour glucose elevation (≥155 mg/dl). Patients who met the exclusion criteria or whose visceral fat index (VFI) data were not available were excluded, leaving 50 patients included in the study. A control group of 48 healthy individuals with normal glucose tolerance (NGT) and matching demographic characteristics was selected based on the OGTT.

The inclusion criteria for the study were adult male or female patients over the age of 18, who had undergone a 75-gram standard OGTT and had normal fasting plasma glucose levels and 2-hour plasma glucose levels.

The exclusion criteria for the study were patients under the age of 18, with a diagnosis of diabetes, thyroid dysfunction, kidney failure, liver failure, use of antidepressants, cerebrovascular disease, cardiovascular disease, use of any medication, previously diagnosed glucose intolerance (diabetes/pre-diabetes), use of oral antidiabetic or diabetogenic medications, diagnosis of hypertension or use of hypertension medications, cancer or hematologic disease, smoking or alcohol consumption, and pregnant patients.

The following were measured using retrospective data from the biochemistry laboratory of our hospital: fasting plasma glucose (using GLUC Hk Gen.3,800 tests by Cobas C kit, UV test hexokinase method), total cholesterol (by Cobas Integra CHOL 2 Hico 400 tests kit), triglyceride (TG Gen.3 200 tests, Cocas C, enzymatic colorimetric method with Integra kit), high-density lipoprotein (HDL-C Gen.3, 200 tests, Cobas C, homogeneous enzymatic colorimetric method with integrated kit), LDL cholesterol level (using Friedewald's formula [LDL=Total cholesterol- (VLDL + HDL); VLDL=TG/5] when triglyceride level was under 400 mg/dl).

In our study, there was no patient and control group with triglyceride levels above 400 mg/dl. C-reactive protein (Cobas C 501 particle surface expanded immunoturbidimetric assay) and insulin (Insulin Elecsys 100 T. kit) were tested with electrochemiluminescence method using cobas®e601 brand device and original Roche diagnostic kits (Roche Diagnostic GmbH, Sandhofer Strasse 116, D-68305 Mannheim).

Hemogram parameters (hemoglobin, white blood cell, platelet, neutrophil, lymphocyte, MPV, PDW) were measured by flow cytometric impedance method on an automatic whole blood count device (Mindray BC 6800, Shenzhen, China). Simply division of neutrophils by lymphocytes and platelets by lymphocytes was used in calculation of NLR and PLR, respectively.

HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) score was calculated using [plasma fasting glucose x plasma fasting insulin level] / 405 formula.

Values above HOMA-IR ≥2.7 were considered insulin resistance.

Statistical Analysis

Data were analyzed using IBM Statistical Package for Social Sciences 21.0 (Chicago, IL, USA). Descriptive statistics are given as a number, percentage, mean, and standard deviation. The chi-square test was used to compare categorical variables between groups. Kolmogorov-Smirnov test, Shapiro-Wilks test, and histograms were used in normality analysis of study variables.

The t-test was used in independent groups to compare the numerical variables that fit the normal distribution among the independent groups. The Mann-Whitney U test was used to compare the numerical variables that did not fit the normal distribution among the independent groups. Pearson correlation analysis was performed for variables that conform to the normal distribution, and Spearman correlation analysis was used for variables that do not, in correlation analysis. For the analysis of the relationship between two variables, For statistical significance, $p < 0.05$ was taken as the limit value.

RESULTS

Fifty patients and forty-eight healthy people were included in the study. Of the 50 patients, 66.0% (n=33) of subjects were female, and 34.0% (n=15) of those were male. Among the 48 healthy people, 68.8% (n=33) of individuals were female, and 31.2% (n=15) of those were male. There was no statistically significant difference between the two groups in terms of gender (p=0.772). The mean age was 45.2±13.3 years in the patient group and 44.4±13.3 years in the control group. There was no statistically significant difference between the groups regarding age (p= 0.775)

The weight, height, and BMI did not statistically differ between the two groups (p=0.685, 0.787, and 0.647, respectively) (**Table 1**). The patients' mean plasma glucose levels after OGTT for the 0-hour, 1-hour, and 2-hour were 92.2±5.8 mg/dl, 178.4±18.9 mg/dl, 115.2±16.0 mg/dl, respectively. The control group's mean plasma glucose levels after OGTT were 92.0±8.2 mg/dl at the 0-hour, 116.5±20.7 mg/dl at the 1-hour, and 97.9±16.9 mg/dl at the 2-hour. In the patient group, plasma glucose values at the first hour (p <0.001) and at the second hour (p <0.001) were significantly higher than the control group. Fasting plasma glucose was not significantly different among study groups (p=0.210) (**Table 2**).

Table 1. Results of anthropometric measurements

Variable name	Patient group (n=50) *	Control group (n=48) *	p value **
Age (years)	45.2±13.3	44.4±13.3	0.775
BMI (kg/m²)	32.4±8.0	31.7±7.3	0.647
Weight (kg)	88.7±21.2	86.0±16.9	0.685
Height (m)	1.657±0.083	1.652±0.087	0.787

* Mean±standard deviation is given.
** p <0.05 was taken as the limit value of significance.

Table 2. OGTT results

Variable name	Patient group (n=50) *	Control group (n=48) *	p value **
OGTT 0-hour (mg/dl)	92.2±5.8	92.0±8.2	0.210
OGTT 1-hour (mg/dl)	178.4±18.9	116.5 ±2 0.7	**<0.001**
OGTT 2-hour(mg/dl)	115.2±16.0	97.9±16.9	**<0.001**

* Mean±standard deviation is given.
** p <0.05 was taken as the limit value of significance.

There was no statistically considerable difference between the two groups in terms of HbA1c (p=0.44). The mean fasting insulin value was 17.7±12.0 µIU/ml in the patient group and 13.5±9.6 µIU/ml in the control group. Fasting insulin levels were significantly higher in the patient group (p=0.041). The mean HOMA–IR values of patients and controls were 4.09±2.84 and 3.02±2.2, respectively. The HOMA – IR values were found to be significantly higher in the patient group than in the control group (p=0.027). CRP was not statistically different between study and control groups (p=0.814). See in **Table 3**.

Table 3. HbA1c, fasting insulin, HOMA–IR and CRP results

Variable name	Patient group (n=50) *	Control group (n=48) *	p value **
HbA1c (%)	5.5±0.3	5.7±0.6	0.440
Fasting insulin (µIU/ml)	17.7±12.0	13.5±9.6	**0.041**
HOMA–IR	4.09±2.84	3.02±2.25	**0.027**
CRP (mg/L)	2.78±2.12	2.37±1.33	0.814

* Mean±standard deviation is given.
** p <0.05 was taken as the limit value of significance.

Hemoglobin of healthy subjects was 14±1.7 g/dl. Blood hemoglobin level in study group was not statistically different than the controls (p=0.112). Mean WBC was higher in OGTT group (8240±1607/mm³) compared to control subjects (7519±1861/mm³) (p=0.013). The numbers of neutrophils of study and control groups were 4908±1404/mm³, and 4497±1327/mm³, respectively (p=0.114). Lymphocyte count was 2626±718 / mm³ in OGTT group and 2255±597/mm³ in control group. There was a considerable statistical difference between each group (p=0.008). The two groups did not significantly differ regarding platelet count (p=0.518). There was no statistically significant difference between the two groups in terms of MPV (p=0.814). NLR was not significantly different between study and control groups (p=0.29). The platelet-lymphocyte ratio (PLR) was 106.4±28.8% in study group and 121.4±38% in control group (p=0.043). **Table 4** shows hemogram parameters study groups.

Table 4. Complete blood count values of the study population

Variable name	Patient group (n=50) *	Control group (n=48) *	p value **
Hemoglobin (g/dl)	14.6±1.8	14.0±1.7	0.112
White blood cell count (count/mm³)	8240±1607	7519±1861	**0.013**
Neutrophil count (count/mm³)	4908±1404	4497±1327	0.114
Lymphocyte count (count/mm³)	2626±718	2255±597	**0.008**
Platelet count (count/mm³)	266645±55931	258847±60474	0.518
MPV (fL)	9.94±1.28	10.0±1.10	0.814
PCT (%)	0.25±0.05	0.24±0.07	0.671
NLR (%)	2.03±0.95	2.09±0.72	0.290
PLR (%)	106.4±28.8	121.4±38.0	**0.043**

* Mean±standard deviation is given.
** p <0.05 was taken as the limit value of significance.

As shown in **Table 5**, there was no statistically significant correlation between OGTT 1-hour glucose and the number of platelets (r=0.048; p=0.643), MPV (r=-0.014; p=0.895), PCT (r=0.004; p=0.972), NLR (r=-0.064; p=0.540) and CRP (r=0.253; p=0.102).

Table 5. Correlation of complete blood count, CRP, HbA1c, insulin and HOMA-IR results with OGTT 1-hour plasma glucose

Variable name	Correlation coefficient	p value **
Hemoglobin	0.243	**0.018**
White blood cell count	0.318	**0.002**
Neutrophil count	0.217	**0.035**
Lymphocyte count	0.288	**0.005**
Platelet count	0.048	0.643
MPV	-0.014	0.895
PCT	0.004	0.972
NLR	-0.064	0.540
PLR	-0.233	**0.024**
CRP	0.253	0.102
HbA1c	-0.049	0.704
Fasting insulin	0.286	**0.018**
HOMA–IR	0.322	**0.007**

* The correlations of the variables with OGTT 1st hour glucose were examined in all subjects.
** p <0.05 was taken as the limit value of significance.

There was a statistically significant positive correlation between OGTT 1-hour glucose and hemoglobin (r=0.243; p=0.018), white blood cell count (r=0.318; p=0.002),

neutrophil count (r=0.217; p=0.035) and lymphocyte count (r=0.288; p=0.005). There was a statistically significant negative correlation between OGTT 1-hour glucose and PLR (r=-0.233; p=0.024).

No statistically significant correlation was found between OGTT 1st hour glucose and HbA1c (r=-0.049; p=0.704). A statistically significant positive correlation was found between OGTT 1-hour glucose and fasting insulin (r=0.286; p=0.018) and HOMA-IR (r=0.32; p=0.007) values of the study groups.

DISCUSSION

In this study, we investigated the markers of chronic inflammation including MPV, NLR, and PLR in patients with elevated 1st hour during OGTT. The MPV and NLR values were not different in the patient group, and PLR was significantly lower in the patient group in our study. Besides, the number of white blood cells and insulin levels were significantly higher in the patients.

The 155 mg/dl threshold for 1-hour plasma glucose after OGTT was first identified in San Antonio Heart Study (SAHS) over 1611 patients without diabetes. In this study, the patients were followed for an average of 7-8 years. It was shown that plasma glucose elevation after OGTT predicted the risk of type 2 DM (16.7%) that would develop after 7-8 years with higher sensitivity than IGT (threshold 140 mg/dl).[17] When the literature is reviewed, the most comprehensive study is by Bardini et al.[18], including 1062 patients. According to this study, patients were divided into four groups according to whether they were prediabetic and whether their plasma glucose levels were higher than 155 in OGTT. According to the results of the study, significant increases in fibrinogen level and white blood cell count were found in patients with plasma glucose above 155 mg/dl in the first hour compared to the other patients. The number of white blood cells increased in our study similarly.

This study showed that OGTT 1st hour glucose >155 mg/dl is an actual threshold for subclinical inflammation, dyslipidemia, and insulin resistance; therefore, this threshold value should be considered in order to identify patients with high cardiovascular risk.[18]

In addition, previous studies have shown that elevated glucose levels are associated with obesity, hypertension, hypercholesterolemia, metabolic syndrome and left ventricular diastolic dysfunction. It was shown that carotid artery intima thickness increased, the prevalence and incidence of diabetic retinopathy were significantly increased, eGFR was lower, and the high levels of ALT and GGT were associated with elevated 1-hour glucose levels.[7-9,19,20]

In another study of methods for predicting the development of type 2 diabetes, it was shown that the high plasma glucose concentration during the first hour of OGTT was higher in predicting the risk of developing future Type 2 DM compared with HbAlc alone. According to another study, 1-hour plasma glucose concentration during OGTT was found to have a stronger correlation with insulin secretion, insulin resistance, and insulin secretion/insulin resistance index compared with 2-hour plasma glucose concentration, and 1-hour plasma glucose concentration was reported to be more potent in predicting diabetes.[21,22] It is known that MPV and NLR values are increased in prediabetes and diabetes subjects compared to the normal population. In addition, studies have shown that MPV increases in diseases such as DM, acute coronary syndrome, stroke, preeclampsia, and hypercholesterolemia.[23-26]

In a retrospective study of 1876 subjects, the relationship between MPV and plasma fasting glucose levels in the general population was investigated, and MPV was found to be higher in prediabetic patients than in normoglycemic subjects. Moreover, MPV and fasting glucose levels were found to be higher in patients with higher glucose levels than those with low glucose levels, not only in prediabetics but also among patients with normal fasting blood glucose.[13] In the literature, there is only one study, conducted with 48 patients and 48 controls, related to impaired glucose tolerance. As a result of this study, it was found that MPV was significantly higher in the impaired glucose tolerance group than the control group, and MPV was positively correlated with plasma glucose levels at the 2-hour after OGTT in the impaired glucose tolerance group.[14]

In literature, it has been shown that low preoperative PLR may be associated with an increased incidence of postoperative complications regardless of age, BMI, operative procedure, and disease stage, according to studies on PLR.[27] In the previous studies, it was reported that PLR value increased in advanced stages of diabetes despite the decrease in the prediabetic and early diabetic period.[16] From the point of view of PLR, our result was consistent with the previously described decrease in PLR in the prediabetic and early diabetic periods.

In our study, BMI values were above 30 in the control group, similar to the patient group. The fact that MPV, CRP, and NLR values of controls were identical to the patient group may be related to this situation. MPV and CRP values have already been shown to be higher in obese individuals than in normal individuals.[28,29]

When the previous studies were examined, insulin, HOMA-IR, CRP, and white blood cell count were found to be higher in the prediabetic group compared to individuals with normal glucose tolerance.[30-33]

Similar to these results, in our study, insulin levels were remarkably higher in patients with isolated 1-hour elevation during OGTT. We assume that insulin and HOMA-IR levels increase due to the compensatory rise in beta cell function, which begins many years before the diagnosis of diabetes. In fact, in the British Whitehall II study, it was observed that insulin secretion remained constant over the 13-year observation period and showed a remarkable compensatory increase 3-4 years before the diagnosis of diabetes. These results indicate that insulin resistance initiates years before the development of diabetes.[34] Accordingly, we found elevated WBC count in OGTT group compared to controls in present study.

In another study examining the effects of white blood cell levels on the development of diabetes, a total of 352 non-diabetic patients (272 NGT and 80 IGT) were included in the study, and it was found to be significantly higher in patients with IGT (8,470±2,153) than patients with NGT (8,000±1,973).[35]

When 272 patients were prospectively examined, high white blood cell levels predicted progression from NGT to diabetes. Furthermore, in this study, elevated white blood cell levels were shown to be associated with a decrease in insulin sensitivity. Collectively, this data indicates the

role of inflammation in insulin resistance and subsequent development of type 2 diabetes.[35]

It is also thought that activation of the immune system causes a decrease in insulin sensitivity, and its result contributes to developing type 2 diabetes. Interleukin-6 (IL-6), a potent white blood cell differentiation factor, produced primarily on adipose tissue, is associated with insulin resistance.[36,37] Therefore, it can be said that IL-6 can be a factor that increases the white blood cell and causes insulin resistance.[37] Association between inflammation markers (CRP) and prediabetes was well established in the literature. A study consisted of 15,010 adults reported that prediabetic subjects have higher CRP levels than other individuals.[30] There was only a slight increase between prediabetic and diabetic subjects in term of CRP. These findings suggest that onset of diabetes could be related with inflammatory modulation. There are other recent studies supporting the relationship between prediabetes and CRP elevation.[31,32] However, CRP was not significantly different between study and control groups in present work.

In terms of the limitations of the study, firstly, the design of our study was retrospective, and the patients who had isolated 1st hour with standard OGTT between 1 January 2016 and 31 December 2017 were screened.

Therefore, other markers of inflammation, such as IL-6 and high-sensitivity CRP, could not be studied. The other limitation of our study was that the BMI values of the patient and control groups were above 30. The similarity of parameters such as MPV and CRP in the patient and control groups may be related to this situation. On the other hand, when the literature is reviewed, inflammation markers such as MPV, NLR, and PLR have not been studied in patients with isolated 1-hour plasma glucose elevation during oral glucose tolerance test, and this is the first study in this field.

CONCLUSION

Isolated first hour hyperglycemia in oral glucose tolerance test is associated with insulin resistance, therefore, cautiously clinical follow-up is warranted for those subject. Interventions to reduce first hour hyperglycemia in OGTT may yield further benefit in delaying and prevention of overt diabetes. We think that isolated 1st hour hyperglycemia in OGTT should not be classified as normal since it is associated with increased fasting insulin and HOMA-IR levels.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Kırıkkale University Clinical Researches Ethics Committee (Date: 02.10.2018, Decision No: 15/36).

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

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

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

Data Availability Statement: Data will be made available by the corresponding author on reasonable request.

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Original Article

The relationship between albumin level and the development of acute kidney injury and mortality in critically COVID-19 patients

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ABSTRACT

Aims: TThe impact of the coronavirus pandemic, which began in 2019, has considerably diminished; however, its effects still persist. While respiratory symptoms have been prominent during the pandemic, acute kidney disease has emerged as a significant contributor to morbidity and mortality. This study aims to demonstrate that serum albumin levels can serve as a predictor for acute kidney injury (AKI) and mortality, owing to their cost- effectiveness and feasibility for use across various healthcare centers. The goal is to contribute to the reduction of AKI development and mortality rates.

Methods: The study was conducted by analyzing data from a total of 350 patients admitted to intensive care units of a training and research hospital due to COVID-19 between March 1, 2020, and April 30, 2021. Of these patients, 179 (51%) were male, and 171 (49%) were female. The data were examined retrospectively. Patients were categorized into two groups based on serum albumin levels: 2.5 mg/dl (severe hypoalbuminemia) and 2.5-3.5 mg/dl (mild hypoalbuminemia). Subsequently, the patients were further categorized into groups based on the presence or absence of AKI, and these groups were statistically compared. Demographic data, clinical information, and laboratory values of the patients were assessed. The diagnosis of acute kidney injury (AKI) was made according to KDIGO criteria. Data were compared using the SPSS version 24 software.

Results: Among the 350 patients included in the study, 115 had serum albumin levels ?2.5 mg/dl (severe hypoalbuminemia), and 235 had levels in the range of 2.5-3.5 mg/dl (mild hypoalbuminemia). Among those who developed AKI, the average albumin level was found to be 2.68 mg/dl, whereas in the group without AKI, the average albumin level was 2.76 mg/dl. Out of the total, 201 (57%) patients developed AKI, and 82% of them experienced mortality. In contrast, among the 149 (43%) patients who did not develop AKI, the mortality rate was 42%. Further subgroup analysis revealed the highest mortality rate of 88% among patients with severe hypoalbuminemia and AKI development. Conversely, the lowest mortality rate of 40% was observed in patients with mild hypoalbuminemia and no AKI.

Conclusion: This study aims to establish that low serum albumin levels should be regarded not only as a negative acute-phase reactant but also as a predictive factor for complications including acute kidney disease development and mortality. Lower albumin values are correlated with higher complication rates and increased mortality. Additionally, due to its widespread availability and low cost, serum albumin is a cost-effective diagnostic tool that can be utilized in almost any healthcare setting.

Keywords: COVID-19, hypoalbuminemia, acute kidney injury, intensive care unit, mortality

INTRODUCTION

According to the current data of the World Health Organization, approximately 769 million Coronavirus dissease–19 (COVID-19) cases have been seen worldwide and approximately 7 million of them have died.[1] Although the most common cause of COVID-19 infection-related mortality is acute respiratory failure, it is known that COVID-19 infection causes serious complaints by involving the cardiological, gastrointestinal, hepatological, nephrological, neurological, hematological, ocular and cutaneous systems in addition to respiratory system complaints.[2] Kidneys have a special importance among these organs affected by COVID-19 infection. The rate of developing acute kidney injury in those with COVID-19 infection is 28%. This rate increases up to 46% in those who are hospitalized and

followed up in the intensive care unit.[3] The mortality rate of patients who develop AKI due to COVID-19 infection is more than 5 times higher than that of those who do not develop AKI.[4]

Therefore, identifying high-risk patients for the development of AKI among COVID-19-related hospitalized patients, closely monitoring high-risk patients for the development of AKI, and taking measures to prevent the development of AKI, if possible, preventing the development of AKI damage is very important in order to increase the survival of patients and prevent the development of morbidity. Various tests have been developed for this purpose and are known to be useful in the early diagnosis of AKI. These can be listed as Cystatin-C, NGAL and KIM-1.[5] However, these tests are used only for clinical research purposes because they are expensive and not available in most centers. Therefore, they are not cost effective.

In this study, we aimed to evaluate the predictive ability of serum albumin level in predicting the development of AKI, morbidity and mortality in patients diagnosed with COVID-19 and treated in the intensive care clinic.

METHODS

Ethics

The study was carried out with the permission of Health Sciences University Gazi Yaşargil Training and Research Hospital Ethics Committee (Date: 28.04.2021, Decision No: 2021/840), and it was conducted in accordance with the Declaration of Helsinki.

Setting and Participants

This retrospective, single-center and observational study included patients aged 18 and over who were treated with a diagnosis of COVID-19 infection in the intensive care unit of a training and research hospital between 01.03.2020-30.04.2021. The participants were diagnosed with COVID-19 infection by PCR method. Patients with previously diagnosed glomerulonephritis or nephrotic syndrome, end-stage renal failure, end-stage heart failure, cirrhosis, malnutrition and protein-losing enteropathy, and patients under 18 years of age were not included in the study.

Patient Characteristics and Procedures

For all participants, demographic characteristics such as age and gender; clinical data such as diabetes hypertension, coronary heart disease, blood pressure value at the time of admission, initial oxygen support, length of hospital stay, need for dialysis, type of discharge; laboratory findings such as albumin amount, white blood cell count, neutrophil count, lymphocyte count, hemoglobin, platelets, glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, potassium, sodium, procalcitonin, ferritin, blood gas and C-reactive protein (CRP) were learned from the patient files retrospectively. Those with albumin values between 2.5 g/dl and 3.5 g/dl were defined as patients with mild hypoalbuminemia, and those with <2.5 g/dl were defined as patients with severe hypoalbuminemia (**Table 1**).

AKI development status in the patients was decided using the Kidney Dissease Improving Global Outcomes-Acute Kidney Injury (KDIGO-AKI) criteria and the patients were divided into 2 groups: those who developed AKI and those who did not develop AKI.

Table 1. Baseline characteristics of participants

Characteristic	Albumin≤ 2.5 n:115	2.5≤Albumin<3.5 n:235	p value
Age (year) mean±SD	69.5 (13.6)	65.4 (14.1)	**0.011**
Gender (%)	32.4±8.0	31.7±7.3	0.356
Male	17.4	33.4	
Female	15.4	33.7	
Mean blood pressure±SD (mm/Hg)			0.286
Systolic	124 (20.4)	126 (21)	
Diastolic	74.1 (13.5)	75.7 (13.8)	
Chronic diseases (%)			
Dm	8	24.6	0.122
HT	15.1	36.3	0.162
CAD	10	16.6	0.252
Initial oxygen support (%)			**0.002**
Mask+nasal	10	24	
Reservoir mask	4.2	12.8	
High flow	1.7	2	
CPAP	6.5	19.7	
Mechanical ventilation	9.4	8.2	
Hospitalization duration mean±SD	13.8 (min:2-max:90)	14.1 (min:2-max:129)	0.303
Need for dialysis (%)			0.422
Yes	4	6.3	
No	28.9	60.9	
Need for positive inotropes (%)			0.139
Yes	14	23.1	
No	18.9	44	
Albumin infusion (%)			**0.022**
Yes	21.4	35.1	
No	11.4	32	
Anti-inflammatory treatment (%)			**0.697**
Yes	14	27.1	
No	18.9	40	
Infective parameters (mean±SD)			
Crp	150 (84)	139 (80)	0.232
Procalcitonin	1.8 (4.5)	1.2 (3.9)	**0.009**
Ferritin	947 (776)	767 (654)	**0.016**
Hemogram parameters (mean±SD)	Albumin≤ 2.5 N:115	2.5≤Albumin<3.5 N:235	p value
Hgb	12.2 (2)	13.7 (8.7)	**<0.001**
Plt	269 (109)	266 (103)	0.86
Wbc	14.4 (6.7)	12.4 (6.7)	**0.003**
Neu	12.8 (6.6)	10.7 (6.3)	**0.001**
Lym	0.96 (0.62)	1.1 (1)	0.213
Neu/lym	21.5 (22)	14.2 (13.9)	**0.001**
Biochemical parameters (mean±SD)			
Urea	65 (47.5)	49.4 (27.3)	**0.002**
Sodium	138.7 (6.4)	135.7 (6)	**<0.001**
Potassium	4.3 (0.66)	4.23 (0.6)	0.496
Calcium	8.9 (0.5)	8.8 (0.5)	**0.034**
ALT	53.5 (75)	35 (27)	**0.01**
AST	58 (70)	45 (40)	0.104
Total bilurubin	0.9 (1.5)	0.6 (0.46)	**0.006**
D-dimer (mean±SD)	3089 (6718)	1513 (4007)	**<0.001**
Blood gas parameters (mean±SD)			
PH	7.35 (0.12)	7.38 (0.1)	**0.356**
HCO3	21.9 (5.5)	22.4 (4.2)	**0.585**
Lactate	2.9 (2.3)	2.8 (2.3)	0.785
AKI (n %)			**0.039**
Yes	75 (65)	126 (53)	
No	40 (34)	109 (46)	
Discharge type (n %)			**0.001**
Alive	25 (21.7)	92 (39.1)	
Death	90 (78.3)	143 (60.9)	

Dm: diabetes mellitus, HT: Hipertension, CAD: Coronary Artery Disease, Cpap:Continuous positive Airway Pressure, Crp: C-reaktive protein, Hgb: hemoglobine, Plt:platelet, Wbc:white blood cell, Neu: Neutrophile, Lym: Lymphocite, Ney/Lym: Neutrophile Lymphocite ratio, ALT: Alanine transaminase, AST: Aspartate transaminase, Hco3: Bicarbonate, AKI:acute Kidney Injury

The effect of the degree of hypoalbuminemia on the development of AKI and mortality and the mortality rates in patients who developed AKI were compared between the groups (Table 2).

Table 2. Albumin and acute kidney injury subgroups

Albumin(mg/dl)	n (%)	Acute kidney injury	n (%)
≤2.5 (severe hypoalbuminemia)	115 (67%)	Developed	201 (57%)
2.5-3.5 (mild hypoalbuminemia)	235 (33%)	Non-developed	149 (43%)
Total	**350 (100)**	**Total**	**350 (100)**

AKI:Acute kidney injury

Statistical Analysis

Statistical analyzes in our study were performed using IBM SPSS (version 24.0) package program. The suitability of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov test). Normally distributed numerical variables were analyzed using the "t test in independent groups" between two groups. Numerical variables that were not normally distributed were analyzed using the "Mann Whitney U test" between the two groups. "Chi-square analysis" and "Fisher's exact test" were used to compare nominal data. One Way Anova test was used to compare more than two groups. The power of all scoring models in the prediction of the mortality rate was tested with the receiver operator characteristics (ROC)-area under curve (AUC) analysis. ROC analysis was also used to state cut-off values and their sensitivity and specificity to estimate the risk of mortality in the ICU. Results are expressed with a 95% confidence interval. In statistical analysis, p values below 0.05 were considered statistically significant.

RESULTS

A total of 350 patients were included in our study. 179 (51%) of the participants were male. The total average age was 66.83 (min: 22-max: 102). The average age of men was 64.1±13.8 and the average age of women was 69.6±13.9. The initial albumin value was ≤2.5 mg/dl (severe hypoalbuminemia) in 115 of 350 patients and 2.5-3.5 mg/dl (mild hypoalbuminemia) in 235 patients. The mean initial creatinine in the severe hypoalbuminemia group was 1.15 (0.84) mg/dl, and in the mild hypoalbuminemia group, the initial creatinine average was 1.06 (0.49) mg/dl. The number of patients who developed AKI was 201 (57%) and AKI did not develop in 149 (43%) patients. The average albumin level was found to be 2.94 mg/dl in the mild hypoalbuminemia group that developed AKI, and 2.2 mg/dl in the severe hypoalbuminemia group that developed AKI.

When the follow-ups of the patients were examined, it was determined that hypoalbuminemia was correlated with AKI and mortality. When patients who developed AKI were evaluated, the rate of AKI development was found to be 53% in patients with mild hypoalbuminemia and 65% in patients with severe hypoalbuminemia ($p<0.05$). Death occurred in 166 (71.2%) of 201 patients who developed AKI. While death occurs in 69% of patients with mild hypoalbuminemia who develop AKI; this rate was found to be 73.3% in patients with severe hypoalbuminemia who developed AKI. AKI did not develop in the remaining 149 (43%) patients. The number of deaths in this group was 67 (44%). In our study, the total mortality rate was 66.6%. Death rate was 60.9% in the mild hypoalbuminemia group and this rate was 78.3% in the severe hypoalbuminemia group. This rate is statistically significant with the degree of low albumin level. (AUC:0.653; $p<0.05$). When the subgroups were compared among themselves, the highest mortality rate was seen in the patient group with severe hypoalbuminemia and AKI. The lowest mortality rate was seen in the group with mild hypoalbuminemia and without AKI (Table 3, 4).

Table 3. Acute kidney injury and mortality rates according to hypoalbuminemia groups

	AKI developed (n%)	Resulted in death (n%)
Mild hypoalbuminemia	126 (53.6)	143 (60.9)
Severe hypoalbuminemia	75 (65.2)	90 (78.3)
Total	**201 (57.4)**	**233 (66.5)**

AKI:Acute kidney injury

Table 4. Mortality rates according to hypoalbuminemia and acute kidney injury subgroups

	Mild Hypoalbuminemia (n%)	Severe Hypoalbuminemia (n%)
AKI non-developed	44 (40)	23 (59)
AKI developed	100 (79)	66 (88)
Total	**144 (61)**	**89 (77)**

AKI:Acute kidney injury

When the AKI groups were compared among themselves, statistical significance was detected in terms of age, length of stay, WBC count, neutrophil count, potassium level, D-dimer level and procalcitonin levels (Table 5).

Table 5. Comparison of acute kidney injury groups

Characteristic	AKI developed n:201	AKI non-developed n:149	p value
Age	68	65	**0.037**
Systolic blood pressure	124	127	0.303
Diastolic blood pressure	75	75	0.404
Hospitalization duration	12.3	15.8	**0.01**
Wbc	13.6	12.3	**0.045**
Neu	11.9	10.74	**0.047**
Lym	1.08	1.06	0.26
Neu/Lym	18	14.73	0.085
Hgb	13.5	12.91	0.934
Plt	271	262	0.487
ALT	44.2	38	0.183
AST	52	47	0.372
Total bilurubin	0.69	0.72	0.82
Calcium	8.8	8.9	0.469
Sodium	137	136	0.281
Potassium	4.3	4.1	**0.002**
CRP	147	136	0.085
D-dimer	2468	1440	**0.03**
Ferritin	891	740	0.142
Procalcitonin	1.8	1.05	**0.000**
Albumin	2.68	2.78	0.063

AKI: Acute kidney injury, Wbc: white blood cell, Neu: neutrophil, Lym: lymphocit, Hgb: hemoglobin, Plt: platelet, ALT: alanine aminotranferase, AST: aspartate aminotranferase

DISCUSSION

Our study was conducted with a total of 350 patients in a large center during the COVID-19 pandemic, by dividing patients with hypoalbuminemia into subgroups and

examining their effects on AKI development and mortality retrospectively. 179 (51%) of the participants were men and 171 (49%) were women. The death rate due to COVID-19 generally varies between 1.4-8%.[6] However, the development of acute kidney injury in addition to COVID-19 in patients followed in intensive care may cause the mortality rate to increase up to 80%, as some studies show.[7,8] Therefore, predicting AKI will play a key role in preventing mortality. In our study, in parallel with previous studies on albumin, it was determined that hypoalbuminemia caused both the development of AKI and an increase in mortality. However, unlike other studies, it is important that our study is conducted according to albumin levels and provides different perspectives.

In a meta-analysis by Silver et al.[3], which included 53 studies with COVID-19 patients and 30,657 patients, the rate of AKI development in non-intensive care patients was 12%, while this rate ranged between 35-57% in patients hospitalized in intensive care. In terms of AKI etiology, acute tubular damage stands out as the most common cause in patients followed in intensive care due to COVID-19.[9] Risk factors for the development of AKI are age, body mass index, acute circulatory and respiratory system failures, chronic liver disease, congestive heart failure, infections, peripheral vascular occlusive diseases, cancers, invasive procedures and high-risk surgeries.[10] Another important reason that precipitates the development of AKI is low albumin level.[8,11,12] In addition, markers that can predict AKI cases that occur due to intensive care hospitalization or various etiological reasons have been defined.[5] The most well-known of these are cystatin-C, NGAL (Neutrophil gelatinase-associated lipocalin) and KIM-1 (kidney injury molecule-1).

When the studies on this subject were reviewed, hypoalbuminemia was found to be a predictor for the development of AKI in both non-intensive care and intensive care patients, and it was also shown that the presence of hypoalbuminemia caused an increase in mortality.[11-13] Additionally, in a meta-analysis conducted by Hansrivijit et al.[13] in 2021, including 168,740 patients, it was shown that every 1 mg/dl decrease in albumin level caused a 1.68-fold increase in the development of AKI and a 1.18-fold increase in mortality. In the same study, it was determined that the risk for AKI development and mortality began to increase at albumin levels lower than 3.2 mg/dl. Studies on the effect of albumin level on the development of AKI and mortality are often designed to compare normal albumin levels with albumin levels ≤3.5 mg/dl.[7,14] Yang et al.[7] in a retrospective study with 740 patients were divided into 4 groups according to albumin levels. The highest mortality rate was found in the group with the lowest albumin level. Additionally, in a study conducted by Uyanık et al.[14] in Turkiye, the relationship between albumin values at the time of diagnosis and mortality was examined. The average albumin level was found to be 2.87±0.66 g/dl in deceased patients and 3.28±0.64 g/dl in living patients, and these values were statistically significant.

In our study, unlike previous studies, we aimed to retrospectively examine the relationship between serum albumin level and the development of AKI and mortality in COVID-19 patients and especially in intensive care patients. In our study, in parallel with the literature, a statistically high correlation was detected between the decrease in albumin level and the development of acute kidney injury and mortality (**Table 6**). However, in our opinion, it is important to conduct our study with patient groups with mild and severe hypoalbuminemia in terms of providing new perspectives.

Table 6. Albumin roc analysis in terms of Acute Kidney Injury development

Risk factor	AUC (95%)	Cut-off	P	Sensitivity (%)	Specificity(%)
	0.558 (0.497-0.619)				201 (57%)
Albumin	235 (33%)	2,65	0.064	45.3	37.6

AKI:Acute Kidney Injury

In the mild hypoalbuminemia group, the incidence of AKI was 53% and the mortality rate was 60%. In the group with severe hypoalbuminemia, the incidence of AKI was 65% and the mortality rate was 78.3%. When subgroup examinations were made, the highest mortality rate, reaching 90%, was seen in the group with severe hypoalbuminemia and AKI development; the lowest mortality rate, 40%, was found in the group with mild hypoalbuminemia and no AKI. As a result, as the albumin level decreased, more acute kidney disease and more death rates were detected. In our study, the total acute kidney injury incidence rate was found to be 57.4%, and the total death rate was 66.6% (**Table 7, 8**).

Table 7. Comparison of groups according to discharge method

Characteristic	Resulted in death n: 223	Not resulted in death n: 117	p value
Age	68.62	63.26	**<0.001**
Systolic blood pressure	124.52	128.9	**0.043**
Diastolic blood pressure	74.22	77.23	**0.013**
Hospitalization duration	13.3	14.89	**<0.001**
Wbc	13.78	11.64	**0.007**
Neu	12.23	9.81	**0.002**
Lym	0.97	1.28	**<0.001**
Neu/Lym	19.6	10.75	**<0.001**
Hgb	13.4	13	0.78
Plt	267	268	0.89
Alb	2.64	2.85	**<0.001**
Urea	60	43.4	**<0.001**
Cre	1.14	0.98	**0.003**
E-GFR	68	77	**0.003**
ALT	44.6	35.5	0.11
AST	53.2	43.7	0.13
Total bilurubin	0.71	0.69	0.69
Calcium	8.88	8.9	0.68
Sodium	137	135.8	0.12
Potassium	4.24	4.2	0.86
Crp	153	122	**0.001**
D-dimer	2284	1526	**0.03**
Ferritin	912	656	**0.001**
Procalcitonin	1.62	1.22	**<0.001**

Wbc: white blood cell, Neu: neotrophil, Lym: lymphocit, Hgb: hemoglobin, Plt: platelet, Alb: albumin, Cre: creatinine, E-GFR: estimated glomerular filtration rate, ALT: alanine aminotranferase, AST: aspartate aminotranferase

Table 8. Albumin Roc analysis for mortality

Risk factor	AUC (95%)	Cut-off	p	Sensitivity (%)	Specificity(%)
	0.653 (0.591-0.715)				201 (57%)
Albumin	235 (33%)	2,75	0.000	60.1	36.8

When the groups that developed and those that did not develop AKI were compared, there was a statistical significance between the groups in terms of age, length of stay, WBC, neutrophil count, potassium, d-dimer and procalcitonin. The average age of patients who developed

AKI was higher than those who did not develop AKI. All inflammation markers were detected higher in the group that developed AKI. There was a high correlation especially between the high initial procalcitonin value and the rate of AKI development (p<000). Similar risk factors were identified in the study conducted by Candido de Almeida et al.[15] Although there was no statistical significance between the mean albumin level in the groups that developed AKI and those that did not, there was a lower albumin level in the group that developed AKI (2.68 mg/dl versus 2.78 mg/dl).

When the effects of the parameters in our study on mortality were examined, age, hospitalization time, initial lymphocyte count, neutrophil/lymphocyte ratio, albumin level, initial urea, procalcitonin levels were found to be statistically highly significant (p<0.00). These findings were consistent with previous studies.[9,16] In studies conducted on this subject, male gender, diabetes, hypertension and coronary artery disease have also been identified as risk factors for mortality.[16] However, this could not be confirmed in our study (p>0.05). As mentioned before, this may be due to the difference in the patient group selected for our study.

Limitations

Since the patients included in our study were selected from patients hospitalized during the most intense period of the pandemic period, and as a natural result of retrospective studies, sufficient information could not be obtained about the patients' proteinuria, basal creatinine values and urine output amounts. Additionally, patients with normal albumin were requested to be included in the study as a control group, but only 4 of the patients examined in the same period were suitable for our study. Therefore, a control group could not be created. We continued our study by comparing subgroups of patients with hypoalbuminemia among themselves. In order to clarify this situation, prospective, large-scale, better designed studies are needed to predict the relationship between albumin values and AKI development, after eliminating the deficiencies that prevent us from giving clearer messages based on our study.

CONCLUSION

With this study, we aimed to show that low albumin is a predictive factor for the development of acute kidney disease and complications including mortality, rather than considering it only as an acute phase reactant. In our study, lower albumin levels were found to be associated with more complications and higher mortality rates. The availability of albumin in every center and the fact that it is a low-cost test is important in terms of cost-effectiveness. Other prospective, more comprehensive studies are needed to elucidate this issue.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Gazi Yaşargil Training and Research Hospital Ethics Committee (Date: 28.04.2021, Decision No: 2021/840), and it was conducted in accordance with the Declaration of Helsinki.

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

Referee Evaluation Process: Externally peer-reviewed.

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Review

COVID-19 infection: antiviral therapy

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ABSTRACT

This review summarizes the current literature on antiviral drugs used in the treatment of coronavirus disease 2019 (COVID-19). The pandemic caused by COVID-19 is an important cause of mortality and morbidity all over the world and in Turkey. COVID-19 infection is a viral infection caused by the SARS-CoV-2 virus that can affect many organs, such as the heart, gastrointestinal system, and central nervous system, especially the lungs. Many anti-microbials have been tried in the treatment of COVID-19 in the past few years. Today, there are some antiviral drugs that have clinically proven efficacy in the treatment of COVID-19 and are still in use.

Keywords: COVID-19, SARS-CoV-2, clinical trials, current treatment, antiviral drugs

INTRODUCTION

The disease caused by SARS-CoV-2 has been named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). It can cause respiratory illnesses ranging from mild symptoms to serious ones. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is in the genus Betacoronavirus, family *Coronaviridae*.[1] It was declared a "pandemic" by the World Health Organization (WHO) in March 2020. Since then, numerous clinical and experimental studies have been conducted to determine effective approaches for prevention and treatment.[2,3]

According to the data from the Ministry of Health, 17,232,066 confirmed COVID-19 cases and a total of 102,174 deaths due to COVID-19 were reported in Turkey until March 2023.[3] According to the data of the Ministry of Health, a total of 152,725,380 doses of the COVID-19 vaccine were administered until September 24, 2023, and the number of people who received a single-dose vaccine was 57,959,115, while the number of people who received a double-dose vaccine was 53,194,534.[4,5] According to the World Health Organization's report dated January 15, 2024, 701,742,393 confirmed cases, 6,968,842 deaths due to COVID-19, and 672,730,354 cases recovered from COVID-19 were reported worldwide.[4]

COVID can present with many different clinical presentations. Main clinical symptoms of the COVID-19 infection include fever, cough, shortness of breath, and chest pain. These symptoms may be accompanied by headaches, sore throats, and taste and smell disturbances. The most common imaging finding in viral pneumonia caused by COVID-19 is the detection of bilateral peripherally located ground-glass opacities on computed tomography (CT) imaging. Although COVID-19 mostly involves the lungs, involvement of the cardiovascular system, gastrointestinal system, and central nervous system can also be observed. WHO estimates that about 80% of COVID-19 cases recover without the need for hospital treatment, 15% become seriously ill and require oxygen (O2), and about 5% of cases require intensive care. The main cause of death in COVID-19 patients leads to a "cytokine storm syndrome" responsible for organ damage, acute respiratory distress syndrome (ARDS), and respiratory failure. The primary site of SARS-CoV-2 morbidity is the respiratory tract. However, extrapulmonary manifestations affecting the heart, liver, kidneys, brain, intestine, pancreas, testes, ovaries, breast, uterus, and placenta are also common. This can be attributed to the high expression of angiotensin-converting enzyme-2 (ACE-2) in these tissues. Another important mechanism underlying the pathophysiology of multi-organ damage secondary to SARSCoV-2 infection involves direct viral endothelial damage, which can induce inappropriate thrombin generation by inhibition of fibrinolysis and activation of complement pathways, triggering microthrombi accumulation and microvascular dysfunction.[2]

Many anti-bacterial, anti-parasitic, and anti-viral drugs have been tried in the treatment of COVID-19 in the past few years. Some antiviral drugs with proven efficacy are currently used in the treatment of COVID-19. In the past years, chloroquine, hydroxychloroquine, ivermectin, and nitazoxanide were among the parasitic drugs; azithromycin was among the antibacterial drugs; and lopinavir/ritonavir, ribavirin, darunavir-cobicistat, umifenovir, favipiravir, and remdesivir were among the antiviral drugs used in the treatment of COVID-19.[3,6,7] In the COVID-19 pandemic, the development and widespread use of inactivated vaccines and mRNA vaccines, as well as the use of antiviral drugs effective against SARS-CoV-2, contributed to the decrease in SARS-CoV-2-related mortality and morbidity rates.

In this article, antiviral drugs currently used in the treatment of COVID-19 disease and clinical and in vitro studies with these drugs are summarized.

ANTIVIRAL DRUGS IN COVID-19

Antiviral agents reported against COVID-19 mainly include polymerase inhibitors, protease inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors, entry and uncoating inhibitors, and other antivirals (Table 1).[8]

Table 1. Antiviral drugs used to treat COVID-19

Polymerase inhibitors
..... Remdesivir
Molnupiravir
Paxlovid (nirmatrelvir/ritonavir)
Old antiviral drugs
.....Favipiravir
Lopinavir/ritonavir
Pegylated interferon Lambda

Antiviral drugs act by interfering with the SARSCoV-2 replication cycle to reduce viral load and its subsequent pathological effects. Mechanisms of action include inhibition of virus entry via the ACE2 receptor and/or TMPRSS2, viral membrane fusion and endocytosis, or viral proteases and RdRp. This class of drugs has a vital role in preventing the progression of COVID-19 disease because viral replication is more active during early infection.[2]

Polymerase Inhibitors

Remdesivir: Remdesivir is the first antiviral drug approved by the FDA for COVID-19. It is a nucleotide analog prodrug. Its active metabolite, an adenosine analog, can bind to viral RNA-dependent RNA polymerase (RdRp) and inhibit viral replication by causing premature termination of RNA transcription.[2]

It has a broad spectrum of antiviral in vitro activity against other pathogenic RNA viruses, including Middle East respiratory syndrome (MERS), SARS-CoV-1, and bat CoV viruses. The World Health Organization (WHO) issued a conditional recommendation in 2020 against the use of remdesivir in hospitalized patients regardless of severity of illness, despite the lack of sufficient evidence at the time that remdesivir could improve survival or other clinical outcomes. The WHO recommendation reported that there was insufficient evidence to support the use of remdesivir.[3]

Later, in April 2022, following the emergence of new data from clinical trials, WHO updated its recommendations and recommended the use of remdesivir in mild or moderate COVID-19 patients at high risk of hospitalization.[2]

In a clinical trial of non-hospitalized COVID-19 patients, safety was found to be acceptable after 3 days of remdesivir treatment, while the risk of hospitalization or death was reported to be reduced by 87% compared to placebo. Another clinical trial reported that remdesivir outperformed placebo.

It was also reported that adults hospitalized for COVID-19 and lower respiratory tract infections had a shorter recovery time after receiving remdesivir treatment. In contrast to these studies, multicenter studies in China reported no statistically significant difference in the clinical condition of COVID-19 patients receiving remdesivir compared to standard care. In addition, it was reported that remdesivir combined with baricytinib, a Janus kinase inhibitor, was more effective than remdesivir alone in terms of shortening the recovery time of COVID-19 patients and accelerating the improvement of their clinical symptoms.[8]

The US Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Infectious Diseases Society of America (IDSA), and the National Institute for Health and Clinical Excellence (NICE) in their latest guidelines recommend the use of remdesivir in hospitalized and non-hospitalized adult and pediatric patients (age ≥28 days and body weight ≥3 kg) with "mild to moderate COVID-19." In addition, to reduce the risk of disease progression, the NIH recommends co-administration of remdesivir with dexamethasone for hospitalized COVID-19 patients requiring O2 supplementation. Remdesivir is administered intravenously (IV) over 30-120 minutes at a dose of 200 mg (loading dose) on day 1, followed by a maintenance dose of 100 mg/day. For pediatric patients (less than 40 kg), the loading dose on day 1 is 5 mg/kg, followed by a maintenance dose of 2.5 mg/kg/day.[2] The recommended total duration of treatment for non-hospitalized patients is 3 days. In hospitalized patients, it is 5 days or until the patient is discharged. However, if the patient does not improve clinically, the clinician may extend the treatment period up to 5 days, and the total treatment period should not exceed 10 days.[9]

The most common side effect of remdesivir is nausea. It may also increase liver transaminases and prothrombin time and cause hypersensitivity reactions. Chloroquine and hydroxychloroquine reduce the antiviral activity of remdesivir; therefore, they are not recommended to be administered together. The dose of Remdesivir should be adjusted for patients with renal impairment. It is not recommended for use in patients with a glomerular filtration rate (eGFR)<30 ml/min. Remdesivir is well tolerated during pregnancy, and the rate of serious side effects is low.[2]

Molnupiravir: Molnupiravir is another oral antiviral drug that targets viral replication. It is a prodrug that joins viral RNA strands mimicking the nucleoside cytidine or uridine and is converted to β-D-N4-hydroxycytidine (NHC), leading to 'error catastrophe' during viral replication.[2]

Molnupiravir, an oral prodrug of N-hydroxycytidine, has previously demonstrated a high barrier to resistance development with broad in vitro antiviral activity against multiple RNA viruses.[10]

It has activity against coronaviruses, including SARS-CoV-2. It has been reported to reduce the risk of hospital admission or death by approximately 50% in non-hospitalized COVID-19 patients. A study to evaluate the efficacy and safety of molnupiravir treatment in non-hospitalized, unvaccinated adults with mild-to-moderate COVID-19 suggested that the risk of hospitalization or death due to COVID-19 in unvaccinated adults may be reduced by early treatment with molnupiravir. Another study reported that molnupiravir was active against the three dominant circulating variants of SARS-CoV-2 (delta, gamma, and mu) and showed a moderate antiviral effect.[8]

Molnupiravir was also tested in prophylaxis after domestic contact with patients with COVID-19. In the study, COVID-19 infection rates up to day 14 were 6.5% in those receiving molnupiravir prophylaxis and 8.5% in those receiving placebo, with no statistically significant differences

reported. Although molnupiravir was well tolerated in prophylaxis, it was reported that its failure to meet the predetermined superiority criterion may be partially affected by the pre-existing high immunity in the study population.[11]

The FDA, NIH, IDSA, and NICE guidelines recommend the use of molnupiravir in non-hospitalized adult patients with "mild to moderate COVID-19" to reduce the risk of disease progression "only when Paxlovid or remdesivir cannot be used." The dose of molnupiravir is 800 mg orally every 12 hours for 5 days, starting within 5 days of symptom onset.[2,11]

Strizki et al.[10] evaluated the antiviral activity and potential for resistance development of molnupiravir against SARS-CoV-2 omicron variants (BA.1, BA.1.1, BA.2, BA.4, BA.4.4.6, BA.5, BQ.1.1, XBB.1 and XBB.1.1.5), alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), lambda (C.37), and mu (B.1.621) variants in Vero E6 cells using cytopathic effect assays. In the study, it was reported that molnupiravir maintained antiviral activity in all major SARS-CoV-2 variants and no viral resistance to this drug was detected; therefore, molnupiravir has a high barrier to resistance development.

The most common side effects of molnupiravir are nausea, diarrhea, and dizziness. Neither drug interactions nor contraindications have been reported due to the limited available data. However, it is not approved for COVID-19 patients aged 18 years and younger due to bone and cartilage growth and is not recommended for pregnant or breastfeeding women. In addition, molnupiravir is not authorized by the FDA for pre- or post-exposure prophylaxis for COVID-19. Due to its lack of clinical benefit, molnupiravir is not authorized for the treatment of hospitalized COVID-19 patients.[2]

In a one-to-one matched cohort study with molnupiravir by Butt et al.[12], 1459 patients were treated with molnupiravir in a study that included patients with COVID-19 for the first time. Molnupiravir use was not associated with a reduction in hospitalization and mortality within 30 days of COVID-19 diagnosis. The study reported that a group of patients who presented as asymptomatic benefited from molnupiravir.

Bernal et al.[13] included 1433 COVID-19 patients in their randomized, double-blind, placebo-controlled study with molnupiravir. Of the patients, 716 received molnupiravir treatment, and 717 received placebo treatment. In the study, the risk of hospitalization or death from any cause by day 29 was 7.3% (28 of 385 patients) with molnupiravir and 14.1% (53 of 377 patients) in the placebo group, with a statistically significant lower risk reported in the molnupiravir-treated group. One patient died on day 29 in the molnupiravir group, compared to nine deaths in the placebo group. In conclusion, early treatment with molnupiravir was reported to significantly reduce the risk of hospitalization or death in at-risk, unvaccinated adults with the COVID-19 infection.

Paxlovid (nirmatrelvir/ritonavir): Paxlovid is the first FDA-approved oral antiviral drug against COVID-19. It is a combination of nirmatrelvir, which inhibits the main protease (Mpro) of SARS-CoV-2, and ritonavir, a cytochrome P450-3A4 inhibitor, thereby slowing the metabolism of nirmatrelvir. This combination provides a longer effect. The half-life of nirmatrelvir allows a dosing interval of 12 hours. It is the first oral antiviral medicine approved for COVID-19. The FDA and the most recent guideline (NIH, IDSA, and NICE) versions recommend the use of Paxlovid in non-hospitalized adult and pediatric (≥12 years and ≥40 kg) patients with "mild to moderate COVID-19" to reduce the risk of disease progression.[2,11]

Side effects of Paxlovid include diarrhea, taste disturbance, hypertension, and myalgia. It is not recommended for patients with severe renal or hepatic impairment. It should be used with caution in patients with liver diseases, abnormal liver enzymes, or hepatitis. Use of Paxlovid in people with uncontrolled or undiagnosed HIV-1 infection may induce HIV-1 drug resistance. Paxlovid is contraindicated in patients with a history of clinically significant hypersensitivity reactions. Because it is a CYP-3A4 inhibitor, it is contraindicated in patients taking drugs metabolized by CYP-3A4, such as alfuzosin, colchicine, propafenone, amiodarone, ergotamine, statins, sildenafil, midazolam, and triazolam. Paxlovid dose should be adjusted in patients with eGFR≤60 mL/min. Paxlovid is not recommended for patients with an eGFR<30 ml/min.[2,9,11]

Lewnard et al.[14] investigated the efficacy of the drug in preventing hospital admissions and death in 7274 people who tested positive for SARS-CoV-2 who received nimatrelvir-ritonavir treatment and 126 152 people who did not receive treatment in a cohort study in the United States. In the study, 5,472 (75.2%) people receiving treatment and 84,657 (67.1%) people not receiving treatment were tested within 5 days of symptom onset. The study found that nirmatrelvir-ritonavir had an overall estimated effectiveness of 53.6% in preventing hospitalization or death within 30 days of a positive SARS-CoV-2 test, increasing to 79.6% when nimatrelvir-ritonavir was given within 5 days of symptom onset. In the subgroup of patients tested within 5 days of symptom onset and discontinued on the test day, the estimated efficacy of nimatrelvir-ritonavir was 89.6%. In conclusion, in a setting with high levels of COVID-19 vaccine uptake, nimatrelvir-ritonavir was reported to effectively reduce the risk of hospitalization or death within 30 days of a positive SARS-CoV-2 test in outpatients.

In a study conducted in the United States, nimatrelvir-ritonavir was reported to have greater efficacy in adults aged 65 years and older compared to adults aged 65 years and older. However, studies conducted in the United States and Hong Kong reported that efficacy did not differ according to age, immunity, or the presence of comorbidities.[14-16]

In a retrospective viral cohort study, the efficacy of nimatrelvir-ritonavir was investigated in outpatients with COVID-19, including BA.4 and BA.5, in Colorado, United States. The study found an association between nimatrelvir-ritonavir treatment and a reduction in all-cause 28-day hospitalization, all-cause mortality, and emergency department visits. The researchers reported that nirmatrelvir-ritonavir was effective in first-line treatment in adults with acute SARS-CoV-2 infection who were not hospitalized during an omicron period, including BA.4 and BA.5 sub-variants.[17]

Old Antiviral Drugs in COVID-19

Favipiravir: Like remdesivir, it is an RdRp inhibitor. It is a prodrug purine analogue, and its activated phosphoribosylated form (favipiravir-RTP) inhibits viral RNA polymerase activity and genome replication. Favipiravir was approved in Japan in 2014 for the treatment of influenza viruses. Due to the urgency of COVID-19, favipiravir was redesigned for the treatment of mild COVID-19 cases without

hospitalization and has been used off-label. However, NIH, IDSA, and NICE guidelines do not recommend or endorse the use of favipiravir for the treatment of COVID-19.

In vitro studies have revealed that favipiravir may be effective against SARS-CoV-2. However, there is controversy about its efficacy against COVID-19 in clinical trials. A meta-analysis showed that favipiravir reduced mortality by 30%, but this finding was not statistically significant. Clinical evidence supports the safety and tolerability of short-term use of favipiravir. The most commonly reported side effects of favipiravir are elevated liver transaminases, bilirubin, and uric acid, gastrointestinal disorders, chest pain, and teratogenicity; therefore, it is contraindicated in pregnancy.[2]

Shah et al.[18] compared the efficacy of favipiravir with standard therapy in the PIONEER open-label, phase 3 randomized controlled multicenter study. Of the 499 people included in the study, 251 received favipiravir and standard care, and 248 received standard care only. There was no significant difference between those who received favipiravir and standard care compared to those who received standard care only in the time to recovery in the overall study population. In post-hoc analyses, patients aged <60 years who received favipiravir and standard care showed a faster recovery rate compared to patients who received standard care only. Of the 251 patients who received favipiravir and standard care, 27 (11%) of 251 patients experienced 36 serious adverse events, compared to 33 serious adverse events in 27 (11%) of the 248 patients who received standard care only. These adverse events were reported as infectious, respiratory, and cardiovascular events in order of frequency. There was no significant difference between the groups in terms of serious adverse events per patient.

Favipiravir was found to be ineffective in the treatment of COVID-19 compared to standard treatment in randomized controlled trials and was largely withdrawn from use or replaced by more effective antiviral drugs.

Lopinavir/ritonavir: Lopinavir/ritonavir is a protease inhibitor approved by the FDA in 2000 for the treatment of HIV. Ritonavir is added because it is a cytochrome P450-3A4 inhibitor that slows the metabolism of lopinavir. This combination has been shown to inhibit SARS-CoV-1 and MERS-CoV replication in vitro and has been reported to reduce mortality due to ARDS in clinical trials. In an open-label, randomized, phase II study in the early phase of COVID-19, the triple combination of interferon beta-1b, ribavirin, and lopinavir/ritonavir was reported to shorten hospital stays in patients with mild to moderate COVID-19.[2,8]

Lopinavir/ritonavir did not show clinical efficacy in non-hospitalized COVID-19 patients in two randomized controlled trials. The NIH and IDSA do not recommend the use of lopinavir/ritonavir for the treatment of COVID-19 in hospitalized or non-hospitalized patients or for post-exposure prophylaxis. The most commonly reported side effects include nausea, vomiting, diarrhea, abdominal pain, loss of appetite, bloating, metallic taste, paresthesia, pruritus, prolonged QT interval, and hepatotoxicity, as well as drug interactions due to CYP3-A4 inhibitory activity.[2]

Evaluated the efficacy of nirmatrelvir-ritonavir and molnupiravir in outpatients when the Omicron variant was circulating. The study showed no difference in the risk of 30-day or 31 to 180-day hospitalization or death between matched participants treated with nirmatrelvir or molnupiravir. Nirmatrelvir-ritonavir was reported to be effective in reducing 30-day hospitalizations and deaths. Molnupiravir appeared to provide a benefit in terms of 30-day mortality but no benefit in hospitalization. No further reduction in mortality from 31 days to 180 days was observed with either antiviral.[20]

Pegylated Interferon Lambda

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes weak expression of type III interferons in infected cells, which are naturally produced as an early defense barrier line in upper respiratory tract infections. Interferon lambda, a type III interferon, is a member of a new cytokine family with antiviral effects that is highly similar to type I interferons (IFN-α and IFN-β).[21]

IFN λ (type 3 interferon) is secreted from virus-infected cells, macrophages, and dendritic cells. It stimulates antiviral activity in cells. Activates and regulates cellular components of innate immunity; initiates stimulation of the acquired immune response. It activates apoptosis-stimulating molecules and stimulates the progression of infected cells to apoptosis.[22]

Pegylated interferon lambda (PegIFN-lambda) has been applied in many clinical trials involving viral hepatitis agents and COVID-19 and has been shown to have a good safety and side effect profile. Pegylated interferon lambda has been shown to have broad-spectrum antiviral activity in multiple cell cultures, animal models, and clinical trials.

Reis et al.[22] investigated the effect of pegIFN-lambda on hospitalization within 28 days or observation longer than 6 hours in the emergency department (primary endpoint) in patients with acute COVID-19 in a prospective randomized controlled study. The study included 931 patients who received a single subcutaneous 180 µg pegIFN-lambda treatment and 1018 patients who received placebo treatment as a control group. The primary endpoint was 2.7% in the pegIFN lambda group and 5.6% in the control group. In the same study, the frequencies of hospitalization, death, and adverse events in the peg IFN lambda group and control groups were reported as 2.3%, 3.9%, 0.1%, 0.4%, 0.8%, and 1.1%, respectively. In conclusion, the researchers reported that hospitalization or emergency department visits (observation longer than 6 hours) in patients with mild to moderate COVID-19 were significantly reduced with a single dose of peg IFN lambda.

The main antiviral agents used in COVID-19 treatment, their mechanisms of action, adverse drug reactions, and drug interactions are summarized in the **Table 2**.

CONCLUSION

As a result of, although there are some antiviral drugs with proven efficacy in the treatment of COVID-19 in outpatients, we believe that antiviral drugs that are also effective against new variants of SARS-CoV-2, can be used in inpatients and prophylaxis, have a high resistance barrier, and have few side effects should be developed.

Table 2. Major antiviral agents used in the treatment of COVID-19, their mechanisms of action, adverse drug reactions, and drug interactions*

Antiviral medicine	Mechanism of action	Adverse drug reactions	Drug interactions
Remdesivir	RNA-dependent RNA polymerase inhibitor	Gastrointestinal disorders (nausea, vomiting), elevated transaminases, and infusion-related reactions (hypotension, diarrhea, tremor) Prolonged prothrombin time, hypersensitivity reaction	CYP3A4 enzyme stimulants reduce efficacy
Lopinavir-ritonavir (Kaletra)	3CL protease inhibitor, one of the main protease enzymes of SARS-CoV-2 virus	Gastrointestinal disorders (nausea, vomiting, diarrhea), elevated transaminases, increased bleeding, hyperlipidemia, hyperglycemia, insulin resistance, QT prolongation, risk of renal dysfunction	Inhibitor and substrate of CYP3A4 Substrate of CYP2D6
Favipiravir	RNA-dependent RNA polymerase inhibitor	Gastrointestinal disorders (nausea, vomiting, diarrhea), hyperuricemia, elevated transaminases, decreased neutrophil count	Inhibitor of CYP2C8, aldehyde oxidase and xanthine Enhances the toxic effects of pyrazinamide
Molnupiravir	Molnupiravir increases the frequency of viral RNA mutations in human and animal models and disrupts SARS-CoV-2 replication.	Nausea, diarrhea, and dizziness. Contraindicated in pregnant and lactating women and under 18 years of age.	No drug interactions have been reported so far
Nirmatrelvir-ritonavir	Nirmatrelvir inhibits the main protease (Mpro) of SARS-CoV-2, ritonavir is a P4503A4 inhibitor, slowing the metabolism of nirmatrelvir.	Diarrhea, taste disturbance, hypertension, and myalgia. Not recommended in severe hepatic and renal failure. It should be used with caution in patients with liver disease, hepatitis, and elevated liver enzymes. Use in patients with HIV-1 infection may induce HIV-1 antiviral resistance.	It is a CYP-3A4 inhibitor. Contraindicated in patients taking drugs metabolized by CYP-3A4 such as colchicine, propafenone, amiodarone, ergotamine, statins, sildenafil, midazolam, triazolam

(*) Part of references 2,23,24 is cited

ETHICAL DECLARATIONS

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Review

Loss of appetite, weakness and chronic fatigue: current approach

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ABSTRACT

Fatigue and chronic fatigue are frequently encountered complaints in clinical practice, and their etiology is difficult to determine. In addition to increasing patient dissatisfaction due to the lack of clarification of the etiology, it brings about a significant increase in cost due to the fact that patients consult multiple physicians. In this review, current clinical practices, including especially overlooked points in the etiology of weakness and fatigue, investigations that should be planned, diagnosis, treatment, and lifestyle recommendations, are reviewed.

Keywords: Loss of appetite, weakness, fatigue, chronic fatigue syndrome

LOSS OF APPETITE

Appetite is generally defined as the desire for food and is known as a common symptom encountered by physicians. It can manifest itself as a consequence of many clinical conditions and can lead to patient dissatisfaction and inadequate treatment compliance.

Appetite is regulated by hormonal effects. Ghrelin, known as the appetite hormone, is generally responsible for appetite regulation. Ghrelin is a peptide hormone that is mainly produced in the gastric fundus.[1] In addition to appetite regulation, ghrelin is also effective for energy homeostasis and carbohydrate metabolism.[2]

Many organic causes of anorexia have been described. However, it is not possible for clinicians to rule out all these causes. Therefore, a detailed anamnesis and physical examination should be performed, and the underlying etiology should be determined according to the accompanying symptoms and findings. The most common causes of anorexia are summarized in Table 1.[3]

Table 1. Common causes of loss of appetite

• Acute or chronic infections
• Gastroesophageal reflux, *H. pylori* infection
• Dyspepsia
• Nausea, vomiting
• Diarrhea, constipation
• Gastroenteritis
• Intestinal parasitoses
• Dysphagia
• Anemia (especially iron deficiency anemia)
• Zinc deficiency
• Acute renal failure
• Psychological reasons

WEAKNESS AND FATIGUE

Chronic fatigue and weakness are common complaints frequently encountered by all clinicians and often difficult to treat. The main reason for the difficulty in its treatment is the difficulty in making the diagnosis that leads to the clinical presentation. The reason for this situation is that it can occur as a result of many organic and psychiatric disorders. On the other hand, weakness and chronic fatigue can be observed without any underlying disease.

Weakness and chronic fatigue are complaints frequently encountered in all health institutions, especially among primary care physicians. Even a large proportion of patients presenting with other complaints complain of weakness and fatigue. In studies, it was found that these complaints were present in patients presenting to outpatient clinics at rates ranging between 10% and 40%.[4]

Basic evaluation and routine investigations are performed on patients with complaints of weakness and chronic fatigue. As a result of the examinations, no pathology is usually detected, psychological causes are considered, and patients are referred to psychiatry physicians. This significantly increases the workload of psychiatric physicians. Moreover, the examinations performed on these patients do not detect any psychiatric problems in a large proportion of them. In addition to the workload for the physicians, this situation is also annoying for the patients.[4,5]

The increase in workload does not only affect psychiatric physicians. These patients, for whom no clear diagnosis can be made, are referred to a wide variety of specialty physicians and cause an increase in the workload of all clinicians. Studies have shown that nearly 50% of patients with complaints of weakness and chronic fatigue are seen by five specialty physicians. However, many of them still remain inconclusive.

Patients' daily lives and work performances are also negatively affected because their complaints do not go away.[5]

At this point, patients' expectations from physicians are that a clear diagnosis should be made, preferably a pharmacologic treatment should be initiated, and all complaints should disappear in a short time. However, as mentioned, in the majority of these patients, even a treatable organic cause cannot be detected.[5,6]

As the duration of fatigue and weakness increases, the frequency of patients being psychologically affected by this condition increases, and some long-term side effects are observed in patients. Long-term side effects that occur in these patients over time are summarized in Table 2.[6]

Table 2. Long-term side effects in people with weakness and chronic fatigue

Common muscle and joint pains	Depression and anxiety
Exhaustion after physical activities	Sexual dysfunction
Headaches with a new onset	Decreased sleep quality
Impaired memory and concentration	≥30.00

Another important problem for patients with complaints of weakness and chronic fatigue is deciding which specialty physician to consult. These complaints may be the initial symptoms of diseases, followed by many branches, thus requiring a holistic perspective. The branch with this holistic perspective is primarily family physicians, while internal medicine specialists are preferred as another option for adults.[5-7]

DIAGNOSTIC EVALUATION

As in almost all branches of medical practice, the first approach for patients with complaints of weakness and chronic fatigue should be anamnesis and physical examination. With a detailed and careful physical examination, many diagnostic clues can be found. It should be kept in mind that conditions such as musculoskeletal problems, lumbar and cervical disc herniation, osteoarthrosis, and fibromyalgia, which can be detected by physical examination, may cause intensity and severe fatigue.[7]

After a detailed anamnesis and physical examination, initial investigations must be ordered. In patients presenting with weakness and chronic fatigue, initial investigations should include a complete blood count, blood biochemistry, CRP, sedimentation level, thyroid hormone level, vitamin D, vitamin B12, urinalysis, PA chest radiography, and ECG if necessary. If significant pathologies are detected in these tests, further investigations should be planned. Initial evaluation tests and conditions that may be relevant are summarized in Table 3.[8]

ETIOLOGY

Many diseases and factors have been identified as the etiologies of chronic fatigue and weakness. The general diagnostic approach is based on the exclusion of many of these causes. It has been shown that less than 20% of the etiologic causes identified are due to organic pathologies. Approximately 80% are psychological and lifestyle-related conditions. Psychological and lifestyle-related conditions are summarized in Table 4.[9]

Table 3. Initial evaluation tests for weakness and fatigue and related conditions

Complete blood count	In particular, about 1/3 of women of reproductive age are anemic. Anemia is one of the leading causes of fatigue and weakness.
Blood biochemistry test	Abnormalities in liver function tests and enzyme elevations may present with weakness and fatigue depending on the cause. Gilbert's syndrome with elevated indirect bilirubin is also a common cause. Renal function tests and electrolyte disorders, especially hyperpotassemia, may also cause these complaints.
Hormone tests	Especially thyroid hormone disorders, Addison's disease with cortisol deficiency, and pituitary insufficiency should be investigated. First of all, TSH should be requested, and morning fasting plasma cortisol levels should be checked in suspicious cases. Vitamin B12, folic acid, and vitamin D levels should also be checked. Deficiencies of these are common causes of weakness and fatigue. These symptoms may be observed in patients with a history of diabetes and prediabetes due to insulin resistance and high blood sugar. HBA1c, insulin level, and OGTT should be requested if necessary.
Other	P-A chest radiography, ECG, complete urinalysis, CRP, and erythrocyte sedimentation rate should be ordered if not taken recently. In patients with symptoms and signs, USG of the whole abdomen should be ordered if necessary.

Table 4. Psychological and lifestyle-related conditions that may cause fatigue and weakness

Psychological disorders and mood disorders	It is caused by all psychological disorders, especially depression.
Eating disorders	It is observed in all disorders, primarily due to anorexia and bulimia.
Sleep disorders	Insomnia and obstructive sleep apnea syndrome
Unhealthy lifestyle	Work problems, economic problems, sedentary life, lack of regular exercise, inadequate and unhealthy diet, smoking, alcohol use, insufficient rest
Drug and substance use	Alcohol, caffeine, psychotropic drugs, antihistamines, cardiovascular drugs, reserpine, methyldopa

Obstructive sleep apnea syndrome is a syndrome that develops due to upper airway obstruction during sleep. It is characterized by intermittent awakenings, decreased oxygen saturation, decreased sleep quality, fatigue, and daytime sleepiness. The most prominent risk factors include male gender, obesity, alcohol and smoking, endocrine disorders, and family history.[10,11] The organic causes of chronic fatigue and weakness are compiled in Table 5, and they account for less than 20% of the identified causes.

Table 5. Organic causes of fatigue and weakness

Infections	Viral, bacterial, etc.
Metabolic disorders	Diabetes, thyroid dysfunction, pituitary insufficiency, Addison's disease, etc.
Hematologic diseases	Anemia, leukemia, metal intoxications
Renal diseases	Acute and chronic renal failure
Liver diseases	
Rheumatologic diseases	Fibromyalgia, Sjögren's syndrome, polymyalgia rheumatica, giant cell arteritis, polymyositis and dermatomyositis, inflammatory bowel disease, sarcoidosis, chronic fatigue syndrome, etc.
Neurological diseases	Parkinson's disease, multiple sclerosis, etc.
Cardiac problems	Coronary artery disease, congestive heart failure
Respiratory system diseases	Chronic obstructive pulmonary disease, asthma, etc.

CHRONIC FATIGUE SYNDROME

Chronic fatigue syndrome (CFS) is a disease that is often overlooked in etiology and requires detailed questioning. Chronic fatigue syndrome can be defined as a disease that lasts longer than 6 months, increases with exertion, has an unexplained cause, and may progress with impairment in daily activities and cognitive functions. It has been found that up to 2 million people in the USA are affected by this condition; it is more common in women than in men, and it is usually found in other family members.[12,13]

Although the etiology and pathophysiologic mechanisms of the disease have not been clearly demonstrated, there are conditions thought to be effective. These can be listed as infectious causes, immune system disorders, and hormonal disorders.[14-17]

Although the diagnosis is basically based on the exclusion of all other causes, diagnostic criteria have been determined by guidelines. The diagnostic criteria for CFS are compiled in **Table 6**.[18]

Table 6. Diagnostic criteria for chronic fatigue syndrome

At least three of these symptoms are required for a diagnosis:
• Fatigue lasting more than 6 months, of recent onset, not restricted by exertion, and not demonstrated by exercise tests
• Restriction in professional, educational, social, and personal activities compared to the period before the disease
• Fatigue after exertion
• Inability to rest with sleep
At least one of the following symptoms is also required for diagnosis:
• Cognitive impairment
• Orthostatic intolerance

Laboratory tests are usually normal in CFS. The aim is to rule out all other pathologic conditions. Although there is no specific treatment for CFS, symptomatic and non-treatment therapies may be recommended.

Early diagnosis of organic causes of chronic fatigue can significantly improve the patient's quality of life by enabling diagnosis and treatment of the underlying medical condition. Some tips to help early diagnosis: Fatigue lasting longer than six months, accompanied by other symptoms (fever, weight loss, muscle aches, joint pains, sleep problems, difficulty concentrating), presence of risk factors (family history of chronic disease, weak immune system).[19,20]

RECOMMENDATIONS FOR WEAKNESS AND CHRONIC FATIGUE

In these patients, treatment of the underlying conditions should be planned first. However, since a significant etiology cannot be detected in most of them, symptomatic treatments, lifestyle changes, and exercise are recommended. Nonsteroidal anti-inflammatory drugs are especially recommended as symptomatic treatments. Possible recommendations for these patients are summarized in **Table 7**.[21-23]

Table 7. Recommendations for patients with weakness and chronic fatigue

• Eating patterns, sleep patterns, and regular exercise
• Avoiding inadequate and unhealthy nutrition, reaching and maintaining the ideal weight
• Recommendations for adequate rest and quality sleep
• Gradual transition away from sedentary life to regular active exercise
• Approaches to work problems that cause serious anxiety and psychiatric support, if necessary
• Suggestions for adjustments to household expenditures and the economic situation
• Suggestions for organizing social activities and friendships
• Recommendations for balancing mental health

CONCLUSION

Weakness, fatigue and loss of appetite are among the most common applications to outpatient clinics in clinical practice. We tried to summarize current clinical practices, including the points to be considered in the etiology of this condition, the examinations to be planned, diagnosis, treatment and lifestyle recommendations.

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Review

Investigation of the effects of Ramadan and intermittent fasting on material and spiritual health

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ABSTRACT

One of the most important problems for humanity is maintaining health. It is much easier and more cost-effective to protect it than to fix it after it has deteriorated. Modern medicine has also caught up with this point in recent years and has started to give more importance to preventive medicine practices, as Islam has been emphasizing for 1400 years. For this reason, preventive medicine practices such as intermittent fasting and eating less, which are recommended both in Islam and in scientific studies, are very important in terms of protecting health, reducing health expenditures and the workload of hospitals. In this study, we have compared the Qur'an and hadiths, which are the main sources of Islam, with the current medical literature datas. We have shown that they both point to the same points and make recommendations in the same parallel, such as intermittent fasting. With this study, which is the first and original in this respect, we aimed to contribute to the protection and improvement of both individual and social health and to reduce health expenditures and the workload of hospitals.

Keywords: Ramadan, intermittent fasting, spiritual health

INTRODUCTION

One of the greatest treasures of humanity is health, and one of the most important problems is to protect it. It is much easier and more cost-effective to protect health than to correct it after it has deteriorated. For this reason, preventive medicine and health measures are much more important than diagnosis and treatment medicine, which are efforts to correct health after it has deteriorated. Modern medicine has also caught up with this important point in recent years and has started to attach more importance to preventive medicine, as Islam has done for 1400 years. Scientific studies are also focusing more and more on this subject.

Fasting, one of the most important acts of worship in Islam, is of great importance in terms of preventive medicine. The Qur'an states: "O you who believe! Fasting has been enjoined upon you on the numbered days, as it was enjoined upon those before you, that you may beware. (...) "Ramadan is the month in which the Qur'an was sent down as a guide to mankind, and as clear proofs of the truth and the difference between the truth and the error. So let those of you who realize the month of Ramadan fast in it."[1]

The Prophet also said: "Islam is based on five things: To testify that there is no god but Allah and that Muhammad is the Messenger of Allah, to pray, to pay zakat, to perform Hajj, and to fast in Ramadan."[2]

The practice of fasting, which lasts for one month a year, has many worldly and ethereal benefits. In this article, we will first present some hadiths about the importance of fasting, and then we will focus on the benefits of fasting for human psychology (spirituality) and physical health based on both hadiths and modern medical data.

A. THE IMPORTANCE OF FASTING

Some hadiths about the importance of fasting in Ramadan are as follows:

It was narrated from Abu Hurayrah (r.a) that the Messenger of Allah (s.a.w.) said: "Allah azza wa jalla said: "All deeds are for the son of Adam, except fasting, which is for me. Fasting is a shield (against Hellfire). When one of you is fasting, let him not speak ugly words or shout. If someone curses him or wants to fight him, let him say, "I am fasting, I am fasting." I swear by Allah, in Whose might is the soul of Muhammad, that the smell of the mouth of the fasting person is more pleasant in the sight of Allah than the smell of musk. There are two joys for the fasting person. When he breaks his fast, he rejoices in his fast. When he meets his Lord, he rejoices in his fast (the reward for fasting)."[3] In a narration of Muslim, it is narrated that "The reward for every good deed is multiplied for the son of Adam from ten times to seven hundred times. Allah Almighty said, "Except fasting. Surely fasting is for me. I will give its reward."

It was narrated from Abu Said (r.a) that the Messenger of Allah (s.a.w.) said:

"If a servant fasts for a day in the way of Allah, Allah will remove his face from the fire of Hell by a distance of seventy years because of that one day's fast."[4]

One of the Companions, Abu Umama (r.a), said: "O Messenger of Allah! Order me a deed!" He said, "Fast, for there is no worship equal to fasting." I again said, "O Messenger of Allah! I said, "Order me a deed!" He said, "Fast, for there is no worship equal to fasting. I said again, "O Messenger of Allah! I said again, "Order me a deed!" He said, "Fast, for there is no worship equal to fasting. Later on, the narrators narrated that Abu Ummamah's house's stove did not work during the daytime for food, and that he spent all his days fasting, and would only break his fast if there were guests. It is also said that his wife and servant fasted.[5]

It was narrated from 'Abdullah b. 'Umar (r.a) that the Messenger of Allah (saw) said:

"The Qur'an and fasting will intercede for the servant on the Day of Resurrection. Fasting says, "My Lord! I have restrained him from eating and lustful desires, so grant me the right to intercede for him!" And the Qur'an says, "I restrained him from sleeping at night, so grant me the right to intercede for him! And they both intercede (Allah accepts their intercession)."[6]

B. EFFECTS OF RAMADAN FASTING ON MENTAL HEALTH

Fasting is first and foremost an act of worship. However, there are many worldly and ethereal benefits in this act of worship. The worldly benefits can be divided into two parts: benefits for the soul and benefits for the body. Here, we will first focus on some of the spiritual benefits, and then on the physical benefits to the human body.

1. Fasting is a Training of Patience and Willpower

Fasting teaches people patience and strengthens their willpower. Athletes improve their bodies through constant training. A weightlifter develops his arm muscles because he constantly lifts heavy barbells. An athlete who is constantly practicing running develops leg muscles. A Muslim who fasts also practices patience and learns to be patient. All sins are actually committed because of impatience. A person who gets used to patience learns to discipline him lower self. Someone who abstains even from halal things during fasting gains a sense of resistance against haram. Fahrettin al-Razi, commenting on the verse that explains that fasting leads to taqwa, says: "If people are very fond of something, it is very difficult to stay away from it. In the life of this world, the things that people are most in love with - compared to other things - are eating, drinking and marriage. If it is easy for you to give up eating, drinking and marriage out of fear of Allah, it will be easier and lighter for you to give up other things out of fear of Allah."[7]

Because of these characteristics, the Prophet (s.a.w.) said, "Fasting is half of patience."[8] Another hadith says, "Patience is half of faith."[9] Therefore, it is possible to say that fasting is ¼ of faith.

2. Fasting and Lower Self-control

Hunger cuts the lust of the lower self and breaks the inclination towards the desires of the soul. Eating too much, on the other hand, causes the lust to be aroused and the limbs to turn towards sin. As a matter of fact, our Prophet (s.a.w.) said, "O community of young people! Get married if you are able! For marriage is more conducive to closing the eyes to forbidden things and protecting against fornication. And those who cannot afford marriage, fast! Fasting will remove his lust."[10] If a person eats a lot of food, his lower self becomes aroused and he goes to sin. Even if he does not sin for fear of Allah, he cannot control his eyes. Even if he can control his eyes, his mind is occupied with bad things. Sometimes he cannot stop thinking about immoral things even in prayer.

Imam al-Ghazali is of the opinion that fasting will prevent all evil desires, not just lust. He states: "Eating too much food is the mother (of bad morals). Because all lusts come from the stomach. For example, eating too much increases sexual desires tendency towards women. When the desire to eat a lot and get married overcomes a person, the love of property and fondness for riches arises from this. Because possessing these two things is only possible through property and riches. And from the love of wealth comes the love of authority and position. Because without authority and position, it is difficult to earn property and become rich. When these two things are acquired, many evils arise from them, such as arrogance, envy, hatred, enmity and so on. The source of all these is the stomach."[11] Therefore, fasting is a means to save people from all these spiritual diseases.

Many Sufis have drawn attention to this feature of fasting. Imam Sharani said, "When the lower self is hungry, it becomes like a weak child, and when it is full, it becomes like a ravaging lion."[12]

3. Hunger and Science

Hunger causes the heart to become pure, intelligence and clairvoyance to open. Eating too much causes the heart to become dull and the intellect to diminish. Abdulkarim al-Qushayrî said, "Hunger has become an attribute of Sufis. Hunger is one of the pillars of jihad against the nafs. The Sufis gradually accustomed themselves to starvation and restrained themselves from eating and drinking. Thus, they found the fountains of wisdom in hunger. There are many life stories narrated from them on this subject."[14]

Abū Suleiman Darānī said, "Continue to starve, for it weakens the nafs, softens the heart, and results in heavenly knowledge." Shiblî, one of the wise men, said, "Whenever I was hungry, I saw doors opening from my heart to wisdom and signs." Lokman physician also said to his son, "O my son! When the stomach is full, the idea sleeps, wisdom becomes silent, the body becomes lazy and unable to worship." Bayazid al-Bestâmî also said, "Hunger is like a cloud. When a person is hungry, the heart showers wisdom."[15]

4. Effects of Fasting on Depression, Memory and Cognitive Function

Recent studies have demonstrated the positive effects of calorie restriction and fasting in the treatment of depression, and research on this subject has been accelerated. Igwe et al.[16] said that, reviewed the literature on the neurobiological mechanisms associated with calorie restriction and intermittent fasting and summarized in their article published in 2021: "Factors that may play a role in the health effects of dietary manipulations such as intermittent fasting and calorie restriction include changes in free fatty acids, ketone bodies, neurotransmitters, cyclic adenosine monophosphate response element binding protein (CREB), brain-derived neurotrophic factor (BDNF), cytokines, euxin, ghrelin, leptin, reactive oxygen species and autophagy. Many of these factors are potential contributors to the improvement of symptoms of depression."

In another related article titled " Effects of Intermittent Fasting, Caloric Restriction, and Ramadan Intermittent Fasting on Cognitive Performance at Rest and During Exercise in Adults.", Anissa Cherif et al said that: "There are several types of intermittent fasting. One of them is Ramadan fasting, a religious practice in Islam in which healthy adult Muslims do not eat or drink during daylight hours for 1 month. Other religious practices in Islam (Sunnah of the Prophet) also encourage Muslims to practice intermittent fasting outside of Ramadan. Several cross-sectional and longitudinal studies have shown that intermittent fasting has significant effects on physical and intellectual performance, affecting various aspects of body physiology and biochemistry that may be important for athletic success. Moreover, recent findings have revealed that immunological variables also play a role in cognitive function and that intermittent fasting may influence the relationship between cytokine expression in the brain and cognitive impairments, including memory impairments.". In this article emphasizing the physical benefits of fasting as well as its benefits on memory and other cognitive functions.[17]

In another important recent study, the fact that overnutrition and obesity cause both physical and mental problems is summarized as follows: "The American Medical Association recently recognized obesity as both an illness and a leading cause of preventable death and chronic disease. This association is not only linked to physical health outcomes, however, as obesity has also been extensively associated with mental illness as well. Both obesity and severe mental illness decrease quality of life and are associated with an increase in disability, morbidity, and mortality, and when they occur together, these adverse health outcomes are magnified. Despite educational campaigns, increased awareness, and improved treatment options, the high prevalence of mental illness and comorbid obesity remains a serious problem."[18]

C. FASTING AND PHYSICAL HEALTH

As we have mentioned above, fasting is first and foremost an act of worship and servitude to Allah. It has a great contribution to one's spirituality. But fasting also has great benefits in terms of physical health. In fact, the Prophet (PBUH) said, "Fast and be healthy." In another narration, it is reported that Allah revealed to Jesus (a.s.) the following: "(O Jesus!) Tell the congregation of the sons of Israel to fast for my sake. I will give health to their bodies and increase their (hereafter) rewards."[19] These narrations point to both the material and spiritual aspects of fasting and suggest that a healthy life is possible through fasting.

In recent years, many scientific studies on the benefits of fasting for human health have been conducted and presented to the public. For example, at the first international congress on "Ramadan and Health" in Casablanca in 1994, 50 comprehensive studies on the medical ethics of fasting were presented. Papers in various fields presented at this congress showed that fasting has been shown to contribute to human well-being and has not caused any deterioration in the health and basic health status of any patient. Abstaining from food at prescribed intervals has been found to be not only physically harmless to a healthy person, but also beneficial. On the other hand, it has also been stated that patients suffering from primary diabetes or serious conditions such as coronary artery disease, kidney stones, etc. are exempt from fasting and should not fast.[20]

1. The Effect of Fasting on Obesity and Weight Control

The Prophet emphasized the importance of eating less in various hadiths. For example, a hadith on this subject is as follows: "Man has never filled a vessel more evil than his stomach. But a few morsels are enough to sustain onelower self. If he must eat, he should reserve one-third of his stomach for food, one-third for drink, and one-third for his breath."[21]

The medical importance of the Prophet's encouragement to eat less has been confirmed by medicine today. Today, medical research shows that eating too much food is the cause of many diseases. In fact, those who eat too much are exposed to obesity. Records of international organizations such as the World Health Organization (WHO), the World Agriculture and Food Organization (FAO) and the World Food Programme (WFP) show that while about one billion people in the world suffer from hunger, many more face the problem of obesity.[22]

People who are overweight and obese are at higher risk of heart attacks, strokes, high cholesterol, high blood pressure, vascular occlusion, diabetes, heart disease and cancer. Fourteen percent of cancer deaths in men and 20 percent of cancer deaths in women have been attributed to obesity.[23]

Fasting and eating less is an opportunity to be healthy. Fasting can be beneficial for obesity patients by helping weight control with a regular, balanced iftar and sahur.

Although there are many articles on the subject, an article titled "The role of low-calorie diets and intermittent fasting in the treatment of obesity and type 2 diabetes" summarizes: "Intermittent fasting (IF) involves caloric restriction every day, either once or several days a week or as an extension of night fasting. The results of recent clinical trials have shown that intermittent fasting in patients with obesity can lead to reductions in body fat mass and improvements in metabolic parameters. These beneficial effects are not only due to loss of body mass, but also to activation of metabolic pathways specific to fasting conditions."[24]

2. Fasting and Metabolism

Ramadan fasting regulates the body's metabolic processes. Fasting rests the organs of the digestive system and directs the body to use its energy more effectively.

An article published in 2022 titled "Intermittent Fasting and Metabolic Health" emphasized the benefits of fasting on metabolism. Izzah Vasim and colleagues describe obesity as an epidemic, highlighting the ongoing pressure it places on public health outcomes, the difficulties in its treatment, and the need for new and effective approaches to weight control. They then focused on different methods, including fasting, intermittent fasting, full-day fasting and time-restricted eating as approaches to improve weight control and metabolic outcomes. They stated that with dietary programs that are only allowed for 6 hours, such as fasting for up to 18 hours, especially during the long summer months, fatty acids are converted into ketones and that stimulation of this metabolism leads to very positive metabolic effects in the body, such as improvements in dyslipidemia and blood pressure.[25]

In their article published in 2019, Nader Lessan and Tomader Ali made the following observations from a Ramadan Fasting Perspective: "Intermittent fasting (IF) is gaining popularity as a way to lose weight. Ramadan fasting (RF) is practiced by millions of adult Muslims worldwide for one month each year. It entails a major shift from normal eating patterns to special nighttime eating. RF leads to intermittent

depletion and replenishment of liver glycogen. The early part of the fasting day (morning) is spent with carbohydrate dominance as the main fuel, but as the time to break the fast approaches in the afternoon and at sunset (iftar), lipid becomes more dominant. The practice of observing RF is accompanied by changes in sleep and activity patterns, as well as circadian rhythms of hormones such as cortisol, insulin, leptin, ghrelin, growth hormone, prolactin, sex hormones and adiponectin. Understanding intermittent fasting is of direct interest to many religious observers and may have wider potential implications for weight loss strategies. This review examines the existing knowledge on different aspects of energy balance in RF as a common model to learn from, as well as mapping strategies for healthier outcomes in such settings."[26]

There are many studies on the effects of long-term fasting in current literature. One of these is the work of Stephen Keenan and his colleagues. They compared two types of energy restriction models in their randomized controlled study. They compared the outcomes of fasting twice a week as in the sunnah of the our Prophet Muhammad (S.A.W.) with continuous energy restriction. They noted that high levels of compliance and reported low levels of hunger were seen with both diet methods throughout the intervention period, and that both were well tolerated in the short and medium term. These results revealed that when combined with resistance training, both methods reductions blood lipids, with greater reductions observed in the intermittent fasting group.[27]

3. Fasting, Autophagy and Detoxification

Before moving on to the subject of autophagy, "Everything has a zakat. The zakat of the body is fasting."[28] The hadith will help us to understand the subject better. In Islam, zakat is a financial worship. Zakat means cleanliness. In other words, the property for which zakat is paid is cleansed of impurities. Indeed, the Prophet said, "Zakat is the dirt (of people's property)."[29]

Since zakat is the dirt of property and the property that is zakatized is cleansed, it is possible to say that the Prophet's saying "Fasting is the zakat of the body" means that the body is cleansed of dirt through fasting. It is also confirmed by scientific studies that fasting accelerates the process of removing toxins from the body. This contributes to healthy cell renewal by providing detoxification. As a matter of fact, autophagy also refers to this.

Japanese scientist Yoshinori Ohsumi scientifically proved the effect of fasting on human health by demonstrating that cells are renewed through fasting. For this proof, he won the Nobel Prize in 2016.[30,31]

Autophagy is part of the cellular response to prolonged starvation, such as fasting, and other stress situations, such as exercise. It has an important role in embryo development and cell metamorphosis, elimination of bacteria and viruses invading the cell after infection, elimination and regeneration of damaged proteins and organelles in cells, stem cell activation, detoxification and thus slowing down aging. Damage or inadequate functioning of the autophagy mechanism is associated with many diseases such as cancer, diabetes, Parkinson's, etc. Mutations in autophagy genes can lead to genetic diseases. Along with all these, fasting is one of the most important factors that trigger autophagy.[32]

CONCLUSION

In the light of all this information and the literature, we can say that long-term fasting practices such as fasting can of course be practiced with different methods, but its continuity, making it a lifestyle, is very important for the continuation and improvement of health. A regular practice such as fasting can easily ensure this. In this respect, it is clear that fasting practiced regularly with a sense of worship and responsibility will result in a disciplined lifestyle and the protection of material and spiritual health. Therefore, we believe that the recommendation of fasting by modern medicine as well as Islam, and its acceptance as one of the most important preventive medicine practices, is very important for both individual and public health, and for reducing the workload and health costs of hospitals.

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Case Report

Does Gitelman syndrome really save bone?

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ABSTRACT

Gitelman syndrome is a renal tubular disease characterized by hypokalemia, hypomagnesemia and hypocalciuria. It has been suggested that Gitelman syndrome may affect bone metabolism by different mechanisms. This case report discusses a young male patient with chronic hypomagnesemia, recurrent fractures, and osteopenia due to Gitelman syndrome.

Keywords: Gitelman syndrome, hypomagnesemia, osteopenia, osteoporosis

INTRODUCTION

Gitelman syndrome is an inherited kidney disease characterized by impaired sodium chloride (NaCl) reabsorption in the distal tubule. Clinically, it is differentiated from other tubulopathies with hypomagnesemia, hypokalemia, normocalcemia and hypocalciuria.[1] There are studies showing that Gitelman syndrome has variable effects on bone metabolism.[2,5]

This case report discusses a patient with Gitelman syndrome who applied to the outpatient clinic with extensive bone pain and recurrent fractures.

CASE

A twenty-eight-year-old male patient was admitted to the endocrinology outpatient clinic with complaints of joint and bone pain for two years. He had no additional complaints in the physician query. He had two ankle fractures, one finger fracture, and two forearm fractures in his history. All of them occurred in childhood secondary to trauma. But he was investigated due to his history of multiple fractures. The patient was diagnosed with Gitelman syndrome at the age of four. He didn't have growth retardation. Due to Gitelman syndrome, spironolactone intake and magnesium potassium supplementation have been recommended. He did not use the drug because gynecomastia developed after using spironolactone, and he also took magnesium and potassium tablets rarely.

On physical examination, height was 174 cm and weight 62 kg. Blood pressure was 117/87 mmHg, and pulse rate was regular at 101/min. There was no shortening in his height. The patient's laboratory tests showed findings supportive of Gitelman syndrome (Table 1, 2).

Table 1. BMD data

	2011	2022
Lumbar 4 z score	-0.6	-0.7
Femur neck z score		-1.2
Femur total z score		-2.2

Table 2. Laboratory data at the time of application

	Patients results	Normal ranges
C. calcium ˜	8.86 mg/dl	8.8-10.6
Sodium	141 mmol/l	136-145
Phosphor	3.3 mg/dl	2.5-4.5
Albumin	53 g/l	35-52
Potassium	2.85 mmol/l	3.5-5
Magnesium	0.54 mmol/l	0.6-1.07
25 OH vit D3	21.8 qg/l	30-80
Hemoglobin	16.5 g/dl	12.5-16
GFR ¥	117.7 ml/dk/1.7	>90
Creatinine	0.85 mg/dl	<0.9
Parathormone	49.3 pg/ml	15-68.3
Prolactin	11.2 qg/l	4.6-21.4
Total testosterone	541 ng/l	191-663
DHEA-SO4 §	198 qg/l	160-449
TSH	2.78 mıU/ml	0.4-4.2
Renin	21.8 n/ml/hour	0.1-6.56
Aldosteron	30.7 ng/dl	>30
24 hours urine calcium	17 mg/day	100-321

˜ Corrected calcium, ¥ Glomerüler filtration rate, § Dehidroepiandrosteron sulfat

DISCUSSION

Hypokalemia, hypomagnesemia and hypocalciuria were observed. The patient's bone mineral densitometry (BMD) measurements were consistent with osteopenia (Femur total Z score: -2.2). Primary or secondary hypogonadism, thyrotoxicosis, primary hyperparathyroidism, vitamin D deficiency, smoking or alcohol use that caused secondary osteoporosis were investigated in the patient. He said he does not smoke or drink alcohol. Intact parathormone(PTH), thyroid stimulating hormone(TSH) and total testosterone levels were normal. But the 25(OH)D level was low. No height loss or chondrocalcinosis was observed in the vertebral radiographs. Oral calcium and vitamin D therapy were given to patient and it was recommended the patient to continue magnesium and potassium oral replacement therapy.

The different effects of electrolyte imbalance observed in patients with Gitelman syndrome on bone metabolism were evaluated in experimental and clinical studies.

Some studies suggested that this syndrome constituted an advantageous condition for bone formation. In a study conducted in mice with homozygous knockout of the NCC gene, it was stated that duodenal calcium absorption and calcium deposition in the bone increased, and osteoblast activity accelerated.[2]

Another study, performed on 45 patients with Gitelman syndrome, reported that the bone mineral density (BMD) of the patients increased compared to the healthy controls in high-resolution peripheral bone tomography. Also, it was found that the trabecular bone structures were thinner but denser.[3] Similar results were found in another study with dual-energy x-ray absorptiometry (DEXA).[4]

However, osteoporosis was also seen in cases with Gitelman syndrome. In a case report presented by Nakamura et al.[5], osteopenia developing in a patient with Gitelman syndrome was associated with hypocalcemia.

In the study of Wan X et al.[6], it was reported that cases with heterozygous mutations in the SLC12A3 gene associated with Gitelman syndrome experienced twice as many fractures as those who did not carry this gene.

Our case applied to the outpatient clinic with complaints of fracture attacks due to trauma and common bone pain. Osteopenia was detected as a result of BMD. According to the study conducted by Gennari et al.[7], the causes of bone loss in men might be related to genetic, environmental, hormonal, and some disease-specific factors. It was reported that about half of men with osteoporosis have alcohol use, hypogonadism, and glucocorticoid intake. In our patient estrogen and testosterone values were in the normal range. There was no glucocorticoid use or alcohol intake. Also the patient wasn't using antiepileptic and immunosuppressive drugs. His PTH and TSH values was normal range. Vitamin D deficiency causes osteoporosis because it causes a decrease in the renewal of bone mineralization and secondary hyperparathyroidism. To protect skeletal health, the 25(OH) D level would be deemed at least 20 ng/ml.[8] In our patient, 25(OH)D vitamin level was 21 ng/ml and the PTH value was within normal limits.

When the drugs he used were questioned, it was learned that he took the potassium and magnesium supplements rarely. According to the laboratory data he had hypomagnesemia and hypokalemia for a long time. Hypomagnesemia, one of the electrolyte imbalances seen in Gitelman syndrome, might also have adverse effects on the bone structure because it was seen that hypomagnesemia might directly play a role in the development of osteoporosis by reducing osteoblastic activity, bone formation, and volume.[9]

A four-year study by Tucker et al.[10] on men revealed that a diet rich in magnesium and potassium was associated with higher bone mineral density and lower bone loss.

In the study of Sara et al.[11] conducted on magnesium and osteoporosis, it was shown that magnesium deficiency caused osteoporosis directly and indirectly. In the body, 60% of magnesium was found in bone, most of which is found on the surface of hydroxyapatite. Hypomagnesemia was associated with decreased bone hardness, decreased osteoblast activity, and increased osteoclast activity due to a reduction in hydroxyapatite crystals. Because the patient did not use magnesium medications regularly, laboratory findings mostly showed hypomagnesemia. So osteopenia and fractures can be connected with hypomagnesemia in our case to. It was also reported that magnesium deficiency, which was used as a cofactor in parathyroid hormone (PTH) synthesis, might lead to a decrease in PTH synthesis and serum vitamin D levels.

Another study conducted by Bigi et al.[12] suggested that collagen in the bone was richer in magnesium and that bone quality might deteriorate in hypomagnesemia.

CONCLUSION

Although it is known that trabecular bone structures are thinner but denser in patients with Gitelman syndrome, there is not enough data on the frequency of fractures. Although bone density seems to increase in Gitelman syndrome, our patient has osteopenia and multiple fractures. Therefore changes in collagen structure and hypomagnesemia might decrease BMD, increase bone fragility in these patients. So BMD follow-up is recommended in patients with Gitelman syndrome who have long standing hypomagnesemia.

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