e-ISSN: 2791-9250

DAHUDER MEDICAL JOURNAL

Volume 3 · Issue 3 · July 2023

DAHUDER MEDICAL JOURNAL

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

INTERNATIONAL EDITORIAL BOARD MEMBERS

Table of Contents

Original Articles

Case Report

Original Article

DOI: 10.56016/dahudermj.1253273

DAHUDER Medical Journal
e-ISSN: 2791-9250

Validity and reliability of the hypoglycemia confidence scale for patients with type 1 diabetes

Gokhan Sahin[1], Baris Önder Pamuk[2], İsmail Demir[1]

[1]Department of Internal Medicine, University of Health Sciences Izmir Bozyaka Training and Research Hospital, Izmir, Turkey
[2]Department of Endocrinology and Metabolic Diseases, İzmir Katip Celebi University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Objectives: This study aims to assess the validation and reliability of the Turkish adaptation of the Hypoglycemic Confident Scale and to investigate its relationship between the Hypoglycemia Fear survey, WHO Well-Being Index, Hba1c, sociodemographic characteristics and variables.

Method: The survey consists of a total of 81 questions concerning the sociodemographic status, clinic status variables, and the Hypoglycemic Confidence Scale formed by 35 standard questions and 46 scale questions.

Result: In this study, assessment of the reliability of the scale was achieved by internal consistency and test-retest methods, and the Cronbach alpha internal consistency reliability coefficients were 0.814 in the first test and 0.885 in the second test. It was observed that the responses given to the items of the Hypoglycemic Confidence Scale at two separate times were consistent with one another. The overall correlation of the scale ($r = 0.927$, $p < 0.0001$) was positive and highly significant ($p < 0001$). A significant, inverse, and moderate correlation was found between HbA1c values and Hypoglycemic Confidence Scale total scores ($p < 0,0001$, $r = -0,479$). Similarly, a higher hypoglycemic confidence score was observed to be associated with higher WHO Well-Being Index score and lower hypoglycemic fear.

Conclusion: This study shows that the Hypoglycemia Confidence Scale created by Polonsky et al. is a valid and reliable scale that can be put into use in our country.1 The Hypoglycemic Confidence Scale may be beneficial in diabetic patient follow-up and achieving treatment goals in diabetic patients.

Keywords: Hypoglycemia, Hypoglycemic Confidence Scale, Hypoglycemia Fear Scale, WHO Well-Being Index

Hypoglycemia is one of the most frightening complications of diabetes and diabetes treatment. It is also often considered the major limiting factor in effective glycemic contro.[1] Fear of being hypoglycemic develops in patients over time and this fear complicates the treatment and increases the cost.[2]

While insulin therapy is often considered the most effective treatment for controlling hyperglycemia when administered properly, data from previous National Health and Nutrition Examination Survey research suggest that patients using insulin therapy alone have the worst control over hyperglycemia, probably due to the severity of their diabetes and fear of hypoglycemia.[3]

Therefore, over the past decade, studies have been designed to assess and understand the anxiety about hypoglycemia among patients with diabetes have

Received: *February 19, 2023****; Accepted:*** *June 1, 2023****; Published Online:*** *July 29, 2023*

How to cite this article: *Sahin G, Pamuk BÖ, Demir İ. Validity and reliability of the hypoglycemia confidence scale for patients with type 1 diabetes. DAHUDER MJ 2023,3(2):76-84. DOI: 10.56016/dahudermj.1253273*

Address for correspondence: *Gökhan Şahin, MD., Izmir Bozyaka Training and Research Hospital, Karabağlar, İzmir, Turkey*
E-mail: gkhn7sn@gmail.com

been primarily focused on fear and anxiety. These studies suggest that hypoglycemic fear is negatively correlated with glycemic control and life quality. In an accordance with that, efforts to intervene have been primarily designed to alleviate or completely overcome this fear. Lately, studies on hypoglycemia have been focused on a new concept, hypoglycemic confidence. The concept of hypoglycemic confidence encompasses a sense of personal strength and comfort derived from the belief that one has the necessary resources to stay safe from the problems associated with hypoglycemia. In other words, it emphasizes the thoughts on one's ability to avoid hypoglycemic problems. Therefore, it can be considered as representing the positive side of hypoglycemic fear and avoidance.[4] As new medication and devices are developing to reduce the risk of severe hypoglycemic episodes from happening, one of our goals should be not only to ensure that the patient feels less anxious and stay safe from the hypoglycemic attacks; we should also help the patient to feel safer and more confident about themselves. For this purpose, a nine-item "Hypoglycemic Confidence Scale" was developed by Polonsky *et al*. in 2017.1 The Hypoglycemic Confidence Scale is a self-report scale that assesses how safe and comfortable diabetic patients feel about their ability to avoid hypoglycemia-related problems. It is approved for use in adults with type 1 diabetes and type 2 diabetes patients administered with insulin.

METHODS

This study aims to assess the validity and reliability of the Turkish adaptation of the Hypoglycemic Confidence Scale. This study was conducted on 114 patients consisting of 80 women and 34 men diagnosed with type 1 diabetes. In the study, a survey created by the researcher was used to collect data for the Hypoglycemia Confidence Scale, the WHO-5 Well-Being Index, the Hypoglycemia Fear Survey, and the sociodemographic characteristics of the participants. Some of the questions concerning hypoglycemia that are involved in the sociodemographic data survey were obtained from the 'Diabetes Symptoms Checklist', which was validated by Terkes *et al*.[5] The WHO 5 Well-Being Index, which was validated in Turkish by Eser E., is a survey that consists of 5 questions and asses that how the person has been feeling during the past 2 weeks.[6] It consists of a total of 81 questions. Informed consent forms of the participants were obtained from a section in the introduction part of the questionnaire, explaining the research and asking them to participate. 146 volunteered patients with type 1 diabetes who applied to Izmir Katip Celebi University Department of Internal Medicine and Endocrinology Outpatient Clinic of the Faculty of Medicine between April 2018 and April 2019, over the age of 18, diagnosed with diabetes over a year, literate, capable of filling out the form on their own participated in the study. Diabetes patients who meet the inclusion criteria were included in the study after they were informed that their data will be confidential. The survey was completed through face-to-face interviews or patients filling out the forms by themselves. Ethics committee approval was obtained from Katip Celebi University Non-Interventional Clinical Research Ethics Committee (with decision number 110, dated 21.03.2018).

While gathering patients' data, 146 type 1 diabetic patient who met the criteria were reached, but 32 of the forms were excluded from the study due to incomplete filling. Consequently, our study is carried out with 114 type 1 diabetes patients' data. 30 patients from the same participant group was possible to reach afterward and was able to take the same survey. The Hypoglycemic Confidence Scale is a 9-item self-report scale that dwells upon 3 matters, which assess the degree of how secure and comfortable the diabetic patients feel about their ability to avoid hypoglycemia-related problems.

1-Confidence about staying safe from hypoglycemia at certain critical times. (5 items, such as driving, exercising, sleeping, etc.)

2-Self-confidence (3 items, such as having the confidence about sensing the hypoglycemia before it is too low and acting accordingly)

3-Presumed partner trust (one item; Patients presume how his/her partner feels about his/her ability to avoid serious problems due to hypoglycemia)

After the scale was translated into Turkish by the researcher, it was reviewed by two endocrinologist faculty members and a competent English lecturer, and necessary changes were made. Afterward, it was presented to the committee, which includes an academician physician, a psychologist, and a dietitian that works with diabetes and in diabetes-related fields, and then the scale was shaped into its final form. After the last changes were made, it was given to 5 people with different education levels and evaluated in terms of readability and intelligibility. Scaling scored as "I do not trust at all (1), I trust very much (4)" as in a 4-point Likert type. No cut-off value is used whereas

the average score is used (Fig. 1).

Statistical analysis of the study data was achieved by the IBM SPSS 22 statistical program. Since the variables had non-normal distribution; nonparametric tests were used in our study. Non-normal distribution of the data was identified by visual (histogram and probability graphs) and analytical (skewness and kurtosis coefficients, Kolmogorov–Smirnov/Shapiro-Wilk tests) analyses. Kolmogorov–Smirnov and Shapiro-Wilk analysis result was < 0.001, showing that the data has non-normal distribution. Descriptive statistics, Kruskal Wallis, Mann-Whitney U, Chi-square, Spearman correlation, Cronbach Alpha analysis, and regression analysis tests were used as statistical methods. for statistical significance, an error level of 5% and, p - value of < 0.05 was considered statistically significant. Confirmatory factor analysis (CFA) was achieved by the AMOS statistical package program.

RESULTS

Sociodemographic Findings

This study was carried out on 114 participants. 80 of the participants were women and 34 of the participants were men. Median age of the participants was 27,24 ± 10,28 (minimum 18, maximum 58). In the matter of education, 16.7% of participants (n = 19) had secondary school education or below, 35.1% (n = 40) were high school graduates, 48.2% (n = 55) were a university graduates or had a higher education level. The average duration of diabetes of the participants was 12.04 ± 9.87 years (minimum 1 – maximum 50 years), the average of their last measured HbA1c was 7.89 ± 1.60% (5.2% minimum – maximum 13.9%).

95.6% (n = 109) of the participants received a diabetes education whereas 4.4% (n = 5) of the participants did not receive a diabetes education. While 74.62% (n = 85) of the participants thought that they received a good education, 25.4% (n = 29) thought that they received a bad education. 92.1% (n = 105) of the participants stated that they received hypoglycemia training, 7.9% (n = 9) of the participants stated that they did not receive a hypoglycemia training. Among the patients who received a diabetes education, %81.6 (n = 93) state that they received a good education, whereas %18.4 stated that they received a bad

HYPOGLYCEMIC CONFIDENCE SCALE

How confident are you that you can avoid serious problems with hypoglycemia?	I do not trust.	A little	I trust.	I'm Very Confident
1. While doing sports				
2. While you sleep				
3. While driving				
4. Socializing				
5. When you are alone				

How confident are you that you can do the following?	I Never Trust	A Little Confidence	Moderately Confident	I'm Very Confident
6. That you can avoid serious problems caused by hypoglycemia				
7. Be aware of hypoglycemia and take precautions before your blood sugar drops too much.				
8. That you can continue to do the things you truly want to do in life, despite the risks of hypoglycemia.				
9. If you have a spouse or partner, what is your estimate of your partner's belief in you that we can overcome serious problems that may arise from hypoglycemia?				

Fig. 1. Hypoglycemic confidence scale

education. It was determined that 5.5% (n = 6) of the participants who stated that they have received a diabetes education did not receive hypoglycemia training. 1.9% (n = 2) of the participants who have received a hypoglycemia training stated that they did not receive a diabetes education. A statistically significant and positive correlation was found between blood glucose level dropping below 70 mg/dl and hypoglycemia symptoms occurring in the last week ($p < 0.0001$ r = 0.686).

Hypoglycemic Confidence Scale Validity Reliability Findings

Factor Analysis

The predetermined factor structure of the scale was assessed with confirmatory factor analysis. If a previously validated scale is going to be adapted into another culture, in order to test the construct validity of the scale in question, recommended use of method is to perform a direct confirmatory factor analysis without doing a re-exploratory factor analysis.[7] In confirmatory factor analysis, the factor loads of the

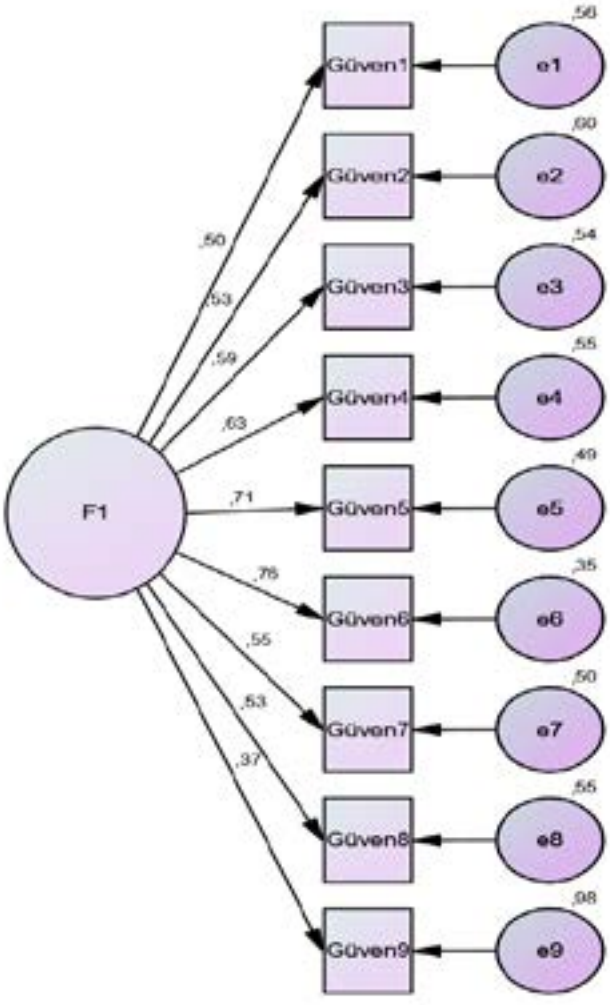

Fig. 2. Diagram of Hypoglycemic Confidence Scale Confirmatory Factor Analysis

the scale should be above 0.32.[8] In the study in which the scale was first developed, factor loads ranged from 0.52 to 0.92. According to the structural equation theory of the analysis, it was observed that the item variance values in the Turkish scale varies between 0.37 and 0.76 and the adaptation is satisfactory (Fig. 2). It was observed that the single-factor structure of the scale also is in fit.

Confirmatory factor analysis (DFA) was achieved by the AMOS statistical package program. Testing of the fit of the tested model with the analyzed data was achieved by Chi-square test. Chi-square/degrees of freedom, Comparative Fit Index (CFI), Standardized Root Mean Square Residual (SRMR) which indicates the mean difference between the model's explained covariance and observed covariances, Root Mean Square Error of Approximation (RMSEA), Goodness of Fit Index (GFI), Adjusted Goodness of Fit Index (AGFI) of the Tested model was calculated. In confirmatory factor analysis, CMIN criteria showed a good fit; GFI, CFI, AGFI, RMSEA and RMR criteria showed acceptable fit. In conclusion; It was determined that the findings obtained from the collected data of the Turkish scale were consistent with the theoretical structure and were valid (Table 1).

In the reliability studies of the research, Cronbach alpha internal consistency coefficient and test-retest correlation coefficient were assessed. Internal consistency reliability requires that the items of the scale have a certain conceptual structure and requires items to measure the same structure in relation to one another.[9] The Cronbach alpha internal consistency reliability coefficients of the Hypoglycemic Confidence Scale were found to be 0.814 in the first calculation and 0.885 in the second calculation. A Cronbach Alpha coefficient of $0.80 \leq a < 1.00$ indicates that the reliability of the scale is high. The Cronbach Alpha reliability coefficient of the "Hypoglycemic Confidence Scale" was determined to be highly reliable. The findings show that the internal reliability of the scale is sufficient.

In the test-retest method used in the scale reliability study; scale is re-applicated to the same group after a certain interval (between 2 and 4 weeks) (Time-invariant) and the relationship between two re-application is assessed with the Pearson product-moment correlation coefficient.[9] The correlation coefficient is defined as the correlation between the groups obtained by testing the scale twice under

Table 1. **Hypoglycemic confidence scale (HCI) factor loads and regression coefficients for items**

Index	Good fit*	Acceptable fit	Hypoglycemic Confidence Scale (HCS)
CMIN/D($\chi^{2/sd}$)	< 2	< 5	1.668
GFI	> 0.95	> 0.90	0.918
CFI	> 0.95	> 0.90	0.927
AGFI	> 0.95	> 0.85	0.864
RMSEA	< 0.05	< 0.08	0.077
RMR	< 0.05	< 0.08	0,052

CMIN: Chi-square, GFI: Goodness of Fit Index, CFI: Comparative Fit Index, AGFI: Adjusted Goodness of Fit Index, RMSEA: Root Mean Square Error of Approximation, RMR: Root Mean Square Residual

Table 2. **Test-Retest Mean Scores and Comparison**

Scale and subscale	Hypoglycemic Confidence Scale Score		Analyze results	
	First Take X ± SS	Second Take X ± SS	r	*p*
HCS Overall score	2.82 ± 0.59	2.92 ± 0.64	0.927	.000

similar conditions and with a short time interval. The correlation coefficient should be approximately 1 and be above 0.70 at least. The most suitable value is 0,80.[10] According to the analyzes in the study, responses for the items of the Hypoglycemic Confidence Scale at two separate times were consistent with one another. The overall correlation of the scale (r = 0.927, $p <$ 0.0001) was positive and highly significant ($p <$ 0001). This result shows that the scale is not affected by time, assesses the same situation, and is consistent (Table 2). According to the research results, the analyzes showed that the Hypoglycemic Confidence Scale is a valid and reliable test for the Turkish sample.

The hypoglycemic fear survey (HFS) was developed to assess the fear of hypoglycemia in individuals with diabetes.[11] Turkish validity and reliability study of HFS was conducted by Erol *et al*. in 2009 and the total scale Cronbach's alpha coefficient of HFS was found r = 0.9 . The scale consists of two factors, behavior and anxiety, and a total of 32 items of 5-point Likert type. In the behavior factor, 15 items are asked to patients about their practices to prevent their glucose levels from dropping low within six months. In the anxiety factor, 17 items are asked of patients about how often

Table 3. **The relationship between the participants' total score of HAI and its variables**

Variables	Spearman's correlation coefficient	*p*
Age	-0,134	0,15
Duration of Diabetes	0,033	0,72
HbA1C	**-0,479**	**<0,001**
BMI	-0,166	0,07
WHO Index Score	**0,417**	**<0,001**
HFS total score	**-0,385**	**<0,001**
HFS (behavioral)	**-0,243**	**0,009**
HFS (anxiety)	**-0,331**	**<0,001**

Table 4. **Comparison of Mean HCS Scores According To Control Visit Frequency**

Control Visit Frequency	n	HCS Mean Score	SS	Kruskal-Wallis	*P* value
Control Visit Frequency for Diabetes					
Bimonthly	18	2,86	0,56	8,368	**0,015**
Every 3-6 months	85	2,87	0,57		
Once a Year	11	2,31	0,58		
Perception of Quality of Life in Participants					
Bad	11	2,55	0,31	8,908	**0,012**
Moderate	56	2,73	0,57		
Good	47	2,98	0,61		

Table 5. Comparison of Independent Variable and Mean Scores Of HCS

	n	Mean Score of HCS	SS	Mann Whitney-U	P value
Exercise					
Yes	87	2,88	0,58	-2,299	**0,021**
No	27	2,60	0,54		
Number Of Measurements of Blood Glucose Per Day					
4 or less	87	2,72	0,56	-2,265	**0,008**
5 or more	27	3,04	0,58		
Diabetes Education Wellness Perception					
Yes	85	2,89	0,56	-2,218	**0,027**
No	29	2,59	0,60		
Hypoglycemia Training Wellness Perception					
Yes	93	2,89	0,58	-2,983	**0,003**
No	21	2,42	0,49		
Practice of Nutrition Therapy for Diabetes					
Yes	79	2,90	0,60	-2,366	**0,018**
No	35	2,63	0,51		

they feel anxious due to a decrease in glucose level within six months.

The total mean of the participants' responses to the Hypoglycemic Fear Scale was found to be 1.58 ± 0.68. The mean response to the behavior sub-factor was found to be 1.43 ± 0.70. The mean response to the anxiety sub-factor was found to be 1.71 ± 0.91. The Turkish validity and reliability analysis of the WHO Well-Being Index (Eser *et al*. 1999) was carried out and it consists of five single-factor and six-point Likert-type questions. The lowest score is 0 and the highest score is 25. Scores below 13 indicate poor quality of life and should be evaluated for depression. The mean score of the participants' WHO Well-Being Index was found to be 13.81 ± 4.78. In our study, a statistically significant and weak inverse correlation was found between the WHO Well-Being Index score and the Hypoglycemic Fear Scale score (p = 0.019, r =-0.219). No significant correlation was found between HFS, WHO Index, and HbA1c values.

A significant, inverse and moderate correlation was found between the participants' HbA1c values and their Hypoglycemic Confidence Scale total scores (p < 0.0001, r = -0.479). A statistically significant and moderately positive correlation was found between the WHO Index score and the Hypoglycemic Confidence Scale score (p < 0.0001, r = 0.417). Statistically significant weak inverse correlation was found between the total score of HFS and HCS score (p < 0.0001, r = -0.385). Similarly, weak and inverse correlations were found between HFS sub-factors. No significant correlation was found between other variables (Table 3).

A statistically significant relationship was found between the control visit frequency of the participants for diabetes and the participants' perception of quality of life (p = 0.012) and their Hypoglycemic Confidence Scale scores (p = 0.015). Determining the group that made the difference in control visit frequency was achieved by using a nonparametric post-hoc (Tamhane) test and a statistically significant difference was found between those who went for a check-up between 3-6 months and those who went once a year (p = 0.030) (Table 4).

Exercising status (p = 0.021), number of blood glucose measurements per day (p = 0.008), perception of quality of life (p = 0.012), diabetes education wellness perception (p = 0.027), hypoglycemia training wellness perception (p = 0.021). 0.003) practice state of nutritional therapy for diabetes (p = 0.018) of the participants was found to be statistically significantly correlated with the hypoglycemia confidence scale

Table 6. Hierarchical Regression Analysis (Hypoglycemic Confidence Scale)

Model	R	R Square	Adjusted R Square	Durbin-Watson	ANOVAF	ANOVAp
1	0,461[a]	0,213	0,11	1,810	2,273	0,13[a]
2	0,476[b]	0,226	0,11		2,066	0,20[b]
3	0,616[c]	0,379	0,28		3,993	< 0,0001[c]

Table 7. Excluded Variables in Regression.

Model		Beta	t	*p*	Partial Correlation
2	Hypoglycemic Fear Behavior	0,126[b]	1,317	0,191	0,131
	Hypoglycemic Fear Anxiety	0,052[b]	0,561	0,576	0,056
3	Hypoglycemic Confidence Scale	-0,444[c]	-4,919	< 0,0001	-0,445

(Table 5).

In our study, we investigated the efficiency of the Hypoglycemic Confidence Scale after removing all the factors that may influence the HbA1c level. To achieve this, we used the hierarchical regression analysis method and the durbin-watson coefficient was calculated to be between 1.5 and 2.5, which is acceptable. In the first step, we analyzed demographic situations that could have an effect. In the second step, sub-factors of the Hypoglycemic Fear Scale were included in the analysis. Finally, in the third step, we studied the effect of the Hypoglycemic Confidence Scale on HbA1c independently from other factors (Table 6). As a result of our analysis, it was found that the HCS score alone is associated with HbA1c independently from other factors (significantly and inversely correlated). (Table 7).

First step a: Age, gender, marital status, education level, exercise status, smoking, alcohol consumption

Second step b: Hypoglycemic Fear Scale anxiety, Hypoglycemic Fear Scale behavior

Third step c: Hypoglycemic Confidence Scale

Dependent variable: HbA1c

In our study, we analyzed the relationship between the Hypoglycemic Confidence Scale and these independent variables one by one such as age, education status, income status, place of residence, housemates, occupation, smoking, alcohol consumption, exercise, diabetes education status, hypoglycemia training status, or to have an additional disease, and we found no statistically significant difference in-between.

DISCUSSION

In this study, confirmatory factor analysis was used to investigate the validity and reliability of the scale, reliability was also calculated using internal consistency and test-retest methods. In the study of Polonsky *et al*., factor loadings ranged from 0.52 to 0.92.[1] The factor loads of the items in our study ranged from 0.37 to 0.76 and were above the acceptable factor load value of 0.32. The Cronbach alpha internal consistency reliability coefficients were found to be 0.814 in the first test and 0.885 in the retest. The findings showed that the internal reliability of the scale is sufficient and thus can be put into use in our country as a reliable scale. According to the analyzes in the study, it was observed that the responses given to the items of the Hypoglycemic Confidence Scale at two separate times were consistent with one another. The overall correlation of the scale ($r = 0.927$, $p < 0.0001$) is positive and highly significant ($p < 0001$). This result shows that the scale is time-invariant, assess the same situation and is consistent.

In the study of Polonsky *et al*., the average of the responses given to the hypoglycemia confidence scale items by patients was found to be 3.06 ± 0.59.[1] Demographic data in the study suggested that the degree of confidence in hypoglycemia was independent from age, gender, duration of diabetes, and type of diabetes. The only exception to these is the education level; higher education was found significantly associated with higher HCS scores.

In our study, the average of the responses to the hypoglycemia confidence scale was found to be 2.82 ± 0.59. Likewise, in our study, no significant relationship was found between age, gender, duration of diabetes, and HCS. On the contrary, no relationship was found between educational status and the Hypoglycemic Confidence Scale in our study. Moreover, no statistically significant relationship was found between the Hypoglycemia Confidence scale and the variables that are additionally investigated in this study; such as BMI, age, education level, income status, place of residence, housemates, occupation, smoking, alcohol consumption, exercise, diabetes education status, hypoglycemia training status, additional disease presence, presence of diabetes complications or having attacks of hypoglycemia. Considering that it may be related to the sociodemographic data, we added exercising status ($p = 0.021$), number of blood glucose measurements per day ($p = 0.008$), diabetes education wellness perception ($p = 0.027$), hypoglycemia training wellness perception (0.003) practice state of nutritional therapy for diabetes ($p = 0.018$) into the analysis and found a statistically significant correlation

with the hypoglycemia confidence scale. In addition, the relationship between the control visit frequency of patients for diabetes ($p = 0.015$) and the participants' perception of quality of life ($p = 0.012$) and their Hypoglycemic Confidence Scale scores were found statistically significant.

Similar to Polonsky *et al*'s study, we observed a significant, inverse, and moderate correlation between the HbA1c values and the Hypoglycemic Confidence Scale total scores of the participants ($p < 0.0001$, r = -0.479).1 Once again similar to Polonsky *et al*. study, higher hypoglycemic confidence was found to be associated with higher scores on the WHO Well-Being Index and lower hypoglycemic fear. A statistically significant and moderately positive correlation was found between the WHO Index and the Hypoglycemic Confidence Scale ($p < 0.0001$, r = 0.417).1 A statistically significant weak inverse correlation was found between the total score of HFS and the HCS score ($p < 0.0001$, r = -0.385). Likewise, weak and inverse correlations were observed in HFS sub-factors. A statistically significant and weak inverse correlation was found between the WHO Index and the Hypoglycemic Fear Scale ($p = 0.019$, r = -0.219). In our study, no significant relationship was found between the HFS, WHO Index Score and HbA1c values.

In the study of Polonsky *et al*., evaluation of the independence of the relationship between HCS and HbA1c values was achieved by hierarchical regression analysis, and an independent effect of HCS on HbA1c was observed only in type 2 DM patients administered with insulin.[1] Hierarchical regression analysis of the study revealed that HCS was significantly and inversely correlated with HbA1c alone independently from other factors $p < 0.0001$, r = -0.445).

Turkish adaptation of the Hypoglycemia Confidence Scale created by Polonsky *et al*. is a valid and reliable scale that can be put into use in our country.[1] HCS should be put into use in our country and the HCS score of diabetes patients should be evaluated, and the HCS score should be aimed to use in the plan the improving the patients' HCS score. In addition, since the relationship between the Hypoglycemic Confidence Scale and HbA1c is statistically significant and inversely correlated independently from other factors, the use of this scale in the follow-up of diabetic patients will be beneficial for achieving the treatment goal.

CONCLUSION

Turkish adaptation of the Hypoglycemia Confidence Scale created by Polonsky *et al*. is a valid and reliable scale that can be used in the follow-up of diabetes patients in our country.[1] Although, our study is carried with type 1 diabetes patients, we suggest that a reliability and validity study of the HCS scale should also be conducted with type 2 diabetes patients. Further studies are needed on this subject that should be conducted with larger and variable patient groups.

Conflict of Interest

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

Funding Sources

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

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of İzmir Katip Celebi University Faculty of Medicine, İzmir, Turkey. (Decision number: 110, date: 21.03.2018).

Authors' Contribution

Study Conception: BÖP, GŞ, İD; Study Design: İD, GŞ; Literature Review: GŞ; Critical Review: BÖP, GŞ, İD; Data Collection and/or Processing: GŞ, İD; Analysis and/or Data Interpretation: GŞ, İD; Manuscript preparing: GŞ, İD.

REFERENCES

1. Polonsky WH, Fisher L, Hessler D, Edelman SV. Investigating hypoglycemic confidence in type 1 and type 2 diabetes. Diabetes technology & therapeutics. 2017;19(2):131-6.
2. Williams SA, Shi L, Brenneman SK, Johnson JC, Wegner JC, Fonseca V. The burden of hypoglycemia on healthcare utilization, costs, and quality of life among type 2 diabetes mellitus patients. Journal of Diabetes and its Complications. 2012;26(5):399-406.
3. Cheung BM, Ong KL, Cherny SS, Sham P-C, Tso AW, Lam KS. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. The American journal of medicine. 2009;122(5):443-53.
4. Leiter LA, Yale J-F, Chiasson J, Harris S, Kleinstiver P, Sauriol L. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. Can J Diabetes. 2005;29(3):186-92.

5. Terkes N, Bektas H. Psychometric evaluation of the Diabetes Symptom Checklist–Revised in patients with type 2 diabetes in Turkey. Japan Journal of Nursing Science. 2016;13(2):273-83.
6. Unit PR. WHO (Five) Well-Being Index. Hillerød, Denmark: WHO Collaborating Center for Mental Health, Frederiksborg …; 1998.
7. Kahn JH. Factor analysis in counseling psychology research, training, and practice: Principles, advances, and applications. The counseling psychologist. 2006;34(5):684-718.
8. Tabachnick BG, Fidell LS. Principal components and factor analysis. Using multivariate statistics. 2001;4(1):582-633.
9. Gürbüz S, Şahin F. Sosyal bilimlerde araştırma yöntemleri. Ankara: Seçkin Yayıncılık. 2014;271.
10. Polit DF, Beck CT. Generalization in quantitative and qualitative research: Myths and strategies. International journal of nursing studies. 2010;47(11):1451-8.
11. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes care. 1987;10(5):617-21.

Original Article

DOI: 10.56016/dahudermj.1279501

DAHUDER Medical Journal
e-ISSN: 2791-9250

The value of procalsitonin in determining the severity acute pancreatitis cases

Ali Zeynettin[1], İsmail Demir[1], Hüseyin Sinan Akay[2]

[1]Departman of Internal Medicine, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey
[2]Departman of Internal Medicine, Atatürk Training and Research Hospital, Yeşilyurt, İzmir, Turkey

ABSTRACT

Objectives: Many markers and indication systems are being used to indicate the prognosis of acute pancreatitis. Our study was planned to investigate the importance of procalcitonin(PCT) in patients with severe pancreatitis in terms of predicting prognosis by comparing C-reactive protein , modified CT severity index, and duration of hospitalization.

Methods: In our cross-sectional retrospective study, 30 patients who were hospitalized with a diagnosis of A. pancreatitis were included in the study. Our study was conducted from January 2013 to January 2019 at Katip Çelebi University. PCT, CRP, duration of hospitalization, gender, age, CRE, CA, pleural effusion, and modified CT severity scores were recorded in all patients.

Results: Of the 30 patients included in the study,13 (43.33%) were male and 17(56.66%) were female. The presence of stones in 80% of patients was detected in 6.7% of patients due to hypertriglestrimia. The PCT value was found to be a minimum of 0.0 ng/ml, a maximum of 39.68 ng/ml, and an average of 1.97 ng/ml. There is a significant relationship between the PCT value and the length of hospitalization for the patients. The hospitalization period was a minimum of 3 days, a maximum of 23 days, and an average of 10.13 days in the 30 patients studied. It was determined that there was a statistically significant relationship between PCT and length of stay (r = 0.437; p 0.016).

Conclusion: In patients with A. pancreatitis, the evaluation of PCT, CRP, and modified CT severity index can be used to estimate the duration of hospitalization.

Keywords: acute pancreatitis, procalcitonin, modified CT severity index, CRP

Acute pancreatitis (AP) is known as the reversible inflammation of the pancreas. This inflammatory event may remain localized in the pancreas and may spread to the peripancreatic tissues and other organ systems.[1] The annual incidence of acute pancreatitis ranges from 13 to 45 per 100,000 people, with the incidence in men being more frequent than in women. Gallstones are responsible for 80-90% of acute pancreatitis cases and analysis is responsible for 10-20%. Alcoholism increases the incidence of gallstones in men and women. 10-15% of the cases are severe acute pancreatitis and 80% are syncretizing pancreatitis.[2]

It can be seen in acute pancreatitis from mild interstitial edema to necrotizing pancreatitis and infected pancreatic necrosis. It can occur in varying degrees from abdominal pain to hypotension, fluid sequestration, metabolic disorders, sepsis, and death.

Received: *April 8, 2023;* ***Accepted:*** *July 21, 2023;* ***Published Online:*** *July 29, 2023*

How to cite this article: *Zeynettin A, Demir İ, Akay HS. The value of procalsiton in determining the severity acute pancreatitis cases DAHUDER MJ 2023,3(3):85-90. DOI: 10.56016/dahudermj.1279501*

Address for correspondence: *Ali Zeynettin, MD., Associate Professor, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey*
E-mail: ataz6@hotmail.com

Diagnosis of the disease; patient history, physical examination, serological markers, and radiological scoring systems have been developed to date. Ranson, APACHE II, and Atlanta classifications are the most used ones.[3] Many studies have proven the relationship between Ranson, APACHE-II, Glasgow, and Balthazar CT Severity Index and Serum procalcitonin in the prediction of acute pancreatitis.[4, 5]

In our study, we aimed to investigate the relationship between procalcitonin values, course of the disease, and length of hospitalization in patients with mild, moderate, and severe pancreatitis.

METHODS

Our study included 30 patients hospitalized with the a diagnosis of A. pancreatitis in Katip Çelebi University Atatürk Training and Research Hospital Gastroenterology, General Internal Medicine clinics between January 2013 and January 2019. Our study was supported by decision number 36 of the institutional ethics review board dated 14.02.2018.

The study was planned as retrospective in one center. The diagnosis of acute pancreatitis was made according to the coexistence of at least two or more of the following criteria in patients presenting with acute abdominal pain:

of back pain in the epigastric region,

-The presence of 3 times or more elevation in serum amylase and lipase values,

-Verification of pancreatitis table with imaging methods

In our study, a modified computed tomography (CT) severity index (Balthazar record) was used to classify the severity of the disease. Contrast-enhanced CT is recommended for imaging patients with AP and evaluating the severity of AP.[6] This scoring; The degree of necrosis was developed based on the presence of inflammation and fluid collections. The maximum score is 10, if the score is ≥ 6, there is a serious disease.

Patients were treated using accepted AP standard management. Oral intake for all patients was stopped immediately after hospitalization. Fluid therapy was administered, electrolyte disturbance was regulated, and analgesics were given. Systemic antibiotics were applied when necessary. Endoscopic retrograde cholangiopancreatography was performed in the first 24 hours in patients with suspected biliary angiography. Although the sensitivity and specificity of all these systems to predict severe AP vary between 55% and 90% depending on the timing of the record and the cutoff values of the parameters used, these recording systems required at least 48 hours to complete. In the study, CTs were taken 48-72 hours after admission.

According to the Atlanta criteria, mild and severe acute pancreatitis were differentiated in all patients and these numbers were recorded.

Since the patients recruited in our study were hospitalized in the emergency department, and because procalcitonin could not be measured in emergency conditions, the procalcitonin level was requested on the day of admission to our service. Procalcitonin was measured using Serum PCT concentration. A chemiluminescent immunoassay (LUMItest PCT, Brahms Diagnostica, Berlin, Germany). Analytical test sensitivity is about 0.1 ng/mL. Functional test sensitivity (20% coefficient of variation between tests) is approximately 0.3 ng/mL. In PCT, blood samples were centrifuged for 10 minutes (3,000 rotations per minute at -4 °C). Serum was removed and stored at -80 °C until being used for biochemical analysis.

Using the hospital computer system (probel), the age, gender, max proc, max CRP, Urea, Creatinine, Calcium, modified CT severity index score of the patient, pleural effusion, clinical follow-up notes, epicrisis notes and the duration of staying at the hospital were included. In addition, the number of surgical interventions (in numbers and types), ERCP requirements, interventional radiology procedures, and mortality, if any, during the hospitalization were recorded.

Blood samples were taken from the AP diagnosed hospitalized patients from the emergency department or polyclinics immediately after hospitalization. These blood tests were performed on the PCT Siemens Advia Centaur XPT immunoassay device (Siemens Healthcare GmbH, Erlangen, Germany). The reference range of the PCT kit is 0-0.1ng/mL. CRP, ALT, amylase, lipase, and Ca measurements were measured by the Abbott Architect c16000 spectrophotometer device. (Abbott Park, Illinois, USA) CRP reference range is 0-0.5 mg/dL, ALT reference range is 0-55 U/L, amylase reference range 25-125 U/L, lipase reference range 8-78 U/L, Ca reference range is 8.5-10.5 mg/dL. WBC was performed on a Sysmex XN 1000 complete blood count. (Wakinohama-Kaigandori Chuo-ku, Japan) WBC reference range 4-10 10 9 /L' was evaluated.

Statistical analysis

SPSS-24 software program was used for statistical analysis. The normality of numerical data was evaluated with the Shapiro-Wilk test. Normally distributed numerical data were expressed as mean and standard deviation, and non-normally distributed data were expressed as median and interquartile range. Independent Student's t-test was used to compare normally distributed data, and the Mann-Whitney U test was used to compare non-normally distributed data. The chi-square test and Fischer Exact test were used to compare categorical variables. Spearman correlation analysis was used to analyze the relationship between activity level and clinical variables.

RESULTS

Thirty patients with a definite diagnosis of acute pancreatitis were included in the study. The number and percentage of male patients was 13 (43.33%) and 17 (56.66%) were female; The youngest patient was 38 years old and the oldest patient was 93 years old. The mean age was 57.55 and the standard deviation was ± 16.3. Biliary causes were determined in 86.67% of patients, hypertriglyceridemia in 6.67% of patients, and drug-related in 6.67%. In the modified CT severity index 2 patients (6.7%) with pancreatic inflammation in acute pancreatitis with 0 points, 2 patients with 5 (16.7%) points, and 23 patients with 4 points (76.7%) were recorded. The number of patients with a pancreatic necrosis score of 0 was 25 (83.3%), 2 patients were 4 (13.3%), and the number of patients with 4 patients was 1 (3.39%). In the grading of extra pancreatic complications, the number of patients with a record of zero was 12 (40%), and the number of patients with a record of 2 was determined as 18 (60%). The number of patients with a modified CT severity index total recorded of 0 is 1 (3.3%), the number of patients with 2 is 6 (20%), the number of patients with 4 is 6 (20%), number of patients with 6 is 12 (40%), number of patients with 8 The number of patients with a record of 4 (13.3%) and a record of 10 was determined as 1 (3.3%). The minimum value of procalcitonin, which can be used to predict poor prognosis in patients diagnosed with acute pancreatitis, was 0.0ng/mL, and the maximum detected value was found to be 39.6800 ng/mL, with a mean of 1.9783 ± 7.2907. The minimum hospitalization period of the patients was 3 days, the maximum was 23 days, and the mean was 10.133 ± 5.20 days. The lowest value seen in CRP was 0.100, and the highest value was 32.2700, with an average of 15,639 ± 9,127. The lowest value of Creatinine was found to be 0.4600 and the highest value of 2.200 was found to be 0.845 ± 0.3068. BUN's lowest value 6 highest value is 29.00 mean of 14.36 ± 6.96. The lowest value of Calcium was 7.30 mg/dL and the highest value was 9.800 mg/dL with an average of 8.2933 ± 0.525. One of the systemic complications of acute pancreatitis is pleural effusion. In our study, the number of patients with pleural effusion was 14 (46.7%) and the number of patients without pleural effusion was found to be 16 (53.3%). Our study was conducted on a total of 30 patients aged between 38 and 93. In this study, the mean age was 57.55 years, and there was no statistically significant relationship between the investigated parameters and age and gender. In this study, we investigated the correlation of PCT values measured at admission with different parameters in patients hospitalized with the diagnosis of acute pancreatitis. The procalcitonin value was found to be a minimum of 0.0 ng/mL, maximum of 39.68 ng/mL average 1.97 ng/mL. There is a significant relationship between the procalcitonin value and the length of hospital stay of the patients. The hospitalization period was a minimum of 3 days, a maximum of 23 days, and an average of 10.13 days in 30 patients studied. It was determined that there was a statistically significant relationship between procalcitonin and length of hospital stay ($r = 0.437$; $p < 0.016$). In 30 patients investigated, CRP levels were found to be minimum of 0.1 mg/dL, a maximum 32.27 mg/dL, and a mean of 15.6393 mg/dL ($r = 0.653$; $p < 0.001$). It was determined that the relationship between the length of stay and modified CT severity index total score and the level of relationship with CRP were closed. CT severity index total scoring was found to be a minimum of 0, maximum of 10, and mean 5 No correlation was found between the modified CT severity index and PCT (p : 0.539). However, a positive correlation was found between the Modified CT severity index and CRP (p : 0.539), but a positive correlation was found between the Modified CT severity index and CRP ($p < 0.001$). In 30 patients studied, a negative correlation was found only with the modified CT severity index total score of serum calcium levels ($r= -0.483$; $p < 0.007$) The maximum calcium level was 9.8000 mg/dL and the minimum level was 7.3000 mg/dL.

DISCUSSION

Various recording systems are used to determine clinical severity and prognosis in acute pancreatitis. The main systems are Ranson criteria, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Multiple Organ System Score (MOSS), Modified Glasgow, and Modified CT severity index scores.

The annual incidence of acute pancreatitis ranges from 13 to 45 per 100,000 people.[7] Clinical symptoms and signs in acute pancreatitis may vary depending on the age and severity of the attack. Sudden onset of abdominal pain, nausea, vomiting, and abdominal distention are common symptoms and signs.[8] The most common of these symptoms are abdominal pain felt in the epigastric region or the left upper quadrant. Although pain is often severe, it is not proportional to the severity of the disease.[9] Although in many studies there are differences between countries in the etiology, gallstones and alcohol are blamed in 90% of the cases. While alcohol occupies the first place in the etiology of AP in western countries, biliary causes are the first in our country.[10, 11] In our study, consistent with the literature, biliary causes were found in 86.67% of patients, hypertriglyceridemia in 6.67%, and drug-related in 6.67% of patients. The rate of acute biliary pancreatitis in women was 56.66%. The higher incidence of gallstone pancreatitis in women may be due to the higher incidence of gallstones in women, but the risk of developing gallstone pancreatitis is relatively higher in men than in women (relative risk12 vs. 25).[12] It is known that gender does not cause an increase in the severity and mortality of acute pancreatitis.[13] In our study, no significant difference was found between the male and female gender in terms of mortality and complications. It is more mortal in advanced age.[14, 15] In our study, pancreatitis was found with a similar frequency in both genders, which is consistent with the literature. Contrast-enhanced CT is considered the gold standard for the diagnosis of acute pancreatitis and the assessment of the severity of the disease.[16, 17] He found the diagnostic value of CT for acute pancreatitis to be 75-90%,18 CT defines anatomical structures better and can reveal complications such as pancreatic inflammation and necrosis.[19] CT is also helpful in determining clinical severity and prognosis. In acute pancreatitis, the pancreas may be normal at a rate of 14-28% on CT. Normal pancreas is generally associated with good clinical outcomes. The modified CT severity index provides standard grading for acute pancreatitis scoring to CT findings. In this score system, the degree of inflammation and necrosis in the pancreas defines the clinical severity. Although the subject of which tests should be requested in the diagnosis of acute pancreatitis is still controversial, an early CT scan comes to the first when the benefits of the Modified CT severity index score are taken into consideration. It is stated that routine CT repetition is not required during follow-up in patients whose Modified CT severity index score is between 0-3 in the early period, but control CT is recommended in this patient group in case of unexpected clinical worsening, abscess, pseudocyst and other complications.

In the study of Vriens et al., it was reported that early determination of the Modified CT severity index is an important prognostic indicator in determining complications and mortality. The higher the modified CT severity index score, the higher the mortality rate. While the mortality rate is 0% in patients with an index of 0-2, it is accepted as 17% in patients with an index of.[7-10, 13] There are many studies supporting this view.2 However, in the study of De Waele et al. in 2007, no correlation was found between the Modified CT severity index and mortality.[15, 17] In our study, a significant correlation was found between the modified CT severity index score and mortality, which is consistent with many studies in the literature. Our study shows that there is a significant correlation between the modified CT severity index score and the length of hospital stay ($p < 0.000$).

In the study of Zrnic et al., it was observed that CRP levels and disease severity were correlated in patients with AP. This is useful in predicting complications that may occur.[18] In the study of Dambrauskas et al., CRP and leukocyte values were found to be important distinguishing parameters in the development of infected pancreatic necrosis.[10] Similarly, in the study of Schütte et al., it was shown that erythrocyte sedimentation rate and CRP were successful in determining the severity of acute pancreatitis in the first 24 hours.[11] The synthesis of CRP starts very rapidly after a single stimulant, and serum concentrations rise above 5 mg/L around 6 hours, reaching pixelum concentrations around 48 hours. The plasma half-life of CRP is approx.

It is 19 hours and the only determinant of the circulating concentration of CRP is the rate of synthesis. Therefore, stimulation of CR production reflects the severity of pathological processes. CRP concentration is a very useful nonspecific biochemical marker for inflammation. CRP measurement provides important contributions in screening for organic

disease, monitoring the response to inflammation and infection treatment, and detecting concomitant infection in immunocompromised individuals.

In our study, it was determined that the high level of CRP affects the length of stay in line with the literature. It was observed that patients with high CRP values were hospitalized longer ($p < 0.001$).

In large study groups, procalcitonin was found to be more successful in demonstrating the severity of pancreatitis and the risk of developing necrosis compared to other inflammatory markers.[12, 13] In a prospective international multicenter study, it has been proven that procalcitonin plays a role in the development and prognosis of pancreatitis. In the study of Rau et al., procalcitonin and CRP values were compared and procalcitonin was found to be a more valuable marker in early diagnosis and prognosis. It has been shown that Ranson criteria and CRP level are correlated with the development of severe acute pancreatitis, but procalcitonin level is more effective when compared to procalcitonin level.[15] In our study, no correlation was found between the procalcitonin values at the time of hospitalization and the modified CT severity index score. However, in our study, a significant correlation was found between the procalcitonin value obtained at the first hospitalization of the patient and the duration of hospitalization ($p < 0.016$).

found prolonged hospitalization (≥ 8 days) in 46 (20%) of 231 mild AP patients.[16] The main determinants of prolonged hospitalization are symptoms associated with ongoing pancreatitis. Direct healthcare costs related to AP exceed $2.6 billion annually[16], with two-thirds of these costs associated with hospitalization.[17] The mean hospitalization period of the patients hospitalized with AP was 5.8 days in 1997 and 6.4 days in 2003. In the last ten years, the rate of hospitalization has decreased to 4.7 days.[5] This is probably due to a better understanding of the pathophysiology of AP and earlier diagnosis and treatment of complications. It is also an increase in awareness of reducing the cost of health care.

According to the experience of Harkirat Singh et.al.[18], a significant proportion of mild AP patients stay in the hospital longer than 4-5 days. The main reasons for long-term hospitalization are the presence of comorbidity, longer periods of fasting, ongoing abdominal pain, oral refeeding intolerance, the need for abdominal imaging and endoscopic retrograde cholangiopancreatography (ERCP) during hospitalization, and inadequate hydration therapy.

CONCLUSION

Acute pancreatitis was observed more frequently in women than in men. According to our study, biliary causes were the most common etiology, followed by hyperlipidemia and medication, respectively. According to our study, the duration of hospitalization can be estimated by calculating the CRP, procalcitonin, and modified CT severity index score, which may be related to the length of stay. Significant cost savings can be made and the mortality of the disease can be reduced by reducing the length of stay with symptom treatment and enteral nutrition of the patients. A single measurement of procalcitonin may not be sufficient to determine the prognosis, follow-up is more meaningful. Measurements should be made at 24-hour intervals. Larger prospective studies are needed to reveal the relationship between the severity of acute pancreatitis and serum procalcitonin.

Conflict of Interest

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

Funding Sources

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

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Izmir Katip Celebi University, İzmir, Turkey. (Decision number: 14.02.2018, date: 14.02.2018).

Authors' Contribution

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

REFERENCES

1. Carroll JK, Herrick B, Gipson T, Lee SP. Acute pancreatitis: diagnosis, prognosis, and treatment. Am Fam Physician. 2007 May 15;75(10):1513-20. PMID: 17555143.
2. Stone HH, Fabian TC, Dunlop WE. Gallstone pancreatitis: biliary tract pathology in relation to time of operation. Ann Surg. 1981 Sep;194(3):305-12. doi: 10.1097/00000658-198109000-00008. PMID: 6168240; PMCID: PMC1345356.

3. Lee DW, Cho CM. Predicting Severity of Acute Pancreatitis. Medicina (Kaunas). 2022 Jun 11;58(6):787. doi: 10.3390/medicina58060787. PMID: 35744050; PMCID: PMC9227091.
4. Herrmann MG, Dobrowolski SF, Wittwer CT. Rapid beta-globin genotyping by multiplexing probe melting temperature and color. Clin Chem. 2000 Mar;46(3):425-8. Erratum in: Clin Chem. 2004 Jun;50(6):1111. Erratum in: Clin Chem. 2004;50(5):982. PMID: 10702535.
5. Rau B, Steinbach G, Gansauge F, Mayer JM, Grünert A, Beger HG. The potential role of procalcitonin and interleukin 8 in the prediction of infected necrosis in acute pancreatitis. Gut. 1997 Dec;41(6):832-40. doi: 10.1136/gut.41.6.832. PMID: 9462219; PMCID: PMC1891610.
6. Huang QL, Qian ZX, Li H. A comparative study of the urinary trypsinogen-2, trypsinogen activation peptide, and the computed tomography severity index as early predictors of the severity of acute pancreatitis. Hepatogastroenterology. 2010 Sep-Oct;57(102-103):1295-9. PMID: 21410075.
7. Papachristou GI, Clermont G, Sharma A, Yadav D, Whitcomb DC. Risk and markers of severe acute pancreatitis. Gastroenterol Clin North Am. 2007 Jun;36(2):277-96, viii. doi: 10.1016/j.gtc.2007.03.003. PMID: 17533079.
8. Mitchell RM, Byrne MF, Baillie J. Pancreatitis. Lancet. 2003 Apr 26;361(9367):1447-55. doi: 10.1016/s0140-6736(03)13139-x. PMID: 12727412.
9. Warndorf MG, Kurtzman JT, Bartel MJ, Cox M, Mackenzie T, Robinson S, Burchard PR, Gordon SR, Gardner TB. Early fluid resuscitation reduces morbidity among patients with acute pancreatitis. Clin Gastroenterol Hepatol. 2011 Aug;9(8):705-9. doi: 10.1016/j.cgh.2011.03.032. Epub 2011 Apr 8. PMID: 21554987; PMCID: PMC3143229.
10. Sargent S. Pathophysiology, diagnosis and management of acute pancreatitis. Br J Nurs. 2006 Oct 12-25;15(18):999-1005. doi: 10.12968/bjon.2006.15.18.22025. PMID: 17077771.
11. DiMagno MJ, DiMagno EP. New advances in acute pancreatitis. Curr Opin Gastroenterol. 2007 Sep;23(5):494-501. doi: 10.1097/MOG.0b013e3282ba566d. PMID: 17762554; PMCID: PMC3474362.
12. Moreau JA, Zinsmeister AR, Melton LJ 3rd, DiMagno EP. Gallstone pancreatitis and the effect of cholecystectomy: a population-based cohort study. Mayo Clin Proc. 1988 May;63(5):466-73. doi: 10.1016/s0025-6196(12)65644-4. PMID: 3361956.
13. Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006 Oct;101(10):2379-400. doi: 10.1111/j.1572-0241.2006.00856.x. PMID: 17032204.
14. Suppiah A, Malde D, Arab T, Hamed M, Allgar V, Smith AM, Morris-Stiff G. The prognostic value of the neutrophil-lymphocyte ratio (NLR) in acute pancreatitis: identification of an optimal NLR. J Gastrointest Surg. 2013 Apr;17(4):675-81. doi: 10.1007/s11605-012-2121-1. Epub 2013 Feb 1. PMID: 23371356.
15. Kendir Ö. T. , Ağın M. , Yılmaz H. , Sarı Gökay S. , Tumgor G. Evaluation of Acute Pancreatitis Patients: Single Center Five Years' Experience. J Contemp Med. 2021; 11(3): 262-266.
16. Sargent S. Pathophysiology, diagnosis and management of acute pancreatitis. Br J Nurs. 2006 Oct 12-25;15(18):999-1005. doi: 10.12968/bjon.2006.15.18.22025. PMID: 17077771.
17. Tran DD, Cuesta MA. Evaluation of severity in patients with acute pancreatitis. Am J Gastroenterol. 1992 May;87(5):604-8. PMID: 1595648.
18. Singh H, Gougol A, Mounzer R, Yadav D, Koutroumpakis E, Slivka A, Whitcomb DC, Papachristou GI. Which Patients with Mild Acute Pancreatitis Require Prolonged Hospitalization? Clin Transl Gastroenterol. 2017 Dec 7;8(12):e129. doi: 10.1038/ctg.2017.55. PMID: 29215631; PMCID: PMC5746601.

Original Article

DOI: 10.56016/dahudermj.1326075

DAHUDER Medical Journal
e-ISSN: 2791-9250

The relationship of serum bilirubin level with histopathological parameters in patients with nonalcoholic fatty liver disease

Ali Kirik[1], Cemal Nuri Ercin[2], Hasan Gurel[3], Ali Fuat Cicek[4], Ali Cem Yekdes[1], Sultan Turel[5], Serkan Tapan[6], Teoman Dogru[7]

[1]Department of Internal Medicine, Balikesir University, School of Medicine, Balikesir, Turkey
[2]Department of Gastroenterology, University of Health Sciences, Gulhane School of Medicine, Ankara, Turkey
[3]Department of Gastroenterology, University of Health Sciences, Education and Research Hospital, Samsun, Turkey
[4]Department of Pathology, University of Health Sciences, Gulhane School of Medicine, Ankara, Turkey
[5]Department of Internal Medicine, Health Ministery Education and Research Hospital, Nigde, Turkey
[6]Section of Biochemistry, ENA Laboratory, Ankara, Turkey
[7]Department of Gastroenterology, Balikesir University, School of Medicine, Balikesir, Turkey

ABSTRACT

Objectives: Non-alcoholic fatty liver disease (NAFLD) is among the most common causes of chronic liver disease and is known as a part of metabolic syndrome (MetS), and the role of bilirubin in the pathogenesis of NAFLD is unclear. This study aimed to evaluate the relationship between bilirubin levels and histopathological findings in patients with NAFLD having no confounding factors such as morbid obesity, diabetes mellitus (DM), and hypertension.

Methods: A retrospective analysis of clinical and laboratory data of patients with biopsy-proven NAFLD was performed. The relationship between the bilirubin levels and histopathologic findings was evaluated.

Results: The subjects in the nonalcoholic steatohepatitis (NASH) group had greater AST ($p < 0.001$) and ALT ($p < 0.001$) levels than the non-NASH group. We found no difference between NASH and non-NASH groups regarding bilirubin levels. The levels of AST (p = 0.001), ALT ($p = 0.011$), insulin ($p = 0.029$), and HOMA-IR index ($p = 0.027$) were higher in fibrosis group comparing non-fibrosis group. However, bilirubin levels were not different comparing the fibrosis and non-fibrosis group. We couldn't find any relation between bilirubin levels and other parameters in correlation analysis.

Conclusion: We couldn't find any relation between the bilirubin levels and histopathological findings of the patient with NAFLD having no confounding factors such as morbid obesity, DM, and hypertension. The difference, shown in the other studies, may be the effect of other diseases related to MetS.

Keywords: NAFLD, NASH, fibrosis, bilirubin

Non-alcoholic fatty liver disease (NAFLD), a component of the metabolic syndrome (MetS), is the most common chronic liver disease worldwide. NAFLD is a disease characterized by lipid accumulation in the liver, often without secondary causes such as alcohol and steatogenic medication.[1]

The pathogenic mechanisms responsible for the

Received: *July 12, 2023****; Accepted:*** *July 26, 2023****; Published Online:*** *July 29, 2023*

How to cite this article: *Kirik A, Ercin CN, Gurel H, Cicek AF, Yekdes AC, Turel S, at al. The relationship of serum bilirubin level with histopathological parameters in patients with nonalcoholic fatty liver disease DAHUDER MJ 2023,3(3):91-96. DOI: 10.56016/dahudermj.1326075*

Address for correspondence: *Ali Kirik, Asst. Prof., Department of Internal Medicine, Balikesir University, School of Medicine, Cagis, Balikesir, 10145, Turkey*
E-mail: alikirik87@hotmail.com

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

development of NAFLD are complex. The key points are mainly dysregulation of fatty liver accumulation (FLA), development of hepatic insulin resistance (IR), and hyperinsulinemia. Oxidative stress is one of the leading causes of chronic inflammation and fibrosis in the liver, especially hepatocyte necrosis. In addition, increased FLA levels predispose to oxidative stress that leads to hepatic inflammation and fibrosis.[1,2] Also, it was shown that cardiovascular disease (CVD) is a more common cause of death among NAFLD patients comparing liver disease.[3,4] Also, elevated biochemical markers of atherosclerosis and systemic inflammation are often found in patients with NAFLD.5 It is interesting that CVD can be diagnosed without traditional risk factors in patients with NAFLD.[6] So, it is accepted that every patient with NAFLD should be screened for CVD and vice versa.[7]

Bilirubin is the final product molecule resulting from the breakdown of heme molecule. When the level is in the physiologic range, bilirubin has cytoprotective and beneficial metabolic effects, but it is potentially toxic if high.[8] It is reported that serum bilirubin significantly contributes to total antioxidant capacity.[9] The antioxidant effect of bilirubin molecule, which has lipid peroxidation inhibitory property, can be as strong as antioxidant vitamin E.[10] Both bilirubin and the enzymes involving bilirubin metabolism have some effects. It was shown that heme oxygenase, responsible for the degradation of heme to biliverdin, stimulated insulin products, and reduced insulin resistance.[11] In clinical studies, it was found that higher levels of bilirubin were inversely associated with IR and MetS.[12] Also, bilirubin is suggested to have a protective effect in atherogenesis, coronary artery disease (CAD), and peripheral arterial disease (PAD).[13,14]

In light of these data, the current literature's relationship between serum bilirubin level and histopathological findings such as steatohepatitis and fibrosis in patients with NAFLD remains unclear. In the study presented here, it was aimed to examine the relationship between serum bilirubin levels with steatohepatitis and fibrosis in biopsy proven NAFLD patients.

METHODS

Study design and population

In this study, biopsy-proven NAFLD patients followed in the gastroenterology clinic of a tertiary university hospital were examined retrospectively. Demographic, clinical, laboratory and biopsy data of the patients were enrolled. The study was approved by the local ethics committee of Balikesir University Medical School (date: 14.10.2020; no: 2020/179) and was complied with according to the Helsinki Declaration. In this study, which included patients diagnosed with NAFLD through liver biopsy, the main exclusion criteria were chronic alcohol use, hemochromatosis, wilson's disease, presence of viral hepatitis, type 2 DM, morbid obesity, and any other major diseases.

Clinical examination and laboratory analyses

The BMI of the patients, whose waist circumference (WC) was measured from the midpoint between the lowest rib margin and the iliac crest was evaluated using the formula obtained by dividing the weight by the square of the height. Hemoglobin (Hb), white blood cell (WBC), and platelet (PLT) levels were determined by an ABX Pentra 120 automatic hematology analyzer used for whole blood counts. Fasting plasma glucose (FPG), liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT)] and cholesterol profile [triglyceride (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C)] levels were measured by enzymatic colorimetric methods. The Friedewald Formula calculated low-density lipoprotein cholesterol (LDL-C).[15] The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula determined the IR level.[16]

Liver histology

Liver biopsy materials of the patients were stained with Hematoxylin and eosin (H&E) dye and examined by a single specialist pathologist. On the other hand, Masson's trichrome stain was used to examine the fibrosis levels. Finally, histopathological findings were evaluated according to Kleiner *et al*.17, and fibrosis staging were evaluated according to Brunt *et al*.[18] NAFLD activity score (NAS) was evaluated by adding the scores obtained from steatosis, lobular inflammation and hepatocellular ballooning, and NASH was defined as a NAS $\geq$ 5. Fibrosis staging was graded on a scale from 0 to 4.

Statistically analysis

Statistical analyses were performed by SPSS 22 (Statistical Package for the Social Sciences, version

22). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the assumption of normality. Parametric values were reported as the mean ± standard deviation, and non-parametric values were reported as the median (25.-75. percentiles). Mann-Whitney U-test and independent samples t-test evaluated differences between groups as appropriate. For possible relationships, Spearman and Pearson correlation analyses were performed between two parametric values. $P < 0.05$ was accepted as statistically significant.

RESULTS

Descriptive and comparative statistics of NASH and Non-NASH groups are summarized in Table 1. The distribution of age, BMI, and WC were not different between the NASH and non-NASH groups. Among the biochemical parameters, the subjects in the NASH group had greater AST ($p < 0.001$) and ALT ($p < 0.001$) levels than the non-NASH group. The distribution of age, BMI, and WC did not differ between the fibrosis and non-fibrosis groups. The levels of AST ($p = 0.001$), ALT ($p = 0.011$), insulin ($p = 0.029$), and HOMA-IR index ($p = 0.027$) were higher in the fibrosis group comparing the non-fibrosis group (Table 2).

We found no difference between NASH [direct bilirubin = 0.15 (0.10-0.22), indirect bilirubin = 0.63 (0.42-0.90)] and non-NASH groups [direct bilirubin = 0.15 (0.11-0.20), indirect bilirubin = 0.58 (0.40-0.77)] regarding bilirubin levels (respectively $p = 0.888$, $p = 0.286$). Additionally, there was no difference between with fibrosis group [direct bilirubin = 0.15 (0.11-0.20), indirect bilirubin = 0.17 (0.11-0.20)] and

Table 1. Descriptive and comparative statistics of NASH and Non-NASH groups

Variables	Values		*p*
	NASH n =53	Non-NASH n =76	
Age (years)	31.13 (± 5.86)	32.83 (± 6.20)	0.120***
BMI (kg/m²)	28.20(26.07-29.77)*	28.40 (26.50-31)*	0.450**
WC (cm)	100 (96-105)*	98.50 (96-104)*	0.745**
FPG (mg/dL)	94.06 (± 11.07)	92.73 (± 11.09)	0.507***
TC (mg/dL)	201.92 (± 44.24)	205.45 (± 45.29)	0.664***
LDL-C (mg/dL)	119.80 (± 33.67)	128.58 (± 35.60)	0.170***
TG (mg/dL)	160.50 (122-265.25)*	166 (108-251)*	0.600**
HDL-C (mg/dL)	38 (35-44.75)*	41 (36.75-46)*	0.156**
ALT (U/L)	121(95-166.50)*	91 (64.50-115.25)*	**<0.001****
AST (U/L)	56 (41.50-65.50)*	44.50 (35-53.75)*	**<0.001****
GGT (U/L)	60 (46.25-81.50)*	58 (44-87.75)*	0.814**
Direct bilirubin (mg/dL)	0.15 (0.10-0.22)*	0.15 (0.11-0.20)*	0.888**
Indirectbilirubin(mg/dL)	0.63 (0.42-0.90)*	0.58 (0.40-0.77)*	0.286**
UricAcid (mg/dL)	6.67 (5.73-7.23)*	6.58 (5.70-7.07)*	0.390**
Hb (g/dL)	16.12 (± 0.95)	15.63 (± 0.97)	**0.008*****
WBC (x 10³)	7100 (6100-8600)*	7150 (6200-8675)*	0.968**
Plt (x 10³)	225829.79 (± 41730.14)	244147.06 (± 54433.10)	0.054***
Insulin (µU/mL)	14.45 (10.37-20.21)*	12.48 (9.56-20.16)*	0.361**
HOMA-IR	3.39 (2.34-4.79)*	2.78(2.10-4.95)*	0.411**
Hs-CRP (pg/mL)	2.02 (1.25-3.12)*	2.03 (1.16-3.50)*	0.810**

NASH: nonalcoholic steatohepatitis; BMI: Body mass index; WC: waist circumference; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglicerides; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; Hb: Hemoglobin; WBC: White blood cell; Plt: platelet; HOMA-IR: homeostasis model assessment for insulin resistance; Hs-CRP: high-sensitivity C-reactive protein

*median(25.-75. Percentiles)

** Mann Whitney U test

*** Independentsample t- test

Table 2. Descriptive and comparative statistics of fibrosis and non fibrosis groups

Variables	Values		*p*
	With Fibrosis n = 84	Without Fibrosis n = 45	
Age (years)	32.44 (± 6.61)	31.56(± 5.01)	0.396***
BMI (kg/m²)	28.40 (26.10-30.50)*	28.20 (26.42-29.85)*	0.723**
WC (cm)	100 (96-105)*	98 (97-102)*	0.542**
FPG (mg/dL)	93.83 (± 10.71)	92.23 (± 11.74)	0.437***
TC (mg/dL)	203.34(± 47.73)	205.27 (± 38.90)	0.818***
LDL-C (mg/dL)	123.95 (± 38.48)	126.82 (± 27.73)	0.633***
TG (mg/dL)	167 (115-261)*	155.50 (110-253.75)*	0.820**
HDL-C (mg/dL)	40.50 (36-47)*	40 (35-43.75)*	0.276**
ALT (U/L)	111 (85.50-148.75)*	89 (69.50-114)*	**0.011****
AST (U/L)	51.50 (40-64.75)*	41 (35-51.50)*	**0.001****
GGT (U/L)	58 (44-77)*	59 (45-90)*	0.797**
Direct bilirubin (mg/dL)	0.15 (0.11-0.20)*	0.17 (0.11-0.20)*	0.527**
Indirectbilirubin (mg/dL)	0.60(0.40-0.80)*	0.60 (0.40-0.82)*	0.976**
UricAcid (mg/dL)	6.67 (6.06-7.18)*	6.38 (5.58-7.13)*	0.174**
Hb (g/dL)	15.87 (± 1.06)	15.73 (± 0.82)	0.461***
WBC (x 10³)	7100 (6250-8525)*	7200 (6050-8850)*	0.799**
Plt (x 10³)	241256.41 (± 50103.38)	226972.97 (± 49869.54)	0.155***
Insulin (µU/mL)	15.25 (10.27-23.91)*	11.41 (9.31-16.13)*	**0.029****
HOMA-IR	3.63 (2.34-5.43)*	2.48 (2.09-4.06)*	**0.027****
Hs-CRP (pg/mL)	2.11 (1.30-3.45)*	1.75 (1.11-2.89)*	0.257**

BMI: Body mass index; WC: waist circumference; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglicerides; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; Hb: Hemoglobin; WBC: White blood cell; Plt: platelet; HOMA-IR: homeostasis model assessment for insulin resistance; Hs-CRP: high-sensitivity C-reactive protein
*median(25.-75. Percentiles)
** Mann Whitney U test
*** Independentsample t- test

without fibrosis groups [direct bilirubin = 0.60 (0.40-0.80), indirect bilirubin = 0.60 (0.40-0.82)] regarding bilirubin levels (respectively $p = 0.527$, $p = 0.976$).

DISCUSSION

In this study, we investigated the bilirubin levels among subjects with biopsy-proven NAFLD grouped as either with or without NASH and with or without fibrosis who have no confounding factors such as hypertension, DM, and obesity. We couldn't find any difference in comparing the groups. Including only the subjects free from any confounding factor is an important feature of the present investigation.

Bilirubin exerts an antioxidant effect by inhibiting the activity of NAD(P)H oxidase, which paves the way for the formation of superoxide radicals.[19] However, bilirubin has anti-inflammatory effects, which inhibit the formation of fibrogens via heme oxygenase-1.[20] At the same time, it is shown that higher bilirubin levels are inversely associated with insulin level, IR, and DM, the factors defined in the pathogenesis of NAFLD. From a cardiovascular perspective, it is stated that elevated bilirubin levels are also related to the reduced risk of CVD, including CAD, stroke, and PAD.[12]

A cross-sectional study of 17,348 participants compared the subjects with and without ultrasonography diagnosed NAFLD. The bilirubin levels were significantly low in the NAFLD group. It is emphasized that NAFLD, which is observed to be associated with serum bilirubin level, decreases with the increase in bilirubin level.[21] Chang Y *et al.* conducted a prospective cohort study among middle-aged Korean workers with no evidence of liver disease and no major risk factors for liver disease. The patients evaluated within the scope of the study were

followed up for a period of seven years and checked with USG at certain periods. Interestingly, it has been observed that higher direct bilirubin levels result in a reduced risk of developing NAFLD, even adjusting for various metabolic parameters, including obesity, IR, DM, history of CVD, and malignancy. They stated the effect of oxidative stress and IR in the pathogenesis of NAFLD and the association between low serum bilirubin levels and increased HOMA-IR and insulin levels. Interestingly, they found the persistence of the association between increased direct bilirubin and lower incidence of NAFLD after adjusting for a variety of measures of IR and after restricting the analysis to participants with no evidence of IR. In conclusion, they reported that the protective role of direct bilirubin in these patients is independent of IR.[22] In parallel with the previous study, Tian J *et al*. found a relationship between low direct bilirubin levels. They reduced NAFLD risk among the middle-aged and elderly Chinese population. They explained this as the anti-inflammatory effect of bilirubin, especially direct bilirubin, inhibiting oxidative stress and IR and altering glucose metabolism. The important part of these results was that this association was independent of classical risk factors, including liver enzymes, DM, MetS features, CAD, and other classical metabolic risk factors.[23]

Two studies evaluate the relationship between bilirubin levels and histopathologic findings in patients with NAFLD. In a retrospective study including the patients' biopsy-proven NAFLD, they investigated the relationship between the unconjugated bilirubin (UCB) levels and histopathological findings. They found that unconjugated hyperbilirubinemia was inversely associated with NASH. They speculated that these findings are because of the inhibition of the pathogenesis of NASH via the potent antioxidant, anti-inflammatory and anti-fibrogenic effect of UCB.[24] Another study, including two hundred and eighty-five patients with biopsy-confirmed NAFLD, investigated the relationship between steatosis, inflammation, and fibrosis with UCB levels. They found that UCB levels were decreased in patients with NASH and advanced inflammation and fibrosis. Also, they demonstrated by logistic regression analysis that low UCB levels are independently associated with advanced liver inflammation and fibrosis. These results were interpreted as a lack of the effect of UCB, the main endogenous lipid antioxidant, leading to the progression of liver injury in patients with NASH.[25] Conversely, we couldn't find any relation between bilirubin levels with histological findings in our study participants. In these studies, some of the participants in NAFLD groups were diabetic, obese, or hypertensive. Still, in our study, none of the patients had confounding factors for NAFLD, such as morbid obesity, DM, and hypertension. We think that the real relationship between the bilirubin and histological findings in NAFLD can be evaluated in this unique group. The low bilirubin levels in patients with NAFLD found in these studies can be the effect of the other confounding factors seen in MetS.

Limitations

This study has several limitations. Since our study is cross-sectional, it does not reflect all NAFLD patients. Secondly, all participants were men, and it remains to be determined if these results were similar even in women. Finally, HOMA-IR index has been used for the evaluation of insulin resistance and is not the gold standard method.

CONCLUSION

In light of these data, it was found that serum bilirubin level was not different in either the steatohepatitis group or the fibrosis group compared to the control group in biopsy-proven NAFLD patients. It is thought that conducting our study in a patient group without confounding factors such as morbid obesity, DM, and hypertension will contribute positively to the literature. On the other hand, randomized controlled studies are needed to understand the role of bilirubin in the development and progression of NAFLD.

Conflict of Interest

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

Funding Sources

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

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Balikesir University, School of Medicine Balıkesir, Turkey. (Decision number: 2020/179, date: 14.10.2020).

Authors' Contribution

Study Conception: CNE,AK, TD; Study Design: CNE,AK, TD; Supervision; CNE, TD; Materials: ST, AÇ; Data Collection and/or Processing: ST, AÇ; Analysis and/or Data Interpretation: ACY, ST; Literature Review: CNE,AK, TD; Critical Review: CNE, TD; Manuscript preparing: CNE, AK, TD.

REFERENCES

1. Fang YL, Chen H, Wang CL, Liang L. Pathogenesis of non-alcoholic fatty liver disease in chil-dren and adolescence: From "two hit theory" to "multiple hit model". World J Gastroenterol. 2018 ;24(27):2974-2983.
2. Sonmez A, Dogru T, Ercin CN, Genc H, Celebi G, Gurel H, et al. Betatrophin Levels Are Re-lated to the Early Histological Findings in Nonalcoholic Fatty Liver Disease. Metabolites. 2021;11(7):425.
3. Oni ET, Agatston AS, Blaha MJ, Fialkow J, Cury R, Sposito A, et al. A systematic review: burden and severity of subclinica lcardiovascular disease among those with nonalcoholic fatty liver; should we care? Atherosclerosis 2013; 230(2):258-267.
4. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fat-ty liver disease. N Engl J Med. 2010; 363(14):1341-1350.
5. Dogru T, Kirik A, Gurel H, Rizvi AA, Rizzo M, Sonmez A. The Evolving Role of Fetuin-A in Nonalcoholic Fatty Liver Disease: An Overview from Liver to the Heart. Int J Mol Sci. 2021;22(12):6627.
6. Pacifico L, Chiesa C, Anania C, Merulis AD, Osborn JF, Romaggioli S, et al. Nonalcoholic fatty liver disease and the heart in children and adolescents. World J Gastroenterol 2014; 20(27):9055–9071.
7. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64(6):1388-1402.
8. Erlinger S, Arias IM, Dhumeaux D. Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. Gastroenterology 2014; 146(7):1625-1638.
9. DiNicolantonio JJ, McCarty MF, O'Keefe JH. Antioxidant bilirubin works in multiple ways to reduce risk for obesity and its health complications. Open Heart. 2018;5(2):e000914.
10. Neuzil J, Stocker R. Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting plasma and low density lipoprotein lipid peroxidation. J Biol Chem 1994; 269(24):16712-16719.
11. Ndisang JF, Jadhav A. Up-regulating the hemeoxygenase system enhances insulin sensitivity and improves glucose metabolism in insulin-resistant diabetes in Goto-Kakizakirats. Endocrinol 2009; 150(6):2627-2636.
12. Lin LY, Kuo HK, Hwang JJ, Lai LP, Chiang FT, Tseng CD, et al. Serum bilirubin is inversely associated with insulin resistance and metabolic syndrome among children and adolescents. Atherosclerosis 2009; 203(2):563-568.
13. Jain V, Ghosh RK, Bandyopadhyay D, Kondapaneni M, Mondal S, Hajra A, et al. Serum Bili-rubin and Coronary Artery Disease: Intricate Relationship, Pathophysiology, and Recent Evi-dence. Curr Probl Cardiol. 2021;46(3):100431.
14. Perlstein TS, Pande RL, Beckman JA, Creager MA. Serum total bilirubin level and prevalent lower-extremity peripheral arterial disease: National Health and Nutrition Examination Survey (NHANES) 1999 to 2004. Arterioscler Thromb Vasc Biol 2008; 28(1):166-172.
15. 15.Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18(6):499-502.
16. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, et al. Homeosta-sis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000; 23(1):57-63.
17. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Nonalco-holic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005; 41(6):1313-1321.
18. Brunt EM. Nonalcoholic fatty liver disease: what the pathologist can tell the clinician. Dig Dis 2012; 30(1):61-68.
19. Takei R, Inoue T, Sonoda N, Kohjima M, Okamoto M, Sakamoto R, et al. Bilirubin reduces visceral obesity and insulin resistance by suppression of inflammatory cytokines. PLoS One. 2019;14(10):e0223302.
20. Leal EC, Carvalho E. Heme Oxygenase-1 as Therapeutic Target for Diabetic Foot Ulcers. Int J Mol Sci. 2022 Oct 10;23(19):12043.
21. Kwak MS, Kim D, Chung GE, Kang SJ, Park MJ, Kim YJ, et al. Serum bilirubin levels are in-versely associated with nonalcoholic fatty liver disease. Clinical and Molecular Hepatology 2012; 18(4):383-390.
22. Chang Y, Ryu S, Zhang Y, Son HJ, Kim JY, Cho J, et al. A cohort study of serum bilirubin levels and incident non-alcoholic fatty liver disease in middle aged korean workers. PLoS ONE 2012; 7(5):e37241.
23. Tian J, Zhong R, Liu C, Tang Y, Gong J, Chang J, et al. Association between bilirubin and risk of non-alcoholic fatty liver disease based on a prospective cohort study. Sci Rep 2016; 6(1):31006.
24. Hjelkrem M, Morales A, Williams CD, Harrison SA. Unconjugated hyperbilirubinemia is in-versely associated with non-alcoholic steatohepatitis (NASH). Aliment Pharmacol Ther 2012; 35(12):1416-1423.
25. Salomone F, Volti GL, Rosso C, Grosso G, Bugianesi E. Unconjugated bilirubin, a potent en-dogenous antioxidant, is decreased in patients with non-alcoholic steatohepatitis and advanced fibrosis. J Gastroenterol Hepatol 2013; 28(7):1202-1208.

Case Report

DOI: 10.56016/dahudermj.1263226

DAHUDER Medical Journal
e-ISSN: 2791-9250

Erythema nodosum: A clinical sign of acute pancreatitis

Yasemin Çöl[1], Dilara Turan Gökçe[2], Meral Akdoğan Kayhan[2]

[1]Department of Internal Medicine, Bilkent City Hospital, Ankara, Turkey
[2]Department of Gastroenterology, Bilkent City Hospital, Ankara, Turkey

ABSTRACT

Although pancreatic pathologies are primarily and mostly manifested by abdominal complaints, they can also occur with other organ systems. Erythema nodosum is the most common variant of panniculitis.[1] In this study, we present a patient with acute pancreatitis who developed erythema nodosum.

Keywords: Erythema nodosum, pancreatitis, panniculitis

Pancreatic pathologies such as acute and chronic pancreatitis, autoimmune pancreatitis and pancreatic cancer often present with gastrointestinal system symptoms. These may sometimes be accompanied by cutaneous symptoms that precede even the abdominal findings.[2]

Erythema nodosum is the most common clinicopathological variant of panniculitis. It is a cutaneous reaction consisting of inflammatory, tender, nodular lesions usually located in the pretibial region, which regresses within 3-6 weeks. This condition may be associated with a wide variety of pathologies including infections, sarcoidosis, rheumatological diseases, inflammatory bowel diseases, drugs, autoimmune disorders, pregnancy and malignancies.[3] Erythema nodosum is divided into acute and subacute/chronic forms. The acute classical form usually affects the bilateral legs in young women, while it can rarely be seen on the forearm and thigh. It may take days, weeks or months, but heals without sequelae. The subacute/chronic form is called "Erythema nodusum migrans". It is mostly seen on the extensor surface of the tibia. There is no ulceration, scarring or tenderness. Unlike the acute form, it can last for years, not days.[4]

CASE PRESENTATION

A 36-year-old female patient applied to the emergency department with complaints of abdominal pain, jaundice, darkening of the urine color and redness on the anterior of the leg, which had been present for 2 days. The lesions of the patient's anterior leg started approximately 24-36 hours after the abdominal pain in both pancreatitis attacks. The patient also suffered pancreatitis three months earlier. Aspartate aminotransferase (AST):201 U/L, Alanine aminotransferase (ALT):255 U/L, alkaline phosphatase (ALP):423 U/L, gamma glutamyl transferase (GGT):230 U/L Amylase:2115 U/L Lipase:3157 U/L Total Bilirubin:9.5 mg/dl Direct Bilirubin:6,6 mg/dl White Blood Count:7,85x10^9/L Glucose: 90 mg /dl C-Reactive Protein:90 mg/L Lactate dehydrogenase:336 U/L were in the patient's admission laboratory examinations. The patient with epigastric, girdle-style pain was hospitalized for further examination and treatment with a preliminary diagnosis of pancreatitis.

In the contrast-enhanced tomography of the abdomen taken in the emergency department of our

Received: *March 10, 2023****; Accepted:*** *June 13, 2023****; Published Online:*** *July 29, 2023*

How to cite this article: *Çöl Y, Turan Gökçe D, Akdoğan Kayhan M. Erythema nodosum: A clinical sign of acute pancreatitis .DAHUDER MJ 2023,3(X):97-99. DOI: 10.56016/dahudermj.1263226*

Address for correspondence: *Yasemin Çöl, MD. Bilkent City Hospital, Ankara, Turkey*
E-mail: unubuyukyasemin@gmail.com

hospital, the intrahepatic bile ducts were dilated in all lobes, the common bile duct diameter was 15 mm, and it was thinning distally. There were stone-mud densities in the lumen distal to the common bile duct, the pancreatic parenchyma was mildly edematous, inflammatory density increases in the peripancreatic fat planes and a moderate amount of peripancreatic free fluid were present. When the patient was admitted to the emergency service of our hospital, his temperature was 37.1 C, heart rate was 89/min, BP: 112/66 mm/hg, and saturation was 99 on room air. The general condition of the patient was moderately conscious, oriented and cooperative, Glasgow Coma Scale (GCS): 15 and Ranson score: 0. Biliary pancreatitis was initially considered in the patient.

On physical examination, there was tenderness in the right upper quadrant of the abdomen and no signs of acute abdomen. Respiratory and heart sounds were normal and pretibial edema was not detected. There were nodular hyperemic lesions of approximately 1 cm that faded by pressing on both legs, with the left tibia dominant on the anterior surface (Fig. 1A). Erythema nodosum were identified as the patient's lesions, which were assessed in conjunction with dermatology. It was learned that the patient had an attack of pancreatitis 3 months ago. The patient stated that the same lesions were present in the previous pancreatitis attack. Autoimmune pancreatitis was not considered due to the detection of 15 milimeters stones in the gallbladder in the hepatobiliary ultrasonography taken in the patient's pancreatitis attack 3 months ago.

In the endoscopic ultrasonography performed by us, the common bile duct was 7.9 millimeters at the level of the hilus and ended by thinning distally. No pathology was observed in the common bile duct. Left intrahepatic bile ducts were minimally prominent in the central part. Pancreas was voluminous and hypoechoic lobulations were observed in the parenchyma (secondary to pancreatitis?). Rheumatic diseases were not considered in the differential diagnosis of erythema nodosum due to the regression of the lesions after the acute pancreatitis episode resolved. There were no features suggesting a rheumatological disease in the patient's system investigation and examination.

In the follow-up of the patient who was treated for pancreatitis and planned for cholecystectomy, improvement in blood parameters was observed, and Ranson score was 0 at the 48th hour. The patient's skin lesions regressed at 48 and 72 hours (Fig. 1B).

DISCUSSION

Skin findings are a rare complication of pancreatitis.[2] However, it has been known for a long time that patients with pancreatitis have skin findings.[5] Also pancreatic panniculitis; It can also mimic other forms of panniculitis such as erythema nodosum, erythema induratum, traumatic, infectious or α1-antitrypsin deficiency panniculitis.[6]

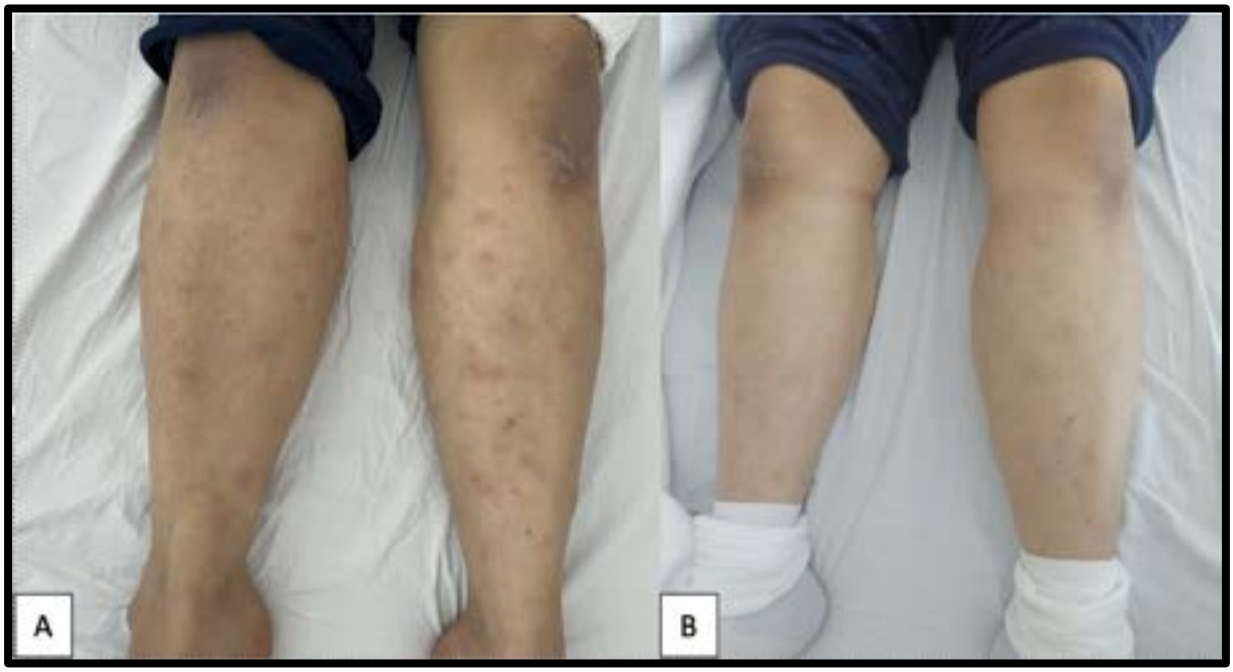

Fig. 1. Erythema nodosum at the patient's admission (A) and at the 72nd hour of hospitalization (B)

It has been thought that skin lesions in acute pancreatitis may be associated with the prognosis of the disease, but it has been reported in the literature that skin lesions are also present in non-severe acute pancreatitis cases, as in our case. In our case, the patient's Ranson score was 0 and the patient's clinic began to improve within 72 hours.

CONCLUSION

Skin lesions in pancreatitis, although rare, can be seen. Skin lesions are mostly not associated with abdominal pathologies by clinicians. However, the presence of skin manifestations of pancreatitis should be kept in mind in the differential diagnosis.

Conflict of Interest

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

Funding Sources

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

Authors' Contribution

Study Conception: DTG; Study Design: YÇ; Supervision; MAK; Data Collection and/or Processing: YÇ, DYG; Analysis and/or Data Interpretation: YÇ; Literature Review: YÇ; Critical Review: DTG; Manuscript preparing: YÇ.

REFERENCES

1. Kelati, A., Meziane, M., Soughi, M., & Mernissi, F. (2016). L'érythème noueux, une complication des teignes à Trichophyton mentagrophytes [Erythema nodosum due to tinea]. Archives de pediatrie : organe officiel de la Societe francaise de pediatrie, 23(7), 727–730. https://doi.org/10.1016/j.arcped.2016.04.014.
2. Miulescu R, Balaban DV, Sandru F, Jinga M. Cutaneous Manifestations in Pancreatic Diseases-A Review. J Clin Med. 2020 Aug 12;9(8):2611. doi: 10.3390/jcm9082611. PMID: 32806580; PMCID: PMC7464368.
3. Mert A. Eritema Nodozum: 9 Yillik Deneyim. Cerrahpaşa Tıp Dergisi. 2002; 33(1): 47-59
4. Akif Karababa, Serap Utaş. Panniculitis. J Clin Pract Res. 1998; 20(2): 176-183.
5. Requena L, Requena C. Erythema nodosum. Dermatol Online J. 2002 Jun;8(1):4. PMID: 12165214.
6. Laureano A, Mestre T, Ricardo L, Rodrigues AM, Cardoso J. Pancreatic panniculitis - a cutaneous manifestation of acute pancreatitis. J Dermatol Case Rep. 2014 Mar 31;8(1):35-7. doi: 10.3315/jdcr.2014.1167. PMID: 24748910; PMCID: PMC3989096.

Case Report

DOI: 10.56016/dahudermj.1312590

DAHUDER Medical Journal
e-ISSN: 2791-9250

Exertional rhabdomyolysis-induced "normokalemic" severe acute kidney injury. A case report and a brief literature review

Alper Tuna Güven[1], Rüya Özelsancak[2]

[1]Department of Internal Medicine, Division of General Internal Medicine, Başkent University Faculty of Medicine, Ankara, Turkey
[2]Department of Internal Medicine, Division of Nephrology, Başkent University Adana Hospitals, Adana, Turkey

ABSTRACT

Rhabdomyolysis is the breakdown of the muscle cells with the resultant leakage of intracellular components. Hyperkalemia and hyperphosphatemia may occur during the disease course, as well as acute kidney injury due to blockade of the tubules by myoglobin released from the muscle cells. Electrolyte disturbances are generally more severe than acute kidney injuries. We would like to report a patient who was diagnosed with exertional rhabdomyolysis-induced acute kidney injury due to vigorous swimming and who required hemodialysis but lacked hyperkalemia. The discrepancy between the severe acute kidney injury and lack of hyperkalemia was remarkable. A brief literature search also revealed several patient reports with hypo- and normokalemia despite experiencing acute kidney injury. Pathophysiologic explanations for this discrepancy include exercise-induced increased kaliuresis and intracellular shifting of potassium.

Keywords: Rhabdomyolysis, acute kidney injury, potassium, exercise, dialysis

Rhabdomyolysis is a disorder characterized by muscle necrosis and the release of muscle contents into the circulation. There are multiple causes of rhabdomyolysis, including but not limited to exercise, trauma, drugs, toxins, electrolyte disturbances, and inherited metabolic or muscle disorders. Rhabdomyolysis severity may range from asymptomatic muscle enzyme elevations to life-threatening disease due to electrolyte imbalances (i.e., hyperkalemia and hyperphosphatemia) and acute kidney injury (AKI).[1] In the event of an AKI, the severity of hyperkalemia is expected to become disproportionate to the severity of kidney injury.[2] Exertional rhabdomyolysis is associated with unique pathophysiologic changes regarding kidney injury and potassium since vigorous exercise has been shown to lower potassium levels by several mechanisms.[3, 4, 5] Herein, we present a case of exertional rhabdomyolysis-induced acute kidney injury that we think is of particular importance due to the reversely disproportioned severity between acute kidney injury (AKI) and potassium levels.

CASE PRESENTATION

The patient is a 27-year-old male who was admitted to the emergency department with recent-onset nausea and vomiting. He states he had cola-colored urine output after swimming for long hours four days ago,

Received: *June 10, 2023****; Accepted:*** *June 25, 2023****; Published Online:*** *July 29, 2023*

How to cite this article: *Güven AT, Özelsancak R. Exertional rhabdomyolysis-induced "normokalemic" severe acute kidney injury. A case report and a brief literature review DAHUDER MJ 2023,3(3):100-104. DOI: 10.56016/dahudermj.1312590*

Address for correspondence: *Alper Tuna Güven, MD., Taşkent Caddesi (Eski 1. Cadde) 77. Sokak (Eski 16. Sokak) No:11 06490 Bahçelievler, Ankara, Turkey*
E-mail: alper.tuna.guven@gmail.com

Table 1. Exertional rhabdomyolysis induced acute kidney injury patients in the PubMed search

Case[Ref.]	Age/Sex	Body Temperature (°C)	Creatinine (mg/dL)	Potassium (mmol/L)	CK (U/L)	Underlying disease	Medication - Herbal products	Rhabdomyolysis cause	Possible additional factors	Mortality
1[6]	21/M	41.0	2.1	4.2	1100	-	-	Military training	Heat stroke	-
2[7]	21/M	37.3	1.9	4.5	426	-	Herbal supplement	Military training	Ephedra	-
3[8]	25/M	38.2	2.3	*	5555	-	-	Military training	Influenza infection	-
4[9]	19/M	36.1	2.3	5.2	536	Sickle cell trait	-	Football training	Sickle cell trait	+
5[10]	31/M	41.7	1.9	6.7	7482	-	-	Obstacle marathon	Heat stroke	-
6[11]	36/M	39	2.1	6.2	2975	-	Ephedrine	Half marathon run	Ephedrine	-
7[12]	50/M	N/A	1.8	*	2306	Hypertension, gastroesophageal reflux disease, osteoarthritis, insomnia	Hydrochlorothiazide, omeprazole, sildenafil, codeine/acetaminophen, Hydroxyzine, fat burn X	Daily sports exercise	Fat burn X	-
8[13]	25/M	36	1.1	5.5	38280	-	Androgenic steroids	Gym exercise	Androgenic steroids	-
9[14]	N/A /M	N/A	4.9	3.1	>40000	N/A	NSAID	Endurance run	-	-
10[14]	N/A / M	N/A	3.4	4.9	38218	N/A	NSAID	Endurance run	-	-
11[14]	N/A / M	N/A	4.4	2.8	>40000	N/A	NSAID	Endurance run	-	-
12[15]	41/M	40.3	12	5.3	112300	-	-	10 km run	Heat stroke	-
13[16]	19/M	37.1	8.3	6.2	10127	hereditary renal hypouricemia	-	Gym exercise	-	-
14[17]	19/M	37.0	1.9	4.2	587600	-	-	26 km run	-	-
15[18]	39/M	N/A	8.1	4.9	26320	-	-	4 km run	Alcohol Abuse	-
16[19]	32/M	N/A	1.3	4.6	>100000	N/A	N/A	Endurance run	Diarrhea	-
17[19]	47/F	N/A	1.1	4.1	15636	-	N/A	Endurance run	-	-
18[19]	35/M	N/A	4.8	5.2	>100000	-	N/A	Endurance run	-	-
19[19]	41/M	N/A	7.1	5.9	122347	-	N/A	Endurance run	-	-
20[20]	20/M	39.4	2.8	2.1	27947	Sickle cell trait	-	Military training	Heat stroke	+
21[21]	19/M	36.7	13.6	3.5	850	-	-	Wrestling	Dextroamphetamine use	-
22[22]	25/M	40.5	8.1	4.8	6409	-	-	Police recruitment training	Heat stroke	+
23[23]	33/F	N/A	12.2	6.1	11500	Hypothyroidism	Levothyroxine	Marathon run	Hypothyroidism	-
24[24]	19/M	N/A	1.6	3.2	2545	-	-	Football play	Cold water immersion	-
25[25]	26/M	37.5	2.7	5.6	2112	Sickle cell trait	-	Military training	Sickle cell trait	+
26[26]	23/M	N/A	1.5	5.8	36640	Graves' disease	-	Weight lifting	Thyrotoxicosis	-
27[27]	33/M	38.3	2.3	4.8	133240	-	Creatine, ephedrine.	Military training	Crash diet, Creatine, ephedrine	+
28[28]	25/F	>40	3.2	3.0	1600000	-	-	Hiking	Heat stroke	-
29[29]	31/M	N/A	1.3	4.5	59159	-	protein supplements, caffeine, pseudoephedrine,	Resistance training	Protein supplements, caffeine, pseudoephedrine	-
30[30]	19/M	38.3	1.9	4.6	408545	Sickle cell trait, asthma	-	Football play	Sickle cell trait, heat stroke	-
31[31]	20/M	40	3.2	4.7	23500	-	-	Military training	Heat stroke	-
32[32]	32/M	N/A	2.8	5	114383	Hypertension, hypothyroidism, gastroesophageal reflux disease, inflammatory bowel disease	Esomeprazole, levothyroxine, irbesartan–hydrochlorothiazide, metoprolol succinate, metoclopramide, dicyclomine, oxycodone, acetaminophen, phentermine	Furniture lifting	Phentermine	-
33[33]	25/M	N/A	4.4	4.4	2268	-	-	Military training	-	-
34[34]	57/M	N/A	9.4	6.4	3389	Hypertension, hyperlipidemia	Ramipril, atorvastatin	Trekking	Atorvastatin	-
35[35]	59/M	Afebrile	2.5	4.6	>18000	N/A	N/A	Brisk walk	Alcohol	-
36[36]	22/M	37.3	6	4.2	100000	Sickle cell trait	-	Military training	Sickle cell trait, diarrhea	+

CK: Creatine Kinase, N/A: Not applicable

* Potassium level was written as "normal"

but the urine had turned to its normal color the day after. He was deconditioned, and strenuous swimming took place on a very hot and humid day. He did not have any prior disease or medication history, and he denies substance abuse. He did not have any diarrhea or abdominal pain prior to admission. His vital signs, including body temperature, were in the normal range. Blood tests revealed stage 3 AKI (creatinine = 8.07 mg/dL), moderate transaminase elevation (ALT = 214 U/L, and AST = 384 U/L), and marked creatine kinase (CK) elevation (CK = 14.851 U/L). Urinalysis showed mild protein and moderate hemoglobin and myoglobin but a lack of red blood cells. The electrolyte levels were as follows: sodium = 132 mmol/L, potassium = 4.0 mmol/L, and phosphorus = 6.7 mg/dL. The uric acid level was 13.1 mg/dL, the TSH level was 0.94 mIU/L, and the blood gas analysis was unrevealing. Abdominal ultrasound showed mild hepatosteatosis and increased renal echogenicity. He was diagnosed with exertional rhabdomyolysis-induced AKI, so vigorous hydration was started. After hydration, he became fluid overloaded and his creatinine did not improve; therefore, hemodialysis was initiated. He was discharged after a week with residual kidney impairment.

DISCUSSION

We presented an untrained young man who swam for several hours during a hot and humid weather and experienced exertional rhabdomyolysis. Our patient is noteworthy with regards to the discordance between the level of kidney injury and potassium levels. One would expect hyperkalemia during a rhabdomyolysis course that has caused stage 3 AKI. There are several explanations for this discrepancy and include several mechanisms: Firstly, heat and exercise-induced sweating, and tachypnea caused direct potassium loss and intracellular potassium shift, respectively. Secondly, exercise-generated heat and exercise-induced water loss led to aldosterone overproduction and resultant kaliuresis.[3] Finally, ongoing urine output and vomiting might have played a role in potassium loss.

A brief literature review was performed via PubMed in order to compare our case with the existing literature. Search keywords were as follows: ((exercise) OR (exertional)) AND (rhabdomyolysis). Only case reports, letters, and observational studies that were conducted in humans over 18 years old were included. Search results included 441 studies. Studies that included patients without acute kidney injury, patients without data regarding kidney function and potassium level, patients with inherited metabolic disorders, inborn errors of metabolism, storage disorders, muscle disorders, malignant hyperthermia, drug-related rhabdomyolysis, and non-exertional rhabdomyolysis were excluded. Of the remaining 31 studies,[6-36] patients were found to have exertional rhabdomyolysis with acute kidney injury. Of the 36 patients, 4 were hypokalemic, 18 were normokalemic, and 14 were hyperkalemic. Creatinine levels, mortality, body temperature, and CK levels upon admission to the emergency department were not different between these 3 groups. Table 1 illustrates the characteristics of these patients.

Further systematic reviews should be conducted to search for and describe the features associated with non-hyperkalemic exertional rhabdomyolysis. Findings may challenge the dogma that clinicians should expect hyperkalemia during rhabdomyolysis regardless of the kidney injury and assert the finding that hypokalemia or normokalemia may occur during exertional rhabdomyolysis even in the presence of severe kidney injury.

CONCLUSION

Conflict of Interest

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

Funding Sources

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

Authors' Contribution

Study Conception: ATG; Supervision; RÖ; Data Collection and/or Processing: ATG; Literature Review: ATG; Critical Review: RÖ; Manuscript preparing: ATG.

REFERENCES

1. McMahon GM, Zeng X, Waikar SS. A risk prediction

score for kidney failure or mortality in rhabdomyolysis. JAMA Intern Med. 2013;173(19):1821-1828. doi:10.1001/jamainternmed.2013.9774
2. Lordon RE, Burton JR. Post-traumatic renal failure in military personnel in Southeast Asia. Experience at Clark USAF hospital, Republic of the Philippines. Am J Med. 1972;53(2):137-147. doi:10.1016/0002-9343(72)90124-6
3. Poortmans JR. Exercise and renal function. Sports Med. 1984;1(2):125-153. doi:10.2165/00007256-198401020-00003
4. Wang AY, Li PK, Lui SF, Lai KN. Renal failure and heatstroke. Ren Fail. 1995;17(2):171-179. doi:10.3109/08860229509026254
5. Aizawa H, Morita K, Minami H, Sasaki N, Tobise K. Exertional rhabdomyolysis as a result of strenuous military training. J Neurol Sci. 1995;132(2):239-240. doi:10.1016/0022-510x(95)00144-q
6 Pereira F, Moraes R, Bavel D, Lorenzo AR, Tibirica E. Exertional Rhabdomyolysis after Military Training Paralleled by Systemic Microvascular Dysfunction and Plasma Cytokine Increase: A Case Report. Arq Bras Cardiol. 2019;113(2):294-298. Published 2019 Sep 2. doi:10.5935/abc.20190165
7. Stahl CE, Borlongan CV, Szerlip M, Szerlip H. No pain, no gain--exercise-induced rhabdomyolysis associated with the performance enhancer herbal supplement ephedra. Med Sci Monit. 2006;12(9):CS81-CS84.
8. Tseng GS, Hsieh CY, Hsu CT, Lin JC, Chan JS. Myopericarditis and exertional rhabdomyolysis following an influenza A (H3N2) infection. BMC Infect Dis. 2013;13:283. Published 2013 Jun 21. doi:10.1186/1471-2334-13-283
9. Anzalone ML, Green VS, Buja M, Sanchez LA, Harrykissoon RI, Eichner ER. Sickle cell trait and fatal rhabdomyolysis in football training: a case study. Med Sci Sports Exerc. 2010;42(1):3-7. doi:10.1249/MSS.0b013e3181ae0700
10. Aquilina A, Pirotta T, Aquilina A. Acute liver failure and hepatic encephalopathy in exertional heat stroke. BMJ Case Rep. 2018;2018:bcr2018224808. Published 2018 Jul 30. doi:10.1136/bcr-2018-224808
11. Rhidian R. Running a risk? Sport supplement toxicity with ephedrine in an amateur marathon runner, with subsequent rhabdomyolysis. BMJ Case Rep. 2011;2011:bcr1120115093. Published 2011 Dec 13. doi:10.1136/bcr.11.2011.5093
12. Hannabass K, Olsen KR. Fat burn X: burning more than fat. BMJ Case Rep. 2016;2016:bcr2015213374. Published 2016 Jan 25. doi:10.1136/bcr-2015-213374
13. Braseth NR, Allison EJ Jr, Gough JE. Exertional rhabdomyolysis in a body builder abusing anabolic androgenic steroids. Eur J Emerg Med. 2001;8(2):155-157. doi:10.1097/00063110-200106000-00015
14. Bruso JR, Hoffman MD, Rogers IR, Lee L, Towle G, Hew-Butler T. Rhabdomyolysis and hyponatremia: a cluster of five cases at the 161-km 2009 Western States Endurance Run. Wilderness Environ Med. 2010;21(4):303-308. doi:10.1016/j.wem.2010.06.012
15. Hart LE, Egier BP, Shimizu AG, Tandan PJ, Sutton JR. Exertional heat stroke: the runner's nemesis. Can Med Assoc J. 1980;122(10):1144-1150.
16. Chakraborty S, Sural S. A young patient of hereditary renal hypouricaemia presenting with exercise-induced rhabdomyolysis and acute kidney injury. Ann Clin Biochem. 2013;50(Pt 3):271-273. doi:10.1258/acb.2012.012017
17. Al Badi A, Al Rasbi S, Alalawi AM. Exercise-Induced Rhabdomyolysis: A Case Report and Literature Review. Cureus. 2020;12(8):e10037. Published 2020 Aug 26. doi:10.7759/cureus.10037
18. Daher Ede F, Silva Júnior GB, Brunetta DM, Pontes LB, Bezerra GP. Rhabdomyolysis and acute renal failure after strenuous exercise and alcohol abuse: case report and literature review. Sao Paulo Med J. 2005;123(1):33-37. doi:10.1590/s1516-31802005000100008
19. Ellis C, Cuthill J, Hew-Butler T, George SM, Rosner MH. Case report: exercise-associated hyponatremia with rhabdomyolysis during endurance exercise. Phys Sportsmed. 2009;37(1):126-132. doi:10.3810/psm.2009.04.1693
20. Ferster K, Eichner ER. Exertional sickling deaths in Army recruits with sickle cell trait. Mil Med. 2012;177(1):56-59. doi:10.7205/milmed-d-11-00106
21. Hamilton RW, Gardner LB, Penn AS, Goldberg M. Acute tubular necrosis caused by exercise-induced myoglobinuria. Ann Intern Med. 1972;77(1):77-82. doi:10.7326/0003-4819-77-1-77
22. Hassanein T, Perper JA, Tepperman L, Starzl TE, Van Thiel DH. Liver failure occurring as a component of exertional heatstroke. Gastroenterology. 1991;100(5 Pt 1):1442-1447.
23. Nelson SR, Phillips AO, Hendry BM. Hypothyroidism and rhabdomyolysis in a marathon runner. Nephrol Dial Transplant. 1993;8(4):375-376.
24. Kahanov L, Eberman LE, Wasik M, Alvey T. Exertional rhabdomyolysis in a collegiate american football player after preventive cold-water immersion: a case report. J Athl Train. 2012;47(2):228-232. doi:10.4085/1062-6050-47.2.228
25. Kerle KK, Nishimura KD. Exertional collapse and sudden death associated with sickle cell trait. Mil Med. 1996;161(12):766-767.
26. Kim HR, Kim SH, Oh DJ. Rhabdomyolysis after a regular exercise session in a patient with Graves' disease. Nephrology (Carlton). 2012;17(3):307-308. doi:10.1111/j.1440-1797.2011.01528.x
27. Kuklo TR, Tis JE, Moores LK, Schaefer RA. Fatal rhabdomyolysis with bilateral gluteal, thigh, and leg compartment syndrome after the Army Physical Fitness Test. A case report. Am J Sports Med. 2000;28(1):112-116. doi:10.1177/03635465000280010401
28. Pattison ME, Logan JL, Lee SM, Ogden DA. Exertional heat stroke and acute renal failure in a young woman. Am J Kidney Dis. 1988;11(2):184-187. doi:10.1016/s0272-6386(88)80210-5
29. Pearcey GE, Bradbury-Squires DJ, Power KE, Behm DG, Button DC. Exertional rhabdomyolysis in an acutely detrained athlete/exercise physiology professor. Clin J Sport Med. 2013;23(6):496-498. doi:10.1097/JSM.0b013e318291d39e
30. Shelmadine BD, Baltensperger A, Wilson RL, Bowden RG. Rhabdomyolysis and acute renal failure in a sickle cell trait athlete: a case study. Clin J Sport Med. 2013;23(3):235-237. doi:10.1097/JSM.0b013e3182625a37
31. Sherner JH, Yuan CM. A 20-year-old army private with leg pain, fever, and collapse during a forced road march. Mil Med. 2002;167(4):363-366.
32. Steidl KE, Darko W, Probst LA, Noviasky JA, Nasser S. Rhabdomyolysis associated with phentermine. Am J Health Syst Pharm. 2010;67(22):1929-1932. doi:10.2146/ajhp090395
33. Tietjen DP, Guzzi LM. Exertional rhabdomyolysis and acute renal failure following the Army Physical Fitness Test. Mil Med. 1989;154(1):23-25.
34. Unnikrishnan D, Satish B. Exertion-induced rhabdomyolysis in a patient on statin therapy. Nephrol Dial Transplant. 2005;20(1):244. doi:10.1093/ndt/gfh578

35. West H. Rhabdomyolysis associated with compartment syndrome resulting in acute renal failure. Eur J Emerg Med. 2007;14(6):368-370. doi:10.1097/MEJ.0b013e32823a3c8b
36. Zimmerman J, Granatir R, Mummert K, Cioffi R. Sickle crisis precipitated by exercise rhabdomyolysis in a patient with sickle cell trait: case report. Mil Med. 1974;139(4):313-315.