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Diagnostic Significance of Chemerin and Chitinase 3-Like Protein 1 Levels in Cholelithiasis

Kolelitiaziste Kimerin ve Kitinaz 3-Benzeri Protein 1 Düzeylerinin Tanısal Önemi

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Abstract

Objectives: Cholelithiasis is a common gallbladder disease that refers to the formation of gallstones. In this study, we investigated the relationship between Cholelithiasis and Chitinase 3-like-1 protein (Chi3L1) and Chemerin levels.

Materials and Methods: Our study was conducted in 88 individuals, 44 of whom were healthy and 44 of whom had cholelithiasis. Chemerin and Chi3L1 serum levels were measured by enzyme-linked immunsorbent assay-ELISA method. The results were then analyzed using SPSS.

Results: When cholelithiasis patient groups were compared with healthy groups, a significant increase was found in Chemerin levels in cholelithiasis patients (6.28-4.68, p<0.001). Chi3L1 concentration values were not statistically different between groups (p=0.460). After receiver operating characteristic analysis, the Chemerin result was statistically significant in predicting disease [p<0.001, area under the curve: 0.795 (0.697-0.893)], Chi3L1 was statistically insignificant in predicting disease. While the difference between the patient and control groups in terms of creatinine, albumin, amylase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, direct bilirubin, sodium, and calcium was statistically significant (p<0.05), the difference between Chi3L1 concentration and creatinine and total protein was statistically significant (p<0.05).

Conclusion: Our study suggests that chemerin may be a new biomarker in the diagnosis of cholelithiasis. In addition, since our study has not been done before, it can bring a new perspective to the literature.

Key Words: Cholelithiasis, Chemerin, Chitinase 3-Like-1

Öz

Amaç: Kolelitiazis, toplumda sık görülen ve safra taşı oluşumunu ifade eden bir safra kesesi hastalığıdır. Bu çalışmada, kolelitiazis ile kitinaz 3-benzeri protein 1 (Chi3L1) ve kimerin düzeyleri arasındaki ilişki araştırılmıştır.

Gereç ve Yöntem: Çalışmamız 44'ü sağlıklı ve 44'ü kolelitiazisli olmak üzere 88 birey üzerinde yürütülmüştür. Kimerin ve Chi3L1 serum düzeyleri enzyme-linked immunsorbent assay-ELISA yöntemi ile ölçülmüştür. Sonuçlar daha sonra SPSS kullanılarak analiz edilmiştir.

Bulgular: Kolelitiazis hasta grupları sağlıklı gruplarla karşılaştırıldığında, kolelitiazis hastalarında kimerin düzeylerinde anlamlı bir artış bulundu (6,28-4,68, p<0,001). Chi3L1 konsantrasyon değerleri gruplar arasında istatistiksel olarak farklı değildi (p=0,460). Alıcı işletim karakteristiği analizinden sonra, kimerin sonucu hastalığın öngörülmesinde istatistiksel olarak anlamlıydı [p<0,001, eğri altında kalan alan: 0,795 (0,697-0,893)], Chi3L1 hastalığın öngörülmesinde istatistiksel olarak önemsizdi. Hasta ve kontrol grupları arasında kreatinin, albümin, amilaz, alanin aminotransferaz,

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Öz

aspartat aminotransferaz, gama glutamiltransferaz, direkt bilirubin, sodyum ve kalsiyum açısından fark istatistiksel olarak anlamlı iken (p<0,05), Chi3L1 konsantrasyonu ile kreatinin ve total protein arasındaki fark istatistiksel olarak anlamlıydı (p<0,05).

Sonuç: Çalışmamız, kimerinin kolelitiazis tanısında yeni bir biyobelirteç olabileceğini düşündürmektedir. Ayrıca çalışmamız daha önce yapılmadığı için literatüre yeni bir bakış açısı getirebilir.

Anahtar Kelimeler: Kolelitiazis, Kimerin, Kitinaz Benzeri-3 Protein 1

Introduction

Gallstones are one of the most common biliary system disorders in the world with a prevalence of 15-20% in western countries (1-4). In addition, it is one of the most common diseases affecting emergency room patients with epigastric pain, nausea, vomiting, abdominal pain and loss of appetite (5). The pathogenesis of gallstones is believed to be multifactorial and likely develops from interactions between various genetic and environmental factors, such as age, gender, ethnicity, family history, obesity, rapid weight loss, and pregnancy (6). The direct and indirect consequences of gallbladder disease represent billions of dollars in cost and cause a huge health burden that increases every year (7,8). Most patients have gallstones diagnosed during an abdominal ultrasound performed for another reason (9). Gallbladder diseases include various disorders of the gallbladder and bile ducts. Cholelithiasis refers to the formation of gallstones and can occur with or without obvious symptoms. Symptomatic gallbladder disease refers to biliary colic or pain as a result of gallstone formation. Asymptomatic gallbladder disease refers to gallstones that are present but remain in the gallbladder, which are not obstructive and do not cause discomfort (10). The causes of gallbladder disease are multifactorial. Factors that affect hepatic cholesterol production, gallbladder function (stasis or inflammation), bile acid production, or intestinal absorption of cholesterol and bile acids can all contribute to gallstone formation (11-15). Gallstone formation is characterized by three main pathways. If the liver produces more cholesterol than bile can dissolve, the excess cholesterol may precipitate into crystals. Crystals become trapped in the gallbladder mucus, producing gallbladder sludge. Over time, the crystals can grow to form stones and block the ducts, eventually causing gallstone disease. Bilirubin, a yellow pigment obtained from the breakdown of red blood cells, is secreted into bile by liver cells. Some hematological conditions cause the liver to make too much bilirubin through the breakdown of hemoglobin. This excess bilirubin can also lead to gallstone formation. If the gallbladder does not empty effectively, bile can become concentrated and form gallstones. Each stone has a unique set of risk factors. In the diagnosis of gallstones, ultrasound, complete blood count, prothrombin time, partial thromboplastin time, lipase, amylase, alkaline phosphatase (ALP), total bilirubin, and urine analyzes are performed first.

Chemerin is a widely occurring multifunctional secreted chemotactic and adipokine protein involved in immune cell migration, osteoblastogenesis, angiogenesis, myogenesis, and glucose homeostasis. Chemerin is regulated by nuclear receptor agonists, metabolic signaling proteins and intermediates, and proinflammatory cytokines (16). Chitinase 3-like-1 (Chi3L1) is a glycoprotein in a number of human cancers and is characterized by chronic inflammation and tissue remodeling. In many human neoplasms, including cancers of the breast, colon, prostate, ovaries, brain, thyroid, lung, and liver, elevated serum levels are associated with poor prognosis and short-term survival. Increased serum Chi3L1 is also associated with disease severity in rheumatoid arthritis (RA), osteoarthritis, liver fibrosis, inflammatory bowel disease, and bacterial septicemia (17).

Since Chemerin and Chi3L1 proteins are associated with many inflammatory conditions and their combined association with cholelithiasis has not yet been investigated, we planned to examine this disease group and these biomarkers in our study. The high prevalence of cholelithiasis in the community and the lack of a specific biomarker are the reasons for our study design. The aim of our study was to investigate whether chemerin and Chi3L1 protein levels differ in patients with cholelithiasis and healthy individuals and whether these proteins would be useful as biomarkers in disease diagnosis.

Materials and Methods

Patients

The patient group was determined to be 44 patients who were diagnosed with cholelithiasis in Sivas Cumhuriyet University Hospital, General Surgery Clinic, without age and gender discrimination. We chose this group of patients because cholelithiasis is common and therefore patients can be obtained more easily. The diagnosis of cholelithiasis was made by evaluating together the ultrasound results and biochemical parameters in patients with abdominal right upper quadrant pain. Patients whose diagnosis was not confirmed by radiological methods, patients with malignant tumors, patients receiving chemotherapy, patients taking anti-psychotic drugs because they may have too many interactions and patients with a history of right upper quadrant trauma were excluded from our study.

Controls

The healthy control group consisted of 44 individuals who applied to Sivas Cumhuriyet University Hospital, General Surgery Clinic. Ultrasound and biochemical parameters were evaluated in these individuals, and those who were not diagnosed with cholelithiasis were included in the study. Individuals with gallstones were excluded from the study. The healthy control group was randomly selected to be similar to the patient group, regardless of age and gender.

Measurement of Serum Chemerin and Chi3L1 Levels

In our study, venous blood samples were taken into serum tubes. The samples were then centrifuged (2000xg, 10 minutes). The samples were stored for later use in the study. Serum Chemerin (ELK Biotechnology, Catalog No: ELK1953, China) levels were measured using a human enzyme-linked immunsorbent assay kit (ELISA). The range of detection was 0.16-10 ng/mL with <8% intra-assay and <10% inter-assay variation coefficient. The minimum measurable amount was 0.069 ng/mL. Chi3L1 (ELK Biotechnology, Cat. No. ELK1991, China) levels were also measured via an ELISA kit. The range of detection was 31.25-2000 pg/mL with <8% intra-assay and <10% inter-assay variation coefficient. The minimum measurable level was 13.5 pg/mL. Chemerin and Chi3L1 levels in serum samples were measured in microplate reader device.

Ethical Consideration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The ethics committee approval has been granted from our institution. Ethics committee approval was obtained for our study from Sivas Cumhuriyet University Faculty of Medicine Clinical Research Ethics Committee; with the decision of the dated 11.01.2022 and numbered 2022-01/04.

Statistical Analysis

SPSS Statistics software (Version 22, SPSS Inc., Chicago, IL, USA) was used. Frequencies (n) and percentages (%) were used to present all demographic and categorical data. The chi-square test was used to conduct the statistical analysis of proportion comparison between case-control groups. Descriptive statistics were reported using mean ± standard deviation (SD) for normally distributed numerical data and median (quartiles: Q1, Q3) for non-normally distributed numerical data. The Shapiro-Wilk test was used to determine whether the data were distributed normally. To compare numerical data between case and control groups, the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data were used. Using Chemerin and Chi3L1 concentration values, a receiver operating characteristic (ROC) analysis was used to distinguish the patient group from the control group. The area under the ROC curve (AUC) was calculated with 95% confidence intervals. The AUC scale was 0.9-1 for excellent, 0.8-0.9 for good, 0.7-0.8 for fair, 0.6-0.7 for poor, and 0.5-0.6 for very poor. Following the ROC analysis, the best cut-off points for the Chemerin and Glycoprotein concentration values found significant in ROC analysis was determined using the Youden index (highest sensitivity and specificity). Statistical significance level was considered as $p<0.05$.

Results

In the study, a total of 88 data, 44 patients and 44 control groups, were analyzed. Statistical findings for the comparison of sociodemographic characteristics and concentration values between research groups are shown in Table 1. The distribution of sex ratios was similar (p=1.000). 31.8% (n=14) of the patient and control groups were male and 68.2% (n=30) were female. The mean age of the patients was 64.97±10.35 years. In controls, the mean age was 62.25±11.32 years Table 1. Chemerin concentrations were significantly different between the groups (p<0.001, Table 1). Chemerin concentrations of the cholelithiasis group (6.28) were significantly higher (4.88) (p<0.001, Table 1). The boxplot showing the distribution of Chemerin concentration values between the groups is shown in Figure 1. Chi3L1 concentration values were not different between groups (p=0.460, Table 1). The boxplot showing the distribution of Chi3L1 concentration values between the

Table 1: Comparison of socio-demographic and concentration values between case and control groups

		Case (n=44)	Control (n=44)	p-values
Gender	**Male**	14 (31.8%)	14 (31.8%)	1.000[a]
	Female	30 (68.2%)	30 (68.2%)	
Age		64.97±10.35	62.25±11.32	>0.001[b]
Chemerin (ng/mL)		6.28 (5.65-8.28) (6.89±1.7)	4.68 (4.17-5.88) (5.32±1.62)	**<0.001**[c]
Chi3L1 (pg/mL)		5.15 (3.96-6.96) (5.55±1.93)	3.68 (4.88-6.62) (5.95±3.66)	0.460[c]

[a]Chi-square test with n (%)
[b]Student's t-test with mean ± SD
[c]Mann-Whitney U test with median (Quartiles: Q1-Q3) and (mean ± SD)
SD: Standard deviation, Chi3L1: Chitinase 3-like-1 protein

groups is shown in Figure 2. Statistical study was performed to determine whether Chemerin and Chi3L1 concentrations were significant parameters in the prediction of disease. Chemerin concentration was statistically significant in predicting disease [p<0.001, AUC: 0.795 (0.697-0.893), Figure 1]. ROC analysis results of chemerin concentration values for disease prediction, sensitivity, selectivity, and positive predictive values (PPV) and negative predictive values (NPV) are shown in Table 2. The discrimination power (ROC area under the curve) for Chemerin was almost good. The best cut-off point for the chemerin concentration was determined as 5.31, and the sensitivity and specificity values for case-control discrimination for this cut-off were 88.6% (74.6-95.7) and 70.5% (54.6-82.8) with confidence intervals, respectively. PPV and NPV with confidence intervals were 75% (60.8-85.6) and 86.1% (69.7-94.8), respectively. According to ROC analysis results, Chi3L1 was statistically insignificant in the prediction of disease [p=0.460, AUC: 0.546 (0.424-0.667), Table 2, Figure 2]. The groups were compared between the patient and control groups in terms of creatinine, albumin, amylase, ALP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma glutamyltransferase (GGT), blood urea nitrogen (BUN), direct bilirubin, sodium, calcium and potassium. While the difference between the patient and control groups in terms of line, albumin, amylase, ALT, AST, creatinin, GGT, direct bilirubin, sodium, and calcium was statistically significant (p<0.05), the difference in other parameters was found to be insignificant (p>0.05) (Table 3).

In addition, the correlation between Chemerin and Chi3L1 concentrations and these parameters was investigated in the patient and control groups. While the correlation between BUN and Sodium parameters of Chemerin concentration in the patient group was statistically significant (p<0.05), the difference between Chi3L1 concentration and Creatinine and total protein was statistically significant (p<0.05).

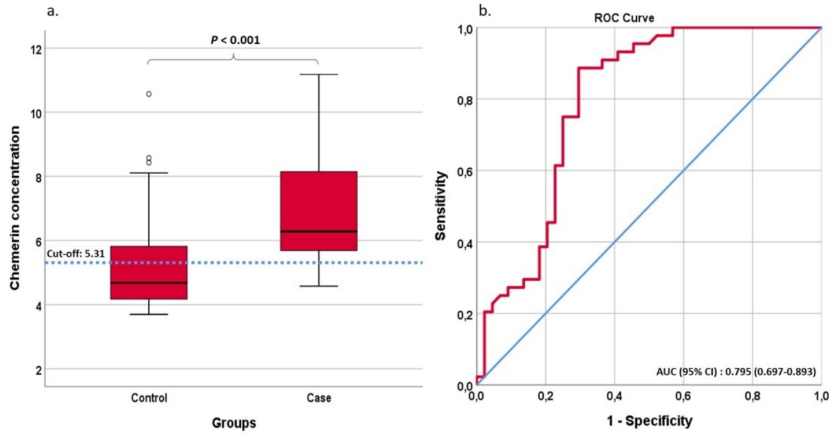

Figure 1: a) Boxplot showing the distribution of Chemerin concentration values between the case and control groups. **b)** The area under the ROC curve for case-control discrimination by Chemerin concentration values

ROC: Receiver operating characteristic

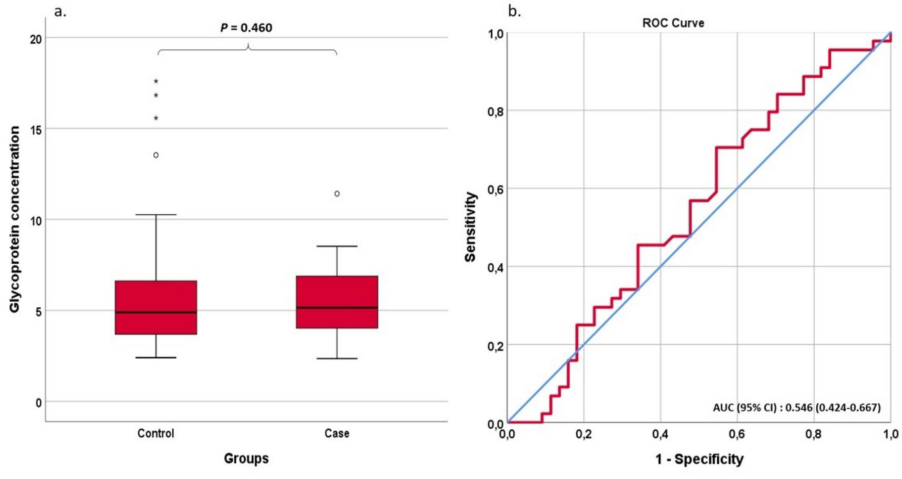

Figure 2: a) Boxplot showing the distribution of Chi3L1 concentration values between the case and control groups. **b)** The area under the ROC curve for case-control discrimination by Chi3L1 concentration values

ROC: Receiver operating characteristic, Chi3L1: Chitinase 3-like-1 protein

Table 2: ROC analysis results, sensitivity, specificity, and positive-negative predictive values for the success of Chemerin and Chi3L1 concentration values in disease prediction

	Chemerin	Chi3L1
AUC (95% CI)	0.795 (0.697-0.893)	0.546 (0.424-0.667)
P values	**<0.001***	0.460
Cut-off	5.31	-
Sensitivity	88.6% (74.6-95.7)	-
Specificity	70.5% (54.6-82.8)	-
PPV (True positive)	75% (60.8-85.6)	-
NPV (True negative)	86.1% (69.7-94.8)	-

*Statistically significant
AUC: Area under the ROC curve, CI: Confidence interval, PPV: Positive predictive values, NPV: Negative predictive values, ROC: Receiver operating characteristic, Chi3L1: Chitinase 3-like-1 protein

Table 3. Comparison of the biochemical parameters of the patient and healthy control group

	Group	N	Mean	SD	25%	50%	75%	p-value
Glucose (mg/dL)	Patient	44	79.96	64.76	2.00	43.35	100.50	p=0.801
	Control	44	75.65	47.20	4.47	9.75	90.00	
BUN (mg/dL)	Patient	44	19.74	10.83	11.47	27.30	43.00	p=0.166
	Control	44	21.27	17.53	12.45	34.50	40.25	
Creatinine (mg/dL)	Patient	44	1.43	0.61	0.68	0.70	3.13	p=0.048*
	Control	44	0.55	0.28	0.90	0.56	2.75	
T. Protein (g/L)	Patient	44	63.10	28.41	6.68	2.70	6.13	p=0.071
	Control	44	53.68	10.64	5.74	3.00	7.60	
Albumin (g/L)	Patient	44	22.97	19.05	0.68	2.70	6.13	p=0.001*
	Control	44	35.73	30.03	6.82	6.00	11.23	
Amylase (U/L)	Patient	44	113.61	68.24	68.67	94.58	179.50	p=0.001*
	Control	44	54.64	47.40	14.25	46.57	80.50	
ALP (U/L)	Patient	44	50.00	39.50	0.89	31.43	73.25	p=0.793
	Control	44	37.08	29.48	14.05	27.31	61.75	
ALT (U/L)	Patient	44	26.81	12.92	7.15	12.05	38.25	p=0.011*
	Control	44	9.99	9.15	0.67	13.05	17.75	
AST (U/L)	Patient	44	23.97	4.98	4.60	18.06	34.97	p=0.002*
	Control	44	9.27	8.08	0.27	9.94	17.00	
LDH (U/L)	Patient	44	148.04	81.20	70.25	142.09	212.25	p=0.950
	Control	44	139.75	43.98	138.03	142.08	173.50	
GGT (U/L)	Patient	44	70.94	54.62	27.00	68.06	99.25	p=0.001*
	Control	44	26.24	25.99	4.42	21.00	28.75	
T. Bilurubin (mg/dL)	Patient	44	1.45	1.02	0.77	0.79	0.75	p=0.496
	Control	44	0.96	0.43	0.71	0.39	0.01	
D. Bilurubin (mg/dL)	Patient	44	0.472	0.34	0.19	0.49	0.75	p=0.002*
	Control	44	0.28	0.231	0.00	0.13	0.57	
Sodium (mmol/L)	Patient	44	137.52	55.02	137.03	140.56	184.50	p=0.002*
	Control	44	131.99	73.749	132.07	138.01	142.00	
Potassium (mmol/L)	Patient	44	4.32	3.41	4.43	5.10	4.12	p=0.172
	Control	44	4.39	3.02	4.41	4.51	4.75	
Calcium (mg/dL)	Patient	44	5.18	3.96	4.82	6.01	8.80	p=0.015*
	Control	44	9.52	8.03	7.74	9.11	9.65	

*p<0.05, Mann-Whitney U testi
BUN: Blood urea nitrogen, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartat Aminotransferase, LDH: Lactate dehydrogenase, GGT: Gamma glutamyltransferase, SD: Standard deviation

Discussion

Chemerin protein is predominantly seen in liver, lung and white adipose tissue. When cholelithiasis patient groups were compared with healthy groups, we found a significant increase in chimerin levels in cholelithiasis patients. Therefore, the findings of our study suggests that chemerin may be a new biomarker in the diagnosis of cholelithiasis. When cholelithiasis patient groups were compared with healthy groups, no significant difference was found in Chi3L1 protein levels. However, this result may change with studies with a larger population.

Gonzalez-Ponce et al. (18) studied 210 patients with severe and mild RA. Chemerin levels were found to be high in 89 of these patients and RA activity was found to be severe. Another study by Haberl et al. (19) examined 45 HBV-infected, HCV-infected, and uninfected patients. In their study, they found that the levels of HCC chemerin associated with HCV were essentially unchanged. They found that chemerin protein was induced in HCC patients, HBV tumors. In 2016, Chang et al. (20) worked with obese patients and found an increase in chemerin levels. Important factors such as gender and age, which are likely to influence the mechanism between obesity and this protein, were also investigated. It has been reported that the chemerin levels in the serum of the patients remain stable for a long time and the forms of this protein change slowly. It has been determined that chemerin is highly associated with obesity. In a study that included 54 children and adolescents with gallstones and 26 controls, serum levels of chemerin were investigated by ELISA. In this study, chemerin concentrations were found to be higher in normal weight children and adolescents with cholelithiasis when compared to the control group. Obese children and adolescents with gallstones have significantly higher chemerin levels than healthy controls (21). Xu et al. (22) found that chemerin increased in lung cancer. According to this study, tumor size, regional lymphatic metastasis and spread to another tissue were significantly associated with high serum chemerin levels. Dozens of studies on chymine have been published this year. Some of the most important of these are studies related to common diseases. For example, Pankiewicz and Issat (23) reported that blood chemerin levels were elevated in patients with pre-eclampsia and positively correlated with disease severity. In an important manuscript published by Hu et al. (24) in 2023, it was shown that vascular chimerin levels are associated with tone and have a role in the pathogenesis of obesity-associated hypertension. According to an important animal experimental study by Liu et al. (25), chimerin protein has a protective effect for cardiomyopathy. As can be seen in the literature, except for one study, studies with chimera were conducted on different diseases. This makes our study more valuable. In our study, chemerin concentrations of the Cholelithiasis group were found to be significantly higher than the control group, in line with the studies mentioned. According to ROC analysis, Chemerin was found to be statistically significant in disease prediction.

Chi3L1 is a protein produced by many cells, including immune system cells and malignant tumor cells. In our current study, no significant difference was found between the two groups. According to ROC analysis, Chi3L1 is statistically insignificant in disease prediction. In contrast to our study, Ko et al. (26) studied Chi3L1 protein in patients with idiopathic normal pressure hydrocephalus (iNPH), idiopathic Parkinson's disease, mild cognitive impairment, Alzheimer's disease and healthy subjects. Chi3L1 levels were found to be higher in iNPH patients than in other groups. Jin et al. (27) studied Chinese chronic hepatitis B patients and serum Chi3L1 levels and their findings suggest that Chi3L1 serum levels are associated with fibrosis stage and Chi3L1 may be an important biomarker for fibrosis. Hoste et al. (28) examined 660 patients for the diagnosis of this disease and reported that Chi3L1 levels were elevated in patients with stage 2 or 3 AKI. Huang et al. (29) claimed that Chi3L1 levels are often correlated with aggressive and metastatic tumors. It has been reported that ChiCL1 levels are associated with esophageal tumor size, but not with survival in patients with esophageal carcinoma. ROC analysis results showed that Chi3L1 levels could detect esophageal carcinoma with absolute accuracy. In 2020, Cheng et al. (30) examined patients with thyroid cancer and their Chi3L1 levels, and it was found that high Chi3L1 levels were associated with recurrence in patients with differentiated type thyroid carcinoma. In our study, however, no difference was found between the groups in Chi3L1 concentration values. It has been reported that CHI3L1 can be used in the evaluation of prognosis in some studies with HCC patients (31,32), but no study has investigated CHI3L1 protein levels in cholelithiasis disease. Comprehensive studies are needed to evaluate CHI3L1 levels in the diagnosis of Cholelithiasis.

Our results suggest that Chemerin protein may be used as a biomarker for the diagnosis of cholelithiasis.

Study Limitations

The limitations of our study include the small patient population and the fact that many protein levels may be affected due to the complex pathogenesis of cholelithiasis.

Conclusion

Chemerin levels were found to be significantly increased in the serum of patients with cholelithiasis. However, Chi3L1 levels were not different between the patient and control group. After ROC analysis, Chemerin could use for the prediction of disease while Chi3L1 was not statistically significant. Although it requires more studies, it is thought that chemerin can be used as a biomarker in the diagnosis of cholelithiasis. Chemerin

levels were found to be significantly increased in the serum of patients with cholelithiasis. However, Chi3L1 levels did not differ between patients and controls. After ROC analysis, Chemerin could be used for disease prediction, while Chi3L1 was not statistically significant. Although more detailed studies are needed, it is thought that chemerin can be used as a biomarker in the diagnosis of cholelithiasis.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for our study from Sivas Cumhuriyet University Faculty of Medicine Clinical Research Ethics Committee; with the decision of the dated 11.01.2022 and numbered 2022-01/04.

Informed Consent: Detailed information about the study was given to the participants and consent forms were obtained from these individuals.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ö., G.G., Ö.T., Concept: A.Ö., C.Z., G.G., Ö.T., Y.S., Design: A.Ö., M.A.G., C.Z., Data Collection and Processing: M.A.G., G.G., A.T., Ö.T., Analysis or Interpretation: M.A.G., C.Z., T.A., A.T., Y.S., Literature Search: A.Ö., T.A., A.T., Writing: A.Ö., T.A., Y.S.

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