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Relationship between pancreatic cancer and Maresin 1

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ABSTRACT

Aims: Pancreatic cancer is the 4th most common cause of death from cancer. In addition, pancreatic cancer is the most common primary malignant tumor of the pancreas. There are many risk factors for pancreatic cancer, including age, certain genetic syndromes, smoking, diabetes, alcohol abuse and obesity. In our study, we aimed to evaluate the role of Maresin 1 (MaR1), which is responsible for the resolution of inflammation, in the pathogenesis of pancreatic cancer and its differential power between chronic pancreatitis and pancreatic cancer.

Methods: The study included 47 patients diagnosed with pancreatic cancer, 32 patients diagnosed with chronic pancreatitis, and 30 volunteers without any additional disease who applied to the internal medicine polyclinic for routine control, who applied to our clinic since October 2021 and accepted to participate in the study. MaR1 levels were measured using the ELISA technique from blood samples obtained from these volunteers.

Results: In our study, MaR1 level was 374.42 (97.27-74.129) pg/ml in the pancreatic cancer group, 491.39 (252.66-949.28) pg/ml in the chronic pancreatitis group and 558.53 (286.94) in the healthy control group. -886,68) pg/ml was measured. There was a significant difference between the pancreatic cancer patients group and the chronic pancreatitis patients and healthy control group. In the pancreatic cancer patient group, MaR1 level was found to be lower than the chronic pancreatitis group (p=0.01). In our ROC analysis, the discriminative performance of MaR1 (AUC=0.651; [95%CI: 0.535-0.754]; p=0.0169 values) was found to be high in predicting patients with pancreatic cancer according to the patient group with chronic pancreatitis. For MaR1 ≤315.52 cut-off point sensitivity was 36.17% and selectivity was 90.62%.

Conclusion: Proinflammatory cytokines, which have a role in the pathogenesis of pancreatic cancer, increase as a result of the decrease in lipid mediators involved in resolution pathways. Reduction of MaR1 may trigger chronic inflammation and pancreatic carcinogenesis. MaR1 may make an important diagnostic contribution in clinical practice in predicting the progression of patients with chronic pancreatitis to pancreatic cancer.

Keywords: Pancreatic cancer, chronic pancreatitis, inflammation, resolution, Maresin 1

INTRODUCTION

Among the causes of death worldwide, malignancies take second place after cardiovascular system diseases.[1] Pancreatic ductal adenocarcinomas (PDAC) are among the cancers with an aggressive course compared to other cancers.[2] Pancreatic cancer, which is ninth in frequency in our country, ranks fourth in terms of mortality1 with a survival rate of 10-15% in a 5-year period.[3] The incidence of pancreatic cancer is higher in men than in women.[4] The disease is frequently seen in the age range of 65-69 in men and 75-79 in women.[5]

At the mention of pancreatic cancer, the pancreas ductal adenocarcinoma (PDAC) and its variants come to mind. PDAC accounts for approximately 85% of all pancreatic neoplasms. As a result of incomplete resolution of acute inflammation, the inflammatory response may become chronic and progress to fibrosis. If complete resolution is achieved, the spread of inflammation can be prevented and as a result, the tissues can be restored functionally and structurally.[6]

Mediators produced from omega-3 and omega-6 play an active role in inflammation resolution. Deficiencies in polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and omega-3 fatty acid derivatives, which have immunomodulatory effects, inhibit resolution of inflammation leading to chronic inflammation. Maresins are DHA derivatives secreted from macrophages involved in the resolution of inflammation. Maresin 1 (MaR1) is synthesized in macrophages after several enzymatic reactions with 14-lipoxygenation (LOX) of DHA. An increase in pro-inflammatory cytokines can cause chronic inflammation, cancer formation, and proliferation of cancer.

Maresins areinvolved in the resolution of inflammation as theydecrease proinflammatory cytokines and suppress the communication between molecules involved in proliferation. Thus, theycan prevent the formation of cancer as well as suppress inflammation.[7-9]

This study aimed to evaluate the role of MaR1, a mediator of inflammation resolution, in the pathogenesis of pancreatic cancer and its potential to differentiate between chronic pancreatitis and pancreatic cancer. This is the first clinical study to show the relationship between pancreatic cancer and MaR1.

METHODS

Patient Selection and Study Method

The study included 47 patients diagnosed with pancreatic cancer and 32 patients diagnosed with chronic pancreatitis at the Gastroenterology Outpatient Clinic of the Faculty of Medicine of Kırıkkale University, and 30 volunteers without any disease who applied to the Internal Medicine Polyclinic for routine check-up.

This thesis study was carried out with the permission of Kırıkkale University Faculty of Medicine Clinical Researches Ethics Committee (Date: 05.10.2021, Decision No: 16/01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion Criteria for the Study

1. Patients over the age of 18,
2. Patients with newly diagnosed pancreatic cancer,
3. For the control group, patients with a new and old diagnosis of chronic pancreatitis,
4. Another control group with individuals without health problems,
5. Patients and healthy individuals who accepted and signed the informed consent form,

Blood was drawn from patients who had taken omega-3 supplements in the last 1 week, frompatients using non-steroidal anti-inflammatory and acetylsalicylic acid 1 week after drug discontinuation, and from patients who had not consumed fish in the last week.

Exclusion Criteria for the Study

1. Being under the age of 18,
2. Patients with any other pancreatic disease besides pancreatic cancer and chronic pancreatitis,
3. Patients with pancreatic metastases or other malignancies,
4. Patients and healthy individuals who did not accept and sign the informed consent form,
5. For the healthy control group; Patients with
   A. Diabetes mellitus
   B. Chronic kidney disease
   C. Obesity
   D. Collagen tissue diseases
   E. Thyroid diseases
   F. Anemia
   G. Acute infection
   H. Hyperlipidaemia
   I. Those with a diagnosis of inflammatory bowel disease
   J. Those with pancreatic disease
   K. Individuals with a history of using fish, omega-3 supplements, and non-steroidal drugs at least once in the last week.

Laboratory Analysis Methods

Blood samples were taken from the patients included in the study after at least 12 hours of fasting. The blood taken for routine examinations was centrifuged in 2 cc tubes (13×100, 5 mL plastic tube with Vacutainer gel) at 5000 rpm for 5 minutes, and the separated serum samples were transferred to sterile Eppendorf tubes. Serum samples were stored in a deep freezer at -80°C. All samples were studied concurrently and those with hemolysis were excluded from the study. C-reactive protein was studied with the Cobas C 501 particle surface expanded immunoturbidimetric test using the Roche cobas® c501 brand device and original Roche diagnostic kits (Roche Diagnostic Gmbh, Sandhofer Strasse 116, D-68305 Mannheim). Hemogram parameters (hemoglobin, white blood cell, platelet, neutrophil, lymphocyte) were studied with the flow cytometric impedance method in an automatic complete blood count device (Mindray BC 6800, Shenzhen, China). Glucose (GLUC Hk Gen.3,800 tests Cobas C kit with UV test hexokinase method), aspartate transaminase (Cobas Integra ASTL 500 tests kit with UV absorbance method), alanine transaminase (Cobas Integra ALT 500 tests kit with UV absorbance method), alkaline phosphatase (Cobas Integra ALP 500 tests kit with UV absorbance method), gammaglutamyl transferase (Cobas Integra GGT 500 tests kit with UV absorbance method), total bilirubin, direct bilirubin (Cobas Integra ALP 500 tests kit with the colorimetric method), albumin (Cobas Integra ALB Gen. 2 300 tests kit by colorimetric method), creatinine (CREAJ Gen.2, 700 tests, Cobas C, Integra kit using photometric method), sodium (Na, Gen.2 300 tests, Cobas c, Integra kit using colorimetric method) were studied using the Roche cobas® c501 brand device and original Roche diagnostic kits (Roche Diagnostic Gmbh, Sandhofer Strasse 116, D-68305 Mannheim). CA 19.9 and CEA levels were studied by chemoluminescence method using cobas® e601 brand device and original Roche diagnostic kits.

The Maresin 1 Elisa kit was prepared as follows:

- 50 µl of standard diluent was added to each tube.
- 100 µl of standard (1350 pg/ml) was added to the 5th tube.
- 100 µl was transferred from the 5th tube to the 4th tube.
- 50 µl was transferred from the 4th tube to the 3rd tube and the dilution process was continued as in 6th tube
- Undiluted standard is high standard (1350 pg/ml), diluent (empty well) was accepted as zero standard.

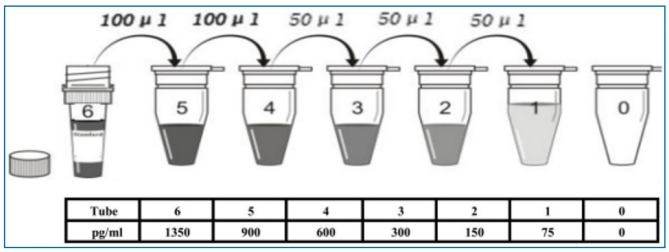

Figure 1. Preparation of standard solution with Elisa kit

Statistical Analysis

Descriptive statistics are presented as frequency (n) and percentage (%) for categorical variables, and mean±standard deviation (SD) or median (IQR) values for continuous variables. The assumption of normality was checked with the Shapiro-Wilk test. Pearson chi-square test was used to analyze

the relationships between categorical variables. In cases where the assumption of normality is not satisfied, Mann-Whitney U test was used to compare numerical variables between the two groups, while the Kruskal Wallis test (post-hoc test: Bonferroni test) was used to compare the three groups. In cases where the assumption of normality is provided, student T test was used to compare numerical variables between the two groups, while the one-way ANOVA test (post-hoc test: Tukey test) was used to compare the three groups.

Diagnostic performance and threshold values of MaR1, total bilirubin, CEA and CA-199 values were evaluated with ROC (Receiver Operating Characteristic) analysis in distinguishing the disease group diagnosed with pancreatic cancer and chronic pancreatitis compared to the control group and distinguishing KSK patients from the benign biliary disease group. Analysis results are presented with area under the curve (AUC), threshold value, sensitivity and specificity values, and 95% confidence intervals (CI). Youden index method was used to determine the optimal threshold value. Spearman correlation test was used for the relationships between ordinal or non-normally distributed continuous variables. All analyzes were performed with the IBM SPSS 21.0 package program (IBM Corp. Armonk, NY). P values less than 0.05 were considered statistically significant.

RESULTS

A total of 109 participant, including 47 newly diagnosed pancreatic cancer patients, 32 patients with chronic pancreatitis, and 30 healthy control group, were included in the study. Demographic characteristics of the whole population are presented in Table 1 in detail. The mean age was 69.40±9.77 years for the pancreatic cancer group, 58.06±8.01 years for the chronic pancreatitis group and 61.46±8.74 years for the control group. While the mean age did not differ significantly between the chronic pancreatitis group and the healthy group (p=0.420), it was higher in the pancreatic cancer group than the other groups (p<0.05). The rate of male was lower in the pancreatic cancer group than the other groups (Pancreatic cancer group: 63.8% vs. Chronic pancreatitis group: 75% vs. Control group: 73.3%, p=0.040), while the gender distribution did not differ significantly between the chronic pancreatitis and control groups (p>0.05).

The rate of smoking user was higher in the chronic pancreatitis group than the other groups (Pancreatic cancer group: 38.3% vs. Chronic pancreatitis group: 62.5% vs. Control group: 33.3%, p=0.040), while it did not differ significantly between the pancreatic cancer and control groups (p>0.05). The rate of alcohol user was higher in the chronic pancreatitis group than the other groups, while it was higher in the pancreatic cancer than the control groups (Pancreatic cancer group: 38.3% vs. Chronic pancreatitis group: 62.5% vs. Control group: 33.3%, p=0.040), while the gender distribution did not differ significantly between the pancreatic cancer and control groups (p>0.05) (**Table 1**).

The rate of patients with diabetes mellitus were higher in the pancreatic cancer than the chronic pancreatitis group (25.5% vs. 9.4%, p <0.001). The rate of patients with hypertension were higher in the pancreatic cancer than the chronic pancreatitis group (31.9% vs. 12.5%, p<0.001). The proportion of patients with coexistence of diabetes mellitus and hypertension were lower in the pancreatic cancer than the chronic pancreatitis group (29.8% vs. 37.5%, p<0.001) (**Table 1**).

Table 1. Demographic characteristics of patients according to study groups

Variables	Pancreatic cancer n=47	Chronic pancreatitis n=32	Control group n=30	p
Age, years	69.40±9.77	58.06±8.01	61.46±8.74	<0.001*
Gender, n (%)				<0.04**
Female	17 (%36.2)	8 (%25)	8 (%26.7)	
Male	30 (%63.8)	24 (%75)	22 (%73.3)	
Smoking				
User	18 (%38.3)	20 (%62.5)	10 (%33.3)	0.04**
Non-user	29 (%61.7)	12 (%37.5)	20 (%66.7)	
Alcohol, n(%)				
User	12 (%25.5)	11 (%34.4)	2 (%6.7)	0.03**
Non-user	35 (%74.5)	21 (%65.6)	28 (%93.3)	
Diabetes mellitus, n (%)	12 (%25.5)	3 (%9.4)	-	<0.001**
Hypertension, n (%)	15(%31.9)	4(%12.5)	-	<0.001**
Diabetes mellitus+ hypertension, n (%)	14(%29.8)	12(%37.5)	-	<0.001**

*Anova test ** Chi-square test

Median FPG, CRP, AST, ALT, ALP, GGT, total bilirubin, and direct bilirubin values were higher in the pancreatic cancer group compared to the chronic pancreatitis and control groups (p<0.05 for each parameter). While median albumin value was higher in the control group compared to the other groups, it was lower in the pancreatic cancer group compared to the other groups (p<0.001). Median WBC and PLT values were higher in the pancreatic cancer and chronic pancreatitis group than in the control group (p<0.001 for each parameter). While median LDH value was lower in the control group compared to the other groups, it was higher in the pancreatic cancer group compared to the other groups (p<0.001). The median MaR1 value was 374.42 (97.27-74.129) pg/mL in the pancreatic cancer patient group, 491.39 (252.66-949.28) pg/ mL in the chronic pancreatitis group, and 558.53 (286.94-886.68) pg/ mL in the control group. MaR1 value was lower in pancreatic cancer patients compared to chronic pancreatitis and control groups (p=0.001). MaR1 levels did not differ significantly between chronic pancreatitis and control groups (p=0.370).

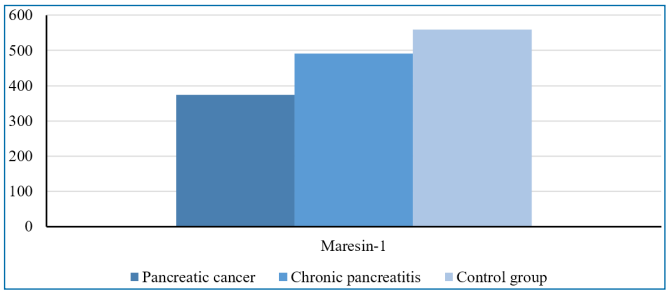

Figure 2. Maresin-1 values between groups

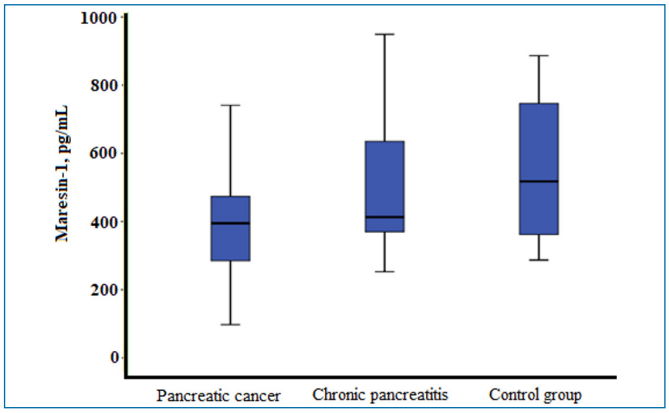

Figure 3. Distribution of Maresin-1 levels between groups

Table 2. Distribution of biochemical parameters between groups

Variables	Pancreatic cancer n=47	Chronic pancreatitis n=32	Control group n=30	p
FBG, mg/dL	147.42 (70-292)	117.81 (68-285)	100.76 (63-137)	<0.001*
CRP, mg/L	55.34 (0.7-446)	6.25 (0.5-22)	5.03 (0.1-21)	<0.001*
AST, IU/L	96.36 (9-433)	31.96 (9-96)	20.00 (10-70)	<0.001*
ALT, IU/L	122.51 (8-736)	36.65 (9-180)	20.90 (7-76)	<0.001*
TBIL, µmol/L	4.67 (0.2-21)	0.74 (0.3-1.45)	0.70 (0.3-1.30)	0.001*
DBIL, µmol/L	4.03 (0.1-18)	0.46 (0.1-1.45)	0.27 (0.1-1.6)	<0.001*
Albumin, g/dL	3.67 (2.1-5.6)	4.14 (3-5)	4.55 (3.9+5.18)	<0.001*
WBC, x109 /L	10.85 (3-90)	8.01 (4.7-14)	7.73 (3.5-13.2)	<0.001*
PLT, x109 /L	263.48 (120-673)	226.91 (148-380)	275.6 (183-563)	<0.001*
CEA, ng/m	95.99 (1.9-1000)	4.77 (0.5-20)	-	0.015*
CA19-9,U/mL	554.0 (120-1000)	18.27 (1.8-100)	-	<0.001*
ALP, IU/L	372.72 (60-1055)	106.25 (26-450)	70.40 (20-130)	<0.001*
GGT, IU/L	449.70 (14-1790)	61.68 (3-213)	45.90 (11-87)	<0.001*
LDH	289.36 (118-700)	189.65 (90-373)	90.1 (12-222)	<0.001*
HGB, g/dL	11.36 (4.6-16.2)	13.1 (8.5-17)	14.15 (10.9-16.4)	<0.001*
Maresin-1, pg/mL	374.42 (97.27-741.29)	491.39 (252.66-949.28)	558.53 (286.94-886.68)	0.001*

* Kruskal Wallis testi

The distribution of patients diagnosed with pancreatic cancer by stage was as follows: 3 patients (6.4%) stage 1A, 2 patients (4.3%) stage 1B, 1 patient (2.1%) stage 2A, 5 patients (% 10.6) stage 2B, 12 patients (25.5%) stage 3, 24 patients (51.1%) stage 4 (**Table 3**).

Table 3. Pancreatic cancer staging chart

Stage	n=47
1A	3 (6.4%)
1B	2 (4.3%)
2A	1 (2.1%)
2B	5 (10.6%)
3	12 (25.5%)
4	24 (51.1%)

The patients were grouped according to their stage as Stage 1-2 (group 1) and Stage 3-4 (group 2). MaR1 (p=0.725), CEA (p=0.142), CA19-9 (p=0.440), total bilirubin (p=0.580) values did not differ significantly between group 1 and group 2. The values of MaR1, CEA, CA19-9, and total bilirubin according to tumor stage of patients diagnosed with pancreatic cancer are summarized in **Table 4**.

Table 4. Distribution of parameters according to tumor stage in pancreatic cancer

Variables	Stage 1-2 n=11	Stage 3-4 n=36	p
CEA, ng/m	17.62 (5.3-20.8)	119.94 (13.8-1000)	0.142*
CA19-9,U/mL	489.27 (0.8-1000)	573.79 (42.-1000)	0.440*
TBIL, µmol/L	3.77 (0.3-5.6)	4.95 (2.8-21.0)	0.580*
Maresin-1, pg/mL	381.31 (99.17-467.18)	372.32 (97.27-741.29)	0.725*

* Mann-Whitney U testi

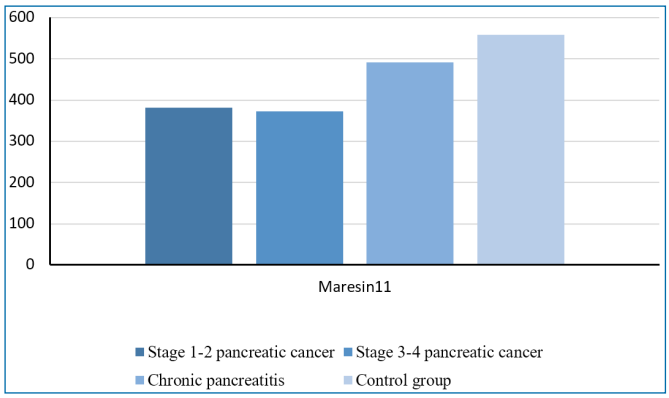

Figure 4. Maresin 1 values by pancreatic cancer stage

The relationship between LDH and MaR1 levels in the pancreatic cancer group was not statistically significant (r=0.286, p=0.051). A negative correlation was found between ALP and MaR1 levels in the control group (r=0.363, p=0.049) (**Table 5**).

Table 5. Relationship between Maresin 1 and other parameters

Variables	Pancreatic cancer n=47		Chronic pancreatitis n=32		Control group n=30	
	r	p	r	p	r	p
Tumor stage	-0.230	0.879	-	-	-	-
Tumor size	-0.340	0.820	-	-	-	-
CEA	0.140	0.347	0.074	0.697	-	-
CA 19-9	0.024	0.873	-0.101	0.593	-	-
FBG	0.018	0.906	0.149	0.416	0.254	0.175
LDH	0.286	0.051	0.015	0.936	0.354	0.055
HGB	-0.084	0.575	0.135	0.460	0.299	0.108
WBC	-0.029	0.849	-0.322	0.362	0.201	0.286
PLT	-0.065	0.662	-0.140	0.443	-0.055	0.771
CRP	0.116	0.429	0.712	0.347	0.246	0.225
AST	0.080	0.595	0.024	0.895	0.144	0.449
ALT	-0.104	0.487	-0.183	0.316	0.129	0.498
ALP	0.066	0.659	-0.030	0.870	0.363	0.049
GGT	0.034	0.821	-0.107	0.561	0.096	0.561
TBIL	-0.152	0.308	-0.036	0.847	-0.266	0.847
DBIL	-0.131	0.379	0.010	0.996	-0.190	0.996
Albumin	0.136	0.362	0.070	0.968	-0.274	0.968

*Spearman korelasyon testi

MaR1 values showed high diagnostic performance in predicting patients with pancreatic cancer compared to the control group (AUC=0.752, 95% CI=0.641-0.844, p<0.001). The threshold value of MaR1 in predicting pancreatic cancer was ≤492.08 with 85.11% sensitivity and 60.00% selectivity. Total bilirubin values showed high diagnostic performance in predicting patients with pancreatic cancer compared to the control group (AUC=0.719, 95% CI=0.605-0.816, p<0.001). ALP values showed high diagnostic performance in predicting patients with pancreatic cancer compared to the control group (AUC=0.946, 95% CI=0.870-0.985, p<0.001). The threshold value of ALP in predicting pancreatic cancer was >111 with 85.11% sensitivity and 96.67% selectivity. GGT values showed high diagnostic performance in predicting patients with pancreatic cancer compared to the control group (AUC=0.899, 95% CI=0.809-

0.956, p<0.001). The threshold value of GGT in predicting pancreatic cancer was >87 with 78.72% sensitivity and 100% selectivity.

The diagnostic performances of MaR1 and total bilirubin in differentiating patients with pancreatic cancer did not differ (AUC=0.752 for MaR1 vs. AUC=0.719 for total bilirubin, p=0.687). GGT showed superior diagnostic performance compared to MaR1 in distinguishing patients with pancreatic cancer (AUC=0.752 for MaR1 vs. AUC=0.899 for total bilirubin, p=0.034).

MaR1 values showed high diagnostic performance in predicting patients with pancreatic cancer compared to the chronic pancreatitis patients (AUC=0.651, 95% CI=0.535-0.754, p=0.017). The threshold value of MaR1 in predicting pancreatic cancer than chronic pancreatitis patients was ≤315.52 with 36.2% sensitivity and 90.62% selectivity.

The diagnostic performances of MaR1 and CEA in differentiating patients with pancreatic cancer did not differ than chronic pancreatitis group (AUC=0.651 for MaR1 vs. AUC=0.827 for CEA, p=0.289). CA19-9 showed superior diagnostic performance compared to MaR1 in distinguishing patients with pancreatic cancer (AUC=0.651 for MaR1 vs. AUC=0. 978 for CA19-9, p<0.001).

DISCUSSION

Chronic pancreatitis is a fibrotic process with recurrent attacks that is difficult to treat. Macrophage infiltration is important in the progression of fibrosis and is an important risk factor in the development of pancreatic cancer.[10-12]

MaR1 has been shown to reduce macrophage infiltration and fibrosis development in chronic pancreatitis. This current study supports the studies in the literature. When 32 patients with chronic pancreatitis were compared with 30 healthy control groups, the mean MaR1 level was found to be 491.39 (252.66-949.28) in the chronic pancreatitis group, while it was 558.53 (286.94-886.68) in the healthy control group. However, no significant difference was found between the groups (p=0.370). The small sample size may have affected the statistical significance, but it was thought that MaR1 would be a marker in predicting inflammation.

In the study by Yingying Lu et al.[13] published in 2021, an acute and chronic pancreatitis model was developed on experimental animals, and the effect of MaR1 replacement was investigated. Acute pancreatitis was induced by Caurelein injection. The chronic pancreatitis model was obtained with 50 µg/kg caerulein injection 5 days a week for 4 weeks. 5 groups were formed as control, caurelein, caurelein+0.2 ng/mouse, caurelein+2 ng/mouse, caurelein+10 ng/mouse. Mice with acute pancreatitis given MaR1 showed reduced edema, inflammation, and necrosis in pathological examination compared to mice with acute pancreatitis not given control MaR1. Caerulein stimulation of the pancreas in mice developed acute pancreatitis. Chronic pancreatitis was created when this stimulation became permanent. It was determined that fibrosis and macrophage infiltration were significantly less in the chronic pancreatitis group given 2 ng/dl MaR1 compared to the Caurelein group.

In a previous study by Jung et al.[14] where MaR1 replacement was given to mice on a fatty diet, hepatic steatosis was reduced as a result of adenosine monophosphate-activated protein kinase / sarcoendosplasmic reticulum calcium ATPase 2b (AMPK/SERCA2b)-mediated reduction of stress in the endoplasmic reticulum (ER).

In a study by Morris et al.[15] including 73 pancreatic cancer patients, 115 patients with chronic pancreatitis, and 19 patients with cholangiocellular carcinoma, CA19-9 levels were reported to be significantly higher in malignant diseases than in benign diseases. Median values were calculated as 653 U/ml for pancreatic cancer, 19 U/ml for chronic pancreatitis, and 408 U/ml for cholangiocellular carcinoma. In the differentiation of benign and malignant pathologies, a cut-off point of 70.5 U/ml was determined, with a sensitivity of 82.1% and a specificity of 81.3%. In our study, CEA, CA 19-9 and MaR1 levels were compared in patients diagnosed with pancreatic cancer and chronic pancreatitis. CEA and CA 19-9 levels were found to be significantly higher in patients with pancreatic cancer. In ROC analysis, there was a significant difference between the areas under the curve. The cutoff point for the CA 19-9 value was determined as 100 U/ml, the sensitivity was determined as 82.98% and the specificity as 100%.

In a study conducted by Gu et al.[16] through developing sepsis models on mice, it was determined that after MaR1 replacement with the obstruction method in the cecum, the cytokine levels involved in inflammation decreased through the lipoxin A4 receptor/cyclic adenosine monophosphate/ reactive oxygen species (ALX/cAMP/ROS) activation, and a significant regression was observed in developing lung damage.

To the best of our knowledge, this is the first clinical study in the literature investigating the relationship between serum MaR1 levels in patients with pancreatic cancer. In our study, 47 patients with pancreatic cancer, 32 patients with a diagnosis of chronic pancreatitis, and 30 healthy individuals as a control group were included. The mean age of pancreatic cancer patients was higher than that of chronic pancreatitis and healthy controls, this was consistent with the occurrence of the disease in advanced age. However, age distributions were similar between chronic pancreatitis and the healthy group.

The diabetes rate in patients with pancreatic cancer was found to be higher when compared to patients with chronic pancreatitis, which is consistent with the literature.[17-20]

MaR1 level was significantly lower in patients diagnosed with pancreatic cancer compared to chronic pancreatitis and healthy control groups. However, MaR1 levels of patients did not differ according to tumor stage. ROC analysis showed that MaR1 has high sensitivity and selectivity in differentiating pancreatic cancer patients from chronic pancreatitis and healthy controls (85.11% for sensitivity, %60 for specificity, and MaR1 ≤492.08 for cutoff point). Although the MaR1 level was observed to be low in chronic pancreatitis patients compared to the control group, it was not significant. These results suggested that MaR1 could be used as a biomarker to predict inflammation in patients with pancreatic cancer and chronic pancreatitis.

The strengths of our study are the exclusion of patients who had used a food supplement containing omega-3 PUFA, NSAIDs or consumed fish in the last 1 week prior to the study. An important limitation of this study was the inability to measure MaR1 measurements at the tissue level and the low sample size.

CONCLUSION

In our study, we evaluated the role of MaR1 in the pathogenesis of pancreatic cancer. We compared it with the tumor markers CA 19-9 and CEA. According to our literature review, this is the first clinical study showing the relationship between pancreatic cancer and MaR1. MaR1 can be a marker for distinguishing patients with pancreatic cancer from chronic pancreatitis and healthy control groups. It has been shown that it can predict inflammation in patients with chronic pancreatitis. Prospective studies with more patients and longer follow-ups are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: This thesis study was carried out with the permission of Kırıkkale University Faculty of Medicine Clinical Researches Ethics Committee (Date: 05.10.2021, Decision No: 16/01).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

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