EXPERIMENTAL STUDY

Changes in cytokines and chemokines in an acute pancreatitis model

Erdem Kınacı,[1] Mert Mahsuni Sevinc,[2] Anil Demir,[2] Emre Erdogan,[3] Fatih Alper Ahlatci,[4] Ufuk Oguz Idiz[2]

[1]Department of Liver Transplantation and HPB Surgery, Basaksehir Cam and Sakura City Hospital, İstanbul-*Türkiye*
[2]Department of General Surgery, Istanbul Training and Research Hospital, İstanbul-*Türkiye*
[3]Ercis Martyr Ridvan Cevik State Hospital, Van-*Türkiye*
[4]Depatment of Pathology, Corlu State Hospital, Tekirdag-*Türkiye*

ABSTRACT

BACKGROUND: The immune response secondary to inflammation that develops in acute pancreatitis plays an important role in the clinical course of the disease. This study aims to evaluate the changes in various cytokines and chemokines according to the severity of pancreatitis.

METHODS: Twenty-one female Wistar albino rats were divided into three equal groups. The control group received no intervention. Intraperitoneal cerulein was administered to the other groups once per hour for five hours at doses of 50 μg/kg and 80 μg/kg for the mild and severe pancreatitis groups, respectively. The development of pancreatitis and its severity level were confirmed by histological evaluation after euthanization. Blood samples were taken from all rats to measure levels of Interleukin-10 (IL-10), Interferon gamma (IFN-γ), C-X-C Motif Chemokine Ligand 1 (CXCL-1), Monocyte Chemoattractant Protein-1 (MCP-1), Tumor Necrosis Factor alpha (TNF-α), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), IL-18, IL-12p70, IL-1β, IL-17A, IL-33, IL-1α, and IL-6. Additionally, the Schoenberg inflammation scores of pancreatic tissues were evaluated.

RESULTS: The acute pancreatitis model was successfully induced in all cases within the study groups, according to histopathological examination. It was found that the levels of CXCL-1, MCP-1, and IL-6 were statistically significantly higher in rats with pancreatitis, with these parameters being elevated in the group with severe pancreatitis. In correlation analyses, MCP-1 and IL-6 showed a moderate correlation with the severity of pancreatitis.

CONCLUSION: CXCL-1, MCP-1, and IL-6 exhibit predictive characteristics for the occurrence and clinical course of pancreatitis. Our results highlight the production and working pathways of these cytokines as potential targets for therapeutic intervention.

Keywords: Acute pancreatitis; severity; cytokine; chemokine; cerulein.

INTRODUCTION

The clinical course of acute pancreatitis (AP) varies widely, ranging from asymptomatic cases to multi-organ failure and, in severe cases, death. Accurately predicting the course and severity of AP is a significant challenge for clinicians. Objective findings are essential for evaluating the severity of AP.[1,2]

The etiological spectrum of AP is broad, with cellular damage initiated by inflammatory pathways in the acinar cells of the pancreas, primarily due to the inappropriate activation of proenzymes produced and stored in the normal acinar cells.[3]

Numerous experimental studies have investigated the pathophysiology of AP, focusing on the examination of serum cytokine levels. These studies highlight the involvement of various

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Address for correspondence: Erdem Kınacı
Department of Liver Transplantation and HPB Surgery, Basaksehir Cam and Sakura City Hospital, İstanbul, Türkiye
E-mail: erdemkinaci@gmail.com

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inflammatory cells, including macrophages, neutrophils, and lymphocytes, as well as proinflammatory cytokines such as Interleukin-1 (IL-1), IL-6, IL-8, and Tumor Necrosis Factor alpha (TNF-α).[4] The activation of macrophages and the secretion of cytokines in AP have been correlated with the severity of inflammation. Experimental models have shown elevated serum levels of IL-1 and TNF-α, while antagonists for these cytokines demonstrate potential in reducing the severity of AP. Another proinflammatory cytokine, IL-6, peaks within 24-48 hours following the onset of AP. Meanwhile, IL-8, acting as a chemokine, is associated with the severity of inflammation.[5]

Various scoring systems and laboratory markers have been utilized to assess the severity of AP. Although several markers possess potential predictive value, most are impractical for routine use due to their insufficient predictive accuracy. Examples of these markers include C-reactive protein (CRP), blood urea nitrogen (BUN), serum creatinine, urinary trypsinogen activation peptide, procalcitonin, polymorphonuclear elastase, pancreatic-associated protein, serum amylase, lipase, calcium, procarboxypeptidase-B, procarboxypeptidase-B activator, trypsinogen 2, phospholipase A2, serum amyloid protein-A, substance-P, antithrombin III, platelet-activating factor, IL-1, IL-6, IL-8, TNF-α, soluble TNF receptor, and angiopoietin-2.[6-11] Despite extensive research, the search for a highly predictive marker continues. In this study, we aimed to investigate multiple inflammatory parameters that have previously been studied individually, in a comprehensive analysis to compare their predictive power.

MATERIALS AND METHODS

This study received approval from the Local Ethics Committee for Animal Experiments at XXX University (Approval Number: 2021/19), adhering to the regulations outlined in the Declaration of Helsinki for the care and use of laboratory animals.

Twenty-one female Wistar albino rats, with an average weight of 385 grams and an average age of nine months, were divided into three equal groups. The rats were housed in standard plastic cages covered with iron wire netting and fed a specialized pellet-type feed formulated for small experimental animals.

The first group was designated as the control group, receiving no intervention. In the second group, 50 μg/kg of cerulein was administered intraperitoneally once per hour for a total of five times, designated as the mild pancreatitis group. Similarly, for the severe pancreatitis group, 80 μg/kg of cerulein was administered intraperitoneally once per hour for a total of five times. The development of pancreatitis and its severity were confirmed by histological evaluation post-euthanasia. Eight hours after the injection of cerulein, blood samples were taken from all rats and centrifuged. The levels of plasma IL-10, Interferon gamma (IFN-γ), C-X-C Motif Chemokine Ligand 1 (CXCL-1), Monocyte Chemoattractant Protein-1 (MCP-1), TNF-α, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), IL-18, IL-12p70, IL-1β, IL -17A, IL-33, IL-1α, and IL-6 were measured using flow cytometry (Cube 8™, Sysmex, Japan, cat. no. CY-S-3068R_V3) with a cytokine and chemokine measurement kit (LEGENDplex™ Rat Inflammation Panel, Biolegend, USA, cat. no. 740251). Subsequently, a laparotomy was performed on all animals, and pancreatic tissues were collected for histopathological examination to confirm the AP model. Pancreatitis status was evaluated under 100x magnification stained with Hematoxylin & Eosin. Additionally, Schoenberg's score[12] for pancreatitis was calculated for each group to demonstrate the severity of AP. After the laparotomy, rats were euthanized by cervical dislocation.

Statistical Analysis

A power analysis was conducted considering a type I error of 0.05 and a power of 0.8. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0. The distribution of variables was assessed with the Kolmogorov-Smirnov test. The Kruskal-Wallis test was employed for independent and non-normally distributed data. For normally distributed data with significant differences in the analysis, the Tukey test was used for homogeneous variances, and the Tamhane's T2 test was used for inhomogeneous variances as a post hoc analysis. For non-normally distributed data, the Mann-Whitney U test was applied for two-group comparisons following the Kruskal-Wallis test. The Chi-square test and Fisher's Exact Test were used for qualitative data. The Pearson correlation coefficient (0.00-0.19: very weak, 0.20-0.39: weak, 0.40-0.59: moderate, 0.60-0.79: strong, 0.80-1.0: very strong) was utilized for correlation analysis according to disease severity.

RESULTS

The comparisons of mean values of cytokines and chemokines between the rats with and without AP are presented in Table 1. Additionally, changes according to the severity of AP are outlined in Table 2. There were no significant changes in the levels of IL-10, IFN-γ, TNF-α, GM-CSF, IL-18, IL-12p70, IL-1β, IL -17A, IL-33, and IL-1α according to both the presence and severity of AP.

CXCL-1, MCP-1, and IL-6 levels were significantly higher in rats with AP, as indicated in Table 1. When the three groups were subjected to statistical analysis together, changes in CXCL-1, MCP-1, and IL-6 levels were significantly different between the groups (p-values: 0.001, 0.009, and 0.006, respectively) (Table 2). In the subgroup analysis, CXCL-1 levels were significantly higher in the mild-AP group compared to the control group and were also significantly higher in the severe-AP group compared to the mild-AP group, with p-values of 0.008 and 0.003, respectively. However, for MCP-1 and IL-6, there was no significant difference between the control group and the mild-AP group, while the differences between the severe-AP group and the mild-AP group were significant (p=0.008 for MCP-1 and p=0.004 for IL-6).

Table 1. Changes in cytokine and chemokine levels in animals with acute pancreatitis

	Control Group (n=7)	Pancreatitis Group (n=14)	P value
IL-10 pg/ml (median-IQR)	0.57-0.00	0.57-0.02	0.198
IFN-γ pg/ml (median-IQR)	1.95-0.00	1.95-0.10	0.198
CXCL-1 pg/ml (median-IQR)	4.97-2.21	159.30-261.54	<0.001
MCP-1 pg/ml (median-IQR)	1584.32-324.32	2367.22-2122.45	0.002
TNF-α pg/ml (median-IQR)	1.95-0.00	1.95-0.00	1.000
GM-CSF pg/ml (median-IQR)	17.38-0.00	17.38-0.00	1.000
IL-18 pg/ml (median-IQR)	10.06-0.00	10.06-0.00	0.480
IL-12p70 pg/ml (median-IQR)	1.75-0.00	1.75-0.00	1.000
IL-1β pg/ml (median-IQR)	6.84-0.00	6.84-0.00	1.000
IL-17A pg/ml (median-IQR)	1.56-0.00	1.56-0.00	1.000
IL-33 pg/ml (median-IQR)	6.55-0.00	6.55-0.00	0.306
IL-1α pg/ml (median-IQR)	1.60-0.00	1.60-0.94	0.586
IL-6 pg/ml (median-IQR)	2.27-0.00	26.86-53.22	0.005

Table 2. Changes in cytokine and chemokine levels by pancreatitis severity

	Control Group (n=7)	Mild Pancreatitis (n=7)	Severe Pancreatitis (n=7)	P value
IL-10 pg/ml (median-IQR)	0.57-0.00	0.57-0.36	0.57-0.00	0.296
IFN-γ pg/ml (median-IQR)	1.95-0.00	1.95-0.40	1.95-0.00	0.365
CXCL-1 pg/ml (median-IQR)	4.97-2.21	60.46-568.53	160.85-144.03	0.001
MCP-1 pg/ml (median-IQR)	1584.32-324.32	1990.90-2369.51	2744.45-1533.92	0.009
TNF-α pg/ml (median-IQR)	1.95-0.00	1.95-0.00	1.95-0.00	0.990
GM-CSF pg/ml (median-IQR)	17.38-0.00	17.38-0.00	17.38-0.00	1.000
IL-18 pg/ml (median-IQR)	10.06-0.00	10.06-0.00	10.06-0.00	0.368
IL-12p70 pg/ml (median-IQR)	1.75-0.00	1.75-0.00	1.75-0.00	1.000
IL-1β pg/ml (median-IQR)	6.84-0.00	6.84-0.00	6.84-0.00	1.000
IL-17A pg/ml (median-IQR)	1.56-0.00	1.56-0.00	1.56-0.00	1.000
IL-33 pg/ml (median-IQR)	6.55-0.00	6.55-0.00	6.55-0.00	0.589
IL-1α pg/ml (median-IQR)	1.60-0.00	1.60-3.75	1.60-2.46	0.735
IL-6 pg/ml (median-IQR)	2.27-0.00	2.27-49.95	29.98-144.34	0.006

Histopathological appearances in a sample from each group are shown in Figure 1. The AP model was successfully induced in all cases within the study groups, according to histopathological examination. The median Schoenberg scores for the control group, the mild, and the severe pancreatitis groups were 1 (range 0-1), 5 (range 4-5), and 9 (range 8-11), respectively. Histopathological examination results showed that the AP model was induced with appropriate severity levels in each group. The correlation between Schoenberg scores and changes in the levels of cytokines and chemokines was examined. The correlation map is shown in Figure 2. It was determined that MCP-1 and IL-6 showed a moderate correlation with the severity of pancreatitis (r=0.56 and r=0.51, respectively).

DISCUSSION

Immune dysregulation in AP can lead to hyperinflammation, systemic inflammatory response syndrome (SIRS), and multi-organ dysfunction syndrome (MODS).[13] An intense proinflammatory response causes the clinical manifestations of SIRS and MODS, or multi-organ failure (MOF). This robust proinflammatory response triggers the clinical manifestations of SIRS and MODS, followed by a compensatory anti-inflammatory response syndrome (CARS), characterized by decreased levels of IFN-γ and an increase in anti-inflammatory cytokines such as IL-10 and Transforming Growth Factor Beta (TGF-β).[14] Numerous mediators are involved in the complex mechanisms underlying the development of

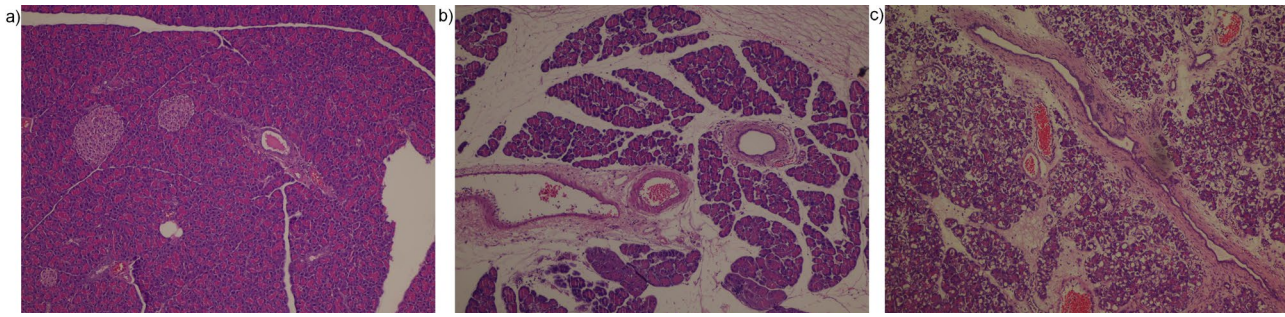

Figure 1. Histopathologic images of pancreatitis stained with Hematoxylin & Eosin x100 magnification **(a)** control group, **(b)** mild pancreatitis, **(c)** severe pancreatitis).

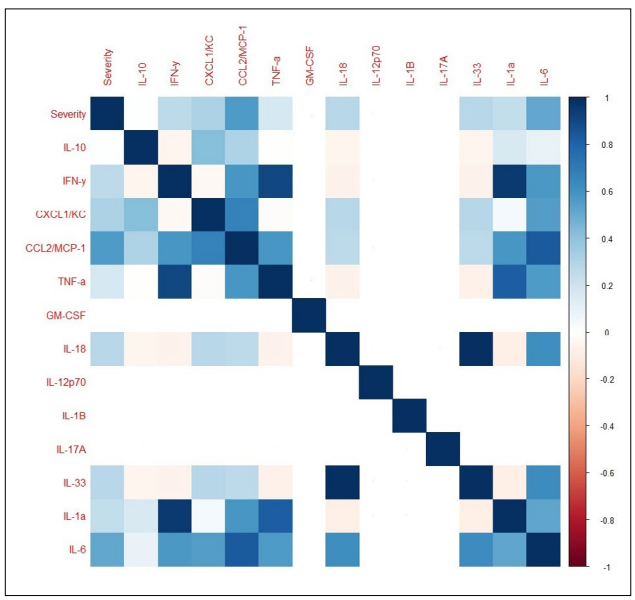

Figure 2. Correlation heatmap of cytokines and chemokines according to the severity of pancreatitis.

AP. Studies related to the effects of these mediators, their predictive values, and their potential as treatment pathways are ongoing. Our study focused on 13 mediators and revealed that CXCL-1, MCP-1, and IL-6 were significant in diagnosing AP and predicting its severity.

MCP-1, a chemokine involved in almost all inflammatory processes, emerges as a major player in AP, exhibiting a correlation with its severity. Pancreatic satellite cells have been identified as the primary source of MCP-1 during pancreatic inflammation.[15-18] These cells not only secrete MCP-1 but also release cytokines and chemokines during an oxygen burst in developing AP, presenting a potential target for drugs aimed at mitigating pancreatitis.[19] MCP-1 was also one of the significant chemokines in our study. According to our results, it seems logical to focus on molecules that target the MCP-1 pathway.

CXCL-1 plays a crucial role in inflammatory reactions by serving as a chemoattractant for neutrophils through the CXCR2 receptor.[20] Despite limited literature on the association between CXCL-1 and AP, we identified two relevant studies. In one study, CXCL-1 messenger ribonucleic acid (mRNA) expression was observed to increase up to 8-fold in pancreatic acinar cells of an ex vivo pancreatitis model.[21] In another study, elevated serum CXCL-1 levels were noted in a cerulein-induced pancreatitis model in mice.[22] Our study's findings align with these results, indicating a significant role for CXCL-1 in both diagnosing AP and assessing its severity in our model.

IL-6 is employed in certain centers to identify patients at risk of developing severe AP.[23] While numerous studies have documented elevated serum levels of IL-6 in complicated AP, the reported increases vary significantly across studies. Consequently, establishing a definitive cutoff value for IL-6 to predict the severity of AP proves challenging. A recent meta-analysis of clinical studies acknowledged the predictive value of IL-6 in determining the severity of AP. However, the analysis emphasized the difficulty in defining a precise cutoff value for this purpose.[24] Consistent with these findings, our results indicate a significant elevation in IL-6 levels for both diagnosing AP and predicting its severity.

Elevated IL-1 has been consistently reported in AP, with numerous studies highlighting the pivotal role of IL-1 and IL-1 receptors in its pathogenesis.[25,26] It has been shown that IL-1 receptor gene-deficient mice or treatment with an IL-1 receptor antagonist have demonstrated regression in cerulein-induced chronic pancreatitis in mice.[26] The IL-1 converting enzyme (ICE) is responsible for secreting IL-1β from pro-IL-1β. In the experimental pancreatitis model, the ICE inactivator has shown a reduction in histological grading and death rates associated with AP.[27] Additionally, elevated IL-1β serum levels have been associated with the development of AP.[28] In our study, contrary to the findings in the literature, no significant increase was found in the levels of IL-1α and IL-1β in rats with AP. Furthermore, no correlation was observed between the severity of pancreatitis and the levels of IL-1α and IL-1β.

TNF-α, a key player in inflammation, is released from damaged pancreatic cells and varying immune system cells, triggering the release of other cytokines, such as IL-6 and IL-8, as a direct response.[29] Most studies have associated higher serum TNF-α levels with the severity of AP.[30,31] However, a contrasting perspective is presented by Paajanen et al., who

concluded that peripheral blood TNF-α concentration has no clinical value in assessing the severity of AP.[32] Similar conflicting data are also available for MCP-1, a chemokine, in a relatively small number of studies in the literature. In one study, chemokines such as MCP-1 and MCP-3, which are related to monocyte trafficking, and cytokines such as IL-6, IL-10, and IL-15, which play roles in inflammation, were significantly increased in patients with severe AP. However, TNF- α has been reported to be unchanged in the same study.[33] On the other hand, in another study evaluating peripheral blood cytokines in patients with AP, serum levels of IL-2, IFN-γ, TNF-α, IL-4, IL-5, and IL-10 were significantly increased in all forms of AP, with the highest values found in severe AP.[34] In our study, the values of IFN-γ and TNF-α were almost the same in both the control group and the AP group, and they had no significant relation with the severity of pancreatitis. According to our results, it appears that IFN-γ and TNF-α have no value in the diagnosis or in predicting the severity of AP. However, consistent with data available in the literature and mentioned above, our study found an increase in MCP-1 levels associated with the severity of AP.

In addition to the aforementioned parameters, IL-18, IL-33, and IL-10 were also included in our study. There was no observed correlation between changes in the blood levels of these three cytokines and the presence or severity of AP, according to our results. IL-18, a member of the IL-1 family of cytokines, plays a role in various aspects of the innate and adaptive immune systems, sharing some features with IL-1β.[35] The literature suggests an increase in IL-8 levels in patients with acute and chronic pancreatitis, with higher levels associated with more severe AP.[36,37] IL-33, also a newer member of the IL-1 cytokine superfamily, binds to a complex mediating the function of the ST2L/IL1 receptor helper protein.[14] While various studies highlight the crucial role of IL-33 in the pathogenesis of chronic pancreatitis and possibly pancreatic cancer, there are limited studies on its role in AP. An experimental study, however, found that IL-33 activates acinar cell proinflammatory pathways and exacerbates acute pancreatic inflammation in mice.[38] IL-10, produced by activated immune cells such as monocytes/macrophages, Treg, and Th cells,[39] is known to have a protective role. IL-10 gene-deficient mice exhibit an increased inflammatory response and lung damage during acute and chronic pancreatitis.[40] In an experimental AP model, a reduction in lung injury and mortality was achieved with IL-10 agonist treatment.[41] IL-10 was also found to be related to the severity of AP.[42] In studies based on various rodent models of AP, IL-10 has been reported to reduce serum amylase, serum lipase, pancreatic edema, necrosis, and bleeding levels by decreasing the production of inflammatory cytokines from macrophages.[43] However, our study found no relationship between IL-10 levels and either the occurrence of pancreatitis or its severity.

The primary limitation of our study lies in its reliance on a rat model. Ethical considerations constrained our study to a limited number of rats. The nature of the animal research prevented daily monitoring of blood value changes, precluding a correlation with clinical findings. Additionally, variability in the lower limit of blood values, depending on the laboratory, can be regarded as a limitation.

CONCLUSION

Our study underscores the undeniable role of the immune system in AP. The immune components, including cytokines and chemokines, contribute not only to the onset of AP but also play a pivotal role in determining its continuation and the severity of inflammation. Our results highlight the association of CXCL-1, MCP-1, and IL-6 with the occurrence of pancreatitis and its severity. All three components are part of the innate immune system and actively participate in the early phases of inflammation. Consequently, the pathways involving the activity of CXCL-1, MCP-1, and IL-6 merit further investigation as potential targets for preventing severe AP and its complications.

Ethics Committee Approval: This study was approved by the Bezmialem Foundation University Ethics Committee (Date: 22.02.2021, Decision No: 2021/19).

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DENEYSEL ÇALIŞMA - *ÖZ*

Akut pankreatit modelinde sitokin ve kemokinlerdeki değişimler

Erdem Kınacı,[1] Mert Mahsuni Sevinc,[2] Anil Demir,[2] Emre Erdogan,[3] Fatih Alper Ahlatci,[4] Ufuk Oguz Idiz[2]

[1]Başakşehir Çam ve Sakura Şehir Hastanesi, Karaciğer Nakli ve HPB Cerrahisi Kliniği, İstanbul, Türkiye
[2]İstanbul Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul, Türkiye
[3]Erciş Şehit Rıdvan Çevik Devlet Hastanesi, Genel Cerrahi Kliniği, Van, Türkiye
[4]Çorlu Devlet Hastanesi, Patoloji Depatmanı, Tekirdağ, Türkiye

AMAÇ: Akut pankreatitte gelişen inflamasyona sekonder immün yanıt, pankreatitin klinik seyrinde önemli rol oynamaktadır. Bu çalışmanın amacı pankreatit şiddetine göre çeşitli sitokin ve kemokinlerdeki değişiklikleri birlikte ortaya koymaktır.

GEREÇ VE YÖNTEM: Yirmi bir adet Wistar dişi albino sıçan üç eşit gruba ayrıldı. Kontrol grubuna herhangi bir müdahale yapılmadı. Hafif ve şiddetli pankreatit gruplarına sırasıyla 50 µg/kg ve 80 µg/kg dozlarında beş saat boyunca saatte bir kez intraperitoneal cerulein uygulandı. Pankreatit gelişip gelişmediği ve varsa şiddet düzeyi sakrifikasyon sonrası histolojik değerlendirme ile doğrulandı. Tüm sıçanlardan kan örnekleri alındı ve IL-10, IFN-γ, CXCL-1, MCP-1, TNF-a, GM-CSF, IL-18, IL-12p70, IL-1β, IL-17A, IL-33, IL-1α, IL-6 düzeylerine bakıldı. Ayrıca pankreas dokularının Schoenberg inflamasyon skorları da değerlendirildi.

BULGULAR: Histopatolojik incelemeye göre çalışma gruplarının tüm vakalarında akut pankreatit modeli başarıyla sağlandı. Pankreatitli sıçanlarda CXCL-1, MCP-1 ve IL-6 parametrelerinin istatistiksel olarak anlamlı derecede yüksek olduğu, şiddetli pankreatitli sıçanlarda ise CXCL-1, MCP-1 ve IL-6 parametrelerinin istatistiksel olarak anlamlı derecede yüksek olduğu belirlendi. Korelasyon analizinde MCP-1 ve IL-6 pankreatit şiddeti ile orta düzeyde korelasyon göstermektedir.

SONUÇ: CXCL-1, MCP-1 ve IL-6, pankreatit gelişimi ve seyrinin nasıl olacağını göstermede anlamlı görülmüştür. Bu sitokinlerin üretim ve etki yolakları akut pankreatitin medikal tedavisi için potansiyel hedefler olarak değerlendirilebilir.

Anahtar sözcükler: Akut pankreatit; kemokin; sitokin; serulein; şiddet.

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