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■ Research Article

Relationship between the severity of acute pancreatitis and vitamin D level in geriatric patient population

Geriatrik hasta popülasyonunda akut pankreatit şiddeti ile D vitamini düzeyi arasındaki ilişki

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Abstract

Aim: It is important to determine the severity of acute pancreatitis (AP) and its prognosis. The aim of this study is to research the efficiency of vitamin D level on the severity of acute pancreatitis in geriatric population.

Material and Methods: Files of 4108 patients were analyzed retrospectively. Serum vitamin D levels of total 404 patients (geriatric 160 (n:160); non-geriatric 244 (n:244)) were compared between mild, moderate and severe groups according to revised Atlanta classification for acute pancreatitis. Relationship between the severity of acute pancreatitis and vitamin D levels were analyzed.

Results: No significant difference was observed in non-geriatric patients in terms of vitamin D levels according to the Atlanta classification for acute pancreatitis. However, there were significant differences both between mild and moderate groups and between moderate and severe groups in geriatric patients ($p < 0.005$). AP was more severe in patients with a low vitamin D level ($p < 0.005$).

Conclusion: We have concluded that vitamin D levels may be insufficient to predict the severity of acute pancreatitis considering age factor, which is a substantial indicator of its prognosis. Vitamin D levels have been found out to be efficient in the severity of disease in geriatric acute pancreatitis patients compared to non-geriatric ones.

Keywords: Acute pancreatitis, Atlanta classification, geriatric population, vitamin D

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Öz

Amaç: Akut pankreatitin (AP) şiddetini ve prognozunu belirlemek önemlidir. Bu çalışmanın amacı geriatrik popülasyonda D vitamini düzeyinin akut pankreatitin şiddeti üzerindeki etkinliğini araştırmaktır.

Gereç ve Yöntemler: 4108 hastanın dosyaları retrospektif olarak analiz edildi. Toplam 404 hastanın (geriatrik 160 (n:160); geriatrik olmayan 244 (n:244)) serum D vitamini düzeyleri akut pankreatit için revize Atlanta sınıflamasına göre hafif, orta ve şiddetli gruplar arasında karşılaştırıldı. Akut pankreatitin şiddeti ile D vitamini düzeyleri arasındaki ilişki analiz edildi.

Bulgular: Akut pankreatit için Atlanta sınıflamasına göre D vitamini düzeyleri açısından yaşlı olmayan hastalarda anlamlı bir fark gözlenmedi. Ancak, geriatrik hastalarda hem hafif ve orta gruplar arasında hem de orta ve şiddetli gruplar arasında anlamlı farklılıklar vardı ($p < 0,005$). D vitamini düzeyi düşük olan hastalarda AP daha şiddetli idi ($p < 0,005$).

Sonuç: Prognozun önemli bir göstergesi olan yaş faktörü göz önüne alındığında, D vitamini düzeylerinin akut pankreatitin şiddetini öngörmeye yetersiz olabileceği sonucuna vardık. D vitamini düzeylerinin geriatrik akut pankreatit hastalarında geriatrik olmayanlara kıyasla hastalığın ciddiyetinde etkili olduğu bulunmuştur.

Anahtar Kelimeler: Akut pankreatit, Atlanta sınıflandırması, geriatrik popülasyon, D vitamini

Introduction

Acute pancreatitis (AP) is an inflammatory process progressing with clinical, morphological, and functional changes. The cell injury due to early activation of pancreatic proteases, constitutes the basic pathophysiology of acute pancreatitis (1).

The prevalence of AP, which is associated with high mortality and morbidity, is increasing all over the world. The annual AP incidence reported in the USA varies from 4.9 to 35 per 100,000 population (2,3). Gallstones and alcohol are the most common reasons of AP (4).

Most of AP attacks are mild and self-limited and are manageable with symptomatic treatment. A serious clinical condition with a higher mortality rate up to 30% may occur in around 20% of the patients (5).

Various scoring methods including clinical, laboratory and radiological criteria have been developed in order to determine the severity of the disease in patients at risk and to determine the treatment correctly. Various scoring methods including clinical, laboratory, and radiological criteria have been developed in order to determine the severity of the disease in patients at high risk and to decide on the treatment approach. Ranson criteria, Imrie scoring system (Modified Glaskow 2), Acute Physiology and Chronic Health Evaluation II (APACHE II), Tomography Severity Index (CTSI), Bedside Index of Severity in Acute Pancreatitis (BISAP), Balthazar Score (BT Severity Index), and Atlanta Classification are the most common ones (6). Although each method is separately guiding, they have complicated processes and several challenges (7).

Atlanta classification based on clinical and radiological features have been defined in 1992 and revised in 2012. The severity of AP is classified as mild, moderate, and severe based on the presence of local complications in CT and that of organ failure (8).

The mechanism contributing to an increase in pancreas injury and pancreatic necrosis is mainly based on hyperinflammation (1). As the information obtained increases, the relationship between ap and metabolic diseases gains importance day by day.

Several recent studies have revealed that serum vitamin D level is closely related to the severity of AP and its prognosis (9-11).

Vitamin D is a biomarker having receptors in many organs of human body, which plays an important role on most diseases including diabetes mellitus (DM), cardiovascular diseases, cancer, infectious diseases, and otoimmune diseases. Vitamin D deficiency is commonly accepted as serum 25-hydroxyvitamin D level (25OHD) < 10 ng/ml (< 25 nmol/l) because lower values are associated with rickets and/or osteomalacia. However, values < 20 ng/dl and < 10 ng/dl are defined as insufficiency and deficiency, respectively, by the World Health Organization (WHO) (12). On the other hand according to the Turkish Endocrine and Metabolism Society; levels above 20 ng / ml (50 nmol / L) is sufficient for bone health, levels between 30 and 50 ng / ml (75-125 nmol / L) are sufficient for extra-bone effects. And while the levels between 10 and 20 ng / ml (25-50 nmol / L) are considered as vitamin D insufficiency, levels < 10 ng / ml (25 nmol) / L) are considered as vitamin D deficiency (13).

It is estimated that almost 1 billion people around the world have vitamin D deficiency. That there are different outcomes related to vitamin D in different countries, even in different parts of the same country, has been revealed by studies conducted before. It has also been revealed that vitamin D deficiency has been experienced by 40% to 100% of the elderly males and females in Europe and America. This rate is quite high in those people staying at nursing homes. Similarly, that vitamin D deficiency is common in our country has been revealed in some studies.

It is indicated that vitamin D has a great role on innate and acquired immunity. There are several published reports

indicating how it plays a role on the protection of human body against pathogens and also supporting the idea that it may be used for medical purposes in acute and chronic infections. Vitamin D deficiency is also associated with the severity of various diseases. On the other hand, it has been revealed that it has a basic role on defence against antibiotic-resistant pathogens, increases resistance to sepsis in animal models, and speeds up the healing process of epithelial injury.

Based on the effects of macrophages and of T cells on acute pancreatitis prognosis and the process of necrosis, the association between the severity of AP and vitamin D levels have been demonstrated in limited studies (11), and as far as we know, there is no study conducted in geriatric population concerning to this matter in literature.

In this study; We aimed to investigate the potential effect of serum vitamin D level as a predictor for determining the severity of AP in geriatric patients and nongeriatric patients under 65 years of age at the time of admission.

Material and Methods

Files of 4108 patients who were hospitalized in Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Department of Internal Medicine, between the dates of January 2015 and March 2019 were analyzed retrospectively. 404 patients diagnosed with AP who have had a CT scan were included in the study. AP is diagnosed by the presence of the following 2 factors:

1. Abdominal pain,
2. Serum amylase and/or lipase levels more than 3 times the upper limit of normal,
3. Radiological signs

The severity of AP was classified as mild, moderate, and severe based on Atlanta classification for Acute Pancreatitis (14). Vitamin D levels were considered as follows: A level below 10 ng/ml as severe deficiency, between 10 ng/ml and 20 ng/ml as deficiency, and above 20 ng/ml normal (15). Patients were divided into two groups: the geriatric group over 65 years of age and the non-geriatric group under 65 years of age.

Patients under the age of 18, those with a history of pancreatic and patients with chronic or recurrent pancreatitis were excluded from the study. Age, gender, etiologic causes, comorbid diseases, duration of hospitalization, antibiotic use in postpancreatic period and laboratory data of patients were determined (Table 1 and 2). Acute pancreatitis severity and serum vitamin D levels were compared according to Atlanta classification between geriatric and non-geriatric group.

Our study has been approved by Clinical Research Ethics Committee of University of Health Sciences, xxxxxx Training and Research Hospital (Date: September 7, 2020; Decree no: 95/04) and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

SPSS Statistics Version 21.0 (IBM®, Chicago, The USA) was used for statistical analysis of our data. Normality of distribution was checked by a combination of visual inspection (histogram and probability charts) of data points and the analytical method Shapiro-Wilk normality test. Descriptive statistics were expressed as mean and standard deviation in normally distributed numerical data whereas median and minimum-maximum range in those not showing normal distribution. However, descriptive statistics were expressed as numbers and percentages in nominal data. Normally distributed numerical variables were analyzed by "Independent T-test" between two groups, "One-Way ANOVA test" between three groups, and "Paired Sample T-test" within the group. Numerical variables that did not show normal distribution were compared using the "Mann-Whitney U test" between the two groups and the "Kruskal-Wallis test" between the three groups. On the other hand, nominal values between two groups were evaluated using "Chi-Squared" test or "Fisher's Exact test". P-values below 0.05 were accepted as statistically significant in this study.

Results

Mean age of all patients included in this study was 62 years. The mean age for patients under and over the age of 65 was 50 and 77, respectively. Compared with both groups in terms of comorbid diseases; hypertension, DM, and chronic obstructive pulmonary disease (COPD) were seen more in the group above 65 years, although steatosis was more common in the group below 65 years ($p < 0.05$). Cholelithiasis, an etiologic factor of AP, and antibiotic use in post-pancreatic period were found out to be higher in geriatric group ($p < 0.05$). Moreover, the duration of hospitalization in the group above 65 years was 7 days longer than the other one ($p < 0.05$).

A statistically significant difference was found between the geriatric and non-geriatric groups in terms of the ratio of the mild group and the moderate-severe group defined according to the atlanta classification for AP ($p < 0.05$). 72.5% of patients had mild AP and 27.5% had moderate-severe AP in the non-geriatric group whereas the ratios were 57.5% and 42.5% in the geriatric group, respectively ($p < 0.001$). It was observed that the severity of AP had increased in elderly patients. The distribution of the sociodemographic characteristics of the patients according to the age factor is shown in Table 1.

There were also statistically significant differences between the geriatric and non-geriatric groups in terms of the level of change in laboratory values ($p < 0.05$). Calcium, magnesium, and albumin levels were found to be lower whereas Erythrocyte sedimentation rate (ESR), C-Reactive

Protein (CRP), Haemoglobin A1C (HbA1C) and bilirubin levels were found to be higher in the geriatric group compared to nongeriatric group. In the geriatric group; Vitamin D levels were below 10 ng / ml in 86 patients, between 10 and 20 ng / ml in 50 patients and below 10 ng / ml in 24 patients. In the non-geriatric group vitamin D levels were less than 10 ng / ml in 136 patients, between 10-20 ng / ml in 85 patients and were less than 10 ng / ml 23 patients. No statistical significant difference was detected between two groups (p=0.221). The distribution of laboratory parameters of the patients by age factor is demonstrated in Table 2.

Considering the severity of AP, mean age was significantly higher in the moderate-severe group than in the mild group (65 (21-97) and 57.5 (20-98), respectively, p<0.001). Antibiotic usage rate in post-pancreatic period were 28.6% and 60.7%, respectively, in mild and moderate-severe AP (p<0.001). Hospitalization durations were 5.5 (2-19) and 9 (2-29) days in the mild and the moderate-severe groups, respectively (p<0.001). The distribution of the sociodemographic characteristics of the patients according to the severity of AP is shown in Table 3.

ESR, CRP, and parathormone (PTH) were detected to be higher whereas albumin and phosphore levels were detected to

be lower in the moderate-severe group compared to the mild group in the analysis carried out between laboratory parameters and the severity of AP. The difference was statistically significant (p<0.05). No significant relationship between the other parameters and the severity of AP was detected. The distribution of laboratory parameters of the patients according to the severity of AP is demonstrated in Table 4.

66.5% of AP patients constitute the mild group, 30.6% the moderate group and 2.9% the severe group. In non-geriatric group, %72.5 (n:177) of patients constitute the mild group, %26.2 (n:64) the moderate group and %1.3 (n:3) the severe group. No statistically significant data was found regarding the difference in vitamin D levels between mild, moderate and severe groups. However, there was a significant difference between the mild group (%57.5 (n:92)), the moderate group (%37.5 (n:60)) and the severe group (%5 (n:8)) in the geriatric patient group in terms of vitamin D levels (p=0.017). When vitamin D levels of all patients were compared between groups determined according to Atlanta Classification; there were statistically significant differences both between moderate and severe groups and between mild and severe groups. (p<0.005). Relationship between vitamin D levels and the severity of AP is demonstrated in Table 5.

Table 1. Distribution of Sociodemographic Characteristics by Age

Sociodemographic characteristics			All patients (N=404)	< 65 years (N=244)	≥ 65 years (N=160)	P value
Age		Median (min-max) N (%)	60 (20-98)	50 (20-64)	77 (65-98)	
Gender	Female		247 (61.1)	141 (57.8)	106 (66.3)	0.088†
	Male		157 (38.9)	103 (42.2)	54 (33.8)	
Comorbidity		N (%)				
	Hypertension		114 (28.2)	36 (14.8)	78 (48.8)	<0.001†
	Diabetes Mellitus		68 (16.8)	28 (11.5)	40 (25)	<0.001†
	COPD		27 (6.7)	9 (3.7)	18 (11.3)	0.003†
			156 (38.6)	105 (43)	51 (31.9)	0.024†
Etiology		N (%)				
	Cholelithiasis		269 (66.6)	151 (61.9)	118 (73.8)	0.013†
	Drug		19 (4.7)	13 (68.4)	6 (31.6)	0.464 †
			7 (1.7)	5 (75)	2 (25)	0.547†††
CT signs		N (%)				
	Pankreatitis (-)		107 (46.1)	63 (43.8)	44 (50)	0.354†
Pankreatitis (+)		125 (53.9)	81 (56.3)	44 (50)		
Antibiotic use in post pancreatitis stage			166 (38.9)	76 (31.1)	83 (51.9)	<0.001†
Duration of Hospitalization		Median (min-max)	6 (2-29)	6 (2-28)	7 (2-29)	0.001††
Atlanta Classification		N (%)				
	Mild		269 (66.6)	177 (72.5)	92 (57.5)	0.002†
Moderate-severe		135 (33.4)	67 (27.5)	68 (42.5)		

CT:Computerized Tomography; COPD: Cronic Obstructive Pulmoner Disease † Pearson Chi-Squared" test; †† Man Whitney U Test ; ††† Independent Groups T Test; †††† Fisher Exact Testi

Table 2. Distribution of Laboratory Parameters by Age

Laboratory Parameters			All Patients (N=404)	< 65 years (N=244)	≥ 65 years (N=160)	P value
		N (%)				
Vitamin D (ng/dl)	<10		222 (55)	136 (55.7)	86 (53.8)	0.221†
	10-20		135 (33.4)	85 (63)	50 (31.3)	
	>20		47 (11.6)	23 (48.9)	24 (15)	
		Mean±sd				
		Phosforus (mg/dL)	3.0±0.7	3.0±0.7	2.9±0.7	0.348†††
		Median (min-max)				
		Calcium (mg/dL)	9.3 (6.5-12)	9.3 (6.9-11.1)	9.2 (6.5-12)	0.004††
		Triglyceride (mg/dL)	109 (27-3705)	109 (38-3705)	109 (27-312)	0.374††
		CRP (g/L)	56 (2-427)	38 (2.9-427)	74 (2-325)	<0.001††
		ESR (mm/h)	23.5 (1.4-114)	19.5 (1.4-114)	29 (2-95)	<0.001††
		Albumin (g/dL)	3.5 (2.2-5.6)	3.6 (2.6-5.6)	3.4 (2.2-4)	<0.001††
		Magnesium (mg/dL)	1.8 (1.1-3.6)	1.9 (1.5-3.6)	1.8 (1.1-2.3)	0.001††
		HbA1c (%)	5.8 (4.4-19)	5.7 (4.4-19)	6.0 (4.8-14.1)	0.001††
		Amylaz (U/L)	1190 (94-10778)	1230 (94-10778)	1092 (118-5518)	0.145††
		Lypaz (U/L)	3327 (102-26064)	3497 (243-26064)	3135 (102-19025)	0.146††
		Parathormone (ng/L)	50 (1.4-284)	43 (1.4-284)	58.5 (3-276)	<0.001††

CRP:C-Reactive Protein; HbA1C: Haemoglobin A1C; ESR: Erythrocyte sedimentation ratio. † Pearson Chi-Squared" test, †† Man Whitney U Testi ; ††† Independent Groups T Testi;

Table 3. Distribution of Sociodemographic Characteristics by Severity of Acute Pancreatitis

			Atlanta Classification		P value
			Mild	Moderate-severe	
Sociodemographic Characteristics					
Age		Median (min-max)	57.5 (20-98)	65 (21-97)	<0.001††
		N (%)			
Gender	Female		165 (61.3)	82 (60.7)	0.907†
	Male		104 (38.7)	53 (39.3)	
		N (%)			
Kombidite	Hypertension		72 (26.8)	42 (31.1)	0.360†
	Diabetes Mellitus		46 (17.1)	22 (16.3)	0.839†
	COPD		17 (6.3)	10 (7.4)	0.680†
	Steatosis		98 (36.4)	58 (43)	0.203†
		N (%)			
Etyology	Cholelithiasis		179 (66.5)	90 (66.7)	0.980†
	Drug		15 (5.6)	4 (3)	0.242†
	Ethanol		5 (1.9)	2 (1.5)	1.000†††
		N (%)			
CT findings	Pankreatit (-)		95 (70.9)	12 (12.2)	<0.001†
	Pankreatit (+)		39 (29.1)	86 (87.8)	
Antibiotic use in post pancreatitis stage			77 (28.6)	82 (60.7)	<0.001†
Duration of Hospitalization		Median (min-max)	6 (2-19)	9 (2-29)	<0.001††

CT:Computerized Tomography; COPD: Cronic Obstructive Pulmoner Disease † Pearson Chi-Squared" test; †† Man Whitney U Test ; ††† Fisher Exact Testi

Table 4: Distribution of Laboratory Parameters by Severity of Acute Pancreatitis

Laboratory Parameters		N (%)	Atlanta Classification		P value
			Mild	Moderate-severe	
Vitamin D (ng/dl)	<10		155 (57.6)	67 (49.6)	0.146†
	10-20		88 (32.7)	47 (34.8)	
	>20		26 (9.7)	21 (15.6)	
		Mean ± sd			
Phosphorus (mg/dL)			3.1±0.6	2.8±0.8	0.007†††
		Median (min-max)			
Calcium (mg/dL)			9.3 (6.5-12)	9.2 (6.9-10.9)	0.219††
Trygliseride (mg/dL)			112 (38-3193)	102 (27-3705)	0.201††
CRP (g/L)			38 (2.9-427)	95 (2-416)	<0.001††
ESR (mm/h)			22 (1.4-114)	27 (2-95)	0.040††
Albumin (g/dL)			3.5 (2.4-5.1)	3.4 (2.2-5.6)	0.011††
Magnesium (mg/dL)			1.9 (1.2-3.6)	1.8 (1.1-2.6)	0.320††
Amylaz (U/L)			1055 (105-10778)	1272 (94-8168)	0.082††
Lipaz (U/L)			3258 (102-26064)	3579 (162-22923)	0.652††

CRP: C-Reaktif Protein; ESR: Erythrocyte sedimentation ratio † Pearson Chi-Squared test; †† Man Whitney U Test; ††† Independent Groups T Test

Table 5. The Relationship Between Vitamin D levels and The Severity of Acute Pancreatitis

		N(%)	Atlanta classification			p value
			Mild (N=269)	Moderate (N=124)	Severe (11)	
<65 age			177 (65.8)	64 (51.6)	3 (27.3)	0.463
≥ 65 age			92 (34.2)	60 (48.4)	8 (72.7)	0.017
		Median (min-max)				
Vitamin D Level (ng/dL)	All patients		9 (0-47)	10.6 (0.6-119.6)	6.8 (2.4-9.4)	A**B*C*
	<65 age		9.4 (2.6-38)	9.8 (1.4-51)	6.3 (6-8.6)	A**B**C**
	≥ 65 age		8.2 (0-47)	12.5 (0.6-119.6)	6.9 (2.4-9.4)	A*B*C**

Pancreatitis

A: Comparison of Mild Group and Moderate Group; B: Comparison of Mild Group and Severe Group; C: Comparison of Mild Group and Severe Group. *-p<0,05; **-p≥0,05. Kruskal Wallis Test was used in comparison of 3 groups and Mann Whitney U Test was used in comparison of 2 groups.

Discussion

Due to the rapid increase in the elderly population all over the world, there is an increase in the incidence, severity and mortality of all diseases in this population. One of these diseases is AP.

The high mortality and morbidity of AP have caused to be conducted more studies to determine its prognosis and to take required precautions. Although there are few publications in the literature showing the relationship between vitamin D and the severity of AP, there is no study conducted in the geriatric population so far (11).

In a prospective study conducted by Bang et al. In patients with acute pancreatitis, vitamin D levels were measured at 0 and 48 hours, and vitamin D levels were shown to decrease in the first 48 hours. This has been attributed to the increased use of vitamin D due to the inflammatory process in AP (9,10). Increased macrophages during inflammation reduce the formation of 1.25 OH vitamin D by decreasing the 25

OH-vitamin D level (16). As a result, hypercalcemia, which exacerbates inflammation is prevented. In this study, a negative correlation of vitamin D level with CRP in AP was shown, and it was suggested that vitamin D could be considered as a negative acute phase reactant.

Hummel et al have revealed that 25 OH-vitamin D and CYP24A1 expressions increase in the inflamed pancreatic tissue (17). On the other hand, El-Mahdy et al demonstrated that etiologic factors may be associated with the severity of AP, and vitamin D receptor (VDR) cannot predict the severity of the disease (5).

In the first and only study conducted by Huh et al. with 242 patients with AP, which investigated the relationship between vitamin D level and the severity of pancreatitis, 28.5% of the patients were found to have vitamin D deficiency and it was found that vitamin D deficiency could be used as an independent factor in predicting severe AP (OR 5.37, 95% CI

1.13-25.57) (11). Although there were mostly elderly people, no distinction was made especially regarding age in the study. Although it differs from other studies in the literature because it takes the age factor as a criterion, when the results of the study are evaluated regardless of age we obtained similar results in our study. On the other hand, we could not detect any relationship with vitamin D levels and the severity of AP in the non-geriatric group considering age factor which has kept in mind that the increase in AP severity may be derived from age factor rather than vitamin D levels. The severity of AP has been detected to be higher in the geriatric population, which has been an expected outcome.

Kara et al have revealed that the severity of AP and duration of hospitalization in geriatric population is higher than in non-geriatric population (18). Similar results have been indicated in the other studies (19-21).

Age factor, various laboratory parameters, and long-term duration of hospitalization is are the most prominent indicators of severe AP (5). Some laboratory parameters such as CRP, procalcitonin, albumin, and lactate dehydrogenase (LDH) have been evaluated in several studies. In compliance with the literature, we have found CRP levels to be higher, and albumin levels to be lower in severe AP (22-24). We have also found a relationship between vitamin D levels and the severity of AP in the geriatric group in particular. The study conducted by Huh et al had been consisting of the elderly patients. The reason of why the relationship between vitamin D levels and the severity of AP has not been detected in the non-geriatric group may be derived from this difference.

Our study has some limitations. First, only one method has been preferred to evaluate the severity of AP, although there are some other methods like RANSON, BISAP, and CTSI. Second, the cause-effect relationship between vitamin D levels and the severity of AP cannot be evaluated due to the retrospective study design of our study.

In conclusion, vitamin D deficiency is more common in the elderly and the levels are affected by many factors such as age, gender, geographical location and race (12,25,26). This may prevent vitamin D from being a prognostic factor for AP. We think that multicenter and prospective studies are needed on the relationship between vitamin D and AP, especially in the geriatric population.

Conclusion

Vitamin D level is a guiding factor for most studies thanks to its being an easily accessible test and its well-known role on inflammation. It is also found out to be associated with the severity

of AP. However, issues such as the fact that vitamin D levels are affected by many factors and the lack of consensus in the world in terms of insufficiency / deficiency, limit making a general inference. Additional studies are needed, especially on elderly patients.

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Declarations

Availability of data and materials: All data are freely available for scientific purposes.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

MT and CG contributed to the conception and design of the work, acquisition, analysis, interpretation of data, drafting, revision, and final approval of the work. All authors had the data access and contributed to the article.

Ethical conduct of research

Research ethics approval dated September 7, 2020 and numbered 95/04 has been received from Clinical Research Ethics Committee of University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital and informed consents have also been taken from all patients in accordance with the Declaration of Helsinki.

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