



The role of Pentraxin-3 and Angiopoietin-1 in the inflammation pathway in chronic kidney disease

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Abstract

Aim: Angiopoietin-1 and Pentraxin-3 are new generation biomarkers in the inflammation pathway that have been studied in CKD and other inflammatory diseases. This study aims to investigate the relationship of Pentraxin-3 and Angiopoietin-1 in the inflammation pathway in chronic kidney disease (CKD).

Materials and Methods: Our study was planned single-center, prospective, cross-sectional study. This study includes 25 healthy volunteers, 29 predialysis cases, 34 cases in routine hemodialysis program. Blood was drawn after 12 hours of fasting. In addition to routine biochemical tests, Pentraxin-3 Angiopoietin-1, 1,25 hydroxy Vitamin D levels were measured. Age and gender parameters, BUN, creatinine, e-GFR values of the cases were recorded.

Results: Pentraxin-3 levels were not statistically significant for all three groups ($p = 0.993$). For angiopoietin-1 levels, statistical significance was found between all three groups ($p < 0.001$). While 25 hydroxy Vit D levels were not statistically significant between all three groups ($p = 0.329$), by comparison with 1,25 dihydroxy Vit D levels, a statistically significant difference was found for all three groups ($p < 0.001$). There was a positive low-level relationship ($r = 0.023$) between creatine and Pentraxin-3, and this relationship was not statistically significant ($p = 0.832$). There is a moderate positive correlation ($r = 0.593$) between creatine and Angiopoietin-1 and this relation is statistically significant ($p < 0.001$). A simple regression model was established for creatine and angiopoietin-1.

Conclusion: Since Pentraxin-3 is accepted as an acute phase reactant in the literature, no significant relationship was found between all groups in our study either. Angiopoietin-1 levels were found to be increased in CKD cases and we found statistically significant results. Angiopoietin-1 can be considered as a useful biomarker for the follow-up and treatment of CKD.



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Introduction

Chronic kidney disease (CKD) is seen as an important public health problem in Turkey and all over the world. The progressive course of the disease leads to the development of the need for renal replacement therapy over time. In addition to causing loss of workforce, this situation also leads to a significant increase in health expenditures. Considering all these reasons, it is important to slow down the progression of CKD [1]. Pentraxin-3 can be considered an acute phase protein. Pentraxin-3 is the most important member of the long pentraxin family, first discovered [2, 3]. Under normal conditions, serum levels are low,

less than $2 < \text{ng/ml}$ in human plasma [4]. Pentraxin-3 is an acute phase reactant similar to C-Reactive Protein in structure and function [5]. In recent studies, Pentraxin-3 level has been associated with increased mortality in patients with vascular diseases [6]. Pentraxin-3 is synthesized in mononuclear phagocytic cells, endothelial cells, myeloid dendritic cells, fibroblasts, smooth muscle cells, and synovial cells. Pentraxin-3 has an important role in regulating the innate immune response. It contributes to the opsonization and clearance of apoptotic and necrotic cells [7].

Angiopoietins are the main regulators of angiogenesis. Angiopoietins take different roles in various steps of pathological and physiological angiogenesis. Apart from angiogenesis, they also have roles in inflammation. Although there

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are 4 isoforms, the best known ones are Angiotensin-1 and Angiotensin-2. Angiotensin-2 triggers inflammation, mediates vascular regression, increased permeability, and angiogenesis. Angiotensin-1 shows anti-inflammatory properties, reduces endothelial cell permeability, increases vascular stability through healing in pericytes, and stimulates the growth of muscle cells in smooth muscles [8].

This study aims to investigate the relationship of Pentraxin-3 and Angiotensin-1 in the inflammation pathway in chronic kidney disease (CKD).

Materials and Methods

Ethical approval was obtained from Ordu University Clinical Research Ethics Committee for our study (Date: 18.02.2021, Decision No: 2021/37). In this study, 29 patients in the predialysis stage, who were diagnosed with CKD, not yet undergoing dialysis, and applied to the nephrology outpatient clinic of our hospital between 01.03.2021 and 31.08.2021 were included in addition to 34 patients who were in the routine hemodialysis program in the hemodialysis unit of our hospital. Finally, 25 healthy volunteers were included in the study among the healthy volunteers who applied to the nephrology outpatient clinic and did not have any abnormality in the examination and physical examination findings. A total of 88 cases were included in our study. At all stages of our study, the Declaration of Helsinki was adhered to. An informed consent form was signed by all subjects who agreed to participate in the study. In the cases included in our study, CKD stages and the amount of albuminuria were defined according to the KDIGO (Kidney Disease Improving Global Outcomes 2012) guideline [9]. In CKD staging, G1 is accepted as GFR (ml/min/1.73m²) ≥ 90 (normal or high), G2; 60-89 (ml/min/1.73m²), G3a; 45-59 (ml/min/1.73m²), G3b; 30-44 (ml/min/1.73m²), G4; 15-29 (ml/min/1.73m²), and G5 is accepted as < 15 (ml/min/1.73m², Kidney failure). Again, the proteinuria level was classified as A1 albumin/creatinine ratio < 30 mg/g, A2, 30-300 mg/g, A3, > 300 mg/g, as stated in the KDIGO guide [7].

Our study was planned as a single-center, prospective, cross-sectional study. Our study did not include patients diagnosed with malignancy, patients under the age of 18 and over the age of 90, patients with acute renal failure, patients who underwent renal transplantation, immunosuppressed patients, patients who received corticosteroid therapy in the last 3 months or still receiving corticosteroid therapy, patients with active infection at the time of admission, patients with chronic inflammatory disease, patients taking immunomodulatory drugs (such as interleukin antagonists), and patients who did not accept the study.

Blood samples were taken from each case after 12 hours of oral intake restriction. Gender and age values of the cases were recorded. Routine biochemical tests are requested from patients who apply to our nephrology outpatient clinic. Routine examinations of biochemical levels; hemogram, glucose, BUN, creatinine, e-GFR values, potassium, calcium, phosphorus, magnesium, uric acid, albumin, C-reactive protein (CRP), spot urine albumin/creatinine (UACR), HbA1c, ferritin, Parathormone (PTH)

Table 1. Gender comparison by groups

Group	Gender		Test Statistics ¹	p
	Female	Male		
Healthy Volunteers	19 (76.0) ^a	6 (24.0) ^b	12.464	0.002
Predialysis Patients	9 (31.0) ^a	20 (69.0) ^b		
Dialysis Patients	13 (38.2) ^a	21 (61.8) ^b		

1: Chi-square Test Statistic, a-b: There is no difference between groups with the same letter for each line.

levels were examined in the clinical biochemistry laboratory of Ordu University Training and Research Hospital. The opened laboratory results were recorded separately for each event by looking at the information operating system of our hospital. In addition, 25 hydroxy vitamin D (25 OH Vit D) and 1,25 dihydroxy vitamin D (1, 25 OH Vit D), Pentraxin-3, Angiotensin-1 levels were also measured in the same laboratory.

For serum Pentraxin-3 and Angiotensin-1 levels, 2 ml venous blood samples were taken from the patients in a gel biochemistry tube, after centrifugation at 4000 rpm for 10 minutes, their serums were separated into a separate ependorf and kept at -80 C until the study was conducted. Pentraxin-3 and Angiotensin-1 levels were measured via ELISA method.

Statistical Analysis

Data were analysed with IBM SPSS V23. Conformity to normal distribution was examined by Kolmogorov-Smirnov. ANOVA analysis was used to compare normally distributed groups. The Kruskal Wallis test was used in the analysis of groups that did not show normal distribution. The relationship between the variables was examined by Spearman correlation analysis. Mean ± standard deviation and median (minimum – maximum) values for all variables were given in descriptive statistics tables. Chi-square test was used to compare categorical data and categorical data were presented as frequency (percentage). The frequency distributions of the data are given in the frequency table. Significance level was taken as p < 0.050. Graphs showing mean and standard deviation values by groups for Pentraxin, angiotensin, 25 hydroxy Vit D and 1,25 dihydroxy Vit D are presented. Correlation table was given for the relationship between the data and regression analysis was given for the size of the relationship between the data.

Results

Our study included 41 female (46.59%) and 47 male (53.41%) cases. Groups depend on gender (p=0.002). While the proportion of females in healthy volunteers was 76%, the male ratio was 24%. While the male ratio in predialysis patients was 69%, the female ratio was 31%. While the male ratio in dialysis patients was 61.8%, the female ratio was 38.2%. Groups and gender relations are presented in Table 1.

Descriptive statistical values of the analyzed variables are presented in Table 2.

Table 2. Descriptive statistical values

	Mean ± Standard Deviation.	Median (Min-Max)
Age (years)	59.56 ± 13.71	59 (20 - 88)
BUN(mg/dl)	36.36 ± 21.58	37.6 (4.3 - 89.9)
Creatinine (mg/dl)	3.57 ± 2.88	2.31 (0.42 - 11.12)
Pentraxin-3(ng/ml)	58.54 ± 87.66	42.3 (9.15 - 604.71)
Angiopoeitin-1(pg/ml)	0.77 ± 0.41	0.75 (0.1 - 2.55)
25hydroxy Vitamin D(ng/ml)	14.68 ± 7.74	14 (3.82 - 51.4)
1.25 dihydroxy Vit D(ng/ml)	32.6 ± 21.3	30.6 (5 - 108.1)
MPV (FL)	10.34 ± 0.98	10.2 (8.5 - 13.4)
Albumin (gr/dl)	4.2 ± 0.47	4.2 (2.4 - 5.1)

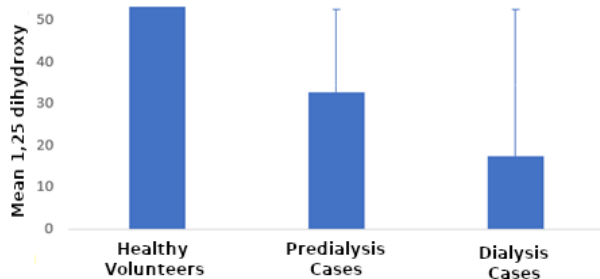


Figure 1. 1.25 dihydroxy Vit D values by groups

No significant difference was found between the MPV values of the groups ($p=0.693$). A significant difference was found between the albumin values of the groups according to the Kruskal-Wallis test statistic ($p < 0.001$). The median albumin score of healthy volunteers was 4.5, different from the other two groups. The median albumin score of predialysis patients is 4.3, which is different from the other two groups. The median albumin score of dialysis patients is 3.93, which is different from the other two groups. There was no significant difference between the 25 hydroxy vitamin D values of the groups ($p=0.329$). According to the Kruskal-Wallis test statistic, no significant difference was found between the 25 hydroxy vitamin D values of the groups ($p=0.329$).

There was a significant difference between the 1,25 dihydroxy vitamin D values of the groups ($p < 0.001$). The median score of 1.25 dihydroxy vitamin D of healthy volunteers was 51.3, different from the other two groups. The median score of 1.25 dihydroxy vitamin D of predialysis patients is 33, which is different from the other two groups. The median score of 1.25 dihydroxy vitamin D of dialysis patients is 14.1, which is different from the other two groups. The 1,25 hydroxy Vit D levels of the groups are presented in Table 3.

The graph of the 1.25 hydroxy Vit D levels of the groups is presented in Figure 1. No significant difference was found between the Pentraxin-3 values of the groups ($p=0.993$). The relationship between the Pentraxin-3 values of the groups is presented in Table 4.

Pentraxin-3 values by groups are presented in Figure 2. There was a significant difference between the

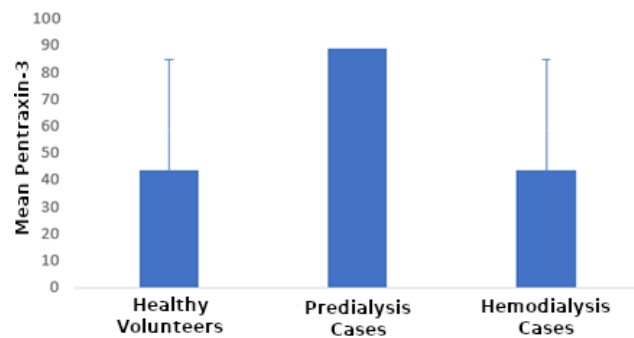


Figure 2. Pentraxin-3 values by groups

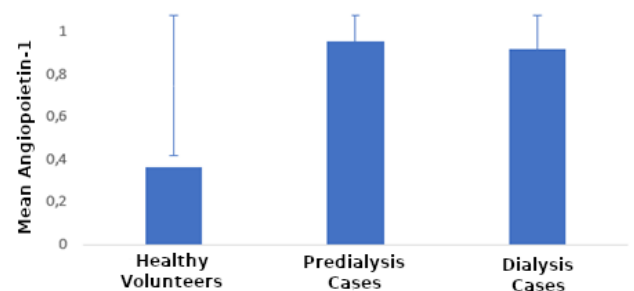


Figure 3. Angiopoeitin-1 levels of the groups

Angiopoeitin-1 values of the groups ($p < 0.001$). The median angiopoietin score of healthy volunteers was 0.36, different from the other two groups. The median angiopoietin score of predialysis patients was 0.94, and the median angiopoietin score of dialysis patients was 0.93, and there was no difference between them. The relationship between the Angiopoeitin-1 values of the groups is presented in Table 5. Angiopoeitin-1 values of the groups are presented in Figure 3. Correlation analysis was performed between creatinine values and Pentraxin-3, Angiopoeitin-1, 25 Hydroxy Vit D and 1.25 dihydroxy Vit D. An important laboratory finding of CKD progression is elevated creatinine. Our correlation analysis findings are presented in Table -6. There was a positive low-level relationship ($r=0.023$) between creatine and Pentraxin-3, and this relationship was not statistically significant ($p=0.832$). There was a moderate positive correlation ($r=0.593$) between creatine and Angiopoeitin-1, and this relation was statistically significant ($p < 0.001$). There was a very low positive correlation ($r=0.006$) between creatine and 25 OH Vit D, and this relationship was not statistically significant ($p=0.955$). There was a moderate negative correlation ($r=0.687$) between creatine and 1.25 dihydroxy Vit D and this relation was statistically significant ($p < 0.001$). Further statistical analysis was performed between creatine and Angiopoeitin-1, Pentraxin-3, 25 hydroxy Vit D and 1.25 dihydroxy Vit D. Our regression analysis results are presented in Table 7.

A simple regression model was established for creatine and Pentraxin-3. The created regression model was not found to be statistically significant ($F=0.781$, $p=0.379$) and $R^2=0.009$. A simple regression model was established for creatine and angiopoietin-1. The created regression model was found to be statistically significant ($F=13.409$

Table 3. 1, 25 hydroxy Vitamin D values between group

Group	Mean±Standard Deviation.	Median (Min-Max)	Test Statistics1	p
Healthy Volunteers(ng/ml)	53.12 ± 18.09	51.3 (23.3 - 108.1)a	42.699	< 0.001
Predialysis Patients (ng/ml)	32.67 ± 17.02	33 (6.97 - 73.6)b		
Dialysis Patients (ng/ml)	17.46 ± 12.52	14.1 (5 - 51.6)c		

1: Kruskal Wallis test statistics,

Table 4. Pentraxin-3 values between groups

Group	Mean±Standard Deviation.	Median (Min-Max)	Test Statistics1	p
Healthy Volunteers(ng/ml)	43.4 ± 17.41	42.3 (9.15 - 77.74)	0.015	0.993
Predialysis Patients(ng/ml)	88.92 ± 147.78	40.02 (13.72 - 604.71)		
Dialysis Patients(ng/ml)	43.75 ± 17.25	45.73 (10.29 - 75.46)		

1: Kruskal Wallis test statistics

, $p < 0.001$) and $R^2=0.135$. The estimated angiotensin value is equal to $(0.58+0.05*\text{creatinine})$ value. A simple regression model was established for creatinine and 25 hydroxy Vit D. The created regression model was not found to be statistically significant ($F=0.665$, $p=0.417$) and it was obtained as $R^2=0.008$.

A simple regression model was established for creatinine and 1.25 dihydroxy Vit D. The created regression model was found to be statistically significant ($F=53,685$, $p < 0.001$) and it was obtained as $R^2=0.384$. The estimated value of Creatinine is equal to $(6.29-0.08*1.25 \text{ dihydroxy Vit D})$.

With the regression model we created, it was again statistically proven that there was a significant relationship between Pentraxin-3 levels and CKD. Our regression model results confirmed our H1 hypothesis once again. The relationship between 1,25 hydroxy Vit D, which is the active form of Vitamin D, and CKD is a known fact. However, the reason for including it in the analysis here is to ensure the relationship between CKD and Angiotensin-1 levels. That is, taking 0.05 times the creatinine value and adding 0.58 gives the Angiotensin -1 value. The opposite is also true. The creatinine value of the case can also be calculated by finding the angiotensin-1 level.

Discussion

In our study, a significant relationship was found between Angiotensin-1 levels and CKD. Angiotensin-1, which plays a role in angiogenesis and inflammation, can be a guiding biomarker in the early diagnosis and treatment planning of CKD patients. No relationship was found between Pentraxin-3 levels and CKD. In our study, it was proved again that Pentraxin-3, which has a role in inflammation, is a marker more like an acute phase reactant. The relationship between 1,25 hydroxy Vit D, which is the active form of Vitamin D, and CKD is a known fact. The determination of this relationship in our study, confirmed our hypothesis about the relationship between Angiotensin -1 and CKD.

The study of David S et al. [10] showed that Angiotensin-2 levels in CKD Stage 5 patients receiving maintenance dialysis treatment are associated with widespread atherosclerosis, and moreover, it is associated with high

mortality. David S et al. did not find a relationship between Angiotensin-1 levels and CKD progression, and they stated that the relationship between Angiotensin-2 levels and CKD was significant.

In a case-control study conducted by Anderson et al. [11], Pentraxin-3, Angiotensin-1 levels, and VEGF-A (Vascular Endothelial Growth Factor -A) levels were examined in cases with and without CKD diagnosis. The authors examined the relationship between angiogenic factors and CKD. Unlike our study, the authors found VEGF-A and Pentraxin -3 levels to be increased in CKD, while they found Angiotensin-1 levels to be low. Investigative authors stated that multicenter prospective studies with larger populations are needed to understand whether angiogenic factors play a role in CKD progression [11]. Our results are inconsistent with the work of Anderson et al. The fact that they conducted their studies as a different geographical region and higher patient population and only 2 groups (patients diagnosed with CKD and healthyvolunteers) are different aspects of our study. We think that our results may have differed for these reasons.

Tsai et al. [12] investigated the relationship between Angiotensin-1 and Angiotensin-2, VEGF-A levels and subclinical cardiovascular disease in CKD patients by including Echo parameters. They found a positive correlation between high angiotensin-2 levels, low angiotensin-1 levels and the development of ischemic heart disease in CKD patients [12]. Although they found a positive correlation between low angiotensin -1 levels and the development of ischemic heart disease in CKD patients, we found a positive correlation between high angiotensin -1 levels and CKD progression in our study. Our study results do not coincide with the study of Tsai et al.

Loganathan et al. [13], in their experimental study, accelerated the progression to chronic kidney disease by causing low Angiotensin-1 in rats. The presence of tubulointerstitial fibrosis is a harbinger of progressive decline in kidney function, regardless of the underlying cause. In the experimental model they created based on this scientific fact, the authors proved with electron microscopic results that low levels of angiotensin-1 increase renal fibrosis, that is, accelerate the course of chronic kidney disease. Our results

Table 5. Angiotensin-1 values between groups

Group	Mean±Standard Deviation.	Median (Min-Max)	Test Statistics1	p
Healthy Volunteers (pg/ml)	0.36 ± 0.1	0.36 (0.2 - 0.56)a	45.325	< 0.001
Predialysis Patients (pg/ml)	0.95 ± 0.47	0.94 (0.1 - 2.55)b		
Dialysis Patients (pg/ml)	0.92 ± 0.28	0.93 (0.39 - 1.84)b		

1: Kruskal Wallis test statistics, a-b: There is no difference between groups with the same letter.

Table 6. Correlation analysis

	Pentraxin-3	Angiotensin-1	25 OH Vit D	1.25 OH VitD
Creatine	r=0.023 ; p=0.832	r = 0.593 ; p < 0.001	r=0.006 ; p=0.955	r=-0.687 ; p < 0.001

r:spearman's rho

are in contrast with the study of Loganathan et al. In our study, we found angiotensin-1 levels higher in predialysis and dialysis patients compared to healthy volunteers. This can be explained by the fact that the study of Loganathan et al. is an experimental study and our study is a clinical study.

Pentraxin-3, also known as long pentraxin, is an acute phase reactant that plays an important role in the immune system, and can induce acute or chronic inflammation by activating the first component of the classical complement cascade [14].

In a study by Abu Seman et al. [15] in Malaysia, they examined serum Pentraxin-3 levels in patients with Type-2 diabetes mellitus and in patients with diabetic nephropathy. The authors found that serum Pentraxin-3 levels were low in patients with Type-2 diabetes mellitus and in patients with diabetic nephropathy (15).

In the study of Sjöberg et al. [16], they claimed that Pentraxin is a biomarker that indicates renal damage before the development of CKD. They stated that as the GFR level decreased in the elderly, Pentraxin-3 levels increased. They also stated that Pentraxin -3 levels were high even in the early stages of CKD. In our study, when CKD cases and healthy volunteers were compared, we found that there was no difference between Pentraxin-3 levels in all groups. Our results do not coincide with the study of Sjöberg et al.

A review by Ristagno et al. [17] states that Pentraxin-3 is elevated as an indicator of tissue damage in acute myocardial infarction, heart failure, and cardiac arrest and that it is a new and highly predictive biomarker for cardiovascular diseases. Ristagno et al. stated that Pentraxin -3, an acute phase reactant, is a good biomarker for acute cardiovascular diseases. CKD is a chronic process, so it is an expected result that we did not obtain significant results in our study.

In a study by Dubin et al. [18] in a large population study including 2824 multicenter CKD cases from different ethnicities, they reported that they found a strong and linear relationship between elevated pentraxin-3 levels and low GFR levels in CKD, especially in coloured. The authors also stated that increased Pentraxin -3 levels in CKD patients were also associated with increased cardiovascular disease [18]. Our study is a single-center and narrow-population study. The inconsistency of our results may be

related to the difference in our study populations.

Myamoto et al. [19] examined Pentraxin-3 levels in obese patients with end-stage renal disease. When the Pentraxin -3 levels of the cases undergoing hemodialysis incidentally and those undergoing continuous hemodialysis were compared, Pentraxin-3 levels were found to be higher in the cases undergoing continuous hemodialysis.

Suliman et al. [20] found Pentraxin-3 levels higher in hemodialysis patients compared to the control group in a study in which they compared end-stage renal disease patients and the control group. Multicenter and multi-ethnic data were evaluated. Although not statistically significant, Pentraxin-3 levels were found to be higher in the predialysis group and moderately higher in the hemodialysis group compared to the control group in our study. Our results are in partial agreement with the study of Suliman et al.

Another noteworthy situation in this study is that using 1.25 dihydroxy Vit D is more meaningful than the use of 25 hydroxy Vit D in determining vitamin D levels, which are determinant in the prognosis and complications of the disease in CKD patients. Vitamin D deficiency is a well-known condition in both the general population and those with chronic kidney disease (CKD). In the study of Levin et al. [21], it was claimed that although serum 25 hydroxy Vit D may be a good indicator of vitamin D status in healthy individuals, 1.25 dihydroxy Vit D would be a more appropriate indicator for mineral metabolism and bone turnover in patients with CKD. Our study also supports this literature finding. In our study, there was no significant difference in 25 hydroxy Vit D levels between all 3 groups. The 1.25 dihydroxy Vit D levels were found to be highest in healthy volunteers, low in predialysis patients, and quite low in hemodialysis patients, and statistical significance was found between the groups.

There are some limitations of our study. First of all, the fact that it is single-centered and performed in a relatively narrow population is the first limiting factor. Measuring Pentraxin-3 and Angiotensin-1 levels in smaller subgroups homogenized by age or gender would have resulted in much more meaningful results. The second limiting factor is the lack of age and/or gender homogenization for biomarker measurements.

As a result; Although in the literature mostly a relationship was found between increased Angiotensin-2 levels and CKD and endothelial dysfunction, we found high

Table 7. Regression analysis

	β_1 (95% CI)	SE	β_2	t	p
Creatine-Pentraxin-3					
Constant	68.85 (39.12 - 98.58)	14.957		4.603	< 0.001
Creatine	-2.89 (-9.4 - 3.61)	3.272	-0.095	-0.884	0.379
Creatine-Angiopoietin-1					
Constant	0.58 (0.45 - 0.71)	0.066		8.847	< 0.001
Creatine	0.05 (0.02 - 0.08)	0.014	0.367	3.662	< 0.001
Vit 25 OH D-Creatine					
Constant	3.09 (1.77 - 4.4)	0.662		4.667	< 0.001
Vit 25 OHD	0.03 (-0.05 - 0.11)	0.040	0.088	0.816	0.417
Vit 1.25 D Hydroxy-Creatine					
Constant	6.29 (5.41 - 7.18)	0.444		14.174	< 0.001
Vit125 D Hydroxy	-0.08 (-0.11 - -0.06)	0.011	-0.620	-7.327	< 0.001

Angiopoietin-1 levels in CKD cases in our study. Although a decrease in CKD cases was detected in the literature with angiopoietin-1 levels, our finding in our study that increased angiopoietin-1 levels with CKD progression made a new contribution to the literature. Angiopoietin-1 can be considered as a useful biomarker for the follow-up and treatment of CKD. No correlation was found between our Pentraxin-3 levels and CKD progression. While a relationship was found between elevated Pentraxin-3 levels and CKD in the literature, Pentraxin-3 levels were found to be similar between our groups in our study. We believe that our study sheds light on the literature in terms of different results. We believe that multicenter studies with a large population are needed in order to reach definitive results for both biomarkers.

References

- Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. *JAMA* 2019;322(13):1294-304
- Kim SB, Lee KH, Lee JU, Ann HW, Ahn JY, Jeon YD, et al. Long pentraxin 3 as a predictive marker of mortality in severe septic patients who received successful early goal-directed therapy. *Yonsei Med J.* 2017;58(2):370–9.
- Haliloglu M, Bilgili B, Bilginer H, Kasapoglu US, Sayan I, Aslan MS, et al. A new scoring system for early diagnosis of ventilator-associated pneumonia: LUPPIS. *Arch Med Sci.* 2020;16(5):1040–8.
- Bottazzi B, Garlanda C, Cotena A, Moalli F, Jaillon S, Deban L, The long pentraxin PTX3 as a prototypic humoral pattern recognition receptor: interplay with cellular innate immunity. *Immunological Reviews* 2009; 227(1):9–18.
- Inforzato A, Reading PC, Barbati E, Bottazzi B, Garlanda C, Mantovani A. The “Sweet” Side of a Long Pentraxin: How Glycosylation Affects Ptx3 Functions in Innate Immunity and Inflammation. *Front Immunol* 2013;3 Article ID 407. <https://doi.org/10.3389/fimmu.2012.00407>
- Latini R, Maggioni AP, Peri G. Prognostic significance of the long pentraxin PTX3 in acute myocardial infarction *Circulation* 2004;110(16):2349–54.
- Ozer Balin S, Sagmak Tartar A, Uğur K, Kilinc F, Telo S, Bal A et al. Pentraxin-3: A new parameter in predicting the severity of diabetic foot infection? *Int Wound J* 2019;16(3):659–64.
- Fagiani E, Lorentz P, Kopfstein L, Christofori G. Angiopoietin-1 and -2 Exert Antagonistic Functions in Tumor Angiogenesis, yet Both Induce Lymphangiogenesis *Cancer Res*; 71(17); 5717–27.
- KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2013;3(1):19-112.
- David S, John SG, Jefferies HJ, Sigrist MK, Kumpers P,

- Kielstein JT et al. Angiopoietin-2 levels predict mortality in CKD patients *Nephrol Dial Transplant* 2012 (27): 1867–72 doi: 10.1093/ndt/gfr551
- Anderson CE, Lee Hamm L, Batuman G, Kumbala DR, Chen CS, Kallu SG et al. The association of angiogenic factors and chronic kidney disease *BMC Nephrology* 2018;19(117):1-8
- Tsai YC, Lee CS, Chiu YW, Kuo HT, Lee SC, Hwang SJ et al. Angiopoietin-2, Angiopoietin-1 and subclinical cardiovascular disease in Chronic Kidney Disease *Sci. Rep* 2016; 6, 39400; doi: 10.1038/srep39400
- Loganathan K, Salem Said E, Winterrowd E, Orebrand M, He L, Vanlandewijck M, et al. (2018) Angiopoietin-1 deficiency increases renal capillary rarefaction and tubulointerstitial fibrosis in mice. *PLoS ONE* 13(1):1-18 e0189433.
- Fornai F, Carrizzo A, Forte M, Ambrosio M, Damato A, Ferrucci M, et al. The inflammatory protein Pentraxin 3 in cardiovascular disease. *Immunity & Ageing.* 2016;13(1):5-9 DOI 10.1186/s12979-016-0080-1
- Abu Seman N, Witasap A, Mohamad WNW, Anderstam B, Brismar K, Stenvinkel et al Evaluation of the Association of Plasma Pentraxin 3 Levels with Type 2 Diabetes and Diabetic Nephropathy in a Malay Population *J Diabetes Res.* 2013; 2013: 298019.
- Sjöberg B, Qureshi AR, Heimbürger O, Stenvinkel P, Lind L, Larsson A et al. Association between levels of pentraxin 3 and incidence of chronic kidney disease in the elderly *J Intern Med.* 2016 ; 279(2): 173–9.
- Ristagno G, Fumagalli F, Bottazzi B, Mantovani A, Olivari D, Novelli D et al. Pentraxin 3 in Cardiovascular Disease *Front Immunol.* 2019; 10: 823. doi: 10.3389/fimmu.2019.00823
- Dubin R, Shlipak M, Li M, Ix JH, de Boer I, Jenny N et al. Racial differences in the association of pentraxin-3 with kidney dysfunction: the Multi-Ethnic Study of Atherosclerosis *Nephrol Dial Transplant.* 2011 Jun; 26(6): 1903–1908. doi: 10.1093/ndt/gfq648
- Miyamoto T, Rashid Qureshi A, Heimbürger O, Bárány P, Carrero K, Sjöberg B, Lindholm B, Stenvinkel P, Carrero JJ. Inverse relationship between the inflammatory marker pentraxin-3, fat body mass, and abdominal obesity in end-stage renal disease. *Clin J Am Soc Nephrol.* 2011 ;6(12):2785-91. doi: 10.2215/CJN.02320311. PMID: 22157708; PMCID: PMC3255358.
- Suliman ME, Yilmaz MI, Carrero JJ, Qureshi AR, Saglam M, Ipcioglu OM, Yenicesu M, Tong M, Heimbürger O, Barany P, Alvestrand A, Lindholm B, Stenvinkel P. Novel links between the long pentraxin 3, endothelial dysfunction, and albuminuria in early and advanced chronic kidney disease. *Clin J Am Soc Nephrol.* 2008;3(4):976-85. doi: 10.2215/CJN.03960907. Epub 2008 Apr 16. PMID: 18417746; PMCID: PMC2440283.
- Levin A, Le Barbier M, Er L, Andress D, Sigrist MK, Djurdjev O. Incident isolated 1,25(OH)(2)D(3) deficiency is more common than 25(OH)D deficiency in CKD. *Journal of Nephrology.* 2012;25(2):204-10. DOI: 10.5301/jn.2011.8429. PMID: 21688248.