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

Murat Cihan\textsuperscript{a,*}, Ahmet Karatas\textsuperscript{b}, Ebru Canakci\textsuperscript{c}, Mervegul Kaya\textsuperscript{d}

\textsuperscript{a}Ordu University, Training and Research Hospital Department of Medical Biochemistry, Ordu, Turkey. 
\textsuperscript{b}Ondokuz Mayis University, Department of Nephrology, Samsun, Turkey. 
\textsuperscript{c}Ordu University, School of Medicine, Department of Anesthesiology and Reanimation, Ordu, Turkey 
\textsuperscript{d}Ordu University Training and Research Hospital, Department of Family Medicine, Ordu, Turkey

Abstract

\textbf{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).

\textbf{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.

\textbf{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.

\textbf{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.

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 < 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
are 4 isoforms, the best known ones are Angiopoietin-1 and Angiopoietin-2. Angiopoietin-2 triggers inflammation, mediates vascular regression, increased permeability, and angiogenesis. Angiopoietin-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 Angiopoietin-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 31.08.2020 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, c-GFR values, potassium, calcium, phosphorus, magnesium, uric acid, albumin, C-reactive protein (CRP), spot urine albumin/creatinine (UACR), HbA1c, ferritin, Parathormone (PTH) 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, Angiopoetin-1 levels were also measured in the same laboratory.

For serum Pentraxin-3 and Angiopoetin-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 ependor and kept at -80 C until the study was conducted. Pentraxin-3 and Angiopoetin-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, angiopoetin, 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

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

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 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 vitamin D levels of the groups are presented in Table 3.

The graph of the 1.25 hydroxy vitamin 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

Angiopoietin-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 Angiopoietin-1 values of the groups is presented in Table 5. Angiopoietin-1 values of the groups are presented in Figure 3.

Correlation analysis was performed between creatinine values and Pentraxin-3, Angiopoietin-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 Angiopoietin-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 Angiopoietin-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 R2=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
Atherosclerosis, and moreover, it is associated with high levels in CKD Stage 5 patients receiving maintenance dialysis treatment are associated with widespread atherosclerosis. Our hypothesis about the relationship between Angiopoietin-1 and CKD is a known fact. The relationship between 1,25 hydroxy Vit D, which is the active form of Vitamin D, and CKD is a known fact. However, 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 healthy volunteers) are different aspects of our study. We think that our results may have differed for these reasons.

In a case-control study conducted by Anderson et al. [11], Pentraxin-3, Angiopoietin-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 Angiopoietin-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 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 Angiopoietin-1 and Angiopoietin-2, VEGF-A levels and subclinical cardiovascular disease in CKD patients by including Echo parameters. They found a positive correlation between high angiopoietin-2 levels, low angiopoietin-1 levels and the development of ischemic heart disease in CKD patients [12]. Although they found a positive correlation between low angiopoietin -1 levels and the development of ischemic heart disease in CKD patients, we found a positive correlation between high angiopoietin -1 levels and CKD progression in our study. Our study results do not coincide with the study of Tsai et al.

In our study, a significant relationship was found between Angiopoietin-1 levels and CKD. Angiopoietin-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 Angiopoietin -1 and CKD.

The study of David S et al. [10] showed that Angiopoietin-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 Angiopoietin-1 levels and CKD progression, and they stated that the relationship between Angiopoietin-2 levels and CKD was significant.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean±Standard Deviation</th>
<th>Median (Min-Max)</th>
<th>Test Statistics1</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Volunteers(ng/ml)</td>
<td>53.12 ± 18.09</td>
<td>51.3 (23.3 - 108.1)a</td>
<td>42.699</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Predialysis Patients (ng/ml)</td>
<td>32.67 ± 17.02</td>
<td>33 (6.97 - 73.6)b</td>
<td></td>
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</tr>
<tr>
<td>Dialysis Patients (ng/ml)</td>
<td>17.46 ± 12.52</td>
<td>14.1 (5 - 51.6)c</td>
<td></td>
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</tbody>
</table>

Table 4. Pentraxin-3 values between groups

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

Discussion

In our study, a significant relationship was found between Angiopoietin-1 levels and CKD. Angiopoietin-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 Angiopoietin -1 and CKD.

The study of David S et al. [10] showed that Angiopoietin-2 levels in CKD Stage 5 patients receiving maintenance dialysis treatment are associated with widespread atherosclerosis, and moreover, it is associated with high
are in contrast with the study of Loganathan et al. In our study, we found angiopoietin-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 Angiopoietin-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 Angiopoietin-2 levels and CKD and endothelial dysfunction, we found high
Angiopoetin-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

1. Chen TK, Kucely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. JAMA 2019;322(13):1294-304

Table 7. Regression analysis

<table>
<thead>
<tr>
<th></th>
<th>β1 (95% CI)</th>
<th>SE</th>
<th>β2</th>
<th>t</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Creatine-Pentraxin-3</td>
<td>68.85 (39.12 - 98.58)</td>
<td>14.957</td>
<td>4.603</td>
<td>&lt; 0.001</td>
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<td>Creatine</td>
<td>-2.89 (-9.4 - 3.61)</td>
<td>3.272</td>
<td>-0.095</td>
<td>-0.884</td>
<td>0.379</td>
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<tr>
<td>Creatine-Angiopoetin-1</td>
<td>0.58 (0.45 - 0.71)</td>
<td>0.066</td>
<td>8.847</td>
<td>&lt; 0.001</td>
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<tr>
<td>Creatine</td>
<td>0.05 (0.02 - 0.08)</td>
<td>0.014</td>
<td>0.367</td>
<td>3.662</td>
<td>&lt; 0.001</td>
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<tr>
<td>Vit 25 OH D-Creatine</td>
<td>3.09 (1.77 - 4.4)</td>
<td>0.662</td>
<td>4.667</td>
<td>&lt; 0.001</td>
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<tr>
<td>Vit 25 OH D-Creatine</td>
<td>0.03 (-0.05 - 0.11)</td>
<td>0.040</td>
<td>0.088</td>
<td>0.816</td>
<td>0.417</td>
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<tr>
<td>Vit 125 D Hydroxy-Creatine</td>
<td>6.29 (5.41 - 7.18)</td>
<td>0.444</td>
<td>14.174</td>
<td>&lt; 0.001</td>
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</tr>
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<td>Vit 125 D Hydroxy-Creatine</td>
<td>-0.08 (-0.11 - 0.06)</td>
<td>0.011</td>
<td>-0.620</td>
<td>-7.327</td>
<td>&lt; 0.001</td>
</tr>
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Statistical analysis