



# Association between serum levels of pentraxin-3, mannose binding lectin and high sensitivity C-reactive protein with renal transplantation

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Received 13 June 2022

Accepted 19 Sep. 2022

Published online 9 Feb. 2023

**Keywords:** Pentraxin-3, Mannose binding lectin, High sensitivity C-reactive protein, Kidney transplantation, Transplant rejection

## Abstract

**Introduction:** Chronic kidney disease (CKD) may increase morbidity and mortality. Therefore, early detection of inflammation in kidney transplant recipients with a high risk of transplant rejection is important.

**Objectives:** This study was conducted to compare serum levels of pentraxin-3 (PTX-3), mannose binding lectin (MBL) and high sensitivity C-reactive protein (hs-CRP) in patients with chronic renal failure before and after transplantation.

**Patients and Methods:** This cross-sectional study was carried on 18-80 years old patients receiving immunosuppressive therapy who underwent kidney transplantation in Shahid Beheshti hospital of Babol in 2016. Before transplantation, one week later and two months after transplantation, the serum levels of PTX-3, MBL and hs-CRP were determined. Complications including acute transplant rejection and urinary tract infection were recorded since inflammatory markers were evaluated and compared at the time of complication.

**Results:** The mean age of the patients was 42.07±12.47 years. Transplant rejection and urinary tract infection occurred in 3 (10%) and 4 (13.3%) of patients, respectively. Patients over 55 years of age and those with hypertension had significantly more complications ( $P=0.03$  and  $P=0.02$  respectively). Two months after transplantation, PTX-3 and MBL levels were significantly lower (PTX-3; 10.84±15.88 versus 18.75±24.31 ng/dL,  $P=0.001$  and MBL; 764.3±771.35 versus 1157.9±1299.75 ng/dL,  $P=0.006$ ). In patients with complications, PTX-3, MBL and hs-CRP levels were 16.73±27.98 ng/dL, 710.0±613.19 ng/dL and 8.43±12.10 mg/L, respectively. No significant difference was found between inflammatory markers in complicated and uncomplicated patients. Comparison of changes in PTX-3, MBL and hs-CRP levels before and after transplantation showed a significant difference two months following transplantation compared to pre-transplantation and also one week after it for PTX-3 and MBL (PTX-3:  $P=0.001$  and  $P=0.009$ , respectively; MBL:  $P=0.006$  and  $P=0.03$ , respectively).

**Conclusion:** Based on the results of this study, PTX-3 and MBL levels can be considered for determining the inflammatory status of kidney transplant patients and the prognosis of transplantation.

**Citation:** Firouzjahi A, Hajian Tilaki K, Ghorbani H, Shamsi Jamkhaneh N, Akbari R. Association between serum levels of pentraxin-3, mannose binding lectin and high sensitivity C-reactive protein with renal transplantation. Immunopathol Persa. 2023;x(x):e34419. DOI:10.34172/ipp.2023.34419.

## Introduction

Chronic kidney disease (CKD) characterized by chronic inflammation is associated with increased risk of morbidity and mortality. Causes of inflammation include primary kidney disease, oxidative stress, malnutrition, activation of the immune system by dialysis, infections, and genetic factors (1). Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD) patients (2). Successful kidney transplantation improves the quality of life and reduces the risk of death in most patients compared to maintenance dialysis (3-5). These patients have many associated complications due to underlying ESRD or its consequences. After transplantation, patients receive severe immunosuppressive therapy, which

## Key point

In a study on 30 patients receiving immunosuppressive therapy who underwent kidney transplantation, the serum levels of pentraxin-3 (PTX-3), mannose binding lectin (MBL) and high sensitivity C-reactive protein (hs-CRP) were determined. No significant difference was found between inflammatory markers in complicated and uncomplicated patients. Comparison of changes in PTX-3, MBL and hs-CRP levels before and after transplantation showed a significant difference in two months after transplantation compared to pre-transplantation and one week after it for PTX-3 and MBL.

predisposes them to infections, malignancy, and cardiovascular disease; therefore, they need constant follow-up and care (6).

Early detection of inflammation in kidney transplant recipients with a high risk of transplant rejection is important. There is a



growing interest in the value of pre-transplant inflammatory markers as a predictor of transplant outcome. However, the effects of inflammation on connective tissue function after kidney transplantation are unclear (7).

The most common inflammatory marker studied so far is C-reactive protein (CRP), an acute-phase protein belonging to the pentraxin family (8), which is produced in the liver and is the most important component of the inflammatory syndrome (9). Since, it increases rapidly in response to inflammation, unlike other acute-phase proteins, it only increases in inflammatory conditions and therefore there is no ambiguity in its interpretation (10). Serum CRP levels in adults with CKD increase even in the early stages (11,12). Its serum level is higher in dialysis patients. High serum CRP level predicts the occurrence of heart disease and death in dialysis patients (11). Little is known about the predictive value and role of CRP, as well as the serum level of pentraxin in post-transplant patients, while these patients benefit greatly by identifying a non-invasive biomarker that can predict adverse events (13). Recent studies have shown that an increase in pentraxin-3 (PTX-3) level is associated with clinical outcomes in the 5<sup>th</sup> stage of CKD at the start of kidney transplant treatment (14,15).

Mannose binding lectin (MBL), also called mannose binding protein, is a calcium-dependent C-type lectin made by the liver and plays an important role in the innate immune system and activation of the complement system. The association between MBL and diseases is relatively complex, and the MBL acts as a double-edged sword. Both decrease and increase in serum MBL levels are associated with various diseases. In renal transplantation, low-serum MBL levels are associated with a higher risk of infection and high serum levels are a risk factor for mild inflammation, post-transplant diabetes, and subclinical transplant rejection, with poor transplant outcomes. The predictive value of MBL on connective tissue survival is discussed previously (16).

PTX3 is a 6.40 kd protein that belongs to a large family of pentraxin protective proteins (17). It is not synthesized in the liver however it is produced in various cells including dendritic cells, macrophages, fibroblasts, and vascular endothelial and epithelial cells (14,18,19). This substance also produced in other tissues such as the heart and kidney in response to inflammatory mediators like lipopolysaccharide and interleukin 1 beta (IL-1 $\beta$ ) and tumor necrosis factor alpha (TNF- $\alpha$ ) (18). PTX3 can be used as an inflammatory marker in renal disease that may be associated with endothelial dysfunction, malnutrition, proteinuria, risk of cardiovascular disease, and increased mortality (18,20).

The lectin pathway is one of the complement pathways which after binding of microorganisms (bacteria, viruses, fungi and parasites) to MBL and activation of MASP (mannose-binding associated serin protease), the lectin complement pathway is then activated. The MBL gene is

located on the 10<sup>th</sup> chromosome. Due to the existence of gene mutations, there are different variations in several populations and races (21). Common assessments of renal allograft function generally include serum creatinine levels and proteinuria evaluation. Some patients with evidence of allograft dysfunction or proteinuria may need a kidney biopsy to assess the cause of the disorder (6).

## Objectives

Since no comprehensive study has evaluated the serum levels of acute-phase proteins in kidney transplantation, this study aimed to compare the serum levels of PTX3, MBL, and hs-CRP in determining the inflammatory status before and after kidney transplantation in patients with chronic renal insufficiency.

## Patients and Methods

### Study design

This cross-sectional study was carried on ESRD patients who underwent kidney transplantation in 2016 at Shahid Beheshti hospital of Babol. Patients with a diagnosis of chronic renal failure in the age group of 18-80 years with a minimum duration of dialysis for six months were included. Patients with a history of myocardial infarction or cerebrovascular accident, infection, hospitalization or surgery in the last month and patients with chronic liver disease, pulmonary embolism, pericarditis, severe pulmonary hypertension, malignancy, inflammatory diseases, diabetic foot, kidney transplantation treated with high dose steroids and immunosuppressive agents as well as nonsteroidal anti-inflammatory drug users were excluded.

The sample size was 30 cases based on 80% power. After obtaining written informed consent, information about each patient including age, sex, history of smoking and alcohol consumption, systolic and diastolic blood pressure, medications used, complications, history of diabetes, hyperlipidemia, ischemic heart disease, and complications within 2 months after transplantation (acute rejection of transplantation and urinary tract infection) were recorded and the level of markers was checked at the time of complication.

Five milliliters blood sample was obtained from patients before initiation of immunosuppressive therapy, before transplantation, one week and two months following transplantation (when the level of immunosuppressive drugs was reduced to the maintenance level) in the morning and after 12 hours of fasting. CRP level was measured with high sensitivity with Parsazmoon kit and immunoturbidimetric method, while pentraxin and MBL levels were measured with BT-Humann kit by ELISA (enzyme-linked immunosorbent assay) method. CKD was defined as the presence of renal impairment presenting with urinary albumin secretion >30 mg/day or decreased renal function with a glomerular filtration rate (GFR) <30 mL/min/1.73 m<sup>2</sup> for three months or more (22).

All patients were visited by a nephrologist and all tests were performed in the laboratory of Rouhani hospital in Babol.

### Statistical analysis

After data collection, they were analyzed by SPSS software version 16.0, and the correlation between qualitative variables and Fisher's exact test was analyzed. In addition, repeated measurement analysis was used for comparison of patients before transplantation, one week and two months after it. The changes in PTX-3, MBL, and hs-CRP markers before transplantation, one week later, and within 2 months after transplantation were analyzed using a multivariate analysis of variance. *P* value <0.05 was considered to be statistically significant.

### Results

Thirty patients including 17 male and 13 females were included in the study. The mean age of the patients was  $42.07 \pm 12.47$  years. Complications in patients included transplant rejection in three patients (10%) and urinary tract infection in four patients (13.3%) (Table 1).

Two months after transplantation, PTX-3 ( $P=0.001$ ) and MBL ( $P=0.006$ ) levels were significantly lower than before transplantation (PTX-3 =  $10.84 \pm 15.88$  and  $18.75 \pm 24.31$  ng/dL, respectively; MBL =  $764.3 \pm 771.35$  and  $1157.9 \pm 1157.9$  ng/dL, respectively), however serum hs-CRP level had no significant change (Table 2). The

mean PTX-3, MBL, and hs-CRP levels in patients with complications were  $16.73 \pm 27.98$  ng/dL,  $710.0 \pm 613.19$  ng/dL, and  $8.43 \pm 12.10$  mg/L, respectively.

No statistically significant difference was found between inflammatory markers in complicated and uncomplicated individuals (Table 3). PTX-3 ( $P<0.001$ ) and MBL ( $P=0.006$ ) markers were significantly different two months after transplantation and one week after transplantation (PTX-3:  $P=0.009$ , MBL:  $P=0.03$ ), however serum hs-CRP marker level was not significantly different (Table 4).

Patients with age >55 years had significantly more complications ( $P=0.02$ ). No statistically significant association was found between complications in men and women ( $P=0.43$ ). The prevalence of transplant complications in patients with hypertension compared to patients without hypertension was statistically different (57.1% versus 13%, respectively,  $P=0.03$ ).

PTX-3 and MBL did not significantly change one week after transplantation and before it ( $P=0.90$  and  $P=0.73$ , respectively). However, two months following transplantation, they were significantly different from pre-transplantation and also one week after it ( $P>0.05$ ). There was no significant difference in hs-CRP two months after transplantation compared to one week before it ( $P>0.05$ ).

### Discussion

According to the present study, PTX-3 and MBL decreased significantly one week and two months after kidney

**Table 1.** Demographic characteristics of the patients by condition and prevalence of complications

		Complication		Total	P value
		Positive	Negative		
Age (y)	<40	2 (13.3)	13 (86.7)	15 (100)	0.02
	40-55	1 (11.1)	8 (88.9)	9 (100)	
	>55	4 (66.7)	2 (33.3)	6 (100)	
Gender	Male	5 (29.4)	12 (70.6)	17 (100)	0.43
	Female	2 (15.4)	11 (84.6)	13 (100)	
Smoker	Yes	5 (20)	3 (60)	5 (100)	0.565
	No	2 (40)	20 (80)	25 (100)	
Alcohol consumption	Yes	6 (22.2)	2 (66.7)	3 (100)	1.00
	No	1 (33.3)	21 (77.8)	27 (100)	
IHD	Yes	3 (60)	2 (40)	5 (100)	0.068
	No	4 (16)	21 (84)	25 (100)	
DM	Yes	3 (50)	3 (50)	6 (100)	0.120
	No	4 (16.7)	20 (83.3)	24 (100)	
HLP	Yes	3 (42.9)	4 (57.1)	7 (100)	0.306
	No	4 (17.4)	19 (82.6)	23 (100)	
HTN	Yes	4 (57.1)	3 (42.9)	7 (100)	0.03
	No	3 (13)	20 (87)	23 (100)	
DBP	Yes	3 (15)	17 (85)	20 (100)	0.181
	No	4 (40)	6 (60)	10 (100)	
SBP	Yes	1 (9.1)	10 (90.9)	11 (100)	0.215
	No	6 (31.6)	13 (68.4)	19 (100)	

*P* value was calculated by merging the two groups of transplant rejection and UTI using Fisher's exact test.

IHD: Ischemic heart disease; DM: Diabetes Mellitus; HLP: High lipoprotein; HTN: Hypertension; DBP: Diastolic blood pressure; SBP: Systolic blood pressure

**Table 2.** Comparison of PTX-3, MBL, and hs-CRP before, one week after, and 2 months after transplantation

	Mean ± SD			P value <sup>a</sup>
	Pretransplant	One week after the transplant	2 months after transplant	
PTX-3 (ng/dL)	18.75 ± 24.31	18.54 ± 23.65	10.84 ± 15.88	0.001
MBL (ng/dL)	1157.9 ± 1299.75	1217.9 ± 1286.17	764.3 ± 771.35	0.006
hs-CRP (mg/L)	8.87 ± 13.03	9.29 ± 24.07	2.88 ± 4.62	0.07

P value was driven using F-test for comparison between groups in repeated measurement analysis.

**Table 3.** Comparison of PTX-3, MBL, and hs-CRP based on complications

Complication		Mean ± SD			P value <sup>a</sup>	P value <sup>b</sup>
		Pretransplant	One week after transplant	Two months after transplant		
PTX-3 (ng/dL)	Yes	17.81 ± 3.05	15.73 ± 26.28	14.41 ± 23.83	0.02	0.99
	No	19.63 ± 22.71	19.40 ± 23.35	9.75 ± 13.13		
MBL (ng/dL)	Yes	1122.0 ± 1235.61	785.0 ± 891.85	656.0 ± 694.4	0.01	0.57
	No	1168.3 ± 1235.61	1349.40 ± 1374.38	797.26 ± 804.93		
hs-CRP (mg/L)	Yes	5.26 ± 10.32	6.44 ± 9.46	5.55 ± 8.27	0.22	0.99
	No	6.75 ± 13.95	10.15 ± 27.12	2.07 ± 2.57		

<sup>a</sup> P value was driven from repeated measurement analysis using F-test for comparison of in linearity variation of mean within group.

<sup>b</sup> P value was driven from repeated measurement analysis using F-test for comparison between groups with and without complication.

**Table 4.** Comparison of changes in PTX-3, MBL and hs-CRP before and after kidney transplantation

Two by two comparison		Mean difference	95% CI	P value <sup>a</sup>	
PTX-3 (ng/dL)	Pretransplant	One week later	0.021	-3.17; 3.57	0.90
	Posttransplant	2 months later	7.91	3.34; 12.47	0.001
	One week later	2 months later	7.70	2.07; 13.34	0.009
MBL (ng/dL)	Pretransplant	One week later	-60	-432.07; 303.07	0.73
	Posttransplant	2 months later	393.60	121.77; 665.42	0.006
	One week later	2 months later	453.60	57.86; 849.34	0.03
hs-CRP (mg/L)	Pretransplant	One week later	-2.42	-7.28; 2.45	0.32
	Posttransplant	2 months later	3.98	-0.43; 8.39	0.07
	One week later	2 months later	6.40	-2.36; 15.16	0.15

<sup>a</sup> P value was driven using paired t test in multiple comparison.

transplantation, since serum hs-CRP level did not change significantly during this period. The overall incidence of transplant complications in this study was 23.3%. Patients older than 55 years and those with hypertension had significantly more complications. The difference between markers in complicated and uncomplicated individuals was not significant.

The transplant rejection rate was 10% in our study; MBL level decreased significantly during the two months of follow-up. This decrease could be related to transplant rejection and other complications. However, the MBL level was not significantly associated with complications at the three measured times. Therefore, studies with a higher sample size are recommended on this subject. The results of the study by Ibernon and colleagues showed that a low-serum MBL level is a chronic inflammatory response that affects transplant outcomes (23).

Likewise, in the study by Puente et al, patients with lower MBL levels in the pre-transplant period presented the first

post-transplant infection episode earlier (24). In the study by Bay et al, low levels of functional MBL were associated with decreased kidney graft survival; while, low-MBL level and male gender were independent risk factors of graft loss when adjusted for age (25).

Furthermore, in the study by Puente and colleagues, patients with lower MBL levels in the pre-transplant period presented the first post-transplant infection episode earlier and patients with low serum MBL levels had more episodes of CMV disease than those with normal levels, although these differences were not statistically significant (24). These findings indicate the potential role of MBL in the prevention of CMV infection after renal transplantation and MBL deficiency may be a significant risk factor for the development of CMV infection in renal transplant recipients which necessitate the prophylaxis for CMV (26). Our study was similar to the study by Puente et al in decreasing MBL level during follow-up time but we found no significant association between transplant

complications and MBL level during follow-up. Studies with larger sample sizes and case and control groups to determine this association are recommended. Our study was designed to report changes in marker levels.

We found no significant association between MBL level with infection and transplant rejection. Nevertheless, liver transplant recipients of MBL-deficient livers had a higher risk of bacterial infection, pneumonia and septic shock compared with recipients of MBL-deficient livers in the study by Lombardo-Quezada and colleagues (27). In the study by Bouwman et al, the association between low MBL levels and increased infection in transplant patients was reported, and high levels were associated with inflammatory diseases and transplant rejection (13). Due to the high level of infection (13.3%) and transplant rejection (10%) in our study, decreased MBL may be associated with them. Further studies with larger sample sizes and consideration of the control group are needed to determine this association.

According to our study, changes in PTX-3 after transplantation were significant. Contrary to our findings, Gursu et al suggested that PTX-3 may not help diagnose inflammatory conditions after kidney transplantation and CRP may be better than PTX-3 as a marker of inflammation (28). In their study, after transplantation, the mean CRP and IL-6 levels decreased but the PTX-3 and TNF- $\alpha$  levels did not change and a significant correlation was found between IL-6 and CRP before and after transplantation. They found no significant association between TNF- $\alpha$  and hs-CRP hypersensitivity before transplantation, but a significant correlation was reported after transplantation. There was no significant association between IL-6 and PTX-3, TNF- $\alpha$  and PTX-3, or hs-CRP and PTX-3 before or after transplantation (28). The findings of the study by Gursu and colleagues were contrary to us and the reason for this difference is unclear.

In our study, PTX-3 decreased significantly over two months, which could be associated with a good long-term prognosis for transplantation. The study by Imai et al was in line with our study. In a non-rejection biopsy (before and after the restoration of blood flow and biopsy protocol), the incidence of PTX-3 remained uniformly low, whereas, in transplant rejection biopsy, PTX-3 was significantly higher. Treatment of acute renal transplant rejection resulted in a significant reduction in PTX-3 and PTX-3 was positively associated with a degree of renal transplant dysfunction and acute regression scores of Banff classification. This study suggests that PTX-3 may be an existing histological marker of acute renal transplant rejection (29). However, an increase in PTX-3 levels is a factor in acute graft rejection. Therefore, a slight increase in PTX-3 within a week may be associated with a high link rejection in our study.

In the present study, no significant changes in hs-CRP level were observed during one week and two months after transplantation compared to pretransplantation.

Contrary to our study, Dahle et al found that elevated hs-CRP and IL-6 levels were independently associated with graft loss, death, and doubling of serum creatinine, and were associated with long-term consequences of grafts in transplant recipients (30).

In the study by Abbas et al, the plasma level of PTX-3 was significantly increased in CKD patients compared to the control group. There was also a gradual increase in PTX-3 with an increasing CKD stage from 3 to 5. On the other hand, the level of PTX-3 in patients with concomitant CKD and cardiovascular diseases (CVD) had a significant increase compared to CKD patients without CVD (17). The study by Tong et al showed that PTX-3 has a higher predictive value of mortality than CRP (31). As mentioned in these studies, PTX-3 is significantly higher in patients with renal complications than in normal people. It is considered that a low MBL level is associated with transplant complications. Finally, in the study by Satomura et al study, serum MBL level was higher in patients with chronic renal failure (32).

### Conclusion

In our study, in the long-term, the serum level of MBL decreased significantly, which could indicate a lower prognosis in these patients. Therefore, further studies are needed to prove this finding. Also, the PTX-3 level increased slightly in the short time and decreased significantly over two months and was associated with a good prognosis in patients. The hs-CRP level was not significantly correlated with transplant complications at different times after transplantation. Marker levels in patients with transplant complications did not significantly differ from those without complications. In our study, PTX-3 decreased significantly over two months. Therefore, measuring the levels of PTX-3 and MBL markers can be useful in determining the inflammatory status and prognosis of kidney transplantation.

### Limitations of the study

We had a limitation in our study. Due to the high cost of MBL and PTX-3 kits, we were unable to increase the sample size and this small sample size may have reduced the power of the study.

### Authors' contribution

Conceptualization: AF, HG and RA.

Methodology: AF, HG, RA and KHT.

Validation: KHT.

Formal analysis: KHT.

Investigation: HG and NSHJ.

Data curation: HG and NSHJ.

Writing—original draft preparation: HG, NSHJ and RA.

Writing—review and editing: RA.

Supervision: AF and RA.

Project Administration: AF and RA.

All authors participated in proofing the final draft of the manuscript, revised it and confirmed the final submitted manuscript.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Babol University of Medical Sciences approved this study (MUBABOL.HRI.REC.1395.118). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from pathology thesis of Dr. Nazila Shamsi Jamkhaneh at this university (Thesis#9503016).

### Funding/Support

The authors of this article express their gratitude to the officials of Babol University of Medical Sciences, for approving and funding this project (Grant #3973).

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