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ORIGINAL ARTICLE

Serum and Urine Monocyte Chemoattractant Protein-1, Macrophage Colony-stimulating Factor, and Neopterin as Sensitive Biomarkers for Assessment of Renal Parenchymal Damage in Children With Chronic Kidney Disease

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Abstract

Background: **Chronic Kidney Disease is postulated to be a constitutional pathology with interlacing between different etiological and pathogenic factors, which lead to ESRD. These pathogenic factors such as monocyte chemoattractant protein-1 (MCP-1), Neopterin and macrophage colony-stimulating factor (MCSF) control migration of mediators that cause damage of renal tissue and play a role in the process inflammation.**

Aim: **Confirming the presence of the sensitive markers for renal parenchymal damage, monocyte chemoattractant protein-1, neopterin, and macrophage colony-stimulating factor in patients' urine and serum as well as the progression of those patients to end-stage renal disease.**

Methodology and patients: **This prospective case-control study, which included two equal groups of forty candidates each, was conducted at the hospitals affiliated with Al-Azhar University. Twenty patients receiving regular hemodialysis for chronic kidney disease with mean age of (9.60 ± 1.85), they were 10 males and 10 females (Group 1). Twenty apparently healthy children with mean age was (8.15 ± 2.76), they were 10 males and 10 females (group 2).**

Results: **With a *P* value of 0.001, there is a statistically significant variation between the studied groups in terms of serum levels of MCP-1 and neopterin. With a *P* value of 0.072, there is no statistically significant difference between the studied groups in terms of serum levels of MCSF. Regarding urinary levels of MCP-1, MCSF, and Neopterin, there is a statistically significant difference between the three groups with a *P* value 0.001.**

Conclusion: **MCP-1, Neopterin and MCSF can be future biomarkers for early detection of renal affection in patients with CKD and can be useful for prognosis of progression of CKD.**

Keywords: Biomarkers, Chronic kidney disease, Hemodialysis, Monocyte chemoattractant protein-1, Macrophage colony-stimulating factor, Neopterin

1. Introduction

Chronic kidney disease (CKD) is defined as structural or functional kidney abnormalities (abnormal urine analysis, imaging studies, or histology) that last for at least three months with or without decreased glomerular filtration rate (GFR), or GFR was less than 60 ml/min/1.73 m^2 surface area, by the Kidney Disease and Outcome Quality Initiative (K/DOQI) working group of the National Kidney Foundation of the United States.[1]

Immune response factors are stimulated to migrate to the sites of inflammation in chronic kidney disease (CKD), which leads to renal fibrosis.[2] The progression

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and irreversibility of renal damage are caused by this process.[3]

Early stages of cell migration are influenced by monocyte chemoattractant protein-1 (MCP-1) and macrophage colony-stimulating factor (MCSF), which draw monocytes to areas of inflammation and promote their maturation into macrophages.[4]

Both adults receiving hemodialysis and children with focal segmental glomerulosclerosis have the MCP-1 gene polymorphism.[4,5]

Neopterin differs from these inflammatory mediators in that it is produced as a result of provoked cell migration and the ensuing inflammation rather than as a stimulant. Both monocytes and macrophages release neopterin in response to stimulation. Additionally, this substance might function as an immune response biomarker. Patients with nephrosis, CKD, and those receiving hemodialysis all had elevated levels of neopterin in their serum and urine.[6,7] A risk marker for renal allograft rejection is neopterin8.

2. Methodology and patients

At the hospitals affiliated with Al-Azhar University, we conducted this case-control study. Twenty CKD patients receiving regular hemodialysis were included in the study (Group 1), and twenty children who appeared to be in good health and whose age and sex matched those of the cases were included as a control group (Group 2). The patients were selected from the Al-Azhar University Hospitals' Pediatric Nephrology Unit and Hemodialysis Unit between June 2021 and December 2022. The Study was divided into two groups:

Group 1: Twenty children known to have chronic kidney disease and on regular hemodialysis, their age was range from 8 to 16 years with mean age of 9.60 ± 1.85. They were 10 males and 10 females.

Group 2: Twenty children, ages 3 to 12, who appeared to be in good health, with a mean age of 8.15 2.76. They were 10 males and 10 females.

2.1. Inclusion criteria

Group 1: The age group is 3–16 years and both sexes will be included, on regular hemodialysis for at least 12 months.

Group 2: Twenty children who appeared to be in good health and matched the patients' age and sex.

2.2. Exclusion criteria

Group 1: Patient less than 3 years or more than 16 years, on regular hemodialysis for less than 12 months, with acute or chronic inflammatory conditions, malignancy, diabetesmellitus, cardiovascular diseases or patients with anuria.

Group 2: Children with family history of renal diseases.

2.3. Ethics-related matters

Before including the parents of the control group and patients in the study, an informed consent was obtained from each parent. The Al-Azhar Faculty of Medicine's and Pediatric Department's ethical review boards both approved the study. The parents of the studied groups were informed about the study's procedures, goal, potential advantages, and risks. Both the patients and the controls had the option of leaving the study at any time and without explanation.

The following procedures were applied to all patients and controls:

2.3.1. Full history

A complete history is taken, including the patients' ages, the cause of their ESRD, any family history of renal disease or hypertension, how long they have been receiving dialysis, how often they take medications, how often they get sick, and any symptoms that might point to other systemic conditions.

2.3.2. Clinical examination

Body mass index (BMI), height (cm), blood pressure, and a full clinical examination are performed.

2.3.3. Lab investigations

Serum alkaline phosphatase, Complete blood count, Liver functions (SGOT, SGPT), Serum creatinine and urea, Serum electrolytes, Serum intact parathyroid hormone (iPTH) level.

The serum and urine concentrations (were done just before hemodialysis cession in hemodialysis patients) of Macrophage Colony-Stimulating Factor (MCSF), Neopterin and Monocyte Chemoattractant Protein- (MCP-) 1 evaluated by commercially available ELISA kits. The urine levels will be evaluated as regard random sample, ratio to creatinine level and fractional excretion using the following formula (Urinary level/serum level)÷(Urine creatinine/Serum creatinine) × 100).

2.3.4. Sampling requirements

The specimen can be preserved by being kept at −20 °C after collection. Centrifugation of the serum for 20 min at a speed of 2000–3000 rpm is used to remove the supernatant. Using a sterile container to collect urine, centrifuge it for 20 min at a speed of 2000–3000 rpm to remove the supernatant.

2.4. Statistical analysis

IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp) was used to gather and analyze data. Number and percent were used to plot numerical data. The Shapiro-Wilk test was employed to validate the distribution's uniformity. The range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR) were used to describe numerical data. The 5% level revealed remarkable results. Operating Characteristic Curve (ROC) performance is deemed satisfactory when the area is above 50% and best performance for the test when the area is above 100%.

3. Results

Our study revealed that Obstructive uropathy was the most frequent etiology of CKD in our study (Tables 1 and 2). Serum transferases were reduced in Group 1 as compared to Group 2. Serum phosphate, ALP and PTH were significantly higher in patient groups than control. Serum potassium was reduced in Group 1 in comparison to Group 2. The eGFR for Group 1 is (3.60–10.20) with mean is (6.57 ± 1.62), while it is (90.0–146.0) with mean is (122.2 ± 16.28) (Table 3). Regarding serum levels of MCP-1 and neopterin, there is a significant difference between the studied groups; however, there are no significant differences regarding MCSF. Regarding urinary levels of MCP-1, MCSF, and Neopterin, there is a significant difference between the studied group. In terms of the urinary levels of the three biomarkers in relation to the creatinine ratio, there are clear differences between the study groups. Regarding the fractional excretion of the three biomarkers, there are significant differences between the studied groups (Tables 4 and 5).

Figs. 1–3.

4. Discussion

Different etiological and pathological factors of onset and development contribute to the complex

Table 2. Etiology of ESRD in group 1 and revealed most common cause is obstructive uropathy, followed by glomerulonephritis then idiopathic.

Etiology of ESRD	Number (%)
Obstructive Uropathy	7 (35.0)
Glomerulonephritis	6 (30.0)
Idiopathic	3 (15.0)
Alport Syndrome	2 (10.0)
Cystinosis	1 (5.0)
Lupus Nephritis	1 (5.0)

Table 3. Showing descriptive analysis of the studied groups in light of the outcomes of the lab. In terms of the laboratory results, there is a big difference between the groups that were studied.

Laboratory investigations	Group 1 ($n = 20$)	Group 2 ($n = 20$)	P
SGOT (mg/dl)			
Min.–Max.	2.0–46.0	31.0–43.0	<0.001[a]
Mean ± SD.	17.40 ± 10.90	36.70 ± 3.61	
SGPT (mg/dl)			
Min. – Max.	7.0–45.0	37.0–49.0	<0.001[a]
Mean ± SD.	21.50 ± 8.63	42.75 ± 3.88	
Urea (mg/dl)			
Min.–Max.	84.0–209.0	23.0–39.0	0.001[a]
Mean ± SD.	130.0 ± 34.24	30.20 ± 4.46	
Creat. (mg/dl)			
Min.–Max.	6.10–16.0	0.34–0.49	<0.001[a]
Mean ± SD.	9.04 ± 2.53	0.42 ± 0.04	
Total Ca (mg/dl)			
Min.–Max.	6.70–9.80	8.80–10.10	<0.001[a]
Mean ± SD.	8.61 ± 0.85	9.36 ± 0.45	
Phosph. (mg/dl)			
Min.–Max.	3.60–14.30	3.80–5.30	<0.001[a]
Mean ± SD.	8.50 ± 2.97	4.57 ± 0.50	
PTH (pg/ml)			
Min.–Max.	6.3–17.61	13–65	<0.001[a]
Mean ± SD.	421.8 ± 125.60	31.2 ± 5.4	
Alkaline Phosphatase *(u/l)*			
Min.–Max.	29–1158	22–403	<0.001[a]
Mean ± SD.	370.2 ± 106.7	87.6 ± 65	
K (mmol/l)			
Min.–Max.	3.80–5.10	3.90–4.90	0.026[a]
Mean ± SD.	4.23 ± 0.42	4.54 ± 0.30	
eGFR ml/min/1.73 m^2 surface area 1			
Min.–Max.	3.60–10.20	90–146	<0.001[a]
Mean ± SD.	6.57 ± 1.62	122.2 ± 16.28	

Standard deviation, or SD.
p: *P* value for comparing between the studied groups.
[a] Statistically significant at $P \leq 0.05$.

Table 1. Demographic data of studied patients ($n = 20$ for each group).

Data on demographics	Group 1 ($n = 20$) Number (%)	Group 2 ($n = 20$) Number (%)	P
Sex			
Male	10 (50.0)	10 (50.0)	0.338
Female	10 (50.0)	10 (50.0)	
Age (years)			
Min.–Max.	8.0–16.0	3.0–12.0	0.106
Mean ± SD.	9.60 ± 1.85	8.15 ± 2.76	
Median (IQR)	9.0 (8.0–10.0)	8.0 (5.5–10.0)	

Group 1, 20 patients, with a mean age of 9.60 1.85 and ten male and ten female patients.20 controls in Group 2; 10 men and 10 women; mean age, 8.15 2.76.

Table 4. Serum levels of markers, urine levels of markers, U markers/Cr ratio and fractional excretion of biomarkers (%) in studied groups.

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	P
Markers (ng/ml) (Serum)			
MCP-1			
Min.–Max.	43.04–856.3	42.76–68.21	0.001[a]
Mean ± SD.	237.2 ± 187.8	55.93 ± 7.83	
Median (IQR)	243.8 (72.9–344.5)	56.96 (50.0–61.8)	
Neopterin			
Min.–Max.	2.89–14.09	1.69–42.07	0.007[a]
Mean ± SD.	6.85 ± 3.86	5.65 ± 8.65	
Median (IQR)	5.25 (4.0–11.1)	3.68 (2.9–5.0)	
MCSF			
Min.–Max.	0.18–1.80	0.25–4.30	0.072
Mean ± SD.	0.71 ± 0.48	0.60 ± 0.88	
Median (IQR)	0.50 (0.42–0.85)	0.42 (0.31–0.51)	
Markers (ng/ml) (Urine)			
MCP-1			
Min.–Max.	148.6–417.5	51.98–77.98	<0.001[a]
Mean ± SD.	280.8 ± 77.01	63.14 ± 6.57	
Median (IQR)	265.2 (234.4–351.0)	62.51 (58.0–67.6)	
Neopterin			
Min.–Max.	2.71–16.95	0.92–7.22	<0.001[a]
Mean ± SD.	8.53 ± 4.60	4.17 ± 1.88	
Median (IQR)	9.21 (4.0–12.5)	4.02 (2.8–6.0)	
MCSF			
Min.–Max.	0.38–1.93	0.37–0.84	<0.001[a]
Mean ± SD.	0.88 ± 0.32	0.48 ± 0.10	
Median (IQR)	0.86 (0.70–1.01)	0.47 (0.41–0.52)	
Markers (ng/mg creatinine) (U Markers/Cr ratio)			
MCP-1			
Min.–Max.	18.20–77.86	0.35–1.32	<0.001[a]
Mean ± SD.	47.74 ± 17.83	0.77 ± 0.27	
Median (IQR)	42.70 (38.0–60.3)	0.77 (0.57–0.91)	
Neopterin			
Min.–Max.	381.4–2935.0	8.10–120.30	<0.001[a]
Mean ± SD.	1427.8 ± 823.8	51.44 ± 29.37	
Median (IQR)	1338.0 (604.5–2312.0)	47.61 (27.2–72.4)	
MCSF			
Min. – Max.	53.17–286.30	3.31–9.28	<0.001[a]
Mean ± SD.	150.3 ± 63.21	5.83 ± 2.03	
Median (IQR)	155.6 (101.0–192.2)	5.57 (4.2–7.2)	
Fractional excretion of Biomarkers (%)			
MCP-1			
Min.–Max.	0.27–11.50	0.00–0.01	<0.001[a]
Mean ± SD.	3.03 ± 2.48	0.01 ± 0.00	
Median (IQR)	2.55 (1.5–3.6)	0.0 (0.0–0.01)	
Neopterin			
Min. – Max.	0.19–7.71	0.00–0.02	<0.001[a]
Mean ± SD.	2.71 ± 2.17	0.01 ± 0.00	
Median (IQR)	2.29 (0.82–4.21)	0.01 (0.00–0.01)	
MCSF			
Min. – Max.	0.39–6.61	0.0–0.01	<0.001[a]
Mean ± SD.	2.72 ± 1.92	0.01 ± 0.0	
Median (IQR)	1.96 (1.3–4.0)	0.01 (0.0–0.01)	

Regarding serum biomarkers, there are notable differences between the study groups (with the exception of serum MCSF). Significant differences exist between the studied groups in terms of urinae biomarkers. Inter Quartile Range is IQR.Standard deviation, or SD. p: The P value used to compare the studied groups.

[a] Statistically significant at P 0.05.

pathology of CKD. Long-standing structural and functional kidney problems that result in renal impairment are a well-known sign of chronic kidney disease (CKD).[9] Clinically, increased MCP-1 expression in kidney biopsies and increased urinary level has been proved in an entity of glomerulonephritis associated with monocyte/macrophage infiltration, such as immunoglobulin A (IgA) nephropathy, lupus nephritis, vasculitis and Goodpasture's disease.[10] Numerous studies have discovered that cases of

Table 5. Prognostic performance for MCP-1, Neopterin and MCSF were used to distinguish between groups 1 (n = 20) and 2 (n = 20).

	AUC	*P*	95% C.I	Cut-off	Sensitivity	Specificity	PPV	NPV
MCP-1								
Serum	0.836	<0.001[a]	0.689–0.983	>61.23	80.0	75.0	76.2	78.9
Urine	1.000	<0.001[a]	1.0–1.0	>77.98	100.0	100.0	100.0	100.0
U MCP-1/Cr ratio	1.000	<0.001[a]	1.0–1.0	>1.32	100.0	100.0	100.0	100.0
Fractional excretion	1.000	<0.001[a]	1.0–1.0	>0.01	100.0	100.0	100.0	100.0
Neopterin								
Serum	0.726	0.014[a]	0.567–0.885	>4.03	75.0	55.0	62.5	68.7
Urine	0.760	0.005[a]	0.605–0.915	>4.35	75.0	60.0	65.2	70.6
U MCP-1/Cr ratio	1.000	<0.001[a]	1.0–1.0	>120.3	100.0	100.0	100.0	100.0
Fractional excretion	1.000	<0.001[a]	1.0–1.0	>0.015	100.0	100.0	100.0	100.0
MCSF								
Serum	0.694	0.036[a]	0.527–0.861	>0.42	75.0	60.0	65.2	70.6
Urine	0.910	<0.001[a]	0.803–1.017	>0.53	90.0	85.0	85.7	89.5
U MCP-1/Cr ratio	1.000	<0.001[a]	1.0–1.0	>9.28	100.0	100.0	100.0	100.0
Fractional excretion	1.000	<0.001[a]	1.0–1.0	>0.014	100.0	100.0	100.0	100.0

Area Under a Curve, or AUC. Value of *P* Value of probability.
Confidence Intervals (CI) Negative predictive value (NPV).
Positive predictive value (PPV).
[a] Significant statistically at *P* 0.05.

nephrotic syndrome, chronic and acute glomerulonephritis, and various stages of chronic kidney disease are associated with higher serum or urine neopterin levels,[8,11] Furthermore, it has been established that patients with end-stage renal disease (ESRD) who receive regular hemodialysis have higher neopterin levels, which are correlated with the length of hemodialysis.[12] In particular, the differentiation of macrophages is correlated with nephritis. Higher levels of circulating MCSF in mice promote the development of lupus nephritis, increase the number of monocytes in the blood, and influence the inflammatory phenotype of these monocytes as they differentiate into macrophages.[13]

In terms of MCP-1, we discovered that there was a significant difference in serum levels between the studied groups (*P* value 0.001), with CKD patients having higher serum levels than the control group. This finding is consistent with *Musia et al.*[14] who noted that the serum rank was increased in CKD patient in comparison to normal.

In addition, our study is in agreements with *Vianna et al.*,[15] that have a study for the link of MCP-1 and dyslipidemia in glomerular diseases and found that serum level of MCP-1 was higher in CKD patients. Moreover, *Gregg et al.*,[16] who studied the association of MCP-1 with death and atherosclerosis events in chronic kidney diseases,

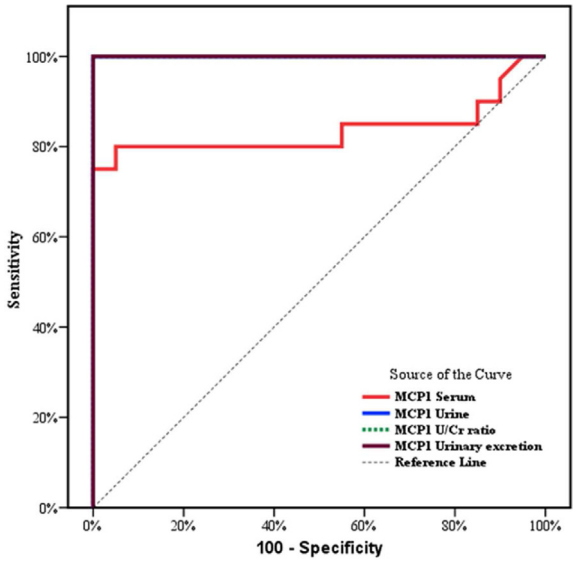

Fig. 1. MCP-1's ROC curve for separating group 1 (n = 20) from group 3 (n = 20).

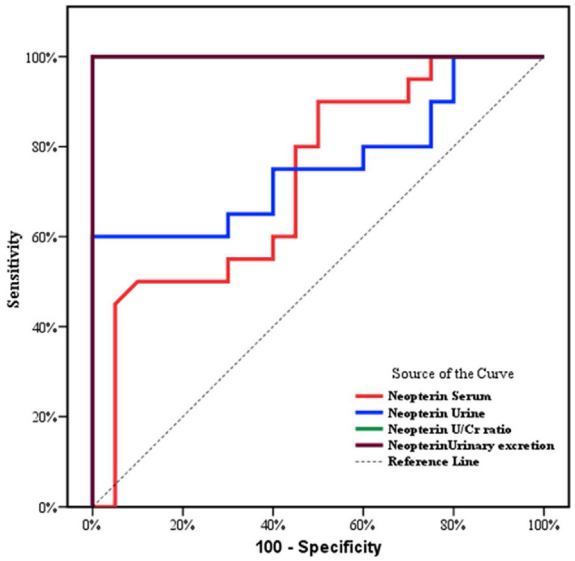

Fig. 2. Neopterin's ROC curve for separating group 1 (n = 20) from group 2 (n = 20).

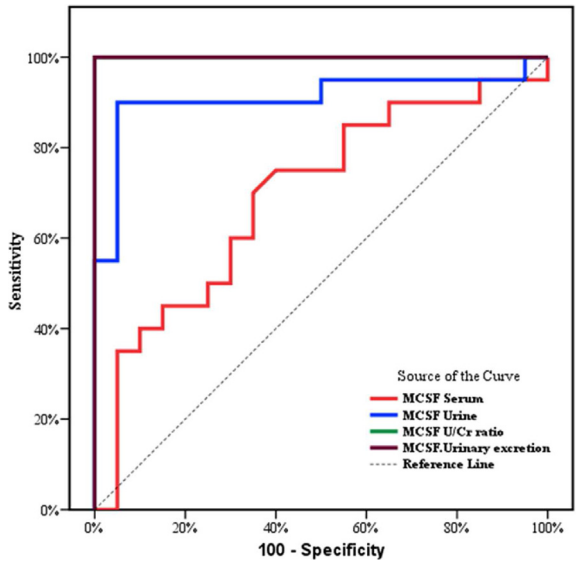

Fig. 3. ROC curve for MCSF to distinguish between groups 1 and 2 (n = 20).

they found that MCP-1 was higher in CKD patients than control groups and negatively associated with eGFR.[16] According to *urinary level* of MCP-1, we found that there was significant difference (*P* value < 0.001) between CKD groups and control groups. However, for accurate assessment we studied the urinary MCP-1/creatinine ratio, we found that there was significant differences between the CKD groups in comparison to control (*P* value < 0.001). This is in agreement with ***Musiał et al.,***[14] found that the urinary level was increased in CKD patient in comparison to normal children. According to *fractional excretion* of MCP-1, we found that there was significant differences between the CKD groups in comparison to control (*P* value < 0.001) and between CKD patients on hemodialysis in comparison to patients on conservative management. This is in agreement with ***Musiał et al.,***[14] who found that the serum level was increased in CKD patient in comparison to normal children.

As regard MCSF, no significant difference among the patients and controls according to serum level of MCSF. This is in disagreement with ***Musiał et al.,***[14] as they hat CKD patients' serum levels were higher than those of healthy children.

According to *urinary level* of MCSF, we found a significant difference between the CKD group and control group (*P* value 0.001). However, for accurate assessment we studied the urinary MCSF/creatinine ratio, We discovered that the CKD groups significantly differed from the control group (*P* value 0.001). This concurs with the findings of ***Musial et al.***[14] who found that the urinary level was increased in CKD patient in comparison to normal children.

According to *fractional excretion* of MCSF We discovered that the CKD groups significantly differed from the control group (*P* value 0.001). This is in line with what ***Musia et al.,***[14] said as they found that the serum level was increased in CKD patient in comparison to normal children.

As regard Neopterin, we found that there were major difference (*P* value < 0.001) of *serum level* of Neopterin. This was in agreement with ***Lhee et al.,***[7] ***Üniivar& Aslanhan,***[12] ***and Musiał et al.***[14] who found that serum Neopterin was significantly increased in CKD patient in comparison to normal population. According to *urinary level* of Neopterin, We discovered that there was a significant difference between the CKD group and the control group (*P* value 0.001). However, for accurate assessment we studied the urinary Neopterin/creatinine ratio, We discovered that the CKD groups significantly differed from the control groups (*P* value 0.001) and between CKD patients on hemodialysis in comparison to patients on conservative management. This is consistent with ***Lhee et al.,***[7] and ***Musiał et al.,***[14] as they noted that the urinary level was increased in CKD patients in comparison to the normal population. According to *fractional excretion* of Neopterin, We discovered that there were significant differences in the CKD groups compared to the control group (*P* value 0.001) and between CKD patients receiving hemodialysis and those receiving conservative management. This is in line with what ***Musia et al.,***[14] said, as they noted that CKD patients' serum levels were higher than those of healthy children.

4.1. Conclusion

MCP-1, Neopterin and MCSF can be future biomarkers for early detection of renal affection in patients with CKD and can be useful for prognosis of progression of CKD.

Conflicts of interest

Authors declare that there is no conflict of interest, no financial issues to be declared.

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