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The Dynamics of C-reactive Protein Associated with Nutritional Status Changes in Kidney Failure Patients at Initiation and After 3 Months of Dialysis

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Abstract: Among kidney failure patients, especially those on dialysis, malnutrition is associated with poor outcomes. Malnutrition is a multifactorial process, including inflammation, which can be measured by C-reactive protein (CRP). The objective is to evaluate the dynamics of CRP associated with nutritional status changes in kidney failure patients at initiation and after 3 months of dialysis. A prospective cohort study using a consecutive sampling method consisting of 40 kidney failure patients who received initial dialysis at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia from January-March 2020. Nutritional status was evaluated with Subjective Global Assessment (SGA), and CRP was measured at the initial dialysis and after 3 months. All subjects received nutritional education at the beginning. Nutritional status was defined as well-nourished (WN, SGA A) and malnourished (MN, SGA B and C), then classified into 4 groups denoting nutritional changes: Group 1 (WN to WN), Group 2 (MN to WN), Group 3 (WN to MN), and Group 4 (MN to MN). ANOVA, paired t-test, and chi-square test (significance p<0.05) were used for statistical analyses. Subject's mean age was 50.5±14.8 years old; 52.5% were male. Diabetes and obstructive nephropathy were the most frequent underlying diseases, both had a prevalence of 35%. At initiation, the prevalence of malnutrition was 77.5%; after 3 months, it was 70%. The highest proportion of Group 4 were female (62.5%) and those with diabetes (45.9%). Among all subjects, mean CRP decreased (9.4±32.3 mg/dL) after 3 months. While mean CRP based on nutritional changes, Group 2 had the highest reduction (18.8±26.8 mg/dL), and Group 3, CRP increased (17.5±17.0 mg/dL). C-reactive protein is negatively associated with nutritional status changes in kidney failure patients after 3 months of dialysis. Malnutrition was higher in female subjects and those with diabetes.

Keywords: Kidney Failure, Dialysis, Nutritional Status, Inflammation, C-Reactive Protein

1. INTRODUCTION

Kidney failure is a permanent and end-stage chronic kidney disease process, characterized by a glomerular filtration rate <15ml/min/1.73m^2. Patients with kidney failure require renal replacement therapy, dialysis, or kidney transplant.[1] According to the Global Burden of Disease (GBD) Study 2017, 0.041% of kidney failure patients were on dialysis.[2] The Indonesian Renal Registry (IRR) 2018 reported there were 132,000 kidney failure patients on dialysis.[3] Both studies reported increased prevalence in comparison with past studies.

Kidney failure patients, especially those on dialysis, face many challenges throughout their lives. One of these challenges is malnutrition.[4] Since 2008, the International Society of Renal

Nutrition and Metabolism (ISRNM)
has recommended using protein-energy wasting (PEW) as aterm to describe the malnutrition process in kidney failure. Prevalence of PEW in kidney failure patients on dialysis is 18-75%, with varied based on the method used to evaluate nutritional status.[4,5] PEW is associated with poor outcomes, including a higher risk of morbidity and mortality.[5,6] Therefore, nutritional status should be monitored regularly to ensure early detection of malnutrition, and maintenance or improvement of nutritional status. Protein-energy wasting is a multifactorial process, in which inflammation plays an important role. Dialysis also contributes to inflammation. Inflammation is associated with higher PEW, muscle catabolism, and mortality.[5,6] Inflammation can be measured with CRP, which is an acute-phase reactant produced in the liver as a response to inflammation. Higher CRP values indicate greater inflammation.[7]

This study's objective is to evaluate the dynamics of CRP and its association with nutritional status changes in kidney failure patients at initiation of dialysis and after 3 months.

2. METHODS

Research Design

This was a prospective cohort study at Dr. Wahidin Sudirohusodo Hospital in Makassar, South Sulawesi Indonesia.

Research Subjects

All kidney failure patients over 18 years old who started dialysis were recruited with consecutive sampling from January 2020 until March 2020. Subjects who met inclusion criteria and who were willing to participate signed informed consents. The only exclusion criteria was decrease of consciousness.

Research Tools

All subjects were evaluated using Subjective Global Assessment (SGA), as recommended by the IRR; this included obtaining each patient's medical history and performing a physical examination. Nutritional status was categorized as SGA A (well-nourished/WN), SGA B (mild to moderate malnourished/MN), and SGA C (severe malnourished/MN). For laboratory measures, CRP was examined at Dr. Wahidin Sudirohusodo Hospital.

Research Data Collection

All subjects' demographics were recorded, including age, sex, and underlying diseases. For laboratory evaluation, CRP was measured both at the initiation and after 3 months of dialysis.

Initial nutritional status was evaluated with SGA, and categorized into SGA A, B, and C. All subjects were given nutrition education at the beginning of dialysis. After 3 months of dialysis, nutritional status was re-evaluated using SGA, and patients were classified into 4 groups according to nutritional status changes: Group 1 (WN to WN), Group 2 (MN to WN), Group 3 (WN to MN), and Group 4 (MN to MN).

Research Data Analysis

Statistical analysis was performed with SPSS V22.0. Statistical analysis was performed using descriptive statistical calculation and frequency distribution, as well as an ANOVA statistical test, paired t-test, and chi-square test. Results were significant if $p<0.05$.

Ethical Clearance

This study protocol was approved by the Health Research Ethics Commission of Universitas Hasanuddin, Medical Faculty, following the ethical recommendations from the Helsinki Declaration of 1975, with approval letter number 196/UN4.6.4.5.31/PP36/2020.

3. RESULTS

Subject Characteristics

There were 40 patients enrolled in this study from January 2020 until March 2020, with 21 males (52.5%) and 19 females (47.5%). Subjects ranged in age from 20-75 years, with a mean age of 50.5±14.8 years. The most frequent underlying diseases were diabetes and obstructive nephropathy, with a prevalence of 35% each. (Table 1)

Nutritional Status Changes After 3 Months of Dialysis

Table 2 illustrates the proportion of patients with various nutritional statuses at initiation of dialysis and 3 months later. At initiation, the prevalence of malnourished kidney failure patients (SGA B and C) was 77.5%, while after 3 months dialysis, it was 70%.
Table 3 illustrates that Group 1 consisted of males only; in contrast, Group 4 had a higher proportion of females. However, these findings were not statistically significant (p=0,056). In Group 4, a higher

proportion of patients had diabetes compared to other underlying diseases.

C-Reactive Protein Associated with Nutritional Status Changes at Initiation of Dialysis and After 3 Months

Table 4 describes mean CRP at initiation and after 3 months of dialysis according to changes in each group's nutritional status. Subjects in Groups 1 and 3 had lower CRP values of 13.5±9.3 mg/dL and 7.4±6.3 mg/dL, respectively. In comparison, subjects in Groups 2 and 4 had higher CRP values of 28.1±34.2 mg/dL and 35.9±36.1 mg/dL, respectively. After 3 months of dialysis, subjects in Groups 1 and 2 had lower CRP values of 6.1±3.4 mg/dL and 9.2±7.9 mg/dL, respectively. In contrast, subjects in Groups 3 and 4 had higher CRP values, (24.8±22.3 mg/dL and 24.4±21.5 mg/dL, respectively).

When compared at initial dialysis treatment and after 3 months, mean CRP was decreased by 9.4±32.3 mg/dL. However, a comparison of nutritional status changes in all 4 groups revealed that only Group 3 experienced an increased CRP of 17.5±17.0 mg/dL. In contrast, subjects in

Group 2 had the greatest reduction in CRP with decreases of 18.8±26.8 mg/dL. Although, none was statistically significant.

4. DISCUSSION

Forty subjects were enrolled in this study, with a mean age of 50.5±14.8 years. According to the IRR's 2018 report, the highest proportion of kidney failure was found in individuals between the ages of 45-64 years.[3] As kidney function naturally decreases with aging, age alone is a risk factor for kidney failure. Also, underlying diseases that may cause kidney failure are more prevalent in older individuals, including diabetes and hypertension.[8]

Regarding sex, the proportion of males on dialysis was higher (52.5% male). GBD 2017 and IRR 2018 also reported a higher proportion of males on dialysis, despite the fact that a higher proportion of women were diagnosed with kidney failure.[2,3] This may be because men tend to experience a more rapid decline in kidney function.[2] Neugarten and Golestaneh reported estrogen has a protective role toward kidney function in female experimental models. However, in human, other factors such as lifestyle, culture, and socioeconomic may have influence.[9]

In our study, the most prevalent underlying diseases were diabetes and obstructive nephropathy, with a proportion of 35% each. In contrast, the GBD 2017 report found the most prevalent underlying diseases were diabetes and hypertension [2], while in Indonesia, the most prevalent were hypertension and diabetes.[3] Other studies by Prakash et al. and Oluseyi and Enajite also reported diabetes as the most prevalent underlying disease in kidney failure.[10,11]

Initially, the proportion of malnourished subjects in our study was 77.5%. According to the Kidney Disease Outcomes Quality Initiative, the prevalence of malnutrition in kidney failure patients on dialysis was 18-75%, varied based on the method used to evaluate nutritional status .[4] In another study, Prakash et al. reported the prevalence of malnutrition was 65%, while Ghorbani et al. found the prevalence of malnutrition was 29.7%.[10,12] These differences in malnutrition statistics are likely due to differences in food intake, therapy management, and methods used to evaluate nutritional status.[12,13] At the end of our study, the prevalence of malnourished subjects decreased to 70%. Improved nutrition status in kidney failure patients on dialysis was also reported by Kwon et al., who found that the prevalence of malnourished subjects decreased from 36.8% to 11.9% after 12 months of dialysis.[14]

After routine dialysis for 3 months, the subjects in this study were stratified into groups according to nutritional status changes; we found a higher proportion of female subjects with malnutrition compared to males. Similar results were also reported by Ghorbani et al., who found a higher proportion of malnutrition in females, and noted that female is a predictive factor in malnutrition.[12] However, different results were reported by Yigit, who found no difference in malnutrition between both sex.[15]

At the end of our study, diabetes was the most prevalent underlying disease in Group 4. Compared to other underlying conditions, diabetes is most associated with poor outcomes, due to the role insulin resistance plays in higher muscle catabolism. Also, diabetes is an independent risk factor for inflammation, and both muscle catabolism and inflammation are factors in the etiology of malnutrition.[16,17]

In this study, at the initiation of dialysis and after 3 months of treatment, CRP was consistently lower in well-nourished subjects and higher in malnourished subjects. In contrast, Group 2 (MN to WN) experienced the greatest reduction in CRP, while Group 3 (WN to MN) experienced increased CRP. We found that inflammation has a negative association with nutritional status, and suggest that it may play an important role in kidney failure patients' prognosis.

Naturally, all kidney failure patients experience low-grade inflammation.[18] Inflammation in kidney failure is associated with poor outcomes and a higher risk of mortality, especially in patients with concurrent cardiovascular disease.[7,16] The exact cause of inflammation in kidney failure is still being studied. The higher levels of pro-inflammatory mediators were found in kidney failure patients compared to a healthy control group. This is presumably due to decreased elimination and/or increased regeneration of pro-inflammatory mediators that precipitate inflammation. Other factors, including age, sex, comorbidities such as diabetes and infection, and genetics also have a role in promoting inflammation.[16]

Inflammation is also a factor in the etiology of malnutrition in kidney failure, especially in patients on dialysis, and with increased dialysis duration.[5] Dialysis is associated with activation of an inflammatory cascade characterized by increased CRP and the pro-inflammatory mediator IL-6.[19] In a study by Kaur et al., higher CRP was found in kidney failure patients on dialysis compared to the control group.[20] High CRP is also associated with a decrease in nutritional status and its associated parameters. Studies by Ghorbani et al. and Yigit reported similar results, noting that CRP has a negative association with nutritional status and albumin.[12,15]

Patients with kidney failure, especially those on dialysis, have a high prevalence of malnutrition. Regular evaluation of nutritional status is important for early detection of malnutrition and for developing proper nutrition interventions to help patients to meet optimal nutrient requirements.[21] The National Kidney Foundation and the Academy of Nutrition and Dietetics recommend management of daily calories, daily protein intake, and other micronutrients to ensure adequate intakes.[22]

In our study, subjects were given nutrition education by members of the clinical nutrition department at the beginning of dialysis, as a part of the nutritional management protocol for patients with kidney failure. A study by Vijaya et al. reported improvement in nutritional status in subjects with regular nutrition education by a professional dietitian compared to the control.[23] Another study by Campbell et al. showed decreased CRP in subjects with regular nutrition education compared to the control.[24]

This study is the first at Dr. Wahidin Sudirohuso Hospital, Makassar, Indonesia to evaluate the dynamics of CRP in 40 kidney failure patients at initiation of dialysis and after 3 months. We suggest nutrition evaluation, nutritional education, and CRP measurement should be conducted regularly among dialysis patients. A limitation of this study is that we didn't control for other factors that might affect CRP, such as comorbidities and dialysis. Thus, a larger-scale and multi-center study, with controls for other factors affecting CRP, would help provide a better understanding of the dynamics of CRP and its relation to nutritional status changes in Indonesia.

Table 1 : **Subject characteristics at initial dialysis**

Variable		N	%
Age, mean (year)		50.5 ± 14.8	
Sex			
	Male	21	52.5
	Female	19	47.5
Underlying disease			
	Diabetes	14	35
	Hypertension	10	25
	Obstructive nephropathy	14	35
	Glomerulonephritis	2	5

Table 2: Prevalence of nutritional status at initiation and after 3 months of dialysis

	Initial	3 Months
Well-nourished (SGA A), n(%)	9(22.5)	12(30)
Malnourished (SGA B and C), n(%)	31(77.5)	28(70)

Table 3 :Nutritional status changes after 3 months of dialysis based on sex and underlying disease

		Nutritional Status Changes					
			Group 1	Group 2	Group 3	Groups 4	
		Total	WN to WN	MN to WN	WN to MN	MN to MN	
		(n = 40)	(n = 5)	(n = 7)	(n = 4)	(n = 24)	*P*
Sex							
	Male, n(%)	21(52.5)	5(100)	4(57.1)	3(75)	9(37.5)	0.056*
	Female, n(%)	19(47.5)	0(0)	3(42.9)	1(25)	15(62.5)	
Underlying disease							
	Diabetes, n(%)	14(35)	0(0)	2(28.6)	1(25)	11(45.9)	
	Hypertension, n(%)	10(25)	2(40)	4(57.1)	1(25)	3(12.5)	
	Obstructive Nephropathy, n(%)	14(35)	3(60)	1(14.3)	2(50)	8(33.3)	
	Glomerulonephritis n(%)	2(5)	0(0)	0(0)	0(0)	2(8.3)	
*significant if p<0.05. WN well-nourished; MN malnourished							

Table 4 : Comparison of C-reactive protein in nutritional status changes at initiation

and after 3 months of dialysis							
			Nutritional Status Changes				
			Group 1	Group 2	Group 3	Group 4	
		Total	WN to WN	MN to WN	WN to MN	MN to MN	
		(n = 40)	(n = 5)	(n = 7)	(n = 4)	(n = 24)	*P*
CRP, initial mg/dL		28.9 ± 32.7	13.5 ± 9.3	28.1 ± 34.2	7.4 ± 6.3	35.9 ± 36.1	0.274 *
CRP, 3 months, mg/dL		19.4 ± 19.5	6.1 ± 3.4	9.2 ± 7.9	24.8 ± 22.3	24.4 ± 21.5	0.102 *
Delta CRP, mg/dL		-9.4 ± 32.3	-7.5 ± 7.4	-18.8 ± 26.8	17.5 ± 17.0	-11.5 ± 37.1	0.334 *
*significant if p<0.05. WN well-nourished; MN malnourished							

5. CONCLUSION

Our study found that in kidney failure patients 3 months after initiation of dialysis, CRP was negatively associated with nutritional status changes. A high prevalence of malnutrition was seen in female subjects and those with diabetes.

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Conflict Of Interest
The authors have no potential or relevant conflicts of interest to declare.

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