

**THE COMBINATION OF PROBIOTIC AND CALCIUM CARBONATE DECREASE MONOCYTE COUNT OF END-STAGE RENAL DISEASE PATIENT**Ari Yulistianingsih¹✉, Taufik Maryusman², Mohammad Sulchan¹, Shofa Chasani³¹Departemen Ilmu Gizi, Fakultas Kedokteran, Universitas Diponegoro, Indonesia²Program Studi S1 Ilmu Gizi UPN "Veteran" Jakarta, Indonesia³Bagian Penyakit Dalam, Fakultas Kedokteran, Universitas Diponegoro, Indonesia**Article Info***Article History:*

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Elevated monocyte count is correlated to the decrease of renal function and disease progressivity on end-stage renal disease (ESRD) patients. Probiotic that utilize lactobacillus species is known to play a role in maintaining immunity system balance by inducing the monocyte apoptosis. The combination between probiotic and calcium carbonate could increase probiotic colonization in the gastrointestinal tract. The aim of this study was to analyze the effect of probiotic and calcium carbonate combination toward reduction of monocyte count on ESRD patient at Rumah Sehat Terpadu Dompot Dhuafa Bogor Hospital. This study was true experimental research with randomized pre-post test control group design. Twenty four ESRD patient were randomly enrolled into treatment group (n=12) and control (n=12). The treatment group received probiotic and calcium carbonate, whereas control group received standardized calcium carbonate for 21 days. There was a significant decrease of monocyte (p=0.03) after administration of probiotic and calcium carbonate.

Introductions

End-stage renal disease (ESRD) is defined as structural or functional abnormality of renal function with reduced glomerular filtration rate, presence of albuminuria, or both of those occurring for ≥ 3 months (Inker, 2014). End-stage renal disease is a risk factor for cardiac disease and other systemic complications. The main causes of ESRD in developing countries are diabetes mellitus and hypertension. Global Burden of Disease put ESRD at the 27th rank as world's highest mortality cause at 1990 and raised into 18th rank at 2010 (Jha, 2013). The percentage of ESRD patient undergoing hemodialysis in Indonesia was 84% on 2014 according to Indonesian Renal Registry report.

The province with highest ESRD cases was West Java province with 3654 number of cases (IRR, 2014).

Renal function damage may influence metabolic balance and glomerular filtration resulting in a condition where the kidney is unable to excrete urea, resulting in urea accumulation in the blood. In general, ESRD patients undergoing hemodialysis are experiencing uremia, hence there would be imbalance between pro- and anti-inflammation and also immune system imbalance. This condition is aggravated by malnutrition which is usually found in ESRD patient (Cohen, 2012). Several studies explained that monocyte count is a predictor of vascular disease and

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atherosclerosis in ESRD patient (Ghattas, 2013). Otherwise, decreasing glomerular filtration rate is related to the increase in monocyte count (Ganda, 2013).

Conservative therapy is one of treatment for ESRD patient. Conservative therapy through medication, nutritional therapy, and precise functional nutrients could improve immune system and nutrient absorption. Probiotic is food supplement originated from living microbes or culture of living microorganism; when given in adequate amount it could maintain gut microflora balance and boost immune system. *Lactobacillus* probiotics are lactic acid bacteria that are commonly used in food industry because they have medicative and therapeutic potency. Systemic inflammation and urea accumulation (uremia) play a role in the pathogenesis of cardiac and vascular disease among ESRD patients caused by gut flora disorder. *Lactobacillus* is expected to increase nutrient absorption, decrease gastrointestinal tract disorder, and increase immune response (Mafra, 2014). The first probiotic product patented to maintain renal health is capsule probiotic (Renadyl™) consisted of *S. thermophilus* KB 19, *L. acidophilus* KB 27, dan *B. longum* KB 31 strains, containing 3 billion CFU per capsule. This probiotic could decrease uremia toxin accumulation in the blood of ESRD patient (Ranganathan, 2013). Studies on probiotic supplement from *Lactobacillus casei* Shirota strain showed that there was a reduction of leukocyte and improvement in renal function as shown through increased GFR on gastroenteritis patients with acute kidney injury (Akoglu, 2015).

Recently, most probiotic products are packaged in capsule form in order to be easily consumed. Studies on the 3rd and 4th stage of chronic kidney disease revealed that probiotic supplementation in form of capsule (Renadyl™) for 4 months with the highest dosage of 270×10^9 CFU per day is safe and well tolerated (Ranganathan, 2013). This study utilized probiotic supplementation in the form of Lacidofil™ capsule consisting of *Lactobacillus helveticus* Rossell -52 and *Lactobacillus rhamnosus* Rosell -11 strains with total bacteria of 2.0×10^9 CFU given as 2 capsules per day, which is a safe from and within safety tolerance

limit. *Lactobacillus rhamnosus* GG could prevent apoptosis induced by cytokines on gut epithelial cell by blocking tumor necrosis factor (TNF) (K Gogineni, 2013). The utilization of probiotic and calcium carbonate combination is known to increase the number viable cell in gastrointestinal tract (Zhao, 2009).

Studies aiming to understand the effect of probiotic strain *Lactobacillus* toward monocyte count in ESRD patient has not been reported yet. Therefore, the authors were interested to analyze the effect of probiotic and calcium carbonate combination on changes in monocyte count among ESRD patients at Rumah Sehat Terpadu Dompot Dhuafa Bogor Hospital.

Methods

This study was true experimental study with randomized pre-post test control group design conducted in Hemodialysis Unit Rumah Sehat Terpadu Dompot Dhuafa Hospital, Bogor, West Java, Indonesia on February – March, 2017. Subjects were randomly divided into two groups consisting of treatment group and control group. Subject inclusion criteria were 1) ESRD patient undergoing hemodialysis for >3 months, 2) male or female aged 18-60 years old, 3) having good nutritional status measured by anthropometry. Exclusion criteria were 1) HIV/AIDS patient, 2) patients consuming immunosuppressant and immunomodulator medications, 3) patient with high fever. Drop out criteria were died or admitted into Intensive Care Unit (ICU).

The sample size was determined by minimal sample measurement formula. To prevent drop out possibility of sample, the researchers added reserve samples as much as 20%. Sample size needed for each groups were 13 subjects, therefore the total sample size needed were 2×13 subjects = 26 subjects. Treatment group received intervention in form of combined probiotic at a dosage of 2×10^9 CFU, 2 capsules per day, and calcium carbonate 500 mg x 3 tablets per day for 21 days. Control group only received standardized intervention which was calcium carbonate 500 mg x 3 tablets per day for 21 days. Intervention was monitored by intake compliance form.

Lacidofil™ capsule containing *Lactobacillus helveticus* Rossell-52 0.1×10^9

CFU and *Lactobacillus rhamnosus Rosell-11* 1.9×10^9 CFU with total bacteria count 2.0×10^9 CFU was used as the probiotic in this study. Product safety for Lacidofil™ in Indonesia is in accordance to FAO/WHO 2002 standard, which is containing living bacteria in order to maintain gut flora balance, having adequate amount (containing 2 billion bacteria), and being registered at North America and Europe based on clinical research. Monocyte count was conducted before and after intervention by laboratory staff using flow cytometry method and hematology analyzer tools. Nutritional intake data was obtained through 24 hours food recall method. Data results of nutritional intake were determined using Nutrisurvey 2007 program and compared with Nutritional Adequacy Rate (NAR) 2013. Statistical analysis was based on independent t-test and paired t-test. Subjects received written informed consent before being enrolled to study. This study had obtained Ethical Clearance agreement from Health Research Ethics Committee, Faculty of Medicine, Universitas Diponegoro Semarang (No.149/EC/FK-RSDK/IV/2017).

Results and Discussions

Number of research subjects fulfilling inclusion and exclusion criteria was 26 subjects and were divided into control and treatment

group with simple randomization method. During the research, there were 2 drop outs, leaving 24 remaining subjects. Subjects' characteristic (Table 1) showed that treatment group was mostly male, whereas control group was mostly female. Dialysis Outcomes and Practice Patterns Study (DOPPS) prospective study mentioned that hemodialysis patient was mostly male because average GFR value of male patients was higher than female (Bohlke, 2008). However, *US Renal Data System* (USRDS) reported that Chronic Kidney Disease prevalence in 2007-2012 was higher among females (15.1%) than males (12.1%) (USRDS, 2016).

Chronic Kidney Disease (CKD) is a multifactorial disease affected by many risk factors including hypertension, type II DM, heart disease, and asthma. According to past illness, several subjects in the treatment group had a history of hypertension (N=10; 83.3%), meanwhile in the control group some had type II DM (n=5; 41.7%) and hypertension (n=5; 41.7%). *Indonesian Renal Registry* reports on 2014, the main cause of CKD is hypertension, as many as 37% (IRR, 2004). *Cross sectional* research on 2011 by Eva at Bogor concluded that subjects with hypertension and type II DM had higher risk, 3.7 times and 2.5 times

Table 1. Subject Characteristics Description

Characteristics	Treatment Group (n=12)		Control Group (n=12)	
	n	%	n	%
Gender				
Male	7	58.3	5	41.7
Female	5	41.7	7	58.3
Disease History				
Diabetes	1	8.3	5	41.7
Hypertension	10	83.3	5	41.7
Cardiac disease	0	0	1	8.3
Asthma	1	8.3	1	8.3
Nutritional Status				
Under	1	8.3	1	8.3
Normal	6	50	7	58.3
Over	5	41.7	4	33.3
Duration of Hemodialysis (months)				
4 – 12	8	66.7	9	75
13 – 24	1	8.3	2	16.7
25 – 36	1	8.3	1	8.3
37 – 48	2	16.7	0	0

Source : Primary Data

Table 2. Subject Characters in the Beginning of the Research

Character	Treatment group (n=12)				Control group (n=12)				p
	Med	Min	Max	Mean±SD	Med	Min	Max	Mean±SD	
Age (year)	44.5	24	63	44.2±11.5	52	33	60	48.7±9.7	0.31 ^a
Monocyte count (%)	8	4	17	8.8±3.7	7	5	10	7.4±2	0.28 ^a

^aIndependent t-test

Table 3. Nutrition Intake and Consumption Level

Variable	Treatment Group (n=12)	Control Group (n=12)	p
Nutrition Intake			
Vitamin C (mg)	40.68±26.4	21.2 (3-145.1)	0.2 ^b
Vitamin A (µg)	827.9 (33.4-4746.5)	652.5 (130.3-3445.7)	0.53 ^b
Zinc (mg)	4.54±1.6	3.68±1.1	0.13 ^a
Consumption Level (%)			
Vitamin C	49.3±34.1	28.2 (4-193.5)	0.25 ^b
Vitamin A	156.4 (5.6-949.3)	127.3 (21.7-689.1)	0.53 ^b
Zinc	39.8±16.2	32.8±8.9	0.2 ^a

a : *Independent t test* b : *Mann-Whitney*

respectively, for developing CKD (Sulistiowati, 2015).

Most subjects in the treatment (n=8; 66.7%) and control (n=9; 75%) group had been on hemodialysis therapy less than 13 months. Of 6 (50%) subjects in the treatment group and 7(58.3%) subjects of control group had normal nutrition index. Chi-yuan research mentioned that 58% people with CKD had normal body mass index (BMI). A high BMI is a risk factor for developing CKD (Hsu, 2006), whereas other studies defined that BMI >40 kg/m² was not related to mortality caused by heart disease and non-malignancy in CKD patients. The duration of hemodialysis affects the health and life quality of CKD patients. A research stated that there was significant difference between quality of life and psychological and physical dimension in CKD patients after being treated with hemodialysis (Supriyadi, 2013).

The mean age was 44.2 years old (treatment group) and 48.7 years old (control group) with the youngest and oldest age was 24 years old and 63 years old, respectively. In 2010, globally, almost end stage renal disease developed in patients aged more than 65 years old (USRDS, 2016). Therefore, in this research CKD can be developed in 24 years old patient. The normal monocyte count based on references was 2-8%. Mean monocyte

count was in the normal range in both group (8.8±3.7% n treatment group with the highest value being 17%, meanwhile in control group it was 7.4±2% with the highest value being 10%). There was no statistical difference in mean age and monocyte count between two groups at the beginning of the research (p>0.05) (Table 2).

Mean intake of vitamin C (40.68), vitamin A (1251.6 mg), and zinc (4.54mg) was higher in treatment group than control group with consecutive mean 31.65 mg, 1215.6 µg, and 3.68 mg but there was no statistically significant difference in intake between the two groups (p>0.05). Mean consumption level of vitamin C (49.3%), vitamin A (236.8%), and zinc (39.8%) was higher in treatment group than control group with consecutive percentages 40.1%, 222.9%, 32.8%. Therefore, mean consumption level of vitamin c and zinc in both groups were in deficit category (<70%), in contrast with vitamin A consumption level which was in high category (>100%).

CKD patients have decreased vitamin and mineral intake due to malnutrition and gastrointestinal disorder. Current research is concordance with other studies in which vitamin C intake in CKD patients were low due to potassium restriction. Oxalates, metabolite of ascorbic acid, in urine and serum were elevated in CKD patients who received ascorbic

Table 4. The Effect of Probiotic and Calcium Carbonate Combination on Monocyte Count.

Variable	Treatment Group (mean ± SD)	Control Group (mean ± SD)	p
Monocyte count			
Before treatment	8.8±3.7	7.4±2.0	0.28 ^b
After 21 days	7.2±3.1	8.6±2.5	0.23 ^b
Δ monocyte count (%)	-1.6±2.2	1.2±2.5	0.01 ^b
p	p=0.03 ^a	p=0.13 ^a	

^apaired t-test ^bindependent t-test

supplementation. High dose of vitamin C was not recommended for CKD patients since it increased risk for hyperoxalosis. Furthermore, recent study investigated that consumption of 500mg vitamin C daily in non-CKD patients at risk of oxalate stone formation did not increase oxalate excretion in urine (Steiber, 2011). Vitamin A consumption was high in both groups, which was consistent with the theory that CKD patients had higher level of vitamin A in serum. The responsible mechanisms are decreased RBP (retinol binding protein) catabolism as main transporter, or elevation blood retinol in CKD patients. It means that vitamin A supplementation is not needed for CKD patients.

Ho was accepted according to statistical analysis $p < 0.05$, in which there was no difference between Vitamin C, vitamin A, and Zinc intake in both group ($p < 0.05$). Most of the subjects consume rice-vegetables only, rice-egg white, or rice-tempeh only in every meal. Moreover, CKD patients had lower food intake due to gastrointestinal disorder including decreased appetite, nausea, and vomiting due to haemodialysis (Yani, 2017).

Table 4 shows the influence of probiotic and calcium carbonate combination on monocyte count. Monocyte count decreased 1.6% in treatment group and increased 1.2% in control group. There was significant difference in monocyte count between the two groups after intervention ($p = 0.01$), as well as the difference in monocyte count before and after administration of probiotic and calcium carbonate combination ($p = 0.03$).

Non-specific immune response, including mononuclear cell (monocyte and macrophage) and polymorphonuclear cell, plays a role as the first defence. Monocyte act as antigen presenting cells for microbes,

tissue regeneration process, pathogenesis of inflammation, and atherosclerosis. Monocyte count in control group was significantly decreased ($p = 0.03$) and this was in accordance to the study by Gleeson et al, which found that probiotic (*Lactobacillus casei Shirota*) administration to infected athletes could reduce monocyte count (Gleeson, 2011). In contrast, other studies found that probiotic administration for 4 weeks did not affect phagocytosis activity and cytokine secretion of mononuclear cells (Seifert, 2011). The differences in outcome might be caused by different probiotic dose, duration of intervention and food intake. After the intervention, the average number of monocyte in control group tend to elevate. This could be due to Diabetes mellitus which was found more in control group than treatment group. The responsible mechanism for monocyte count increase in DM patients was not fully understood. Total peripheral leucocyte, monocyte, and neutrophil were elevated in line with diabetic nephropathy. Nephropathy diabetic patients was significantly related to total leucocyte count.

Mucosal immune system protects mucous membrane from pathogenic microbe invasion, protect antigen uptake, and prevent abnormal immune response. *Mucosal-associated lymphoid tissue* (MALT) is aggregation of nonencapsulated organized lymphoid tissue that is populated by T cells, B cells, and APC (*antigen-presenting cells*) or dendritic cells. MALT play an important role in selecting mechanism and intensity of an effector to avoid tissue damage and excessive immune response, especially in regulating the balance between pro- and anti- inflammatory cytokine (Kataoka, 2013).

Some In-vitro studies investigated that *L. helveticus* met the criteria for probiotic since

its characteristics includes the capability to defend against pathogenic bacteria, survive in gastrointestinal tract, and its existence in epithelial cells. Moreover, in vivo study in animals showed that *L. helveticus* could stimulate immune system, improve defence against pathogenic bacterial, influence gastrointestinal tract (GIT) microbiota population, and prevent GIT infection. Protective effect was found when *L. helveticus* was taken orally (Skrzypczak, 2015). *Lactobacillus rhamnosus Rosell-11* has benefits for GIT and immune system, especially defending against pathogens in GIT and urinary tract. *Lactobacillus rhamnosus* prevent pathogenic bacteria growth in GIT. Goldin dan Gorbach investigated that *L. rhamnosus* was resistant to stomach acid. A study on patients with renal disease elucidate that *L. rhamnosus* could be transported through GIT resistant to vancomycin antibiotic (Manley, 2007).

Lactobacillus rhamnosus GG act on monocyte and macrophage by increasing INF , IL-12, and IL-18 production and NF- κ B induction (Kusumaningsih, 2014). Ex vivo research stated that mononuclear and polymorphonuclear phagocytic activity increased following *L. rhamnosus* HN001 and *B. lactis* HN109 consumption. The known mechanism was that *Lactobacillus rhamnosus* and *Lactobacillus helveticus* produce inhibitor substances (lactic acid and bacteriomycin) for epithelial cells adhesion (Delcenserie, 2008). This process helps the normal flora to dominate, stimulate mucus production, metabolic activity that reduce microbe toxin, help food digestion, and balance the inflammatory cytokine and interleukin.

Calcium carbonate is the standard intervention for end-stage renal disease. KDOQI (*Kidney Disease Outcomes Qualitative Initiative*) suggested that calcium carbonate administration for CKD patients on hemodialysis was aimed to manage calcium and phosphor concentration as well as bone calcification. The combination of calcium carbonate with lactic acid strain probiotic is expected to increase calcium carbonate absorption since it needs acidic condition to dissolve well in small intestine (Houtkooper, 2017). Furthermore, administration of probiotic containing *Lactobacillus* strain can

increase viable cell up to 150-220% (Zhao, 2009). However, other studies suggested that addition of calcium phosphate in *Lactobacillus helveticus R002* and *Lactobacillus rhamnosus R0011* probiotic supplementation could increase the number of *Lactobacillus spp* viable cell, while calcium carbonate could not (Dahl, 2016).

Conclusion

There was a significant decrease in monocyte count in the treatment group ($p=0.03$). Monocyte count decreased by 1.6% in treatment group and increased by 1.2% in control group. There was significant difference in monocyte count between the two groups after intervention ($p=0.01$). The limitations of this study are uninvestigated components of the drugs that could influence subject's appetite and nutrition absorption, no investigation on subjects' microflora status that could influence probiotic absorption, and each subject's diagnosis was not mentioned. Our suggestion was an addition of probiotic supplementation for CKD patients which could reduce monocyte count.

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