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ORIGINAL ARTICLE

Title

Correlation between Dialysis Vintage and Vitamin D and Bone Mass Density on Patients with Chronic Kidney Disease Undergoing Hemodialysis In Zainoel Abidin Hospital

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Editor:

Jonathan Barratt

*Received 23 September 2019, revised 26 March 2020, accepted 1 April 2020, published 20 April 2020***Abstract**

Background: Bone mineral disorders in chronic kidney disease (CKD-MBD) is one of the complications that occurs due to systemic disorders of minerals and bones in chronic kidney disease (CKD). This syndrome is one or a combination of laboratory abnormalities (phosphate, parathyroid hormone, and vitamin D), bone disorders (turnover, mineralization, volume, linear growth, and strength), and/or vascular calcification or other soft tissue. It is associated with high mortality and morbidity in CKD patients. To determine the relationship of vitamin D levels and bone mineral density (BMD) examination with the hemodialysis vintage in CKD patients undergoing hemodialysis at RSUD Dr. Zainoel Abidin.

Methods: This study is a cross-sectional study held in Zainoel Abidin Hospital, Banda Aceh, Indonesia, from January until May 2017. We include all patients who received twice-weekly hemodialysis for at least 3 months. Patients who received corticosteroids in the past 2 weeks, pregnant, suffering from endocrine disorders or malignancy, autoimmune diseases, and thalassemia, and menopausal women, were excluded. Laboratory examination and Bone Densitometry were performed before a single hemodialysis session. Data were analyzed using the Spearman Rank Correlation test.

Results: Thirty patients were analyzed from 196 hemodialysis patients. The proportion of patients that have vitamin D insufficiency was 56.6%. The proportion of patients that have with normal vitamin D was 43.3%. The proportion of patients that have osteoporosis was 30% and 56.6% were osteopenia based on bone densitometry examination. The magnitude of the Spearman Rank Correlation coefficient between vitamin D levels and the duration of hemodialysis in CKD patients is -0.552 with a p-value

0.002. The magnitude of the Spearman Rank Correlation coefficient between BMD and hemodialysis time in CKD patients is -0,397 with a p-value of less than 0.030.

Conclusion: There was a correlation between dialysis vintage with vitamin D levels and bone densitometry.

Keywords: vitamin D, bone mineral density, hemodialysis

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BACKGROUND

Chronic kidney disease (CKD) is associated with high mortality and morbidity because it can cause a variety of serious complications. Mineral Bone Disorder (CKD MBD) is a clinical syndrome that occurs due to systemic disorders in mineral and bone metabolism in CKD. This syndrome includes one or a combination of the following: laboratory abnormalities that occur due to impaired metabolism of calcium, phosphate, parathyroid hormone (PTH), and vitamin D, and bone disorders in terms of turnover, mineralization, volume, linear growth, and strength, vascular calcifications or other soft tissues. One example is renal osteodystrophy.¹

Research by Tjekyan et al in Palembang showed that 72.5% of 142 CKD patients have hyperphosphatemia.² Research by Yauri et al in Manado found that serum calcium levels decreased (< 8.3 mg / dL) in 51.21%

male subjects and 38.23% female CKD subjects. And serum phosphate levels increase (> 4.5 mg / dL) in 34 men out of a total of 41 subjects, whereas in women 27 out of a total of 34 subjects. The prevalence of patients with hypocalcemia ($\text{Ca} < 8.4$ mg / dl), hyperphosphatemia ($\text{P} > 4.6$ mg / dl), hyperparathyroidism (intact PTH > 65 pg / ml) will increase as the glomerular filtration rate decreases.

The purpose of this study was to determine the correlation of vitamin D levels and Bone Mineral Density (BMD) examination with the duration of hemodialysis in CKD patients undergoing hemodialysis at dr. Zainoel Abidin General Hospital.

METHODS

This study is a cross-sectional study from January until May 2017 in the hemodialysis unit at dr. Zainoel Abidin Hospital, Banda Aceh. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all participating patients.

We include all patients who received twice-weekly hemodialysis for at least 3 months. Patients who received corticosteroids in the past 2 weeks, pregnant, suffering from endocrine disorders, malignancy, autoimmune diseases and thalassemia, and menopausal women were excluded. The estimated size of the study sample using a sample size formula was 30 hemodialysis patients.

Measurement of vitamin D levels was carried out by the clinical laboratory improvement amendments (CLIA) method, by taking the patient's blood 5 ml before dialysis. Bone mineral density (BMD) examination was conducted at Prince Nayef Bin Abdul Azis Hospital - Syiah Kuala University (Darussalam). Spearman Rank Correlation was used to determine the correlation between vitamin D and BMD levels with hemodialysis vintage.

RESULTS

Thirty patients were analyzed from 196 hemodialysis patients. The proportion of patients that have vitamin D insufficiency was 56.6%. The proportion of patients that have with normal vitamin D was 43.3%. Most of the patients were male (60 %). Overall, most patients were aged between 41 and 50 years. Most of the patients were married. Most patients have normal BMI (36.7%), with details of 5 people (16.7%) have vitamin D insufficiency levels and 6 people (20.0%) with vitamin D levels normal according to Table 1.

The proportion of patients that have osteoporosis was 30% and 56.6% were osteopenia based on bone densitometry examination. The others were normal bone densitometry (13.3%). Of the 18 male subjects, 33.3% of them have osteopenia, while of the 12 female patients, 23.3% have osteopenia. Most of the patients were aged between 41-50 years (36.7%), with details of 6 BMD osteopenia, and 5 BMD osteoporosis. Majority of patients have BMI normoweight (Table 2).

Vitamin D levels are normally distributed, while the hemodialysis vintage data are not normally distributed (Table 3). So the correlation used is the Spearman rank correlation. The magnitude of the Spearman Rank Correlation coefficient between vitamin D levels and the duration of hemodialysis in CKD patients is -0.552 with a p-value 0.002. This shows that the relationship between vitamin D levels with hemodialysis duration is strong and significant. The magnitude of the Spearman Rank Correlation coefficient between BMD and hemodialysis time in CKD patients is -0,397 with a p-value of less than 0.030. This shows that the relationship between BMD and hemodialysis duration is strong and significant.

DISCUSSION

Chronic kidney disease (CKD) is associated with high mortality and morbidity because it can cause a variety of serious complications. Mineral Bone Disorder (CKD MBD), which is a clinical syndrome that occurs due to systemic disorders in mineral and bone metabolism in CKD. This syndrome includes one or a combination of the following: laboratory abnormalities that occur due to impaired metabolism of calcium, phosphate, parathyroid hormone (PTH), and vitamin D, bone disorders in terms of turnover, mineralization, volume, linear growth, and strength, vascular calcifications or other soft tissues. One example is renal osteodystrophy.¹

Chronic kidney disease is characterized by low levels of 25 (OH) vitamin D (calcidiol), low levels of 1.25 (OH) 2vitamin D (calcitriol), and calcitriol resistance.⁴ Valkovskystudy show that high prevalence of 25 (OH) vitamin D deficiency (96%) and a decrease in bone densitometry in patients undergoing hemodialysis.⁵

Risk factors for osteoporosis are age (≥ 65 years for women and ≥ 70 years for men), history of glucocorticoid therapy for more than 3 months, smoking, alcohol consumption, rheumatoid arthritis, and other autoimmune diseases, endocrine diseases (hyperthyroidism, hypothyroidism, Cushing's syndrome), CKD, and malignancy.⁶

Table 1. CharacteristicsOf Subjects

	Vitamin D					
	Insufficient		Normal		Total	
	N	%	N	%	N	%
Gender						
Male	8	26.7	10	33.3	18	60.0
Female	9	30.0	3	10.0	12	40.0
Age						
≤ 30 years	6	20.0	2	6.7	8	26.7
31 - 40 years	3	10.0	3	10.0	6	20.0
41 - 50 years	6	20.0	5	16.7	11	36.7
51 - 60 years	2	6.7	3	10.0	5	16.7
Marital status						
Single/Widower	5	16.7	2	6.7	7	23.3
Married	12	40.0	11	36.7	23	76.7
Body Mass Index						
Underweight	5	16.7	1	3.3	6	20.0
Normoweight	5	16.7	6	20.0	11	36.7
Overweight	4	13.3	4	13.3	8	26.7
Obese grade I	2	6.7	2	6.7	4	13.3
Obese grade II	1	3.3	0	0.0	1	3.3

Table 2. Subject's baseline characteristics according to bone densitometry

Table 2. Subject's baseline characteristics according to bone densitometry

Subject Characteristics	BMD							
	Osteoporosis		Osteopenia		Normal		Total	
	N	%	N	%	N	%	N	%
Gender								
Male	6	20.0	10	33.3	2	6.7	18	60.0
Female	3	10.0	7	23.3	2	6.7	12	40.0
Age								
≤ 30 years	2	6.7	6	20.0	0	0.0	8	26.7
31 - 40 years	0	0.0	4	13.3	2	6.7	6	20.0
41 - 50 years	5	16.7	6	20.0	0	0.0	11	36.7
51 - 60 years	2	6.7	1	3.3	2	6.7	5	16.7
Marital Status								
Single/Widower	2	6.7	5	16.7	0	0.0	7	23.3
Married	7	23.3	12	40.0	4	13.3	23	76.7
Body Mass Index								
Underweight	4	13.3	2	6.7	0	0.0	6	20.0
Normoweight	1	3.3	10	33.3	0	0.0	11	36.7
Overweight	3	10.0	2	6.7	3	10.0	8	26.7
Obese grade I	1	3.3	2	6.7	1	3.3	4	13.3
Obese grade II	0	0.0	1	3.3	0	0.0	1	3.3

Table 3. Test for normality of Vitamin D levels and duration of hemodialysis.

Variable	Shapiro-Wilk	p-value
Kadar vitamin D	0,950	0,174
Lama hemodialysis	0,801	< 0,001

Tabel 4. Spearman rank correlation test results.

Variable	N	Correlation Coefficient	p-value
Kadar vitamin D - Lama Hemodialysis	30	- 0,552	0,002
BMD - Lama Hemodialysis	30	- 0,397	0,030

The prevalence of osteoporosis in hemodialysis patients varies and depends on various factors, including the dialysis method, area examined for the bone scan, and gender.⁷ According to the study by Ebeling et al (2000), weight gain can increase osteoporosis risk. A study Hiiang et al(2009) showed weight loss and serum albumin are associated with low bone mass in patients undergoing hemodialysis. In women, estrogen deficiency before menopause is associated with a decrease in BMD. In men, testosterone deficiency is associated with decreased BMD. In CKD, estrogen has an important role in the development of bone mass in women who experience uremic.⁶

The KDIGO 2009 guideline did not recommend for patients with stage 3a to 5D CKD to undergo routine BMD examination, because BMD could not predict fracture risk as occurs in the general population, and BMD cannot determine the type of renal osteodystrophy. But KDIGO 2017 recommends patients with stage 3a to 5D CKD with the occurrence of GMT-CKD and/or risk factors for osteoporosis to have BMD to assess the risk of fracture if the results will influence the therapeutic decision. The updated reason is that there are many new prospective studies that low BMD results predict the incidence of fractures in patients with stage 3a to 5D CKD, and may influence the decision to do a bone biopsy.⁸

In patients with stage 3 to 5D CKD, KDIGO recommends that vitamin D levels be checked, and repeated for comparison of initial values and therapeutic interventions. KDIGO states that vitamin D deficiency and insufficiency can be corrected using recommended therapeutic strategies in the general population

Saafan FH's research and colleagues observed that 27% of hemodialysis patients had normal bone mineral density (BMD), 53% osteopenia, and 20% osteoporosis. There was also a significant negative correlation between BMD and the age of patients undergoing hemodialysis, body weight, body mass index, duration of hemodialysis, serum phosphorus, and serum iPTH.

There is a positive correlation between BMD and gender, height, and serum calcium.

Increased bone resorption and bone formation in patients with long periods of hemodialysis predispose patients to osteoporosis. Other risk factors that can predispose to increase the incidence of osteoporosis, such as acidosis. Adequate dialysis sessions will remove excessive phosphate and restore calcium balance, preventing bone resorption. Vitamin D increases calcium absorption and maintains the homeostasis of calcium

CONCLUSION

The study concludes that the levels of vitamin D and BMD have a statistically significant negative correlation with the duration of hemodialysis in CKD patients undergoing hemodialysis in RSUD dr. Zainoel Abidin Banda Aceh.

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ORIGINAL ARTICLE

Title

Haemodialysis Central Line-Associated Blood Stream Infections: Incidence, Risk factor, and Antibigram

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Abstract

Background Central-line associated bloodstream infection (CLABSI) is one of the complications of using a temporary HD catheter and also increases patient's morbidity and mortality. Identifying CLABSI risk factors and causative micro-organisms are important for setting prevention policies. There were no data regarding CLABSI in hemodialysis in Indonesia

Objective: This study identified the epidemiology and risk factor of HD CLABSI and to aid in the choice of empiric antibiotics therapy given to patients with HD CLABSI

Method: This study was an analytical observational study with a cross-sectional design conducted at the Inpatient Installation of Dr. Soetomo General Hospital in August 2018 - January 2019. The study population was patients with installed non-tunneled double lumen hemodialysis catheters for more than two calendar days. The inclusion criteria in this study were the patient 18-60 years old and any clinical presentation of fever, chills, and or hypotension. HD patients who presented with other sources of infection were excluded from the study. Data analysis was performed using SPSS v.23.

Results: In this study, 42 subjects were included in the composition of male: female 24: 18, with an average age of 49.62 years. The incidence of CLABSI is 11,3 /1000 catheter days. The results of blood cultures by gram-negative bacteria were 51.86%, and gram-positive bacteria were 48.14%. The most frequent causal organism found was *Staphylococcus aureus* by 25.9%. Based on gram-staining, *Staphylococcus aureus* was 53.84% of the gram-positive bacteria found, whereas the most frequent gram-negative bacteria was *Enterobacter clo-*

acae (53.84%). Antibiotics that have the highest sensitivity to gram-positive bacteria are Fosfomycin, Teicoplanin, and Chloramphenicol. Antibiotics that have the highest sensitivity to gram-negative bacteria are Cefoperazone Sulbactam, Imipenem, and Meropenem. There was a statistically significant relationship between DM and CLABSI events (OR = 3.896; p 0.037). There was a statistically significant relationship between hypoalbuminemia and the incidence of CLABSI (OR = 4,524; p 0,023).

Conclusion: This study found *S. aureus* was the most common cause of CLABSI. Our study was unusual as a high prevalence of gram-negative bacteremia was found in HD patients. Diabetes mellitus and hypoalbuminemia increase the risk of CLABSI in hemodialysis patients.

Keywords: chronic kidney disease, CLABSI, antibiogram, diabetes mellitus, hypoalbuminemia

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INTRODUCTION

Temporary vascular access by central venous catheter (CVC) is widely used in hemodialysis. The incidence of central line-associated bloodstream infection (CLABSI) is one of the complications of using a temporary HD catheter, and is one of the causes of

HD patient morbidity and mortality. The relative risk of bacteremia is nearly seven times in dialysis catheter use compared to native arteriovenous fistulas.^{1,2} Some studies mention factors that influence the risk of CLABSI events, including advanced age, diabetes mellitus, anemia, hypoalbuminemia, hyperferritinemia, catheter insertion, and duration of in situ catheter placement.^{2,3} Identifying bacterial profile and CLABSI risk factors is important for setting prevention policies.⁴

There was no data regarding CLABSI in hemodialysis in Indonesia. This research aimed to evaluate the incidence of CLABSI, the bacterial profile of CLABSI, and risk factor diabetes mellitus and hypoalbuminemia in Soetomo General Hospital, as a national referral hospital.

METHODS

The study was an analytical observational study with a cross-sectional design. The study was conducted in the hemodialysis unit of Soetomo General Hospital on September 2018 – February 2019. The subjects were consecutively recruited based on inclusion criteria. Our hospital ethics and research committee approved all subjects.

The population in this study were the patients of routine dialysis who have inserted a non-tunneled catheter for >2 calendar days. The inclusion criteria in this study were the patient 18-60 years old and any clinical presentation of fever, chills, and or hypotension. The exclusion criteria in this study were other sources of infection besides the confirmed hemodialysis catheter with clinical examination, laboratory, and radiological examinations as indicated, patients who had hemodialysis catheters installed in the femoral region, and patients who had received antibiotics before the CLABSI diagnosis was established. All subjects of the study were subjected to the following: full history taking and clinical examination, chest x-ray, and laboratory test which included: complete blood count, serum albumin, blood glucose, blood culture, and bacterial sensitivity from peripheral samples.

One set of blood cultures peripheral vein were taken from each patient. The peripheral blood culture was

taken from a vein in the median cubital fossa or the flexor aspect of the forearm. A sterile zone was then demarcated by draping the area with a sterile sheet. The sterile zone was created by cleaning the area with 70% alcohol, followed by 10% povidone-iodine in a circular motion starting from the center and moving outwards, and the site was left to dry. All operators wore plastic gowns, face masks, and sterile gloves to prevent contamination of the blood culture. The blood cultures were then sent to our microbiology laboratory for culture and antibiotic sensitivity tests. All cultures isolated were tested using the Clinical and Laboratory Standards Institute (CLSI) 2013 protocol.

The diagnosis of CLABSI was based on two criteria of CDC 2017 guidelines⁵

1. The central line was in place for >2 calendar days on the date of the event, with the day of device placement being Day 1.
2. Any of the following Laboratory-Confirmed Bloodstream Infection (LCBI) criteria
 - a. Patient of any age has a recognized pathogen identified (i.e., an organism which is not on the NHSN common commensal list) from one or more blood specimens by culture or non-culture based microbiologic testing method AND Organism(s) identified in the blood is not related to an infection at another site.
 - b. Patient of any age has at least one of the following signs or symptoms: fever (>38.0oC), chills, or hypotension AND Organism(s) identified from blood is not related to an infection at another site, AND the same NHSN common commensal is identified from two or more blood specimens drawn on separate occasions, by culture or non-culture based microbiologic testing method.

Data were analyzed statistically using SPSS 22nd version. Qualitative data were presented in the form of sums and percentages, whereas quantitative data were presented as mean values and standard deviation. The chi-square test was performed to compare independent variables (diabetes mellitus and hypoalbuminemia) between the groups of patients with and without CLABSI. Threshold for significant p-value is < 0,05 with 95 % confidence interval.

RESULT

The number of research subjects was 42 HD patients in the inpatient installation of RSUD dr. Soetomo in the period August 2018 - January 2019 and fulfilled the inclusion and exclusion criteria. General characteristics data are summarized in table 1. In this study, the number of male samples was 24 people (57.1%), and female samples were 18 people (42.9%). The median age in CLABSI patients was 49.6 years with an age range of 20-60 years, whereas in patients without CLABSI it was 48.7 years with an age range of 32-60 years. The mean length of CLABSI patients undergoing HD in 13.64 weeks, and patients without CLABSI, it is 6.47 weeks.

Table 1. General Characteristics of the patients

Category	Frequency	
	CLABSI n= 25	No CLABSI n= 17
Gender		
Male	13	11
Female	12	6
Age (years)		
Median ± SD	50.76 ± 12.35	48.71 ± 10.99
Range (Min-Max)	(20-60 years)	(32- 60 years)
Double lumen catheter location		
Right Subclavian	22 (88%)	17 (100 %)
Right Jugular	3 (12%)	0 (0 %)
Duration of undergoing HD		
Mean ± SD (weeks)	13.64 ± 9.69	6.47 ± 3.93
Duration of double lumen catheter		
Mean ± SD (weeks)	12.6 ± 6.86	6,71 ± 3.90

The results of blood culture were dominated by gram-negative bacteria at 51.86%, while gram-positive bacteria at 48.14%. *S.aureus* is the most frequent bacterial cause of CLABSI of 25.9% and in the gram-positive group of 53.84%. *E. cloacae* is a bacterium that causes CLABSI in the gram-negative group

of 42.85%. The organisms isolated are shown in Table 2.

Table 2. Bacterial isolates from 25 blood cultures

	Count (%)
Gram-positive organism	
<i>Staphylococcus aureus</i>	7 (53.84 %)
<i>Staphylococcus haemolyticus</i>	2 (15.38 %)
<i>Enterococcus faecalis</i>	1 (15.38 %)
<i>Methicillin-resistant staphylococcus aureus</i>	1 (7.69 %)
<i>Corynebacterium matruchotti</i>	1 (7.69 %)
Total	13 (48.14%)
Gram-negative organism	6 (42.85%)
<i>Enterobacter cloacae</i>	2 (14.28 %)
<i>Acinetobacter baumannii</i>	2 (14.28 %)
<i>Escherichia coli</i>	2 (14.28 %)
<i>Stenotrophomonas maltophilia</i>	1 (7.14 %)
<i>Pseudomonas aeruginosa</i>	1 (7.14 %)
<i>Pantoea agglomerans</i>	14 (51.86 %)
Total	14 (51.86 %)
Total for organism	27 (100 %)

In this study, the results were that the incidence of CLABSI with comorbid DM was 17 people (68%) and non-DM patients were eight people (32%). While in the group of patients without CLABSI who had DM comorbidities of 6 people (35.3%) and non-DM patients, 11 people (64.7%). Table 5 shows the distribution of the incidence of CLABSI in HD patients with and without DM.

Table 3 Antibiotic Sensitivity Test Results against Gram-positive Bacteria

Antibiotic	Sensitive	Intermediate	Resistant
Amikacin	-	-	-
Tobramycin	-	-	-
Gentamycin	7/12 (58.33%)	-	5/12 (41.66%)
Aztreonam	-	-	-
Amoxicillin clavulanic acid	7/9 (77.78%)	-	2/9 (22.22%)
Ampicillin	2/11 (18.18 %)	-	9/11(81.82%)
Ampicillin-Sulbactam	-	-	-
Penicillin G		-	
	2/12 (16.67 %)		10/12 (83.33%)
Pepiracillin tazobactam	-	-	-
Oxacillin		-	
	7/10 (70%)		3/10 (30 %)
Cephazolin	-	-	-
Ceftazidime	-	-	-
Cefotaxime	-	-	-
Ceftriaxone	-	-	-
Cefoperazone-Sulbactam	-	-	-
Cotrimoxazole	7/12 (58.33)	-	5/12 (41.67%)
Tetracyclin	6/9	-	3/9
	(66.67 %)		(33.33 %)
Chloramphenicol	9/10(90%)	-	1/10 (10 %)
Erythromycin	8/12 (66.67%)	1/12 (8,33 %)	3/12 (25%)
	8/12 (66.67 %)	-	
Clindamycin	7/8	-	4/8 (33.33 %)
	(87.5 %)		
Quiniopristin-dalfopristin			1/8 (12.5 %)
Ciprofloxacin	6/8 (75 %)	-	2/8 (25 %)
Levofloxacin	6/9	1/9 (11,11 %)	2/9 (22.22%)
	(60.6 %)		
Moxifloxacin	9/11 (81.82 %)	-	2/11
			(18.18 %)
Fosfomycin	11/11	-	-
	(100 %)		
Teicoplanin	10/11 (90.9%)	-	1/11 (9.1 %)
Imipenem	-	-	-
Meropenem	-	-	-
Ertapenem	-	-	-

Table 4. Antibiotic Sensitivity Test Results Against Gram-negative Bacteria

Antibiotic	Sensitive	Intermediate	Resisten
Amikacin	12/13 (92.3%)	-	1/13 (7.6 %)
Tobramycin	-	-	-
Gentamycin	9/12 (75 %)	-	3/12 (25 %)
Astreonam	5/13 (38.46%)	-	8/13 (61.54%)
Amoxicillin clavulanic acid	1/13 (7.7%)	-	12/13 (92.3%)
Ampicillin	1/13 (7.7%)	-	12/13 (92.3%)
Ampicillin-Sulbactam	2/13 (15.38%)	1/13 (7.7%)	10/13 (76.92%)
Pepiracillin tazobactam	9/12 (75 %)	1/12 (8.33 %)	2/12 (16,67 %)
Cephazolin	1/13 (7.7%)	-	12/13 (92.3 %)
Ceftazidime	9/14 (64.28%)	-	5/14 (35.71 %)
Cefotaxime	6/13 (46.15%)	1/13 (7.7%)	6/13 (46.15 %)
Ceftriaxone	7/13 (53.84 %)	1/13 (7.7%)	5/13 (38.46 %)
Cefoperazone-Sulbactam	11/12 (91.67%)	-	1/12 (8.33%)
Cotrimoxazol	11/14 (78.57%)	-	7/9 (21.42%)
Tetracyclin	7/12 (58.33%)	-	5/12 (41.67%)
Chloramphenicol	7/12 (58.33%)	-	5/12 (41.67%)
Ciprofloxacin	9/13 (69.23%)	-	4/13 (30.77%)
Levofloxacin	10/14 (71.42%)	1/14 (7.14%)	3/14 (21.42%)
Fosfomycin	5/12 (41.67%)	1/12 (8.33%)	6/12 (50 %)
Imipenem	11/12 (91.67%)	-	1/12 (8.33%)
Meropenem	11/12 (91.67%)	-	1/12 (8.33%)
Ertapenem	-	-	-

Table 5. Distribution of CLABSI patients with and without DM

	CLABSI	
	Yes	No
With DM	17 (68%)	6 (35.3%)
Without DM	8 (16%)	11 (64.7%)

In this study, antibiotics that had the highest sensitivity to gram-positive bacteria were Fosfomycin (100%), Teicoplanin (90.9%), and Chloramphenicol (90%). While antibiotics that have the highest resistance to gram-positive bacteria are Penicillin G (83.33%) and Ampicillin (81.82%). The results of the test results for antibiotic sensitivity to gram-positive are summarized in Table 3.

In this study, antibiotics that had the highest sensitivity to gram-negative bacteria were Sulbactam Cefoperazone (91.67%), Imipenem (91.67%), and Meropenem (91.67%). In this study, there was 1 CLABSI event with the bacterium *Acinetobacter baumannii*, which was resistant to all antibiotics. While antibiotics that have the highest resistance to gram-negative bacteria are Amoxicillin-clavulanic acid (92.3%), Ampicillin (92.3%), and Cephazolin (92.3%). Ceftriaxone antibiotics that are used as empirical therapy at this time for CLABSI events only have a sensitivity of 53.84%. The data from the test results for antibiotic sensitivity to gram-negative are summarized in Table 4.

The results of the comparison test with chi-square obtained a p-value of 0.037 which is less than the significance level of 0.05 (5%), so it can be concluded that there are significant differences in CLABSI patients with and without DM. The results of OR 3.896 means that patients with a DM have a risk of 3.896 times higher for the CLABSI compared with patients without DM.

In this study, albumin levels in the CLABSI group were divided into two groups, namely the group ≤ 3.5 g / dL as many as 19 people (76%) and > 3.5 g / dL as many as six people (24%). The albumin level in the patients without the CLABSI group was divided into two groups, namely the group ≤ 3.5 g / dL as many as six people (35.3%) and > 3.5 g / dL as many as 11

people (64.7%). Table 6 shows the distribution of the incidence of CLABSI in HD patients with and without hypoalbuminemia.

Table 6. Distribution of CLABSI patients with and without hypoalbuminemia

	CLABSI	
	Yes	No
$\leq 3,5$ g/ dL	19 (76 %)	6 (35.3%)
$> 3,5$ g/ dL	6 (24 %)	11 (64.7%)

The results of the comparison test with chi-square obtained a p-value of 0.023 which is less than the significance level of 0.05 (5%), so it can be concluded that there are significant differences in CLABSI patients with and without hypoalbuminemia. The results of OR 4.524 means that patients with hypoalbuminemia have a risk of 4.524 times higher for the CLABSI compared with patients without hypoalbuminemia.

DISCUSSION

The results of this study found the CLABSI incidence rate of 11.3 per 1000 catheter-days. This result is consistent with the research of Abdulrahman et al., where the incidence of CLABSI was 11.3 per 1000 catheter-days.⁶ Sahli et al. study showed different results where a higher incidence of CLABSI was obtained, namely 16.6 per 1000 catheter days.⁷ This is because, in the Sahli et al. study, the insertion of HD catheters in the femoral area was 79.6%. Femoral insertions have a higher risk of infection than insertions in the internal and subclavian jugular.¹

S. aureus was the most common cause of CLABSI in this study. This is consistent with the research analysis by Saxena et al. in 7 HD centers, which stated *S. aureus* as the cause of 21.9 - 60% of CLABSI. A class of cell surface adhesins – MSCRAMMs specifically interacts with extracellular matrix components and plays an important role in host tissue colonization, invasion, and as a key factor for *S. aureus* virulence.¹ Additionally, *S. aureus* elaborates glycocalyxes which promote the bacterial colonization and spread of infection even further.⁸

Our study was unusual as a high prevalence of gram-negative bacteremia was found in HD patients. As compared to previous studies, our study showed an increasing trend of gram-negative bacteremia. Alexandraki et al. investigated the five-year pattern of organisms isolated from HD patients with catheter infection, which showed a significant increase in the incidence of single gram-negative organisms and polymicrobial bacteraemias.⁹ This trend was consistent with the pattern of catheter infection in nondialysis patients. The high prevalence of gram-negative bacteria may be due to the immunocompromised state of patients, contaminated infusate, and misuse of antibiotics.¹⁰

In this study, antibiotics that had the highest sensitivity to gram-negative bacteria were Sulbactam Cefoperazone (91.67%), Imipenem (91.67%), and Meropenem (91.67%). In this study, there was 1 CLABSI occurrence with the bacterium *Acinetobacter baumannii*, which was resistant to all antibiotics. The study by Chandra et al. the 42 CLABSI events showed a phenomenon of increased resistance to the cephalosporin and carbapenem groups namely Imipenem (77%), Ampicillin Sulbactam (75%), and Ceftazidime (60%). This is due to the research of Chandra et al. 27% of the causes of CLABSI were obtained in the gram-negative group, *Acinetobacter baumannii*.¹¹

In this study, it was found that in HD patients with DM, there was an increase in risk factors for CLABSI with OR 3.896. This supports the research report by Lamaire et al., a multicenter retrospective cohort study with multivariate analysis involving four dialysis installations in 1749 research subjects, showing DM was a significant risk factor for CLABSI (OR 2.37; 95% CI 1.65 - 3.39).¹² In the study of Sahli et al. on 104 research subjects showed DM was an independent risk factor for the incidence of CLABSI with a value of $p < 0.01$.⁷ Ghonemy et al. also reported in his study with 119 study subjects showing DM was a risk factor for CLABSI with a value of $p < 0.001$.¹³

Diabetes mellitus is a risk factor for infection due to various disorders of the immune system, including humoral, cellular, and innate immunity that contributes to the pathogenesis of CLABSI in diabetic patients. In patients with DM, there is a decrease in the ability of

mobilization, chemotaxis, phagocytosis, and impaired adherence function, from PMN.¹⁴ Diabetes mellitus, which is also associated with a decrease in cell-mediated immunity (CMI) function. Diabetes causes a decrease in lymphocyte transformation against excitatory PHA (phytohemagglutinin) in uncontrolled people with diabetes mellitus. T lymphocyte counts decrease, especially CD4, which results in decreased CD4: CD8 ratio due to reduced insulin levels or decreased insulin activity.¹⁵

In this study, it was found that in HD patients with hypoalbuminemia, there was an increase in risk factors for CLABSI with OR 4.524. Ghonemy et al. also reported in his study with 119 study subjects that hypoalbuminemia was a risk factor for CLABSI with a value of $p < 0.008$.¹³ A retrospective study with multivariable logistic regression analysis by Fysaraki et al. of 142 episodes of bloodstream infection in hemodialysis patients showing hypoalbuminemia was a risk factor for CLABSI (OR 1.976; 95% CI).¹⁶

The risk of hypoalbuminemia in HD patients is related to malnutrition, loss of nutrients through the dialysis process, increased protein catabolism, and blood contact with the dialyzer membrane which activates the complement system and monocytes thereby releasing catabolic proinflammatory cytokines.¹⁷ Serum albumin is a marker of nutrition, inflammation, and predictor of death in hemodialysis patients.¹⁸

This study has limitations due to not having the data on what could be the cause of these infections. Future studies should include analysis between risk factors such as hand hygiene practices, water sources, and the incidence and prevalence of CLABSI.

CONCLUSION

This study found *S. aureus* was the most common cause of CRBSI. Our study was unusual as a high prevalence of gram-negative bacteremia was found in HD patients. Diabetes mellitus and hypoalbuminemia increase the risk of CRBSI in hemodialysis patients.

ETHICAL CLEARANCE

This research had been approved by the Ethics Committee before the study conducted.

CONFLICT OF INTEREST STATEMENT

The authors declare that there was no conflict of interest in this research.

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AUTHOR CONTRIBUTION

All authors have contributed to all process in this research, preparation, drafting, review, and approval of this manuscript

DISCLOSURE

The author reports no conflicts of interest in this research.

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ORIGINAL ARTICLE

Title
Association between the Biofilm of Double-Lumen Catheter and Blood Culture in Hemodialysis Patients with Suspected Central Line-Associated Bloodstream Infection

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Abstract

Background: Blood culture examination is still the gold standard for diagnosis of central line-associated bloodstream infection (CLABSI). CLABSI is also often associated with biofilm formation which can cause recurrent bacteremia and antibiotic resistance thereby increasing mortality and morbidity.

Objective: This study aims to analyze the relationship between the biofilms of the double-lumen catheter and blood cultures in hemodialysis patients with suspected CLABSI.

Method: This was an analytic observational study with a cross-sectional design to determine the relationship of biofilms and blood culture on patients aged >18 years with routine HD and suspected CLABSI at Dr. Soetomo General Hospital in August 2019 - November 2019. The examination of biofilm on DLC was done using the test tube method was measured with a nephelometer. The biofilm result is positive if ≥ 0.36 MF and negative if < 0.36 MF. Blood was cultured with a 3D BacT/ALERT tool in the Clinical Microbiology Installation Laboratory of Dr. Soetomo General Hospital.

Results: Of the 33 subjects, 45.5% were men and 54.5% were women, with an average age of 49.06 ± 1.5 years. The most common cause of CKD is hypertension (54.5%). The median length of HD was 3 months, ranging from 1-8

months. DLCs were mostly inserted at the right subclavian vein (87.9%) and installed with a mean duration of 77.94 ± 5.22 days. The majority (66.7%) had a normal nutritional status. The mean albumin level was 3.28 ± 0.07 g/dL. There was biofilm growth in 16 subjects (48.5%). The evaluation of blood culture revealed 15 positive results (45.5%). The analysis between biofilm density and CLABSI found significant differences between the two groups ($p=0.024$). From the chi-square test, the association of biofilms with blood culture in HD patients with suspected CLABSI obtained a p-value of 0.001.

Conclusion: Patients with suspected CLABSI and positive bacteria growth in blood cultures had biofilm in DLC. The density of biofilms in DLC is higher in positive blood culture CLABSI cases.

Keywords: chronic kidney disease, CKD, Double lumen catheter, Biofilm, Blood culture, Infection, CLABSI

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INTRODUCTION

Chronic Kidney Disease (CKD) is a major public health problem with an increasing number of events and when it reaches the terminal stage it requires hemodialysis (HD) as a substitute for kidney function to survive.^{1,2} Non-tunneled double lumen catheter (DLC) is one of the most frequently used vascular access for HD patients in Indonesia. Aside from thrombosis, infection is one of the most severe complications of catheter use for dialysis. HD catheter infection is thought increase mortality >50% and also causes significant morbidity in the dialysis population.^{3,4} Data on HD catheters usage showed at least 80,000 reported cases of central line-associated bloodstream infection (CLABSI) occur in intensive care units every year.⁵ In Dr. Soetomo General Hospital Surabaya reported that 32.3% of HD patients with a non-tunneled double lumen catheter had CLABSI.⁶

There are four known mechanisms of CLABSI. The first is microbial migration through catheter insertion lesion. These microbes can originate from the patient's skin, or through medical personnel. Second is the colonization of the catheter lumen. The third is direct contamination by bacteria that circulate in the bloodstream. Meaning the patient already has an infection in the bloodstream, and then the microbes adhere to the catheter when passing through it. Fourth is catheter lumen contamination related to infusion, both at the time of installing infusion (intrinsic) and at the time of usage (medical intervention).⁷ Diagnosis of bloodstream infections mainly relies on blood culture to detect bacteremia because a positive culture is not always followed by clinical symptoms of infection.⁸ However, the examination of culture requires a long time and is expensive, also at the end of incubation, false identification of positive cultures and false-negative results often occur.⁹ In addition to blood culture tests, biofilm examination or bacterial colonization of DLC can help in the diagnosis and management of patients.

Biofilm is a mucopolysaccharide matrix produced by the colonization of micro-organisms on the surface of the catheter. Biofilms can protect pathogenic microorganisms from innate immunity, antimicrobial agents, and disinfectants, making these pathogens difficult to eradicate.^{10,11} Biofilms

will undergo dispersion (release) which causes microbial biofilms to enter the bloodstream and leads to bacteremia.^{12,13} It is reported that 65% of the incidence of infection in developed countries is related to the formation of microbial biofilms which further aggravates the condition of bacteremia into recurrent bacteremia.¹⁴ Ramanathan et al. reported biofilm density is related to CLABSI conditions. Biofilm examination can be an option because it gives faster results than blood culture, and besides that biofilms are not affected by the surrounding environment (host and environment).¹⁰

Research data on the relationship between biofilms and CLABSI are still minimal in Indonesia. The author intends to prove that there is a correlation between the non-tunneled double lumen catheter biofilm of HD patients with CLABSI incidents based on blood culture. It is expected that with this research, the relationship between biofilms and blood cultures of those suspected with CLABSI can be more evident so that better management can be applied in CKD patients with HD that experience CLABSI.

METHODS

This study has a cross-sectional design and a population of CKD patients with a double-lumen HD catheter in the outpatient, inpatient and HD installation of Dr. Soetomo General Hospital Surabaya during August – November 2019. Patients aged >18 years and have undergone routine HD with suspected CLABSI. The exclusion criterion for this study was if other sources of infection were found such as respiratory and urinary tract infections.

Suspected CLABSI patients are patients with DLC as dialysis vascular access and experience one of the following symptoms: fever (>38°C), chills, or unexplained hypotension, and no signs of infection elsewhere. Then the diagnosis of CLABSI is based on the 2017 CDC criteria, by fulfilling one of the Laboratory Confirmed Bloodstream Infection criteria: a) Patients who are identified having pathogenic organisms from one or more blood specimens through a culture method based on microbiological methods & organisms that are identified in the blood and are not related to infections elsewhere; b) All patients who experi-

ence one of the following symptoms: fever ($>38^{\circ}\text{C}$), chills, or hypotension & organisms identified in the blood are not related to infection elsewhere & the same commensal organism is found on two or more examinations at the same time differ through the method of culture based on microbiological methods.¹⁵

Biofilm examination: The isolates obtained from DLC were put into BHI liquid, incubated 24 hours at 37°C and then cultured in MH media. Biofilm measurement was carried out using a nephelometer machine with positive results if ≥ 0.36 MF, negative results if < 0.36 MF.^{16,17}

The data collected will be processed and presented in textual, tabular and graphic forms. All research data were tested for normality with the Shapiro-Wilk test. A Chi-square test is used to analyze the relationship between two nominal scale variables. A significant result is achieved if the p-value < 0.05 with a 95% confidence interval. All data will be analyzed using the SPSS program version 25.0.

RESULTS

Of the 33 total subjects, the majority (54.5%) were female. The mean age of the study subjects was 49.06 ± 1.5 years with a range between 34-73 years. The etiology of CKD in this study was mostly caused by hypertension (54.5%). The median duration of HD was 3 months with a range of 1-8 months. The most frequent location of double lumen catheter placement in this study was the right subclavian vein found in 29 subjects (87.8%). The complete profiles of subjects could be observed in table 1.

Based on blood culture examination, there were 15 subjects (45.5%) with positive results and confirmed the diagnosis of CLABSI. Regarding the pathogenic bacteria in blood cultures, 10 specimens showed growth of gram-positive bacteria with *Staphylococcus aureus* as the most pathogens (20%) revealed. Furthermore, from the antibiotic sensitivity test, 100% of bacteria are sensitive to several antibiotics including Teicoplanin, Vancomycin, Linezolid and Trimethoprim. On the other hand, an antibiotic with a 100% resistant rate was Cephazolin. Data on blood culture results and antibiotic sensitivity tests are summarized in table 2 and table 3.

In this study, from 33 subjects, biofilm growth was obtained in 16 subjects (48.5%). Biofilm growth was then evaluated based on several parameters that can affect it including DLC insertion location, duration of DLC attachment, and antibiotic use during double lumen catheter placement. There were no significant differences resulted in all parameters (Table 4).

Of the 16 subjects with biofilm growth, 12 (80%) of them had positive blood cultures while 4 subjects (22.2%) did not. Whereas in the other 17 subjects with negative biofilms, the majority (77.8%) of subjects did not have bacterial growth in their blood cultures. Before analyzing the relationship of biofilms with CLABSI events, researchers found that there were significant differences in biofilm density ($p=0.024$; 95% CI) between patients with positive and negative culture in CLABSI groups (Figure 1), in which the biofilm density the negative CLABSI group were lower than the positive CLABSI group (table 5). Further analysis with the chi-square test (table 6) showed a significant relationship between biofilms and the incidence of CLABSI based on blood cultures ($p=0.001$; 95% CI).

DISCUSSION

From the basic characteristics, there are more female subjects than men. Research by Saleh et al. also showed the dominance of female subjects (61%).¹⁸ The mean age of the subjects was 49 years, with the youngest age at 34 years and the oldest at 73 years. This is consistent with the 2013 Basic Health Research data and also data from the Indonesian Renal Registry (IRR).^{19,20} Other studies also obtained an average age of 48.9 years.²¹ As for the etiology of CKD, this study reported hypertension as the most common cause (54.5%). Data from IRR 2017 support these results where 51% of CKD patients with HD are caused by hypertension.

Regarding the catheter, 87.8% of the double lumen catheters were inserted at the subclavian vein. In contrast, other studies have more insertion in the femoral²² and jugular^{8,23}. The rationale of selecting subclavian insertion site is due to easier mobilization and lower risk of infection compared to femoral and jugular insertion sites.^{8,22-24}

Table 1. General Characteristics of the patients

Category	Total (%)
	n=33
Gender, n (%)	
Male	15 (45.5)
Female	18 (54.5)
Age, years	
Mean $\pm$ SD	49.06 $\pm$ 1.5
Range (Min-Max)	34 – 73
ESRD etiology, n (%)	
DM	13 (39.4)
HT	18 (54.5)
Autoimmune	2 (6.1)
Duration of HD, month	
Median	3
Range (Min-Max)	1-8
Double Lumen Catheter Location, n (%)	
Right subclavian vein	29 (87.8)
Right jugular vein	2 (6.1)
Femoral vein	2 (6.1)
Double Lumen Catheter Duration of Installment, days	
Mean $\pm$ SD	77.94 $\pm$ 5.22
Range (Min-Max)	31 – 151
Nutritional Status, n (%)	
Underweight	3 (9.1)
Normal	22 (66.7)
Overweight	7 (21.2)
Obese	1 (3.0)
Albumin, g/dL	
Mean $\pm$ SD	3.28 $\pm$ 0.07
Range (Min - Max)	2.5 – 3.9

Table 2. Blood Culture Result

Types of microorganism	n
Gram-positive bacteria	
<i>Staphylococcus aureus</i>	3 (20%)
<i>Staphylococcus epidermidis</i>	2 (13.3%)
<i>Methicillin-resistant staphylococcus aureus</i>	2 (13.3%)
<i>Staphylococcus haemolyticus</i>	2 (13.3%)
<i>Enterococcus faecalis</i>	1 (6.7%)
subtotal	10 (66.7%)
Gram-negative bacteria	
<i>Enterobacter cloacae</i>	2 (13.3%)
<i>Acinetobacter baumannii</i>	1 (6.7 %)
<i>Escherichia coli</i>	2 (13.3 %)
subtotal	5 (33.3%)
Total	15 (100 %)

Table 4. Characteristic of Biofilm Growth

Category	Total (%)	Frequency		p value
		Biofilm positive	Biofilm negative	
	n=33	n= 16 (48,5%)	n= 17 (51,5%)	
Double Lumen Catheter Location				
Subclavia Dextra	29 (87,8)	12 (75)	17 (100)	0,68
Jugular Dextra	2 (6,1)	2 (12,5)	0 (0)	
Femoral	2 (6,1)	2 (12,5)	0 (0)	
Double Lumen Catheter Duration of Installment, days				
Mean $\pm$ SD	77,94 $\pm$ 5,22	87,69 $\pm$	71,12 $\pm$	0,11
Range (Min - Max)	(31-151)	8,79	5,00	
Prior use of Antibiotics				
Yes	10 (30,3)	7 (43,75)	3 (17,65)	0,10
No	23 (69,7)	9 (56,25)	14 (82,35)	

Table 5. Distribution of biofilm density with and without CLABSI

	Total	CLABSI		p value
	Mean	Positive	Negative	
	n=33	n=15	n=18	
Biofilm density	0.31 $\pm$ 0.02	0.38 $\pm$ 0.04	0.26 $\pm$ 0.03	0.024

Table 3. Antibiotic Sensitivity Test Results

Antibiotic	Sensitive	Intermediate	Resistant	Total
Aminoglycoside				
Amikacin	5 (83,3%)	-	1 (16,7%)	6
Tobramycin	-	-	-	-
Gentamycin	6 (40%)	1 (6,7%)	8 (53,3%)	15
Beta-lactam Penicillin				
Astreonam	1 (16,7%)	-	5 (83,3%)	6
Amoxicillin clavulanic acid	2 (14,3%)	1 (7,1%)	11 (78,6%)	14
Ampicillin	1 (7,7%)	-	12 (92,3%)	13
Ampicillin-Sulbactam	1 (16,7%)	-	5 (83,3%)	6
Penicillin G	1 (12,5%)	-	7 (87,5%)	8
Oxacillin	2 (25%)	-	6 (75%)	8
Piperacillin	2 (40%)	1 (20%)	2 (40%)	5
Piperacillin tazobactam	4 (66,7%)	2 (33,3%)	-	6
Beta-lactam Cephalosporin				
Generasi I				
Cephazolin	-	-	5 (100%)	5
Generasi III				
Ceftazidime	2 (33,3%)	-	4 (66,7%)	6
Cefotaxime	2 (28,6%)	-	5 (71,4%)	7
Ceftriaxone	2 (28,6%)	-	5 (71,4%)	7
Cefoperazone-Sulbactam	5 (83,3%)	-	1 (16,7%)	6
Sulfa-Trimethoprim				
Cotrimoxazol	6 (40%)	-	9 (60,%)	15
Trimethoprim	1 (100%)	-	-	1
Tetracyclin	5 (35,7%)	1 (7,1%)	8 (57,1%)	14
Chloramphenicol	10 (76,9%)	-	3 (23,1%)	13
Macrolides				
Erythromycin	5 (55,6%)	2 (22,2%)	2 (22,2%)	9
Clindamycine	5 (62,5%)	-	3 (37,5%)	8
Quinolon				
Quinopristin-dalfopristin	5 (83,3%)	-	1 (16,7%)	6
Ciprofloxacin	4 (28,6%)	-	10 (71,4%)	14
Moxifloxacin	7 (70%)	1 (10%)	2 (20%)	10
Levofloxacin	4 (36,4%)	1 (9,1%)	6 (54,5%)	11
Lain-lain				
Fosfomycin	7 (70%)	-	3 (30%)	10
Vancomycin	2 (100%)	-	-	2
Linezolid	2 (100%)	-	-	2
Imipenem	4 (80%)	1 (20%)	-	5
Meropenem	5 (83,3%)	-	1 (16,7%)	6
Ertapenem	-	-	-	-
Teicoplanin	9 (100%)	-	-	9

Still related to the catheter, the mean duration of the double lumen catheter installation in this study was 77.94 days. This differs from 2 other studies that have a longer mean duration of 138 days¹⁰ and 214 days²⁵. However, both studies used tunneled DLC. Based on blood culture results, 15 subjects were confirmed CLABSI positive with 10 of them having growth of gram-positive bacteria. Several other studies have shown similar results with the percentage of gram-positive bacteria growth ranging from 61.5 – 75%.^{10,23,26} *Staphylococcus aureus* becomes gram-positive bacteria which accounts for 40 – 80% in the majority of catheter infection cases.²⁷⁻²⁹ This is in line with this research. In the sensitivity tests, all pathogens are still sensitive to some antibiotics. One research by Gafor et al. with a period of 6 months in 28 study subjects, also obtained antibiotics with 100% sensitivity, including vancomycin, meropenem, imipenem, amikacin, and trimethoprim. The vancomycin regimen is recommended as an empirical systemic antimicrobial therapy. A study in India states that teicoplanin is effective with a 100% sensitivity test on CLABSI caused by *S. Aureus*. As for gram-negative, meropenem, imipenem, and amikacin can be an option.^{4,26,28}

Figure 1. Distribution of Biofilm Density between CLABSI Groups

Figure 1. Distribution of biofilm density between subjects with positive and negative blood culture results.

Table 6. Analysis of Biofilm Growth and Blood Culture

	Culture		Total (%)	p value
	(+)	(-)		
Biofilm positive	12 (80%)	4 (22,2%)	16 (48,5%)	0,001
Biofilm negative	3 (20%)	14 (77,8%)	17 (51,5%)	
Total	15(100%)	18(100%)	33 (100%)	

In this study, the majority (48.5%) of subjects had results of biofilm growth. In theory, almost all (99.9%) microorganisms can form biofilms on various surfaces. The ability to form biofilms has been reported in a large number of bacterial species such as *P. Aeruginosa*, *S. Epidermidis*, *E. Coli* spp, *S. Aureus*, *E. Cloacae*, *K. Pneumoniae*.³⁰ Researchers also analyzed several factors that could influence colonization and biofilm growth and it was discovered that the duration of DLC insertion, location, duration of CDL installation, and history of antibiotic use did not produce significant differences. Research by De Freitas et al. ($p = 0.11$)⁸ and Kang et al. ($p = 0.304$)³¹ also got insignificant results on the duration of DLC installation. However, a study in Brazil reported that the location of the insertion gave a significant effect ($p=0.03$).⁸ Different types and brands of DLC could affect the results of the study, whereas previous studies used tunneled DLC which has a longer duration of installation than that of non-tunneled DLC.

The results of the analysis present that there is a significant

difference in density ($p=0.024$; 95% CI) between subjects with positive and negative blood culture results. Furthermore, the chi-square test showed a significant relationship between biofilms and the blood culture of suspected CLABSI patients ($p=0.001$; 95% CI). These results are similar to studies in America ($p=0.03$) and Canada ($p=0.02$). Both studies also found significant differences in density and explained that biofilm thickness could increase by up to two-fold in subjects with CLABSI.^{10,25} This proves that biofilms formed from bacterial colonization at the catheter hub can lead to bacteremia.⁵ Biofilms are said to be responsible for 65% of the incidence of catheter-related infections.¹⁴ After the formation of biofilms, bacteria are thought to leave the biofilm itself regularly. By doing this, bacteria can undergo multiplication and rapid spread.³⁰ Biofilms regularly release bacteria into the bloodstream and can cause recurrent bacteremia. Antibiotic resistance in biofilms is also a threat of concern.²⁵

Several limitations of this study are the cross-sectional design with a narrow observation time of the study, so it cannot firmly explain the causal effect between biofilms and blood cultures of CLABSI patients. This study was also conducted at a single center so that it can describe the overall population of HD patients.

CONCLUSION

Patients with suspected CLABSI and positive bacteria growth in blood cultures had biofilm in DLC. This is supported by the results of this study that biofilm is significantly associated with CLABSI based on blood culture. Patients who were confirmed to have CLABSI had significantly higher biofilm density values than the negative CLABSI group. Biofilm could be an alternative examination in evaluating patients with suspected CLABSI. Faster results and its resistance to the surrounding environment are added values for biofilm examinations.

ETHICAL CLEARANCE

This research had been approved by the Ethics Committee before the study conducted.

CONFLICT OF INTEREST STATEMENT

The authors declare that there was no conflict of interest in this research.

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AUTHOR CONTRIBUTION

All authors have contributed to all process in this research, preparation, drafting, review, and approval of this manuscript

DISCLOSURE

The author reports no conflicts of interest in this research.

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CASE REPORT

Title

Case Report: Rhabdomyolysis and Acute Kidney Injury Requiring Dialysis

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*Received 16 December 2019, revised 20 March 2020, accepted 5 April 2020, published 20 April 2020***Abstract**

Background: Acute kidney injury (AKI) with myoglobinuria is the most serious complication of rhabdomyolysis, and can be life-threatening. Acute kidney injury as a complication of rhabdomyolysis is representing about 7 to 10% of all cases of AKI in the United State.^{1,2}

Case Illustration: A 42-year-old man was found with decreased consciousness and strangulated 3 hours before hospital admission. He consumed detergent as a suicide attempt five and one days before hospitalization. The patients have a history of paranoid schizophrenia and hypertension, and had been taking antipsychotic drug risperidone for 2 years irregularly. On physical examination, the patient was not alert with the Glasgow Coma Scale (GCS) of 3, attention and orientation were inadequate and vital signs were stable. Excoriation and hematoma around the neck and ronchi on the lung was found upon examination. Initial laboratory examination showed high leukocytes, low potassium, high alanine aminotransferase, and aspartate aminotransferase, initial creatinine was 1.639 mg/dL then increased to 6.8 mg/dL at the 4th day of care and 9.7 mg/dL on the 6th day with high serum uric acid and low serum calcium. The bicarbonate level in the blood gas analysis is 20.5. Erythrocytes and albumin were found in urinalysis. HCV serology was positive. On cervical x-ray examination showed swelling of the retropharyngeal soft tissue. Chest X-ray showed cardiomegaly and there were infiltrates in the right lung. Kidney ultrasonography showed no abnormality. The patient was diagnosed with acute kidney injury, rhabdomyolysis, paranoid schizophrenia, pneumonia, hypertension, soft tissue injury of the neck after attempted suicide by hanging, and hypocalcemia. The patient received intravenous hydration with

KN2 at 1000 mL daily, antipsychotic drugs, slow-release potassium supplementation, ceftriaxone, and ramipril. The intravenous fluid rate was increased to 1500 mL daily after urine volume decreases on the second day of hospitalization with persistent hyperkalemia. Intermittent conventional hemodialysis was done on the fourth day of hospitalization for 2 sessions. Total 24 hours urine volume was 1000 mL on day 6 of care. Creatinine and creatinine kinase (CK) continued to improve without hemodialysis. After 24 days of hospitalization, he was discharged, with a creatinine level of 1.6 mg/dL and CK 299 IU/L.

Discussion: Patients with AKI due to rhabdomyolysis who receive supportive therapy earlier have better outcomes. Therapy initiation includes prompt volume repletion with a target urine output of approximately 3 ml per kilogram of body weight per hour. In patients who develop oliguria, the administration of intravenous fluids is limited due to volume expansion and pulmonary edema. In these cases, renal replacement therapy is indicated. Intermittent hemodialysis has added benefit to correct volume overload and pulmonary edema. Bicarbonates used to induce urinary alkalization.

Conclusion: Acute kidney injury is the most serious complication of rhabdomyolysis. Fluid overload and electrolyte imbalance need renal replacement therapy.

Keyword: Rhabdomyolysis, AKI, Hemodialysis

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Background

Rhabdomyolysis is a syndrome characterized by the breakdown of skeletal muscle and leakage of intracellular myocyte contents, such as creatine phosphokinase (CPK) and myoglobin into the interstitial space and plasma resulting in AKI.¹ Acute kidney injury associated with myoglobinuria is a serious complication of rhabdomyolysis and can be life-threatening, representing about 7 to 10% of all cases of AKI in the United State. The reported incidence ranges from 13% to 50, but there was no data on AKI due to rhabdomyolysis in Indonesia. Patients with rhabdomyolysis usually present with a clinical picture of volume depletion that is due to the sequestration of water in injured muscles.^{3,4}

Case Illustration

A 42-year-old man was found to be strangled and have decreased consciousness 3 hours before hospital admission. One and five days before admission he ingested detergent mixed with a glass of water due to a suicide attempt and then threw up 3 times. He denied a history of trauma or injury. There were no other symptoms such as coughing, tightness, chest pain or dizziness.

A week before hospitalization, the patient was worried that someone else would kill him. The patient had a history of paranoid schizophrenia and had been taking antipsychotic risperidone for 2 years irregularly. The doctor replaced risperidone with long-acting antipsychotic fluphenazine but he experienced acute dystonia and stopped taking the medicine. Two and a half years ago the patient suffered from anxiety and then received sertraline and clobazam. There was a history of auditory hallucinations and he often got angry and talked to himself seven years ago. He also had a history of hypertension since 1 year ago and the blood pressure was controlled with amlodipine 5 mg 1 time a day.

He has divorced from his wife 7 years ago. He lived with his 80-year-old mother and his 10-year old daughter. Informed consent was obtained from the patient.

On initial physical examination, he was unresponsive with a Glasgow Coma Scale 3, attention and orientation were inadequate. Initial blood pressure was 148/87 mmHg with a pulse rate 100 times per minute, and respiratory rate 20 times per minute. Oxygenation saturation was 100% in room air. Excoriation and hematoma coiled around the neck. Heart rate was regular without murmurs, and ronchi on lung examination and abdomen was soft without tenderness or organomegaly. A Foley catheter was inserted and 50 ml of tea-colored urine was obtained. On the second and third day of hospitalization, urine volume was only 300-350 cc in 24 hours (table 1)

Initial laboratory examination showed hemoglobin 14.5 g/dl, leukocyte 19690/ul, normal sodium, potassium 2.8 mEq/L, alanine aminotransferase 254.7 u/L, aspartate aminotransferase 106 U/L, ureum 13 mg/dl, creatinine 1.639 mg/dl, uric acid 13.2 mg/dl, calcium 7.7 mEq/L. Blood gas analysis showed bicarbonate was 20.5. Urinalysis showed cloudy, leukocytes 2-3/ filed of view, erythrocytes 10-12/ field of view, specific gravity 1.025, PH 5, albumin 2+, HCV serology was positive. HCV RNA and phosphate levels had not been done, and myoglobinuria reagent was not available. The cervical x-ray showed swelling of the retropharyngeal soft tissue. Chest X-ray showed cardiomegaly and infiltrates in the right lung. Kidney ultrasonography showed no abnormality.

The patient was diagnosed with acute kidney injury, rhabdomyolysis, paranoid schizophrenia, pneumonia, hypertension, soft tissue injury of the neck after attempted suicide by hanging, and hypocalcemia.

Figure 1. Laboratory examination: Ureum and Creatinin

Figure 2. Laboratory examination: Creatinine kinase

Initial treatments were intravenous hydration with 1000 mL KN2 for 24 hours and enteral nutrition via nasogastric tube. The patient was prescribed haloperidol 5 mg/day, risperidone 2 mg 2 times a day, slow-release potassium 600 mg 3 times a day, and antibiotic ceftriaxone 2 gram a day. The

Table 1. Laboratory and clinical examination

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 10	Day 14	Day 19	Day 23	Day 27
Ureum (mg/dl)	55		66	112	153		92	112	108	69	43	48
Creatinine (mg/dl)	1.6		6.8	9.7	12		8.9	9.7	7.9	2.7	1.8	1.6
eGFR (ml/min-ute/1.73 m ²)			9.1	5.9	4.6		6.9					
Potassium (mg/dl)	3.3		3.7		4.1		4.3					
CK			23426	22115	10041		1218		345	624	870	505
Urine Volume (cc/24 hours)	800	300	350	250	500	1000	2000	2500	3000	3000	3000	3000
Intravenous fluid (24 hours)	K2N 1000	K2N 1500	NaCl 2000	NaCl 500	NaCl 500	NaCl 500	NaCl 1000	NaCl 1500	NaCl 1500	NaCl 1500	NaCl 1500	NaCl 1500
Oral fluid (NGT)	500	500	1200	1200	1200	1200	1200	1500	1500	1500	1500	1500
Hemodialysis/ Ultra-filtration volume				V 1500		V 1500						

antihypertensive drug was ramipril 5 mg and amlodipine 10 mg once daily.

On the second and third days of treatment, the urine volume was 300-350 cc in 24 hours, therefore the amount of intravenous fluid was increased to 1500 cc in 24 hours, but the patient still experienced oliguria and hyperkalemia. Potassium supplementation was also stopped.

Intermittent conventional hemodialysis was applied on the fourth-day of care. Temporary catheter double-lumen was inserted. The patient was dialyzed for 2 sessions with ultra-filtration volume of 1000 mL, blood flow 180 mL/hours, and dialysate flow 500 ml/hours. the urine volume reached 1000 ml in 24 hours on the sixth day of hospitalization. The last dialysis session was on the 6th day of hospitalization. Creatinine and CK continued to decrease without dialysis. After 24 days of hospitalization, the patient was discharged, with lab results of creatinine 1.6 mg/dL and CK was 299 IU/L. The patient was advised to remain properly hydrated, avoid nephrotoxic drugs, and periodic kidney function evaluation.

Discussion

Rhabdomyolysis is a syndrome characterized by the breakdown of skeletal muscle and leakage of intracellular myocyte contents, such as CPK and myoglobin into the interstitial space and plasma resulting in AKI. Acute kidney injury as a complication of rhabdomyolysis is quite common. The reported incidence ranges from 13% to approximately 50%. It is the cause of renal failure in 5-25% of all cases of renal failure in hospitalized patients.^{1,2}

Rhabdomyolysis usually presents with elevated CPK levels, muscle pain, limb weakness and swelling, and myoglobinuria.⁵ Initial creatinine kinase level in this patient was 23426 mg/dL on day 3rd and 22115 mg/dL on the 4th day. In this

case, the diagnosis of rhabdomyolysis was based on CK levels. Phosphate data are not available and urine myoglobin cannot be performed because reagents are not available. Laboratory findings include urine dipstick positive for blood in the absence of urinary erythrocytes, myoglobinuria, granular casts, epithelial cells in the sediment, and elevated muscle enzymes levels in the serum such as CK, LDH, and aspartate and alanine aminotransferases (AST, ALT), besides elevated serum phosphate and potassium serum levels and initially low serum calcium concentration.^{6,7} In this case, aspartate and alanine aminotransferases increased and erythrocytes and albumin were present in urinalysis.

Causes of rhabdomyolysis usually result in the destruction of muscle cells and the release of intracellular contents into extracellular fluid or circulation. When cells are subjected to mechanical stress, there is an influx of sodium and calcium into the cell, which causes several pathologic processes due to the excess of calcium. Excessive intracellular calcium results in persistent contraction of the myofibers, depletion of adenosine triphosphate (ATP), production of free radicals, activation of vasoactive molecules, release of proteases, and cell death. Afterward, neutrophils invade and amplify the damage with the release of proteases and production of free radicals, and inflammatory myolytic reaction develops. Myoglobin released from lysis of muscular cells does not have a specific binding protein, and it is freely filtered by the glomeruli. Casts are produced after filtration of myoglobin through the glomerular basement membrane that caused brown urine. Water reabsorption causes a rise of myoglobin concentration, and in the presence of acid urine, myoglobin precipitates and forms obstructive casts. Moreover, myoglobin can, through the heme fraction, induce the release of free iron, which catalyzes free radical production and further enhances ischemic tubule damage. In the absence of hypovolemia and acid urine, myoglobin has a less nephrotoxic effect. Another factor that can exacerbate tubular obstruction is the disseminated intravascular coagu-

lopathy associated with rhabdomyolysis due to the activation of the coagulation cascade by the substances released from damaged muscle cells. Acute kidney injury in rhabdomyolysis caused by vasoconstriction, tubular obstruction and tubular injury and hypovolemia.⁸⁻¹² Moreover, cases of AKI and rhabdomyolysis have been described in patients using haloperidol and other neuroleptics, presenting as a neuroleptic malignant syndrome.¹³

Figure 3. Pathophysiology acute kidney injury due to rhabdomyolysis.¹⁴

Elevated serum CK level is enough to establish the diagnosis of rhabdomyolysis. Five times higher than the normal CK level confirm the diagnosis of rhabdomyolysis. The maximum CK level is usually reached during the first 24 hours in 70% of the cases. Magnetic resonance image (MRI) is the method of choice to evaluate the distribution and extension of the affected muscles. Rhabdomyolysis can also be diagnosed with a muscle biopsy. The histopathologic findings usually include loss of cell nucleus and muscular striae with the absence of inflammatory cells.^{13,15-17}

The risk of AKI in rhabdomyolysis is usually low when CPK levels at admission are less than 15,000 to 20,000 U per liter although AKI may be associated with CPK values as low as 5,000 U per liter, usually occurs when coexisting conditions such as sepsis, dehydration, and acidosis are present.⁵ The severity of the disease ranges from asymptomatic elevations in serum CPK to life-threatening electrolyte abnormalities and AKI requiring renal replacement therapy (RRT). The AKI can be severe enough to result in complete loss of renal function leading to end-stage renal disease.⁵ In this case initial creatinine level was 1.639 mg/dL, creatinine increased 6.8 mg/dL on 3th and 9.7 mg/dL on the 4th day.

Patients with rhabdomyolysis that are associated with AKI usually present with a clinical picture of volume depletion that is due to the sequestration of water in injured muscles, pigmented granular casts, reddish-brown urine supernatant, and markedly raised serum CPK. The electrolyte abnormalities that can occur with rhabdomyolysis include hyperkalemia, hyperphosphatemia, hyperuricemia, high anion-gap metabolic acidosis, and hypermagnesemia mainly.^{5,9-10}

Patients with rhabdomyolysis must receive early and prompt treatment. Initial therapy includes volume repletion with normal saline promptly at a rate of approximately 400 ml per hour (200 to 1000 ml per hour depending on the setting

and severity), with target urine output of approximately 3 ml per kilogram of body weight per hour. In a randomized, prospective trial of fluid repletion with ringer's lactate as compared with normal saline in patients with rhabdomyolysis attributed to doxylamine intoxication, 28 patients were randomly assigned to receive one of the solutions. In this study administration of diuretic increased urine volume and decreased myoglobin precipitation, although statistically not significant.¹⁵⁻¹⁸ In this case, our patient developed oliguria, and therefore administration of intravenous fluids is limited due to volume expansion and pulmonary edema.

Bicarbonates can be used to induce urinary alkalization and mannitol to prevent renal failure in patients with rhabdomyolysis. Alkalization of urine can be attempted to reduce the formation of myoglobin casts in renal tubules and prevent Tamm-Horsfall myoglobin precipitation, inhibits the reduction-oxidation cycling of myoglobin and lipid peroxidation, metmyoglobin induces vasoconstriction only in acidic medium. In an experimental study, the association of saline solution, sodium bicarbonate, and mannitol were more effective than hypertonic saline dextran in decreasing oxidant injury in rhabdomyolysis. If CPK exceeds 5,000 IU/L it is advisable to institute aggressive venous hydration, prophylactic bicarbonate, and mannitol. Brown et al performed a study with 2,083 patients with post-traumatic rhabdomyolysis in intensive care unit and concluded that the administration of bicarbonate and mannitol should be reevaluated since they did not prevent renal failure (creatinine > 2.0 mg/dL), dialysis, or mortality in patients with CK levels greater than 5,000 U/L.¹⁸⁻²¹

Renal replacement therapy is considered if resistant hyperkalemia of more than 6.5 mmol per liter, oliguria (<0.5 ml of urine per kilogram per hour for 12 hours), anuria, volume overload, and/or resistant metabolic acidosis (pH <7.1) occurred. In this case, renal replacement therapy was indicated because of oliguria. Intermittent hemodialysis has benefits to correct volume overload and pulmonary edema. Our patient was dialyzed for 2 sessions of 3 hours, with ultrafiltration volume of 1000 mL, blood flow 180 mL/hours and dialysate flow 500 ml/hours. Conventional hemodialysis with high flux filters does not remove myoglobin effectively. The use of highly permeable membranes in continuous venovenous hemofiltration could be a promising treatment because allows for large molecules such as myoglobin to be filtered by convective clearance and helps remove myoglobin. Large pore membranes increase the clearance of solutes with molecular weights in the range of 20–50 kDa, such as immunoglobulin light chains, cytokines, and myoglobin (17.8 kDa).²¹⁻²⁵

Limitations of this case report were lack of ability to generalize, no possibility to establish a cause-effect relationship. **Conclusion:** Acute kidney injury is the most serious complication of rhabdomyolysis. Fluid overload and imbalance electrolyte need renal replacement therapy.

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ORIGINAL ARTICLE

Title

Early Detection of Chronic Kidney Disease In Diabetes Population And Hypertension In Project Sunrise in East Jakarta

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Abstract

Background: Hypertension and diabetes are two of the most prevalent causes of chronic kidney disease (CKD). Screening for kidney disease in primary health facilities in patients with diabetes and hypertension plays a significant role in the early detection of CKD. Dipstick proteinuria is the easiest and widely used method to detect proteinuria in epidemiologic studies, and it is relatively cheaper and easier than examining the urinary ACR, however, some patients with negative proteinuria might have increased urinary albumin-to-creatinine ratio (ACR).

Methods: This is a cross-sectional multicenter descriptive study conducted in four district's community health centers in East Jakarta. Subjects are patients aged > 45 in community health centers and were not enrolled in their respective community health center's Chronic Disease Management Program (Program Pengelolaan Penyakit Kronis). Patients were classified as diabetic, hypertensive, diabetic and hypertensive, and no known history of both diseases. Subjects were then examined for proteinuria using a dipstick examination. Patients with negative proteinuria were then examined for urine ACR. Data analysis was performed in this study with a univariate analysis to describe the characteristics of each variable.

Results: There were 400 subjects included in this study. The majority of subjects were female (76%) and a large proportion of patients was aged 51-69 years (40%). Subjects have hypertension (51%), diabetes (17%), both diabetes and hypertension (26%), and no known history of both (4%). In the group of diabetes patients with negative proteinuria, urinary ACR 30-300 mg/g were found in 4 subjects (16.7%), whereas in patients with both hypertension and diabetes and

negative dipstick proteinuria, urinary ACR 30-300 mg/g was found in 12 subjects (30.8%).

Conclusion: Examination of ACR in subjects with negative dipstick proteinuria shows some subjects have increased ACR. This data should prompt further investigations in the prevalence of albuminuria and reduced glomerular filtration rate in patients with risks of CKD in primary health care settings.

Keywords: CKD, urinary albumin-creatinine-ratio, hypertension, diabetes, proteinuria

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BACKGROUND

Chronic kidney disease (CKD) is a major contributor to world health problems. The increasing prevalence of CKD will be one of the causes of death from 20 diseases worldwide.¹ CKD is defined as kidney damage or decreased glomerular filtration rate of <60 ml/minute/1.73 m² in three consecutive months, with abnormalities found in the histopathological examination and/or imaging examination, and marked with an albumin-to-creatinine ratio (ACR) of > 30 mg/g.² Increased prevalence of CKD and increased risk of death in CKD is found in many low and medium-income countries.³ From the 11th Report of Indonesian Renal Registry in 2018, the incidence of end-stage renal disease (ESRD) needing renal replacement therapy were 30,831, which is significantly higher than the reported 25,446 patients of the previous year.⁴

Experts recommend screening people with risk factors and this has a big impact especially for highly-populated nations.⁵ Hypertension and diabetes are two of the most prevalent causes of CKD.⁶ Screening for kidney disease in primary health facilities in patients with diabetes and hypertension plays a significant role in early detection of CKD.⁷ Prodjosudjadi W et al. reported that about 3% from 9,412 patients were found to have persistent proteinuria, and proteinuria, along with high systolic blood pressure and diabetes mellitus, is a predictor of decreased glomerular filtration rate.⁸

Dipstick proteinuria is the easiest and widely used method to detect proteinuria in epidemiologic studies, and it is relatively cheaper and easier than examining the urinary ACR.⁹ However, 24% of patients with a negative result in dipstick proteinuria examination have an ACR >30 mg/g.¹⁰ In this study, we screened the population within The Sunrise Project, a pilot program aimed at early detection of chronic kidney disease in primary health facilities in the East Jakarta initiated by the Health Office of Jakarta in collaboration with the Indonesian Society of Nephrology and Fresenius Medical Care Indonesia. This project was held in four districts in East Jakarta.

METHODS

This is a cross-sectional multicenter study conducted in four East Jakarta community health centers (Pusat Kesehatan Masyarakat), namely Jatinegara Community Health Center, Cakung Community Health Center, Matraman Community Health Center, and Pasar Rebo Community Health Center. This research was conducted in the period 3-10 October 2019 in The Sunrise Project Program. Subjects were classified as diabetic, hypertensive and diabetic and hypertensive. Subjects were then examined for proteinuria using dipstick examination, and subjects with negative proteinuria using dipstick examination were examined for urine ACR. Data analysis was performed in this study with a univariate analysis to describe the characteristics of each variable. Inclusion criteria were patients aged ≥ 45 years who attended the Sunrise Project, and the exclusion criteria were subjects who were already enrolled in their respective community health center's Chronic Disease Management Program (Program Pengelolaan Penyakit Kronis), and have signs and symptoms of infection. The sampling method was consecutive sampling. The urinary ACR examination was done on patients with negative dipstick proteinuria. Due to the limitation of facilities, a maximum number of 20 patients from each district's community health centers were examined for urinary ACR.

RESULTS

Four hundred patients participated in this study. Over half of the subjects have hypertension (51%), subjects with diabetes mellitus (DM) were 68 patients (17%), and patients

with both DM and hypertension were 104 patients (26%). A large proportion of patients was aged 51-69 years (40%). The majority of the subjects were female (76%). There were 117 diabetic patients with controlled diabetes (29.3%). Diabetic patients who had been diagnosed in less than 5 years before this study were 104 patients (26%). Other characteristic data can be seen in Table 1. In the group of diabetes mellitus patients with negative dipstick proteinuria, there is an ACR <30 mg/g in about 19 patients. Subjects with both DM and hypertension group, 12 patients are having ACR of 30-300 mg/g. In Table 3, the distribution of ACR in patients with diabetes, hypertension and both of them is 65 patients.

DISCUSSION

Over the past 6 years, data from the International Diabetes Federation shows an increasing number whereas in 2017 the figure reached 10.3 million patients.¹¹ In our study, 17% of patients were diabetic and 26% were diabetic concurrent with hypertension, which means 43% of the subjects have diabetes. In diabetic patients with negative dipstick proteinuria, albumin-creatinine ratio levels of 30-300 mg/g can be found in as many as 16.7% and one subject has ACR > 300 mg/g. Albumin-creatinine ratio level of 30-300mg/g can be found in 30.8% in both diabetes and hypertension' patients with negative dipstick proteinuria. Although dipstick proteinuria examination is the preferred method to screen proteinuria due to its sensitivity, specificity, and cost-effectiveness, clinicians must be aware of the possibility of false-negative results. Dipstick proteinuria examination can be affected by the urinary specific gravity, pH, hematuria, antiseptic use in obtaining urine samples, etc. Albumin-creatinine ratio ≥ 30 mg/g is more frequently used when proteinuria of 30-300 mg/g (i.e., microalbuminuria) is known to be related to risk factor for ESRD.⁹ A study by Yamamoto et al found that 24% of patients with negative dipstick proteinuria has ACR of 30-300 mg/g.¹⁰

Poor glycemic control may lead to the production of reactive oxygen species (ROS) which will induce injury to endothelial cells, and increase the risk of cardiovascular diseases. This injury will also affect the glomerular endothelial cells and cause a disruption in the normal glomerular filtration function, causing albuminuria. Persistent albuminuria can cause the tubular cells to produce proinflammatory cytokines, and further damage the endothelial cells and nephrons. Albuminuria is the first sign of renal damage in diabetic patients, rendering screening for albumin and albumin-to-creatinine ratio important in early detection of CKD in the population. Chronic hypertension will also induce proinflammatory cytokines production by endothelial cells, leading to cellular destruction and loss of nephrons. Poorly controlled hypertension will disrupt the regulatory system of the kidney which leads to albuminuria. The role of primary care health professionals in controlling diabetes and hypertension is therefore crucial in curbing the incidence of CKD in these populations.

Table 1. Subjects' baseline characteristics

CHARACTERISTICS	VALUES
DM (%)	68 (17%)
Hypertension (%)	204 (51%)
DM and Hypertension (%)	104 (26%)
Unknown (%)	24 (6%)
Age (%)	
<30 years	2 (0.5%)
30-40 years	16 (4%)
41-50 years	81 (20.3%)
51-60 years	160 (40%)
>60 years	141 (35.3%)
Gender:	
Female (%)	304 (76%)
Male (%)	96 (24%)
Glycaemic control of diabetic patients (n=163)	
Controlled	117 (29.3%)
Uncontrolled	28 (7%)
Unknown	18 (4.5%)
No Answer	237 (59.3%)
Random blood glucose, median (min-max)	121 (67-508)
Duration of diabetes (n=167)	
<5 years	104 (26%)
5-10 years	34 (8.5%)
>10 years	29 (7.2%)
Systolic Blood Pressure, median (min-max)	140 (89-250)
Diastolic Blood Pressure, median (min-max)	80 (50-128)
Blood pressure control of hypertensive patients	
Controlled	217 (54.3%)
Uncontrolled	46 (11.5%)
Unknown	35 (8.8%)
No Answer	102 (25.5%)
Duration of Hypertension (n=298)	
0-5 years	195 (48.7%)
5-10 years	49 (12.3%)
>10 years	54 (13.5%)
History of Kidney Disease (%)	
Yes	29 (7.2)
No	358 (96.8%)
No Answer	13 (3.3%)
Smoking (%)	
Yes	17(4.3%)
No	344 (86%)
Have quitted smoking	22 (5.5%)
No Answer	17 (4.3%)

Table 2. Subjects' characteristics based on proteinuria and urinary albumin-creatinine ratio.

	PROTEINURIA		URINARY ALBUMIN-CREATININE RATIO IN SUBJECTS WITH NEGATIVE DIPSTICK PROTEINURIA			
	Negative	Positive	<30	30-300	>300	Not examined
History of Kidney Disease						
Yes	15	14	3	4	0	22
No	208	150	45	11	1	301
No Answer	6	7		1	0	12
Smoking						
Yes	8	9	2	2	0	13
No	198	146	0	12	1	287
Have quitted smoking	11	11	0	0	0	22
No Answer	12	5	2	2	0	13
Education Level						
Elementary School	35	34	9	1	0	56
Middle School	38	27	9	3	0	53
High School	88	69	15	6	0	136
Undergraduate	51	28	11	1	1	66
Others	6	3	1	1	0	7
No Answer	11	10	3	1	0	17

Table 3. Distribution of Albumin-Creatinine Ratio in Patients with Diabetes, Hypertension and Both Diabetes and Hypertension with Negative Dipstick Proteinuria

Albumin-creatinine ratio (mg/g)	Diabetes mellitus (n=24)	Hypertension (n=2)	DM and Hypertension (n=39)
< 30	19 (79.2%)	2 (100%)	27 (69.2%)
30-300	4 (16.7%)	0	12 (30.8%)
> 300	1 (4.2%)	0	0

The ACR is an examination that costs more when compared to dipstick proteinuria, so the examination was limited. However, it can be seen in table 2, that 171 patients with positive dipstick proteinuria were those at risk for CKD, consistent with the results of several studies.^{12,13} Therefore, the examination of ACR can be allocated to those with risk factors of CKD and negative dipstick proteinuria for cost efficiency.

This study has limitations such as not all patients with negative dipstick proteinuria have their urinary ACR examined due to limited resources. Another limitation is that this study is a cross-sectional study, therefore it cannot follow up on whether the patients have persistent microalbuminuria and

whether they end up developing CKD in the long term. Future studies need to follow-up on patients and the development of CKD in all groups.

CONCLUSION

In our study, it was found that there were subjects with diabetes and/or hypertension with negative dipstick proteinuria, upon further examination showed increased ACR. This study should prompt further investigations in the prevalence of albuminuria and reduced glomerular filtration rate in patients with risks of CKD in primary health care settings. The risk for CKD in the diabetic and/or hypertensive population

in primary health care settings requires more attention, related to the prevention of progression and control of risk factors in primary health facilities because primary health care setting holds a big role in preventing and delaying the onset of CKD.

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DISCLOSURE

By the time of publication, D.L.G. worked at Fresenius Medical Care Indonesia. G.N., A.L., T.D.S., D.O., have nothing to declare.

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