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RELATIONSHIP BETWEEN BODY MASS INDEX AND CREATININE AND UREUM LEVELS IN CHRONIC KIDNEY DISEASE PATIENTS UNDERGOING HEMODIALYSIS AT SANJIWANI HOSPITAL

Putu Dian Amelya Putri Widarani[1], I Wayan Gede Sutadarma[2], Ni Wayan Tianing[3], I Wayan Surudarma[3]
[1]Bachelor of Medicine, Faculty of Medicine, Udayana University
[2]Department of Clinical Nutrition, Faculty of Medicine, Udayana University
[3]Department of Biochemistry, Faculty of Medicine, Udayana University
e-mail: dianamelyaaa@gmail.com

ABSTRACT

Chronic kidney disease (CKD) is a condition characterized by sustained changes in kidney structure and function lasting for more than three months. The hemodialysis (HD) procedure can impact the nutritional status of CKD patients through increased degradation of body proteins. This degradation is reflected in elevated blood levels of creatinine and urea. The aim of this study was to analyze the relationship between body mass index (BMI) and serum creatinine and urea levels in CKD patients undergoing HD at Sanjiwani Hospital, Gianyar. This was an analytical observational study with a cross-sectional design, involving 95 CKD patients undergoing HD who met the inclusion and exclusion criteria. The study population was predominantly male (63.2%), with a median age of 50 years (range 21–63 years). The average BMI was 24.15 ± 4.56 kg/m², the mean serum creatinine level was 9.67 ± 2.83 mg/dL, and the mean serum urea level was 126.08 ± 35.50 mg/dL. Pearson correlation analysis revealed a significant, but weak, positive correlation between BMI and serum creatinine levels ($r = 0.246$, $p = 0.016$). In contrast, the correlation between BMI and serum urea levels was not significant ($r = 0.147$, $p = 0.155$). Based on these results, we conclude that while there is no significant relationship between BMI and serum urea levels, there is a weak, significant relationship between BMI and serum creatinine levels, indicating that higher BMI may be associated with increased serum creatinine levels in HD patients.

Keywords: body mass index, chronic kidney disease, creatinine, urea

Correspondence : gede_sutadarma@unud.ac.id

1. INTRODUCTION

Chronic kidney disease (CKD) is a prevalent global health condition, affecting a significant number of individuals. CKD is defined as kidney damage, characterized by either functional or structural abnormalities, that progresses over a period of at least three months. This condition may occur with or without a reduction in the glomerular filtration rate (GFR) below 60 mL/min/1.73 m².[1] Pathological manifestations of CKD include abnormalities in urine and blood composition, as well as alterations observed in imaging tests.[2] CKD is characterized by being incurable and progressive, often leading to permanent kidney damage.[3] According to data from the World Health Organization (WHO), CKD is a global health condition responsible for approximately 850,000 deaths annually.[4] Research indicates that the global prevalence of CKD across stages one to five has reached 843.6 million people.[5]

According to the 2018 Riskesdas data, the prevalence of CKD in Indonesia is 0.38%, with the highest rate found in North Kalimantan province at 0.64%. In Bali, the incidence of CKD across all hospitals was recorded at 0.44% of the total population, equating to 12,092 cases.[6] The management of CKD aims to improve patients' quality of life through various treatments, including hemodialysis (HD), long-term peritoneal dialysis, and kidney transplantation. HD is a process that filters and cleans the blood using a semipermeable membrane in CKD patients, with the goal of removing metabolic waste products, such as uremic toxins, and restoring the body's electrolyte balance.

HD is usually performed two to three times a week with a duration of approximately four to five hours.[7] Data from the Indonesian Renal Registry (IRR) (2018), reported that CKD patients in Indonesia undergoing HD were 2.7 million.[8] Several studies have shown that the severity of CKD is associated with a poor perception of quality of life among patients. Additionally, malnutrition is a common complication in CKD patients undergoing HD, with a prevalence ranging from 18% to 75%.[9] The results of a recent study, Caglar *et al* evaluated the effect of HD procedures on the induction of IL-6 production and FSR albumin and fibrinogen, two well-known acute phase proteins.

The study showed that during HD, FSR albumin and fibrinogen increased significantly compared to measurements obtained during baseline.[10] Given that whole-body and muscle protein degradation increases linearly during HD and continues for the subsequent two hours post-HD, the concurrent rise in inflammatory markers suggests a potential relationship between these two phenomena, possibly indicating a causal link between inflammation and increased protein degradation. The primary goal of the HD procedure is to remove uremic waste products, however, this process is limited to the partial elimination of uremic solutes, and does not fully clear the uremic burden.[11] Incomplete clearance of uremic waste, along with the formation of urea and creatinine resulting from the breakdown of body proteins induced by the hemodialysis (HD) process and protein intake, contributes to the accumulation of uremic solutes, specifically urea and creatinine.

Creatinine is a product of endogenous metabolism that can assess glomerular function. Meanwhile, urea is a nitrogen product excreted by the kidneys from a protein diet. Normally, the normal value of urea is between 5-20 mg/dL and creatinine is 0.7-1.2 mg/dL. Creatinine is produced in the same amount and excreted through urine with a normal volume of <1.5 mg/dL while the level of urea excreted is 10-50 mg/dL.[12] A study conducted on HD patients at a hospital in Indonesia found an increase in serum creatinine levels among 83 patients, with an average of 11.80 mg/dL in men and 9.73 mg/dL in women. A two-fold increase in serum creatinine levels typically indicates a 50% reduction in kidney function. Additionally, elevated urea levels were observed, with an average of 167.09 mg/dL in men and 164.39 mg/dL in women. A glomerular filtration rate (GFR) decrease of 15% (<15 mL/min) is indicative of kidney failure and uremia.[3]

According to the International Society of Renal Nutrition and Metabolism (ISRNM), one of the indicators used to assess the nutritional status of CKD patients undergoing HD is body mass index (BMI).[13] High levels of creatinine and urea in patients can lead to various complications, such as nausea, anorexia, and metabolic acidosis. In CKD patients, nutritional status is not solely determined by decreased nutritional intake, but rather results from the interaction of multiple factors, including hormonal imbalances, inflammation, increased catabolism, and metabolic disturbances. The nutritional status of CKD patients is a crucial determinant of morbidity and mortality associated with the disease.[9] Toxic urea in plasma closely correlates with markers of inflammation. Uremia also inhibits lipoprotein lipase and liver lipase, leading to impaired lipid degradation and dyslipidemia, which in turn affects the nutritional status of CKD patients.[14] Serum creatinine levels are 95% derived from muscle tissue. Studies suggest that as creatinine waste products accumulate due to kidney failure, muscle atrophy may occur as a result of increased protein catabolism, mediated by the ubiquitin-proteasome system (UPS) and the activation of musculoskeletal myostatin.

The ubiquitin-proteasome system (UPS) degrades muscle proteins, and myostatin can inhibit cell proliferation and muscle synthesis. Increased degradation of body proteins and skeletal muscle is reflected in elevated levels of creatinine and urea in the blood. Research on the relationship between BMI and serum creatinine and urea levels in HD patients is still limited, despite the relatively high prevalence of CKD in Bali. The aim of this study was to analyze the relationship between BMI and serum creatinine and urea levels in CKD patients undergoing HD at Sanjiwani Hospital. The findings of this study are expected to serve as a reference for clinicians in evaluating creatinine and urea levels in CKD patients, helping to minimize the risk of malnutrition.

2. MATERIALS AND METHODS

This research was conducted in February 2024 at Sanjiwani Hospital, Gianyar. The study design is analytical research that used a cross sectional study and has received information on ethical feasibility by the Research Ethics Commission Unit, Faculty of Medicine, Udayana University No. 2578/UN14.2.2.VII.14/LT/2023. The independent variable in this research was the body mass index. Meanwhile, the dependent variables are the creatinine and ureum level. BMI values are categorized based on the World Health Organization criteria, namely undernutrition (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overnutrition (23.0–24.9 kg/m^2), obesity I (25.0-29.9 kg/m^2), and obesity II (≥30 kg/m^2). The normal value for creatinine levels is 0.7-1.2 mg/dL. Meanwhile, the normal value for urea levels is between 5-20 mg/dL. Data collection was carried out in a certain period of time until the number of samples was met. Data collection on each subject was only carried out once.

The research data used were secondary data from patient medical records and primary data from the results of BMI examinations of HD patients at Sanjiwani Hospital. The research sample was taken from CK patients undergoing HD at Sanjiwani General Hospital who met the inclusion and exclusion criteria. The inclusion criteria included patients who had been diagnosed with CKD by a specialist in internal medicine, had undergone HD for at least 3 months, and were aged between 18 and 64 years, regardless of gender. The exclusion criteria included HD patients with impaired consciousness, those who were unwilling to participate in the study, and patients with incomplete medical records. Samples were selected sequentially from patient medical records until the desired number of samples was met.

A normality test was performed using the Kolmogorov-Smirnov test, with data considered to be normally distributed if the p-value was greater than 0.05. All data obtained in this study were analyzed descriptively and the results will be presented in the form of mean ± standard deviation (SD) if the data is normally distributed and in the form of median (minimum-maximum) if the data is not normally distributed. Respondent characteristic data are presented in the form of absolute numbers or percentages. The relationship BMI and serum creatinine and urea levels was analyzed using Pearson's correlation test (for normally distributed data) or Spearman's correlation test (for non-normally distributed data), with a significance level set at $\alpha = 0.05$. The research data were processed using the Statistical Package for the Social Science (SPSS) software version 25 and the data were presented in tabular form.

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RESULTS

Characteristics of Research Subjects

This research was conducted in the Hemodialysis Room and Medical Records Installation of Sanjiwani Gianyar Hospital in February 2024. The number of PGK patients undergoing HD at RSUD Sanjiwani Gianyar who met the criteria for research subjects was 95 people. The data normality test used the Kolmogorov-Smirnov test. The results of the normality test showed that the age data was not normally distributed (p = 0.011). Data on creatinine levels (p = 0.125) and urea (p = 0.111) were normally distributed. The results of the BMI data normality test also showed a normal distribution (p = 0.057). Data are presented in the form of mean ± standard deviation (SD) if normally distributed and in the form of median (minimum-maximum) if the data is not normally distributed. Subject characteristics are shown in Table 1 below. The median age was 50 years with the youngest age being 21 years and the oldest age being 63 years. The number of male subjects was found to be greater than female patients. There were 60 male subjects (63.2%) and 35 female subjects (36.8%).

This study used 95 research subjects, obtained a BMI value of 24.15 ± 4.56 kg/m^2.

The distribution of BMI values in 95 subjects was categorized as undernourished (<18.5 kg/m^2) as many as 6 patients (6.3%), normal (18.5-22.9 kg/m^2) as many as 34 patients (35.8%), overweight (23.0-24.9 kg/m^2) as many as 19 patients (20.0%), obesity I (25.0–29.9 kg/m^2) as many as 28 patients (29.5%), and obesity II (≥30 kg/m^2) as many as 8 patients (8.4%) (Table 1). The results of the analysis of 95 research subjects obtained creatinine levels of 9.67 ± 2.83 mg/dL. The distribution of creatinine levels in 95 subjects was categorized as high (>1.2 mg/dL) in 95 people (100%). No low creatinine levels (<0.7 mg/dL) or normal (0.7-1.2 mg/dL) were found in the subjects. Urea levels in 95 research subjects were 126.08 ± 35.50 mg/dL. The distribution of urea levels in 95 subjects was categorized as high (>20 mg/dL) in 95 people (100%). No low urea levels (<5 mg/dL) or normal (5-20 mg/dL) were found in the subjects (Table 1).

Relationship between Body Mass Index and Creatinine Levels in Chronic Kidney Disease Patients Undergoing Hemodialysis

The results of the correlation analysis using the Pearson correlation test revealed a significant, weak positive relationship between BMI and creatinine levels, with a correlation coefficient of r = 0.246 (p = 0.016). This suggests that an increase in BMI is associated with a corresponding increase in creatinine levels. The interpretation of the correlation strength is as follows: very weak (0.0 - <0.2), weak (0.2 - <0.4), moderate (0.4 - <0.6), strong (0.6 - <0.8), and very strong (0.80 - 1.00).

Table 1. Characteristics of research subjects

Variable	Frequency	Mean ± Standard Deviation (SD)	*p* value
Age (year)		50 (21-63)*	0.011*
Gender			
Men	60 (63.2%)		
Woman	35 (36.8%)		
Creatinine (mg/dL)		9.67 ± 2.83	0.125
Ureum (mg/dL)		126.08 ± 35.50	0.111
BMI (kg/m^2)	• Underweight (6(6.3%)) • Normal (34(35.8%)) • Overweight (19(20.0%)) • Obesity I (28(29.5%)) • Obesity II (8(8.4%))	24.15 ± 4.56	0.057

*: data is not normally distributed (p<0.05) and presented in the form of median(minimum-maximum)

Relationship between Body Mass Index and Urea Levels in Chronic Kidney Disease Patients Undergoing Hemodialysis

The results of the correlation analysis using the Pearson correlation test showed a very weak positive relationship that was not statistically significant between BMI and urea levels, with a correlation coefficient of r = 0.147 (p = 0.155). This indicates that an increase in BMI is not associated with a corresponding increase in urea levels.

DISCUSSIONS

The subjects in this study were 95 CKD patients undergoing HD according to the inclusion and exclusion criteria. The age of the study subjects ranged from 21 to 63 years. The median age of the study subjects was 50 years with the largest proportion being 50-60 years old. This result is not consistent with the findings of a

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study by Sakao *et al*. (2016), which reported that the average age of the study subjects was 65 years and older.[15] Based on global prevalence data, CKD is more common in individuals over 65 years of age compared to those in the 45-64 or 18-44 age groups. Data from the Ministry of Health (2018) also indicates that the prevalence of CKD in Indonesia is highest in the 65-74 age group, accounting for 0.82% of the total population.[6] The decline in kidney function begins at the age of 30-40 years and accelerates at the age of 50-60 years and above, with an average decrease in GFR of 1% per year which is influenced by disease conditions such as hypertension, obesity, and diabetes.[16] The results showing a predominantly younger population in this study are likely influenced by the patients' lifestyle. The increasing prevalence of diabetes, hypertension, and heart disease at younger ages are major drivers of CKD and are closely associated with lifestyle factors.[17]

The subjects of this study were mostly male (63.2%). The same research results were also obtained by Anthoni *et al*. (2019) with a higher proportion of male sufferers than female sufferers.[18] In addition, data from the Ministry of Health (2018) showed that the proportion of male CKD sufferers was greater than female with a ratio of 6:5.[6] Thus, a clear understanding of the relationship between gender and the incidence of CKD is still lacking. Carrero *et al*. (2018) conducted a study suggesting that differences in the incidence of CKD may be attributed to biological factors. Specifically, women may benefit from the protective effects of estrogen, while men may experience a pro-inflammatory and pro-apoptotic effect of testosterone on the kidneys.[19] Health factors such as unhealthy lifestyles and comorbidities are also risk factors for CKD.

The results of observations on 95 subjects of this study, the BMI value category based on the WHO Asia Pacific classification found malnutrition (<18.5 kg/m^2) in 6 patients (6.3%), normal (18.5-22.9 kg/m^2) in 34 patients (35.8%), overweight (23.0-24.9 kg/m^2) in 19 patients (20.0%), obesity I (25.0–29.9 kg/m^2) in 28 patients (29.5%), and obesity II (≥30 kg/m^2) in 8 patients (8.4%). Another study by Anggraini & Adelin (2023) stated that higher BMI is associated with better prognosis in HD patients.[20] Several studies have stated that BMI in HD patients is usually normal and is an indicator to assess overall nutritional status.[21] The BMI values of patients in this study do not align with the theory that, as kidney disease progresses, BMI should decrease in patients.

The results that are inconsistent with this theory are likely due to factors such as dialysis adequacy and the patient's improper dietary habits. Dialysis adequacy refers to the efficiency with which toxins and metabolic waste products are removed from the patient's blood during HD. It is typically assessed using the urea reduction ratio (URR), a quantitative method that measures the percentage of urea cleared during one session of HD. URR, also known as Kt/V, represents the ratio of dialysis time and urea clearance to the volume of urea distribution in body fluids. URR reflects the effectiveness of HD in clearing metabolic waste products. Persistent post-HD BMI may indicate that the volume of fluid retained in the patient's tissues is significant, suggesting that the ultrafiltration and diffusion processes during HD are not functioning properly. BMI can serve as a reliable indicator of kidney function, as an increase in normal BMI is associated with a 0.4% increase in GFR, while an increase in BMI due to obesity is linked to a 1.2% increase in GFR. Consequently, to ensure adequate dialysis function, a high dose of Kt/V is required. Additionally, HD patients are prone to edema due to increased fluid and pressure in the extracellular space, which can also affect BMI measurements.[22]

The results of the research analysis on 95 subjects showed high levels of creatinine and urea. The mean ± standard deviation (SD) of creatinine and urea levels were 9.67 ± 2.83 mg/dL and 126.08 ± 35.50 mg/dL. The increase in creatinine in patients is in accordance with the results of a 2016 study conducted at Dr. Moewardi Surakarta Hospital and Sanjiwani Gianyar Hospital with findings of increased serum creatinine levels in all samples (100%) with an overall average of 6.9 mg/dL.[23] Research by Sanjaya *et al*. (2019) also showed the same results, namely an increase in serum creatinine with an average of 9.07 mg/dL.[24] The results of this study are consistent with the theory that creatinine is a marker of kidney damage. Creatinine is a waste product resulting from the breakdown of muscle proteins in the body and is normally excreted by the kidneys through urine. The reference range for serum creatinine levels in the blood is 0.7–1.2 mg/dL. When kidney damage occurs, particularly to the filtration function, creatinine levels in the blood increase. Elevated creatinine levels above the normal range are correlated with a decreased GFR and indicate impaired kidney function.[25]

This study also showed an increase in urea levels above normal in all subjects (100%). Similar research was also found at Sanjiwani Gianyar Hospital in 2016. Another study at Prof. Dr. R. D. Kandou Manado Hospital and Advent Teling Manado Hospital also found an increase in serum urea with an average of 139.6 mg/dL.[23] Urea is a product of protein metabolism that is often used as a proxy for the severity of CKD and the adequacy of dialysis in clinical conditions.[26] The reference range for serum urea levels in the blood is 5–20 mg/dL. An increase in urea levels is closely related to the extent of GFR impairment. When GFR decreases to 60%, patients may not experience noticeable symptoms, although urea and creatinine levels will rise. As GFR falls to 30%, symptoms such as nocturia, weakness, nausea, decreased appetite, and weight loss begin to appear. If GFR drops below 15%, severe complications arise due to the accumulation of uremic toxins.[23] Serum creatinine and serum urea levels increase along with a decrease in glomerular filtering ability. These two levels reflect the most sensitive damage to the kidneys because the body produces them constantly.

If this study is grouped based on BMI values, the distribution of mean creatinine levels shows an increasing trend along with increasing BMI values. The results of the study showed a significant weak positive relationship between BMI values and creatinine levels with a correlation coefficient value of $r = 0.246$ ($p = 0.016$). Research by Jedrusik *et al*. (2019) said that a higher BMI value is associated with greater muscle mass and creatinine supply, as also seen from 24-hour creatinine excretion.[27] Serum creatinine correlates closely with body weight and even more strongly with lean body mass, which is mainly determined by muscle mass. According to previous theories, as CKD progresses and is influenced by various factors such as complications during HD, the accumulation of uremic toxins, and metabolic changes, there is a decrease in the patient's BMI. This reduction in BMI is accompanied by an increase in creatinine levels, which result from muscle protein degradation. Serum creatinine levels in CKD patients rise in parallel with worsening kidney function. Creatinine, which originates from skeletal muscle, serves as a biomarker for somatic body protein, particularly in end-stage CKD patients with very low GFR. In HD patients with high BMI values, serum creatinine levels due to muscle protein breakdown tend to be elevated. A study by Maherubin *et al*. (2021) also found that mean serum creatinine levels and creatinine clearance were higher in obese women compared to healthy women with normal weight.[28]

Research by Safina *et al*. (2022) found that the average serum creatinine was significantly ($p \leq 0.001$) higher in women with high BMI values compared to women with normal BMI.[29] The figure was also significantly ($p \leq 0.05$) higher in the obese group compared to overweight adult women. Creatinine clearance increases progressively with increasing body weight (including muscle mass, body fat, and water), due to a higher production of creatinine and a greater volume of distribution, accompanied by glomerular hyperfiltration. Additionally, in CKD patients with obesity as a risk factor, high body fat content is associated with early inflammatory processes induced by adipokine production and the HD procedure. This process, in turn, triggers the production of proinflammatory cytokines, which contribute to further muscle breakdown. However, the results of this study contrast with the findings of Lubis *et al*. (2020), which showed no significant relationship between BMI and creatinine levels.[30] This may be due to differences in the frequency distribution of subjects based on BMI categories, where the normal BMI category is greater than the other categories so that statistically the results are not different.

Based on the results of the Pearson rank test, a very weak positive relationship was found that was not significant between BMI values and urea levels with a correlation coefficient value of $r = 0.147$ ($p = 0.155$). These results indicate that an increase in BMI does not cause serum urea levels to also increase and the effect of the relationship between variables is small. The results of this study are not in accordance with the study by Safina *et al*. (2022) which showed a significant relationship between the average serum urea levels in women with BMI values above normal compared to women with normal BMI ($p \leq 0.05$).[29] Several studies have shown that exposure to HD membranes increases protein breakdown. Previous studies have reported increased post-dialysis urea formation and suggested that the HD procedure accelerates protein breakdown.[31] In theory, HD procedures can only partially remove uremic solutes, thereby alleviating the uremic burden to a limited extent. Incomplete clearance of uremic solutes, along with the formation of urea from tissue degradation induced by the dialysis process and protein intake, contributes to the accumulation of these toxins. The buildup of urea in the circulation leads to a significant reflux into the digestive tract, which in turn triggers systemic inflammation.[11]

Based on this theory, the progression of CKD and the influence of the various factors mentioned above are expected to result in a decrease in the patient's BMI and an increase in serum urea levels. The lack of a significant relationship between BMI and serum urea levels in this study may be due to the rate of protein degradation and the inflammatory process. The elevated urea levels observed in all patients suggest ongoing protein degradation caused by inflammation. The rate of protein degradation varies between individuals, as the half-life of proteins in cells can range from minutes to days, with different rates of degradation playing important roles in cell regulation. In response to specific inflammatory signals in CKD patients, proteins can be rapidly degraded. In patients with normal BMI, protein degradation may be more pronounced than in obese patients, due to a more chronic inflammatory state.

The results of a study by Wierzchowska *et al*. (2021) showed that prolonged increases in plasma free fatty acid concentrations in healthy humans decreased protein breakdown by 27%, which could explain previous observations of lower muscle protein breakdown rates in obese patients.[32] This study found that obese subjects had lower body protein levels compared to those with normal BMI. The measurement of creatinine and urea levels is crucial in CKD patients undergoing HD procedures, typically performed every six months to assess dialysis adequacy. The limitations of this study include the potential impact of comorbid diseases and patient supplementation, which may influence the relationship between BMI values and serum urea levels.

SUMMARY AND RECOMMENDATIONS

The conclusion of this study is that there is no significant relationship between BMI values and serum urea levels. However, a weak but significant relationship was found between BMI values and creatinine levels, indicating a tendency for increasing BMI to be associated with higher serum creatinine levels in hemodialysis (HD) patients. Further research is needed to identify additional variables that may correlate with creatinine and urea levels, such as dietary protein intake and the presence of other chronic diseases.

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