International Journal Of Health, Engineering And Technology (IJHET) *E-ISSN 2829 - 8683*
Volume 3, Number 5, January 2025, *Page. 912 - 921*
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The Relationship Between Dietary Protein Intake Restriction and Mortality Risk in Stage V Chronic Kidney Disease Patients With Haemodialysis : Literature Review

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Abstract

Chronic Kidney Disease (CKD) is a condition in which kidney function progressively declines and irreversibly diminishes so that the kidneys are unable to maintain metabolic, fluid and electrolyte balance resulting in uremia and azotemia. One of the kidney replacement therapies in stage 5 of CKD is by hemodialysis procedure. There are 5 – 8 g/dialysis amino acids losses during the hemodialysis (HD) procedured , if protein loss is not replaced with adequate dietary protein intake it will certainly affect malnutrition which can increase the risk of mortality. Inadequate protein intake is associated with protein energy wasting. However, the associated impact of protein intake on mortality remains unclear. Literature review was conducted to identify the effect of protein intake restriction on mortality risk in CKD patients undergoing hemodialysis. Articles were searched through NCBI (The National Center for Biotechnology Information), PubMed/Medline and Science Direct. Prisma Method was used to describe the process of selecting journals in a structured manner so that valid journals are obtained for analysis in this study. The results showed that appropriate management of protein intake for patients undergoing haemodialysis is necessary to prevent malnutrition, high protein intake can increase phosphorus and potassium levels and risk metabolic acidosis, and extensive restriction can lead to malnutrition and death with the hazard ratio 1.33. It is recommended that protein intake in CKD patients undergoing hemodialysis be in the range of 1.0 - 1.2 g/kg/day.

Keyword: Chronic Kidney Disease, Haemodialysis, Protein Intake

INTRODUCTION

Chronic Kidney Disease (CKD) is a kidney disorder that persists for more than or equal to three months characterized by abnormalities in kidney structure or function with or without decreased glomerular filtration rate (eGFR <60 mL/minute/1.73m2) based on pathological abnormalities or signs of kidney damage, including abnormalities in blood or urine composition or abnormalities in laboratory tests (Ministry of Health of the Republic of Indonesia, 2023). The prevalence of CKD in worldwide reached 843.6 million in 2017 and the most prevalent risk factors that increase the risk of CKD such as hypertension, diabetes mellitus and obesity (Kovesdy, 2022)

According to the 2017 Global Burden of Disease data, CKD ranks 12th highest in the worldwide as the leading cause of mortality in people worldwide. The prevalence of CKD in Indonesia is 0.64% with the highest prevalence of CKD in North Kalimantan (0.64%) and the lowest prevalence of CKD in West Sulawesi (0.18%) (Hidayaningsih et al., 2023). Risk factors that can increase the risk of CKD are hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, low physical activity and smoking behavior (Wang et al., 2023). Dialysis in CKD patients can be started if there are one or more of the following conditions, including symptoms or signs caused by kidney failure (serositis, acid-base or electrolyte disorders, pruritus) and the body's inability to control volume status or blood pressure, progressive decline in nutritional status that is refractory to dietary intervention or cognitive disorders and these conditions are often found in LFG 5 and 10 mL/minute/1.73 m2) (Ministry of Health, 2023).

According to The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (KDOQI) guidelines, patients with CKD with hemodialysis are advised to maintain a daily protein intake of 1.0 – 1.2 g/kg/day (Iklizer et al., 2024). A prospective cohort study in 8 hemodialysis outpatient department in Southern China showed that a daily protein intake of 1.0 - 1.4 g/kg/day

was associated with lower mortality from all cases and decreased mortality due to cardiovascular disease in hemodialysis patients (Wang, J et al., 2022). Hemodialysis (HD) is a life-saving therapeutic modality for CKD patients with very low kidney function to remove harmful substances in the body, but the HD procedure can also absorb various nutrients in the body so that there is a decrease in plasma concentration of amino acids during the HD process until 20% in plasma concentration from total amino acids (Hendriks et al., 2020).

Malnutrition has been known to be a major risk factor of morbidity and mortality among hemodialysis patients. There are 75% of hemodialysis patients suffering from malnutrition related to inadequate protein intake. Repeated hemodialysis procedures (2-3 times / week) can reduce protein levels in the body so that it is susceptible to malnutrition (Lee et al., 2020). If protein intake inadequate, there will be a lack of energy and amino acid deficiency so that maintenance of body tissue will be hampered. However, if protein and amino acid intake are excessive, the kidneys and liver will work harder to metabolize and excrete excess nitrogen to prevent acidosis, increased urea and ammonia in the blood (Sulistyowati et al., 2015). Food or supplements with sufficient protein content can be used to improve nutritional status in patients in hemodialysis for a long time and are useful for improving good clinical outcomes in CKD patients who have poor nutritional status at the beginning of hemodialysis therapy (Hendriks et al., 2021).

According to the Pernerfri CKD Nutrition Consensus (2011), CKD patients with Hemodialysis have other factors that can increase the incidence of protein energy malnutrition. Hemodialysis will increase protein catabolism. As much as 4-9 grams of amino acids and 2-3 grams of amino acid peptides will be lost in one hemodialysis session. The use of reusable dialyzers will increase the loss of amino acids and albumin (Pernefri, 2013). Protein is the main source of nitrogen metabolized by the body, these amino acids are used to form proteins and other compounds containing nitrogen or oxidation to produce energy. Nitrogen balance refers to the difference between total nitrogen intake and total nitrogen loss in feces, sweat and urine. In normal adults, nitrogen intake is in accordance with the nitrogen excreted. Positive nitrogen balance occurs when there is more nitrogen intake than nitrogen output, while negative nitrogen balance occurs when nitrogen output exceeds nitrogen intake (Wiji et al., 2021). The relationship between protein intake and mortality in CKD patients undergoing HD still shows inconsistent results, so this study aims to explore further the relationship between protein intake and mortality rates in CKD patients undergoing hemodialysis.

RESEARCH METHODS

The research method used in this study was a literature review to further analyze using secondary data related to protein intake in CKD patients undergoing hemodialysis on mortality rates through library research. The literature review uses a scheme adapted from the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) diagram (Mother et al, 2009).

The database used through Google Science direct, PubMed/Medline and NCBI. The keywords used to obtain articles are "protein intake restriction", "protein Intake", "haemodialysis", "chronic kidney disease", "mortality", chronic kidney disease". Search for studies in English. This study focuses on determining the relationship between protein intake restrictions and decreased mortality in CKD patients undergoing hemodialysis. Articles that meet the criteria include articles discussing protein intake restrictions on decreased mortality in CKD patients undergoing hemodialysis, full-text articles, published in national and international accredited journals and the research design used in the study using longitudinal, cross-sectional and randomized control trials. The year of the literature search that has been published is in the range of 2014 - 2023 or the last 10 years. The exclusion criteria set are non-human research subjects, student final assignments in the

form of thesis, dissertations, theses, non-empirical research, newspaper articles that have not been published through peer review and literature review.

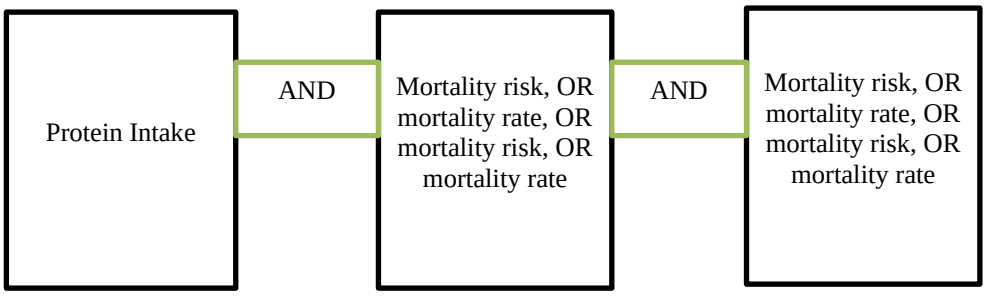

Figure 1. Keywords

RESULTS AND DISCUSSION

Literature review by including inclusion criteria found 6 studies (Bellizzi et al., 2015; Bellizzi et al., 2022; Aryaie et al., 2021; Hasegawa et al., 2020). The countries of origin of the article publications include Italy, Japan, California and Iran with a total of 111,293 respondents. The results of the literature review search were obtained from 3 databases, namely NCBI with 30 articles, Pubmed with 112 articles and Science Direct with 330 articles and the articles were selected using the PRISMA method so that 6 selected research articles were obtained which will be used to discuss the effect of limiting protein intake on the risk of mortality in CKD patients undergoing hemodialysis. The overall study results show that management of protein intake in CKD patients undergoing hemodialysis needs to be carried out to prevent malnutrition which can increase the risk of mortality.

Adequate protein intake play critical roles in HD patients to prevent malnutrition and to reduce the risk of mortality, moreover rerecent studies advised to consume limited plant based protein to control their serum phsoporus and potassium levels and also consumed 50% protein from animal sources to ensure they get enough essential amino acids (Darzi et al., 2023) .Low levels of serum albumin as a biochemical marker indicating protein energy wasting, are strong predictors of higher death risk in HD patients. The recommendation protein intake for HD patients from The National Kidney Foundation is 1.2 g/kg /day due to hypercatabolism factor and protein losses during dialysis (Gurung et al., 2024).

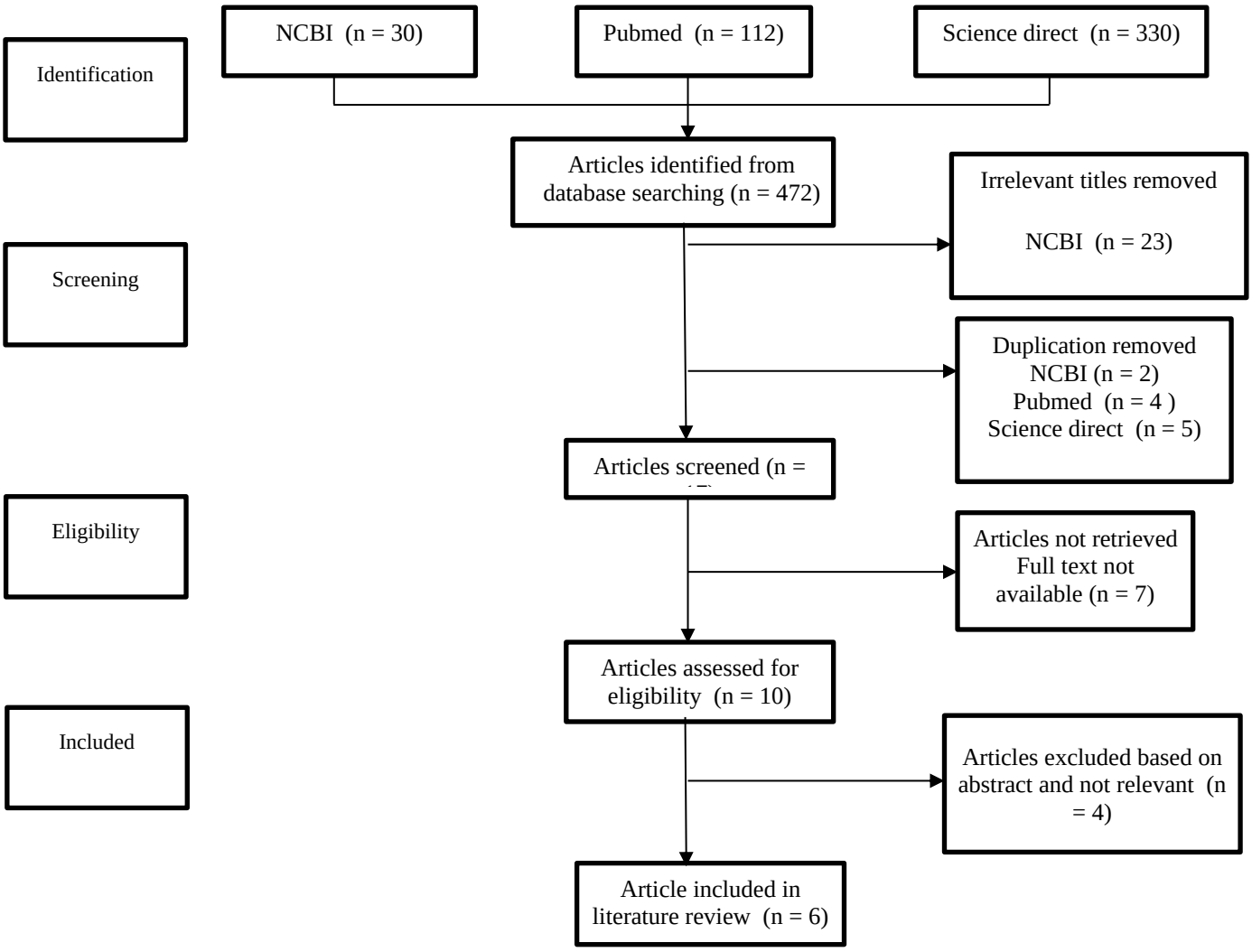

Figure 2. Prisma flow diagram of the literature search strategy

First author	Country	Number of participants	Study design	Analysis Method	Results
Vincenzo Bellizzi (2022)	Italy	Very low protein diet (n = 184), no very low protein diet (n = 334) and unselected patient control group (n = 9,092)	The design of this study is historical cohort studies	Using the propensity score method and the cox regression model used to match groups when starting dialysis to obtain survival analysis and estimate hazard ratios.	*Adjusted hazard ratio*in the group undergoing a very low protein diet compared to the control group, namely 0.59 (0.45 - 0.78). And the provision of a very low protein diet does not increase the risk of mortality during the period of renal replacement therapy.
Hasegawa (2020)	Japan	2,404 hemodialysis patients	The design of this study is prospective cohort	Kaplan Meier and Log rank test were used to compare the normalized protein catabolic ratio (nPCR) and life expectancy of hemodialysis patients.	Patients with nPCR < 1.0 g/kg/day have a high risk of mortality compared to medium (1 – 1.2 g/kg/day) and high (≥ 1.2 g/kg/day)
Vincenzo	Italy	The total number of	A multicenter,	Hazard ratio was	Prescribing a very low protein

Bellizzi (2015)		respondents was 223, divided into 2 groups, namely a very low protein diet (0.35 g/kg/day) consisting of 107 respondents and a low protein diet (0.60 g/kg/day) consisting of 116 respondents.	randomized controlled trial, pragmatic trial comparing the effects of renal outcomes and a low-protein diet in adult patients with grade 4 and 5 CKD.	measured using Fine and Gray regression model. Outcomes of CKD mortality and overall mortality were analyzed using Cox regression model.	diet compared to a low protein diet is still safe to implement but has no additional benefit to the kidneys and patient survival.
Mohammad Aryaie (	Kerman, Iran	The number of respondent in this research was 568 patients from 3 location hemodialysis departement	The study design used was a longitudinal cohort. Information from 568 respondents was retrospectively collected between March 21, 2011 and December 23, 2019 from 3 hemodialysis facilities in Kerma, Iran. Respondents were followed at the start of hemodialysis initiation and ended at kidney transplantation, loss to follow-up, death or end of study on December 23, 2019.	*G estimation* used to determine the causal effect of the protein catabolic ratio on mortality in end-stage CKD patients.	Protein intake <1.2 g/kg/day has a 4.6 times increase in experiencing death compared to respondents who have protein intake ≥ 1.2 g/kg/day. so it can be concluded that inadequate protein intake characterized by a normalized protein catabolic ratio can increase all causes of death in end-stage CKD patients.
Ravel (2013)	California	The number of respondent in this research was 98,488 patient with hemodialysis	The research design used was a prospective cohort and respondents were followed for 8 years from July 1, 2001 – September 30, 2009. And the patients	This study was to determine the increase in normalize protein nitrogen in CKD respondents undergoing hemodialysis with hypoalbuminemia towards reducing the risk of mortality in black, white and Hispanic races. Survival rate was statistically tested using Cox proportional hazard regression.	low protein intake can increase the risk of mortality in HD patients . Low levels of protein nitrogen < 30 g/dl can increase the risk of mortality in HD patients with a hazard ratio of 1.33 compared to protein nitrogen levels ≥ 110 g/dl with a hazard ratio of 0.92 .
Salamah (2024)	Netherlands	The number of respondent in this research 59 hemodialysis patients	The research design is prospective observational study	Spearman correlation was used to evaluate the correlation between protein intake and muscle mass, muscle strength, and Health	Hemodialysis patient with protein intake ≥ 1. 0 g/kg/day have a lower risk mortality rather than patient with protein intake < 1.0 g/kg/day.

	Related Quality of Life (HRQoL).Univariable linear regression analyses were performed to assess the association between protein intake as an independent variable and muscle mass, muscle strength, and HRQoL as dependent variables

Protein-rich foods and snacks during hemodialysis are recommended to increase protein intake during dialysis and are useful for improving nutritional status and survival rates in HD patients. Muscle catabolism during hemodialysis can be prevented and changed to anabolism by consuming foods that have high-quality protein. Consuming 60 grams of protein during hemodialysis can prevent a decrease in amino acid concentrations in the blood (Hendriks et al., 2021). Loss of amino acids during hemodialysis will affect protein synthesis, triggering muscle proteolysis to produce amino acids when the body's energy content is low. In addition, suboptimal food intake can have a negative impact on the survival rate of HD patients. According to several studies, protein intake <0.8 g/kg/day can increase the risk of mortality in HD patients and protein intake <1.2 g/kg /day can increase the risk 4.98 times higher for mortality (Sahathevan et al., 2020).

Excess consumption of amino acid protein is not good for kidney health because if protein is used as an energy source, the NH3 group must be released through the demainiation process and then synthesized into urea. Excess urea in the blood has a negative impact on health so it needs to be excreted through the kidneys in the form of urine. The more protein consumed, the more urea is formed and the higher the burden on the kidneys to remove the urea (Wiji , 2021). In a study conducted by Belizzi et al in 2015 using a historical cohort controlled study design, it was stated that the application of a very low protein diet with 0.3 - 0.4 g/kg/day with amino acid supplementation and ketoacids tablets followed for 3 months in CKD patients undergoing hemodialysis did not increase mortality rates with a hazard ratio of 0.59 (0.45 - 0.78). A prospective cohort study of 1,119 Chinese patients over 18 years of age undergoing hemodialysis in 2014-2015 stated that the proportion of vegetable protein intake normalized to ideal body weight was 0.6 ± 0.2 (SD) g/kg per day followed by a median follow-up of 28 months found 249 respondents died and 146 deaths of respondents were caused by cardiovascular disease. Patients with a proportion of vegetable protein intake was <45%, there was a 17% lower mortality rate for every 5% higher proportion of vegetable protein intake (HR, 0.83 [95% CI, 0.73-0.96]). Among haemodialysis patients with a proportion of vegetable protein intake ≥ 45%, there was a 9% higher mortality rate for every 5% higher proportion of vegetable protein intake (He, Y et al., 2021).

According to a study conducted by Beliizi et al in 2022 with a Randomized Controlled Trial (RCT) research design, shoewd that a very low protein diet (0.35 g/kg/day) and low protein (0.60 g/kg /day) followed for six months is still safe for hemodialysis patients but has no additional benefits to reduce the risk of mortality with HR: 1.12; 95% CI: 0.81, 1.56; p = 0.82) and the results of the study are in line with the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines who argued that CKD patients grade 3-5 are advised to consumed a low protein diet (0.55 - 0.60 g/kg /day) or a very low protein diet (0.28 - 0.43 g/kg/day) with ketoacid analog supplementation to reduce the risk of mortality. Protein energy wasting syndrome has been reported to occur in 18-75% of HD patients, foods with sufficient protein and energy content can help to optimize nutrient intake, restore catabolism from the HD process and increase patient satisfaction so that increasing protein

and energy intake will be associated with improvements in nutritional status, good clinical outcomes, good quality of life , reduced mortality and morbidity risk (Schaminee et al., 2021).

Protein energy wasting is a conditon of reduction body stores of protein and energy fuels and is associated with diminished functional capacity, impaired quality of life and incresed mortality in patient with hemodialysis (Sarav et al., 2018). These patients required a sufficient protein intake with a recommendation of 1.2 g/kg/day compared to healthy individuals because more amino acids are loss from each hemodialysis procedure. nPCR is often used to predict mortality in hemodialysis patients. According to research by Aryaie et al in 2021 using statistical analysis G estimation, inadequate protein intake <1.2 g/kg/day can increase the risk of death 4.6 times higher than protein intake ≥ 1.2 g/kg/day (Aryaie et al., 2021). A study conducted on 10 patients with urine production <100 mL/day undergoing hemodialysis 3 times a week stated that CKD patients who consumed their usual food during HD would loss 12 g of amino acids from the circulation in each session hemodialysis procedure. This is equivalent to the amount of amino acids released into the bloodstream after consuming a regular meal containing 20 – 25 g of protein. Current clinical guidelines recommend that patients on HD consume at least 1.2 g/kg/ day to prevent muscle wasting or sarcopenia. However, most CKD patients fail to meet this protein requirement, the research study showed that the protein intake of CKD patients was only 1.0 g/kg/day, and only 3 patients reported a protein intake of at least 1.2g/kg/day. Inadequate dietary protein intake is a predisposing factor to the development of protein malnutrition, thereby increasing the risk of mortality (Hendriks et al., 2020). Hemodialysis procedure can lead a catabolic state associated with decreased whole body protein synthesis and increased whole body and skeletal muscle breakdown simultaneously. The catabolic effects in HD patients will persist for several hours after the dialysis session ends. Intradialytic administration of protein-rich food has been shown to shift this balance toward a positive protein anabolic state. Hypoalbuminemia is a strong predictor of mortality in HD patients compared to other factors. A study stated that there was an increased risk of mortality in HD patients who had serum albumin <40 g/L (Li, J et al., 2020). The Kidney Disease Outcomes Quality Initiative Clinical Practice (KDOQI) states that the recommendation for protein intake is in the range of 1.2 - 1.4 g/kg/day and the guidelines used in Japan in this study recommend protein intake in the range of 1.0 - 1.2 g/kg/day. These recommendations are lower than the KDOQI guidelines. Patients undergoing hemodialysis are susceptible to malnutrition and weight loss which can lead to poor clinical outcomes. Research conducted by Hasegawa et al in 2020 stated that protein intake <1.0 g/kg/day can increase the risk of death compared to daily protein intake (1.0 - 1.2 g/kg/day) and high protein intake ≥ 1.2 g/kg/day.

Identification and diagnosis of protein energy wasting in HD patients is important because it can reduce quality of life and increase mortality rates. Dietary restrictions and persistent inflammation as well as the presence of uremic toxins contribute to malnutrition (Tan et al., 2019). Hypoalbuminemia is a strong predictor of increased risk of mortality in HD and chronic peritoneal dialysis patients, a study states that malnutrition and inflammation contribute to hypoalbuminemia so that nutritional support is the main thing to improve hypoalbuminemia and clinical outcomes in CKD patients. A prospective cohort study for 8 years in 98,489 HD patients from a multicenter dialysis health care provider stated that low protein nitrogen levels <30 g/dl can increase the risk of mortality in HD patients with a hazard ratio of 1.33 compared to protein nitrogen levels ≥110 g/dl with a hazard ratio of 0.92 and low protein intake can increase the risk of mortality in HD patients (Ravel et al., 2013). Restricting protein intake <0.8 g/kg/day or > 1.4 g/kg/day has been shown to increase the risk of mortality in HD patients. And to meet protein requirements in HD patients, it can be recommended not only to receive nutritional counseling but also to balance it by consuming 200 ml of milk with a protein content of 6 grams and 2 egg whites (66 grams) with a protein content of 7.7 grams per egg in one day in order to meet their daily protein requirements (Li, J et al., 2020).

CONCLUSION

Proper protein intake management for patients hemodialysis still needs to be considered, because high protein intake will have an impact on increasing phosphorus and potassium which increases the risk of metabolic acidosis and uremia. Otherwise extensive restrictions can cause protein energy wasting and malnutrition can lead the risk of morbidity and mortality with the hazard ratio 1.33. So it is recommended to maintain daily protein intake at around 1.0 - 1.2 g/kg/ day according to the KDOQI guidelines to prevent malnutrition and mortality. The importance of the role of the family as a companion to help patients to meet dietary protein requirement in terms of quality and quantity and provide motivation so that patients can increase their food intake adjusted to the needs recommended by KDOQI.

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