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Correlation of eGFR (estimated Glomerular Filtration Rate) with Potassium Levels in Patients with Diabetes Mellitus with Chronic Kidney Failure Complications

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ABSTRACT
Diabetes mellitus is a chronic disease caused by pancreatic metabolic disorders, and is characterized by hyperglycemia due to insulin resistance, insulin deficiency or a combination of both. A common complication in patients with diabetes mellitus is diabetic nephropathy. Diabetic nephropathy is characterized by the presence of microalbuminuria 30 mg/day, then developing into proteinuria accompanied by high blood pressure so that the glomerular filtration rate decreases and causes kidney failure. Chronic kidney failure is characterized by GFR <60 mL/minute/1.73 m2 which lasts for more than three months. eGFR is a more sensitive indicator for measuring kidney damage than serum creatinine because it measures the level of glomerular damage specifically and assesses the filtration function of the kidneys. Decreased kidney function can interfere with potassium metabolism, because potassium excretion is mostly through the kidneys. Disruption of potassium homeostasis can cause hyperkalemia. This study aims to determine the correlation of eGFR with potassium levels in patients with diabetes mellitus who experience complications of chronic kidney failure. The type of research used is observational analytic with a cross-sectional approach. This study was conducted at Syarifah Ambami Rato Ebu Bangkalan Hospital, a type B hospital with A accredited service quality. eGFR examination was carried out using a Cockcroft Gault method and potassium level examination was carried out using the ISE (Ion selective Electrode) method. Data analysis was carried out using the Shapiro Wilk normality test and the Spearman correlation test. The results showed no correlation between eGFR and potassium levels in patients with diabetes mellitus who experienced complications of chronic kidney failure.

Keywords: eGFR; Potassium levels; Diabetes mellitus; Chronic kidney disease

INTRODUCTION
Diabetes mellitus is a chronic disease due to metabolic disorders of the pancreas which cannot produce the hormone insulin optimally (Zulkarnain, 2021). Diabetes mellitus is characterized by hyperglycemia due to insulin resistance, insulin deficiency or a combination of both. The hormone insulin functions to control the use and storage of glucose produced by pancreatic β-cells (Hardianto, 2021). Other organ functions will be disrupted if the insulin deficit is not treated in the long term. These complications include cardiovascular disease, nervous system damage (neuropathy), kidney damage (nephropathy), eye damage (retinopathy) and gangrenous wounds (Federation, 2021).

With half a billion people suffering from diabetes, this number is becoming alarming. About 537 million people had diabetes in 2021. This number is expected to rise to 643 million and 783 million by 2045. The disease also affects more than 1.2 million children and adolescents in 2021. By 2045, IDF estimates that diabetes will increase in the Southeast Asia Region by 68%, which is around 152 million people. Diabetes is the cause of 747,000 deaths in Southeast Asia in 2021. Indonesia is the fifth country in the world with the most people with diabetes mellitus, which is 19.47 million out of 273.8 million total population (Federation, 2021).

Diabetic nephropathy is a complication that often occurs in patients with diabetes mellitus with a percentage reaching 40%. Diabetic nephropathy is characterized by microalbuminuria that increases >30 mg/day, then develops into proteinuria accompanied by high blood pressure so that the glomerular filtration rate decreases and causes kidney failure. Initially high blood glucose levels or hyperglycemia cause glycosylation of basement membrane proteins. The basement membrane thickens and there is a buildup of substances similar to basement membrane glycoproteins in the mesangium so that slowly the glomerular capillaries are squeezed, blood flow is also disturbed which results in glomerulosclerosis and nephron hypertrophy after which diabetic nephropathy occurs (Rivandi and Yonata, 2015).

Diabetic nephropathy will progress to kidney failure, which is the leading cause of death in people with diabetes mellitus (Satria, Decroli and Afriwardi, 2018). Chronic renal failure is irreversible, with eGFR (estimated Glomerular Filtration Rate) or Glomerular Filtration Rate (LFG) < 60 mL/min/1.73 m2 which lasts for more than three months (Nuroini and Wijayanto, 2022).

Creatinine will accumulate in the blood when kidney function is impaired (Nandari, 2015). Creatinine is one of the chemical compounds excreted by the kidneys, mainly through glomerular filtration (Onuigbo and Agbasi, 2015). An elevated serum creatinine concentration is proportional to the amount of functional nephron decline (Nandari, 2015). Creatinine levels are also directly proportional to muscle mass because it is synthesized in skeletal muscle. Men who tend to have higher muscle mass than women will experience a faster increase in creatinine levels when kidney function is impaired. eGFR is a more sensitive indicator to measure kidney damage than serum creatinine. A person with low muscle mass will have normal creatinine levels, despite having a significantly decreased eGFR (Nova, Sartika and Suratno, 2022). eGFR will measure the glomerular function of the kidneys to filter waste from the blood (William and Ludong, 2019).

The kidneys function to maintain the balance of body fluids, by maintaining the concentration of normal values of electrolytes (K, Na, Cl, Ca). Potassium is the main cation in cells, functioning as a guardian of cellular osmolarity, acid-base balance, transmission of nerve stimuli, regulation of heart and muscle function. The total amount of K in the body is about 50-55 mEq/Kg, of which 98% is intracellular and 1-2% is extracellular. Potassium is filtered by the glomerulus, of which 70% is reabsorbed in the proximal tubule, 20% in the henle's arch and 10% is secreted or reabsorbed by the cortical collecting duct. Decreased renal function can lead to abnormal potassium metabolism, as potassium excretion is mostly through the kidneys (Yamada and Inaba, 2021). Disturbances in potassium homeostasis can lead to hyperkalemia or hypokalemia that lead to other serious diseases (DuBose, 2017).

Diabetics are more prone to hyperkalemia, apart from the complications of kidney failure there are two other factors that affect this. The first is hyperosmolarity, which occurs in patients with diabetes mellitus due to hyperglycemia, when the concentration in the blood vessels increases, water with a high potassium content will escape from intracellular to extracellular causing serum potassium to increase, second is insulin deficiency, This hormone plays a role in the synthesis of the Na-K-ATPase enzyme, the Na-K-ATPase enzyme functions to pump potassium from extracellular to intracellular, in patients with diabetes mellitus the quantity of insulin decreases, so that the Na-K-ATPase enzyme does not function properly and potassium levels in the extracellular will increase (Tzamaloukas, 2022). This theory is in accordance with the research of Loutradis, et al (2015) found that chronic renal failure patients with diabetes mellitus have a 25% higher prevalence of hyperkalemia compared to chronic renal failure patients without diabetes mellitus (Loutradis et al., 2015).

The function of potassium is to regulate the contraction and nerve work of the heart muscle, when potassium levels increase the electrical activity of the heart will be disrupted and will cause arrhythmia. Uncontrolled hyperkalemia can cause cardiac arrest or death (Fauziah, 2020). Arrhythmia is an abnormality in the rhythm of the heartbeat, when an arrhythmia occurs the heart will beat faster (tachycardia), slower (bradycardia), or beat with an irregular rhythm. Ventricular arrhythmia is a type of arrhythmia caused by abnormal potassium levels (Andika, Sukohar and Yonata, 2021).

According to research by Ivana (2017), there is an increase in potassium levels in patients with chronic renal failure (Ivana, 2017). According to research by Samsuria and Watuguly (2019), the increase in blood potassium in patients with chronic renal failure is related to creatinine levels, namely the results of a moderate positive correlation between creatinine and potassium (Samsuria and Watuguly, 2019). These results are in accordance with Prabha's research (2017), there are three groups of patients, namely group 1 with creatinine levels < 1.5 mg/dL, group 2 with creatinine levels 1.5-3 mg/dL, and group 3 with creatinine levels > 3 mg/dL, which shows the highest increase in potassium levels occurred in group 2 with a percentage of 51% and group 3 with 74% (Prabha, 2017). Hemodialysis is one of the therapies in chronic renal failure patients to remove body waste substances that cannot be removed optimally by the kidneys, so that creatinine and potassium levels will decrease after doing this therapy. This statement is in accordance with Meilinda's research (2021), namely the average pre-hemodialysis blood potassium level increased by 6.1% from the normal value and decreased by 2.9% post-hemodialysis (Meilinda, 2021).

Based on the description of the problem above, a study will be conducted to determine the correlation of eGFR (estimated Glomerular Filtration Rate) with potassium levels in patients with diabetes mellitus who experience complications of chronic renal failure. Thus it will be known that the relationship between eGFR (estimated Glomerular Filtration Rate) and potassium levels in patients with diabetes mellitus who experience chronic renal failure has a strong or weak negative correlation, so that it can be a basis for reference to prevent other serious complications.

RESEARCH METHOD

Authors The type of research used in this study is analytical observational with cross sectional as an approach method to analyze the level of correlation of eGFR with potassium levels in patients with diabetes mellitus who have complications of chronic renal failure. The research was conducted in February-March at Syarifah Ambami Rato Ebu Bangkalan Hospital for sampling and examination of creatinine levels, potassium levels and calculation of eGFR values.

The population in the study were patients with diabetes mellitus who experienced complications of chronic kidney failure and were treated at Syarifah Ambami Rato Ebu Hospital Bangkalan. The sample in this study was part of the population members determined through purposive sampling with the criteria of having creatinine levels ≥ 2 mg/dL, not yet doing hemodialysis, non-hemolytic and icteric samples, and not suffering from hemolytic anemia and addison's disease, with a sample size of 30. The variables used in this study were eGFR values, potassium levels and diabetes mellitus patients who experienced complications of chronic renal failure. The data collection technique used primary data, namely the results of the examination of creatinine levels, eGFR and potassium levels. The data obtained were analyzed statistically using the Spearman correlation test. This research has passed the ethical feasibility of Poltekkes Kemenkes Surabaya and Syarifah Ambami Rato Ebu Bangkalan Hospital.

RESULT AND DISCUSSION

Results This study was conducted on 30 samples of patients with diabetes mellitus who experienced complications of chronic renal failure and had met the criteria and were treated at Syarifah Ambami Rato Ebu Bangkalan Hospital. The 30 samples were then examined for creatinine levels, eGFR and potassium levels. The research data obtained are presented in the following table:

Table 1. Characteristics of respondents based on gender

Gender	Total	Percentage
Male	14	46,7%
Female	16	53,3%
Total	**30**	**100%**

From table 1, it can be seen that in this study, patients with diabetes mellitus who experienced complications of chronic renal failure based on gender were mostly patients with female gender totaling 16 people or 53.3%. Women are more at risk of developing diabetes mellitus because they generally have less activity which causes a buildup of LDL (*Low Density Lipoprotein*) resulting in an increase in BMI (*Body Mass Index*) and is one of the causes of diabetes mellitus (Agustina *et al.*, 2021). Estrogen and progesterone hormones in women can increase the insulin response in the blood, so that when menopause the insulin response will decrease due to low estrogen and progesterone hormones (Arania *et al.*, 2023).

Table 2. Characteristics of respondents based on age

Age Range	Total	Percentage
31-40 years old	3	10%
41-50 years old	8	26,67%
51-60 years old	10	33,33%
61-70 years	8	26,67%
71-80 years	1	3,33%
Total	**30**	**100%**

From table 2, it can be seen that the age of patients with diabetes mellitus who experience complications of chronic renal failure is mostly in the age range of 51-60 years, namely a total of 10 patients (33.33%), while in the age range 71-80 years has the least number, namely only 1 patient (3.33%). The increased risk of diabetes mellitus occurs at the age of > 40 years, this is due to the aging process so that the ability of pancreatic β cells to produce insulin is reduced. Another cause is a 35% decrease in mitochondrial activity in muscle cells during aging which is associated with an increase in lipids in the muscle and triggers insulin resistance (Komariah and Rahayu, 2020). According to Susilawati and Rahmawati's research (2021), a person aged > 45 years is at 8 times greater risk of developing diabetes mellitus than a person aged < 45 years, due to degenerative factors, namely the decline in body function in metabolizing glucose. Another factor is how long the patient has diabetes mellitus and survives in this condition (Susilawati and Rahmawati, 2021).

Table 3. Characteristics of respondents based on body weight

Body Weight	Total	Percentage
40-50 kg	3	10%
51-60 kg	6	20%
61-70 kg	17	56,67%
71-80 kg	4	13,33%
Total	**30**	**100%**

From table 3, it can be seen that the body weight of patients with diabetes mellitus who experience complications of chronic kidney failure is mostly in the weight range of 61-70 kg, namely a total of 17 patients (56.67%), this weight tends to exceed the normal BMI limit with the average height of the Indonesian population ± 160 cm. Excess weight can cause the hormone adiponectin which functions to increase sensitivity to insulin and increase the effects of insulin to decrease. Fat tissue can secrete fatty acids which, if accumulated in the muscles, will interfere with the work of insulin in the muscles. Increased body weight is also a factor in increasing glucose levels so that the risk of diabetes mellitus increases (Wahyuni *et al.*, 2022). Excess weight will cause an increase in fat stores. Triacylglycerol is a store of fatty acids in adipocyte cells in the form of chemical compounds. Fatty acids in free form can circulate in blood vessels throughout the body, causing oxidative stress called lipotoxicity. The onset of lipotoxicity effects due to the amount of free fatty acids released by triacylglycerols in an effort to compensate for the destruction of excess fat stores will affect adipose and non-adipose tissue, and play a role in the pathophysiology of diseases in various organs such as the pancreas and liver (Rias and Sutikno, 2017). A person with above-normal body weight is also prone to diseases such as hyperglycemia, hypertension, dyslipidemia, atherosclerosis, where these diseases are factors that are closely related to the occurrence of chronic kidney failure (Widiana, 2017).

Table 4. Overview of creatinine levels in respondents

Creatinine Level	Total	Percentage
2.00-3.00 mg/dL	6	20%
3.01-5.00 mg/dL	5	16,67%
≥5.01 mg/dL	19	63,33%
Total	**30**	**100%**

Based on table 4, it is known that patients with diabetes mellitus who experience complications of chronic renal failure have the most creatinine levels ≥5.01 mg/dL, namely 19 patients (63.33%) and creatinine levels of 3.01-5.00 mg/dL owned by the least number of patients, namely 5 people (16.67%). This creatinine examination uses the Architect Plus C4000 tool with the Enzymatic Colorimetric method. Creatinine is the end result of the metabolism of creatine phosphate and muscle creatine, synthesized in the liver, found in blood, muscle and excreted through urine. Creatinine is excreted in the urine through the filtration process in the glomerulus. The diagnosis of renal failure can be made when creatinine levels rise above the normal threshold value. Creatinine levels not only depend on muscle mass, but are also influenced by diet, body activity and health status (Paramita, 2019).

Table 5. Distribution of eGFR values in respondents

Type of Inspection	Minimum Value	Maximum Value	Description	Total	Percentage
eGFR (mL/min/ 1.73 m)^2	3,90	24,59	Normal	0	0%
			Low	30	100%
			Total	30	100%

Description:
Normal eGFR value = > 60 mL/min/1.73 m^2

Based on table 5, the minimum eGFR value is 3.90 mL/min/1.73 m^2 and the maximum value is 24.59 mL/min/1.73 m^2 in patients with diabetes mellitus who have chronic renal failure complications, with 30 patients (100%) having low eGFR values. This eGFR examination uses the *Crockcroft Gault* method, because this method is the most recommended by the *National Kidney Foundation - Kidney*

Diseae Outcome Quality Initiative (NKF-KDOQI) of the three existing methods (Halim, 2017). Things that must be considered in the eGFR examination are when collecting data in the form of gender, age, weight, and creatinine levels so that they are not confused with other respondents by giving sample codes. Another thing that must be considered is that the calculation must be careful and at least repeated twice. *estimated Glomerular Filtration Rate* (eGFR) is a good indicator to assess kidney function. *estimated Glomerular Filtration Rate* will measure how well the kidney's ability to filter waste from the blood. eFGR is measured based on creatinine levels, gender, body weight and age (William and Ludong, 2019). Glomerular filtration is a physiological process to create ultrafiltration of blood as it passes through the glomerular capillaries. Glomerular Filtration Rate is influenced by a variety of diverse pathologic and physiologic conditions. eGFR has been evaluated in large diverse populations and can be applied to general clinical use (Kaitang, Moeis and Wongkar, 2019).

Table 6. Distribution of potassium levels in respondents

Type of Inspection	Minimum Value	Maximum Value	Description	Total	Percentage
Potassium Content (mEq/L)	3,72	8,91	Normal	22	73,33%
			High	8	26,67%
			Total	30	100%

Description:
Normal potassium value = 3.5 - 5.3 mEq/L

Based on Table 6, the minimum value of serum potassium level is 3.72 mEq/L and the maximum value is 8.91 mEq/L. A total of 22 patients (73.33%) had serum potassium levels within normal limits, and 8 patients (26.67%) had high serum potassium levels or outside normal limits. Potassium levels < 3.5 mEq/L are said to be hypokalemia and potassium levels > 5.3 mEq/L are referred to as hyperkalemia. This potassium examination was carried out at Syarifah Ambami Rato Ebu Bangkalan Hospital, which is a type B hospital with accredited service quality A and uses Rapid Chem 744 electrolyte equipment that is routinely calibrated, and uses the ISE (*Ion Selective Electrode*) method, which calculates the number of ions of unknown value. The ion selective membrane in the device will react with the electrolyte in the sample. The membrane is an ion exchanger that reacts to changes in ion electricity resulting in changes in membrane potential. This method has good accuracy, the coefficient of variation is less than 1.5%, has a good quality assurance program, and the calibrator can be trusted (Lestari and Puji, 2018). Things that must be considered when checking potassium are making sure the sample is not hemolytic and icteric, and there are no bubbles because it can affect the test results.

One of the factors causing hyperkalemia is reduced potassium excretion in the kidneys that occurs in renal failure, hyperaldosteronism, cyclosporine use and in cases treated with angiotensin-converting enzyme inhibitors and potassium sparing diuretics. Healthy kidneys have a huge role in maintaining potassium homeostasis in the face of excessive potassium levels. The prevalence of hyperkalemia in patients with chronic kidney disease is estimated to be much higher at around 40-50% than the general population which is only 2-3%. Patients with diabetes and advanced chronic kidney disease are at higher risk. In some patients, potassium levels are still within normal limits, this can happen if the patient is on a low-potassium diet or adjusting their diet (Sandala, Mongan and Memah, 2016).

The results of the study were analyzed with the *Spearman* correlation test to determine whether or not there was a correlation between variables. This *Spearman* correlation test obtained a significance result of 0.208 which indicates that there is no correlation between eGFR and potassium levels in patients with diabetes mellitus who have complications of chronic renal failure. There is no correlation in this research data because more potassium levels in patients are still within normal limits even though the eGFR value is far below normal limits. This result is in line with the research of Thahir & Ukkas (2020) which states that patients with diabetes mellitus do not experience hypokalemia or hyperkalemia (Thahir and Ukkas, 2020). Amalia's research (2016) also stated that there was no significant correlation between the decline in LFG and potassium levels (Amalia, 2016). According to Prasetyorini's research (2018), decreased potassium levels in patients with chronic renal failure due to diarrhea and potassium diet (Prasetyorini, 2018).

There are several factors that can cause blood potassium levels to decrease, including diarrhea and the use of laxatives, the use of drugs, and an increase in the rate of potassium entering the cell (Kardalas *et al.*, 2018). Diarrhea can cause dehydration, renal insufficiency and electrolyte imbalance. Diarrhea and the use of laxatives can result in increased potassium excretion through the mechanism of potassium excretion from extracellular to feces. Potassium levels in the extracelles decrease, resulting in potassium excretion from the intracelles to the extracelles. Drugs such as beta 2 agonists, insulin and diuretics can reduce serum potassium levels. Beta 2 agonists can reduce potassium levels because they stimulate beta 2 adrenergic and trigger Na K^{++} -ATPase pump activity so that potassium will enter the intracell. Insulin can reduce potassium levels, because glucose enters the intracelles and is followed by potassium into the intracelles, so that serum potassium levels decrease (Syahrani, 2019). The use of diuretic drugs can reduce potassium levels according to the mechanism of each class of diuretics that work specifically. Diuretic drugs that are generally most often consumed are loop diuretics, such as furosemide. The mechanism of action of furosemide is by inhibiting the cotransport of Na K^{++} Cl^{-} . Sodium is actively transported out of the cell into the interstitium by a pump that depends on the Na K^{++} -ATPase enzyme in the basolateral membrane. As a result, potassium in the body escapes and causes serum potassium levels to decrease (Wulandari, Nurmainah and Robiyanto, 2015).

The results of this study are not in line with Ivana's research (2017), which states that there is an increase in potassium levels in patients with chronic renal failure. The increase in serum potassium levels in patients with chronic renal failure is due to nephron damage which results in potassium not being excreted by the kidneys, so potassium is carried by the bloodstream and causes hyperkalemia. An increase in potassium can also occur due to a decrease in the glomerular filtration rate (LFG) which can cause impaired potassium excretion and cause hyperkalemia, a decrease in the ability of the glomerular filtration rate (LFG) to transport potassium in the form of excretion into the distal tubules can trigger an increase in blood potassium levels or hyperkalemia and cause death due to potassium poisoning (Ivana, 2017). According to research by Loutradis (2015), chronic renal failure patients with diabetes mellitus have a 25% higher prevalence of hyperkalemia compared to chronic renal failure patients without diabetes mellitus (Loutradis *et al.*, 2015).

The limitation in this study is that the laboratory examination results used are not known whether the examination results are before or after receiving potassium therapy or taking drugs that can reduce potassium levels. Another limitation is that the researchers did not know whether the respondents received insulin therapy or not, did not know whether the respondents experienced diarrhea or not and did not know the potassium intake of each respondent.

CONCLUSION AND RECOMMENDATION

The conclusion of this study is that the eGFR value in patients with diabetes mellitus who experience complications of chronic renal failure has a minimum value of 3.90 mL/min/1.73 m^2 and a maximum value of 24.59 mL/min/1.73 m^2 , with 30 patients (100%) having low eGFR values. Potassium levels in patients with diabetes mellitus who experienced complications of chronic renal failure had a minimum value of 3.72 mEq/L and a maximum value of 8.91 mEq/L, with 22 patients (73.33%) of whom had serum potassium levels within normal limits, and 8 patients (26.67%) had high serum potassium levels or outside normal limits.

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