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Original Article

Electrolyte Dysregulation in Diabetic with Advanced Chronic Kidney Diseases (CKD): Comparative Analysis of CKD Stages 4 and 5

Asbar Tanjung, Riceina Javonda Lembagus Wirawan

Department of Medical Laboratory Technology, STIKes Prima Indonesia, Bekasi, Indonesia

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Correspondence:
Asbar Tanjung
Department of Medical Laboratory Technology, STIKes Prima Indonesia, Bekasi, Indonesia
Email: asbartanjung@gmail.com

Abstract

Background: Electrolyte imbalance is common in both diabetes mellitus (DM) and chronic kidney disease (CKD). While they may occur independently, their coexistence can exacerbate metabolic disturbances, thereby accelerating disease progression and impairing quality of life.

Objective: to investigates the differences in electrolyte profiles between patients with CKD stages 4 and 5 with DM.

Methods: A cross-sectional comparative design study was employed. A hundred participants (50 with CKD stage 4 and 50 with CKD stage 5 with DM) were recruited from a clinical laboratory during May to June 2024. Serum natrium, kalium, and chloride levels were measured alongside urea, creatinine, GFR, and glucose. The Mann-Whitney U test was applied to compare the electrolyte levels between these CKD stages.

Results: Of 100 participants, more men participating in this study (66% vs. 34%). Pre-elderly (45-59 y.o.) was the most predominant (61%), followed by elderly (>60 years, 20%), and adult (26-45 y.o., 19%). Both groups showed elevated urea, creatinine, and glucose levels with reduced GFR, confirming advanced CKD and DM. There was no significant difference in glucose level between stage 4 and stage 5. A significant difference (p=0.001) was observed in natrium levels, with stage 5 CKD patients exhibiting lower levels compared to those in stage 4. In contrast, kalium and chloride levels showed no significant difference (p=0.71 and p=0.81, respectively) in both groups.

Conclusion: This study highlights the specific vulnerability of natrium homeostasis in advanced CKD with diabetes. Natrium dysregulation observed in stage 5 CKD underscores the need for close monitoring and management of sodium levels in this population.

Keywords: Chronic kidney disease, diabetes mellitus, electrolytes, hypernatremia, renal function

Introduction

Chronic kidney disease (CKD) is a global health crisis affecting an estimated 10% of the world's population.[1] CKD progressive characterized by a gradual decline in kidney function leads to inability of the body to effectively regulate metabolism, fluid balance, and electrolytes.[2] CKD was associated with higher rates of mortality, illness, and disability, lower quality of life, and substantial economic costs for both patients and healthcare systems.[3-5]

CKD defined as decrease in kidney function characterized by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for three months or more.[6] Combination of age, hypertension, diabetes mellitus (DM), obesity, proteinuria, abnormal lipid profiles, and environmental factors, such as dietary sodium intake and pollution, were common risk factors can lead to CKD.[7,8] According to Webster *et al*. DM and hypertension constitute the predominant etiologies of CKD in most high-income, middle-income, and many low-income countries.[9] Furthermore, extensive research conducted by Tao P *et al*. revealed that DM and

CKD are multifaceted conditions arising from several factors, while the pathophysiology of both CKD and DM shows significant overlap. Moreover, DM may constitute an independent risk factor for the onset of CKD.[10]

The International Diabetes Federation (IDF) stated that CKD among people with DM is globally common, costly, and associated with high morbidity. It was projected that 784 million people will be living with DM by 2045, up from 537 million in 2021.[11] Individuals who have both DM and CKD face a significantly increased risk of developing kidney failure, cardiovascular problems related to atherosclerosis, heart failure, and dying prematurely.[11] Among people with DM-CKD often progresses without noticeable symptoms, making challenges for early detection and correlated to reduced quality of life, increased morbidity, and higher mortality rates.[12] The co-occurrence of DM and CKD presents a significant clinical challenge, frequently demanding complex therapeutic interventions.[13]

Electrolyte imbalance become a common in both DM and CKD independently. Among DM, hyperglycemia leads to a marked elevation in plasma osmolality, resulting in a dilutional decrease in serum sodium concentration and subsequent disruption of electrolyte balance.[14] Damaged kidneys in CKD can't properly balance electrolytes resulting hyponatremia, hyperkalemia, and hypochloremia.[15] Karinda *et al*. confirmed that common complications in non-dialysis advanced CKD include anemia, hypertension, dyslipidemia, hyperuricemia, and electrolyte imbalances. Specifically, differences in electrolyte imbalances between stage 5 and stage 4 were observed as follows: hyponatremia (66.67% vs. 64.28%), hypernatremia (31.25% vs. 0%), and hypokalemia (16.67% vs. 35.72%).[16] These disturbances are clinically significant because they can trigger life-threatening arrhythmias, neuromuscular dysfunction, fluid imbalance, and increased hospitalization and mortality. Accurate analysis of electrolyte status is therefore essential for optimizing patient management, guiding therapeutic decisions, and preventing complications in CKD-DM.[14,15]

Despite the high burden of CKD among patients with DM, limited studies have investigated electrolyte imbalances specifically in CKD stages 4 and 5 in this population, and more comprehensive data are needed. Therefore, this study aims to investigate differences in electrolyte levels between CKD stage 4 and CKD stage 5 patients with DM to better understand disease progression and identify potential therapeutic targets and interventions.

Methods

This study employed a cross-sectional comparative design to investigate differences in electrolyte levels between patients with stage 4 chronic kidney disease (CKD) and those with stage 5 CKD with diabetes mellitus (DM). The study involved 100 participants (half with CKD stage 4 and half with CKD stage 5 with DM). A total sampling approach was used, in which all eligible participants who routinely underwent medical laboratory checkups during May–June 2024 and met the inclusion criteria were included.

The inclusion criteria were participants diagnosed with CKD and diabetes mellitus (DM) at stage 4 or 5 who provided informed consent. The exclusion criteria were CKD patients with any of the following conditions: hypertension, congestive heart failure (CHF), liver disease, or significant trauma.

Data collected included demographic information, serum creatinine levels, glucose levels, and electrolyte levels (serum sodium, potassium, and chloride). CKD staging was determined based on estimated glomerular filtration rate (eGFR), calculated using the CKD-EPI equation; an eGFR of 15–29 mL/minute was classified as CKD stage 4, and an eGFR of <15 mL/minute was classified as CKD stage 5. Statistical analysis was performed using SPSS 25 (IBM). Descriptive statistics (mean and standard deviation) were used to summarize demographic and clinical characteristics while Mann-Whitney u test was used to compare mean glucose and electrolyte levels between CKD stages 4 and CKD stage 5. A p-value of <0.05 was considered statistically significant. All protocols applied in this research had been approved by *Komite Etik Kesehatan STIKes Prima* Indonesia (Number of ethical clearance: 342/EC/KEPK/STIKES-PI/V/2024). All participants provided written informed consent before participation.

Results

Data from 100 respondents with chronic kidney disease (CKD) were analyzed by frequency distribution according to gender and age category, as well as stage of CKD. These data are summarized in Table 1.

Among the 100 respondents, males constituted the majority (66%), while females

Table 1 Frequency Distribution of Patient Characteristics

Characteristics	n=100	%
Gender		
Male	66	66
Female	34	34
Age		
Adult (26 – 45 years)	19	19
Pre-elderly (45-59 years)	61	61
Elderly (>60 years)	20	20
Stage of CKD		
Stage 4 (GFR 15 – 29 mL/ minute)	50	50
Stage 5 (GFR <15 mL/minute)	50	50

Table 2 Descriptive Statistics of Urea, Creatinine & GFR

Variable	n	Mean ± SD
Serum Urea (mg/dL)	100	117 ± 29
Serum Creatinine (mg/dL)	100	5.34 ± 1.9
GFR (mL/min)	100	13.0 ± 5.4

accounted for 34%. The pre-elderly age group (45–59 years) represented the largest proportion (n=61), followed by the elderly group (>60 years) (n=20), and the adult group (26–45 years), which consisted of 19 respondents.

One hundred patients with CKD were then evaluated for serum urea, serum creatinine, and GFR. The mean values for these measurements were subsequently calculated and are presented in Table 2.

Table 2 show that patients diagnosed with CKD both stage 4 and stage 5 are exhibited elevated serum urea with 117 mg/dL in average (reference range; 10-50 mg/dL), creatinine concentration with 5.34 mg/dL in average (reference range: 0.6–1.3 mg/dL), and GFR with 13.0 mL/min in average (reference range: >60 mL/min).

Table 3 Glucose Level in CKD Grade 4 & 5 with DM

Grade of CKD	n	Median (IQR)	p-value
Grade 4	50	205 (185–232)	0.992
Grade 5	50	204 (180–228)	

**Mann Whitney u test*

One hundred patients with CKD were evaluated for glucose level. The mean values for CKD stage 4 with DM and for CKD stage 5 with DM were separately analyzed and presented in Table 3.

Table 3 show the mean value of glucose level in CKD stage 4 and stage 5 with Table 3 show the mean value of glucose level in CKD stage 4 and stage 5 with DM, in Grade 4 glucose level elevated to 213±32 mg/dL (reference:) while in stage 5 were elevated to 210±32 mg/dL (reference:). There is not significant difference in glucose level between CKD grade 4 and 5 with DM.

The categorized electrolyte imbalance according to electrolyte levels among CKD with DM plotted to CKD stage 4 with DM and CKD stage 5 with DM. Data presented in Table 4 can be seen as follows.

Electrolyte imbalances among patients with CKD stages 4 and 5 with DM were categorized based on serum electrolyte levels, and the distribution is presented in Table 4. Hyponatremia was more prevalent in CKD stage 5 (26 of 50 patients) compared to stage 4 (14 of 50 patients), demonstrating a trend toward increasing hyponatremia with CKD progression. Hyperkalemia was also more common in CKD stage 5 (17 of 50 patients) compared to stage 4 (10 of 50 patients). Hypochloremia was observed in 2 of 50 patients with CKD stage 5 and in 1 of 50 patients with CKD stage 4.

Mann-Whitney-U test demonstrates a highly significant difference in natrium levels

Table 4 Electrolyte Imbalance Distribution Among CKD Grade 4 and 5 with DM

Grade of CKD	Natrium		Kalium		Chloride	
	Hyponatremia	Normal	Normal	Hyperkalemia	Hypochlorite	Normal
Grade 4 (n=50)	14	36	40	10	1	49
Grade 5 (n=50)	26	24	33	17	2	48

Table 5 Mann-Whitney U Test of Mean Electrolyte Levels in CKD Grade 4 and 5 with DM

Electrolyte	Grade CKD	n	Median (IQR)	*p-value
Natrium	CKD Grade 4	50	138.00 (135.00–140.00)	0.001
	CKD Grade 5	50	134.00 (130.00–137.00)	
Kalium	CKD Grade 4	50	4.50 (3.90–5.00)	0.71
	CKD Grade 5	50	4.50 (3.70–5.80)	
Chloride	CKD Grade 4	50	100.50 (99.00–103.00)	0.81
	CKD Grade 5	50	101.00 (99.00–103.00)	

*Mann-Whitney U test

between patients with CKD stage 4 and stage 5 with DM (p=0.001). This strong statistical significance indicates a clear distinction in sodium levels between these two CKD stages in diabetic patients. In contrast, no significant differences were observed in potassium (p = 0.71) or chloride (p = 0.81) levels between the same groups (Table 5).

Discussion

This study conducted among CKD patients specifically CKD stages 4 and 5 with DM. One hundred patients have been recruited to participate to this study, including 50 patients suffer CKD stage 4 with DM and 50 patients suffer CKD stage 5 with DM. Among the 100 respondents, the majority of CKD patients with diabetes were male and belonged to the pre-elderly age group (45–59 years). This study revealed a consistency with study conducted by Behera BP *et al*,. reported that among 244 CKD patients, the largest proportion (42.2%) were aged 46–60 years, followed by 28.7% aged 61–75 years, while younger patients (<30 years) constituted only a small minority (3.3%).[17] According to Lee HJ & Son YJ, older age, female, and having diabetes made end-stage renal disease patients on hemodialysis more likely to become frail.[18]

The observed elevations in serum urea and creatinine, coupled with the significantly reduced GFR (Table 2), strongly confirm the presence of impaired renal function in the study population, consistent with the diagnosis of CKD stages 4 and 5. The mean serum urea level of 117 ± 29 mg/dL, well above the reference range of 10-50 mg/dL, and the mean serum creatinine of 5.34 ± 1.9 mg/dL (reference range: 0.6–1.3 mg/dL) are expected findings in advanced CKD. These markers reflect the reduced capacity of the kidneys to filter waste products from the blood.[5] The corresponding mean GFR of 13.0 ± 5.4 mL/min (reference range: >60 mL/min) further substantiates this impairment, placing the study participants firmly within the CKD stage 4 and 5 categories. The observed mean glucose level of 211 ± 31 mg/dL (reference: <200 mg/dL) across both CKD stages confirms the presence of concomitant diabetes mellitus in the study population. This finding highlights the interplay between these two conditions, which can worsen kidney damage. According to Kumar *et al*. the correlation between diabetes and kidney disease is strong and well-established. Diabetes significantly increases the risk of developing CKD, with diabetic nephropathy being a major cause of end-stage renal disease. Effective diabetes management to control blood sugar is crucial for preventing kidney damage. Conversely, kidney disease itself can also contribute to the development of diabetes.[13]

Electrolytes, crucial in physiological processes, are charged particles that help regulate the body's acid-base equilibrium, blood coagulation, fluid levels, and muscle activity.[19] In this study, of 50 CKD grade 4 and 50 CKD grade 5 patients with diabetes mellitus show the most frequent electrolyte disturbances were hyperkaliemia, hyponatremia, and hypochloremia illustrated a trend of worsening electrolyte imbalance with CKD progression Table 4 Moreover, Electrolyte imbalance was more pronounced in CKD grade 5 than in CKD grade 4. This study in line with study conducted by Dhondup T & Qian Q in 2017 stated that electrolyte imbalances are frequently observed in CKD, with hyponatremia and hyperkalemia being particularly prevalent.[15] Furthermore, a study conducted by Khan RN reported highly significant hyponatremia and hypochloremia among DM patients.[20] According to Renato Watanabe 2020, hyperkaliemia in CKD progression with DM developed as a result of impaired renal excretion along with the

decrease of renal function, metabolic acidosis which promotes potassium movement from the intracellular to the extracellular space, and the use of use of RAAS inhibitors medications to reduce the progression of CKD or to control associated diseases such as diabetes mellitus and heart failure which reduce aldosterone activity and limit potassium elimination. These mechanism at the same time associate with hyperkaliemia in CKD with DM.[21,22] Furthermore, according to Soraya Arzhan *et al*. Hyponatremia in CKD-DM patients associated as a results of impaired renal water handling due to nephron damage and reduced vasopressin responsiveness and compounded by hyperglycemia-induced osmotic water shifts.[23]

CKD is defined as kidney damage infected to low kidney function characterized by GFR below 60 mL/min/1.73 m^2 for at least three months. CKD stage 4 involved a severely reduced GFR of 15-29 mL/min/1.73 m^2 and CKD stage 5 indicated kidney failure with a GFR below 15 mL/min/1.73 m^2.[24,25] In a context of kidney electrolyte regulator, this study examined electrolyte levels in CKD stages 4 and 5 CKD with DM using the Mann-Whitney U test, a highly significant difference in natrium levels was found between the two groups (p=0.001), indicating a clear distinction in natrium regulation as CKD progresses from stage 4 to 5 in this population. However, no significant differences were observed in kalium (p=0.71) or chloride (p=0.81) levels between these same groups (Table 5). The observed difference in natrium levels between CKD stages 4 and 5 suggests that patients in stage 5 require closer monitoring and potentially more aggressive interventions to manage their sodium levels and prevent life-threatening complications, such as hyponatremia or hypernatremia.[19] Furthermore, this study suggests that while natrium imbalances may become more pronounced in later stages of the disease, kalium and chloride levels might be less sensitive to the severity of CKD in these patients, potentially due to compensatory mechanisms that help regulate these electrolytes even in the face of kidney dysfunction.[26]

This study has several limitations. First, it focused exclusively on CKD stages 4 and 5, which restricts the ability to observe electrolyte alterations across the full continuum of CKD progression. The relatively small sample size may further limit the generalizability of the findings. Additionally, the study lacked longitudinal follow-up data on the progression of CKD and DM, preventing the establishment of causal relationships between disease progression and electrolyte disturbances.

In conclusion, this study found a significant difference in sodium levels between CKD stage 4 and stage 5 patients with DM (p=0.001), indicating worsening sodium regulation with advancing disease. While there was a trend toward increased hyponatremia in stage 5, potassium and chloride levels did not differ significantly between the two stages (p=0.71 and p=0.81, respectively). These findings suggest that sodium homeostasis is particularly vulnerable in advanced diabetic CKD.

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