

Impact of Abnormal Serum Electrolyte Levels and Acid-Base Disorders on Clinical Outcomes among Maintenance Hemodialysis Patients

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Abstract

There has been a notable rise in the number of patients diagnosed with chronic kidney disease (CKD) over the years across the world, with most cases subsequently leading to end-stage renal failure. Hemodialysis (HD) remains one of the main treatments for end-stage renal disease (ESRD) worldwide. Despite improvements in dialysis care, the mortality of patients with ESRD on maintenance hemodialysis is persistently high. Abnormal levels of serum electrolytes, pre- and post-dialysis, and acid-base disorders have a crucial influence on clinical outcomes in HD patients. In this review, we aim to discuss the different effects that serum electrolyte levels have on the prognosis of patients on maintenance hemodialysis, particularly sodium, potassium, magnesium, phosphorus and bicarbonate.

Subject Areas

Internal Medicine, Nephrology

Keywords

Chronic Kidney Disease, End-Stage Renal Disease, Hemodialysis, Electrolyte, Acid-Base Disorder

1. Introduction

The number of patients diagnosed with chronic kidney disease (CKD) has increased to a great extent over the years worldwide, with most cases subsequently leading to end-stage renal failure [1]. End-stage renal disease (ESRD) is the irre-

versible deterioration of renal function to an extent that survival is greatly shortened without renal replacement therapy (RRT), either by dialysis or transplantation. The 2016 US Renal Data System (USRDS) Annual Data Report showed the estimated CKD (stages 1 - 5) prevalence in the United States was 14.8% in 2014 and 120,688 new patients with ESRD [2] while another study demonstrated the prevalence of CKD among middle aged and elderly patients in China to be 11.5% [3]. Hemodialysis (HD) remains one of the main treatments for ESRD across the world. The goal of HD is to replace the kidney's excretory function, especially preventing or improving fluid and electrolyte disorders such as fluid overload, hypo-/hypernatremia, hypo-/hyperkalemia, hypo-/hypercalcemia, hypo-/hyperphosphatemia, metabolic acidosis and alkalosis.

2. Prevalence of Serum Electrolytes Abnormalities

A few studies have shown the prevalence of hyponatremia to be higher than that of hypernatremia among maintenance hemodialysis (MHD) patients [4] [5]. In a study of 1549 MHD patients, Waikar *et al.* found the prevalence of hyponatremia to be 29.3% while that of hypernatremia was 18.9% [5]. However, in another study of 11,500 patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS), Hecking *et al.* found the prevalence of mean pre-dialysis serum sodium level lower than 137 mmol/L to be 27% and that of mean pre-dialysis serum sodium level higher than or equals to 140 mmol/L to be 31% [6]. Hyponatremia is a frequently seen electrolyte disorder while hypermagnesemia is also highly prevalent in MHD patients and it tends to be in a higher percentage than hypomagnesemia [7] [8] [9] [10]. In a cohort study of 27,544 MHD patients in the United States, 4729 patients (17.2%) had hypomagnesemia and 6133 patients (22.3%) had hypermagnesemia [10].

Hyperphosphatemia is another commonly encountered electrolyte abnormality in MHD patients. In DOPPS I and DOPPS II, the prevalence of hypophosphatemia among hemodialysis patients was 7.6% and 9.0% respectively and that of hyperphosphatemia was 51.6% and 46.7% respectively [11]. Hypercalcemia also tended to be more prevalent than hypocalcemia in MHD patients as shown in some studies conducted in Japan and the US [12] [13] [14] (**Table 1**). A higher number of HD patients tended to have metabolic acidosis than metabolic alkalosis. In a study by Bommer *et al.* using data from DOPPS, there were 53.0% patients who had metabolic acidosis while only 19.7% had metabolic alkalosis [15]. The prevalence of electrolyte imbalances and acid-base disorders in American and Japanese MHD patients are summarized in **Table 1**.

3. Sodium Disorders

Preserving sodium balance (extracellular fluid volume) is an important task of RRT. While HD is intermittent and salt and fluid intake is a continued process during interdialytic period, maintaining this balance is a difficult task [19]. Hyponatremia (serum sodium concentration <135 mmol/L) [5] is a common electrolyte disorder in patients with ESRD and an increasing number of studies

References	Year (Country)	Type of Study	Number of Subjects	Electrolyte disorder	
				Hyponatremia (<135 mmol/L)	Hypernatremia (>145 mmol/L)
C.M Rhee <i>et al.</i> [4]	2015 (USA)	Observational study	27,180	1939 (7.1%)	549 (2.0%)
				Hypokalemia (<3.5 mmol/L)	Hyperkalemia (>5.5 mmol/L)
Kovesdy <i>et al.</i> [16]	2007 (USA)	Observational study	74,219	6617 (8.9%)	9062 (12.2%)
				Hypomagnesemia (<0.74 mmol/L)	Hypermagnesemia (≥1.15 mmol/L)
Y. Sakaguchi et al. [17]	2013 (Japan)	Observational cohort Study	142,555	28,764 (20.1%)	46,249 (32.4%)
				Hypophosphatemia (<0.9 mmol/L)	Hyperphosphatemia (>1.34 mmol/L)
Nakai <i>et al.</i> [12]	2008 (Japan)	Cross-sectional study	27,404	787 (2.9%)	23,855 (87.0%)
				Hypocalcemia (<2.15 mmol/L)	Hypercalcemia (>2.55 mmol/L)
Rivara <i>et al.</i> [14]	2015 (USA)	Observational cohort study	118,955	5985 (5.03%)	12,844 (10.7%)
				Low serum bicarbonate (<23 mmol/L)	High serum bicarbonate (≥27 mmol/L)
Wu <i>et al.</i> [18]	2005 (USA)	Observational Cohort Study	56,386	35,970 (63.8%)	2207 (3.9%)

Table 1. Prevalence of electrolyte imbalances and acid-base disorders in American and Japanese MHD patients.

showed that low serum sodium is an independent predictor of mortality and has negative health consequences (Table 2).

In their studies, Waikar *et al.* showed that among MHD patients without residual renal function, lower serum sodium concentration was associated with a higher mortality, even after adjustment for demographic, clinical, laboratory, and dialysis-specific covariates [5]. Mandai *et al.*, in an observational cohort study including 332 MHD patients, showed that those with lower serum sodium had an increased risk for infection-related hospitalization [20].

It is important for physicians to prescribe the dialysate sodium concentration according to patients' pre-dialysis serum sodium levels. In a cohort study of 2272 patients on thrice-weekly HD treatment, when using low sodium dialysate (<140 mmol/L), patients with higher pre-dialysis sodium concentration showed better survival than those with lower pre-dialysis sodium concentration [21] while

Authors	Year	Type of study	Number of subjects	Outcomes	HR	95% CI
Waikar [5]	2011	Randomized controlled trial	1549	Risk of death	0.81	0.72 - 0.91
Mandai [20]	2013	Observational study	332	Infection-related hospitalization	2.36	1.10 - 5.04
C. M. Rhee [4]	2015	Observational study	27,180	Mortality	1.45	1.26 - 1.67

 Table 2. Low serum sodium concentration indicates negative outcomes in MHD patients in US and Japan.

Abbreviations: HR: Hazard risk; CI: Confidence interval.

C. M. Rhee *et al.*, in time-varying analyses, found a U-shaped association between pre-dialysis serum sodium levels and all-cause mortality [4].

Low serum sodium level is not only associated with higher mortality but has also been found to be related to other electrolyte disorders, such as hypercalcemia. In a large prospective cohort of incident HD patients, Nigwekar *et al.* showed that hyponatremia is also associated with bone abnormalities. At the time of initiation to dialysis therapy, patients with hyponatremia were noted to have higher prevalences of hypercalcemia (2.2% vs. 1.2%; P = 0.02), elevated alkaline phosphatase levels (20.3% vs. 15.7%; P = 0.002), and hypoparathyroidism (27.5% vs. 20.9%; P < 0.001) compared with patients with normal serum sodium levels [22].

The above studies showed that monitoring pre-dialysis serum sodium level is important so as to provide appropriate sodium dialysate prescription for HD patients and also encourage a proper dietary sodium intake, hence improving HD patients' prognosis [23] [24].

4. Potassium Disorders

Another complication commonly seen in ESRD patients being given HD treatment is hyperkalemia. MHD patients regularly accumulate potassium during the interdialytic period, therefore removal of potassium (K) is one of the most important functions of chronic HD.

Pre-dialysis hyper- and hypokalemia have been found to be associated with a higher risk of electrocardiogram abnormalities and cardiac death [25] [26] [27] [28]. In a large cohort of MHD patients, Kovesdy *et al.* found the association of pre-dialysis hyperkalemia with all-cause and cardiovascular mortality after detailed adjustments for potential confounding variables [16]. In a historical cohort of chronic HD patients, Genovesi *et al.* showed pre-dialysis hyperkalemia to be associated with a 2.7 (CI 95% 1.3 - 5.8)-fold increase in the risk of sudden death [29]. Also, an increasing risk of sudden cardiac arrest among patients with pre-dialysis serum potassium levels above 5.0 mmol/L was observed but no advantage of using low potassium dialysate (<2 mmol/L) was found at any level of serum potassium in a study by Pun *et al.* [27]. However, hypokalemia is also

linked to a high mortality rate. According to Hwang *et al.*, HD patients with lower pre-dialysis levels of both serum potassium and serum sodium were associated with an elevated long-term mortality risk [30]. Patients with lower serum potassium and lower serum sodium levels were characterized by hypoalbuminemia and lower normalized protein catabolic rate (nPCR) level. They were also associated with higher high sensitivity C-reactive protein (hs-CRP) level, and more comorbidity. Their study showed that lower levels of both electrolytes were able to predict the worst long-term prognoses, independent of risk factors like diabetes mellitus, age, gender and HD vintage.

Moreover, significant sudden shifts in electrolytes, particularly potassium, and fluid volume that surround a dialysis session act as triggers and can initiate life-threatening arrhythmias in MHD patients, which is closely linked to sudden cardiac death [31] [32] [33]. Electrocardiogram (ECG) measures related to ventricular repolarization such as QT interval dispersion and QT interval prolongation worsen over the course of a dialysis treatment. In a study by Morris *et al.*, these ECG changes have been shown to be influenced by exposure to potassium during HD, and have been independently associated with cardiovascular mortality in dialysis patients [34] [35]. Also, Jadoul *et al.* found that dialysate with potassium level <3 mEq/L was associated with higher sudden death risk, which was most obvious amongst patients with low pre-dialysis serum potassium levels (<5 mEq/L) [26].

Although appropriately prescribed dialysis therapies still are the main way to control hyperkalemia, dietary strategies should also be used to avoid large fluctuations in serum potassium concentration while ensuring adequate nutrition. The potential beneficial impact of alternative dialysis strategies that would ensure better control of potassium imbalance and prevent marked fluctuations in serum potassium concentration should also be considered.

5. Magnesium Disorders

Magnesium (Mg) is mainly excreted through the renal system and HD patients may have a normal, increased or decreased level of serum magnesium [36]. Higher level of serum magnesium is mostly associated with better prognoses in MHD patients (**Table 3**) and it was found to be associated with lower mortality risk in this group of patients in several studies [10] [37]. In Sakaguchi *et al*'s cohort study, it was shown that the mortality risk of HD patients with hyperphosphatemia was greatly reduced with increasing serum magnesium [17]. A study in Portugal showed an association between lower magnesium levels and increased cardiovascular risk markers and higher mortality in HD patients [38]. Another study found a strong and inverse association between serum magnesium and all-cause mortality, cardiovascular mortality and sudden death in European HD patients [39]. In a prospective study of Japanese HD patients who had secondary hyperparathyroidism (SHPT) by Kurita *et al.* demonstrated that relatively low serum magnesium levels were associated with all-cause death (adjusted HR 1.737, 95 CI 1.200 - 2.512 for lowest quintiles of serum magnesium

Authors	Year Published	Type of study	Number of subjects	Outcomes	HR/OR	95% CI
Sakaguchi [17]	2014	Prospective cohort study	142,069	Increased mortality	OR 0.74	0.56 - 0.97
Ishimura [37]	2007	Observational study	553	All-cause and non-CV mortality	*HR 0.485 [#] HR 0.388	0.241 - 0.975 0.132 - 0.769
Lacson [10]	2015	Observational cohort study	27,544	Low survival	HR 1.6	1.21 - 1.45
João Matias [38]	2015	Prospective study	206	Increased CV and all-cause mortality	°HR 0.82 *HR 0.87	0.72 - 0.95 0.88 - 0.99
de Roij van Zuijdewijn [39]	2015	Randomized controlled trial	365	All-cause and CV mortality.	*HR 0.85 °HR 0.73	0.77 - 0.94 0.62 - 0.85
Kurita [40]	2015	Prospective study	2185	All-cause death CVD, ↓Alb, ↑CRP.	*HR 1.74	1.20 - 2.51

 Table 3. Low serum magnesium levels indicating negative clinical outcomes in HD patients.

Abbreviations: CV: cardiovascular; CVD: cerebrovascular disease; Alb: serum albumin; CRP: C-reactive protein; OR: Odds ratio; HR: hazard risk; \uparrow : Increased; \downarrow : Decreased; *: hazard ratio related to all-cause mortality; #: hazard ratio related to non-CV mortality; C: hazard ratio related to CV mortality.

and HR 1.675, 95% CI 1.254 - 2.238 for second lowest quintiles). They also showed the positive association between serum magnesium levels and serum potassium levels (for Mg \leq 2.3 mg/dl and K \leq 3.5 mEq/L, adjusted odds ratio (AOR) 2.070, 95% CI 1.349 - 3.175, P = 0.001; for Mg > 3.0 mg/dl and K > 6.0 mEq/L, AOR 2.526, 95% CI 1.907 - 3.347, P < 0.001) among HD patients. Moreover, they noted that relatively low serum magnesium levels and the presence of atrial fibrillation (AOR 1.711, 95% CI 1.209 - 2.421, P = 0.002) and cerebrovascular disease (AOR = 1.336, 95% CI 1.035 - 1.725, P = 0.026) are correlated [40].

Recent results have indicated that low intradialytic serum magnesium level was associated with hypotensive episodes during HD [36] [41] [42]. Also, ESRD patients with low serum magnesium level were observed to have a higher and faster rate of vascular calcification [43] [44] [45]. Moreover, lower serum magnesium was associated with higher pulse pressure, left ventricular mass index and the presence of more vascular calcifications [38].

Serum magnesium also has an important influence on other metabolic processes in MHD patients. Several studies have found significant positive association of serum magnesium levels with dyslipidemia in HD patients [46] [47] [48]. However, in another study of 103 HD patients, no relation was found between serum magnesium level and atherogenic lipids [49]. In a prospective study of 206 patients in Portugal, a negative correlation was found between magnesium levels and the presence of diabetes. They also found patients with reduced serum magnesium had a significantly greater age and reduced albumin, unlike

those with increased serum magnesium. In a cross-sectional study of 58 HD patients, a significant negative association was observed between magnesium levels and CRP [50]. Similar findings were illustrated in another study suggesting that low serum magnesium can be a marker for malnutrition [40].

Hence close monitoring of serum magnesium levels, before HD and even during dialysis, is important to avoid negative outcomes.

6. Phosphorus and Calcium Disorders

ESRD is accompanied by profound changes in mineral metabolism. Abnormal mineral metabolism leads to metabolic bone disease [51] and contributes to other clinical problems. Several articles associate hyperphosphatemia, abnormalities in calcium and parathyroid hormone (PTH) levels with increased blood pressure, cardiovascular disease and mortality [11] [52]-[57].

Cardiovascular diseases are one of the most seen causes of death in the HD population and a high level of phosphorus is closely linked to this risk. Hyperphosphatemia causes vascular calcification, coronary atherosclerosis, hyperparathyroidism and smooth muscle proliferation [58]. Lertdumrongluk et al. suggested the link between hyperphosphatemia and increased all-cause and cardiovascular mortality is similar across all age groups, whereas hypophosphatemia is associated with increased mortality only in the elderly HD population [59]. Hence the treatment protocol for phosphorus imbalance should be carefully considered in elderly HD patients other than those belonging to a younger age group. Another study of 12,509 HD patients from the US Renal Data System database by Rubel and Milford showed that serum phosphate greater than 1.62 mmol/L was associated with higher risk for a valvular procedure compared with a phosphate level less than 1.62 mmol (HR 1.47; P = 0.033) [60]. Moreover, Marchais et al. showed that hyperphosphatemia was associated with increased blood pressure, hyperkinetic circulation, increased cardiac work and high arterial tensile stress in a study of MHD patients under 60 years, thus contributing to high cardiovascular morbidity and mortality [52]. A prospective cohort study by X Huang *et al.* of HD patients also showed that serum phosphorus is strongly and independently associated with systolic blood pressure and pulse pressure in the early months of dialysis therapy and up to 2 years later [56].

7. Acid-Base Disorders

Restoring of the alkali consumed in neutralizing the endogenous acids is one of the aims of HD [61]. Optimal pre-dialysis bicarbonate levels by different entities are summarized in Table 4.

Metabolic acidosis plays an important role in the clinical outcome of MHD patients. Several studies showed that very low levels of serum bicarbonate (\leq 17 mmol/L) as well as very high ones (>27 mmol/L) contribute to elevated mortality rates in HD patients [15] [18] [66].

In a large cohort study of more than 56,000 patients, in fully adjusted model, Wu *et al.* associated acidotic patients with serum bicarbonate less than 22 mmol/L

Guidelines	Predialysis bicarbonate level (mmol/L)
2000, 2003 National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NFK-KDOQI) [62] [63]	≥22
Dialysis Outcomes and Practice Patterns Study (DOPPS) [15]	19 - 22
2007 European Best Practice Guidelines (EBPG) [64]	20 - 22
2007 Caring for Australasians With Renal Impairment (CARI) [65]	≥22

Table 4. Optimal pre-dialysis bicarbonate levels by different entities.

with higher death risk [18]. Lowrie *et al.* found death rates to be higher in patients with serum bicarbonate less than 17.5 or greater than 25 mmol/L [66]. Also, Bommer *et al.* associated mid-week predialysis serum bicarbonate \leq 17 mmol/L or >27 mmol/L with elevated mortality, and the lowest mortality was found to be in the range of 20.1 - 21.0 mmol/L [15]. However, another study by Yamamoto *et al* found no relation between pre- and post-dialysis serum bicarbonate levels and all-cause and cardiovascular mortality [67].

Therefore, it is strongly recommended to continuously evaluate patients' preand post-dialysis serum bicarbonate levels, malnutrition, and inflammation and to adjust bicarbonate dialysate concentration accordingly.

8. Conclusion

Electrolytes imbalances and acid-base disorders are frequently encountered complications amongst MHD patients and various factors are important for maintaining their balances. Low levels of sodium, magnesium and high level of phosphate were closely related to poor outcome, while potassium, calcium and bicarbonate showed a U curve with mortality and are preferred to be controlled in an appropriate range.

There is also an inter-relationship between different serum electrolyte levels. Hyponatremia is associated with hypercalcemia and bone abnormalities. Serum magnesium level is positively related with serum potassium level among HD patients. Phosphate abnormalities are commonly combined with calcium abnormalities. Interaction effects on multiple electrolytes should be considered when targeting on a single one.

Management of electrolytes and fluid balance requires a complex mixture of dialysis therapy, medications, dietary intervention, patient and provider education, communication, and patient adherence. Serum electrolyte levels play a crucial role in the prognosis of MHD patients and further research on their effects and management should be encouraged to ensure that this group of patients is given the best and appropriate care.

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Abbreviations

AOR	Adjusted odds ratio
CARI	Caring for Australasians With Renal Impairment
CI	Confidence interval
CKD	Chronic kidney disease
DOPPS	Dialysis Outcomes and Practice Patterns Study
EBPG	European Best Practice Guidelines
ECG	Electrocardiogram
ESRD	End-stage renal disease
HD	Hemodialysis
HR	Hazard risk
hs-CRP	High sensitivity C-reactive protein
K	Potassium
Mg	Magnesium
MHD	Maintenance hemodialysis
NFK-KDOQI	National Kidney Foundation-Kidney Disease Outcomes Quality
Initiative	
nPCR	Normalized protein catabolic rate
PTH	Parathyroid hormone
RRT	Renal replacement therapy
SHPT	Secondary hyperparathyroidism
USRDS	US Renal Data System

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