

The Effect of Acidosis on Albumin Level in Patients Treated With Regular Hemodialysis (Single Center Study)

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Received: August 1, 2018 Accepted: September 24, 2018 Online Published: October 13, 2018

doi:10.5539/gjhs.v10n11p57

URL: <https://doi.org/10.5539/gjhs.v10n11p57>

Abstract

Background: Hypoalbuminemia is the most powerful predictor of mortality in end-stage renal disease on hemodialysis. Metabolic acidosis induces net negative nitrogen and total body protein balance. Some patients undergoing maintenance dialysis have low plasma bicarbonate levels due to inadequate dialysis. We aimed to evaluate the role of metabolic acidosis on serum albumin concentration in patients with end stage renal disease on hemodialysis, and to determine differences of serum bicarbonate level before and after hemodialysis in actual situation.

Methods: This cross sectional comparative study was conducted in the Iraqi Center for Hemodialysis/ Baghdad Teaching Hospital from June to December 2015. It included 100 subjects with end stage renal disease on hemodialysis. They were divided equally into cases with low albumin and comparison group with normal albumin level. Serum bicarbonate and the Kt/V were measured for all subjects before, after, and before next hemodialysis session to show the adequacy of dialysis.

Results: There was a significant association between low bicarbonate and low albumin level in hemodialysis patient and between numbers and duration of dialysis session with albumin. Low Kt/V was significantly associated with hypoalbuminemia. There was no statistically significant association between age and gender with hypoalbuminemia.

Conclusion: This study shows that patients with metabolic acidosis had a lower serum albumin concentration and there was a significant correlation between numbers, duration and adequacy of hemodialysis sessions and albumin level. We recommend to increase the numbers of dialysis centers in Iraq and adjust the bicarbonate doses in dialysate according to patient's bicarbonate levels.

Keywords: acidosis, serum albumin, hemodialysis

1. Introduction

Malnutrition affects 1/3 of hemodialysis (HD) patients and associates with a higher risk of morbidity and mortality. Serum albumin (S. Alb) is a marker of nutrition and inflammation, and hypoalbuminemia is the most powerful predictor of death in patients with ESRD (Yashpal & Kher, 2012).

One of the most powerful regulators of albumin synthesis is availability of dietary protein. Protein calorie malnutrition is clearly a potential cause of reduced albumin synthesis, decreased plasma albumin levels and increased morbidity and mortality in the chronically ill population (Gama-Axelsson et al., 2012). Malnutrition is not the only cause of hypoalbuminemia in this population; otherwise nutritional supplementation should effectively restore albumin pools as it does in patients with hypoalbuminemia caused by protein malnutrition (National Kidney Foundation [NKF-DOQI], 2002).

In addition to being nutritionally modulated, albumin is also a negative acute-phase reactive protein (The Royal College of Pathologists of Australasia [RCPA] Manual, Jun 3, 2015). It is possible that some albumin might be lost across the dialysis membrane in patients on HD, contributing to hypoalbuminemia in them (Kapl, Halley, Lance, &

Graeber, 1995). Metabolic acidosis (MA) is commonly associated with chronic kidney disease (CKD) (Căpușă et al., 2017). With worsening renal function, progressive MA and acidemia can develop (Pourafshar, Pourafshar, & Soleimani, 2018). The prevalence of a serum bicarbonate (S. HCO₃) concentration of <22 meq/L, for example, is <5 percent in CKD stages 1 and 2 and increases to approximately 25 percent in patients with CKD stage 5 (Kovesdy, 2012).

It is believed that the adequacy of dialysis can reduce mortality, increase longevity, and improve the quality-of-life in patients undergoing hemodialysis (Kalender & Tosun, 2014). Effectiveness and adequacy of dialysis depend on many factors including type of filter, dialysis pump rate, dialysis time and speed, the application of high-flux dialyzer, blood flow rate, patient education, diet, and underlying diseases (Saeedi, Zareie, & Javaheri, 2015).

There are five potential mechanisms by which MA contributes to nutritional abnormalities of patients with chronic renal failure (CRF):

- Acidosis is associated with proteolysis, and correction of this acidosis leads to a decrease in protein breakdown in both healthy humans and individuals with CRF. MA may also engender negative nitrogen balance (Carrero et al., 2013).

- Catabolic effects of MA that is mediated by two key mechanisms: First is increased activity of branched-chain ketoacid dehydrogenase (BCKAD) (Pickering et al., 2002) and second is increased activity of the ATP-dependent ubiquitin-proteasome pathway. In a recent study, (Zha & Qian, 2017) demonstrated that an increase in serum total CO₂ was associated with a significant reduction in the muscle content of ubiquitin mRNA as compared to healthy control patients.

- Increases in the pH of the medium even above normal physiologic pH, were associated with progressively higher rates of protein synthesis (Rezende, Brandão de Souza, Modesto Pereira, & Lugon, 2017).

- Insulin resistance is a known complication of CRF. Evidence suggests that this may in part be secondary to MA. Indeed, correction of MA in non-dialyzed patients with CRF enhances insulin-stimulated glucose uptake. Incubation of peritoneal macrophages in an acidic cell culture medium results in an increased production of tumor necrosis factor suggesting a possible link between MA and the inflammatory cascade (Lecker, Goldberg, & Mitch, 2006).

One of the goals of dialysis therapy is to correct the MA. Dialysis therapies, as practiced today, are unable to completely correct MA in a substantial proportion of patients undergoing maintenance hemodialysis (MHD). Moreover, the serum bicarbonate levels in patients undergoing MHD follow a “saw-tooth pattern,” with the lowest bicarbonate levels in the immediate pre-dialysis period (Kalntar-Zadeh, 2016).

Due to the importance of adequacy of dialysis in patients undergoing hemodialysis, evaluating the effectiveness and adequacy of dialysis help policymakers and healthcare professionals to revise their current practice toward more effective dialysis.

The relationship between correction of MA and serum albumin level, as well as the optimal dosage of oral bicarbonate required to maintain S. HCO₃ level within the physiological range has not been studied in the CKD population who are on MHD who are registered in the Iraqi Center for Hemodialysis.

In this present study; we aimed to evaluate the role of MA on S. Alb concentration in patients with ESRD on HD, and to determine differences of S. HCO₃ level before and after HD in actual situation.

2. Patients and Methods

2.1 Study Design & Subjects

This is a hospital-based cross-sectional study conducted at Dialysis Center of Baghdad Teaching Hospital in Medical City/Iraq from June 2015 to December 2015; to measure the risk of low S. HCO₃ and low KT/V on S. albumin level.

We divided the study sample into two groups according to serum albumin level: Cases with S. albumin concentrations at time of study below 3.5 g/dl and comparison cases with S. albumin between 3.5-5.5 g/dl. (Both groups are patients with ESRD and on regular HD)

(KT/V is a number used to quantify HD treatment adequacy, K - dialyzer clearance of urea, t - dialysis time, V - volume of distribution of urea, approximately equal to patient's total body water) (NKF-DOQI, 2015)

A total of 100 ESRD patients on regular HD were included; 50 patients as cases and 50 patients as comparison group (duration of HD ranges between 3months to 4 years).

2.2 Data Collection

After taking consents from all participants, demographic data were taken regarding name, age, gender, underlying disease for CKD, numbers of sessions of HD, duration of each session, and duration of dialysis. S. Alb concentration was monthly measured in all patients (N = 100).

Kt/V was directly measured from the HD machine at the end of the session. Venous blood gas analysis for each participant was done before and after the HD session and before next session of HD.

The dialysis prescription was similar for all participants in this study, which was as follow:

Intermittent conventional HD by B- Braun Dialysis machine 2-3 times/week, 3-4 hours/ session. Low-flux polysulfone hollow fiber dialyzers. Temperature 36.5 °C. HCO₃ level was 31.6 mmol/l. Na⁺ was 145 mmol/l with normal profile. K⁺ = 2 mmol/l, Ca⁺⁺ = 1.5 mmol/l.

Ultrafiltration was according to patient's need. Blood flow according to patient's need and types of vascular access. Dialysate flow was 500 ml/min.

2.3 Inclusion Criteria

All patients with ESRD who undergo regular HD 2-3 sessions/ week; 3-4 hours for each session; at Dialysis Center in Baghdad Teaching Hospital.

2.4 Exclusion Criteria

The exclusion criteria were all patients with suspected hypoalbuminemia due to underlying pathology:

- 1). Chronic liver disease or liver cirrhosis.
- 2). Nephrotic syndrome with active disease.
- 3). Protein losing enteropathy like inflammatory bowel disease.
- 4). Neoplasia, severe systemic illness and diabetes mellitus.

2.5 Measurements

Serum HCO₃ was measured by taking a venous blood sample from central vein to a syringe contained heparin and put it in ice bucket and send them within about 25 minutes to the respiratory care center in Baghdad Teaching Hospital where the blood gas analysis done by special device (ABL800FLEX). A venous HCO₃ ranges between 22-26 mmol/l was considered as normal (Byrne et al., 2014).

Serum Albumin was measured for study group on HD program in same laboratory in the same HD center; by spectrophotometry method by added 1ml of test to 5 l of serum with 5-minute wait at 37 c using RANDOX kit. A value of 3.5-5.5 g/dl was considered as normal (Pathology Harmony Group, 2013).

Kt/V was measured directly during HD session by (B- Braun HD machine) by monitoring the UV light absorbance at selected wave length correspond to dialysate concentration of uric acid or other small molecule weight solute and the ratio of early and late dialysate UV absorption mirror pre-and post- serum uric acid. Normal Kt/V =1.2. (Daugirdas, Blake, & Ing, 2015).

2.6 Statistical Analysis

Statistical analysis was carried out using SPSS version 20. Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as frequencies and percentages. Independent sample t-test was used to compare between two continuous variables. Pearson's chi square (χ^2) test and fisher exact test were used to find the association between the categorical variables. A P- value of ≤ 0.05 was considered as statistically significant. Logistic regression model was used for both groups of patients with ESRD.

3. Results

The overall mean age of cases and comparison group were (47.50±12.25) and (52.16±13.58) years, respectively. There was no significant mean difference of age between cases and comparison group (t=1.801, df= 98, P- value= 0.075). There was no significant difference between study groups by gender with P- value= 0.15 (Figure 1).

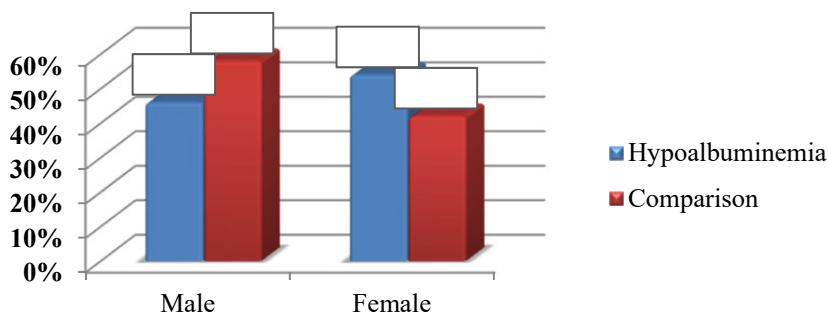


Figure 1. Difference of study groups by gender

There was a statistically significant association with HD sessions and duration between study groups. Cases were 9.33 and 18.86 times more likely to have two sessions of HD for four hours' duration, respectively (Table 1).

Table 1. Comparison of study groups by number and duration of hemodialysis sessions according to time of sessions

Variables	Study groups		χ^2	P. value	Odds Ratio
	Cases	Comparison			
	No. (%)	No. (%)			
Session of HD**:					
Two sessions	32 (64.0)	8 (16.0)	24.000	<0.001*	9.33 (3.60-24.16)
Three sessions	18 (36.0)	42 (84.0)			
Duration of HD:					
3 hrs	22 (44.0)	2 (4.0)	21.930	<0.001*	18.86 (4.12-86.28)
4 hrs	28 (56.0)	48 (96.0)			

*P- value ≤ 0.05 is significant, ** Hemodialysis.

There were significant differences between study groups by HCO₃ according to time of measurement regarding HD sessions. Cases were 66 and 18.86 times more likely to have low HCO₃ before HD sessions and before the next session, respectively. Meanwhile, Cases were 6 times more likely to have low HCO₃ after HD sessions directly (Table 2).

Table 2. Comparison of study groups by serum HCO₃ level according to time of hemodialysis session

Variable	Study groups		χ^2	P. Values	Odds Ratio
	Cases	Comparison			
	No. (%)	No. (%)			
HCO₃ before sessions of HD**:					
Low	45 (90.0)	6 (12.0)	60.864	<0.001*	66.00 (18.77-232.09)
Normal	5 (10.0)	44 (88.0)			
HCO₃ after sessions of HD:					
Low			6.061	0.014*	6.00 (1.24-28.98)
Normal	10 (20.0)	2 (4.0)			

	40 (80.0)	48 (96.0)			
HCO₃ before the next HD session:					
Low	44 (88.0)	14 (28.0)			
Normal	6 (12.0)	36 (72.0)	36.946	<0.001*	18.86 (6.58-54.05)

*P- value ≤ 0.05 is significant, ** Hemodialysis.

There was a significant difference between study groups by Kt/V. Patients with hypoalbuminemia were 45.77 times more likely to have low Kt/V (Table 3).

Table 3. Comparison of Study Groups by Kt/V

Variable	Study groups		χ^2	P. Values	Odds Ratio
	Cases No. (%)	Comparison No. (%)			
Kt/V:					
Low	36 (72.0)	3 (6.0)	45.776	<0.001*	40.28 (10.76-150.86)
Normal	14 (28.0)	47 (94.0)			

There were significant mean differences of HCO₃ before and after sessions of HD, as well as, HCO₃ after sessions of HD and HCO₃ before the next session (Table 4).

Table 4. Mean differences of serum HCO₃ level in cases according to time of hemodialysis sessions

Paired	Groups	Mean± SD [∞]	Paired t-test	P. value
Paired one	HCO ₃ before sessions of HD**	13.51± 2.16	21.435	<0.001*
	HCO ₃ after sessions of HD	18.86± 2.26		
Paired two	HCO ₃ after sessions of HD	18.86± 2.26	15.476	<0.001*
	HCO ₃ before the next session	14.15± 2.35		

*P- value ≤ 0.05 is significant, ** Hemodialysis, [∞] Standard deviation.

Logistic regression model showed that patients with acidosis were 102.8 and 7.88 times more likely to have low HCO₃ before sessions of HD as well as before the next sessions of HD than comparison group, respectively. Patients were 20.46 and 15.9 times more likely to have two sessions of HD as well as 3 hours for duration of HD than comparison group, respectively (Table 5).

Table 5. Logistic regression model for patients with acidosis and comparison group

Variable	Wald	P. value	Odds Ratio	95% C.I. for Odds Ratio	
				Lower	Upper
HCO₃ before sessions of HD[∞]					
Low**					
Normal	11.255	<0.001*	102.83	6.86	1540.40
HCO₃ after sessions of HD					
Low**					
Normal	0.329	0.566	2.39	0.12	47.16

HCO₃ before the next HD					
Low**					
Normal	4.168	0.041*	7.88	1.08	57.28
Kt/V					
Low					
Normal	1.735	0.188	0.11	0.00	2.86
Session of HD					
Two sessions**					
Three sessions	4.612	0.032*	20.46	1.30	321.80
Duration between HD					
3 hrs**					
4 hrs	5.005	0.025*	15.92	1.40	179.85
Age	0.359	0.549	1.02	0.94	1.11
Gender					
Male**					
Female	0.234	0.629	1.59	0.24	10.48
Constant	5.645	0.018	0.00		

*P- value ≤ 0.05 is significant, ** Reference group, Hemodialysis.

Mean S. Alb was (2.34 \pm 0.42) g/dl, (3.77 \pm 0.22) g/dl for cases and comparison respectively (Table 6).

Table 6. Mean values of serum HCO₃, serum Albumin and Kt/V of cases and comparison groups.

HCO ₃ before HD* session meq/L	HCO ₃ after HD session	HCO ₃ before next HD session	Serum Albumin g/dl	Kt/V
Mean \pm SD**	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD
Cases: 13.83\pm 2.53	19.09 \pm 2.44	14.42 \pm 2.82	2.34 \pm 0.42	1.051 \pm 0.15
Control: 19.02\pm 1.71	23.27 \pm 1.84	19.26 \pm 2.19	3.77 \pm 0.22	1.27 \pm 0.22

* Hemodialysis, ** Standard deviation

4. Discussion

In present study, the mean age of cases was (47.50 \pm 12.25) years and the mean age of comparison group was (52.16 \pm 13.58) years. There was no significant mean difference with P. value = 0.075. The study of (Thalacker-Mercer, Johnson, Yarasheski, Carnell, & Campbell, 2014) showed that albumin synthesis has not been found to change with age. While (Ikuko et al., 2007) showed a significant relation with age from 60 years and above. The maximum age in our study was 65 years old. In this study, there was no significant correlation between S. Alb and gender. Insignificant association between gender and low albumin was also shown in (Tayebbeh, & Ahad, 2011) study.

In present study, there was a highly significant correlation between numbers of sessions of HD (2sessions more than 3sessions/week) and duration of session (3hours >4hours/ session) with hypoalbuminemia with P. value = < 0.001. There was 32(64%) cases with 2sessions/ week and 18(36%) cases with 3 sessions/ week while in the comparison group there were only 8(16%) with 2 sessions and 42(84%) with 3 sessions per week. The duration of each session was 3hours in 22(44%) of cases and 4 hours in 28 (56%) of cases while in the comparison group there were 2(4%) with 3hour/ session and 48(96%) with 4 hours per session. Cases were 9 and 18 times more likely to have two sessions of HD for three hours' duration, respectively. The explanation is that patients with 2 sessions/ week and those with 3hour /session received less dialysis dose and were considered to have inadequate dialysis as compared with those of 3 sessions/ week and 4 hours' duration/ session which limit proper correction of acidosis

leading to low albumin level as mentioned previously.

Also, inadequate dialysis may lead to uremia, with consequent, anemia, anorexia nausea, vomiting and poor food intake which also leads to low albumin level. (Hemayati, Lesanpezeski, & Seifi, 2015) described this relation of hypoalbuminemia with dialysis adequacy and consider it significant correlation. In another study (AL-Saedy, Ali, & AL-Kahichy Hayder, 2011) it has been also showed that a significant correlation between dialysis adequacy and malnutrition indicated by low albumin and cholesterol.

In present study, there was a significant correlation between S. HCO₃ and S. Alb level when measured before dialysis session with P- value <0.001, and after dialysis session with P. value <0.001 and before next session with P- value= 0.014. The number of cases who had low HCO₃ level before dialysis session were 45(90%) compared to 6(12%) of comparison group and cases who had normal HCO₃ level were 5(10%) compared to 44(88%) of comparison group. While after HD session the cases who had normal HCO₃ were 40 (80%) compared to 48(96%) of comparison group and only 10 (20%) of cases had low HCO₃ level compared to only 2(4%) of comparison group. The HCO₃ level in cases before next session was normal in 6(12%) of cases compared to 36(72%) of comparison group and low in 44(88%) of cases compared to 14(28%) of comparison group. The mechanisms by which the acidosis causes hypoalbuminemia were discussed earlier. Our explanations to acidosis in our patient could be due to:

- Inadequate dialysis. Duration of dialysis and numbers of session as mentioned above and vascular access. Despite we didn't intake in our study the number of participant who depend on double lumen but it is still important cause of inefficient dialysis in our patient due to low blood flow and high incidence of inflammation and infection.
- Infection. Increase the infection rate leads to acidosis where most of ESRD patient have low immunity and our patients were not well educated about avoidance of contamination and most of them had poor nutrition.
- Nutritional factors where most of our patients were poorly adherent to diet given by specialist or dialysis unit.

Another study had also shown a significant association of low HCO₃ and albumin level with P- value = 0.019 (Tayebbeh, & Ahad, 2011). In a previous study; it was concluded that the treatment of acidosis has reduced whole body protein degradation (Chun-Ting, Shih-Hua, Jin-Shuen, & Yu-Juei, 2013).

In our study, there was a significant difference of study groups by Kt/V. Patients with hypoalbuminemia were 45 times more likely to have low Kt/V with P< 0.001. This correlation was focused by many researches. Sridhar, & Josyula reported that there is a relation between dialysis adequacy and albumin level (Sridhar, & Josyula 2013).

In present study, we compare in paired one between HCO₃ level before and after HD session where the mean of HCO₃ before HD was 13.83 and after HD was 19.09 with P. value<0.001. The paired two compared between HCO₃ level after HD with mean of 19.09 and before next session which was 14.42 with P. value <0.001. This refers that the cases complained from acidosis before HD and this partially was corrected after HD but remained acidosis despite dialysis while before next session of HD.

There would be mild elevation of HCO₃ level before HD in paired two from HCO₃ before HD in paired one. This occurred because there 18 cases have three sessions/ week. So, the HCO₃ before next session in those 18 cases mean midweek session which has better control of acidosis than just 2/ week sessions but statically not significant. So, we need in the cases group especially 2 sessions/ week to increase the dialysis HCO₃ to 35-40mmol/l and according to case instead of 31.6 mmol/l to increase post (HD) HCO₃ and HCO₃ before next session.

In present study, logistic regression model for patients with acidosis and control in ESRD in which the relationship between dependent and independent variables showed that HCO₃ level before session of HD and before next session is statically significant with P <0.001 and P=0.04 respectively, while HCO₃ after HD was statically insignificant, with P= 0.566. The number and duration of sessions were statically significant (P= 0.032, P= 0.025) respectively.

In this logistic regression model, Kt/V was statically insignificant because it depends on the presence of acidosis. In a study by El-Sheikh, & El-Ghazaly in 2016, it was concluded that there is a significant relation between serum total protein and the index of hemodialysis adequacy.

5. Conclusion

This study shows that patients with metabolic acidosis had a lower serum albumin concentration and there was a significant correlation between numbers, duration and adequacy of hemodialysis sessions and albumin level. We recommend to increase the numbers of dialysis centers in Iraq and adjust the bicarbonate doses in dialysate according to patient's bicarbonate levels.

Acknowledgements

The authors declare that there are no competing or potential conflicts of interest. The authors report that there was no funding source for the work that resulted in the article or the preparation of the article. We are grateful for all the medical and paramedical staff in the Iraqi Center for Hemodialysis in Baghdad Teaching Hospital for their work and assistance in completing this study. All authors contributed equally to the study.

Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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