How to Cite:
Mohammed, R. S., Saadi, S. J., & Rasheed, J. I. (2022). The effect of first session dialysis on acid: base status in patients with renal failure. *International Journal of Health Sciences*, *6*(S5), 3478–3491. https://doi.org/10.53730/ijhs.v6nS5.9398

The effect of first session dialysis on acid - base status in patients with renal failure

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***Abstract*---**Background: MA results from the inability of the kidneys to eliminate acid load, leading to HCO_3^- depletion and accumulation of H^+, the more deterioration of renal function the more severity of acidosis, In AKI, acidosis is a traditional and typical complication, and refractory acidosis is an indication for renal replacement therapy. Aim: to study the effect of first dialysis session on acidosis correction. Methods: an interventional study included 33 patients with renal failure presented for 1st time dialysis, we calculated the change in their pH, HCO_3^-, BD, AG and Cl^- to Na^+ ratio caused by dialysis, and studied whether or not this change is related to URR. Results: dialysis had significant effect on pH, HCO_3^- and BD, and there was positive correlation between URR and HCO_3^- difference and negative correlation between both BD difference with HCO_3^- difference, and BD difference with HCO_3^- difference. Conclusion: 1st dialysis session has significant effect on acidosis correction without affecting electroneutrality of the blood.

***Keywords*---** Acid-Base, Kidneys, Hemodialysis.

1. Introduction

1.1 Background:

Acid – base balance is a highly complicated process, functions to keep extracellular pH at a stable level, which ranges between 7.35 – 7.45, providing the best environment for cellular activity and proteins metabolism. Even small change

in concentration of hydrogen (H^+) ion would impair this physiological function. Substances that release H^+ in a solution are called acids, while bases are substances that accept free H^+ and can combine in a solution with an acid resulting in its neutralization. Normally there is continuous production and neutralization of H^+ to achieve stable pH [1,2]. The most important contributor to net endogenous acid production (NEAP) is the diet. Body acids can be classified as volatile (carbonic acid H_2CO_3), and nonvolatile (fixed) acids, also there are organic acids that are metabolizable and nonorganic acids (nonmetabolizable) which the body needs to excrete them in urine [3].

1.2 Endogenous Production of Acids:

H^+ concentration needs to be maintained at an appropriate level, despite NEAP being around 15,000 mEq/day as volatile acids [4], and 70-100 mEq/day as fixed acids [5]. This amount of H^+ comes from carbohydrate, lipid and protein metabolism. The oxidation of these substances results in formation of volatile acid according the equation $CO_2 + H_2O \leftrightarrow H_2CO_3$, also this metabolic pathway will generate intermediary products as H^+ and fixed acids, if not controlled will lead to metabolic acidosis (MA) [4].

1.3 Acid-Base Homeostasis Regulation:

In healthy person, concentration of plasma acids and bases are tightly regulated to achieve a stable pH between 7.35-7.45 [3], this is done by neutralization of the ingested or produced acids by buffers which is the rapid process, or by elimination through the kidneys or the lungs which needs more time.

1.3.1 Neutralization by Buffer Systems:
Bicarbonates (HCO_3^-) and H_2CO_3 represent the most important buffer system, they operate both inside and outside the cells through the reversible reaction ($H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$), the strength in this system lies in its ability to eliminate acids through lungs as CO_2. Other buffers are the proteins, because they have amine group (NH_2) and carboxylic acid (COOH), in plasma they are in anionic form and act as bases by binding excess H^+, they can also act as acids by releasing H^+. another major buffer system is bone carbonate, which respond to acid load by increased release of bone carbonate to act as a buffer, this is supported by noting increased urinary calcium excretion during acidosis [6,7]. Phosphate (PO_4^{3-}) represent intracellular buffer [5].

1.3.2 Pulmonary Acid Excretion:
There is continuous elimination of the volatile acid H_2CO_3 through ventilation, this process is a major regulator of CO_2 pressure to keep stable concentration of carbonic acid in the plasma [3].

1.3.3 Role of Kidneys in Acid Base Regulation:
The kidneys serve to excrete daily produced fixed acids through active secretion of H^+ in tubular fluids [8]. In fact, the kidneys are able to excrete 50-100 mEq of H^+ per day (around 1 mEq/kg/day) representing fixed acids load [9]. They also contribute to maintenance of stable HCO_3^- level through both reabsorption and generation of new HCO_3^- from titratable acid formation which result from

neutralization of excreted H^+ by urinary buffers, generation of new HCO_3^- also results from H^+ excretion and ammonium (NH_4) formation [8]. These highly regulated processes between the kidneys and the lungs result in arterial pH level near 7.40 despite variations in acid or base load.

1.4 Kidney Impairment Effect on MA:

MA results from the inability of the kidneys to eliminate acid load, leading to HCO_3^- depletion and accumulation of H^+ [9]. An inverse relationship exists between the severity of renal function decline and strength of MA, in which the more deterioration of renal function the more severity of acidosis [10]. This involves both chronic kidney disease (CKD) and acute kidney injury (AKI), where wide anion gap (AG) is usually seen, resulting from PO_4^{3-}, small organic anions and sulfate accumulation in bloodstream [11] and reduced excretion of acids and anions [12].

1.5 MA Adverse Effects:

1.5.1 On Kidneys:
When renal function deteriorates, adaptations of the kidneys to improve excretion of acids to maintain normal pH, can cause kidney injury. This is supported by multiple lines of evidence. These adaptations include increase production of ammonia (NH_3) per nephron, to maintain excretion of acids in case of nephron loss, this high concentration of NH_3 enhance cleavage of complement protein C3, resulting in alternative complement pathway activation and tubulointerstitial fibrosis. Another mechanism to increase acid excretion and decrease HCO_3^- includes systemic and renal endothelin-1 upregulation leading to vasoconstriction both systemically and intrarenal, with inflammation induction, oxidative stress and accumulation of extracellular matrix. Acid mediated injury also involves angiotensin II which promotes tubulointerstitial fibrosis [9].

1.5.2 On Other Systems:
MA can induce or exacerbate bone disease, as it decreases vitamin D production, alters parathyroid hormone stimulation and affects end organ response to it, also stimulates bone resorption and inhibiting new bone formation [13]. MA also affects albumin synthesis [14], enhances proteolysis and protein catabolism [15]. MA interferes with insulin binding to its receptor leading to glucose intolerance [16]. It also leads to accumulation of beta 2 microglobulin [17], and increases macrophages release of inflammatory cytokines and formation of inflammatory environment [18]. Most importantly, acidosis with HCO_3^- <22 mmol/L is associated with increased mortality [19].

1.6 Acid-Base Disorder Quantification:

Different methods exist to describe acid-base disorder, of which is the physiological method which relies on the interaction between the lungs and kidneys to control pH [20]. Also, there is the physiochemical (Stewart) method, involving strong and weak ions and their relation to pH [21]. While base excess method based on assessing the change in acid-base status delivered by blood gas analyzers [22].

1.7 Hemodialysis (HD) Role in Correction of Acidosis:

Diffusion of HCO_3^- from the dialysate to the blood and removal of retained anions that participate in the formation of volatile acid is one of the important goals of HD. For patients with renal failure, the highest level of acidosis is present in the period before HD [23]. Some studies support increasing HCO_3^- concentration in chronic HD will decrease the level of acidosis and improves nutritional status [24]. In AKI, acidosis is a traditional and typical complication, and refractory acidosis is an indication for renal replacement therapy [25,26].

1.8 HD Quantification:

The adequacy of HD in clearing solutes is assessed depending on urea kinetics that calculate single pool Kt/V_{urea} (Kt/V) [27,28] which is a numerical value that quantifies adequacy of HD treatment, K stands for dialyzer urea clearance, t duration of dialysis session, V urea volume of distribution which is usually equal to the total body water of the patient [15], practice guidelines of Kidney Disease Improving Global Outcome (KDIGO) recommends achieving a value of at least 1.3 Kt/V in HD for AKI [29]. Hypercatabolism and negative net nitrogen balance occur in AKI, urea production rates may not be constant, and in hemodynamic instability there are regions with altered blood flow, these factors may result in unequal distribution of urea across body compartments, this may affect the adequacy of single pool models because of the variability of urea distribution between AKI and end stage renal disease [30,31]. The other method to assess the delivered small solutes clearance by HD in AKI patients is the urea reduction ratio (URR), which is a reliable and independent of $V_{urea,}$ and relies only on measuring urea pre and post dialysis [32]. The correction of MA by hemodialysis in CKD patients has been studied, and related to albumin and other nutritional parameters [24] and also related to urea kinetics [33]. In our research, we studied the degree of correction of acidosis in patients underwent HD for the 1st time, and whether or not this correction can be correlated with dialysis adequacy

Aim of the study: to study the effect of dialysis on acidosis correction.

2. Patients and Methods

2.1 Selection of The Sample:

An interventional study carried out in Medical City-Baghdad teaching hospital / Iraqi center for dialysis, the studied sample included 33 patients with renal failure presented for 1st time dialysis.
They were enrolled after accepting to take part in the study and fulfilled inclusion criteria.

2.2 Inclusion and Exclusion Criteria:

2.2.1 Inclusion Criteria

- Patients with acute or chronic renal failure required 1st time dialysis.
- Were able to complete 2 hours of HD.

2.2.2 Exclusion Criteria:

- Patients who were unable to complete the dialysis session for any cause.
- Patients already on dialysis.

2.3 Decision of Dialysis:

The decision for the need of dialysis was made by the nephrologists on call, guided by clinical presentation and response to treatment, the indications were one or more of the following:

- Uremic encephalopathy.
- Pericarditis.
- Life-threatening hyperkalemia.
- Refractory acidosis.
- Hypervolemia causing end-organ complications (e.g., pulmonary edema).
- Intractable gastrointestinal symptoms [34].

2.4 Data Collection:

Blood samples were drawn from the patients before starting the dialysis session and again within 5 minutes after session end, the dialysate was stopped for 5 minutes and blood flow decreased to 50 ml/min, blood was taken from arterial side of the dual lumen, and for blood gas analysis, blood was drawn in a heparinized syringe and sent immediately for the blood gas analyzer, samples were measured within 5 minutes. Dialysis was done by B. Braun Dialog + dialysis machine, using polysulfone low flux Diacap Pro (B. Braun) dialyzer with surface area 1.7 m^2, and Sol-Cart B bicarbonate cartridge 650g, and ready to use HCO_3^- solution in mixture 1+34. Device setting was: time 2 hours, sodium (Na^+) 138 mmol/L, HCO_3^- 28 mmol/L, potassium (K^+) 2 mmol/L, ionized calcium (Ca^{+2}) 1.5 mmol/L, chloride (Cl^-) 109 mmol/L, blood flow rate was 200ml/min, dialysate flow was 400ml/min. Blood gases were analyzed using ABL800 FLEX blood gas analyzer (Denmark), electrolytes by Genrui electrolyte analyzer (China), urea and creatinine by Selectra pro M system (Netherlands).

2.5 Calculations:

Acid-base status analysis done by the physiologic method [20,35], which is based on pressure of CO2 (PCO_2) and HCO_3^- concentrations and their effect on pH, to identify the primary disorder and whether or not there is proper compensation or another disorder exist [36] whereas AG is the difference between Na^+ and the sum of HCO_3^- and Cl^- and normal value is 10-12 mmol/L [37]. We also calculated base excess, because it has a prognostic value in critically ill patients [38] and to quantify metabolic component of acid-base disorder [39]. Base excess is defined as the amount of acid or base that is required to titrate whole blood in vitro to a pH of 7.4 at temp 37c and PCO2 of 40 mmHg, and to avoid confusion we used its interchangeable name, base deficit (BD) which is the negative value of base excess [38,40]. We quantified dialysis adequacy by calculating URR to avoid variability in urea distribution across body fluids between AKI and CKD patients that may affect single pool Kt/V. urea reduction ratio was calculated from the following formula: URR = (urea before dialysis – urea after dialysis)/ urea before dialysis [41]. For all patients, we calculated the change in pH, HCO_3^-, BD, AG and Cl^- to

Na^+ ratio (Cl^-/Na^+), all before and after dialysis and called this change a (difference) representing post dialysis value – pre dialysis value, and searched whether or not a relation exists between each parameter difference and dialysis adequacy. The correction of acidosis was measured as HCO_3^- difference, which is the difference between HCO_3^- post dialysis and HCO_3^- pre dialysis. The calculation of Cl^-/Na^+, both before and after dialysis was to check whether or not the correction in acidosis could affect serum electroneutrality, Cl^-/Na^+ also helps identify metabolic acidosis, either due to retention of acids, if $Cl^-$was normal, or loss of HCO_3^- if Cl^- is high [42].

2.6 Normal values:

2.6.1 ABG:

- pH = 7.35 to 7.45.
- pCO2 = 35 to 45 mmHg.
- pO2 = 75 to 100 mmHg.
- HCO3- = 22 to 26 mmol/L.
- O2 Sat = greater than 95%.
- Base deficit = -2 to 2 [20,43].

2.6.2 Biochemistry (according to our lab reference):

- Urea = 15-45 mg/dL.
- Creatinine= 0.72-1.2 mg/dL.
- Na = 135-145 mmol/L.
- Cl = 96-106 mmol/L.
- K = 3.5-5.3 mmol/L.

2.7 Statistical analysis

Data was analyzed using SPSS-28 and presented simply as range, mean with standard deviation, percentage and frequency. Two dependent means difference was tested for significance by paired -t- test. Pearson chi square with Fisher exact or Yate's correction was used to test the significance of different percentages differences. P value considered significant if ≤ 0.05. Significance of correlation between two quantitative variables was calculated by Pearson correlation with its ttest, whereas (r) is the correlation coefficient, values < 0.3, 0.3 - <0.5, 0.5 - <0.7, >0.7 stands for no, weak, moderate and strong correlation, respectively. (r) is either positive (direct) or negative (inverse) correlation. We also calculated r^2 (determination coefficient).

3. Results:

The total enrolled patients are 33, of which 18 were males (54.5%) and 15 were females (45.5). aged between 19 and 70 years old, with mean age of 52.9±11.6 (table 1).

Table 1: demographic data of the patients.

		No	%
Age (years)	<40years	4	12.1
	40---49	6	18.2
	50---59	11	33.3
	=>60years	12	36.4
	Mean±SD (Range)	52.91±11.68 (19-70)	
Gender	Male	18	54.5
	Female	15	45.5

pH of the patients before dialysis ranged between 6.93-7.42 with mean of 7.2±0.11, which increased post dialysis significantly to a mean of 7.30±0.1 (p = 0.0001), pH difference had a mean of 0.107±0.131 (p = 0.0001). there was also significant improvement of HCO_3^- post dialysis with change of mean from 9.62±4.22 to 14.42±4.25, the mean of HCO_3^- difference was 4.79±2.85 (p = 0,0001). BD mean was decreased significantly post dialysis (p 0.0001) from a mean of 16.78±4.99 to 11.22±4.87, and BD difference mean was -5.56±3.80 (p=0.0001). urea is another measurement that had its share of significant change as decreased from a mean of 262.52±81.21 to 154.34±64.50 (p 0.0001). other measurements that changed significantly were PCO2, K^+ and creatinine, as shown in the next 2 tables. on the other hand, Na^+, Cl^-, AG and Cl^-/Na^+ had no significant change in dialysis, as shown in table 2 and table 3.

Table 2: mean with standard deviation and range of the patients' parameters before and after dialysis

	Pre-dialysis	Post-dialysis	P value
pH	7.20±0.11 (6.93-7.42)	7.30±0.10 (7.05-7.52)	0.0001#
HCO_3^- (mmol/L)	9.62±4.22 (1.5-19.3)	14.42±4.25 (3.4-23.0)	0.0001#
PCO_2 (mmHg)	23.73±8.62 (7.2-50.5)	28.57±10.11 (10.1-67.4)	0.0001#
Na^+ (mmol/L)	139.79±8.92 (117-163)	141.24±6.19 (126-154)	0.211
K^+ (mmol/dL)	4.06±1.10 (2.3-6.3)	2.92±0.78 (1.6-5.5)	0.0001#
Cl^- (mmol/L)	101.70±8.58 (85-123)	101.09±5.83 (89-114)	0.592
AG (mmol/L)	28.77±7.68 (14.0-46.8)	26.09±6.79 (15.4-52.5)	0.153
BD (mmol/L)	16.78±4.99 (8.2-27.8)	11.22±4.87 (1.7-23.0)	0.0001#
Urea (mg/dL)	262.52±81.21 (103-411)	154.34±64.50 (22-300)	0.0001#
Creatinine (mg/dL)	10.53±5.69 (2.60-25.0)	6.45±3.62 (1.0-16.2)	0.0001#
Cl^-/Na^+	0.728±0.055 (0.636-0.905)	0.716±0.039 (0.628-0.803)	0.225

-Data were presented as Mean±SD (Range)

#Significant difference between two dependent means using Paired-t-test at 0.05 level.

Table 3: mean and standard deviation of parameters differences

	Mean ±SD	P value
pH difference	0.107±0.131	0.0001#
HCO_3^- (mmol/L) difference	4.79±2.85	0.0001#
AG (mmol/L) difference	-2.68±10.52	0.153
BD (mmol/L) difference	-5.56±3.80	0.0001#
Cl^-/Na^+difference	-0.012±0.056	0.225

-Data were presented as Mean±SD (Range)

#Significant difference between two dependent means using Paired-t-test at 0.05 level.

All patients had high AG acidosis, either alone or mixed with other disorder as shown in table 4.

Table 4: acid-base disorder of the patients

Disorder	No	%
high anion gap acidosis	14	42.4
high anion gap acidosis with respiratory acidosis	10	30.3
high anion gap acidosis with metabolic acidosis	3	9.1
high anion gap acidosis with respiratory alkalosis	3	9.1
high anion gap acidosis with respiratory alkalosis and metabolic alkalosis	2	6.1
high anion gap acidosis with metabolic alkalosis	1	3.0

urea reduction ratio ranged from 15-78 %, and the mean was 42.32±17.03, 69.7% of the patients had URR equal to or less than 40% (table 5).

Table 5: urea reduction ratio levels and percentages among patients

		No	%
URR	10---	4	12.1
	20---	5	15.2
	30---	7	21.2
	40---	7	21.2
	50---	4	12.1
	=>60	6	18.2
	Mean±SD (Range)	42.32±17.03 (15.2-78.6)	

We found a significant positive (direct) correlation between URR and HCO_3^- difference (r = 0.559, p = 0.0001) as seen in figure 1, increasing URR leads to increase in HCO_3^- correction and decrease in acidosis.

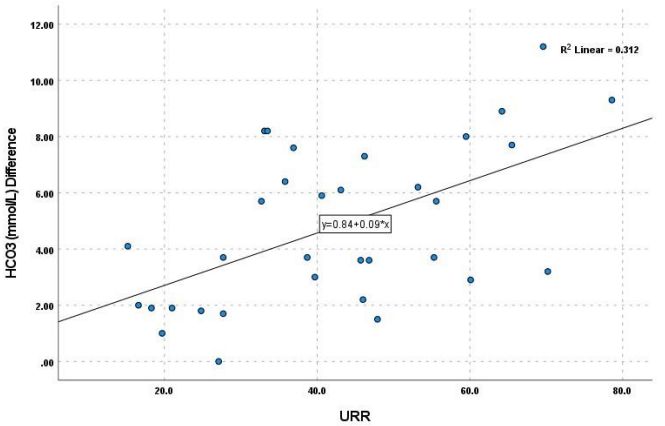

Figure 1: correlation between URR and HCO_3^- difference.

There was also a significant strong inverse correlation between HCO_3^- difference and BD difference (r = -0.825, p = 0.0001), as in figure 2, the more HCO_3^- is corrected the less will be base deficit.

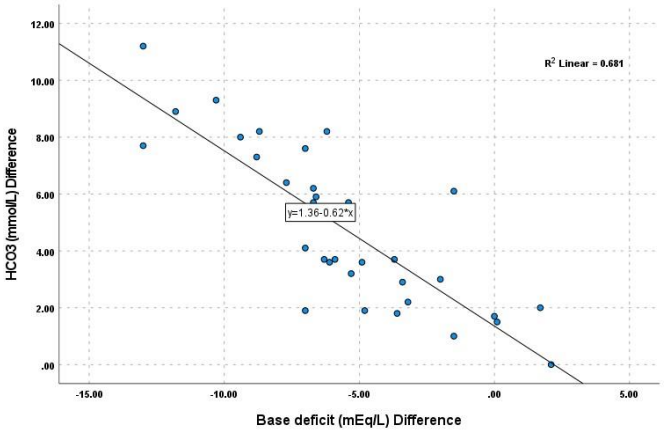

Figure 2: correlation between BD difference and HCO_3^-

BD difference and pH difference had a strong significant inverse correlation (r = -0.731, p = 0.0001), as shown in figure 3.

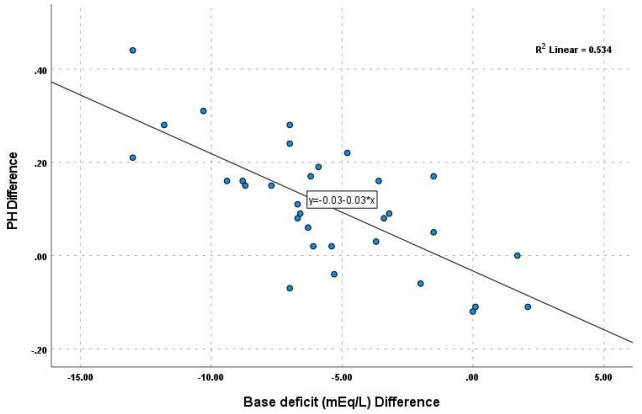

Figure 3: correlation between BD difference and pH difference.

4. Discussion

33 patients who had kidney failure that required dialysis for the first time were investigated for acid-base disorder and the effect of dialysis on acidosis correction. Their mean age was 53±11 years. 54.5% were males and 45.5% were females. Blood urea mean was 262.52±81.21 mg/dL. All of them had high AG MA either alone or combined with other acid-base disorder (table 4). Parameters before dialysis showed that pH mean was 7.20±0.11, while HCO_3^- mean 9.62±4.22, BD mean 16.78±4.99 and AG mean was 28.77±7.68. Compared to a study done by Rocktaeschel J, Morimatsu H, Uchino S, et al. [44], our patients had higher blood urea mean and more severe acidosis evidenced by lower pH, lower HCO_3^-, higher BD and AG, this could be to the fact that many patients are presented late to dialysis either due to delay in seeking proper medical care or due to hesitance in acceptance to do HD. After dialysis, URR mean was 42.32±17.03 %, this is slightly more than the target for URR in AKI HD prescription [45] because of the difference in presenting urea and different body size of the patients with fixed dialysis prescription to all patients. Our result of URR mean also is lower than what is reported by Maurilo Leite Jr et al [33], because their study was done to CKD patients already on HD and higher doses of dialysis and $HCO3^-$ were used, which we can't use because of the risk of disequilibrium syndrome. With this URR mean, the pH difference was 0.107±0.131 (p = 0.0001), to settle in post dialysis pH mean of 7.30±0.10 (p= 0.0001), so we had a significant change in pH towards the normal range. HCO_3^- difference was 4.79±2.85 (p = 0.0001), and post dialysis HCO_3^- increased significantly to 14.42±4.25 (p = 0.0001). BD difference was -5.56±3.80 (p = 0.0001) with post dialysis mean decreased significantly to 11.22±4.87 (p = 0.0001). so, after dialysis the patients had significant improvement in severity of acidosis as evidenced by: (a) elevation in pH which points toward decreased H^+ ions and fixed acids [4], (b) elevation in HCO_3^- through diffusive entry from dialysate to blood to help in buffering acids, (c) decrease in BD which can be understood as decrease in acid accumulation in blood [38,40]. On the other hand, AG didn't change significantly with dialysis, AG difference was -2.68±10.52 (p = 0.153), post dialysis AG mean was 26.09±6.79, and no correlation was found between URR and AG (r = -0.062, p = 0.730). it is well known that AG represents the difference between cations and anions concentrations in plasma [37], and the reason for high AG is retention of acids,

organic anions and PO_4^{3-} which will lead to decrease in HCO_3^- due to its consumption as a buffer for retained acids. So, in a single 1st session dialysis of 2 hours duration, the degree of correction of HCO_3^- will not be enough to change anion gap sufficiently. Cl^-/Na^+ pre dialysis was 0.728±0.055, with normal Cl^- mean level (table 2) indicates acid retention as the main cause of acidosis [42]. Cl^-/Na^+ didn't change significantly after dialysis as the mean post dialysis was 0.716±0.039 (p = 0.225), and Cl^-/Na^+ difference was -0.012±0.056 (p = 0.225), this points towards that the correction of acidosis through dialysis done by adding HCO_3^- to plasma and removal of retained acids and organic anions without affecting electroneutrality of the plasma, and no correlation was found with URR. There was a significant direct correlation between URR and HCO_3^- difference (r = 0.559, p = 0.0001), as URR represents dialysis adequacy and HCO_3^- difference represents MA correction, the more dialysis adequacy the more acidosis correction. this relation explains why dialysis is indicated for the treatment of refractory acidosis [34], we can see that post dialysis HCO_3^- is still in MA range but this is accepted because the patient underwent his first session and will have other sessions for more correction, and severe and rapid correction will put the patients at risk of hypokalemia and enhanced vascular calcification [46]. A similar significant correlation between URR and HCO_3^- difference was found by Maurilo Leite Jr et al [33]. a significant strong inverse correlation was found between HCO_3^- difference and BD difference (r = -0.825, p = 0.0001) as seen in (figure 2), HCO_3^- will diffuse to plasma and acids will be removed, hence more acidosis correction (HCO_3^- difference) leads to less BD (less acid accumulation). BD difference had significant strong inverse correlation with pH difference (r = 0.731, p = 0.0001), by definition, BD can be understood as acid excess in the plasma, so the less acid excess the closer pH to normal. This correlation was demonstrated by Jasso avilla MI et al [47] which showed a significant correlation between BD and pH in diabetic ketoacidosis patients.

5. Conclusion

This study showed that 1st dialysis session has significant effect on acidosis correction noted through changes in pH, HCO_3^- and BD, also a significant correlation was found between dialysis dose and correction of acidosis, and an inverse correlation between both of correction of acidosis with BD difference, and BD difference with pH difference, while no significant effect is noted on AG and Cl^-/Na^+ and no correlation was found with URR.

6. Recommendation:

Studying the effect of dialysis adequacy on acidosis in CKD patients before and after dialysis and its effect on the severity of acidosis before the next session of HD.

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