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# Changing the paradigm of bicarbonate ( $\text{HCO}_3^-$ ) hemodialysis prescription in Portugal: a 24-month prospective study

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## Abstract

**Background:** Metabolic acidosis is common in hemodialysis (HD) patients. The KDOQI guidelines therapeutic goal is pre-dialysis  $\text{HCO}_3^- \geq 22$  mmol/L. The aim of the study was to evaluate an individualized  $\text{HCO}_3^-$  hemodialysis prescription as a preventing factor of metabolic changes.

**Methods:** Twenty-four-month prospective study of patients on online high-flux hemodiafiltration. Every 3 months,  $\text{HCO}_3^-$  blood levels were analyzed and hemodialysis  $\text{HCO}_3^-$  was changed using the following rules:

- $\text{HCO}_3^- > 30$  mmol/L: reduce 4 mmol/L  $\text{HCO}_3^-$
- $\text{HCO}_3^- \geq 25$  mmol/L: reduce 2 mmol/L  $\text{HCO}_3^-$
- $20$  mmol/L  $< \text{HCO}_3^- < 25$  mmol/L: no change
- $\text{HCO}_3^- \leq 20$  mmol/L: increase 2 mmol/L  $\text{HCO}_3^-$
- $\text{HCO}_3^- < 18$  mmol/L: increase 4 mmol/L  $\text{HCO}_3^-$

Data collected comprised demographic information, renal disease etiology, comorbidities, HD treatment information, and lab results. Statistical analysis was performed using SPSS.

**Results:** Thirty-one patients were enrolled and completed the follow-up period. At baseline, average serum pH was  $7.38 \pm 0.06$ , serum  $\text{HCO}_3^- 25.92 \pm 1.82$  mmol/L, and every patient had a 32 mmol/L dialytic  $\text{HCO}_3^-$  prescription. At time point 9, average serum  $\text{HCO}_3^-$  was  $23.87 \pm 1.93$  mmol/L and 58% of the patients had a dialytic  $\text{HCO}_3^-$  prescription of 28 mmol/L. Serum  $\text{HCO}_3^-$  differed with statistical significance during time and approached the reference serum  $\text{HCO}_3^-$  (23 mmol/L) that we have defined as ideal. Through time, the  $\text{HCO}_3^-$  prescription deviated more from the 32 mmol/L initial prescription that was defined as standard.

**Conclusions:** Our findings suggest that the standard  $\text{HCO}_3^-$  prescription of 32 mmol/L should be rethought, as an individualized  $\text{HCO}_3^-$  prescription could be beneficial for the patient.

**Keywords:** Hemodialysis, Bicarbonate, Metabolic acidosis

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## Background

In patients without kidney function, body buffers consumed by acid accumulation are restored by alkali administration during dialysis. The amount of alkali administered during the treatment is dependent on the dialysate bicarbonate ( $\text{HCO}_3^-$ ) concentration and traditionally has been set to avoid marked post-dialysis alkalemia and minimize pre-dialysis acidemia [1].

It was only in the mid-1980s that the detailed studies on metabolic acidosis in chronic kidney disease (CKD) patients gained momentum. Shortly thereafter in 1993, Oettinger and Oliver noted that metabolic acidosis is common in patients with CKD because of the inability of the kidneys to excrete the nonvolatile acid load. Among the many goals of dialysis, the role in the correction of uremic acidosis was recognized. It was noted that despite adequate hours of HD metabolic acidosis remains common and is reported in up to 75% of patients [2].

When  $\text{HCO}_3^-$  replaced acetate as the predominant alkali source for dialysis treatment, bath  $\text{HCO}_3^-$  concentration was set at 35 mEq/L based on historical precedent, with little thought as to what was the ideal concentration. However, the new average values still remained lower than the normal range seen in patients with functioning kidneys, raising concerns about long-term deleterious effects of metabolic acidosis. This is a peculiar form of metabolic acidosis because it is only present intermittently, when serum total carbon dioxide decreases from a high-normal level immediately post-dialysis to its nadir before the next dialysis treatment [3].

In Portugal, the use of dialysate containing  $\text{HCO}_3^-$  is universal. The disseminated use of online high flux hemodiafiltration has allowed a total control of  $\text{HCO}_3^-$  concentration in dialysate prescription. There are no impositions by law on the prescriptions a specific  $\text{HCO}_3^-$  concentration in dialysate.

Metabolic acidosis is a common condition particularly in the end-stage of renal disease (ESRD) patients [4]. It influences the nutritional status with important repercussions on the musculoskeletal system [2, 5]. Metabolic acidosis causes negative nitrogen balance, increased protein degradation, increased essential amino acid oxidation, reduced albumin synthesis, and low appetite [2, 6]. This eventually leads to decreased protein intake, protein energy malnutrition, loss of lean body mass, and muscle weakness [6]. It also has harmful effects on the functioning and structure of the cardiovascular system, thus amplifying morbidity and mortality in uremic patients [5].

Although hemodialysis (HD) is the most important method of correction for the metabolic acidosis of ESRD, the changes in serum  $\text{HCO}_3^-$  levels produced by a HD session are sometimes too abrupt and tempestuous, attracting adverse consequences [5].

Current KDOQI guidelines recommend pre-dialysis or stabilized serum  $\text{HCO}_3^-$  levels should be maintained at/ or above 22 mmol/L [7].

During each HD session, patients are exposed to the  $\text{HCO}_3^-$  bath in the dialysate fluid and can effectively correct metabolic acidosis. Normalization of the pre-dialysis or stabilized serum  $\text{HCO}_3^-$  concentration can be achieved by higher basic anion concentrations in the dialysate and/or by oral supplementation with bicarbonate salts [8].

It is reasonable to speculate that patients with low levels of endogenous acid production are not eating well and many are malnourished, increasing their mortality risk [3].

Acidosis causes the activation of buffer systems involving the accumulation of serum calcium and phosphate ions through bone resorption, with major influence on vascular endothelium and an important role in the development of vascular calcifications [9].

The administration of oral intradialytic  $\text{HCO}_3^-$  has the advantage of a constant buffering acidosis to avoid fluctuations of pre-dialysis and post-dialysis [5].

In the meantime, serum  $\text{HCO}_3^-$  in these patients may be influenced by many variables, such as low or high dietary acid intake, malnutrition and catabolism, oral alkali intake ( $\text{CaCO}_3$  or  $\text{NaHCO}_3$ ), intake of sevelamer hydrochloride or sevelamer carbonate as a phosphate binder, and the concentration of  $\text{HCO}_3^-$  in the dialysate during dialysis treatment [10].

The primary outcome of the study is to evaluate changes in plasma  $\text{HCO}_3^-$  after an individualized  $\text{HCO}_3^-$  hemodialysis prescription. The secondary outcome is to evaluate an individualized  $\text{HCO}_3^-$  hemodialysis prescription as a preventing factor of metabolic changes in a hospital HD facility.

## Methods

We conducted a single-center 24-month prospective study (January 2017–December 2018), at Centro Hospitalar do Médio Tejo, EPE hemodialysis unit.

The Fresenius machine (5008) was used for online high flux hemodiafiltration. Each session had a duration of 4 h with a blood flow rate of 450–500 mL/min.

Every 3 months (9 time points),  $\text{HCO}_3^-$ , calcium ( $\text{Ca}^{2+}$ ), phosphorus ( $\text{P}^+$ ), intact parathyroid hormone (iPTH), C-reactive protein (CRP), and albumin blood levels were analyzed and hemodialysis  $\text{HCO}_3^-$  prescription was changed using the following rules:

- $\text{HCO}_3^- > 30$  mmol/L: reduce 4 mmol/L  $\text{HCO}_3^-$
- $\text{HCO}_3^- \geq 25$  mmol/L: reduce 2 mmol/L  $\text{HCO}_3^-$
- $20$  mmol/L  $< \text{HCO}_3^- < 25$  mmol/L: no change
- $\text{HCO}_3^- \leq 20$  mmol/L: increase 2 mmol/L  $\text{HCO}_3^-$
- $\text{HCO}_3^- < 18$  mmol/L: increase 4 mmol/L  $\text{HCO}_3^-$

We defined the ideal serum  $\text{HCO}_3^-$  as 23 mmol/L.

All out-patients were included.

The data collected included baseline clinical characteristics at the beginning of the study, namely age, gender, kidney disease etiology, and presence of comorbidities with correlation to kidney disease (diabetes mellitus, hypertension). Baseline and every 3-month laboratory findings recorded included  $\text{HCO}_3^-$ ,  $\text{Ca}^{2+}$ ,  $\text{P}^+$ , and iPTH. HD treatment information was also verified, namely Kt/V.

Continuous variables were presented as mean and standard deviation, or median and interquartile range (IQR) for variables with skewed distributions and other nominal variables were presented as number (frequency) and percentage.

Independent-sample *t* tests were used to analyze the mean blood  $\text{HCO}_3^-$  and continuous variable time. Data are presented as a mean [95% confidence interval (CI)].

A Wilcoxon signed-rank test was used to compare the mean baseline  $\text{HCO}_3^-$  prescription with the different time points  $\text{HCO}_3^-$  prescriptions.

A repeat measures ANOVA was used to determine whether there were differences between the means of serum  $\text{HCO}_3^-$  at the different time points.

Correlation between serum  $\text{HCO}_3^-$  and parameters that might be relevant to its concentration were evaluated by the Pearson or Spearman correlation analysis.

Underlying assumptions were met, unless otherwise indicated. A *p* value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 23.0 (Chicago, USA) for Mac OS X.

Informed consent was obtained from the participants. All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Results

The cohort included 125 patients in our hemodialysis unit. However, only 31 (24.8%) completed the follow-up period, since the others died or leave the program to other units. Patient demographic data and characteristics are presented in Table 1.

At baseline, average pH was  $7.38 \pm 0.06$ ,  $\text{HCO}_3^-$   $25.92 \pm 1.82$  mmol/L and every patient had a 32 mmol/L dialytic  $\text{HCO}_3^-$  prescription. At time point 9, average pH was  $7.37 \pm 0.07$ ,  $\text{HCO}_3^-$  was  $23.87 \pm 1.93$  mmol/L and 58% of the patients had a dialytic  $\text{HCO}_3^-$  prescription of 28 mmol/L. The distribution of  $\text{HCO}_3^-$  prescription at time point 9 is presented in Table 2. All detailed information about  $\text{HCO}_3^-$  prescription, laboratory findings (serum  $\text{HCO}_3^-$ ,  $\text{Ca}^{2+}$ ,  $\text{P}^+$ , iPTH, CRP, and albumin), and hemodialysis efficiency are presented in Table 3.

**Table 1** Demographic characteristics of the patients

General characterization (n = 31)	
Mean age $\pm$ SD (yr)	74.26 $\pm$ 12.96
Male sex—no. (%)	20 (65%)
Comorbidities (n = 31)	
Diabetes mellitus—no. (%)	15 (48%)
Hypertension—no. (%)	17 (55%)
CKD etiology (n = 31)	
Cardio-renal syndrome—no. (%)	4 (12.9%)
ADPKD—no. (%)	1 (3.2%)
Chronic Glomerulonephritis—no. (%)	2 (6.5%)
Hypertensive nephroangiosclerosis—no. (%)	1 (3.2%)
Diabetic nephropathy—no. (%)	9 (29%)
Chronic pyelonephritis—no. (%)	4 (12.9%)
Vasculitis—no. (%)	3 (9.7%)
Others—no. (%)	2 (6.4%)
Undetermined—no. (%)	5 (16.1%)

Ab antibody, ADPKD autosomal dominant polycystic kidney disease, CKD chronic kidney disease, no. number, SD standard deviation, yr years

In our sample, gender, diabetes mellitus, hypertension, and kidney disease etiology did not influence the prescription.

A repeated measures ANOVA determined that serum  $\text{HCO}_3^-$  differed with statistical significance during time (*p* = 0.001), and the post Hoc Tukey-Kramer test confirmed those assumptions between time points 1 and 6 (*p* = 0.002), 1 and 7 (*p* = 0.002), 1 and 8 (*p* = 0.001), and 1 and 9 (*p* = 0.009) (Table 4).

Wilcoxon signed-rank test showed that the  $\text{HCO}_3^-$  prescription diverged more in each time point from the 32 mmol/L defined as standard, as showed in Table 5.

We also found that throughout time the serum  $\text{HCO}_3^-$  approached the reference serum  $\text{HCO}_3^-$  (23 mmol/L) that we have defined as ideal, while the  $\text{HCO}_3^-$  prescription differed more each time point from the 32 mmol/L defined as standard (at time point 9, *t* = -4.732, *p* = 0.001).

Throughout time, the blood  $\text{HCO}_3^-$  approached the reference blood  $\text{HCO}_3^-$  level (23 mmol/L) that we have defined as ideal. Initially the serum  $\text{HCO}_3^-$  was significantly higher by a mean of 1.92, 95% CI [1.25; 2.59],

**Table 2**  $\text{HCO}_3^-$  prescription frequency at time point 9

$\text{HCO}_3^-$ prescription (mmol/L)	Frequency (n)	Percentage
34	1	3
32	3	10
30	2	6
28	18	58
26	5	16
24	2	6

**Table 3** Bicarbonate prescription, laboratory findings, and dialysis efficiency through time

	HCO <sub>3</sub> <sup>-</sup> prescription (mmol/L)	Serum HCO <sub>3</sub> <sup>-</sup> (mmol/L)	Serum pH	Serum Ca <sup>2+</sup> (mmol/L)	Serum P <sup>+</sup> (mmol/L)	Serum iPTH (pg/mL)	Albumin (g/dL)	CRP (mg/dL)	Kt/V
<b>(1) Baseline</b>	32	25.92 ± 1.82	7.38 ± 0.06	8.65 ± 0.6	4.27 ± 1.22	228.2 (IQR 365.8)	3.34 ± 0.33	0.7 (IQR 1.8)	1.68 ± 0.35
<b>(2) 3 months</b>	30 (IQR 2)	24.99 ± 1.97	7.37 ± 0.07	8.75 ± 0.47	4.03 ± 1.15	277.3 (IQR 310.75)	3.3 (IQR 0.6)	0.9 (IQR 1.5)	1.61 ± 0.31
<b>(3) 6 months</b>	30 (IQR 2)	24.64 ± 2.21	7.38 ± 0.48	8.7 (IQR 0.6)	3.9 ± 1	339.15 ± 206.52	3.33 ± 0.37	0.35 (IQR 1.5)	1.67 ± 0.36
<b>(4) 9 months</b>	28 (IQR 2)	24.35 ± 1.64	7.315 (IQR 0.06)	8.8 (IQR 0.4)	3.75 ± 1.05	199.5 (IQR 244.7)	3.29 ± 0.46	0.4 (IQR 1.95)	1.61 ± 0.29
<b>(5) 12 months</b>	28 (IQR 2)	23.72 ± 2.21	7.37 ± 0.07	8.71 ± 0.52	3.71 ± 1.24	145.3 (IQR 165.9)	3.37 ± 0.36	0.5 (IQR 0.9)	1.34 ± 0.29
<b>(6) 15 months</b>	28 (IQR 0)	22.44 ± 1.79	7.36 ± 0.07	8.76 ± 0.44	3.91 ± 1.07	209.51 ± 133.235	3.32 ± 0.33	0.5 (IQR 1.15)	1.61 (IQR 0.69)
<b>(7) 18 months</b>	28 (IQR 0)	22.85 ± 1.89	7.38 ± 0.09	8.73 ± 0.21	3.85 ± 1.02	160.3 (IQR 180.6)	3.5 ± 0.31	0.4 (IQR 1.05)	1.73 ± 0.4
<b>(8) 21 months</b>	28 (IQR 0)	23.16 ± 1.4	7.36 ± 0.05	8.8 (IQR 0.4)	3.78 ± 1.22	153.5 (IQR 178.6)	3.45 (IQR 0.52)	0.7 (IQR 1.2)	1.74 ± 0.39
<b>(9) 24 months</b>	28 (IQR 0)	23.4 ± 1.98	7.37 ± 0.07	8.9 (IQR 0.5)	3.68 (IQR 0.9)	181.5 (IQR 243.2)	3.45 (IQR 0.52)	0.5 (IQR 0.7)	1.72 ± 0.37

Note: Continuous variables were presented as mean and standard deviation, or median and interquartile range (IQR) for variables with skewed distributions CRP C-reactive protein, IQR interquartile range

than the value defined as ideal. Lastly, at time point 9, there was no statistically significant mean difference (-0.6, 95% CI [- 1.33; 0.13], *t*(30) = - 1.684, *p* = 0.103).

HCO<sub>3</sub><sup>-</sup> in time point 1 showed a negative correlation with P<sup>+</sup> (*r* = - 0.45, *p* = 0.012) and iPTH (*r<sub>s</sub>* = - 0.47, *p* = 0.014), and a positive correlation with age (*r* = 0.45, *p* = 0.011) at the same time point. At the other time points, there was no correlation with those variables.

**Discussion**

Sajgure et al. conducted a study about the effect of oral HCO<sub>3</sub><sup>-</sup> supplementation in HD patients in correcting metabolic acidosis and its nutritional influence. They reported significant improvements in serum HCO<sub>3</sub><sup>-</sup> and albumin levels after treatment with adequate dosage of

oral sodium bicarbonate supplementation. The improvement in metabolic acidosis was also associated with improvement in nutrition and the clinical and biochemical markers of nutrition [11].

Bozikas et al. study aim was to compare the effect of higher doses of HCO<sub>3</sub><sup>-</sup> based dialysate vs. standard HCO<sub>3</sub><sup>-</sup> bath plus oral bicarbonate therapy [8]. Their observations concluded that increasing the HCO<sub>3</sub><sup>-</sup> in bath results in more prominent post-dialysis alkalemia, however, it is not sufficient to maintain acid-base status during the interdialytic period. Oral HCO<sub>3</sub><sup>-</sup> supplement at a dose of 5 g/day (divided in three daily doses) results in a more balanced acid-base status, avoiding post-dialysis alkalemia. Their conclusion was that the ideal scenario for optimal acid-base management in maintenance HD

**Table 4** Repeated measures ANOVA with a Tukey-Kramer correction

HCO <sub>3</sub> <sup>-</sup> prescription/time	<i>p</i> = 0.0001
Time point 1 to 2	-
Time point 1 to 3	<i>p</i> = 0.606
Time point 1 to 4	<i>p</i> = 0.313
Time point 1 to 5	<i>p</i> = 0.153
Time point 1 to 6	<i>p</i> = 0.002
Time point 1 to 7	<i>p</i> = 0.002
Time point 1 to 8	<i>p</i> = 0.001
Time point 1 to 9	<i>p</i> = 0.009

**Table 5** Wilcoxon signed rank test

Time point	Median score	Z	<i>p</i>
T 1	32	-	-
T 2	30	- 4.58	0.001
T 3	30	- 4.54	0.001
T 4	28	- 4.65	0.001
T 5	28	- 4.56	0.001
T 6	28	- 4.78	0.001
T 7	28	- 4.72	0.001
T 8	28	- 4.68	0.001
T 9	28	- 4.73	0.001
T time point			

patients includes a multifaceted approach of oral and individualized delivery of  $\text{HCO}_3^-$ , instead of a unit-wide prescription that is infrequently changed [8].

In our study,  $\text{HCO}_3^-$  prescription and serum  $\text{HCO}_3^-$  were not influenced by comorbidities like diabetes mellitus and hypertension. Laboratory values like iPTH and  $\text{P}^+$  were correlated with serum  $\text{HCO}_3^-$ , but  $\text{Ca}^{2+}$ , albumin, and CRP were not.

## Conclusion

Our findings suggest that the standard  $\text{HCO}_3^-$  prescription of 32 mmol/L should be rethought, as an individualized  $\text{HCO}_3^-$  prescription could be beneficial for the patient. At this time, we suggest that a prescription of 28 mmol/L should be the new standard.

However, the limitations of our findings include the small sample size. Therefore, further studies with larger samples should be attempted and should assess the correlation between the tight control of bicarbonate with the potential clinical benefits and patient outcomes.

## Abbreviations

$\text{Ca}^{2+}$ : Calcium; CI: Confidence interval; CKD: Chronic kidney disease; CRP: C-Reactive protein; ESRD: End-stage of renal disease;  $\text{HCO}_3^-$ : Bicarbonate; HD: Hemodialysis; iPTH: Intact parathyroid hormone; IQR: Interquartile range;  $\text{P}^+$ : Phosphorus

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## Authors' contributions

All authors approved the final version for publication and take responsibility for its accuracy and integrity. Each author participated actively in the elaboration of the manuscript: I, Rita Valério Alves, was responsible for the conception, analysis, and interpretation of data as well as drafting the article; Hernâni Gonçalves revised the article; Karina Lopes, Flora Sofia, and Ana Vila Lobos provided intellectual content of critical importance to this work.

## Authors' information

Not applicable

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the participants.

## Consent for publication

Not applicable

## Competing interests

All authors have declared that there are no competing interests.

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