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Research Article

The Prevalence of Metabolic Acidosis in Patients with Different Stages of Chronic Kidney Disease: Single-Centre Study

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Keywords
Metabolic acidosis · Chronic kidney disease

Abstract
Background: Metabolic acidosis (MA) is one of the most common consequences of CKD. MA is also a risk factor of CKD progression and increased mortality in these patients. ***Aim:*** The aim of this retrospective, cross-sectional study was to assess the prevalence of MA in different stages of CKD and renal replacement therapy (RRT) modalities – haemodialysis (HD) and peritoneal dialysis (PD). Additionally, the relationship between the prevalence of MA and aetiology of kidney disease was analysed. ***Methods:*** One thousand five patients in different stages of CKD, or modalities of RRT were enrolled into this single-centre cross-sectional study. Forty-one patients were ruled out because of oral bicarbonate supplementation. In the remaining 964 patients (698 CKD stages 1–5, 226 HD, 40 PD), venous blood HCO_3^- concentration, as well as serum Cr and urea concentrations were assessed. MA was diagnosed when blood HCO_3^- concentration was below 22 mmol/L. ***Results:*** The prevalence of MA increased among all stages of CKD. Patients on HD had lower prevalence of MA in comparison with CKD 5 patients with no RRT (38.5 vs. 56.0%; $p = 0.02$) In PD patients, the prevalence of MA was significantly lower than in HD patients (2.5 vs. 38.5%; $p < 0.001$). In the whole study group, there were no significant differences in the prevalence of MA between different aetiologies of CKD (glomerulonephritis 24%, hypertension 23%, diabetes 25%, and tubule-interstitial diseases 24%). Also, when only patients in stages CKD 3–5 were compared, no significant differences in the prevalence of acidosis were found (glomerulonephritis 28%, hypertension 22%, diabetes 24%, and tubule-interstitial 21%). ***Conclusions:*** (1) MA is more frequent in patients with more advanced stages of CKD. (2) RRT reduces the prevalence of MA. (3) In PD patients, MA is rare. (4) Aetiology of CKD seems not to have a significant impact on MA prevalence.

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Introduction

Metabolic acidosis (MA) is among the most common consequences of CKD. The main pathomechanism involved in the development of MA in patents with CKD is the reduced ability of reabsorption of the filtered bicarbonate with concomitant impairment in synthesis of sufficient bicarbonate quantity. As a consequence, failure to neutralize the net endogenous acid load occurs.

The results of studies conducted so far reveal the importance of MA in the etiopathogenesis of the increased morbidity and mortality of CKD patients [1]. There is growing evidence that chronic MA in patients with CKD may cause various adverse effects such as increased parathyroid hormone synthesis and bone resorption, with inhibition of its formation [2]. MA may also contribute to the altered glucose metabolism [3, 4] and to increased protein catabolism, which lead to the development of the MIA (malnutrition – inflammation – atherosclerosis) syndrome [5, 6] and sarcopenia [7, 8]. Moreover, results of multiple studies suggested that MA (with the blood bicarbonate concentration below 22 mmol/L) is an independent factor of accelerated progression of kidney disease [9–12].

It has been shown in several clinical studies that the so-called alkaline diet, as well as alkalizing agents (among others, $NaHCO_3$ and sodium citrate) could in fact postpone the progression of CKD [13–18]. This is why treatment with oral sodium bicarbonate is advised in CKD patients with concomitant MA [19].

Furthermore, some observational studies conducted in CKD patients reported that MA is linked to higher risk of mortality [20, 21]. The increase of mortality in these patients was observed when blood bicarbonate concentrations fell below 23 mmol/L [22]. This seems to imply that target blood bicarbonate concentrations in patients with CKD should be above 22–23 mmol/L.

Thus, the aim of the study was to assess the prevalence of MA in patients with different stages of CKD and with different renal replacement therapy (RRT) modalities – haemodialysis (HD) and peritoneal dialysis (PD). Additionally, the differences in the prevalence of MA depending on the aetiology of kidney disease were analysed.

Material and Methods

A total of 1,005 patients in different CKD stages were enrolled into this retrospective, cross-sectional study. From that studied population, 41 patients were ruled out from further analysis because of oral bicarbonate supplementation. In the remaining 964 patients (573 men and 391 women), peripheral venous blood gases were assessed using a potentiometric method (GEM 3500 Premier analyser – Werfen, Barcelona, Spain). MA was defined as venous blood bicarbonate concentration below 22 mmol/L. Peripheral blood morphology was assessed using the fluorescence flow cytometry method (Sysmex XT-2000I analyser; Sysmex Co., Kobe, Japan); serum Cr and urea concentration were determined using the Beckman-Coulter DxC 600 analyser (Beckman Coulter Inc., Brea, CA, USA). The eGFR was calculated according to the simplified MDRD equation.

Statistical analyses were conducted using the Statistica 10.0 PL software (StatSoft Polska, Cracow, Poland). The Shapiro-Wilk test was used to test the normality of variables, while the ANOVA test with post hoc Newman-Keuls analysis for all pairwise comparisons was used to assess the significance between the differences in quantitative variables. χ^2 test was used to assess the differences in qualitative variables and to compare their distribution (after previous normalization due to the differences in sample sizes of different CKD aetiologies). Correlation coefficients were calculated according to Pearson. As correlation analyses may sometimes

Table 1. Basic characteristics of the studied subgroups

CKD stage/ RRT modality	Gender: female/male	Age, years	Mean eGFR (MDRD), mL/min/1.73 m^2
CKD 1	13/16	42.8 (38.1–47.6)	111.4 (103.4–119.6)
CKD 2	54/89	47.9 (45.6–50.2)	72.6 (70.9–74.3)
CKD 3	141/204	53.0 (51.5–54.7)	43.6 (42.7–44.6)
CKD 4	60/72	53.8 (51.4–56.2)	22.5 (21.6–23.4)
CKD 5	16/34	53.7 (49.6–57.9)	11.1 (10.2–12)
HD	94/132	56.3 (54.1–58.5)	n/a
PD	14/26	50.1 (44.9–55.3)	n/a

RRT, renal replacement treatment; HD, haemodialysis; PD, peritoneal dialysis; eGFR, estimated glomerular filtration rate; n/a, not applicable.

Table 2. Aetiology of CKD in different stages of the disease and dialysis modalities

Aetiology of CKD	Number of patients in different stages of CKD/RRT modality							
	1	2	3	4	5	HD	PD	Total (*N*/%)
Unknown	2	11	38	10	1	10	2	74/8
Glomerulonephritis	20	83	130	46	18	59	21	377/39
Hypertension	1	10	59	31	16	54	1	172/18
Diabetes	2	21	56	28	6	50	8	171/18
ADPKD	0	1	5	1	2	12	2	23/2
Tubulointerstitial nephritis	1	2	11	3	0	10	0	27/3
Othera	3	14	46	13	7	31	6	120/13

RRT, renal replacement therapy; ADPKD, autosomal dominant polycystic kidney disease. [a] Among others: congenital abnormalities, nephrectomies (neoplasms and trauma), iatrogenic (i.e., chemotherapy or others).

reveal just incidental relations, further analyses of univariate regression were conducted to emphasize the causative relation between the variables. The data are presented as means with 95% confidence intervals. Differences were considered significant when $p < 0.05$.

Results

The aetiology of CKD and other demographical data are summarized in Tables 1, 2 and 3. For further analyses, the cohort has been divided into 7 subgroups according to the stage of CKD and dialysis modality.

The venous blood HCO_3^- concentration in CKD 1 patients was significantly higher than in patients in CKD stages 3, 4, and 5, as well as patients on prevalent HD. It was not significantly different than in CKD 2 patients and patients on PD. Similarly, CKD patients had higher blood HCO_3^- concentrations than patients in stages 3–5 and HD patients, but no different than CKD or PD patients. Blood HCO_3^- concentration gradually and significantly decreased among all the stages of CKD and was significantly the lowest in CKD 5 patients not receiving any RRT. HD patients had significantly higher blood HCO_3^- concentration than CKD 5 patients with no RRT, significantly lower than CKD 3 patients and no different than CKD 4 patients. PD patients

Table 3. Prevalence of MA depending on stages and aetiology of CKD – non-dialysed patients

Aetiology of CKD	Stage of CKD					
	1	2	3	4	5	Total (*N*/%])
Unknown	0/2	0/11	4/38	6/10	0/1	10/62 (16)
Glomerulonephritis	3/20	5/83	27/130	17/46	11/18	63/297 (21)
Hypertension	0/1	1/10	5/59	9/31	8/16	23/117 (20)
Diabetes	0/2	2/21	8/56	11/2	3/6	24/113 (21)
ADPKD	0/0	0/1	2/5	0/1	2/2	4/9 (44)
Tubulo-interstitial nephritis	0/1	0/2	2/11	1/3	0/0	3/17 (18)
Othera	0/3	0/14	10/46	7/13	4/7	21/83 (25)

ADPKD, autosomal dominant polycystic kidney disease; MA, metabolic acidosis. [a] Among others: congenital abnormalities, nephrectomies (neoplasms and trauma), iatrogenic (i.e., chemotherapy or others).

Table 4. Blood bicarbonate concentration differences in the studied subgroups

CKD stage/ RRT modality	Blood HCO_3^- concentration, mmol/L	Blood HCO_3^- concentration		
		higher than ($p < 0.05$)	lower than ($p < 0.05$)	no different than ($p < 0.05$)
CKD 1	27.1 (25.8–28.5)	CKD 3, CKD 4, CKD 5, and HD	–	CKD2 and PD
CKD 2	26.3 (25.8–26.8)	CKD 3, CKD 4, CKD 5, and HD	–	CKD1 and PD
CKD 3	24.7 (24.3–25.1)	CKD 4, CKD 5, and HD	CKD 1, CKD 2, and PD	
CKD 4	23.2 (22.5–23.9)	CKD 5	CKD 1, CKD 2, CKD 3, and PD	HD
CKD 5	21.7 (20.5–22.9)	–	CKD 1, CKD 2, CKD 3, CKD 4, HD, and PD	–
HD	22.8 (22.3–23.2)	CKD 5	CKD 1, CKD 2, CKD 3, and PD	CKD 4
PD	27.0 (25.8–28.2)	CKD 3, CKD 4, CKD 5, and HD	–	CKD 1 and CKD 2

RRT, renal replacement treatment; HD, haemodialysis; PD, peritoneal dialysis.

had significantly higher bicarbonate concentrations than patients in CKD 3, 4, 5, or HD patients, and it was no different from the patients in the earliest stages of CKD. The exact values of venous blood HCO_3^- concentrations and the relation between them are presented in Table 4.

Blood haemoglobin concentration in CKD 1 patients was 13.2 (12.4–13.9) g/dL and was not significantly different than the blood haemoglobin concentration in CKD 2 patients – 13.5 (13.2–13.8) g/dL; $p = 0.09$. On the other hand, CKD 3, CKD 4, and CKD 5 patients were characterized by a gradual significant decrease ($p < 0.05$ between every possible combination of CKD stages) in blood haemoglobin concentration – 12.9 (12.7–13.1); 11.2 (10.8–11.6) and 10.1 (9.7–10.6) g/dL. There were no significant differences observed between the haemoglobin concentration of PD and HD patients – it was 10.6 (10.4–10.8 g/dL) and 10.6 (10.1–11.1) g/dL, respectively; $p = 0.61$.

Nevertheless, a significant difference was observed between the percentage of PD and HD patients requiring treatment with erythropoiesis stimulating agents (ESAs) – 30 and 77%, respectively; $p < 0.001$. Also the mean ESAs dose was significantly ($p < 0.001$) lower in PD than in HD patients, 2,158 (777–3,539) and 6,017 (5,323–6,710) units, respectively.

MA was diagnosed in 234 out of 964 enrolled patients (24%). The prevalence of MA varied depending on the CKD stage and/or dialysis modality (Table 5) and was significantly more frequent in each consecutive stage of CKD except CKD 1 and 2, where no significant

Table 5. Prevalence of MA in different stages of CKD

Stage of CKD	Prevalence of MA, %	*p* value	*p* value
CKD 1	10.3		
CKD 2	5.6	0.34	
CKD 3	16.2		0.025
CKD 4	38.9	<0.001	
CKD 5– no RRT	56.0		0.038
HD	38.5	0.023	
PD	2.5		<0.001

MA, metabolic acidosis; RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis.

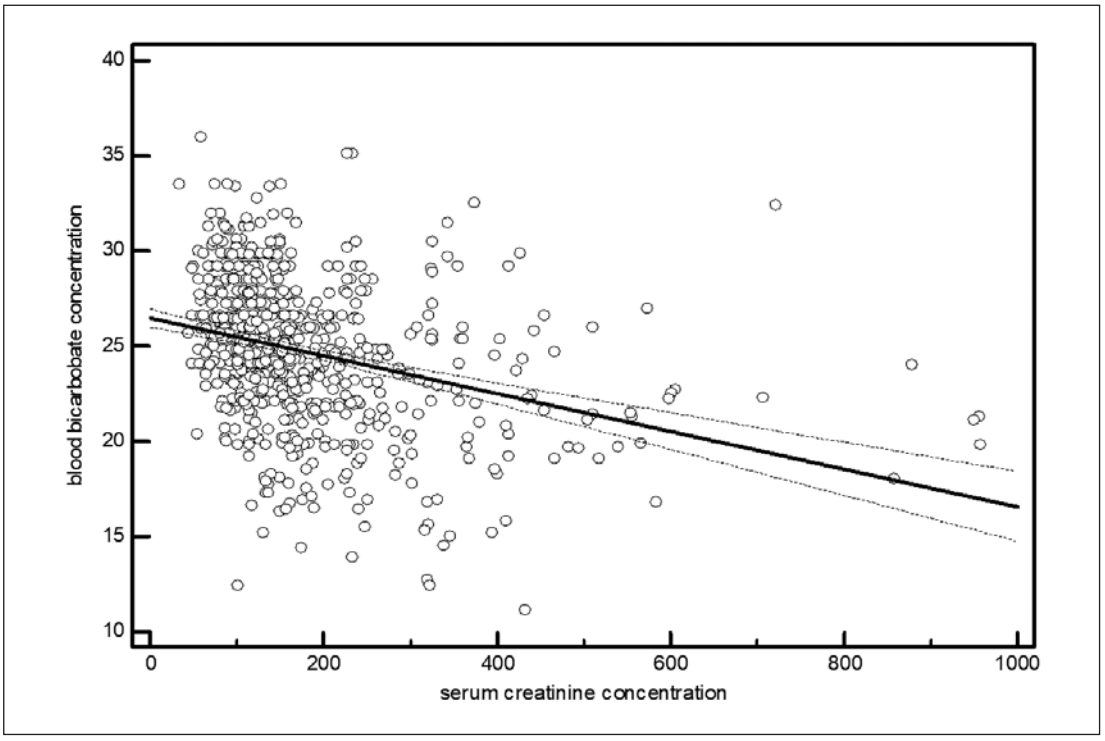

Fig. 1. Correlation between serum Cr concentration and blood bicarbonate concentration in non-dialysed patients with CKD.

difference was found. The trend for the higher prevalence of MA across the stages of CKD was also highly significant, with *p* reaching <0.001.

Interestingly, patients in stage 4 of CKD had the same prevalence of MA as patients on maintenance HD. Moreover, there was a striking difference ($p < 0.001$) between the prevalence of MA in RRT patients depending on the dialysis modality. Patients on PD were less likely to have MA than HD patients. In fact, there was no significant difference in the prevalence of MA in PD patients in comparison to patients in stage 1 or 2 of CKD ($p = 0.73$ and $p = 0.15$, respectively).

There was a significant inverse correlation between the serum Cr concentration and the venous blood bicarbonate concentration ($R = -0.29$; $p < 0.0001$) in patients not receiving RRT (Fig. 1). Similarly, a significant positive correlation ($R = 0.32$; $p < 0.0001$) between the blood

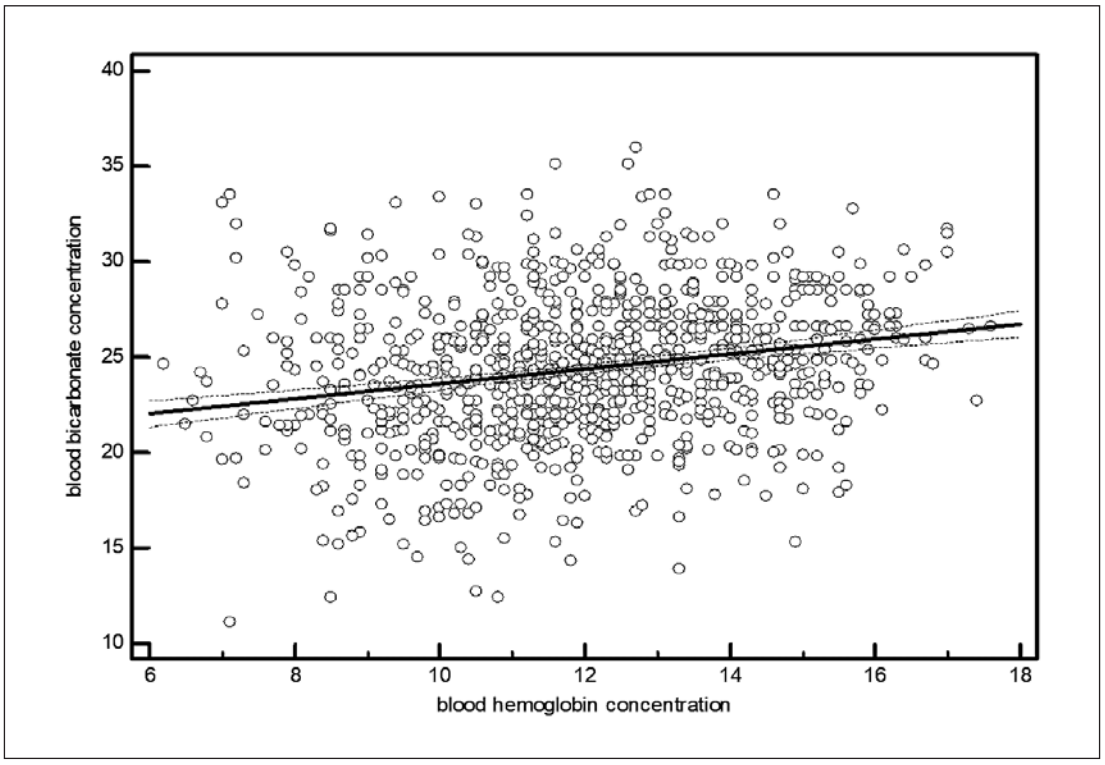

Fig. 2. Correlation between blood haemoglobin concentration and blood bicarbonate concentration in non-dialysed patients with CKD.

bicarbonate concentration and eGFR was found. Both of these relations were found causative in the univariate regression analyses (R^2 = 0.08; p < 0.001 and R^2 = 0.1; p < 0.001, respectively). Moreover, a significant correlation was found between the blood HCO_3^- concentration and blood haemoglobin concentration (R = 0.20; p < 0.0001) and was confirmed in the univariate regression (R^2 = 0.04; p < 0.001 – Fig. 2).

In the RRT patients (both HD and PD together), there was a significant inverse correlation between the blood bicarbonate concentration and the ESAs dose (R = −0.28; p < 0.0001), which was confirmed in the regression analyses (R^2 = 0.08; p < 0.0001). In HD patients alone, a significant inverse correlation was found between the blood bicarbonate concentration and the serum urea concentration before dialysis (R = −0.15; p = 0.018), which was also confirmed in the univariate regression (R^2 = 0.023; p = 0.019).

As far as the impact of kidney failure aetiology on MA prevalence is concerned, in the whole study group, there were no significant differences found (glomerulonephritis 24% MA prevalence, hypertension 23%, diabetes 25%, and interstitial diseases 24%). Nevertheless, the distribution of the frequency of CKD stages was not normal. Therefore, RRT patients were discarded from the comparison as the influence of RRT itself could be a confounder. Also, patients in CKD stages 1 and 2 were discarded. The distribution of the remaining patients was similar, so after normalization for the number of patients in each group, the calculations were redone. Still, no significant differences in the prevalence of acidosis were found (glomerulonephritis 28%, hypertension 22%, diabetes 24%, and interstitial diseases 21%).

Discussion

In this cross-sectional study, the prevalence of MA in a large population of patients in different stages of CKD was analysed. Overall, MA was diagnosed in 24% of the enrolled patients, which seems to be quite more frequent than in a study by Raphael et al. [22] who analysed patients from the CRIC (Chronic Renal Insufficiency Cohort) Study. This discrepancy may be explained by the different approach in patient enrolment. In our study, patients in CKD stages 1–5 as well as RRT patients were analysed, while Raphael et al. [22] studied CKD stages 2–4 patients. On the other hand, MA in our study was significantly less frequent than in an article by Harambat et al. [23], who reported a 43% prevalence of MA in children with CKD stage 3, 61% in CKD stage 4, and 45% in CKD stage 5 (together RRT and non-RRT children), In our study, the prevalence of MA was 16, 39, and 37%, respectively. This is probably due to a higher tendency of acidosis development in children due to the higher amount of protein in diet (especially in adolescents) and more frequent kidney dysplasia, with more pronounced tubule-intestinal damage causing a considerable decrease in HCO_3^- synthesis.

In a study by Skiba et al. [24], a 12% prevalence of MA in kidney allograft recipients was found. This was significantly less than in an eGFR matched control group of CKD patients from their study (19% MA prevalence). Our results show even higher prevalence of MA in non-RRT CKD patients – 21%. This discrepancy in MA prevalence between CKD and KTx patients is also difficult to explain. Synthesis of bicarbonate occurs in the proximal tubule and to a lesser extent in the collecting duct. Available results of experimental studies in animals [25] suggest that renal denervation could prevent the inflammation and fibrosis of the kidney caused by, for example, ischemia/reperfusion injury. Thus, not innervated transplanted kidney could sustain less damage to the compartment crucial in bicarbonate synthesis in comparison to the native kidneys.

What is more, there is a huge discrepancy in the reported prevalence of MA after KTx in studies conducted so far. In a comprehensive meta-analysis done by Mesa et al. [26], it varied from 13 to 40% (when MA was diagnosed with blood bicarbonate concentration <22 mmol/L). It has to be stressed though, that there is a significant difference in the prevalence of MA after KTx depending on the time elapsed after the procedure, which was recently shown by Schulte et al. [27]. In their study, the prevalence of MA decreased after KTx and reached 13% 1 year after the surgery, which is consistent with the results published by Skiba et al. [24] who analysed patients >2 years after KTx.

Results of the current study confirmed that MA is more frequent in the advanced stages of CKD. This is in agreement with previous studies concerning this issue [5, 6]. However, we did not observe significant differences in the prevalence of MA between patients with different CKD aetiology. Different results have been obtained by Caravaca et al. [28] who have shown that MA seems to be less frequent in patients with diabetic nephropathy. These discrepancies are difficult to explain, but might be caused by just an incidental finding in the aforementioned article. They have studied 113 patients, among them, 33 were with diabetic nephropathy, while our group consisted of 964 patients in which 171 had diabetic nephropathy. Also, in their study, patients with diabetic nephropathy had significantly better eGFR than the other CKD patients.

We did observe a striking difference in MA prevalence between patients on HD and PD. Similar results were obtained by Goutham et al. [29]. However, our results cannot be directly compared because of a lot of patients receiving suboptimal RRT in the quoted study. Still, our study underlines the fact that even in a regularly dialysed patient population, patients on PD have higher plasma bicarbonate concentration and lower prevalence of MA in comparison to patients on HD.

In our cohort, a significant decrease in blood haemoglobin was observed among all the stages of CKD – the blood haemoglobin concentration was consistently the lowest among non-dialysed patients in CKD stage 5. This is not surprizing, and it is in agreement with the results of many studies conducted so far. What seems to be more important is that there was a significant inverse correlation between the blood bicarbonate concentration and ESAs dosage in RRT patients, as well as a significant inverse concentration between blood bicarbonate and haemoglobin concentration in non-RRT CKD patients. As these relations were confirmed in regression analyses, it seems that they are not coincidental. This underlines the importance of MA in the development of anaemia in CKD patients. Similar results have been obtained by other authors [30, 31]. Nevertheless, it should be underlined that the exact relationship between anaemia and MA in CKD patients should be studied in future interventional trials aimed to establish, whether more aggressive correction of MA is needed in RRT patients.

Our article has some limitations. The main drawback is the retrospective, cross-sectional character of the study not allowing to fully exclude the possibility of incidental character of observed correlations, although significant dependencies obtained in regression analyses seem to minimize that risk. Also, we did not assess the use of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), or mineralocorticoid receptor antagonists in our studied group. These medications can be associated with suppressing bicarbonate synthesis and acid excretion [32]. However, it seems that the impact of the above-mentioned medications is rather modest, as it was shown by, for example, Raphael et al. [33]. In their study, there was no significant association between the use of ACE-I or angiotensin receptor blockers and the odds of serum bicarbonate <22 mmol/L (only between the coefficients of Δ serum bicarbonate and the use of the aforementioned compounds). Moreover, it was not possible to retrospectively assess our patients' diet, which might be a confounder in the interpretation of our results.

Still, the results of our study seem to imply that in a quite large group of patients, MA is more frequent in the more advanced stages of CKD. RRT reduces the prevalence of MA in general; however, there are some significant differences in the prevalence of MA and bicarbonate concentration depending on the RRT method. Aetiology of CKD seems not to have a significant impact on MA prevalence.

Statement of Ethics

As this was a retrospective study involving only analyses of laboratory measurements and no additional samples from the patients were obtained, nor additional tests conducted, the Medical University of Silesia Ethics Committee decided that Ethics Committee agreement and patients' written consent are not mandatory.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

P.K. was responsible for the gathering of data, data analysis, and the writing of the manuscript. D.C.-M. was responsible for the gathering of data and the writing of the manuscript. B.O. was responsible for the gathering of data. A.H. was responsible for the gathering of data. A.W. was responsible for data analysis and the correction of the manuscript. M.A. came up with the idea of the study and was responsible for data analysis and the correction of the manuscript.

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