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Metabolic Acidosis and Cardiovascular Disease in Patients on Peritoneal Dialysis

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Abstract

Backgroud: Metabolic acidosis, a common condition particularly in end stage renal disease patients, results in malnutrition and inflammation. In this study, we focused on the importance of metabolic acidosis on manifestations of cardiovascular disease in patients on peritoneal dialysis.

Methods: We studied 20 patients on continuous ambulatory peritoneal dialysis (CAPD), 15 males and 5 females, on mean age 61.6 ±11.3 years old. Metabolic acidosis was determined by serum bicarbonate concentrations less than 22mmol/L, which were measured in gas machine. Dialysis adequacy was defined by total Kt/V/week for urea including peritoneal Kt/V for urea and residual GFR (ml/min/1.73m^2). High sensitivity C-reactive protein (hsCRP) was measured using enzyme linked immunoabsorbed assay (ELISA). The concentrations of intact-parathormone (i-PTH) and beta2-microglobulin (beta2M) were measured by radioimmunoassays. Arterial stiffness was measured as carotid-femoral pulse wave velocity (c-f PWV) and augmentation index (AIx). We built a Cox regression analysis to predict coronary artery disease (CAD), congestive heart failure (CHF) and peripheral vascular disease (PVD).

Results: Serum bicarbonate levels were inversely associated to beta2M, i-PTH and AIx (r=-0.451, p=0.04, r=-0.477, p=0.03 and r=-0.569, p=0.009 respectively). Cox- regression analysis revealed significant association of serum bicarbonate levels and PVD having as confounders traditional and specific for these patients risk factors.

Conclusion: Metabolic acidosis may be an independent risk factor for arterial stiffening and peripheral vascular disease manifestation in patients on peritoneal dialysis.

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Running title: metabolic acidosis as a risk factor in peritoneal dialysis

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Introduction

Metabolic acidosis, which is defined by low serum bicarbonate concentrations, is common in end-stage renal disease (ESRD) and is considered an important cause of many metabolic consequences including inflammation, bone disease, oxidative stress and protein-energy wasting [1,2]. The caused by metabolic acidosis disturbancies may contribute to the increased morbidity and mortality in patients on maintenance dialysis.However, the underlying pathophysiological mechanisms for adverse outcomes in patients with low serum bicarbonate level are still unclear.

Additionally, the optimal bicarbonate level to avoid unfavorable clinical outcomes has been not determined yet [3,4]. A recent study has suggested maintaining of serum bicarbonate >22mmol/L for all ESRD patients.Such a value was considered a complete correction of metabolic acidosis, irrespectively to dialysis modality [3]. Peritoneal dialysis, an established treatment modality in ESRD patients, may be more effective in correcting of metabolic acidosis than intermittent hemodialysis, due to the continous provision of peritoneal dialysis treatment. However, a few studies have examined the relationship between serum bicarbonate level and cardiovascular risk and death in dialysis patients.

In this study, we focused on the importance of metabolic acidosis on manifestations of cardiovascular disease in patients on peritoneal dialysis.

Methods

Patients

This is a cross-sectional study of a cohort of 20 peritoneal dialysis (PD) patients, 15 males and 5 females, on mean age 61.6 ±11.3 years old. The data collection became during a time of 60 months, from the 1st of July of 2007 until the end of June of 2012.

The mean time on peritoneal dialysis was 2.8 ± 1.61 years.

We excluded patients < 18 years of age at initiation of PD, patients that had less than 6 months of follow-up and those with autoimmune diseases, infections or malignancy. Also, patients who had been on hemodialysis or received a kidney transplant before the initiation of PD and patients that started PD for other reasons, such as congestive heart failure or acute renal failure, were excluded from the study. All patients underwent urea kitenic analysis including residual renal function and peritoneal equilibration test (PET) for definition of peritoneal membrane categorization [5] every three months of PD initiation.

According to PET, we prescribed the treatment dose and we enrolled in the study patients who were exclusively following continuous ambulatory peritoneal dialysis (CAPD) with 4 changes per day using a combination of 2 changes of 2 L of hypertonic glucose -based solution (3.86% glucose;Baxter Healthcare) and 2 changes of 2 L of semi-hypertonic glucose solution (2.5% glucose; Ariti; Bieffe Medital S.p.A.). Dialysis dose defined according to the formula of Daugirdas by total Kt/V/week for urea including peritoneal Kt/V urea and residual GFR (ml/min/1.73m^2) [6].The patients, who had Kt/V/week for urea < 1.7 were excluded from our study.We used peritoneal liquids in dual backs with a final concentration of bicarbonate equal to 37.5 mmol/L.

The enrolled patients were in a good hydration status, they did not have interdialytic peripheral oedema, high blood pressure, interdialytic orthostatic hypotension or other characteristics of an inaccurate dry body weight.However, patients with pre-dialysis blood pressure ³160/90 (n=11, a ratio of 55%) were considered hypertensive, or if they were receiving anti-hypertensive drugs.2 of the studied patients were current smokers (a ratio of 10%).

At start of study, cardiovascular disease was defined as presence of coronary artery disease (CAD, n=5, 25%), congestive heart failure with an ejection fraction <50% (CHF, n=4, 20%) and peripheral vascular disease (PVD, n=8, 40%). The coronary syndrome was documented by history of myocardial infarction, coronary artery angioplasty or bypass surgery, or clinical signs of angina pectoris.Also, the first and the current cardiovascular events during the study were written down as one event for the studied cardiovascular manifestations.

14 of including in study patients excreted up to 100 ml of urine per day. Calcium channel blockers, beta-blockers or inhibitors of angiotensin II receptors were included in the receiving medications by our patients. Nobody of the enrolled patients received diuretic drugs.Some of the our patients were receiving statin and only calcium-free phosphate binders were prescribed. All of the studied patients were on erythropoetin-a or-β therapy.

The underling renal diseases were hypertensive nephrosclerosis (n=6, 30%), chronic glomerulonephritis (n=5, 25%), polycystic kidney disease (n=3, 15%), diabetic nephropathy (n=4, 20%), and other/unknown (n=2, 10%).

Approval and Consent

The study was approved by the ethics committee of the Hospital "Laiko, University General Hospital of Athens" .Written informed consent was obtained from all subjects.

Blood Collection

Blood samples were obtained by venipuncture in the patients in a twelve hours fasting state during an regular appointment in our Peritoneal Unit. Samples were centrifuged immediately, serum was separated and processed for various assays.

In each subject, three sequences of samples (every month within 3 months) were received for the serum bicarbonate measurements, and their average was used for statistical analysis.The low serum bicarbonate level was considered in combination to low arterial pH (acidemia) and decreased PCO_2.

Laboratory Measurments

Albumin, calcium (Ca) corrected for the albumin levels, phosphate (P), high density lipoproteins (HDL) and low density lipoproteins (LDL) were measured by biochemical analysis and hemoglobin values were also measured. The ratio of LDL / HDL was calculated.

High sensitivity C-reactive protein (hsCRP) and oxidized LDL (ox-LDL) serum concentrations were measured using enzyme linked immunoabsorbed assays (ELISA, Immundiagnostik AG., Germany and Immundiagnostik AG. Stubenwald-Allee, Bensheim respectively) according to manufacturer's specifications.

The concentrations of intact-parathormone (i-PTH) and beta2-microglobulin (beta2M) were measured by radioimmunoassays (CIS bio international/France and Immunotech by Beckman, Czech Republic respectively).

Metabolic acidosis was defined by serum bicarbonate concentrations less than 22.0mmol/L, which were measured in gas machine (Roche, combas b 121) taking care of the blood specimens [7].

Normalized protein catabolic rate for dry body mass (nPCR) was calculated from the urea generation rate [8].Body mass index (BMI) was obtained from height and post-dialysis body weight.

Haemodynamic Measurements

Predialysis peripheral systolic and diastolic blood pressures (SBP and DBP respectively) in enrolled patients were calculated as the mean of 10 measurements during a treatment month using an automatic sphygmomanometer OMRON M4-I (Co Ltd Kyoto Japan). Mean peripheral pre-dialysis BP (MBP) was calculated as: MBP = DBP + 1/3 (SBP - DBP).

Electrocardiographical analysis and M-mode echocardiography were performed the day after dialysis with an Hewlett Packard SONOS 2500 using a 2.25 MHz transducer to estimate the ejection fraction and the ischaemic findings according to the recommendations of the American Society of Echocardiography [9].

Arterial stiffness was measured as carotid-femoral pulse wave velocity (c-f PWV) and carotid augmentation index (AIx) using the SphygmoCor system® (AtCor Medical Pty.Ltd, Sydney, Australia).In each subject two sequences of measurements were performed, and their mean was used for statistical analysis.We recorded the carotido-femoral PWV by positioning one sensor over the right femoral artery and a second sensor over the left carotid artery.The distance between the two sensors was measured with a measuring tape, and three recordings of both pulse waveforms were performed (8-10 heart beats for each recording).The Complior software automatically detected the foot of each pulse waveform from the two arterial sites and then measured the mean distance between the two feet as being the travel time of the wave.PWV was then computed using the formula:

PWV= travel distance/travel time, as previously validated [10].

Central systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), PP, and the time of return of the reflected wave (Tr) were derived.Pressure and time of first peak (P1 and T1) and second peak (P2 and T2), and central augmented pressure (AP) were obtained.Central augmentation index (AIx) was computed (AP= P2-P1; AIx = (AP/PP) x 100) and corrected for a heart rate of 75 beats/minute.

Also, we measured the systolic pressure in both sides of the lower extremities, using a Doppler machine (Huntleigh Healthcare Ltd, UK).Ankle-brachial blood pressure index (ABPI) was calculated as the ratio of the lower values of ankle systolic pressure (pre or posttibial artery), divided by stabilized arm systolic pressure. ABPI values <0.9 were rated as low indicating peripheral vascular disease (PVD) and values up to 1.2 were rated as high.

Data Analysis

Data were analyzed using SPSS 15.0 statistical package for Windows (SPSS Inc, Chicago, Illinois) and expressed as mean ± standard deviation as our data showed normal distribution determined by Kolmogorov-Smirnov test; Differences between mean values were assessed by using Student's *t*-test. Correlations between variables were defined by Pearson and Spearman coefficient and p values less than .05 were considered significant. Because of the duration study was different in our data, correlations between categorical variables were defined by log-rank tests with Kaplan-Meier analysis.We performed a Cox- regression analysis to investigate serum bicarbonate concentrations as a possible independent predictor of the coronary artery disease (CAD), congestive heart failure (CHF) and peripheral vascular disease (PVD) during a time of 5 years, in relation to traditional and specific confounders for peritoneal dialysis patients, such as dialysis adequacy defined by Kt/V/ week for urea, serum albumin, dyslipidemia and hypertension.

Results

Demographical characteristics of the studied population at the time of inclusion are listed in table 1. In our data, 7 patients had serum bicarbonate levels less than 22mmol/L (a ratio equal to 35%).

Serum bicarbonate levels were inversely associated to beta2M, i-PTH and AIx (figure 1), (r=-0.451, p=0.04, r=-0.477, p=0.03 and r=-0.569, p=0.009 respectively).

In table 2, the differences between the groups of patients with serum bicarbonate levels more (n=13) or less (n=7) than 22mmol/L are shown.We observed that the patients with serum bicarbonate levels less than

Table 1: Demographical characteristics of studied patients, n=20.

Characteristic	Valid percent
Sex (males/females)	75 / 25
Diabetes mellitus (yes/no)	20 / 80
Hypertension (yes/no)	55 / 45
Smoking (yes/no)	10 / 90
Coronary artery disease (yes/no)	25 / 75
Congestive heart failure (yes/no)	20 / 80
Peripheral vascular disease (yes/no)	40 / 60

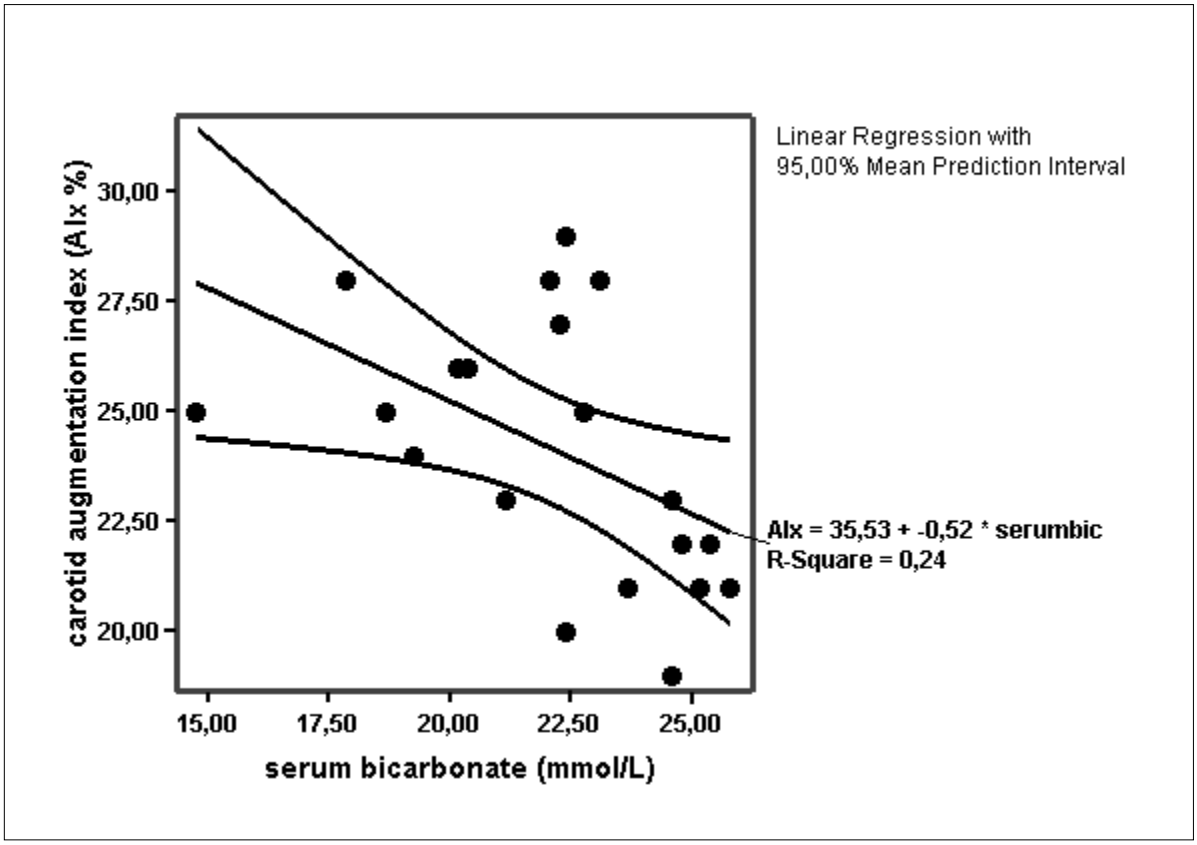

Figure 1: Association between serum bicarbonate levels and augmentation index (AIx) (r=-0.569, p=0.009).

Table 2 : Differences between groups of patients according to lower or higher than 22mmol/L serum bicarbonate levels

	Patients with serum bicarbonate less than 22mmol/L(n=7)	Patients with serum bicarbonate more than 22mmol/L (n=13)
Age (years)	67.5 ± 6.9*	58.3 ± 12
Dialysis vintage (years)	3.1 ± 1.9	2.6 ± 1.4
Total Kt /V/week for urea	1.9 ± 0.20*	2.4 ± 0.5
nPCR (g /Kg /day)	1.4 ± 0.8	1.7 ± 0.4
Urine volume (ml/day)	510.4 ± 166	537.5 ± 256.2
BMI (Kg/m^2)	29.5 ± 6.9	26.4 ± 4.6
Serum bicarbonate (mmol /L)	18.9 ± 2.1*	23.8 ± 1.33
i-PTH (pg/ml)	547.2 ± 383*	216.5 ± 142.4
Hb (gr/dl)	11.2 ± 1.7	12.01 ± 1.4
Albumin (gr / dl)	3.37 ± 0.4	3.7 ± 0.5
LDL/HDL	2.9 ± 1.7	2.5 ± 0.7
hsCRP (mg /L)	14.3 ± 4.5*	9.52 ± 5.9
oxLDL (ng/ml)	50.2 ± 5.9	47.5 ± 22.4
MBP (mmHg)	91.7 ± 16.7	97.1 ± 19.1
ABPI	1.14 ± 0.4	0.9 ± 0.2

*: $p<0.05$

22mmol/L had significantly lower dialysis adequacy defined by smaller Kt/V/week for urea, significantly higher age, hsCRP, and i-PTH, than the group of patients with serum bicarbonate levels more than 22mmol/L. Also, the patients with lower serum bicarbonate concentrations had increased beta 2M, PP, ABPI, AIx, oxLDL and BMI, but they had decreased albumin, nPCR and urine volume comparatively to the patients with higher serum bicarbonate level. In table 3 the comparison between the group of patients according to sex was shown, without any significant difference.

Kaplan-Meier analysis showed that the prevalence of the determined by lower or higher than 22mmol/L serum bicarbonate levels acidosis status on PVD manifestation, was significant (log-rank=3.9, p=0.04, hazard function in figure 2). The relationship between acidosis state and CAD or CHF was not found significant.

Cox-regression analysis revealed significant association of serum bicarbonate levels and PVD (p=0.04, OR=0.69, CI =0.5-0.98) having the dialysis adequacy defined by Kt/V/week for urea, albumin, dyslipidemia and hypertension as confounders (table 4). A such association was found non significant for CAD, either for CHF.

Discussion

In this study we observed that serum bicarbonate levels exhibited a significant inverse association with AIx, which together to pulse wave velocity is an integrated index of vascular function and structure. It estimates the arterial stiffness, which is a strong predictor of cardiovascular mortality in general population and in dialysis patients [11]. Also, in our

Table 3 : Differences between groups of patients according to sex

	Males (n=15)	Females (n=5)
Age (years)	59.7 ± 10.7	67.2 ± 12.1
Total Kt /V/week for urea	2.2 ± 0.3	2.3 ± 0.7
nPCR (g /Kg /day)	1.7 ± 0.6	1.5 ± 0.5
Urine volume (ml/day)	586.3 ± 399.4	266.6 ± 208.1
BMI (Kg/m^2)	27.4 ± 6.1	27.6 ± 3.6
Serum bicarbonate (mmol /L)	22.6 ± 2.3	20.5 ± 4.01
i-PTH (pg/ml)	290.1 ± 236.9	459.2 ± 426.7
Hb (gr/dl)	11.2 ± 1.7	11.01 ± 1.4
Albumin (gr / dl)	3.6 ± 0.5	3.6 ± 0.4
LDL/HDL	2.6 ± 1.26	2.9 ± 0.5
hsCRP (mg /L)	10.2 ± 5.7	14.2 ± 5.5
oxLDL (ng/ml)	45.4 ± 7.4	57.5 ± 35.1
MBP (mmHg)	97.7 ± 15.3	87.8 ± 25.2
ABPI	0.95 ± 0.26	1.12 ± 0.47
AIx	23.9 ± 2.9	24.8 ± 3.5
PP (mmHg)	51.7 ± 24.2	58.2 ± 29.3
Beta2-microglobulin (mg/L)	28.1 ± 7.1	30.6 ± 9.6

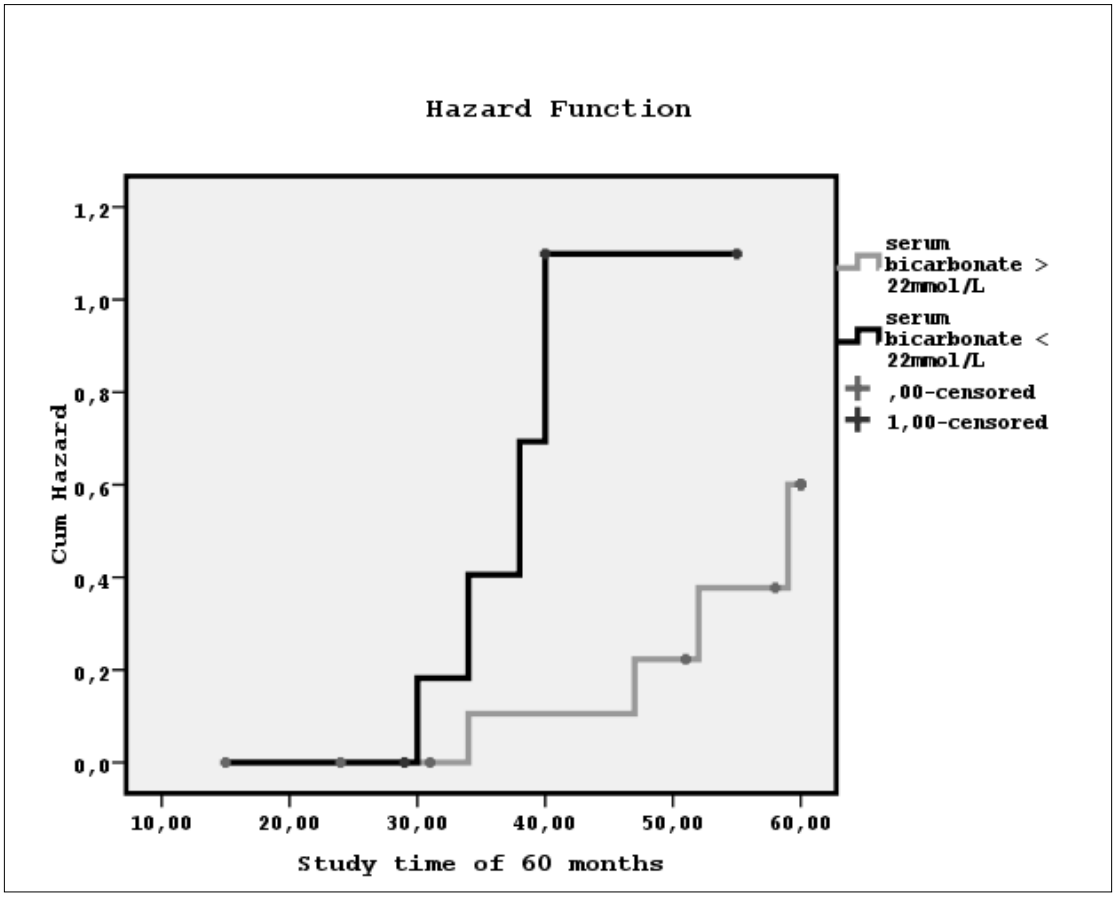

Figure 2. The prevalence of lower or higher than 22mmol/L serum bicarbonate levels on peripheral vascular disease manifestation during a follow up time of 60 months by Kaplan-Meier curve (log-rank=3.9, p=0.04).

Table 4: Cox-regression analysis for the prevalence of serum bicarbonate levels on manifestation of peripheral vascular disease adjusting for confounders.

	p-value	Odds ratio	Confidence interval
Total Kt /V for urea	0.3	0.339	0.03 – 3.29
albumin	0.9	1.04	0.08 – 13.7
LDL / HDL	0.5	0.80	0.4 – 1.57
hypertension	0.3	2.5	0.3 – 17.7
Serum bicarbonate	**0.04**	0.69	0.48 – 0.99

study the patients with low bicarbonate level had higher PP and higher ABPI, another consequences of arterial stiffening and vascular calcification.

Previously, it has been shown the positive relationship between the extent of vascular calcification and arterial stiffness and it may explain the increased cardiovascular events seen in dialysis patients [12]. Additionally, it has already been reported the role of metabolic acidosis on vascular calcification, as the mineral metabolism disturbances act through the existing metabolic acidosis in dialysis patients [13]. The influence of acidosis on vascular calcification is complicated, acting, on the one hand, as a stimulator of the solubility of Ca x P deposits and as a blocker of phosphate uptake by the arterial smooth muscle cells, so acidosis may attenuate vascular calcification [13]. But, on the other hand acidosis promotes inflammation of the arterial wall, releasing cytokines that may induce vascular calcification [14]. The final result of acidosis may be the calcification and the vascular occlusive disease particularly in patients on long dialysis vintage.

Supportingly, we observed that low bicarbonate serum concentrations were shown as an independent risk factor for manifestation of peripheral vascular disease in multivariable analysis, using the Kt/V for urea, albumin, dyslipidemia and hypertension as confounding covariates. Peripheral vascular disease is an atherosclerotic disease, that is frequently associated with coronary disease and patients with PVD are at in increased risk of myocardiac infarction and vascular death [15].

These findings support that metabolic acidosis results in detrimental effects and patients in dialysis with low bicarbonate level should be treated properly.

In the meantime, there is no consensus about the optimal bicarbonate levels in ESRD patients. In a large data from the Dialysis Outcomes and Practice Pattern Study, it has been reported that an increased risk was observed in patients with high (>27 mEq/L) or low (<17 mEq/L) bicarbonate levels [16].Another study of a data of 56,385 hemodialysis patients showed that serum bicarbonate level >22 mEq/L was associated with lower mortality risk [3, 4].

In contrast to intermittent hemodialysis, PD provides continuous dialysis, that could lead to uncommon metabolic acidosis in patients on PD. However, a few studies have addressed this issue in the PD population and they have conflicting results [3, 17]. It has been reported that the mortality risk may be similar or not when serum bicarbonate level is 22 to 24 mEq/L and when they are >24 mEq/L. In addition, according to United Kingdom recommendations a higher threshold of bicarbonate is suggested in PD patients than in hemodialysis patients. In this study, we were considered uncorrected metabolic acidosis in enrolled PD patients, when serum bicarbonate level was <22 mEq/L combined to low arterial pH and decreased PCO_2. Therefore, the low bicarbonate level may be diagnostic

of metabolic acidosis rather than of respiratory alkalosis, another clinical condition that causes decreased bicarbonate level, given the loss of buffering capacity by the kidney in ESRD.

Despite the prevalence of metabolic acidosis in PD patients has not fully explored, several studies have reported that the proportion of patients with serum bicarbonate < 22mmol/L varies widely from 10 to 25% [3,18]. It has been already postulated that performed single and delayed serum bicarbonate measurements in samples, might be responsible for the high proportion of low bicarbonate level [3].

In our study the proportion of serum bicarbonate < 22mmol/L was 35%, due may to very small sample size that led to biased results.

The underlying pathophysiological mechanisms for increased mortality and morbidity in PD patients with low serum bicarbonate levels include chronic inflammation [19] and loss of residual renal function, that has been established to be a powerfull predictor of mortality in patients on dialysis [20,21]. In our study, the patients with low bicarbonate level had significantly higher hsCRP and decreased urine volume as an indicator of residual renal function, than the patients with higher bicarbonate level.In addition, the patients with low bicarbonate had higher i-PTH, beta2M, age and oxLDL in combination to significantly lower total Kt/V/ week for urea, comparatively to the patients with serum bicarbonate >22mEq/L. Supportingly, we observed a significantly inverse relationship between serum bicarbonate level and both, i-PTH and beta2M.

Indeed, metabolic acidosis causes many abnormalities including bone disease and lipoprotein oxidation [22].On the other hand, acidosis *per se* could be worsened by inflammation, rapid loss of residual renal function, old age and inadequate removal of small and middle molecular weight uremic toxins. i-PTH, which is increased in secondary hyperparathyroidism of renal disease, plays a crucial role on calcium homeostasis, and it may be a mediator of pathological calcification associated to metabolic acidosis [23].

The middle-molecule have been recognized as pathogenic substances implicated in the genesis of accelerated atherosclerosis in dialysis patients [24]. Beta2M serves as a surrogate marker of other middle-molecules uraemic toxins and it has been already demonstrated that beta2M is a sighificant predictor of mortality in dialysis patients, independently treatment vintage, diabetes, malnutrition and chronic inflammation, due may to its probable role on immunity and inflammation [25, 26]. On the other hand, preliminary evidence suggested that metabolic acidosis may play a role in the accumulation of beta2-microglobulin seen in dialysis patients [27].

Moreover, in this study we observed that patients with low bicarbonate level had decreased serum albumin and nPCR, but increased BMI, than the patients with serum bicarbonate >22mEq/L. There are controversial opinions about the effect of serum bicarbonate on nutrition. Good dietary intake with high BMI is usually accompanied by high protein intake, that increases acid load and can result in acidosis in uremic patients [18,28]. Conversely, metabolic acidosis *per se* can have a negative impact on nutritional status including increased proteolysis, decreased protein synthesis and endocrine abnormalities [29,30].

There are several limitations in the present study.This is an observational study with a very small sample size.However, we tried to enroll patients in a good status minimizing the risk of inclusion of more sick patients probably connected to serum bicarbonate <22mEq/L. Also, we defined CAPD as an inclusion to study cretirio and no the need for some type of automated peritoneal dialysis according to peritoneal membrane categorization by the PET. Despite the limitations, our findings showed that the peritoneal dialysis patients with serum bicarbonate level <22mEq/L

have a more risk for arterial stiffening and peripheral vascular disease than the patients with serum bicarbonate >22mEq/L, but these findings need further confirmation.

Conclusion

Uncorrected metabolic acidosis may be an independent significant risk factor for arterial stiffening and peripheral vascular disease manifestation in patients on peritoneal dialysis, due may to its association with inflammation, bone disease and increased beta2-microglobulin serum concentrations.

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