

Effect of hemodialysis on blood ammonia level among cirrhotic patients undergoing hemodialysis

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Abstract

Background: Uremia results in a characteristic breath odor (uremic fetor) which is largely due to its high ammonia content. Earlier studies have shown a strong correlation between breath ammonia and blood urea levels and a 10-fold reduction in breath ammonia after hemodialysis in patients with chronic kidney disease. Potential sources of breath ammonia include: (i) local ammonia production from hydrolysis of urea in the oropharyngeal and respiratory tracts by bacterial flora, and (ii) release of circulating blood ammonia by the lungs. While the effects of uremia and hemodialysis on breath ammonia are well known while their effects on blood ammonia are unknown and were explored here.

Methods: Blood samples were obtained from 56 hemodialysis patients (immediately before and after dialysis). Blood levels of ammonia, creatinine, arterial blood gases, and electrolytes were measured.

Results: There was significant fall in serum creatinine following hemodialysis with significant increase in blood ammonia. Moreover, cirrhotic patients with high-bicarbonate showed a significant more increase in ammonia and significant increase in incidence of hyper-ammonemia to that of non-cirrhotic and low-bicarbonate. Furthermore, the increase in serum bicarbonate showed a significant correlation to the change of blood ammonia following dialysis.

Conclusion: The fall in blood creatinine concentration following hemodialysis is paradoxically accompanied by a rise in blood ammonia in hemodialysis subjects, contrasting the reported effect on breath ammonia. The mechanism of the post-hemodialysis rise in blood ammonia may be due alkalotic change in PH. The observed rise in blood ammonia level was directly related to the rise in blood bicarbonate and with aggravation of alkalotic state in cirrhotic patients. The rise in blood bicarbonate is associated with increased incidence of hyper-ammonemia among cirrhotic patients.

Keywords: Uremia, chronic kidney disease, urea, inflammation, dialysis

INTRODUCTION

Prior to the advent of modern laboratory techniques, characterization of the smell of patients' breath was a common tool used by ancient clinicians for the diagnosis of various diseases. A prime example of a disease with a characteristic breath odor is renal failure. The fishy smell of these patients' breath, which is commonly described as uremic fetor primarily due to the presence of large amounts of ammonia in their exhaled air ⁽¹⁾. In an earlier study **Narasimhan et al.** ⁽²⁾ found marked elevation of ammonia (NH₃) concentration in the breath of a group of end-stage renal disease (ESRD) patients. Breath ammonia level in the study population is directly correlated with their blood urea concentration. The fall in urea concentration

was accompanied by a 10-fold drop in breath ammonia level, from 1500 to 2000 ppb before hemodialysis to 150-200 ppb after hemodialysis ⁽²⁾.

Ammonia in the body is derived from two sources: (i) Cleavage of the amino groups of amino acids followed by its conversion to urea by the liver and to ammonium (NH₄) by the renal tubular epithelial cells ^(3,4). Conversion of ammonia to ammonium [NH₃ + H⁺ → NH₄⁺] in the renal level have not been previously investigated. The present study was undertaken to address this issue.

PATIENTS AND METHODS

In this study, Patients were divided into 4 groups:

1- Group I: indicated ESRD, non-cirrhotic with low serum bicarbonate following

dialysis (≤ 22 mEq/L; no=14).

2- Group II: indicated ESRD, non-cirrhotic with high serum bicarbonate following dialysis (>22 mEq/L; no=12).

3- Group III: indicated ESRD, cirrhotic with low serum bicarbonate following dialysis (no=12).

4- Group IV: indicated ESRD, cirrhotic with high serum bicarbonate following dialysis (no=18).

All subjects had been subjected to:

1. Demographic data assessment: (age, sex, height and BMI).
2. History taking: Full history taking focusing on history of hepatic encephalopathy.
4. Thorough clinical examination:
General examination: focusing on assessment of the patient's general condition.
Local examination: focusing on signs of hepatic encephalopathy and ammonia toxicity.
5. ABG before and after hemodialysis.
6. Serum creatinine before and after hemodialysis.
7. Blood ammonia before and after hemodialysis.
8. Hemoglobin before and after hemodialysis.
9. Serum albumin before and after hemodialysis.

The study was approved by the Ethics Board of Al-Azhar University.

Statistical analyses

One-way and Two-way ANOVA, Tukey's post-test, unpaired t-test, Pearson's correlation tests were used in analysis of the data, which were expressed as mean \pm SD. P-values less than 0.05 were considered significant. The data were collected, revised, verified and analyzed statistically.

Blood collection

Blood samples were obtained from the vascular access in the hemodialysis patients immediately before and after a hemodialysis session. Blood ammonia level was measured by the Clinical Laboratory center at UCI Medical Center within 30 minutes of collection. Blood creatinine, urea, electrolytes, hemoglobin, and white blood cells count were measured on automated bioanalyzers at the UCI Medical Center, central laboratory.

RESULTS

There were no statistically significant differences between all groups as regards age, BMI, hypertension, diabetes, smoking, cause of hemodialysis, Child-Pugh score and past history of hepatic encephalopathy (Tables 1 & 2).

Table (1): Comparison between the two groups as regards demographic parameters (using t-test).

	Group	Mean	Std. Deviation	p-value	Significance
Age (years)	Group 1	37.43	13.89	0.4608	NS
	Group 2	40.54	17.38		
BMI (kg/m ²)	Group 1	25.83	5.49	0.305	NS
	Group 2	27.31	5.16		

Table (2): Comparison between the two groups as regard different present history data (using Chi-square test).

		group		p-value	Significance
		Group 1	Group 2		
Sex	Male	20	16	0.6896	NS
	Female	10	10		
HTN	Yes	22	20	0.1128	NS
	No	8	6		
DM	Yes	4	8	0.757	NS
	No	26	18		
Smoking	Yes	9	6	0.5596	NS
	No	21	20		

There was significant fall in serum creatinine following hemodialysis with significant increase in blood ammonia. Moreover, cirrhotic patients with high-bicarbonate showed a significant more increase in

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ammonia and significant increase in incidence of hyper-ammonemia to that of non-cirrhotic and low-bicarbonate. Furthermore, the increase in serum bicarbonate showed a significant correlation to the change of blood ammonia following dialysis (Tables 3 & 6, Figures 1 & 2).

Table (3): Effect of dialysis on arterial blood ammonia among cirrhotic and non-cirrhotic patients

	Group	non-cirrhotic high-bicarbonate	non-cirrhotic low-bicarbonate	Cirrhotic high-bicarbonate	Cirrhotic low-bicarbonate	p-value
Ammonia (μmol/L)	Pre-HD	26.03 ± 0.34	32.61 ± 8	26.49 ± 2.86	28.87 ± 5.8	<0.0001
	Post-HD	24.14 ± 3.53*	27.85 ± 5.023 ^a	17.97 ± 7.02*	32.74 ± 6.19 ^{c*}	
	Δ	-1.89 ± 3.19	4.76 ± 8.61 ^a	-8.52 ± 6.1	3.87 ± 4.54 ^c	

Data are presented as the mean ± S.D (n= 18, 12, 10, 14 for group 1, 2, 3, 4 respectively). 2-way ANOVA followed by post-hoc test; ^a Significant different to group-1 at post-dialysis (p <0.05), ^b Significant different to group-2 at post-dialysis (p <0.05), ^c Significant different to group-3 at post-dialysis (p <0.05), * Significant different to respective group at pre-dialysis (p <0.05).

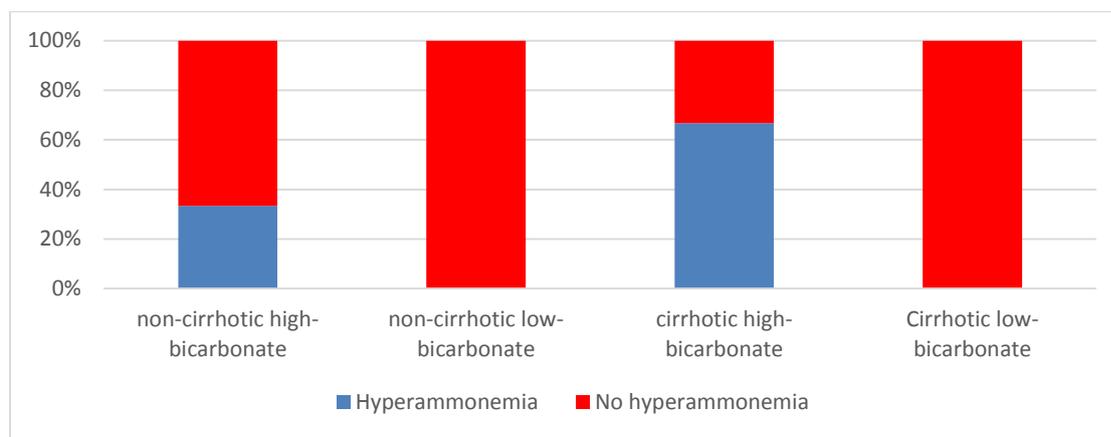


Figure (1): Effect of dialysis on incidence of hyperammonemia (>32μmol/L) among cirrhotic and non-cirrhotic patients

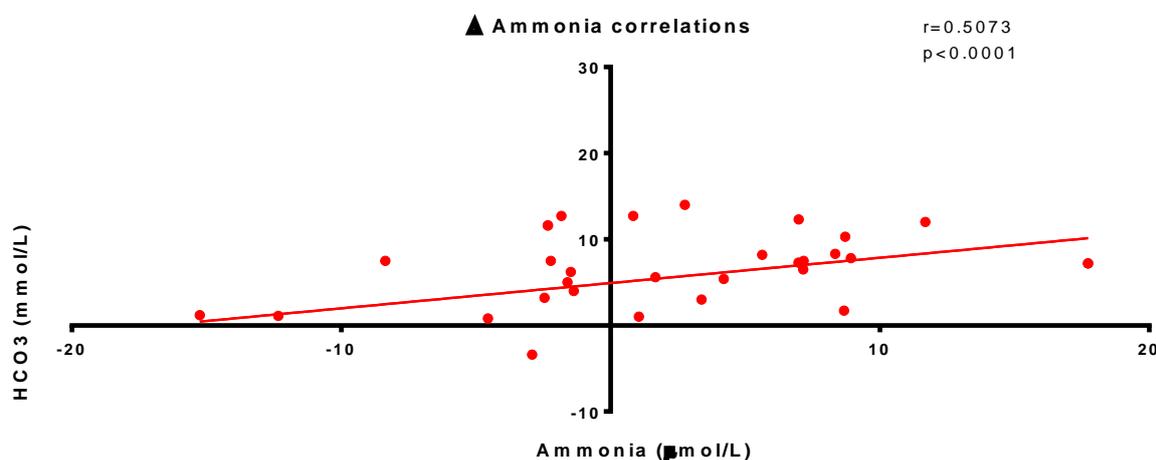


Figure (2): Correlation of blood ammonia and arterial bicarbonate among cirrhotic and non-cirrhotic patients (Pearson correlation test). Correlation coefficient (r-value) considered weak if < 5, strong if > 5 (p-value <0.05).

Concerning arterial gases parameters, there were no statistically significant differences between all groups as regards PO₂. However, cirrhotic patients showed significant decrease in PCO₂ with significant increase in PH in cirrhotic patients due to compensated respiratory alkalosis (p-value >0.05). Moreover, there was no significant correlation with change in blood ammonia following hemodialysis. In addition, there was no significant difference regarding incidence of hyper-ammonemia among all groups. However, there was a significant increase in incidence of alkalosis in cirrhotic group with hypocapnia (Tables 4 & 6).

Table (4): Effect of dialysis on PH, bicarbonate and arterial blood gases among cirrhotic and non-cirrhotic patients

	Group	non-cirrhotic low-biocarb	non-cirrhotic high-biocarb	Cirrhotic low-biocarb	Cirrhotic high-biocarb	p-value
PH	Pre-HD	7.29 ± 0.06	7.28 ± 0.04	7.28 ± 0.05	7.36 ± 0.05	0.7183
	Post-HD	7.39 ± 0.07*	7.37 ± 0.03*	7.36 ± 0.09*	7.45 ± 0.08 ^{bc*}	
	Δ	0.1 ± 0.07	0.09 ± 0.05	0.07 ± 0.07	0.1 ± 0.07	
HCO₃ (mmol/L)	Pre-HD	17.21 ± 0.46	15.9 ± 1.31	21.07 ± 2.9	19.12 ± 2.27	<0.0001
	Post-HD	20.07 ± 2*	23.87 ± 1.26 ^{a*}	21.05 ± 0.79*	26.86 ± 3.11 ^{bc}	
	Δ	2.86 ± 2.47	7.967 ± 1.737 ^a	-0.017 ± 2.609	7.744 ± 3.97 ^c	
pCO₂ (mmHg)	Pre-HD	35.84 ± 3.75	35.73 ± 1.83	31.42 ± 3.85	30.9 ± 4.75	0.0462
	Post-HD	38.88 ± 2.18	39.11 ± 3.39	34.39 ± 5.45	33.5 ± 8.18 ^b	
	Δ	3.04 ± 3.79	3.38 ± 2.94	2.98 ± 4.38	2.6 ± 6.98	
pO₂ (mmHg)	Pre-HD	103.2 ± 21.85	98.65 ± 10.21	58.88 ± 35.49	94.7 ± 32.43	0.3394
	Post-HD	102.84 ± 18.75	119.72 ± 29.38	70.48 ± 31.97	98.96 ± 22.69 ^c	
	Δ	-0.36 ± 21.23	21.07 ± 27.1	11.6 ± 44.67	4.26 ± 30.69	

Data are presented as the mean ± S.D (n= 18, 12, 10, 14 for group 1, 2, 3, 4 respectively). 2-way ANOVA followed by post-hoc test; ^a Significant different to group-1 at post-dialysis (p <0.05), ^b Significant different to group-2 at post-dialysis (p <0.05), ^c Significant different to group-3 at post-dialysis (p <0.05), * Significant different to respective group at pre-dialysis (p <0.05).

Concerning renal parameters, there were no statistically significant differences between all groups as regards hemoglobin, albumin, creatinine, Na and K (p-value >0.05). Moreover, there was no significant correlation with change in blood ammonia flowing hemodialysis. In addition, there was no significant difference regarding incidence of hyper-ammonemia among all groups (Table 5, 6).

Table (5): Effect of dialysis on hemoglobin and different serum biochemistry among cirrhotic and non-cirrhotic patients

	Group	non-cirrhotic low-biocarb	non-cirrhotic high-biocarb	Cirrhotic low-biocarb	Cirrhotic high-biocarb	p-value
Hemoglobin (g/dL)	Pre-HD	10.94 ± 1.84	9.7 ± 2.86	8.8 ± 2.09	8.828 ± 2.43	0.9245
	Post-HD	10.9 ± 1.82	9.68 ± 2.673	8.817 ± 2.202	8.83 ± 2.17	
	Δ	-0.043 ± 0.165	-0.017 ± 0.229	0.017 ± 0.22	0.006 ± 0.31	
Albumin (g/dL)	Pre-HD	3.89 ± 0.3	4.067 ± 0.45	3.817 ± 0.54	3.9 ± 0.32	0.584
	Post-HD	3.86 ± 0.28	4.02 ± 0.42	3.75 ± 0.49	3.88 ± 0.3	
	Δ	-0.029 ± 0.13	-0.05 ± 0.05	-0.067 ± 0.078	-0.022 ± 0.088	
Creatinine (mg/dL)	Pre-HD	7.88 ± 3.76	11.89 ± 1.28	8.845 ± 2.05	9.65 ± 2.43	0.0094
	Post-HD	5.59 ± 2.93*	5.67 ± 0.88 ^a	4.13 ± 1.83*	3.16 ± 1.27 ^{b*}	
	Δ	-2.29 ± 6.09	-6.22 ± 1.19 ^a	-4.71 ± 2.34	-6.49 ± 2.45	
Na (mmol/L)	Pre-HD	129.67 ± 1.048	133 ± 3.4	125.45 ± 4.03	128.24 ± 5.54	0.3469
	Post-HD	134.93 ± 4.69	135.63 ± 3.62*	127.18 ± 4.37	130.11 ± 3.67 ^b	
	Δ	5.26 ± 5.43	2.63 ± 5.76	1.73 ± 5.08	1.87 ± 6.51	
K (mmol/L)	Pre-HD	4.71 ± 0.68	4.6 ± 0.65	4.34 ± 0.29	4.88 ± 1.13	0.3689
	Post-HD	3.6 ± 0.43*	3.28 ± 0.29*	3.34 ± 0.35*	3.43 ± 0.86*	
	Δ	-1.11 ± 0.45	-1.32 ± 0.47	-1 ± 0.61	-1.46 ± 1.1	

Data are presented as the mean ± S.D (n= 18, 12, 10, 14 for group 1, 2, 3, 4 respectively). 2-way ANOVA followed by post-hoc test; ^a Significant different to group-1 at post-dialysis (p <0.05), ^b

Significant different to group-2 at post-dialysis (p <0.05), ° Significant different to group-3 at post-dialysis (p <0.05), * Significant different to respective group at pre-dialysis (p <0.05).

Table (6): Effect of different serum and blood components on level of blood ammonia among cirrhotic and non-cirrhotic patients

	Correlation coefficient	P-value	Significant
Δ ammonia vs. Δ HCO ₃	0.5073	< 0.0001	Yes
Δ ammonia vs. Δ PH	0.05301	0.6980	No
Δ ammonia vs. Δ pCO ₂	0.07769	0.5693	No
Δ ammonia vs. Δ pO ₂	-0.09345	0.4933	No
Δ ammonia vs. Δ Na	-0.185	0.1722	No
Δ ammonia vs. Δ K	0.04976	0.7157	No
Δ ammonia vs. Δ Creatinine	-0.1783	0.1885	No
Δ ammonia vs. Δ Albumin	0.06374	0.6407	No
Δ ammonia vs. Δ HB	-0.1443	0.2886	No

Correlation coefficient (r-value) considered weak if < 5, strong if > 5 (p-value <0.05).

DISCUSSION

Although there have been some limited studies of the effect of regular hemodialysis on blood ammonia, this study prospectively investigated role of regular HD on blood ammonia and incidence of hyperammonemia. This prospective study also detailed the difference between cirrhotic and non-cirrhotic patients on RHD regarding change in ammonia, bicarbonate, PH, biochemical substances and electrolytes. Furthermore, it was to investigate the impact of different intra-dialysis variables including change in bicarbonate, PH, biochemical substances and electrolytes on change of blood ammonia.

The statistical differences regarding patient characteristics (age, sex, BMI, DM, HTN, smoking, cause of HD, cause of cirrhosis, child-pugh and history of HE) among the different groups are insignificant. This comes in agreement with *Rettig et al.* ⁽⁵⁾ and *Schena et al.* ⁽⁶⁾.

Retention of urea in renal failure leads to the rise in its concentration in the body fluids and its heavy influx into the gastrointestinal tract, which is accompanied by marked alteration of the gut microbial flora and dominance of urease-possessing bacteria ⁽⁷⁻⁹⁾. Hydrolysis of urea by microbial urease leads to formation of large quantities of ammonia [NH₂-CO-NH₂ + H₂O CO₂ + 2NH₃]. Most of the ammonia generated in ~~the~~ gut is converted to ammonium hydroxide [NH₃ + H₂O NH₄OH], which accounts for the elevated pH

of the intestinal milieu in patients with renal failure ^(10, 11). There is growing evidence indicating the role of intestinal barrier dysfunction and increased intestinal permeability ⁽¹²⁻¹⁵⁾. Some studies demonstrated massive losses of claudin-1, occludin, and zonula occludens-1 (the key protein constituents of the epithelial tight junction) in the colon, stomach, jejunum, and ileum of rats with CKD ^(14, 16). Other subsequent studies identified the role of urea-derived ammonium hydroxide in the disruption of the intestinal epithelial barrier structure ⁽¹⁶⁻¹⁹⁾. These observations confirm the local production of ammonia from hydrolysis of urea by the microbial flora in the oral, and pharyngeal cavities of uremic patients as the primary cause of their elevated breath ammonia level.

In contrast with elevated breath ammonia, our study revealed that after hemodialysis, ammonia showed a significant increase to that of pre-dialysis. This study doesn't go in line with *Narasimhan et al.* ⁽²⁾ who previously reported that the fall in blood urea level following hemodialysis procedure correlates with a 10-fold drop in breath ammonia level in ESRD patients. This study goes in line with *Vaziri et al.* ⁽²⁰⁾ who observed significantly raised blood ammonia levels in almost half of the subjects.

Moreover, there was a significant increase in PH and HCO₃⁻ after hemodialysis and there was a significant more increase in cirrhotic patients with high-bicarbonate to

that of low-bicarbonate. Furthermore, only the increase in HCO_3^- revealed a significant correlation with the magnitude of rise in blood ammonia level following hemodialysis. Interestingly, there was also a significant increase in incidence of hyperammonemia in high-bicarbonate cirrhotic patients to that of non-cirrhotic and low-bicarbonate groups. These observations may explain the rise of blood ammonia after hemodialysis, due to the acute change in acid-base status from mild acidosis in which the ammonia is held as nonvolatile ammonium (NH_4^+) to the normal or alkalotic states where it exists partly in a volatile state (NH_3).

A second possible mechanism proposed by **Vaziri *et al.*** ⁽²⁰⁾ may explain rise of blood ammonia after HD, is the potential contribution of acute reduction of hepatic perfusion in the setting of ultrafiltration and decreased arterial pressures during hemodialysis. This transient liver ischemia may limit its ability to convert gut-derived ammonia to urea, thus raising systemic ammonia concentrations. Moreover, **Vaziri *et al.*** ⁽²⁰⁾ found a direct correlation between the extents of the fall in MAP with the rise in post-hemodialysis blood ammonia levels in a subset of patients.

Concerning arterial gases parameters, PCO_2 and PO_2 showed insignificant change during dialysis with insignificant correlation to change in blood ammonia. However, cirrhotic patients showed significant decrease in PCO_2 with significant increase in PH in cirrhotic patients to that of non-cirrhotic with high-bicarbonate. However, there was a significant increase in incidence of alkalosis in cirrhotic group with high-bicarbonate and hypocapnia to that of non-cirrhotic and low-bicarbonate. It is well-known that patients with cirrhosis have an acid-base imbalance most commonly hyperventilatory alkalosis with decreased arterial carbon dioxide tension ⁽²¹⁻²⁴⁾. This hypocapnic alkalosis is metabolically compensated especially in class A cirrhosis ⁽²⁵⁾. A balance between hypoalbuminemic alkalosis on the one hand and dilutional, diuretic-induced and unidentified ion acidosis on the other yields a net metabolic (complete or partial) compensation of the respiratory alkalosis in all classes ⁽²⁶⁾. The cirrhotic patient has normal or almost normal pH, but this is the sum of a delicate equilibrium of several acid-

base disturbances, which may be easily disturbed. Thereby, unbalanced in patients with infections, subacute bacterial peritonitis, or hemorrhage, where the cirrhotic patients may be at risk of developing metabolic acidosis or alkalosis earlier and more easily than patients without liver disease ⁽²⁷⁾.

Moreover, in this study, there was an insignificant decrease in PCO_2 in all groups following the dialysis. This coincided with significant increase in pH post-dialysis and this might be due to correction of metabolic acidosis with subsequent diminished respiratory compensation by hypocapnia.

Concerning renal parameters, there was a significant decrease in creatinine and increase in potassium following the dialysis. However, there was no significant difference in albumin, hemoglobin, and sodium during the dialysis. Moreover, there was no significant difference between different groups (cirrhotic vs non-cirrhotic, high-bicarbonate vs low-bicarbonate). Furthermore, there was no correlation between change in ammonia and change in these parameters. These result doesn't go in line with **Narasimhan *et al.*** ⁽²⁾ who previously reported that the fall in blood creatinine level following hemodialysis procedure correlates with a drop in breath ammonia level in ESRD patients.

An inverse relation is known to link blood potassium with renal synthesis and the release of ammonia ⁽²⁸⁾. According to **Zavagli *et al.*** ⁽²⁹⁾ and **Conn** ⁽³⁰⁾ who reported that, in cirrhotic patients-stage I HE with high-normal potassium level, the survival and incidence of hepatic encephalopathy was improved than with low-normal potassium level. They referred this improvement to the induced decrease in blood pH with consequent depression of renal ammonia genesis and rise in the arterial and urine $\text{NH}_4^+/\text{NH}_3$ ratios. These factors reduce the entry of ammonia into the cells and enhance the urinary excretion of this metabolite, respectively. However, in our study, patients with ESRD had a severely inhibited renal ammonia genesis and therefore hyperkalemia will not influence the level of arterial ammonia.

Conclusion

Our study revealed that the fall in blood creatinine concentration following

hemodialysis was paradoxically accompanied by a rise in blood ammonia in hemodialysis subjects, contrasting the reported effect on breath ammonia. The mechanism of the post-hemodialysis rise in blood ammonia might be due alkalotic change in pH. The observed rise in blood ammonia level was directly related to the rise in blood bicarbonate and with aggravation of alkalotic state in cirrhotic patients. The rise in blood bicarbonate was associated with increased incidence of hyper-ammonemia among cirrhotic patients.

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