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Net acid excretion capacity is related to blood hydrogen ion and serum carbon dioxide

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Abstract

Acid-base imbalance due to dietary food patterns has emerged as one of the hypotheses leading to modern-day diseases. This study examined if a new method to assess the renal ability to excrete an acid load, that is, the net acid excretion capacity (NAEC), constructed from net acid excretion (NAE) and urine pH, relates to blood hydrogen ion concentration ([H+]) and serum carbon dioxide concentration ([CO2]). In a second analysis, NAE to pH relationship was examined, and is de facto treated to be linear. This study used historical, cross-sectional data of 58 repeated measurements from 8 subjects for the primary measurements of NAEC, blood [H+], and serum [CO2]. Using fixed models, higher NAEC associated with lower [H+] and higher [CO2]. Using hierarchical models, the interindividual variations in [H+] and [CO2] explained the variations in NAEC. In the second analysis (n = 59), a quadratic NAE to pH relationship (NAE = −846.77 + 341.47 pH − 31.50 pH^2) can be reported. Net acid excretion capacity, a noninvasive tool to assess the renal ability to excrete an acid load, has a physiologic base to it, in that it captures the inherent nonlinear relations of NAE to pH explaining endogenous [H+] retention/excretion. A higher vegetable and fruit consumption might relieve NAEC and allow excess [H+] loss via both renal and respiratory routes.

1. Introduction

Acid-base balance of dietary food consumption has won some recent interest because imbalances in it have been associated with development of the modern-day diseases [1-5]. As a consequence, the physiologic validity of various acid-base indicators, such as the dietary and the anthropometric estimate of organic acid excretion, the dietary unmeasured anion, is in discussion [6,7]. A recent theoretical construct called the *net acid excretion capacity* (NAEC) has been defined as the residues of net acid excretion (NAE) on urine pH [8] and functions as an index of the kidney's ability to excrete an acid load when measurements of NAE and urine pH are available. This NAEC theoretical construct has been successfully shown to decline with aging [6,8]; but it has never been tested if it is related to the endogenous acid-base balance parameters, such as the blood hydrogen ion concentration ([H+]).

Renal function has been reported to be lower with aging and in diseases such as renal failure, diabetes, etc [9-11]. It has been demonstrated that blood pH and plasma bicarbonate in older persons tend toward the lower side of the reference range [12], that is, a greater [H+] retention with aging. The renal function NAEC was also reported to be lower with aging [8]. A decline in NAEC implies a greater [H+] retention by the body, which when uncorrected can lead to acidosis and probably diseases [5,7]. This hypothesis [7], however, requires to be empirically tested.

Net acid excretion capacity can be graphically visualized as the relationship of NAE to pH, originally termed the *hydrogen ion excretion capacity* [13,14]. In the previous study on NAEC, it remained unexplained why the interindividual variations in NAE, having controlled the urine pH, exceeded the interindividual variation in NAE across the physiologic pH range [8]. Protein consumption was suggested as an explanation to the above [8] because protein has been shown to be directly associated with both NAE [15-17] and NAEC [8]. Because of such deliberations, it still remains to be tested if NAEC can serve as an indicator of the renal function to excrete an acid load.

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This study's objectives were to test how and why variations in NAE at a constant pH can exceed variations in NAE across physiologic pH ranges and to thereby test if the theoretical construct of NAEC has any physiologic relevance. Historical data references were used for this present study's empirical testing [18-23].

2. Materials and methods

2.1. Data set

The study was carried out using historical data from 8 participants from 6 original, historical studies reported from 1959 to 1966 with repeated blood and urine measures of acid-base balance [18-23]. Repeated measures from these historical participants were used for the present analysis when NAE was less than 150 mEq/d, that is, the normal Western diet acid loads [4]. As a result, this study's final data set had 59 observations from 8 participants: 11 observations from participant JL [18], 9 observations from participant TW [19], 7 observations from participant AS [20], 6 observations from participant PR [20], 15 observations from participant KEW [21], 6 observations from participant SE(A) [22], 4 observations from participant SE(B) [22], and finally 1 observation from participant AH [23].

Following is a short description of the participants' details from the original studies: Participant JL was a healthy young man on an acid-base balance study with methionine intervention [18]. Participant TW was a healthy young man on balance studies with calcium and magnesium hydroxide intervention [19]. Participant AS was a healthy man on balance studies with soy phosphoprotein intervention; and participant PR, from the same study, was a healthy man with an intervention of 360 g of ground beef steak per day [20]. Participant KEW, a healthy adult man, was on sodium bicarbonate intervention [21]. Participant SE(A) was an adult male patient of acidosis on acid-base balance study; and participant SE(B) was again the same subject on sodium bicarbonate intervention, although at a different time instance [22]. The data on participant SE(A) and participant SE(B), although from the same person, were treated as 2 separate data entities because there were very large differences in the 2 measurement instances. Participant AH was a healthy man on acid-base balance study [23].

2.2. Analyses

The primary outcome variable of interest was NAEC (in milliequivalents per day), which was constructed by building residuals of NAE on urine pH from the 59 observations [8]. The statistical process entails running a linear proc reg procedure with urine pH as the explanatory variable and NAE as the outcome. This generates the residuals of the relationship, which have been defined and used as the NAEC in this study, as in the previous study as well [8]. Analysis 1 had the explanatory variables of blood [H^+] and serum carbon dioxide ([CO2], in millimoles per liter). Subject AH was post hoc excluded because, instead of [CO2], partial pressure of carbon dioxide was reported, reducing the sample size to 58.

For analysis 2, outcome NAE (in milliequivalents per day) was explained with urine pH. This relationship was adjusted for repeated measures on the same participant by offering the identity number (ID) as a covariate. A subanalysis was carried out in this category by a subsampling of 12 readings from 3 participants, 6 observations from participant SE(A), 4 observations from participant SE(B), and 11 observations from participant JL. This subsampling also included measurement of urine nitrogen (in grams per day), with existing exclusion criteria (exclude cases of NAE >150 mEq/d). Because of the very small sample size, instead of offering ID as a covariate, a dummy for each participant was created—D = −1 for SE(A) (patient of acidosis), D = 0 for SE(B) (patient of acidosis with alkali intervention), and D = 1 for JL (healthy person)—to bring out the repeated intraindividual measurements, with an indirect weighting for the basic acid-base status.

2.3. Statistics

Data have been reported as means (confidence intervals) at a significance of $P < .05$. Data were analyzed and the diagrams were generated using SAS procedures (Version 8.2; SAS Institute, Cary, NC). Analysis of variance (1-way) was run across each ID for all variables, and the difference of means was confirmed using Tukey studentized range (honestly significant difference) test.

Analysis 1 (Table 2) was conducted with 3 basic regression runs. Run 1 used procedure generalized linear model (proc glm), run once for [H^+] and once for [CO2], each time once with and once without ID (to adjust for repeated measures on same person). This was to test for fixed effects. Run 2 used procedure mixed (proc mixed), for [H+] and [CO2] fixed effects within the ID class variable. This implied that the repeated measures (on the same person) were a fixed effect within the class variable on the outcome. Run 3 used proc mixed with random nested effects of the [H+] and [CO2] within the class ID.

Analysis 2 (Table 3) shows the outcome NAE explained by pH; all 5 runs used proc glm. Run 3 adjusted for ID using the dummy D. This adjusted for repeated measures on the same person using an arbitrary categorical weighting. Runs 4 and 5 used the subsampling of n = 12, where, in addition to adjusting for D, even nitrogen (index for dietary protein [15,24]) was adjusted for.

3. Results

The basic characteristics of the group (Table 1) show that interindividual variations in urine pH and NAE were relatively low; even so, NAEC, constructed from urine pH and NAE, showed greater variation. Table 2 (a summation of

Table 1
Basic characteristics

ID/study year	Person[a]	n[b]	Blood [H]+ (mmol/L)	Serum [CO2] (mmol/L)	Urine pH	NAE (mEq/d)	NAEC (mEq/d)	$NAEC_{alternate}$ (mEq/d)
1/1959	JL	11	$0.041^{d,e,f}$	$29.1^{d,e}$	6.1	62.6^{d}	$17.7^{d,e,f,g,h,i}$	$71.6^{d,e,f,g,h,i}$
			(0.04-0.04)	(27.8-30.5)	(5.5-6.6)	(26.6-98.6)	(4.4-30.9)	(58.4-84.9)
2/1961	TW	9	0.042^{g}	$30.0^{f,g,h}$	5.8^{d}	79.4^{e}	$24.7^{j,k,l,m,n}$	$78.7^{j,k,l,m,n}$
			(0.04-0.04)	(28.6-31.4)	(5.5-6.2)	(63.9-95.0)	(6.1-43.4)	(60.0-97.3)
3/1962	AS	7	0.042^{h}	$26.5^{d,f,i,k}$	5.5^{e}	60.6^{f}	$-9.5^{d,j,o}$	$44.5^{d,j,o}$
			(0.04-0.04)	(24.5-28.5)	(5.4-5.6)	(46.2-75.0)	(−21.8 to 2.8)	(32.1-56.8)
4/1962	PR	6	0.041^{i}	29.2^{j}	5.2^{f}	66.7^{g}	$-17.6^{e,k,p}$	$36.4^{e,k,p}$
			(0.04-0.04)	(28.8-29.6)	(5.1-5.3)	(54.3-79.0)	(−29.7 to −5.5)	(24.3-48.4)
5/1965	KEW	15	$0.044^{d,j}$	$29.5^{k,l}$	6.1	41.4	$-3.5^{f,l,q,r}$	$50.5^{f,l,q,r}$
			(0.04-0.04)	(28.7-30.3)	(5.5-6.6)	(8.9-73.9)	(−12.4 to 5.4)	(41.6-59.4)
6/1965	SE(A)	6	$0.060^{e,g,h,i,j,k}$	$18.6^{e,g,i,j,l,m}$	5.2^{g}	52.8	$-35.0^{g,m,q,s}$	$19.0^{g,m,q,s}$
			(0.06-0.06)	(18.0-19.2)	(5.1-5.2)	(46.2-59.5)	(−43.1 to −26.8)	(10.9-27.2)
7/1965	SE(B)	4	$0.045^{f,k,l}$	$27.1^{h,m}$	$7.1^{d,e,f,g}$	$-22.3^{d,e,f,g}$	$-15.3^{h,n,t}$	$38.7^{h,n,t}$
			(0.04-0.05)	(26.1-28.0)	(6.8-7.5)	(−35.3 to −9.2)	(−20.3 to −10.3)	(33.7-43.7)
8/1966	AH	1	0.036^{l}	51.0^{b}	6.4	107.0	$78.7^{i,o,p,r,s,t}$	$132.7^{i,o,p,r,s,t}$
	Total		0.044	28.2	5.9	54.0	−6.3	54.0
			(0.04-0.04)	(27.0-29.4)	(5.7-6.1)	(42.2-65.8)	(−6.9 to 6.9)	(47.1-60.8)

Mean with confidence intervals, tested with Tukey test (superscript letters *c* to *t*). $NAEC_{alternate}$ indicates NAEC + 53.97 (mean NAE).

[a] Subjects (details in "Materials and methods").

[b] Number of readings per person.

analysis 1) examines the relationship between NAEC, and [H+] and [CO2]. Models 1 and 3 are similar and report [H+] significant in explaining the variations in NAEC ($P < .001$). Both runs report negative parameter estimate (β) for [H+], indicating that decline in [H+] is related to higher NAEC. In model 5, this relationship is depicted more clearly than in models 1 or 3: NAEC was predominantly explained by interindividual variations in [H+] (model 5 has a better fit with lower Akaike information criteria compared with model 3), which rendered individual measures of [H+] in explaining NAEC not significant. Thus, although the interindividual variations in [H+] were not significant using proc glm, when using proc mixed, these interindividual variations (ID) in [H+] in the hierarchy of analysis are more important than each individual variation in [H+]. Similar results were obtained with [CO2].

Run 1 shows that urine pH alone explains around 66% of the variability in NAE (Table 3). However, if a quadratic term of urine pH is included, the model R^2 increased to 75%. This result shows that the relationship of NAE to pH is not linear, but quadratic (Fig. 1A, B). Finally, in a subsample of 12 (Table 3, model 4), interindividual variability was found to be highly significant (although parameter D was not identical to ID in its adjustment for

Table 2
Relationship of NAEC (outcome variable) with blood [H+] and serum [CO2] (n = 58)

Run	Model	Model	β	*P* value	R^2	AIC
		Proc glm, fixed effects[a]				
1	1	[H+]	−2007.3	<.001	22.9	NA
	2	[CO2]	3.15	<.001	22.3	NA
		Proc mixed, fixed effects within class variable ID[b]				
2	3	[H+]	−2007.3	<.001	NA	525.2
	4	[CO2]	3.15	<.001	NA	525.7
		Proc mixed, random, nested effects within the class variable ID[c]				
3	5	[H+]	−882.3	NS	NA	514.6
	6	[CO2]	.84	NS	NA	515.2

β indicates parameter estimate; *P*, probability value; R^2, the partial contribution of each variable; AIC, Akaike information criteria, an estimate of the fit of a model (the lower, the better); NS, not significant; NA, not applicable.

[a] Also run including identity (ID) to adjust for interindividual repeated measures in NAEC on same person, but was not significant.

[b] Interindividual repeated measures on same person as a fixed effect.

[c] Intraindividual repeated measures of [H+] and [CO2] in the higher category of each person (ID) (interindividual) as a nested effect.

Table 3
Relationship of NAE (outcome variable) and urine pH

Run	Model	β	*P* value	Model R^2
1[a]	Urine pH	−47.8	<.0001	66.2
2[a]	Urine pH	341.5	<.001	
	Urine pH^2	−31.5	<.0001	75.1
3[a]	Urine pH	363.6	.0001	
	Urine pH^2	−33.4	<.0001	
	ID	2.0	NS	75.8
4[b]	Urine pH	−284.2	<.01	
	Urine pH^2	18.3	<.05	
	D	35.2	<.0001	96.2
5[b]	Urine pH	222.4	<.05	
	Urine pH^2	13.7	<.1	
	Urine nitrogen	95.4	<.1	
	Urine $nitrogen^2$	−1.14	<.1	
	D	36.8	<.0001	96.9

Identity (ID) was adjusted for repeated measures on same person. D indicates dummy (−1, 0, and 1 for acidosis patient, acidosis patient with alkali, and healthy person, respectively).

[a] Generalized linear regression (n = 59 in 8 subjects).

[b] Generalized linear regression (n = 12 in 3 subjects) where urine nitrogen measures were also available.

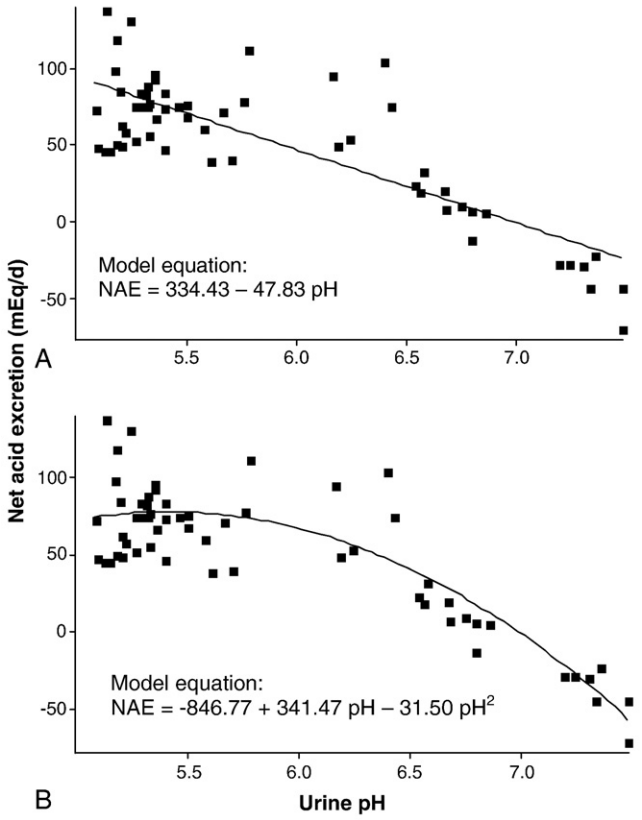

Fig. 1. The linear (A) and quadratic (B) relation of NAE to urine pH.

interindividual variability); and the model R^2 improved to 96% ($P < .0001$). Including urine nitrogen, an index of dietary protein intake, improved model R^2 by 1% (total model R^2 of 97%).

4. Discussion

Using historical data [18-23], this study indicates that the NAEC, previously shown to be lower in older persons [8], correlates inversely with blood [H+] and directly with serum [CO2]. This was supported by the quadratic relationship of NAE with urine pH observed in the present study . These results can be personalized; for example, participant SE(A) (Table 1), a patient of metabolic acidosis with very low NAEC, when placed on an alkali intervention (SE[B]), had an NAEC comparable to that of participant PR, a healthy person on a dietary acid load intervention (beef steak, "Materials and methods"). This supports that the NAEC possibly indexes the renal ability to excrete an acid load.

The study aimed to find out if NAEC has a physiologic base; and present results indicate an interesting relationship between NAEC, and [H+] and [CO2]: higher NAEC correlated with lower [H+] and higher [CO2]. If [H+] is regarded as the fixed acid component and [CO2] the volatile acid component, a recent publication suggested that the fixed acid component could be related to the volatile acid component over lactic acid [7]. Excess lactic acid due to incomplete carbohydrate metabolism might be related to dietary carbohydrate overload [7]. A high carbohydrate consumption has been reported in diets of industrialized nations [1,2,25,26]. The present study's historical participants had a range of dietary intakes/acid precursors, still suggesting that the 2 acid compensation routes might be related. The study finding of higher NAEC with lower endogenous fixed acids ([H+]) implies that, as the endogenous fixed acids increase, the renal compensation of it can be expected to increase [8,9,11,27,28]. The other study finding of a higher NAEC with higher endogenous volatile acids ([CO2]) could imply that NAEC is related to respiratory compensation. Higher [CO2], as already mentioned, could be related to incomplete carbohydrate oxidation [7] and could mean either (*a*) an accumulation of volatile acids or (*b*) an improved excretion of volatile acids. Although a better-designed study is required to elucidate this difference, the present study indicates that, on alkali supplementation, there is a chance that higher NAEC might relate to an improved respiratory compensation. Taking the example of SE(B) again, this participant with metabolic acidosis had a higher [CO2] on alkali intervention. Studies have reported that alkali consumption improves the renal compensation of the fixed acid load [3,17,21]. The present study hints that alkali consumption could improve the respiratory compensation of the volatile acid load in subjects otherwise on/with a high dietary/metabolic acid load. Thus, the need to neutralize dietary acid consumption with alkalis, either via vegetables and fruits and/or alkali salts, as suggested in the previous study [8], has to be reiterated. Practically, this implies that a higher vegetable and fruit consumption might relieve NAEC and allow excess acid loss via both renal and respiratory routes.

This study also indicates that variation in NAE, at a pH, can exceed NAE variations across the physiologic pH range, showing that the NAE to urine pH relationship is not linear but quadratic. Studies using the complete physiologic pH range and treating this inherent quadratic relationship linear, as the practice has been, would have some information loss. Approximating linearity has its advantages; such as simplicity. This study shows that 66% of explained variation in NAE by pH is possible via linear relationships (Fig. 1A). In addition, NAE to pH relationships can be linear in limited pH ranges, as opposed to the complete physiologic pH range [8]. However, perhaps precisely because NAEC is constructed as the linear residues of NAE on pH, it can function as an indicator of the renal ability to excrete acid and, hence, as demonstrated by this study, relates to blood [H+] and [CO2]. This is so because the linear residues of NAE on pH capture the quirkiness of the inherently quadratic relationship of NAE to urine pH.

This study is principally limited in using historical data and by a small sample of 58 measurements on 8 individuals, taking away from extrapolation. Indirect support for the study results can be somewhat inferred

from a relative stability in variations of NAE to pH across industrialized Western nations. This study's historical participants from North America from the last century [18-23] had an interindividual variation of NAE of about 90 mEq at a urine pH of about 5.2 (Fig. 1A) (linear equation: NAE = 334 − 48 pH). The more recent study publishing on the parameter NAEC for the first time used a German sample, which also reported interindividual variations of NAE of about 90 mEq/d at about a urine pH of 5.2 (linear equation for middle pH range: NAE = 392 − 55 pH) [8]. The latter study additionally showed that protein is associated with higher NAEC [8]; even so, protein is also associated with higher acid loads NAE [15-17]. This present study reports a quadratic NAE to pH relationship that explains almost 75% of the model; adding protein to the model explained an additional 1% (highly reduced sampling). Physiologically, it has been shown that dietary protein increases glomerular filtration rate, stepping up renal clearance rates [27,28]. This study would have benefited with glomerular filtration rate measurements also as dietary variables. All these aspects require future research with investigator-generated data.

This study indicates that NAEC has a physiologic relationship with blood [H+] and serum [CO2] and that the relationship of NAE to pH can be quadratic. Physiologically implied, this could allow NAEC to reflect the body's ability to retain/excrete [H+], thereby explaining why NAEC was reported to lower with aging. Dietary consumption of vegetables and fruits might help relieve NAEC and allow an improved acid compensation via not only renal but also respiratory route.

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