Obesity, Anion Accumulation, and Anion Gap Metabolic Acidosis: A Cohort Study

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Key Points

- Obesity is characterized by the accumulation of high serum levels of abnormal, negatively charged solutes and acid.
- Findings were present among patients with normal kidney function, suggesting acid overproduction rather than acid retention.

Abstract

Background Obesity is associated with low serum bicarbonate, an indicator of metabolic acidosis and a CKD risk factor. To further characterize acid-base disturbance and subclinical metabolic acidosis in this population, we examined prospective associations of body mass index (BMI) with elevated anion gap and whether anion gap values in obesity associate with low bicarbonate.

Methods Data from adult outpatients \( n=94,448 \) in the Bronx, New York were collected from 2010 to 2018. Mixed effects models and Cox proportional hazards models were used to examine associations of BMI with elevated anion gap and anion gap metabolic acidosis and of baseline anion gap with incident low bicarbonate and anion gap metabolic acidosis. Anion gap was defined using traditional and albumin-corrected calculations.

Results Greater BMI was associated with higher anion gap over time and with progressively greater risk of developing an elevated anion gap [hazard ratio (HR) for body mass index (BMI) \( \geq 40 \text{ kg/m}^2 \) versus 18 to 25 kg/m\(^2\), 1.32; 95% confidence interval (95% CI), 1.23 to 1.42 for traditional and HR for BMI \( \geq 40 \text{ kg/m}^2 \) versus 18 to 25 kg/m\(^2\), 1.74; 95% CI, 1.63 to 1.85 for corrected]. Higher BMI was also associated with increased risk of developing anion gap metabolic acidosis (HR for BMI \( \geq 40 \text{ kg/m}^2 \), 1.53; 95% CI, 1.39 to 1.69). Among patients with obesity, higher anion gap was associated with increased risk of incident low bicarbonate (HR for fourth versus first quartile, 1.29; 95% CI, 1.23 to 1.44 for traditional and HR for fourth versus first quartile, 1.36; 95% CI, 1.26 to 1.48 for corrected) and higher risk of anion gap metabolic acidosis (HR for fourth versus first quartile, 1.78; 95% CI, 1.59 to 1.99).

Conclusions Obesity is characterized by unmeasured anion accumulation and acid retention or overproduction. Modest elevations in anion gap among patients with obesity are associated with previously unrecognized anion gap metabolic acidosis.

Introduction

Chronic metabolic acidosis and organic anion accumulation are classically associated with advanced CKD (1,2). However, recent research has revealed clinically actionable (3,4) acid retention and anion accumulation in the absence of frank serum electrolyte abnormalities among patients without advanced CKD (5,6). Treatment of this eubicarbonatemic (7) metabolic acidosis prevents GFR decline (4), reduces markers of kidney tissue damage (3), and in patients without CKD, reduces markers of muscle and bone degradation (8,9). Evidence of both eubicarbonatemic and overt metabolic acidosis has also been demonstrated among patients without CKD. In a recent retrospective cohort study, greater body mass index (BMI) was associated with progressively higher risk of low serum bicarbonate (10). This suggests that excess weight may be associated with chronic acid retention or overproduction in the absence of CKD. Patients who are overweight and patients with obesity are a growing population worldwide (11) at risk for CKD (12) and ESKD (13). Metabolic acidosis in this population may represent a novel therapeutic target for preventing kidney function decline (3,4).
This study aimed to further define the relationship between obesity and acid-base disturbance (10) by investigating abnormalities of the serum anion gap as an indicator of organic acid retention. Apart from its diagnostic use (14), the anion gap is predictive of clinical outcomes (6,15). In this context, the incorporation of serum albumin, as the corrected anion gap, may improve the sensitivity for detecting clinical abnormalities and disease risk. In contrast to the traditional anion gap, corrected anion gap elevations are detectable in CKD Stage 2 (6), and they have been associated with mortality risk (6) and relatively higher risk of progression to ESKD (15).

Using data from a diverse outpatient population, a prospective analysis was conducted to examine whether (1) greater BMI is associated with higher risk of incident elevated anion gap and (2) higher anion gap values within this population are associated with low bicarbonate and anion gap metabolic acidosis.

Materials and Methods

Study Population
Adult patients (age ≥18 years) visiting outpatient clinics within the Montefiore Medical Center (MMC) health system between January 1, 2010 and December 31, 2015 were eligible for inclusion if they had complete demographic data, two or more outpatient clinic visits during the study period, two or more basic metabolic panels and serum albumins drawn in the outpatient setting, and a baseline plus at least one subsequent BMI value measured over the study period. Patients were additionally required to have visited an MMC clinic at least once during the year prior to the index date. The index date was defined as the first available anion gap value. Patients were excluded if they had an International classification of diseases (ICD-9) diagnosis within 10 years before or 90 days after the index date for asthma or other lung disease, congestive heart failure, pulmonary hypertension, obesity hypoventilation syndrome or obstructive sleep apnea, inflammatory bowel disease, chronic diarrhea, liver disease, ascites, HIV, AIDS, or any malignancy or if they filled a prescription within 90 days of the index date for diuretics, base equivalents, or antiretroviral medication. Patents with baseline bicarbonate values <15 or >40 mEq/L or baseline BMI values <15 or >60 kg/m² were excluded as outliers (n=636). The study was approved by the institutional review board for MMC/Albert Einstein College of Medicine (institutional review board no. 2018-9100). Informed consent was waived due to the use of deidentified data.

Data Collection
Patient data were obtained from the MMC electronic health record. BMI was calculated as weight in kilograms divided by height in meters squared. Patients who identified as Black Hispanic were included as Hispanic. Patients who did not identify as Black, White, Hispanic, or Asian were a small sample size and were combined with Asian patients in the Asian/other racial and ethnicity category. Baseline comorbidity was defined by the presence of an ICD-9 diagnosis code from 5 years before to 90 days after the index date. Diabetes mellitus was additionally defined by an A1c value ≥6.5% or a prescription for diabetes medication during this index time frame. Income was determined for each patient using the average household income within the patient’s zip code (16).

Only outpatient laboratory values were included in analyses. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula (17). Traditional and corrected anion gap values were calculated (6,15,18,19) from serum electrolytes, and albumin was collected during the same blood draw: traditional anion gap = serum sodium (milliequivalents per liter) - [serum chloride (milliequivalents per liter) + serum bicarbonate (milliequivalents per liter)]; corrected anion gap = traditional anion gap + [4.4 - serum albumin (grams per deciliter)] × 2.5. Incident-elevated anion gap was defined as the first of at least two occurrences after the index date of an anion gap >95th percentile of baseline anion gap values for the total cohort. As there is no standard percentile cutoff for elevated anion gap in previous literature (6,15), this value was chosen because it represents a notable deviation from the mean. Such a degree of elevation is perhaps more likely to represent pathology rather than minor variations in serum electrolytes. Within the MMC laboratory, the normal range for traditional anion gap is 7–16 mEq/L, whereas the mean is not defined. Incident low bicarbonate was defined as the first of at least two bicarbonate values ≤23 mEq/L after the index date. Given the variability in cutoffs for defining low bicarbonate in prior observational studies (20,21), this higher value was chosen to capture more events and increase statistical power. Anion gap metabolic acidosis was defined as the first of at least two occurrences of simultaneous low serum bicarbonate and elevated corrected anion gap. All blood samples for serum electrolytes and albumin were delivered immediately to the laboratory or refrigerated at 4°C–8°C until analyzed centrally within MMC by standardized processes. Serum bicarbonate was measured by the phosphoenolpyruvate carboxylase method, which represents total serum carbon dioxide. There were no changes in analytic methods of serum electrolytes or serum albumin during the study period.

Statistical Analyses
Patient characteristics at baseline were compared across BMI categories by ANOVA for continuous variables and chi-squared tests for categorical variables. The association of baseline BMI and anion gap was examined using linear regression models. The association of BMI with anion gap values over time was examined using multilevel mixed effects models specifying random intercepts and incorporating time-updated BMI, eGFR, and anion gap values. The associations of baseline BMI and incident elevated anion gap with anion gap metabolic acidosis, and of baseline anion gap with incident low bicarbonate and anion gap metabolic acidosis, were examined using Cox proportional hazards models. Time 0 was the date of the first available anion gap value during the study period. Patients were censored at the time of the last available anion gap or bicarbonate value. Covariates for all models were selected a priori and included age; sex; racial and ethnicity; eGFR; income; insurance status; and baseline hypertension, diabetes, and coronary artery disease. A P value of 0.05 was considered statistically significant. Data were analyzed using Stata 13.1 (StataCorp, College Station, TX).
Subgroup and Sensitivity Analyses

Analyses stratified by eGFR group were completed to rule out residual confounding by kidney function (6). Racial and ethnicity subgroups were analyzed due to the previously demonstrated racial and ethnic differences in low bicarbonate risk with greater BMI (10). Stratified analyses by hypertension status (22) and diabetes status (23) were completed to explore potential confounding by comorbidity and medication use. Given the association of dietary acid load and anion gap among patients with moderate CKD (15), an analysis incorporating baseline BUN as a surrogate for dietary protein was also included.

Results

Baseline Characteristics

In total, 94,488 and 94,197 patients were included in cross-sectional analyses of traditional and corrected anion gap, respectively. A small number of patients (n=291, 0.3%) were included in the traditional but not corrected cohort analysis, resulting from differences in available laboratory data. The mean age was 50.3±17 years, 64% were women, 34% were Black, 12% were White, and 36% were Hispanic. At baseline, 35% were overweight, and 43% were obese (class 1 or above). Hypertension, diabetes, and coronary artery disease were more common among patients with greater BMI. Traditional and corrected anion gaps were higher among overweight and obese categories compared with normal weight (Table 1).

Table 1. Baseline characteristics by World Health Organization categories of body mass index

| Characteristics | Body Mass Index, kg/m² |
|-----------------|-----------------------|
|                 | <18.5 | 18.5 to <25 | 25 to <30 | 30 to <35 | 35 to <40 | ≥40 |
| **Patients, n** | 1,049 | 20,041 | 32,664 | 22,594 | 10,726 | 7,414 |
| **Age, yr**     | 43 (23) | 49 (20) | 52 (17) | 51 (15) | 49 (15) | 46 (14) |
| **Women, n (%)**| 766 (73) | 13,046 (65) | 19,531 (60) | 14,481 (64) | 7534 (70) | 5538 (75) |
| **Racial and ethnicity, n (%)** | | | | | | |
| Black           | 330 (32) | 5084 (29) | 10,535 (32) | 8286 (37) | 4201 (39) | 3132 (42) |
| Hispanic        | 316 (30) | 6582 (33) | 11,896 (36) | 8384 (37) | 3885 (36) | 2665 (36) |
| Asian/other race| 247 (24) | 4581 (23) | 6495 (20) | 3705 (16) | 1632 (15) | 1099 (14) |
| White           | 156 (15) | 3074 (15) | 3738 (11) | 2219 (10) | 1008 (9) | 608 (8) |
| **Insurance, n (%)** | | | | | | |
| Commercial      | 583 (56) | 11,981 (60) | 20,323 (62) | 14,246 (63) | 6763 (63) | 4603 (62) |
| Medicare        | 176 (17) | 3333 (17) | 5111 (16) | 3168 (14) | 1299 (12) | 724 (10) |
| Medicaid        | 234 (22) | 3703 (19) | 5627 (17) | 4113 (18) | 2665 (18) | 2665 (18) |
| Self-pay        | 56 (5) | 1024 (5) | 1603 (5) | 1067 (5) | 520 (5) | 331 (5) |
| **Median income by zip code, n (%)** | | | | | | |
| <$30,000        | 190 (18) | 3525 (18) | 6419 (20) | 4768 (21) | 2413 (23) | 1962 (27) |
| $30,000–$49,999 | 471 (45) | 8824 (44) | 15,104 (46) | 10,698 (47) | 5091 (48) | 3370 (46) |
| $50,000–$69,999 | 163 (16) | 3388 (17) | 5223 (16) | 3404 (15) | 1569 (15) | 927 (13) |
| >$70,000        | 83 (8) | 1684 (8) | 2306 (7) | 1380 (6) | 617 (6) | 366 (5) |
| Not specified   | 142 (14) | 2620 (13) | 3612 (11) | 2344 (10) | 1036 (10) | 789 (11) |
| **Baseline diagnoses, n (%)** | | | | | | |
| Hypertension    | 258 (25) | 6927 (35) | 15,368 (47) | 12,173 (54) | 6102 (56.9) | 4212 (57) |
| Diabetes        | 88 (8) | 3118 (16) | 7618 (23) | 6767 (30.0) | 3642 (34) | 2647 (36) |
| Coronary artery disease | 64 (6) | 1356 (7) | 2689 (8) | 1847 (8.2) | 818 (8) | 484 (7) |
| **Baseline laboratory values** | | | | | | |
| eGFR,a ml/min per 1.73 m² | 101 (30) | 93 (26) | 88 (23) | 89 (23) | 91 (24) | 96 (24) |
| BUN,b mg/dl     | 14 (6) | 15 (6) | 15 (6) | 15 (6) | 15 (6) | 14 (6) |
| Serum sodium,c mEq/L | 140 (3) | 140 (3) | 141 (2) | 141 (2) | 141 (2) | 140 (2) |
| Serum chloride,d mEq/L | 103 (3) | 103 (3) | 103 (3) | 103 (3) | 103 (3) | 103 (3) |
| Serum bicarbonate,e mEq/L | 25 (3) | 26 (3) | 26 (3) | 26 (3) | 26 (3) | 25 (3) |
| Serum albumin,f g/dl (n=94,197) | 4.5 (0.4) | 4.5 (0.4) | 4.5 (0.3) | 4.4 (0.3) | 4.4 (0.3) | 4.2 (0.3) |
| **Anion gap, mEq/L** | | | | | | |
| Traditional     | 13 (2.8) | 12.0 (2.6) | 12.2 (2.6) | 12.3 (2.6) | 12.4 (2.6) | 12.4 (2.6) |
| Corrected (n=94,197) | 11.1 (2.8) | 10.9 (2.6) | 11.0 (2.5) | 11.2 (2.5) | 11.5 (2.5) | 11.8 (2.6) |

Continuous variables are reported as means (SD).

aCalculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.
bConversion to Système International units (millimoles per liter): milligrams per deciliter × 0.357 = millimoles per liter.
cConversion to Système International units (millimoles per liter): milliequivalents per liter = millimoles per liter.
dConversion to Système International units (grams per liter): grams per deciliter × 0.1 = grams per liter.

correction

Association of BMI with Anion Gap

After multivariable adjustment, a higher BMI was associated with progressively greater traditional and corrected anion gap, with a greater effect size seen for the latter (Supplemental Figure 1A and B). A slight attenuation of effect was seen at the highest BMI values for traditional (Supplemental Figure 1A) but not corrected anion gap (Supplemental Figure 1B). Analyses using more granular categories of BMI showed these same relationships.
Analyses; 13,972 (15.4%) and 15,477 (16.9%) patients rected anion gap at baseline and were included in these 91,494 patients did not have elevated traditional and cor-
rected anion gaps above the 95th percentiles of baseline values were de-
mons of time-updated BMI with traditional (A and C; n=94,488) and corrected (B and D; n=94,197) anion gap over time according to World Health Organization (WHO) BMI groups (A and B) and smaller BMI categories (C and D). Models were adjusted for age, sex, racial and ethnicity, baseline income, insurance status, eGFR, hypertension, diabetes, and coronary artery disease. Bars denote 95% con-

cides over time, positive associations between BMI and both anion gap measurements were next examined. During a median follow-up period of 4.4 years (interquartile range [IQR], 2.3–6.3), patients had a median of 15.8 mEq/L, respectively. A total of 90,459 and 94,197 anion gap over time according to World Health Organization (WHO) BMI groups (A and B) and smaller BMI categories (C and D). Models were adjusted for age, sex, racial and ethnicity, baseline income, insurance status, eGFR, hypertension, diabetes, and coronary artery disease. Bars denote 95% confidence intervals. *P<0.001; **P=0.01.

(Supplemental Figure 1, C and D). In particular, there was a striking, graded association of higher BMI with greater corrected anion gap throughout the range of overweight and obesity. Longitudinal associations of BMI with each anion gap measurement were then examined. Using more granular categories of BMI, the same strong graded association was seen with both anion gap definitions. Compared with BMI values of 18.5 to <22.5 kg/m², higher traditional and corrected anion gaps were seen even among patients with a BMI of 25 to <27.5 kg/m² (Figure 1, C and D). Although differences in corrected anion gap could be driven by differences in serum albumin associated with obesity (24), results were consistent across quartiles of baseline serum albumin (Supplemental Figure 2).

Association of BMI with Risk of Incident Elevated Anion Gap

Traditional and corrected anion gap values above the 95th percentiles of baseline values were defined as >17.0 and >15.8 mEq/L, respectively. A total of 90,459 and 91,494 patients did not have elevated traditional and corrected anion gap at baseline and were included in these analyses; 13,972 (15.4%) and 15,477 (16.9%) patients developed at least two occurrences of elevated traditional and corrected anion gap, respectively, during the follow-up period. Higher baseline BMI was associated with a progressively greater risk of incident elevated traditional and corrected anion gap (Figure 2, A and B). Again, the effect size was greater for corrected compared with traditional. These associations were confirmed with analyses using more granular categories of BMI (Figure 2, C and D). Compared with patients with a normal BMI, those with a BMI>40 had hazard ratios (HRs) of 1.32 (95% confidence interval [95% CI], 1.23 to 1.42) and 1.74 (95% CI, 1.63 to 1.85) for traditional (Figure 2A) and corrected (Figure 2B) anion gap, respectively. Those with a BMI>45 had HRs of 1.32 (95% CI, 1.18 to 1.48) and 1.90 (95% CI, 1.73 to 2.10) for elevated traditional (Figure 2C) and corrected (Figure 2D) anion gap, respectively. We again observed a J-shaped association of BMI and anion gap (Figure 2), a slight attenuation of effect for traditional anion gap at the highest BMI values (Figure 2, A and C), and a dose-response association of BMI and corrected gap, continuing through the highest categories of BMI (Figure 2D).

Associations of Obesity and Baseline Anion Gap with Risk of Incident Anion Gap Metabolic Acidosis

Next, to examine whether higher BMI was associated not only with risk of developing an elevated anion gap but also, with risk of anion gap metabolic acidosis, we examined the association of BMI with incident co-occurring (simultaneous) elevated corrected anion gap and low
bicarbonate. Over the study period, 7007 (9.3%) of 75,047 patients who did not have either abnormality at baseline developed this outcome. BMI was associated, in a graded fashion, with higher risk (Figure 3). Compared with a normal BMI, values of 30 to 35 and 35 to 40 at baseline were associated with HRs of 1.38 (95% CI, 1.26 to 1.50) and 1.53 (95% CI, 1.39 to 1.69), respectively (Figure 3A). Point estimates were similar and remained significant after exclusion of patients with an eGFR < 90 ml/min per 1.73 m² (Figure 3B).

Finally, we hypothesized that small relative differences of the anion gap represent a state of subclinical anion gap metabolic acidosis and thus, precede the development of more overt disturbances. Among patients with a BMI
Figure 4. Association of baseline anion gap quartile with incident low bicarbonate and anion gap metabolic acidosis. (A) Hazard ratios for incident low bicarbonate according to baseline quartiles of anion gap among patients with obesity (BMI ≥ 30) and normal bicarbonate at baseline (n = 32,500 for traditional and n = 26,637 for corrected). (B) Hazard ratios for anion gap metabolic acidosis among patients with obesity, normal bicarbonate, and normal corrected anion gap at baseline (n = 25,838). Models were adjusted for age, sex, racial and ethnic minority, baseline income, insurance status, eGFR, hypertension, diabetes, and coronary artery disease. Bars denote 95% confidence intervals. HR, hazard ratio. *P < 0.001; †P = 0.05; #P = 0.01.

>30 kg/m² and normal serum bicarbonate at baseline, higher anion gap measurements were independently associated, in a graded fashion, with higher risk of low bicarbonate. The HRs of the highest compared with lowest quartiles of traditional and corrected anion gap were 1.29 (95% CI, 1.23 to 1.40) and 1.36 (95% CI, 1.26 to 1.48), respectively (Figure 4A). Similar results were obtained for patients without obesity (BMI < 30); HRs for highest compared with lowest quartiles, 1.31 [95% CI, 1.23 to 1.38] for traditional and 1.42 [95% CI, 1.34 to 1.50] for corrected anion gap). We also examined the association of baseline corrected anion gap with incident anion gap metabolic acidosis. Among patients with obesity and without these abnormalities at baseline, a similar, graded association was seen across baseline quartiles of corrected anion gap. The HRs of the third and fourth quartiles compared with the first were 1.48 (95% CI, 1.34 to 1.63) and 1.78 (95% CI, 1.59 to 1.99) (Figure 4B).

Subgroup and Sensitivity Analyses

Significant positive associations of greater BMI and incident elevated anion gap were seen across eGFR subgroups (Table 2). Risk was also observed across race and ethnic groups (Supplemental Table 1). Exclusion of patients with hypertension at baseline (Supplemental Figure 3) yielded similar, significant point estimates in comparison with the total cohort for risk of incident elevated traditional (Supplemental Figure 3A) and corrected (Supplemental Figure 3B) anion gap. Greater BMI was associated with greater risk of elevated corrected anion gap among patients with (Supplemental Figure 4A) and without (Supplemental Figure 4B) diabetes mellitus at baseline. There was also a similar risk of anion gap metabolic acidosis among patients without diabetes mellitus (Supplemental Table 2) in comparison with the total cohort (Figure 3A). After additional adjustment for baseline BUN, the relationship between BMI and elevated traditional (Supplemental Figure 5A) and corrected (Supplemental Figure 5B) anion gap was similar to analyses without this variable (Figure 2, A and B). Changing the criteria for anion gap metabolic acidosis to include a bicarbonate cutoff of <22 mEq/L, rather than ≤23 mEq/L, also demonstrated a graded and significant, although slightly attenuated, risk of anion gap metabolic acidosis with higher BMI values (Supplemental Table 3). Lastly, mixed effects models were created that included baseline bicarbonate or corrected anion gap as a covariate in order to examine the average change in these variables by BMI group over the study period (Supplemental Table 4). These analyses demonstrated that greater BMI was associated with a greater rate of decline in serum bicarbonate and a greater increase in corrected anion gap.

Discussion

The results of this study demonstrate that higher BMI is associated with greater risk of developing anion gap elevation and anion gap metabolic acidosis. Additionally, among patients with obesity, even small elevations of the anion gap were associated with higher risk of low bicarbonate and more markedly with higher risk of anion gap metabolic acidosis. Collectively, these findings suggest that patients with obesity may be at risk for both subclinical and overt anion gap metabolic acidosis, a significant CKD risk factor (20,25).

The association between BMI and anion gap was seen across eGFR and race and ethnic subgroups; similar among those with and without diabetes; and unchanged after adjustment for BUN, a surrogate for dietary protein as a source of organic acid (15,26). We observed a consistent risk of elevated anion gap in association with obesity across a range of eGFR categories, including in patients with an eGFR of 30 to <60 ml/min per 1.73 m². Our outcome measurements relied upon at least two occurrences of these abnormalities, suggesting that our findings...
represent a chronic process with potentially significant clinical implications.

A potential source of anions and metabolic acidosis among patients with obesity is endogenous intermediary metabolites and acid production resulting from mitochondrial dysfunction (27). Relative elevations in fasting and postprandial venous and arterial lactate are described widely in patients with obesity (23,28,29) and insulin resistance (23,30,31). Although lactate is a ubiquitous energy substrate and a base equivalent (32) that is shuttled across cell walls and reutilized throughout the body (33), its capacity to act as a base depends upon its reuse for gluconeogenesis or oxidation within mitochondria (34). Patients with obesity and associated metabolic disease are shown to have reduced mitochondrial number (35), protein content (36), and oxidative capacity (36–38) in multiple metabolically active organs, including skeletal muscle (35), adipose tissue (36), and the liver (38). In this way, acid overproduction due to a pathologic reliance upon nonoxidative metabolism may explain our present and prior (10) findings. Other metabolites apart from lactate may also contribute to the observed anion gap elevations. Studies show small (typically <0.2 mmol) elevations in serum pyruvate (39), succinate (40), and other intermediary metabolites (41) as well as potentially diet-independent elevations of glutamate (39), aspartate (39), and anionic amino acid metabolites (42) among patients with obesity compared with healthy controls.

Limitations of this study include that our large dataset, arterial pH measurements were unavailable; therefore, we were unable to confirm the presence of

| Table 2. Association of body mass index with incident elevated traditional and corrected anion gap among eGFR subgroups |
|---------------------------------------------------------------|
| **eGFR, ml/min per 1.73 m²** | **Elevated Traditional Anion Gap** | **Elevated Corrected Anion Gap** |
|--------------------------------|----------------------------------|----------------------------------|
| **Hazard Ratio (95% Confidence Interval)** | **P Value** | **Hazard Ratio (95% Confidence Interval)** | **P Value** |
| >120 (subgroup size: traditional, n=10,188; corrected, n=10,174) | | |
| BMI <18.5 kg/m² | 1.79 (1.20 to 2.66) | 0.01 | 1.81 (1.25 to 2.62) | 0.01 |
| BMI=18.5 to <25 kg/m² | ref | n/a | ref | n/a |
| BMI=25 to <30 kg/m² | 1.06 (0.87 to 1.30) | 0.56 | 0.89 (0.73 to 1.08) | 0.24 |
| BMI=30 to <35 kg/m² | 1.00 (0.81 to 1.24) | 0.99 | 1.09 (0.89 to 1.34) | 0.39 |
| BMI=35 to <40 kg/m² | 1.27 (1.00 to 1.61) | 0.05 | 1.32 (1.06 to 1.65) | 0.05 |
| BMI >40 kg/m² | 1.10 (0.86 to 1.41) | 0.43 | 1.43 (1.15 to 1.78) | 0.01 |
| 90 to <120 (subgroup size: traditional, n=35,770; corrected, n=36,163) | | |
| BMI <18.5 kg/m² | 1.62 (1.16 to 2.25) | 0.01 | 1.70 (1.26 to 2.32) | 0.01 |
| BMI=18.5 to <25 kg/m² | ref | n/a | ref | n/a |
| BMI=25 to <30 kg/m² | 1.15 (1.05 to 1.26) | 0.03 | 1.16 (1.06 to 1.26) | 0.01 |
| BMI=30 to <35 kg/m² | 1.30 (1.18 to 1.43) | <0.001 | 1.41 (1.31 to 1.58) | <0.001 |
| BMI=35 to <40 kg/m² | 1.35 (1.21 to 1.51) | <0.001 | 1.56 (1.42 to 1.73) | <0.001 |
| BMI >40 kg/m² | 1.41 (1.25 to 1.59) | <0.001 | 1.88 (1.69 to 2.10) | <0.001 |
| 60 to <90 (subgroup size: traditional, n=35,482; corrected, n=36,010) | | |
| BMI <18.5 kg/m² | 1.30 (0.91 to 1.85) | 0.15 | 1.50 (1.09 to 2.07) | 0.05 |
| BMI=18.5 to <25 kg/m² | ref | n/a | ref | n/a |
| BMI=25 to <30 kg/m² | 1.04 (0.96 to 1.12) | 0.38 | 1.11 (1.03 to 1.20) | 0.01 |
| BMI=30 to <35 kg/m² | 1.15 (1.06 to 1.25) | 0.01 | 1.38 (1.28 to 1.49) | <0.001 |
| BMI=35 to <40 kg/m² | 1.27 (1.15 to 1.40) | <0.001 | 1.58 (1.44 to 1.74) | <0.001 |
| BMI >40 kg/m² | 1.29 (1.14 to 1.45) | <0.001 | 1.76 (1.58 to 1.97) | <0.001 |
| 30 to <60 (subgroup size: traditional, n=8397; corrected, n=8525) | | |
| BMI <18.5 kg/m² | 0.99 [0.54 to 1.80] | 0.97 | 0.75 [0.40 to 1.41] | 0.38 |
| BMI=18.5 to <25 kg/m² | ref | n/a | ref | n/a |
| BMI=25 to <30 kg/m² | 0.98 (0.87 to 1.11) | 0.75 | 1.01 (0.89 to 1.13) | 0.91 |
| BMI=30 to <35 kg/m² | 1.04 (0.91 to 1.18) | 0.56 | 1.13 (0.99 to 1.28) | 0.07 |
| BMI=35 to <40 kg/m² | 1.03 (0.88 to 1.20) | 0.72 | 1.15 (0.98 to 1.34) | 0.08 |
| BMI >40 kg/m² | 1.18 (0.98 to 1.43) | 0.09 | 1.49 (1.24 to 1.79) | <0.001 |
| 15 to <30 (subgroup size: traditional, n=622; corrected, n=622) | | |
| BMI <18.5 kg/m² | 1.41 (0.43 to 4.61) | 0.57 | Too few observations | n/a |
| BMI=18.5 to <25 kg/m² | ref | n/a | ref | n/a |
| BMI=25 to <30 kg/m² | 1.17 (0.81 to 1.68) | 0.40 | 1.13 (0.78 to 1.65) | 0.52 |
| BMI=30 to <35 kg/m² | 0.83 (0.57 to 1.20) | 0.32 | 0.83 (0.57 to 1.22) | 0.35 |
| BMI=35 to <40 kg/m² | 0.84 (0.52 to 1.35) | 0.47 | 1.00 (0.62 to 1.61) | >0.99 |
| BMI >40 kg/m² | 0.70 (0.42 to 1.18) | 0.18 | 1.05 (0.62 to 1.77) | 0.86 |

The multivariable model was adjusted for age, sex, race/ethnicity, baseline income, insurance status, hypertension, diabetes, and coronary artery disease. BMI, body mass index; 95% CI, 95% confidence interval; ref, reference; n/a, not applicable.
metabolic acidosis. Early in the course of CKD, normal anion gap metabolic acidosis may also be present, which typically precedes anion gap elevations in more advanced disease (43). We suspect that this sequence of events has perhaps attenuated the relationship between BMI and anion gap metabolic acidosis in our results. Additionally, the anion gap is a relatively insensitive diagnostic tool for detecting lactate elevations (44), which may be due to concurrent abnormalities in sodium and other electrolytes masking anion accumulation determined indirectly by calculation. Given that lactate may be a contributor to our findings (23,28,29), our results perhaps underestimate the risk of anion gap elevation associated with obesity. Moreover, although we have demonstrated that greater obesity is associated with greater increases in anion gap over time, these higher levels may still remain within the normal range. Therefore, we may have underestimated the association of obesity with the risk of elevated anion gap, and a longer period of follow-up might have captured a stronger effect size. Mild corrected anion gap elevations (6) and tissue acid retention (45) have been demonstrated in CKD stage 2, which may also influence our results. However, our findings were consistent across eGFR subgroups, and anion gap metabolic acidosis risk with greater BMI was demonstrated even among patients with an eGFR ≥90 ml/min per 1.73 m². Certain medications commonly prescribed for patients with diabetes may influence bicarbonate levels among patients with CKD (46). However, our subgroup analysis excluding baseline diabetes mellitus demonstrated a similar risk of anion gap metabolic acidosis as compared with the total cohort. There may also be residual confounding by respiratory alkalosis with renal compensation among patients within this population. We suspect this is a relatively minor contributor to our findings on the basis of the following evidence. Obesity is more commonly associated with hypo- rather than hyperventilation syndromes (47). Also, greater BMI has been shown to associate with higher, not lower, partial pressure of carbon dioxide in arterial blood levels (48) and lower urine pH (49). Collectively, this suggests a metabolic rather than respiratory cause of low bicarbonate in patients with obesity. The association of low bicarbonate with elevated anion gap further suggests a metabolic cause. Nevertheless, we cannot exclude the possibility that in a subset of patients, the association of higher BMI with lower serum bicarbonate represents respiratory alkalosis. A final limitation is that observational data can only demonstrate correlation and not causation. Future studies are needed to confirm these findings and further define acid-base changes in the setting of obesity.

In conclusion, these results demonstrate that an increasingly populous patient group within the United States (50), those who are overweight and those with obesity, may be at risk of anion gap metabolic acidosis, even prior to the development of CKD. This pathology may be of clinical significance given the risk of adverse kidney disease outcomes among patients with obesity (12).

Disclosures
M.K. Abramowitz reports consultancy agreements with Tricida, Inc.; ownership interest in Aethlon Medical, Inc.; and honoraria from Medscape and the National Kidney Foundation. The remaining author has nothing to disclose.

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Author Contributions
M.K. Abramowitz and D.C. Lambert conceptualized the study; D.C. Lambert was responsible for data curation; D.C. Lambert was responsible for formal analysis; M.K. Abramowitz was responsible for methodology; D.C. Lambert was responsible for project administration; M.K. Abramowitz provided supervision; D.C. Lambert wrote the original draft, and M.K. Abramowitz and D.C. Lambert reviewed and edited the manuscript.

Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0003562021/-/DCSupplemental.

Supplemental Figure 1. Association of BMI with traditional and corrected anion gap.
Supplemental Figure 2. Association of BMI with corrected anion gap over time in subgroups by albumin quartiles.
Supplemental Figure 3. Association of BMI with corrected anion gap among patients without hypertension.
Supplemental Figure 4. Association of BMI with incident elevated anion gap among diabetes subgroups.
Supplemental Figure 5. Association of BMI with incident elevated anion gap adjusted for BUN.
Supplemental Table 1. Association of BMI with incident elevated anion gap adjusted for BUN.
Supplemental Table 2. Association of BMI with incident anion gap metabolic acidosis among subgroup without diabetes.
Supplemental Table 3. Association of BMI with incident anion gap metabolic acidosis (bicarbonate <22 mEq/L).
Supplemental Table 4. Association of BMI with change in bicarbonate and corrected anion gap over the study period.

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