Influence of Medications Containing Acid Salts on Serum Bicarbonate in CKD

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Abstract
Background Many medications are formulated with acid salts. Their effect on acid-base balance in CKD is unclear.

Methods We calculated the acid load (meq/d) from medications prescribed to 74 United States veterans with diabetes and CKD to identify agents with high potential acid load. We also determined cross-sectional associations between the acid load from medications and acid-base parameters after adjusting for demographics, eGFR, protein intake, and other confounders.

Results Of the 125 medications prescribed, 31 (25%) contained an acid salt. Metformin hydrochloride (15.4 meq/d at 2550 mg/d) and gabapentin hydrochloride (13.0 meq/d at 2700 mg/d) were identified as agents with a high potential acid load. Mean daily acid load from medications was 6.6 meq/d in the overall cohort, 14.2 meq/d in the high medication acid load group (≥7.7 meq/d, n=29), and 1.6 meq/d in the low medication acid load group (<7.7 meq/d, n=45). After adjusting for potential confounders, those in the high acid load group had 1.7 meq/L lower total carbon dioxide (CO₂) and 2.2 meq/L higher anion gap than those in the low acid load group. Use of gabapentin alone was not associated with differences in total CO₂ or anion gap. Use of metformin alone was associated with 0.7 meq/L lower total CO₂ and 1.0 meq/L higher anion gap. Use of metformin with gabapentin was associated with 1.8 meq/L lower total CO₂ and 2.4 meq/L higher anion gap. The higher anion gap was not explained by higher serum lactate levels. The acid load from medications was not associated with differences in urinary ammonium, titratable acid, or pH.

Conclusions Medications containing acid salts, particularly metformin hydrochloride and gabapentin hydrochloride, are sources of an exogenous acid load. These agents may influence serum total CO₂ levels and serum anion gap in individuals with CKD.

Clinical Trial registry name and registration number Investigations of the Optimum Serum Bicarbonate Level in Renal Disease, NCT01574157

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Introduction Medications are commonly formulated as salts to increase solubility and bioavailability. Salt formulation also permits large-scale manufacturing and improves palatability (1). The hydrochloride salt is commonly used to improve the bioavailability of basic drugs and helps minimize foul tastes and odors associated with amine compounds in medications. These characteristics of the hydrochloride salt improve patient satisfaction and gastrointestinal absorption (1). Although generally thought to be innocuous, the acid load from medications may adversely affect patients with CKD. Many patients with CKD have impaired kidney acid excretion and are prone to develop metabolic acidosis, which is associated with a number of adverse consequences including bone demineralization, skeletal muscle catabolism, CKD progression, and death (2–6). It is unclear what effect, if any, the acid load from medications has on acid-base balance in patients with CKD.

To investigate this, we used baseline data from a clinical trial testing the effect of oral sodium bicarbonate supplementation on kidney fibrosis and injury markers in United States veterans with diabetic kidney disease and normal serum total carbon dioxide (CO₂) (7). Our objectives were to determine the potential acid load derived from medications, to identify agents with particularly high acid content, and to evaluate cross-sectional associations between the acid load from medications and serum (total CO₂, anion gap, and lactate) and urinary (ammonium, titratable acids, and pH) acid-base measurements in individuals with CKD.

Materials and Methods

Study Population
We analyzed data from all individuals (n=74) who participated in a single-center, randomized, double-
blinded, placebo-controlled trial testing the effect of 6 months of sodium bicarbonate on kidney fibrosis and injury markers (NCT01574157) (7). Key inclusion criteria were being a United States veteran older than 18 years and having type I or II diabetes mellitus and stage 2–4 CKD. Importantly, individuals were eligible if serum total CO$_2$ was 22–28 meq/L at the screening visit and they were not taking agents typically prescribed for the treatment of metabolic acidosis (i.e., sodium bicarbonate, sodium citrate, or potassium citrate). Because participants were randomly assigned to receive either sodium bicarbonate or placebo, we analyzed the baseline data from this cohort, before study medications were administered.

**Determination of the Acid Load from Medications**
Research staff obtained medication, dose, and frequency data from the electronic medical record and reviewed the information with participants for accuracy. Medication data were also reviewed by the investigators and discrepancies were resolved by reviewing the electronic medical record of the participant. Medications were reviewed to determine which were formulated with acid-containing salts (i.e., hydrogen chloride) and the daily dose of each was calculated in milligrams. The daily acid load (meq/d) was determined by dividing the daily dosage (mg/d) by the mol wt of the agent (mg/mmol), factoring the valence of an agent as appropriate. The mol wt of each agent was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/), an open chemistry database of the National Institutes of Health (8).

**Measurements**
Participants collected urine samples for 24 hours under mineral oil (9). Urinary pH, ammonium, and titratable acid were measured by the formalin-titration method (10). Serum lactate was measured enzymatically (LifeSpan Biosciences, Seattle, WA). All other laboratory values were measured by the clinical laboratory. Serum anion gap was calculated as sodium-chloride-total CO$_2$. Total protein intake was calculated using the equation 6.25×(urine urea nitrogen+[weight×0.031]) (11). The GFR was estimated using the CKD-Epidemiology Collaboration formula (12).

**Definitions**
Participants were categorized into two groups, a high acid load group and a low acid load group, determined by the sum of the daily acid content derived from medications. We selected a threshold of 7.7 meq to categorize the participants, reasoning that this is the quantity of acid that would require at least one 650-mg tablet of sodium bicarbonate (7.7 meq of bicarbonate) to counterbalance the acid load from medications. We categorized individuals as having a low or normal serum total CO$_2$ based on the median baseline value in the cohort (23 meq/L).

**Study Oversight**
The study was funded by United States Department of Veterans Affairs (VA) Clinical Sciences Research and Development Service and was approved by the Institutional Review Boards of the University of Utah and VA Salt Lake City Health Care System. All participants signed an informed consent document. The study was performed under the principles embodied in the Declaration of Helsinki. A data monitoring committee, established by the Department of VA Clinical Sciences Research and Development Service, provided oversight of the parent study.

**Statistical Analyses**
Cross-sectional associations between independent and dependent variables were conducted using linear regression models. The odds of having a serum total CO$_2$ ≤23 meq/L was determined using logistic regression. Our principal model adjusted for age, eGFR, urinary albumin-creatinine ratio, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretic use, serum potassium concentration, body mass index, estimated protein intake, and a self-reported history of lung disease. A sensitivity analysis also adjusted for use of calcium-containing medications. The analyses were performed using Stata 16 (StataCorp, College Station, TX).

**Results**

**Acid Load from Medications**
A total of 125 different medications were being used by participants at their baseline visit. The mean (SD) number of medications taken per participant was 11 (4). A total of 31 medications (25%) were formulated with an acid salt. The potential acid load from an individual medication used by at least one participant was broad, ranging from 0.0009 meq/d (tamsulosin hydrochloride, 0.4 mg/d) to 15.4 meq/d (metformin hydrochloride, 2550 mg/d). Figure 1 shows the distribution of the total acid load from medications, which ranged from 0 to 25.2 meq/d. The mean (SD) acid load from medications was 6.6 (7.0) meq/d. Table 1 shows the ten medications with the highest potential acid load that were used by at least one participant in the study. Among these agents, only metformin hydrochloride and gabapentin hydrochloride were identified as contributing a meaningful acid load. The prescribed dosages of metformin hydrochloride (range, 500–2550 mg/d) and gabapentin hydrochloride (range, 200–2700 mg/d) are shown in Table 2.

**Figure 1.** Twenty-nine individuals (39%) in the study had high potential acid load from medications.
per 1.73 m² than those in the low acid load group with a mean (SD) acid load of 1.6 (2.4) meq/d. Almost all (n=27) in the high acid load group were prescribed metformin hydrochloride; approximately half in this group were also prescribed gabapentin hydrochloride. There were no significant differences with respect to demographics, comorbidities, or protein intake between the high and low acid load groups. However, the eGFR and daily urinary ammonium excretion were higher in the high acid load group. Urinary titratable acid excretion, urinary pH, and serum total CO₂ were similar between the high and low acid load groups. However, the cross-sectional associations between use of metformin hydrochloride and gabapentin hydrochloride with acid-base variables are shown in Table 2.

Characteristics of Those with High and Low Potential Acid Load from Medications
A total of 29 individuals (39%) had a high potential acid load from medications (>7.7 meq/d) (Figure 1, Table 3). In this group, the mean (SD) acid load was 14.2 (4.3) meq/d. A total of 45 individuals (61%) had a low acid load from medications (<7.7 meq/d), with a mean (SD) acid load of 1.6 (2.4) meq/d. Almost all (n=27) in the high acid load group were prescribed metformin hydrochloride; approximately half in this group were also prescribed gabapentin hydrochloride. There were no significant differences with respect to demographics, comorbidities, or protein intake between the high and low acid load groups. However, the eGFR and daily urinary ammonium excretion were higher in the high acid load group. Urinary titratable acid excretion, urinary pH, and serum total CO₂ were similar between the high and low acid load groups; although serum total CO₂ was lower among those in the high acid load group with eGFR <45 ml/min per 1.73 m² than those in the low acid load group with similar eGFR. A total of 31 individuals had serum total CO₂ ≤23 meq/L. Although the serum total CO₂ entry criterion for the study was 22–28 meq/L, satisfaction of this criterion was established at the screening visit. At the baseline visit, eight individuals had a serum total CO₂ of 21 meq/L and one had a level of 17 meq/L. Among those in the high acid load group, 52% had a serum total CO₂ ≤23 meq/L as compared with 36% in the low acid load group. There was no difference in serum anion gap or lactate between the groups.

Cross-Sectional Associations between Acid Load from Medications and Acid-Base Variables
Table 4 shows the adjusted cross-sectional associations between each independent and dependent variable. For every SD (7 meq/d) higher potential acid load from medications, serum total CO₂ was 0.7 meq lower and the odds of having a serum total CO₂ ≤23 meq/L were 84% higher, although the latter was not statistically significant. The serum anion gap was also 1.1 meq/L higher. Comparisons between the high and low acid groups showed that those in the high group had 1.7 meq/L lower serum total CO₂, fivefold higher odds of having total CO₂ ≤23 meq/L, and a 2.2 meq/L higher serum anion gap. Serum sodium and chloride were slightly lower and the magnitude of the difference was similar between the two, suggesting the presence of an unmeasured anion. However, there was no variability in serum phosphate or serum lactate levels. Similarly, there were no appreciable differences in urinary ammonium, urinary titratable acid, or urinary pH (Table 4).

Cross-Sectional Associations between Use of Metformin Hydrochloride and Gabapentin Hydrochloride with Acid-Base Variables
Metformin hydrochloride use, not exclusive of gabapentin hydrochloride use, was associated with a 1.2 meq/L lower serum total CO₂, 82% higher odds of having total CO₂ ≤23 meq/L, and a 1.7 meq/L higher serum anion gap (Table 4). Gabapentin hydrochloride use, not exclusive of metformin hydrochloride use, was associated with a 1.0 meq/L lower serum total CO₂, 63% higher odds of having serum total CO₂ ≤23 meq/L, and a 1.2 meq/L higher serum anion gap (Table 4). Use of metformin hydrochloride or gabapentin hydrochloride was not associated with significant differences in serum lactate, urinary ammonium, urinary titratable acid, or urinary pH (Table 4).

Because the analyses of the associations between metformin hydrochloride use and gabapentin hydrochloride use did not exclude use of the other medication, we further analyzed participants in four categories based on their use of each medication (Table 5). Notably, the potential acid load from medications among those taking neither metformin hydrochloride nor gabapentin hydrochloride was low with a mean of 0.2 meq/d. Those taking metformin hydrochloride alone had a higher potential acid load from medications.

Table 1. Ten medications with the highest potential acid load

| Medication                        | Mol Wt (mg/mmol) | Potential Acid Load (mEq)* |
|----------------------------------|------------------|----------------------------|
| Metformin hydrochloride          | 165.6            | 2550 mg=15.4               |
| Gabapentin hydrochloride         | 207.7            | 2700 mg=13.0               |
| Bupropion hydrochloride          | 276.2            | 300 mg=1.1                 |
| Sotalol hydrochloride            | 308.8            | 240 mg=0.8                 |
| Ranitidine hydrochloride         | 350.9            | 300 mg=0.8                 |
| Venlafaxine hydrochloride        | 313.9            | 225 mg=0.7                 |
| Verapamil hydrochloride          | 491.1            | 360 mg=0.7                 |
| Tramadol hydrochloride           | 299.8            | 150 mg=0.5                 |
| Trazodone hydrochloride          | 408.3            | 200 mg=0.5                 |
| Dilitiazem hydrochloride         | 450.9            | 240 mg=0.5                 |

*Refers to the highest dose prescribed to at least one participant in the study.

Table 2. Doses of metformin hydrochloride and gabapentin hydrochloride used by study participants

| Dose (mg/d) | Potential Acid Load (meq/d) | No. of Participants |
|------------|-----------------------------|---------------------|
| Metformin hydrochloride     |                             |                     |
| 500        | 3.0                         | 1                   |
| 1000       | 6.0                         | 12                  |
| 2000       | 12.1                        | 19                  |
| 2550       | 15.4                        | 1                   |
| Gabapentin hydrochloride    |                             |                     |
| ≤600       | 2.9                         | 7                   |
| 900        | 4.3                         | 4                   |
| 1200       | 5.8                         | 5                   |
| 1800       | 8.7                         | 5                   |
| 2700       | 13.0                        | 3                   |
than those taking gabapentin hydrochloride alone (10.6 versus 5.4 meq/d). The highest acid load was among those taking both agents (15.8 meq/d). Metformin hydrochloride use alone was associated with a 1.8 meq/L lower serum total CO2 and anion gap (Table 5). However, use of both agents was associated with a 2.8 meq/L lower serum total CO2 and 4.3 meq/L higher anion gap (Table 5). Serum chloride levels were lower among those taking metformin hydrochloride, either alone or with gabapentin hydrochloride, consistent with accumulation of an unmeasured anion. However, no appreciable difference in serum lactate levels or phosphate (not shown) was observed. The use of these agents alone or in combination was not associated with significant differences in urinary pH, ammonium, or titratable acids (data not shown).

### Discussion

We investigated the cross-sectional relationship between the acid load of medications containing an acid salt and serum and urinary acid-base parameters in individuals with diabetic CKD, most of whom had a normal serum total CO2 at the time of data collection. One of our main goals was to identify agents commonly prescribed in clinical practice that might contribute a significant acid load to individuals with CKD. Although 25% of medications prescribed as part of routine clinical care contained an acid salt, only two contributed a meaningful acid load (metformin hydrochloride and gabapentin hydrochloride) due to their low mol wt and low potency. Indeed, among those not taking metformin hydrochloride or gabapentin hydrochloride, the mean potential acid load derived from medications was <1 meq/d. However, among those in the high acid load group, nearly all of whom were taking metformin hydrochloride and half were taking gabapentin hydrochloride, the mean potential daily acid load from medications was 14.2 meq, which is approximately equivalent to the potential renal acid load of 150 g of beef, chicken, or pork (13). Alternatively, counter-balancing this potential acid load would require consumption of two 650 mg sodium bicarbonate tablets. Hence,

### Use of Base-Forming Agents

We also evaluated use of base-forming agents in the participants. None were prescribed lanthanum carbonate, sevelamer carbonate, or ferric citrate. Seven individuals were taking either calcium carbonate (n=5) or calcium citrate (n=2). Additional adjustment for the use of these agents did not significantly alter the results (Supplemental Tables 1 and 2). Sildenafil citrate was the only other prescribed agent formulated with a base-forming salt. Because this agent is taken as needed and contributes very little base given its high mol wt (667 mg/mol) and potency (100 mg maximum daily dose), we did not consider it in further analyses.

### Table 3. Characteristics of the participants

| Characteristic                          | Total Population (n=74) | High Acid Load (n=29) | Low Acid Load (n=45) |
|----------------------------------------|------------------------|----------------------|---------------------|
| Demographics                           |                        |                      |                     |
| Age, yr                                | 71.6±7.9b              | 70.6±6.9b            | 72.4±8.5b           |
| Male, no. (%)                          | 72 (97)                | 29 (100)             | 43 (96)             |
| White, no. (%)                         | 68 (92)                | 25 (86)              | 43 (96)             |
| Hispanic, no. (%)                      | 7 (9)                  | 2 (7)                | 5 (11)              |
| Comorbidities                          |                        |                      |                     |
| Coronary artery disease, no. (%)       | 15 (20)                | 5 (17)               | 10 (22)             |
| Hypertension, no. (%)                  | 64 (86)                | 25 (86)              | 39 (87)             |
| Systolic BP, mm Hg                     | 128±12b                | 130±11b              | 127±12b             |
| Body mass index, kg/m²                 | 32.8±5.9b              | 33.0±6.8b            | 32.7±5.4b           |
| Protein intake, g/d                    | 87±32b                 | 90±31b               | 80±33b              |
| Medication data                        |                        |                      |                     |
| Metformin use, no. (%)                 | 33 (45)                | 27 (93)              | 6 (13)              |
| Gabapentin use, no. (%)                | 24 (32)                | 16 (55)              | 8 (18)              |
| Insulin use, no. (%)                   | 48 (65)                | 17 (59)              | 31 (69)             |
| Medication acid load, meq/d            | 6.6±7.0b               | 14.2±4.3b            | 1.6±2.4b            |

| Laboratory data                        |                        |                      |                     |
| eGFR, ml/min per 1.73 m²               | 51±18b                 | 62±18b               | 44±14b              |
| Urinary ACR, mg/g                      | 121 (58–370)           | 98 (45–358)          | 149 (64–370)        |
| Serum total CO₂, meq/L                 | 24.2±2.4b              | 23.9±2.4b            | 24.5±2.4b           |
| eGFR <45 ml/min per 1.73 m²            | 24.2±2.4b              | 22.0±1.7b            | 24.6±2.1b           |
| eGFR ≥45 to <60 ml/min per 1.73 m²     | 24.0±2.8b              | 24.1±2.5b            | 23.9±3.1b           |
| eGFR ≥60 ml/min per 1.73 m²            | 24.3±2.4b              | 24.1±2.5b            | 24.9±2.1b           |
| Total CO₂ ≥23 meq/L, no. (%)           | 31 (42)                | 15 (52)              | 16 (36)             |
| Serum anion gap, meq/L                 | 9±3b                   | 9±3b                 | 8±2b                |
| Serum lactate, mmol/L                  | 2.1±0.8b               | 2.2±0.8b             | 2.1±0.8b            |
| Urinary NH₄⁺, meq/d                    | 34±20b                 | 40±25b               | 30±14b              |
| Urinary TA, meq/d                      | 32±15b                 | 33±15b               | 31±15b              |
| Urine pH                               | 5.5±0.4b               | 5.5±0.4b             | 5.5±0.4b            |

ACR, albumin-creatinine ratio; CO₂, carbon dioxide; NH₄⁺, ammonium; TA, titratable acids.

*Expressed as median (interquartile range).

*Expressed as mean±SD.
medications containing acid salts, particularly metformin hydrochloride and gabapentin hydrochloride, are potential and likely unrecognized sources of a significant exogenous acid load.

A second objective was to determine whether the acid load from medications affects serum and urinary acid-base indices. Those in the high potential acid load group had 1.7 meq/L lower serum total CO2 and 2.2 meq/L higher serum anion gap compared with those with a low acid load. Results from prior observational studies suggest that a 1.7 meq/L lower serum total CO2 and 2.2 meq/L higher anion gap. This pattern suggests the presence a dose-response relationship between the acid load from medications and serum total CO2 and anion gap.

| Independent Variable | Each SD Higher (7 meq/L) H+ Load | High versus Low Acid Load | Metformin Usea | Gabapentin Useb |
|----------------------|---------------------------------|--------------------------|----------------|----------------|
| **Serum measurement** |                                 |                          |                |                |
| Total CO2 (meq/L)    | −0.7 (−1.3 to −0.1)             | −1.7 (−3.0 to −0.5)     | −1.2 (−2.4 to 0.0) | −1.0 (−2.2 to 0.3) |
| Odds of total CO2 ≥23 meq/L | 1.84 (0.94 to 3.60)           | 5.03 (1.16 to 21.9)    | 1.82 (0.55 to 6.04) | 1.63 (0.47 to 5.67) |
| Anion gap (meq/L)    | 1.1 (0.5 to 1.7)               | 2.2 (0.9 to 3.4)       | 1.7 (0.5 to 2.9)  | 1.2 (−0.1 to 2.5) |
| Sodium (meq/L)       | −0.6 (−1.4 to 0.3)             | −0.8 (−2.4 to 0.9)     | −1.4 (−2.9 to 0.1) | −0.1 (−1.6 to 1.4) |
| Chloride (meq/L)     | −0.8 (−1.5 to 0.0)             | −0.9 (−2.5 to 0.7)     | −1.6 (−3.0 to −0.2) | −0.2 (−1.6 to 1.3) |
| Phosphate (mg/dl)    | 0.0 (−0.2 to 0.2)              | 0.0 (−0.3 to 0.3)      | −0.1 (−0.4 to 0.2) | 0.1 (−0.2 to 0.4) |
| Lactate (mmol/L)     | 0.1 (−0.2 to 0.3)              | 0.3 (−0.2 to 0.8)      | 0.3 (−0.2 to 0.7) | 0.0 (−0.4 to 0.5) |
| **Urine measurement** |                                 |                          |                |                |
| Ammonium (meq/d)     | 2.8 (−1.2 to 6.9)              | 3.7 (−4.7 to 12.1)     | 3.9 (−3.9 to 11.7) | 2.7 (−5.2 to 10.6) |
| Titratable acid (meq/d) | −0.7 (−3.6 to 2.2)           | 0.0 (−6.0 to 6.1)      | −2.9 (−8.4 to 2.6) | −2.7 (−8.3 to 2.8) |
| Urine pH             | 0.0 (−0.1 to 0.1)              | −0.1 (−0.3 to 0.2)     | 0.0 (−0.2 to 0.2) | 0.0 (−0.3 to 0.2) |

Models adjusted for the following variables: age, eGFR, urinary albumin-creatinine ratio, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretic use, serum potassium concentration, body mass index, estimated protein intake, and a self-reported history of lung disease. Shown are the coefficients (95% confidence intervals). H+, hydrogen ion; CO2, carbon dioxide.

aNot exclusive of gabapentin use.
bNot exclusive of metformin use.

Metformin hydrochloride seems to be particularly likely to influence serum acid-base parameters. Its use alone was associated with 0.7 meq/L lower serum total CO2 and 1.0 meq/L higher anion gap. Although gabapentin hydrochloride use alone was not associated with appreciable differences in serum total CO2 or anion gap, this may be due to the lower acid load from medications in this group (5.4 meq/d) than in the metformin alone group (10.6 meq/d). Nevertheless, gabapentin seems to have an additive effect because users of both agents had mean potential acid load of 15.4 meq/d, 1.8 meq/L lower serum total CO2, and 2.4 meq/L higher anion gap. This pattern suggests the presence a dose-response relationship between the acid load from medications and serum total CO2 and anion gap.

Table 5. Association between use of metformin and gabapentin alone or in combination and acid-base variables

| Variables                        | Group                                      |
|----------------------------------|--------------------------------------------|
|                                  | Metformin Use=No, Gabapentin Use=No(n=32) | Metformin Use=Yes, Gabapentin Use=No(n=18) | Metformin Use=No, Gabapentin Use=Yes(n=9) | Metformin Use=Yes, Gabapentin Use=Yes(n=15) |
| Potential acid load (meq/d)a     | 0.2 (0.5)                                  | 10.6 (3.3)                                  | 5.4 (3.1)                                  | 15.8 (5.6)                                  |
| Serum measurement                 |                                            |                                            |                                            |                                            |
| Total CO2 (meq/L)                 | Reference                                  | −0.7 (−2.3 to 0.9)                         | −0.1 (−2.4 to 2.1)                         | −1.8 (−3.4 to 0.2)                         |
| Chloride (meq/L)                  | Reference                                  | −1.7 (−3.4 to 0.0)                         | 0.1 (−2.4 to 2.6)                         | −1.3 (−3.0 to 0.5)                         |
| Sodium (meq/L)                    | Reference                                  | −1.4 (−3.3 to 0.4)                         | −0.3 (−2.9 to 2.4)                         | −0.7 (−2.5 to 1.2)                         |
| Anion gap (meq/L)                 | Reference                                  | 1.0 (−0.5 to 2.5)                          | −0.3 (−2.4 to 1.9)                         | 2.4 (0.9 to 4.0)                           |
| Lactate (mmol/L)                  | Reference                                  | 0.0 (−0.5 to 0.6)                          | −0.5 (−1.4 to 0.3)                         | 0.3 (−0.3 to 0.9)                          |

Models adjusted for the following variables: age, eGFR, urinary albumin-creatinine ratio, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretic use, serum potassium concentration, body mass index, estimated protein intake, and a self-reported history of lung disease. Shown are the coefficients (95% confidence intervals). CO2, carbon dioxide.

aShown as mean (SD).
We considered whether changes in total CO₂ and anion gap might be explained by lactic acid production, particularly given the association between metformin and lactic acidosis. However, serum lactate levels were not substantially different among those taking this agent alone or in combination with gabapentin hydrochloride. Hence, we do not think that lactate accumulation accounts for the observed changes in total CO₂ or anion gap. Because these agents are not anions, their presence in serum does not account for the changes in the anion gap. The higher anion gap also does not appear to be related to differences in serum phosphate levels. Although the acid load from medications was associated with significant differences in serum total CO₂ and anion gap, there was no appreciable difference in urinary acid excretion, suggesting that kidney acid excretion, and consequently bicarbonate regeneration, was not enhanced. Because study participants had diabetes, hyperaldosteronism may have attenuated the expected increase in kidney acid excretion associated with the acid load. Another possible reason why kidney acid excretion was not enhanced is because most participants had normal total CO₂. Because most participants were not acidicemic, the stimulus to increase kidney acid excretion may have been minimal. Nevertheless, we posit that the acid load from medications is buffered by bicarbonate, however, insufficient kidney acid excretion fails to replace the bicarbonate consumed in the process, leading to a reduction in total CO₂. Although this may explain the lower total CO₂, it does not satisfactorily account for the slightly higher anion gap associated with the use of these agents. The higher anion gap could be explained by differences in serum albumin, sulfate, or urate, for example. However, we did not quantify these in our study.

Importantly, those in the higher acid load group had a significantly higher eGFR. Because metformin hydrochloride and gabapentin hydrochloride have dose restrictions at lower eGFR, it is not surprising that those in the higher acid load group had higher eGFR. Despite the higher eGFR, individuals in the high acid load group had a statistically significantly lower serum total CO₂ after adjusting for eGFR, protein intake, and other potential confounders. Because most individuals in this study had normal serum total CO₂, our results indicate that these changes are apparent within the normal total CO₂ range. Hypothetically, overt metabolic acidosis may ensue with continued use, which might occur at a higher eGFR than typically observed (15). Clinicians should consider these agents as potential contributors to metabolic acidosis in CKD.

Our study has several strengths. Because we obtained the dose of each agent prescribed, we were able to calculate the potential acid load of each medication. Most sources report the mol wt of the pharmacologically active molecule, whereas we used the mol wt of the entire compound (active drug and salt) to improve accuracy. We included measurements of serum lactate and urinary acid excretion, thereby providing a more comprehensive assessment of the acid-base state, and we adjusted for a number of factors that could potentially influence acid-base balance. Although our primary interest was the acid load from medications, we also considered the potential effect of base-producing agents, in particular calcium carbonate and calcium citrate. Adjusting for these medications did not alter the interpretation of the findings. A limitation is that we did not measure serum albumin or other anions that might explain the higher anion gap observed in this study. Hence, the reason for this remains unclear. We may also have underestimated the anion gap in those with hypoalbuminemia. We cannot definitively conclude that use of these agents causes metabolic acidosis given the observational and cross-sectional nature of the study. We were also not able to reliably determine the duration of prior exposure to each agent, and residual confounding remains a possibility.

In conclusion, a quarter of the medications prescribed to our participants as part of routine clinical care contained an acid salt. However, most did not contribute a substantial acid load. On the other hand, metformin hydrochloride and gabapentin hydrochloride were identified as potential sources of a significant exogenous acid load, and they appear to contribute to meaningful differences in serum total CO₂ and anion gap in a dose-dependent manner. These changes do not appear to be related to changes in lactic acid production. Metformin and gabapentin are beneficial for patients, and our results should not discourage their use. Clinicians should recognize that these agents could influence serum total CO₂ and contribute to the development of overt metabolic acidosis in individuals with CKD.

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Author Contributions
J. Gardner and K. Raphael conceptualized the study, were responsible for formal analysis and visualization, and reviewed and edited the manuscript; K. Raphael was responsible for funding acquisition, project administration, resources, software, and supervision; all authors wrote the original draft and were responsible for data curation, investigation, and methodology. All authors contributed significantly to the analysis and interpretation of the data, critically revised the manuscript, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000532019/-/DCSupplemental.

Supplemental Table 2. Association between the use of metformin or gabapentin with acid-base variables, with additional adjustment for use of calcium containing medications.
with additional adjustment for use of calcium containing medications.

References

1. Serajuddin AT: Salt formation to improve drug solubility. Adv Drug Deliv Rev 59: 603–616, 2007
2. Bailey JL, Wang X, England BK, Price SK, Ding X, Mitch WE: The acidosis of chronic renal failure activates muscle proteolysis in rats by augmenting transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway. J Clin Invest 97: 1447–1453, 1996
3. Bushinsky DA, Chahala JM, Gavrilo K, Levi-Setti R: Effects of in vivo metabolic acidosis on midcortical bone ion composition. Am J Physiol 277: F813–F819, 1999
4. Kovessy CP, Anderson JE, Kalantar-Zadeh K: Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant 24: 1232–1237, 2009
5. Navaneethan SD, Schold JD, Attigain S, Jolly SE, Wehbe E, Raina JR, Simon JF, Srinivas TR, Jain AS, Schreiber MJ Jr, Nally JV Jr: Serum bicarbonate and mortality in stage 3 and stage 4 chronic kidney disease. Clin J Am Soc Nephrol 6: 2395–2402, 2011
6. Raphael KL, Wei G, Baird BC, Greene T, Beddhu S: Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. Kidney Int 79: 356–362, 2011
7. Raphael KL, Wei G, Bullshoe T, Tuttle K, Cheung AK, Beddhu S: Sodium bicarbonate supplementation and urinary TGF-β1 in nonacidotic diabetic kidney disease: A randomized, controlled trial. Clin J Am Soc Nephrol 15: 200–208, 2020
8. Kim S, Chen J, Cheng T, Gindulute A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, Bolton EE: PubChem 2019 update: Improved access to chemical data. Nucleic Acids Res 47: D1102–D1109, 2019
9. Cunarro JA, Weiner MW: A comparison of methods for measuring urinary ammonium. Kidney Int 5: 303–305, 1974
10. Raphael KL, Gilligan S, Hostetter TH, Greene T, Beddhu S: Association between urine ammonium and urine TGF-β1 in CKD. Clin J Am Soc Nephrol 13: 223–230, 2018
11. Maroni BJ, Steinman TI, Mitch WE: A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int 27: 58–65, 1985
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman M, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J: CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate [published correction appears in Ann Intern Med 155: 408, 2011]. Ann Intern Med 150: 604–612, 2009
13. Remer T, Manz F: Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc 95: 791–797, 1995
14. Dobre M, Yang W, Pan Q, Appel L, Bellovich K, Chen J, Feldman H, Fischer MJ, Ham LL, Hostetter T, Jaar BG, Kallem RR, Rosas SE, Scialla JJ, Wolf M, Rahman M; CRIC Study Investigators: Persistent high serum bicarbonate and the risk of heart failure in patients with chronic kidney disease (CKD): A report from the Chronic Renal Insufficiency Cohort (CRIC) study. J Am Heart Assoc 4: e001599, 2015
15. Moranne O, Froissart M, Rossert J, Gaucci C, Bobba J, Haymann JP, Mrad MB, Jautou C, Houillier P, Stengel B, Fouqueray B; NephroTest Study Group: Timing of onset of CKD-related metabolic complications. J Am Soc Nephrol 20: 164–171, 2009

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Supplemental Table 1: Association between the acid load from medications and use of metformin or gabapentin with acid-base variables, with additional adjustment for use of calcium containing medications.

| Independent Variable | Each SD Higher (7mEq) H⁺ Load | High vs Low Acid Load | Metformin Use* | Gabapentin Use^^ |
|----------------------|-------------------------------|----------------------|----------------|-----------------|
| **Serum Measurement**|                               |                      |                |                 |
| Total CO₂ (meq/L)    | -0.7                          | -1.7                 | -1.1           | -0.9            |
|                      | (-1.3 to 0.0)                 | (-3.0 to -0.4)       | (-2.3 to 0.1)  | (-2.2 to 0.5)   |
| Odds of total CO₂ ≤ 23 mEq/L | 1.78 (0.89 to 3.53) | 4.78 (1.08 to 21.1)  | 1.69 (0.49 to 5.74) | 1.42 (0.38 to 5.34) |
| Anion Gap (meq/L)    | 0.9 (0.3 to 1.6)               | 1.96 (0.7 to 3.2)    | 1.5 (0.3 to 2.7) | 0.8 (-0.5 to 2.1) |
| Lactate (mmol/L)     | 0.1 (-0.2 to 0.3)              | 0.3 (-0.2 to 0.8)    | 0.3 (-0.2 to 0.7) | 0.0 (-0.5 to 0.5) |
| **Urine Measurement**|                               |                      |                |                 |
| Ammonium (meq/d)     | 2.5 (-1.7 to 6.7)              | 3.1 (-5.5 to 11.6)   | 3.4 (-4.5 to 11.3) | 1.5 (-6.9 to 9.9) |
| Titratable Acid (meq/d) | -0.5 (-3.4 to 2.5) | 0.4 (-5.7 to 6.5) | -2.6 (-8.3 to 3.0) | -2.3 (-8.2 to 3.7) |
| Urine pH             | 0.0 (-0.1 to 0.1)              | -0.1 (-0.3 to 0.2)   | 0.0 (-0.2 to 0.2) | -0.1 (-0.3 to 0.2) |

Models adjusted for the following variables: age, estimated glomerular filtration rate, urinary albumin/creatinine, use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, diuretic use, serum potassium concentration, body mass index, estimated protein intake, self-reported history of lung disease, and use of calcium carbonate or calcium citrate.

Shown are the coefficients (95% confidence intervals).

*Includes individuals also taking gabapentin

^^Includes individuals also taking metformin
Supplemental Table 2: Association between the use of metformin and gabapentin alone or in combination and acid-base variables, with additional adjustment for use of calcium containing medications.

| Group                      | Metformin Use = No Gabapentin Use = No (n=32) | Metformin Use = Yes Gabapentin Use = No (n=18) | Metformin Use = No Gabapentin Use = Yes (n=9) | Metformin Use = Yes Gabapentin Use = Yes (n=15) |
|----------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Potential Acid Load (meq/d)* | 0.2 (0.5)                                     | 10.6 (3.3)                                    | 5.4 (3.1)                                     | 15.8 (5.6)                                    |
| Serum Measurement           |                                               |                                               |                                               |                                               |
| Total CO₂ (meq/L)           | Reference (Reference)                         | -0.7 (-2.3 to 0.8)                            | -0.1 (-2.4 to 2.1)                            | -1.7 (-3.4 to 0.0)                            |
| Chloride (meq/L)            | Reference                                     | -1.8 (-3.5 to -0.1)                           | 0.1 (-2.4 to 2.6)                             | -0.9 (-2.8 to 1.0)                            |
| Sodium (meq/L)              | Reference                                     | -1.4 (-3.3 to 0.5)                            | -0.3 (-3.0 to 2.4)                            | -0.6 (-2.6 to 1.4)                            |
| Anion Gap (meq/L)           | Reference                                     | 1.1 (-0.4 to 2.6)                             | -0.3 (-2.4 to 1.9)                            | 2.0 (0.3 to 3.6)                              |
| Lactate (mmol/L)            | Reference                                     | 0.0 (-0.6 to 0.6)                             | -0.5 (-1.4 to 0.3)                            | 0.4 (-0.3 to 1.0)                             |

Models adjusted for the following variables: age, estimated glomerular filtration rate, urinary albumin/creatinine, use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, diuretic use, serum potassium concentration, body mass index, estimated protein intake, self-reported history of lung disease, and use of calcium carbonate or calcium citrate.

Shown are the coefficients (95% confidence intervals).

*Shown as mean (SD)