

Prevalence of Metformin Use and the Associated Risk of Metabolic Acidosis in US Diabetic Adults With CKD

A National Cross-Sectional Study

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Abstract: The use of metformin in chronic kidney disease (CKD) population has been intensely debated with conflicting evidence. Large population studies are needed to inform risk assessment and therapeutic decision-making. We evaluated the associations among metformin, metabolic acidosis, and CKD in a 10-year nationally representative noninstitutionalized civilian population in the United States.

In this cross-sectional study, a total of 2279 diabetic adults aged 20 years or older in the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2012 were included and had measurements of serum bicarbonate, sodium, potassium, and chloride. The exposure was metformin use. The outcome was subclinical and severe metabolic acidosis defined by serum bicarbonate <23 mEq/L and anion gap >16 mEq/L and by serum bicarbonate <20 mEq/L, respectively.

The prevalence of metformin use decreased from 67.2% among CKD-1 and -2, 40.6% among CKD-3, to 1.3% among advanced CKD-4 and -5. Across CKD stages up to CKD-3b, we observed a tendency of lower levels of serum bicarbonate that was significant in metformin

users with CKD-2 and CKD-3a and marginally significant with CKD-3b compared to nonmetformin users. The corresponding tendency of higher anion gap in metformin users with the estimated glomerular filtration rate >60 mL/min/1.73 m² was also observed. In multiple linear regression analysis, metformin was significantly associated with decreased serum bicarbonate levels ($\beta = -0.45$, 95% CI: -0.73 , -0.17) and increased serum anion gap levels ($\beta = 0.40$, 95% CI: 0.19 , 0.61). The adjusted odds ratio of subclinical high anion gap and severe metabolic acidosis for metformin users was 1.68 (95% CI: 1.11 , 2.55) and 1.31 (0.49 , 3.47), respectively. The association between metformin and serum bicarbonate was significantly modified by CKD status. No interaction was found between metformin and CKD stages for serum anion gap and acidosis.

Metformin is associated with subclinical metabolic acidosis but not with severe metabolic acidosis. The propensity of serum bicarbonate-lowering effect was intensified in advanced CKD; however, such tendency was not associated with the risk of clinically defined acidosis. Our findings highlight a potential of cautious expansion of metformin use among CKD-3b patients with diabetes meriting further investigations.

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Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor, AG = anion gap, ARB = Angiotensin II receptor blockers, CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, ERA-EDTA = European Renal Association – European Dialysis and Transplant Association, FDA = Food and Drug Administration, KDIGO = Kidney Disease, Improving Global Outcomes, MALA = metformin-associated lactic acidosis, NEAP = net endogenous acid production, NHANES = National Health Nutritional Examination Survey, NSAID = nonsteroidal anti-inflammatory drugs.

INTRODUCTION

The globalization of diabetes epidemic, given its micro- and macrovascular complications, imposes enormous economic burden on patients and healthcare systems in both developed and developing economies.¹ Among the diabetic microvascular diseases, chronic kidney disease (CKD) presents significant and unique challenges. Diabetes is the leading cause of end-stage renal disease (ESRD) worldwide.^{2,3} Conversely, CKD is a leading contributor to diabetes-related expenditures, for example, diabetic patients with CKD account for ~30% of total diabetes costs among the US Medicare population in 2011.⁴

Intensive glycemic control may play a critical role to halt or slow down the progression of diabetic kidney disease, and metformin has widely been endorsed as the drug of choice in the initial management of type 2 diabetes,^{5–8} given its low cost and potential pleiotropic benefits, such as weight-neutral effect and

lower cardiovascular mortality.⁹ However, the use of metformin in CKD patients is controversial and in recent years has been intensely debated.¹⁰ On one hand, the US FDA black box warning on rare but potentially fatal metformin associated lactic acidosis (MALA) particularly in patients with renal insufficiency has remained in place since the drug approval in 1994, largely due to the historical experience with phenformin.¹¹ Some researchers have also argued whether there is increasing risk of lactic acidosis in metformin-treated patients with mild to moderate CKD.^{10,12}

On the other hand, there has been increasing calls on the FDA to lift its restrictions to allow greater access to metformin.^{7,13,14} Furthermore, the prevailing guidelines against metformin use in patients with mild to moderate CKD are not being followed consistently in the real world.^{15,16} Such practice has been taking place despite the lack of dosage-reduction regimen available to guide metformin prescription among CKD patients. A recent review on metformin use in diabetic patients with CKD by Inzucchi et al also argues that the increased risk of MALA among patients with mild to moderate CKD, if at all, is insignificant and could be outweighed by the potential benefits from macrovascular outcomes.¹⁷ Meanwhile, the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) formally recommended metformin use in a dose adapted to estimated renal function as the first-line pharmacological therapy in diabetic patients with advanced CKD up to stage 4.¹⁸

To definitively conclude the debate requires randomized controlled trials (RCT) to test specifically whether CKD patients are more susceptible to MALA. However, given the extremely low incidence of MALA, such RCT is cost prohibitive and impractical.¹⁷ To address this issue, we take advantage of the large representative sample of US adults in the National Health Nutritional Examination Survey (NHANES) from 2003 to 2012 to inform this debate. NHANES contains information on utilization of antidiabetic agents that helps to better understand the prescription pattern of metformin among diabetic patients across different CKD stages over the past 10 years in the United States. More importantly, NHANES also collects detailed biomarker data that allow the investigation of the relationship between biomarkers of acidosis and metformin use in this population. The current work provides much-needed insight to inform the use of metformin in type 2 diabetes patients with CKD.

METHODS

Study Population

NHANES 2003 to 2012, conducted by the US National Center for Health Statistics (Hyattsville, MD), used a stratified multistage sampling design to obtain a nationally representative sample of the civilian noninstitutionalized population of the United States. The current study was restricted to diabetic participants 20 years and older ($n = 2297$). The detailed selection process was described in Supplementary Appendix 1 in the online supplement, <http://links.lww.com/MD/A545>. The NHANES 2003 to 2012 cycles were approved by the institutional review board of the National Center for Health Statistics. Oral and written informed consent was obtained from all participants.

Measures of Diabetes Status and Kidney Function

The diabetic patient population was identified as those with a self-reported physician diagnosis and/or the use of

diabetic pills or insulin. The kidney function was evaluated by the estimated glomerular filtration rate (eGFR) using the serum creatinine-based CKD-EPI equation.¹⁹

Chronic kidney disease was defined as eGFR < 60 mL/min/1.73 m². Chronic kidney disease stages were divided into 6 GFR categories according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) as follows: stage 1, eGFR > 90 mL/min/1.73 m²; stage 2, eGFR 60 to 89 mL/min/1.73 m²; stage 3a, eGFR 45 to 59 mL/min/1.73 m²; stage 3b, eGFR 30 to 44 mL/min/1.73 m²; stage 4, eGFR 15 to 29 mL/min/1.73 m²; stage 5, eGFR < 15 mL/min/1.73 m².²⁰ Advanced CKD was defined by an eGFR < 30 mL/min/1.73 m² (stages 4 and 5). Detailed procedures for measurement of serum creatinine were outlined in Supplementary Appendix 1 in the online supplement, <http://links.lww.com/MD/A545>.

Markers of Acidosis

The extent of acidosis was primarily determined by measurement of venous bicarbonate using indirect ion selective electrode (I.S.E.) methodology to quantify the total CO₂ level in serum by a Beckman Synchron LX20 in 2003 to 2006 and a Beckman UniCel[®] Dx C800 Synchron in 2007 to 2012.²¹ The interassay coefficients of variation of quality control–pooled samples analyzed throughout 2003 to 2012 ranged between 1.7% and 5.6%. Serum anion gap (AG) was also assessed to reflect the change in the concentrations of unmeasured anions by the formula: $AG = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$.²² The calculated AG was then corrected for serum albumin using the equation of Figge: $AG \text{ corrected (for albumin)} = \text{calculated } AG + 2.5 (\text{population mean albumin g/dL} - \text{individual albumin g/dL})$.²³ The mean albumin level in our study population was 4.27 g/dL.

Subclinical metabolic acidosis was defined by a serum bicarbonate < 23 mEq/L, whereas high anion gap metabolic acidosis was defined by a serum bicarbonate < 23 mEq/L and an anion gap > 16 mEq/L in accordance with previous NHANES research and clinical analytic studies.^{22,24–26} Severe metabolic acidosis was defined by a serum bicarbonate < 20 mEq/L to approximate MALA.

Dietary Intake and Medication Databases

The NHANES 2003 to 2012 cycle included 2 24-h dietary recalls and appropriate recall quality was observed in ~92% of total interviewed study participants. Detailed procedures were given in Supplementary Appendix 1, <http://links.lww.com/MD/A545>. Data from the first dietary recall were used to estimate net endogenous acid production (NEAP) to approximate daily diet-dependent net acid load, which is negatively associated with serum bicarbonate.²⁷ NEAP was calculated as the following:²⁸

- (1) $NEAP \text{ (mEq/day)} = [54.5 \times \text{total protein intake (gram/day)} / \text{total potassium intake (mEq/day)}] - 10.2$.
- (2) Total protein intake (gram/day) and potassium intake (mg/day) were defined as the daily aggregates of protein and potassium from all food and beverages as calculated using USDA's FOOD and Nutrient Database for Dietary Studies 5 (FNDDS 5.0). The mg/day value of total potassium intake was converted to mEq/day by dividing the atomic weight of potassium, 39.

Information on prescription medications was collected during the household interview. The usage of metformin was defined as participants reported its use during the month that

preceded the interview. Medications that may interfere acid-base status were also obtained. Detailed information of collecting medication database was provided in Supplementary Appendix 1 in the online supplement, <http://links.lww.com/MD/A545>. Further details of other variables including sociodemographic variables and comorbidities were also described in the Supplementary Appendix 1, <http://links.lww.com/MD/A545>.

Statistical Methods

To obtain unbiased point estimates and robust linearized standard errors, statistical analyses were performed using the sample survey commands in STATA version 12.0 statistical software (StataCorp LP, College Station, TX) by adjusting with sampling weights to account for the complex NHANES sampling design. In the current analysis, the 10-year sampling weights for NHANES 2003 to 2012 were calculated by combining the sample weights of each individual NHANES survey cycle (2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012) following the analytical recommendations by the National Center for Health Statistics.²⁹ The 2-sided statistical significance level was set at $\alpha = 0.05$.

The sociodemographic characteristics, biochemical profiles, and the prevalence of metformin use in the sample population were presented as weighted mean \pm standard error and frequency with weighted percentages for continuous and categorical variables, respectively. The prevalence of metformin use corresponding to CKD stages was then analyzed by age categories and sex. We further evaluated the demographic characteristics, NEAP, and markers related to acidosis by CKD and metformin use.

To assess the associations among bicarbonate, corrected anion gap and metformin use, multiple linear regression models were conducted. We also performed multiple logistic regression to estimate the odds ratio of the propensity of metabolic acidosis. Variables for modeling were described in Supplementary Appendix 1, <http://links.lww.com/MD/A545>. We conducted several sensitivity analyses. First, we additionally adjusted for the use of other medications including mineralocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and base precursors, with consistent findings (data not shown). Second, we repeated the analyses with the clinical acidosis defined as serum bicarbonate < 22 mEq/L, showing similar results (data not shown). Whether the association between acidosis and metformin use was modified by the CKD status was explored on a priori grounds and design-adjusted Wald tests were then used to evaluate the significance of multiplicative interaction terms (ie, cross-product terms) in the regression models.

RESULTS

The prevalence of metformin use and chronic kidney disease (CKD) in 2279 diabetic participants on antidiabetic medication was 60.5% ($n=1,347$) and 21.4% ($n=535$), respectively. Mean levels of serum bicarbonate, albumin-corrected anion gap, and NEAP was 25.1, 15.0, and 56.4 mEq/day, respectively. Participants with advanced CKD were older and more likely to be female. Participants with advanced CKD had significantly lower protein and potassium consumption and thus the lower daily dietary net endogenous acid production (NEAP) compared to those without CKD. There was an increased trend in levels of serum sodium, potassium, chloride, and anion gap with increasing stages of CKD up to CKD stage 3b whereas the

opposite trends for serum albumin and bicarbonate concentrations were observed (Table 1).

Prevalence of metformin use decreased significantly in participants with abnormal renal function defined by FDA labeling using serum creatinine and across increasing CKD stages. Only 1.3% of participants with advanced CKD (eGFR < 30 mL/min) were receiving metformin. However, the usage of metformin remained 18.9 and 40.6 %, respectively, in participants with FDA CKD (serum creatinine ≥ 1.5 and ≥ 1.4 mg/dL for men and women, respectively) and stage 3 CKD. The prescription pattern of metformin was generally consistent across sex and age strata. Among diabetic participants with eGFR higher than 90 mL/min, women and middle-aged were more likely received metformin than those with comparable renal function (Fig. 1A). The usage of metformin is significantly less in elder participants with FDA-defined renal failure (Fig. 1B). The prevalence of metformin use by CKD stages across 5 NHANES cycles was also demonstrated (Supplementary Appendix 2, <http://links.lww.com/MD/A545> & Figure S1, <http://links.lww.com/MD/A545>).

In diabetic participants with CKD, metformin users had comparable mean age, BMI, and NEAP to nonmetformin users. Regarding acidosis markers, metformin users had a significant lower serum bicarbonate level but with a comparable level of serum anion gap compared to nonmetformin users (Table 2). In diabetic participants free of CKD, a significant lower serum bicarbonate level and a corresponding higher anion gap were found in metformin users (Table 2). Across CKD stages up to CKD stage 3b, we observed a tendency for significantly lower levels of serum bicarbonate in metformin users with CKD stage 2 and 3a, but only marginally significant lower within CKD stage 3b, as compared to nonmetformin users. The corresponding tendency of higher anion gap in metformin users was also observed; however, the trend was not significant in subjects with CKD stage 3a and 3b (Fig. 2). Between metformin and nonmetformin users, the difference in serum bicarbonate was marginally significant across CKD stages up to CKD stage 3b (P value for interaction = 0.10) whereas the difference in serum anion gap was relatively constant throughout the CKD stages (P value for interaction = 0.99) (Fig. 2).

In multiple linear regression analysis, metformin use was significantly associated with decreased serum bicarbonate levels ($\beta = -0.45$, 95% CI: $-0.73, -0.17$). Other independent variables that were significantly associated with decreased serum bicarbonate levels included increasing age, BMI, eGFR, and diuretics (Supplementary Figure S2, <http://links.lww.com/MD/A545>). While stratified by CKD stages up to CKD stage 3b, the decreasing magnitude of serum bicarbonate level was larger in CKD than in non-CKD subjects (P value for interaction = 0.02) (Fig. 3a). With serum anion gap as the dependent variable, metformin use was significantly associated with an increased serum anion gap ($\beta = 0.40$, 95% CI: 0.19, 0.61). Age, blacks, former and current smoker, NEAP, BMI, eGFR, serum albumin levels, and diuretics use were also associated with an increasing serum anion gap (Supplementary Figure S2, <http://links.lww.com/MD/A545> and Supplementary Table S1, <http://links.lww.com/MD/A545>). Specifically in the case of diuretics use, an increasing anion gap may result from an increase in the net anionic equivalency of plasma protein, as a result of the titration from prevailing alkalemia and an elevation of their concentration due to dehydration.^{22,30} No statistical interaction was found between metformin exposure and CKD stages up to CKD stage 3b on serum anion gap level (P value for interaction = 0.71) (Fig. 3B).

TABLE 1. Characteristics of Diabetic Participants in NHANES 2003 to 2012 by Chronic Kidney Disease Stage*

Sociodemographic	CKD Stage 1 eGFR \geq 90 n = 877 (41.2%)	CKD Stage 2 90 > eGFR \geq 60 n = 885 (37.3%)	CKD Stage 3a 60 > eGFR \geq 45 n = 311 (12.6%)	CKD Stage 3b 45 > eGFR \geq 30 n = 155 (6.3%)	CKD Stage 4 and 5 eGFR <30 n = 69 (2.6%)	P Value [†]
Age (year)	50.9 (0.54)	64.2 (0.55)	69.0 (0.71)	72.9 (1.00)	70.8 (1.39)	<0.01
Female (%)	49.5 (2.5)	48.5 (2.2)	47.3 (4.7)	66.9 (3.5)	78.6 (4.7)	<0.01
Race/ethnicity (%)						<0.01
Non-Hispanic white	56.6 (2.7)	69.6 (2.6)	69.2 (3.9)	75.2 (3.6)	62.8 (6.2)	
Non-Hispanic black	18.2 (1.9)	13.4 (1.7)	17.4 (2.4)	11.1 (2.3)	23.8 (4.9)	
Mexican-American	11.6 (1.5)	7.0 (1.2)	3.4 (0.9)	4.0 (1.5)	8.4 (2.8)	
Others	13.6 (1.5)	10.1 (1.5)	10.0 (2.4)	9.8 (2.7)	5.0 (3.5)	
Education (%)						<0.01
< High school	11.4 (1.2)	14.5 (1.4)	15.0 (2.1)	17.6 (3.4)	15.6 (6.0)	
=High school	37.2 (2.2)	37.6 (2.7)	40.9 (3.4)	45.8 (6.0)	63.6 (6.4)	
>High school	51.5 (2.5)	48.0 (2.8)	44.0 (3.8)	36.7 (5.5)	20.8 (4.8)	
Smoking (%)						<0.01
Never	48.6 (2.5)	50.8 (2.0)	45.1 (3.4)	55.9 (5.4)	59.0 (8.2)	
Former	30.0 (1.9)	36.0 (2.1)	45.4 (3.4)	41.2 (5.4)	35.5 (6.8)	
Current	21.4 (1.7)	13.2 (1.5)	9.6 (1.9)	2.9 (1.2)	5.5 (2.8)	
Alcohol (%)						<0.01
Never	21.9 (2.0)	28.2 (2.5)	23.5 (3.8)	17.5 (3.5)	13.7 (4.8)	
Former	24.3 (1.9)	16.3 (1.9)	18.4 (3.1)	7.1 (2.4)	9.9 (4.0)	
Current	53.8 (2.3)	55.5 (2.4)	58.2 (4.6)	75.4 (4.2)	76.4 (5.0)	
Hypertension (%)	67.6 (2.8)	82.7 (1.8)	89.9 (2.0)	90.4 (2.8)	96.1 (2.4)	<0.01
Body mass index (kg/m ²)	33.4 (0.37)	32.6 (0.32)	33.0 (0.62)	34.0 (0.80)	32.9 (0.70)	0.82
Dietary markers [‡]						
Daily total protein (gm/day)	88.4 (2.07)	75.8 (1.80)	71.9 (2.56)	62.2 (2.31)	57.2 (2.81)	<0.01
Daily total potassium (mEq/day)	72.5 (1.71)	66.5 (1.85)	64.1 (2.50)	57.0 (2.39)	52.7 (3.04)	<0.01
NEAP (mEq/day)	59.3 (1.10)	54.6 (0.89)	54.0 (1.98)	54.8 (2.63)	53.2 (3.35)	<0.01
Biochemical markers						
eGFR (mL/min/1.73 m ²)	104.4 (0.46)	76.4 (0.40)	53.4 (0.31)	37.6 (0.45)	22.9 (0.67)	<0.01
Sodium (mEq/L)	138.2 (0.15)	138.9 (0.12)	139.0 (0.19)	139.3 (0.33)	138.6 (0.65)	<0.01
Potassium (mEq/L)	4.01 (0.02)	4.10 (0.02)	4.19 (0.03)	4.38 (0.05)	4.40 (0.09)	<0.01
Chloride (mEq/L)	102.4 (0.14)	102.8 (0.14)	103.1 (0.26)	103.5 (0.29)	102.8 (0.77)	<0.01
Serum albumin (g/dL)	4.17 (0.01)	4.14 (0.01)	4.06 (0.03)	4.02 (0.03)	3.94 (0.06)	<0.01
Anion gap (mEq/L)	14.8 (0.10)	14.9 (0.09)	15.3 (0.19)	15.8 (0.23)	16.8 (0.27)	<0.01
Bicarbonate (mEq/L)	24.9 (0.13)	25.4 (0.11)	24.9 (0.23)	24.7 (0.21)	23.9 (0.53)	0.13

CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, NEAP = net endogenous acid production, NHANES = National Health Nutritional Examination Survey.

* Characteristics of diabetic participants are given as percentage (standard error) in each category (eg, female) or weighted arithmetic mean (standard error) (eg, age) in each continuous variable.

[†] P values for categorical and continuous variables are derived from Pearson Chi squared test and linear trend test, respectively.

[‡] For levels of dietary markers, n = 850, 861, 302, 148, and 67 for CKD stage 1, 2, 3a, 3b, and 4 and 5, respectively.

The prevalence of metabolic acidosis (venous bicarbonate <23 mEq/L), high anion gap metabolic acidosis (venous bicarbonate <23 mEq/L and anion gap >16 mEq/L), and severe metabolic acidosis (venous bicarbonate <20 mEq/L) in the study population was 14%, 7.4%, and 1.3%, respectively, with a corresponding adjusted odds ratio of 1.38 (95% CI: 1.02, 1.88), 1.68 (1.11, 2.55), and 1.31 (0.49, 3.47), (Fig. 4a, Supplementary Table S2–S3, <http://links.lww.com/MD/A545>). In the subgroup analyses stratified by CKD stages up to CKD stage 3b, the associations between metformin use and metabolic acidosis and between metformin use and high anion gap acidosis were consistent by age, sex, race, weight categories (BMI \leq 25, 25 < BMI \leq 30, and BMI > 30), and diuretics use (Fig. 4B and C).

DISCUSSION

In this large scale, nationally representative, population-based study, we identified the prescription pattern of metformin

across CKD stages in diabetic participants of NHANES 2003 to 2012. Although both major clinical guidelines and FDA recommend avoiding metformin in patients with renal insufficiency, we found the metformin use was not uncommon in diabetics with CKD stage 3 but rarely prescribed in patients with advanced CKD stages 4 and 5. Our findings reflect the discordance between actual prescribing practice of metformin and recommendations of medical standards for diabetes in United States and echo the continuing controversy of whether or not to use metformin in patients with renal insufficiency. However, our study finds empirical evidence for the theoretical concerns about metformin being associated with a higher risk of developing lactic acidosis. In US adults with diabetes, metformin use was associated with a significantly decreasing serum bicarbonate level and a correspondingly increasing trend in serum anion gap. The odds of developing high anion gap metabolic acidosis is 68% higher among the metformin users compared to nonusers and the association is not modified by the CKD status.

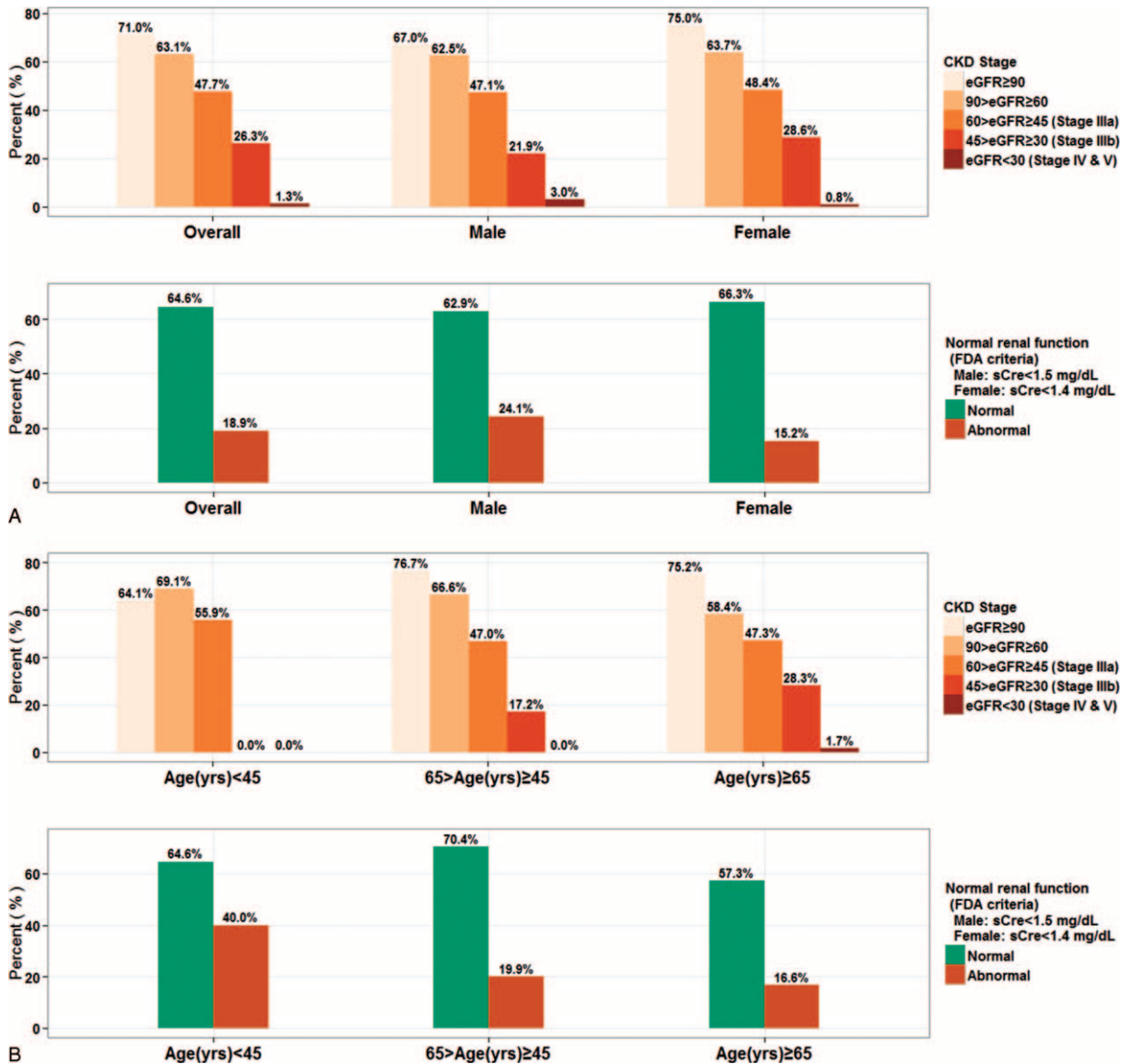


FIGURE 1. (A) Overall prevalence of the metformin use in diabetic participants of NHANES 2003 to 2012 by sex. (B) Overall prevalence of the metformin use in diabetic participants of NHANES 2003 to 2012 by age categories. CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, FDA = Food and Drug Administration, NHANES = National Health Nutritional Examination Survey, sCre = serum creatinine.

Probably the most widely prescribed and the most fundamental initial medical treatment for all diabetic patients with normal renal function, metformin attracts further waves of interest on its potential anticancer effect, obesity prevention, and the cardiovascular protective effect.^{31–33} However, as high prevalence of CKD in diabetic patients, a significant proportion of diabetics are prohibited from the use of metformin for the fear of the potentially fatal lactic acidosis.¹⁷ Because there is apparently no consensus among physicians regarding the risk of MALA in diabetic patients with CKD, as evidenced by the fact that there were a significant number prescribed with metformin (19% by FDA creatinine criteria and 36% based on eGFR criteria), clinical decision-making is particularly challenging to determine what would be in the best interests

of these patients. This observation nevertheless suggests that the safety profile of metformin may be tolerable in diabetic patient with mild-to-moderate CKD (up to stage 3b) since severe metabolic acidosis is rare in this population.

The main glucose-lowering effect of metformin is through the inhibition of gluconeogenesis by reducing the efficiency of respiring mitochondrial oxidative phosphorylation. However, the exact mechanism of metformin induced overproduction of lactate remains disputed. Recent studies have linked metformin to activation of AMP-activated protein kinase (AMPK), suppression of cyclic AMP formation in response to a reduced cellular energy charge^{34–36} and inhibition of the mitochondrial glycerophosphate dehydrogenase (mGPD).^{34,37} If accumulation of metformin exceeds its elimination by the kidney, for

TABLE 2. Acidosis Markers and Relevant Demographics of Diabetic Participants of NHANES 2003 to 2012 Stratified by Chronic Kidney Disease (CKD) Status and Metformin Use Status.^{*,†}

	Non-CKD Participants n = 1762 (78.6%)			CKD Participants n = 535 (21.4%)		
	Metformin (-) n = 603 (32.8%)	Metformin (+) n = 1159 (67.2%)	P Value	Metformin (-) n = 347 (64.1%)	Metformin (+) n = 188 (35.9%)	P Value
Age (year)	57.4 (0.81)	57.2 (0.53)	0.85	70.6 (0.65)	69.8 (0.97)	0.45
Body mass index (kg/m ²)	31.4 (0.37)	33.8 (0.30)	<0.01	33.4 (0.62)	33.0 (0.65)	0.65
NEAP (mEq/day) [‡]	57.6 (1.23)	56.8 (0.86)	0.55	55.6 (1.99)	51.6 (2.18)	0.12
Bicarbonate(mEq/L)	25.4 (0.16)	25.0 (0.10)	0.02	25.0 (0.16)	24.2 (0.22)	<0.01
Anion gap (mEq/L)	14.5 (0.13)	15.0 (0.08)	<0.01	15.6 (0.18)	15.7 (0.20)	0.67

CKD = chronic kidney disease, NEAP = net endogenous acid production, NHANES = National Health Nutritional Examination Survey.

*The distribution of acidosis markers is given as weighted arithmetic mean (standard error).

†CKD was defined by the estimated glomerular filtrate rate <60 mL/min/1.73 m² corresponding to CKD stage 3 to 5.

‡Among non-CKD participants, n is 585 and 1126 for the nonmetformin user and the metformin user, respectively; among CKD participants, n is 334 and 183 for the nonmetformin user and the metformin user, respectively.

example, due to metformin overdose (eg, attempted suicide) or acute renal failure, decompensated lactic acidosis would be established and likely to be irreversible and fatal. Indeed, our study showed a propensity of a lower average level of serum bicarbonate in metformin users compared to nonmetformin users across all CKD stages and this propensity increased with the severity of kidney disease, which implies a greater risk of developing decompensated lactic acidosis in diabetic patients with advanced kidney disease. However this theoretical speculation was not confirmed in this study population as the tendency of clinical significant acidosis with metformin may

be not higher among patients with renal insufficiency.³⁸ To minimize risk of MALA, maintaining chronic compensated acidosis related to metformin by eliminating predisposing factors of mitochondrial dysfunction and decompensation of acid-base buffer systems is paramount, even among diabetic patients with normal renal function, and may be more practical than simply banning its use in CKD population.

Recently, there has been an increasing demand to lift the threshold level of kidney function and allow diabetic patients with mild-to-moderate CKD to receive a metformin-based regimen.^{7,17} Due to the disastrous complication of phenformin-related lactic

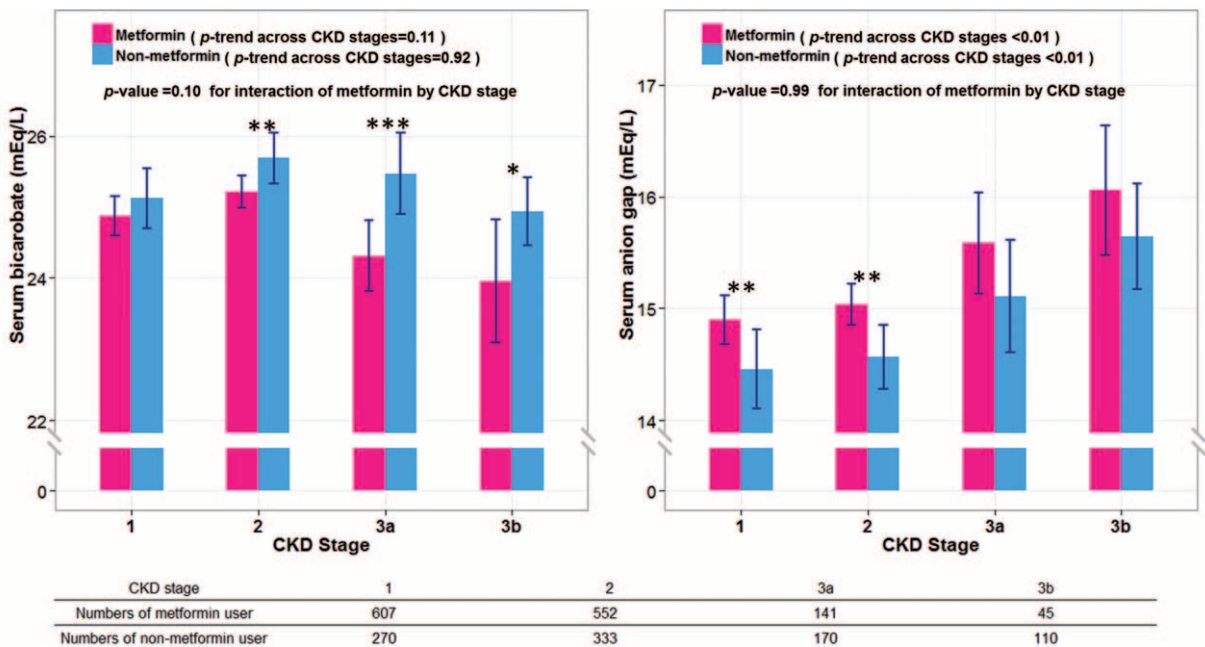


FIGURE 2. Trends of serum bicarbonate and anion gap levels across CKD stages up to stage 3b by metformin use status. Error bar represents the 95% confidence interval of the group mean and the statistical significance is denoted by *0.05 ≤ P < 0.10, **0.01 ≤ P < 0.05, and ***P < 0.01. The test for linear trend was evaluated by modeling the categorical classifications of CKD staging as a continuous variable in design-adjusted simple linear regression models. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

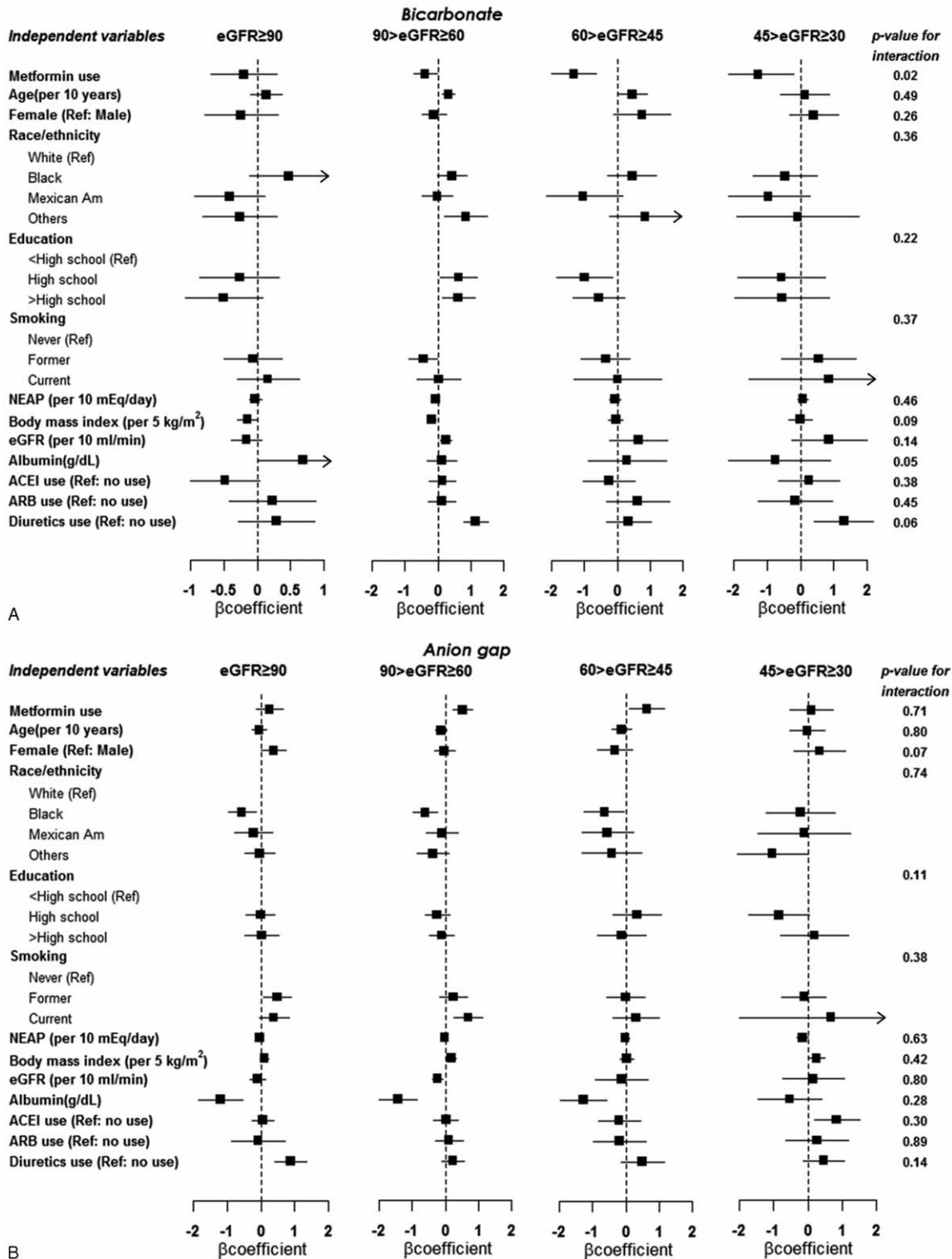


FIGURE 3. (A) Beta coefficients of multiple linear regressions stratified by CKD stages up to stage 3b for metformin and other independent variables with serum levels of bicarbonate as the dependent factor in diabetic participants in NHANES 2003 to 2012. (B) Beta coefficients of multiple linear regressions stratified by CKD stages up to stage 3b for metformin and other independent variables with serum anion gap as the dependent factor in diabetic participants in NHANES 2003 to 2012. ACEI = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blockers, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, NEAP = net endogenous acid production, NHANES = National Health Nutritional Examination Survey.

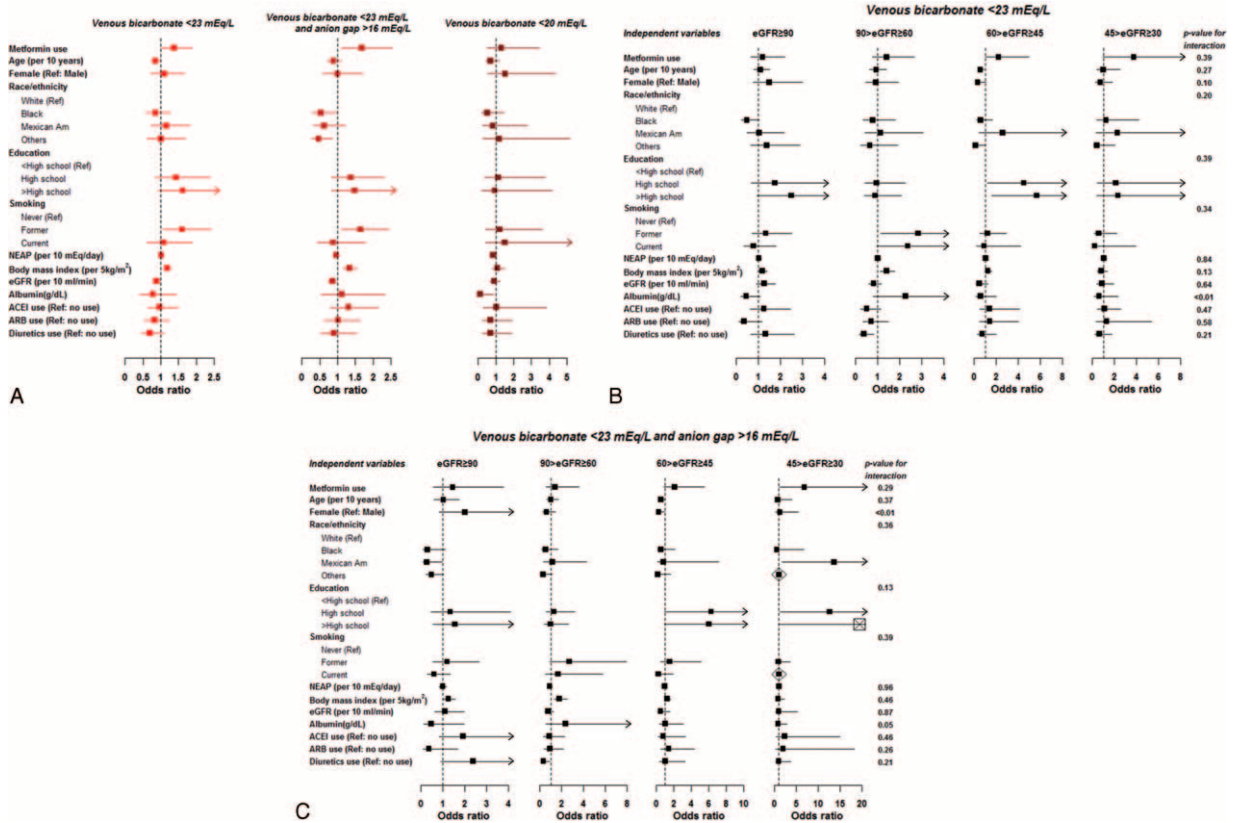


FIGURE 4. (A) Odds ratios of multiple logistic regression for metformin and other independent variables with metabolic acidosis (venous bicarbonate < 23 mEq/L), high anion gap metabolic acidosis (venous bicarbonate < 23 mEq/L and anion gap >16 mEq/L), and severe metabolic acidosis (venous bicarbonate < 20 mEq/L) as dependent factors in diabetic participants in NHANES 2003 to 2012. (B) Odds ratios of multiple logistic regression stratified by CKD stages up to stage 3b for metformin and other independent variables with metabolic acidosis defined by venous bicarbonate < 23 mEq/L as the dependent factor in diabetic participants in NHANES 2003 to 2012. (C) Odds ratios of multiple logistic regression stratified by CKD stages up to stage 3b for metformin and other independent variables with high anion gap metabolic acidosis defined by venous bicarbonate < 23 mEq/L and anion gap >16 mEq/L as the dependent factor in diabetic participants in NHANES 2003 to 2012. The diamond symbol with a central black square indicates empty strata and the square symbol with a cross indicates the estimated effect size beyond the appropriate scale for clear visual display of the information. ACEI = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blockers, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, NEAP = net endogenous acid production, NHANES = National Health Nutritional Examination Survey.

acidosis, FDA has directly forwarded this historical concern to metformin when it was introduced into the US market in 1995 and renal dysfunction was listed as a contraindication in the insert package.¹¹ A recent series of systematic review and meta-analysis of prospective comparative trials or cohort studies did not identify any significant association among metformin use, risk of clinical significant lactic acidosis, and increased levels of lactate.^{17,39} However, findings from pooled data are not conclusive due to a relatively small portion of studies linking to biochemical data and the lack of inter-laboratory standardization. In contrast, our analyses showed that metformin use was significantly associated with the risk of subclinical acidosis with increased anion gap but not with severe acidosis (Supplementary Table S2, <http://links.lww.com/MD/A545>). This novel finding supports the results of prior meta-analysis that metformin is rarely the only trigger of fatal lactic acidosis and echoes the FDA’s historical concern over the potential of predisposing metformin users toward metabolic acidosis.¹¹

Metformin prescribing decision-making in diabetic patients with CKD therefore needs a practical algorithm to

carefully weigh harm-to-benefit ratio according to clinical and therapeutic factors and an educational program for both clinicians and patients to engage awareness of risk factors of MALA and build knowledge about metformin dosing adjustment (Supplementary Figure S3, <http://links.lww.com/MD/A545>). For instance, the potential beneficial effects of a higher bicarbonate concentration and harmful effects of chronic acidosis have been highlighted in a recent review on the progression of CKD.⁴⁰ As demonstrated in the present analysis that a significant propensity of bicarbonate depression is related to metformin use and the effect size is within the range observed in previous studies,^{41,42} it urges caution with respect to the expansion of metformin use particularly in CKD stage 3b population. Clearly, the evidence gap regarding metformin safety and effectiveness for cardiovascular risk, the progression of renal dysfunction, and musculoskeletal complications in CKD population warrants further investigation through prospective experimental research (Supplementary Figure S3, <http://links.lww.com/MD/A545>, a more detailed elaboration was provided in Supplementary Appendix 3, <http://links.lww.com/MD/A545>).

STRENGTHS AND LIMITATION

The main strength of the present study lies in the analysis of a large and nationally representative sample of the noninstitutionalized US population and adequate cases for descriptive analysis stratified by internationally standardized CKD stages. Furthermore, the NHANES prescription medication data were collected by well-trained in-home interviewers through direct verification of reported medications with drug containers. Such an approach allows valid estimates for pharmacological surveillance and helps eliminate recall and ascertainment bias.⁴³ More importantly, NHANES offers a unique opportunity to investigate metformin use and acidosis by integrating biochemical data with anthropometric, food intake, and clinical information.

Some potential limitations of our study should be considered. First, the serum lactate level and blood pH value were not measured in NHANES, which prevented from using lactic acidosis as primary outcome. Second, the sensitivity of anion gap to detect lactic acidosis had been reported as moderate to ~56% to 67% among critically ill patients in retrospective settings, which may lead to a potential misclassification bias.^{44–46} However, whether such concern should be held for general population remains undermined. Furthermore, the outcome misclassification should be nondifferential with respect to metformin use in this nationally representative sample. Another potential source of misclassification bias is the background variation of serum bicarbonate and anion gap levels; nevertheless, the standard error for serum bicarbonate and anion gap was only 0.07 and 0.09 mEq/L, respectively.⁴⁷ Therefore, our findings may underestimate the true association between metformin and metabolic acidosis and are hence likely to provide an overly conservative risk assessment of metformin in CKD population. Third, NHANES recorded “any” use, as opposed to “regular” use, of prescription medication in a short recall period, 1 month, to avoid recall bias. Therefore, our analyses may overestimate the prevalence of anti-diabetics treatment. However, the improved accuracy of current use of metformin would be more timely related to the laboratory data and result in a more sensible analysis. Fourthly, despite the biological plausibility of our findings, NHANES cross-sectional design provides for associations only, not causations. Further, the lack of exact drug dosage information and adherence measures prevents us from investigating the dose–response relationships of interest. Since acidosis statuses was determined based on a single measurement and not available before the use of metformin, our data are not allowed to inform temporality. Fifthly, the possibility of residual confounding from measurement error of confounding variables or unmeasured confounding affecting the association between metformin use and metabolic acidosis could not be completely excluded. For instance, the estimation of NEAP is indirectly derived from a 24-h dietary recall rather than direct measure of dietary intake or quantification of 24-h urine anions and mineral cations. Its measurement error, if there is any, may leave residual confounding. Similarly, other potential undocumented and unmeasured sources of interference on the acid-base balance, such as hydration status, heart failure, and asymptomatic diabetic ketoacidosis or alcoholic ketoacidosis, may not be controlled in this study. Nevertheless, we conducted multiple sensitivity analyses, including adjustment for medications affecting acid-base status and chronic lung disease and the results supported the robustness of our findings. Sixth, the sample size of the metformin users was not large and the risk of type 2 error may not be completely excluded. Lastly, the severity of the defined

metabolic acidosis is considered mild or moderate rather than severe, which is serum bicarbonate less than 10 meq/L corresponding to a blood pH of 7.2. Since acidosis at such a critical level is rarely observed in general population, our findings may not generalize to hospital settings.

CONCLUSION

Despite current guideline recommendations in the United States, in practice, metformin is still commonly prescribed for diabetic patients with mild-to-moderate CKD. We found that metformin is associated with a decreased serum bicarbonate level and a higher risk of high anion-gap subclinical metabolic acidosis, and the bicarbonate-lowering effect of metformin increases as eGFR deteriorates. Our findings support a potential of cautious expansion of metformin use in CKD stage 3b population, as there is no evidence of an increased risk of clinical acidosis. However, the trade-off between metformin’s risk of bicarbonate suppression and advantages in overall survival and cardiovascular benefits needs to be carefully clarified and evaluated by future prospective research to inform clinical practice strategies. In the meantime, to ensure safe usage of metformin in diabetic patients with CKD, proper renal function monitoring, periodic acid-base assessment, and individually tailored patient education and communication must be integral to quality care and among the risk prevention efforts within clinicians’ control.

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