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Are patients with mild to moderate renal impairment on metformin or other oral anti-hyperglycaemic agents at increased risk of contrast-induced nephropathy and metabolic acidosis after radiocontrast exposure?

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AIM: To investigate whether the use of metformin during computed tomography (CT) with radiocontrast agents increases the risk of contrast-induced nephropathy (CIN) and metabolic acidosis after CT in type 2 diabetes patients with mild to moderate renal failure.

MATERIALS AND METHODS: Patient records from January 2015 to December 2017 were reviewed retrospectively. A total of 374 patients were included in the final analysis. Of them, 157 patients received metformin, and 217 patients were taking other oral hypoglycaemic agents (OHAs) during radiocontrast administration.

RESULTS: No significant difference in CIN incidence was observed between the metformin use group and the other OHAs group (p=0.085). Metabolic acidosis after CT was seen in 91 (58%) patients who used metformin and 141 (65%) patients who were taking other OHAs. There was no relationship between metabolic acidosis after CT and the use of metformin (p=0.195). Metabolic acidosis after radiocontrast agent exposure was associated with malignant disease, low serum albumin level, and low serum total CO_2 level at baseline.

CONCLUSION: These data show that other factors, but not metformin use, are associated with metabolic acidosis after radiocontrast agent exposure in patients with reduced renal function. These data support current recommendations that there is no need to discontinue metformin before CT using radiocontrast agents in patients with mild to moderate renal failure.

Introduction

As the frequency of imaging studies using radiocontrast agents has increased, the frequency of radiocontrast agent use has increased in patients with type 2 diabetes. There is

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controversy as to whether patients taking metformin should discontinue use of metformin during the use of radiocontrast agents because of concerns about metformin-induced lactic acidosis.[1–4] Although metformin itself is not a nephrotoxic drug, and therefore, does not directly induce lactic acidosis, radiocontrast agents are nephrotoxic and can cause lactic acidosis in patients who develop contrast-induced nephropathy (CIN)[5]; however, lactic acidosis does not occur in all patients with CIN, and the causal relationship between metformin accumulation and lactic acidosis is unclear.[6] There is no clinical evidence suggesting that metformin should be discontinued in patients with normal renal function, especially in patients who undergo single computed tomography (CT) with minimal use of radiocontrast agents.[3] Furthermore, the most recent guideline from the Royal College of Radiologists advises that there is no need to stop metformin after use of radiocontrast agents in patients with a serum creatinine level within the normal reference range and/or an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2.[7] The American College of Radiology advises that it is not necessary to discontinue the use of metformin during CT with radiocontrast agents, and re-evaluation of renal function is not necessary after the use of radiocontrast agents in patients with an eGFR >30 ml/min/1.73m^2.[8] The Canadian Association of Radiologists Consensus recommends that metformin should be stopped at the time of radiocontrast injection if the patient's eGFR is <45 ml/min/1.73 m^2.[9] The Contrast Media Safety Committee of the European Society of Urogenital Radiology also has updated its guidelines about the use of metformin when radiocontrast is given. They recommend discontinuing metformin from the time of contrast medium administration if the eGFR is <30 ml/min/1.73 m^2.[10] The Royal Australian and New Zealand College of Radiologists also recommends that patients receiving intravenous iodinated contrast media with an eGFR ≥30 ml/min/1.73 m^2 should continue taking metformin.[11] Although these guidelines vary in their method of evaluating renal function, the timing of the discontinuation of metformin, and the timing of the re-evaluation of renal function after the use of radiocontrast agents, most agree that there is no need to discontinue metformin in patients with an eGFR ≥30–45 ml/min/1.73 m^2; however, due to a lack of relevant clinical studies, these guidelines reflect expert opinions or case studies.[7–11] The present study investigated whether the use of metformin during CT with radiocontrast agents increases the risk of CIN and lactic acidosis after CT; however, the lactate concentration is often not measured, so metabolic acidosis was used instead of lactic acidosis. The presence of metabolic acidosis was assessed using serum total CO_2 levels. Serum bicarbonate comprises about 95% of the total CO_2 content; thus, CO_2 is a convenient and informative estimate of serum bicarbonate.[12]

Materials and methods

The records of patients who visited the emergency room and underwent a single CT examination from January 2015 to December 2017 were reviewed. All patient charts were reviewed by the same impartial physician. A total of 461 type 2 diabetic patients with an eGFR between 30 and 59 ml/min/1.73 m^2 underwent CT using iodinated contrast medium. In total, 87 patients were excluded for the following reasons: 51 died immediately after admission because of an underlying disease, five received repeat CT examinations, nine stopped metformin before CT, four were heavy alcoholics (binge drinking on ≥5 days in the past month), and 18 had no data on kidney function after the administration of radiocontrast agents. After exclusion, 374 patients were included in the final analysis. Of these, 157 patients were taking metformin during radiocontrast administration and 217 patients were receiving other oral hypoglycaemic agents (OHAs: sulfonylurea, dipeptidyl peptidase 4 inhibitors, thiazolidinediones, α-glycosidase inhibitors).

Serum creatinine was measured 1–4 days after the administration of radiocontrast agents. Metabolic acidosis was defined as a serum total CO_2 level <23 mmol/l. The definition of CIN was an increase in serum creatinine of ≥25% or an absolute increase of ≥0.5 mg/dl compared to baseline values.[13]

The concomitant use of nephrotoxic agents was also investigated, including the use of diuretics, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, or vasopressors.

Statistical analysis

Data are presented as means±standard deviations or medians (25^{th} to 75^{th} percentile). Comparisons between the two groups were performed using chi-squared or Fisher's exact tests for categorical variables, and Mann–Whitney *U*-test for continuous variables. Logistic regression was used to estimate the odds ratio for metabolic acidosis after radiocontrast agent exposure. Statistical analyses were performed using PASW 18.0 software (SPSS, Chicago, IL, USA). A two-sided *p*-value of <0.05 was considered to indicate significance. The study was approved by the ethics committee.

Results

Baseline characteristics

Table 1 summarises clinical characteristics of the enrolled patients. Significant differences were observed between the metformin group and the other OHAs group in incidence of underlying diseases (cerebrovascular diseases), baseline albumin level, baseline eGFR, and baseline creatinine levels (Table 1). Patients who used metformin had a lower prevalence of cerebrovascular disease than did patients taking other OHAs (Table 1). Furthermore, the baseline eGFR and serum albumin levels were higher in the metformin group than the other OHAs group (Table 1). There was no difference in total serum CO_2 level at baseline between groups. The median metformin dose for the metformin group was 1,000 mg/day (range: 500–1,500 mg/day).

Clinical outcomes

No significant difference in metabolic acidosis and CIN incidence was observed between the metformin group and

Table 1
Baseline clinical characteristics of enrolled patients.

Characteristics	Patients with diabetes using metformin (n=157)	Patients with diabetes using other oral hypoglycaemic agents (n=217)	p-Value
Age (years)	72.9±9.1	72.5±10.0	0.866
Sex, M/F	77/80	135/82	0.015
BMI (kg/m^2)	23.2±3.5	22.9±3.5	0.558
SBP (mmHg)	123.5±22.2	122.9±21.0	0.878
Hypertension	112 (71.3%)	145 (66.8%)	0.368
COPD	13 (8.3%)	17 (7.8%)	1.000
Cardiovascular diseases	40 (25.5%)	59 (27.2%)	0.723
Cerebrovascular disease	3 (1.9%)	28 (12.9%)	< 0.001
Liver cirrhosis	16 (10.2%)	23 (10.6%)	1.000
Malignancy	23 (14.6%)	43 (19.8%)	0.218
Use of nephrotoxic drug	113 (72%)	142 (65.4%)	0.216
Haemoglobin (g/dl)	11.3±2.2	11.1±2.2	0.292
Glucose (mg/dl)	173.0 (129.0–247.0)	193.0 (135.6–269.0)	0.253
Haemoglobin A1c (%)	7.5±1.7	7.4±1.9	0.311
Creatinine (mg/dl)	1.33 (1.18–1.48)	1.43 (1.22–1.64)	< 0.001
eGFR (ml/min)	48.6 (40.3–54.3)	44.3 (37.8–50.8)	0.002
Albumin (g/dl)	3.7±0.6	3.5±0.7	0.003
Uric acid (mg/dl)	6.3±2.1	6.4±2.5	0.995
Total CO_2 (mmol/l)	20.8±4.2	20.6±4.3	0.708
Creatinine after contrast exposure (mg/dl)	1.07 (0.89–1.30)	1.21 (0.93–1.61)	< 0.001
Total CO_2 after contrast exposure (mmol/l)	21.8±3.8	21.2±4.2	0.179

*Data are mean±SD or median (25th percentile-75th percentile).
ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; BMI, body mass index; COPD, Chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

the other OHAs group (Table 2). CIN occurred in eight (5.1%) patients in the metformin group and 22 (10.1%) patients in the other OHAs group. Metabolic acidosis after CT was seen in 91 (58%) patients in the metformin group and in 141 (65%) patients in the other OHAs group (Table 2). No significant relationship was observed between the development of CIN and the presence of metabolic acidosis after radiocontrast exposure (Table 3). The serum creatinine levels before and after the administration of radiocontrast agents were 1.33 (1.18–1.48) mg/dl and 1.07 (0.89–1.30) mg/dl, respectively, in the metformin group (Table 1). This change was statistically significant (p<0.001). There was no aggravation of serum creatinine after CT in the metformin group. The serum total CO_2 levels rose significantly after the administration of radiocontrast agents in the metformin group (before: 20.8±4.2 mmol/l; after: 21.8±3.8 mmol/l; p=0.001). There was also a significant change in serum creatinine in the other OHAs group (1.45±0.29 mg/dl versus 1.36±0.83 mg/dl, p<0.001); however, there was no significant change in serum total CO_2 level after contrast medium exposure in the other OHAs group. Patients with metabolic acidosis after contrast exposure had higher haemoglobin A1c, lower serum haemoglobin, lower serum albumin, and lower serum total CO_2 levels at baseline compared to patients without metabolic acidosis after CT (Table 4). Patients with metabolic acidosis after radiocontrast agent exposure had a higher prevalence of malignant disease than patients without metabolic acidosis. There was no significant difference in age, eGFR, or glucose at baseline (Table 4). There was no relationship between metabolic acidosis after CT and the use of metformin (p=0.195). Logistic regression showed that malignant disease, low baseline albumin level, and low serum total CO_2 level at baseline were associated with metabolic acidosis after exposure to radiocontrast agents. Metformin use before radiocontrast agent administration was not related to metabolic acidosis after radiocontrast agent (Table 5). The relationship between aggravation of serum total CO_2 level after radiocontrast agent exposure and use of metformin was also analysed, and no relationship was found (31.2% versus 35.5%, p=0.438).

Discussion

The present results show that metabolic acidosis after radiocontrast agent administration in patients with reduced renal function (eGFR between 59 and 30 ml/min/1.73 m^2)

Table 2
The development of contrast-induced nephropathy (CIN) and presence of metabolic acidosis after radiocontrast exposure according to use of metformin or other oral hypoglycaemia agents.

	Patients with diabetes using metformin (n=157)	Patients with diabetes using other oral hypoglycaemic agents (n=217)	p-Value
Metabolic acidosis	91 (58%)	141 (65%)	0.195
No metabolic acidosis	66 (42%)	76 (35%)	
CIN	8 (5.1%)	22 (10.1%)	0.085
No CIN	149 (94.9%)	195 (89.9%)	

Table 3
The relationship between development of contrast-induced nephropathy (CIN) and presence of metabolic acidosis after radiocontrast agent exposure.

	Metabolic acidosis (n=232)	No metabolic acidosis (n=142)	p-Value
CIN (n=30)	21 (9.1%)	9 (6.3%)	0.434
No CIN (n=344)	211 (61.3%)	133 (38.7)	

was not associated with metformin use. Metformin has been recommended as the first-choice drug in patients with type 2 diabetes due to its blood glucose-lowering effect, long-term safety, low hypoglycaemic risk, and low risk of weight gain.[14–16] Metformin has been prohibited in patients with renal dysfunction because metformin is removed by the kidneys, and therefore, can accumulate when kidney function deteriorates,[5] which might lead to lactic acid accumulation. Case studies of small numbers of patients have described an association of metformin with lactic acidosis[17,18]; however, the present observational study shows that the incidence of lactic acidosis was not higher in patients taking metformin than in the control group, and there were other risk factors for lactic acidosis in those patients.[19,20] Furthermore, there are controversy about the relationship between radiocontrast use and the occurrence of acute kidney injury (AKI).[21] Other risk factors such as pre-existing renal dysfunction, haemodynamic instability, and exposure to nephrotoxic drugs are associated with the development of AKI.[22,23]

Other studies have shown that metformin clearance is reduced in mild to moderate renal dysfunction, but metformin concentrations remained within the therapeutic range, and lactate levels were normal in patients using metformin. Lim *et al.*[24] found that there was no correlation between kidney function and lactate concentration in patients taking metformin. Although the debate is ongoing, recent observational cohort studies concluded that there was no evidence that metformin is associated with an increased risk of lactic acidosis even in patients with reduced renal function.[20,25] Furthermore, the US Food and Drug Administration recently revised its warnings regarding the use of metformin in patients with reduced kidney function. The new labelling indicates that metformin should not be used in patients with an eGFR <30 ml/min/1.73 m^2. The expansion of metformin use and increased frequency of CT in patients with reduced renal function necessitates questions about whether metformin should be discontinued before CT, and when to restart metformin after CT. Currently, there is no general consensus in the guidelines. Advice on the discontinuation of metformin when a radiocontrast agent is given differs between guidelines.[7–11] This lack of consensus in guidelines is due to a lack of randomised studies, as guidelines are based on expert opinions or case reports. There are few studies about metformin use during the administration of radiocontrast agents.[26,27] Parra *et al.*[26] showed that patients with decreased renal function were at risk for CIN, but not lactic acidosis. Lactic acidosis did not occur in all patients taking metformin who developed CIN after radiocontrast agent administration. These studies included patients with normal renal function (n=67) and mild renal impairment (n=29). Another study of 33 patients using metformin during angiography showed that 29 patients had normal serum creatinine prior to the procedure, and none showed a rise in serum creatinine following angiography. Four patients had abnormal serum creatinine prior to angiography, and all four of these patients showed significant deterioration of renal function; two died from acute renal failure

Table 4
The clinical characteristics according to presence of metabolic acidosis after radiocontrast agent exposure.

	Metabolic acidosis (n=232)	No metabolic acidosis (n=142)	p-Value
Age	72.1±9.6	73.6±9.7	0.176
Sex, M/F	133/99	79/63	0.748
BMI (kg/m^2)	23.2±3.4	22.9±3.6	0.390
SBP (mmHg)	122.4±21.7	124.3±21.3	0.239
Hypertension	159 (68.5%)	98 (69%)	1.000
COPD	19 (8.2%)	11 (7.7%)	1.000
Cardiovascular diseases	57 (24.6%)	42 (29.6%)	0.344
Cerebrovascular disease	20 (8.6%)	11 (7.7%)	0.848
Liver cirrhosis	27 (11.6%)	12 (8.5%)	0.386
Malignancy	50 (21.6%)	16 (11.3%)	0.012
Use of nephrotoxic drug	72 (31.2%)	46 (32.4%)	0.819
Haemoglobin (g/dl)	10.9±2.2	11.7±2.1	0.001
Glucose (mg/dl)	190.5 (134.3–272.5)	167.5 (129.8–245.3)	0.109
Haemoglobin A1c (%)	7.6±1.9	7.3±1.8	0.045
Creatinine (mg/dl)	1.43 (1.19–1.59)	1.33 (1.20–1.48)	0.037
eGFR (ml/min)	45.4 (38.0–51.9)	47.1 (39.5–52.6)	0.149
Albumin (g/dl)	3.4±0.7	3.7±0.6	<0.001
Uric acid (mg/dl)	3.4±2.2	6.3±2.6	0.287
Baseline total CO_2 (mmol/l)	19.2±3.9	23.1± 3.6	<0.001
Metformin	91 (39.2%)	66 (46.5%)	0.195

*Data are mean±SD or median (25th percentile-75th percentile).
ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; BMI, body mass index; COPD, Chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

Table 5
Logistic regression analysis for presence of metabolic acidosis after contrast exposure.

Variables	Presence of metabolic acidosis		
	Exp (B)	S.E.	*p*-Value
Age	0.971	0.016	0.062
Metformin use	0.848	0.265	0.534
Hypertension	0.697	0.299	0.227
Cardiovascular disease	1.254	0.305	0.458
Malignancy	2.480	0.395	0.022
COPD	0.983	0.468	0.983
Baseline albumin	0.536	0.245	0.011
Baseline haemoglobin	0.907	0.067	0.145
Baseline eGFR	1.000	0.017	0.998
Baseline total CO_2	0.701	0.047	<0.001
The development of CIN	0.867	0.482	0.768

Adjusted for age, sex, use of metformin, baseline glucose level, baseline eGFR, uric acid, haemoglobin, systolic pressure, baseline CO_2 level, the development of CIN and the presence of cardiovascular disease, malignancy, COPD, liver cirrhosis, cerebrovascular disease, hypertension, BMI, body mass index; CIN, contrast-induced nephropathy; COPD, Chronic obstructive pulmonary disease; Exp (B), exponentiation of the B coefficient, which is an odds ratio; S.E., standard error around the coefficient for the constant.

and acidosis.[27] The risk of CIN in angiography is different from that in a single CT examination, and the case number of patients with abnormal serum creatinine was small in this study.[27] In the present study, patients had reduced renal function before the use of radiocontrast agents. No correlation was found between serum total CO_2 level and the incidence of CIN, or serum total CO_2 level and the use of metformin. There were cases of CIN after contrast exposure in metformin users in the present study, but the incidence of CIN did not differ between the metformin group and the other OHAs group.

Logistic regression revealed that metabolic acidosis after contrast agent exposure was associated with the presence of metabolic acidosis (low serum total CO_2 level) before radiocontrast agent exposure, low baseline albumin level, and underlying disease (malignant disease). Metformin use during radiocontrast agent exposure was not associated with metabolic acidosis. There were no deaths or severe acidosis requiring therapy after CT in the present study. The discontinuation of metformin in every patient who underwent a single CT examination would result in unnecessary delays in CT or the aggravation of glucose control in diabetic patients with mild to moderate renal failure. The present study has some limitations. First, there were no data on serum lactate levels or serum metformin concentrations. Thus, metabolic acidosis instead of lactic acidosis was defined. Second, metabolic acidosis was estimated by serum total CO_2, rather than by arterial blood gas analysis. This study was conducted retrospectively, and arterial blood gas analysis was not performed after CT. The baseline CO_2 level was lower in the other OHAs group, and thus metabolic acidosis was more frequent in this group. Furthermore, a high percentage of patients had low serum total CO_2 at baseline and the serum total CO_2 level was higher after the administration of radiocontrast agents; this can be explained by hydration and the management of underlying diseases after admission. Thus, a large prospective study is needed to study the precise incidence of lactic acidosis and the effect of metformin on lactic acidosis in patients with reduced renal function after radiocontrast use. Third, the sample size of the present study is small compared to the pooled incidence of metformin-associated lactic acidosis, which is 4.3–5.4 cases per 100,000 patient-years.[3] A larger prospective study is needed to produce more evidence regarding radiocontrast agent use in patients using metformin with an eGFR of 30–59 ml/min/1.73 m^2.

The present results show that metformin use was not related to metabolic acidosis in patients with an eGFR of 30–59 ml/min/1.73 m^2 after radiocontrast agent exposure. Low serum total CO_2 levels before CT, a low baseline albumin level, and underlying malignant disease were risk factors for metabolic acidosis after radiocontrast agent administration. The present study supports recent recommendations that when the eGFR is >30 ml/min/1.73 m^2, there is no need to discontinue the use of metformin during a single CT examination with an intravenous radiocontrast agent.

Conflict of interest

The authors declare no conflict of interest.

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