Impact of continuation of metformin prior to elective coronary angiography on acute contrast nephropathy in patients with normal or mildly impaired renal functions

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Abstract

Objective: Discontinuation of metformin treatment in patients scheduled for elective coronary angiography (CAG) is controversial because of post-procedural risks including acute contrast-induced nephropathy (CIN) and lactic acidosis (LA). This study aims to discuss the safety of continuing metformin treatment in patients undergoing elective CAG with normal or mildly impaired renal functions.

Methods: Our study was designed as a single-centered, randomized, and observational study including 268 patients undergoing elective CAG with an estimated glomerular filtration rate of >60 mL/min/1.73 m^2. Of these patients, 134 continued metformin treatment during angiography, whereas 134 discontinued it 24 h before the procedure. CIN was defined as either a 25% relative increase in serum creatinine levels from the baseline or a 0.5 mg/dL increase in the absolute value that measured 48 h after CAG. Logistic regression analysis was performed to identify independent predictors of CIN and LA after CAG.

Results: Both groups were comparable in terms of demographics and laboratory values. CIN at 48 h was 8% (11/134) in the metformin continued group and 6% (8/134) in the metformin discontinued group (p=0.265). Patients in neither of the groups developed metformin-induced LA. Based on multiple regression analysis, the ejection fraction [p=0.029, OR: 0.760; 95% CI (0.590–0.970)] and contrast volume [p=0.016, OR: 0.022 95% CI (0.010–0.490)] were independent predictors of CIN.

Conclusion: Patients scheduled for elective CAG with normal or mildly impaired renal functions and preserved left ventricular ejection fraction (>40%) may safely continue metformin treatment. *(Anatol J Cardiol 2017; 18: 334-9)*

Keywords: contrast nephropathy, coronary angiography, lactic acidosis, metformin

Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular diseases, such as coronary artery disease, stroke, peripheral artery disease, cardiomyopathy, and heart failure (1). Metformin is the first line oral antidiabetic agent with the highest level of evidence of efficacy in the prevention and treatment of T2DM (2). Metformin improves cardiovascular outcomes in patients with T2DM (3, 4). It acts by reducing glucose synthesis in the liver and increasing glucose uptake and utilization in peripheral tissues. Because coronary artery disease coexists with T2DM currently, majority of the patients scheduled for elective coronary angiography (CAG) will have to use metformin.

The risk of developing contrast nephropathy is higher in patients with T2DM than in those without diabetes (5). Metformin is cleared from the body renally, and diagnostic procedures performed under a contrast agent may result in the development of lactic acidosis (LA) and contrast nephropathy (6, 7). Contrast-induced nephropathy (CIN) is associated with in-hospital mortality and may cause long-term loss of renal functions (8). Therefore, it is important to identify patients who may be at risk of CIN. Cases developing LA secondary to metformin may present with a 50% overall mortality (9).

Knowledge on the use and management of metformin treatment in patients undergoing elective CAG is limited and contradictory (10). Recommendations on the use of metformin during procedures to be performed under a contrast agent are mostly based on studies conducted on the intravenous route or derived from expert consensus statements (11). The generally accepted practice is to discontinue metformin treatment 24–48 h prior to CAG in patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 and to restart usage after checking renal functions 48 h following the procedure. On the other hand, there is no data on the management of metformin treatment in

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routine practice prior to elective CAG and to restart following reassessment of renal functions after 48 h when eGFR >60 mL/min/1.73 m^2 (12).

In our study we aimed to investigate the safety of continuing metformin treatment in patients with T2DM undergoing elective CAG with normal or mildly impaired renal functions (eGFR >60 mL/min/1.73 m^2) in terms of contrast nephropathy and LA.

Methods

A total of 406 consecutive patients on metformin treatment for T2DM scheduled for CAG in our hospital between January 2016 and December 2016 were assessed for eligibility (Fig. 1). Assuming a 21% incidence of CIN in the metformin discontinued group, a sample size of 268 (134 per each group) patients would be required to detect a 70% relative reduction in the incidence of CIN by metformin treatment discontinuation with a 80% power and the conventional 5% 2-sided type 1 error (13). Those diagnosed with acute coronary syndrome and who underwent emergency CAG (n=64), those with eGFR of <60 mL/min/1.73 m^2 (n=44), those with a history of contrast agent exposure in the last 10 days (n=3), those taking oral antidiabetics in addition to metformin for the treatment of T2DM (n=20), those with known contrast allergy (n=2), and those presenting with left ventricular dysfunction (EF <40%) (n=5) were excluded from the study. A total of 268 patients were enrolled in the study. Patients were randomly assigned to two groups according to whether metformin treatment was continued till the day before the procedure. Randomization was performed in 1:1 ratio with computer-generated random numbers. In total, 134 patients continued metformin treatment during CAG (group 1), whereas 134 patients discontinued metformin treatment 24 h before CAG (group 2). Both groups were reassessed at 48 h following the procedure for CIN and LA. eGFR values of patients were calculated 24 h prior to the procedure using the Levey-modified Modification of Diet in Renal Disease (MDRD) formula [183 x (Scr)–1.154 x (Age)–0.203 x (0.742 if female)] (14). The risk of preprocedural CIN was calculated using the validated score specified by Mehran et al. (15) according to the following parameters: hypotension (5 points), intra-aortic balloon pump use (5 points), congestive heart failure (5 points), age >75 years (4 points), anemia (3 points), DM (3 points), serum creatinine levels >1.5 mg/dL (4 points) and amount of contrast volume used (1 point for each 100 cc). CIN was defined as a 0.5 mg/dL or 25% increase in serum creatinine levels versus the baseline level at 48 h following CAG. LA was defined as the post-procedural pH value in arterial blood gas at 48 h <7.35 and lactate level >5 mmoL/L (45 mg/dL) (16). According to the National Cholesterol Education Program Adult Treatment Panel III, hyperlipidemia was defined as the one or more presence of abnormal serum lipid levels ; total cholesterol >200 mg/dL, low-density lipoprotein cholesterol level >100 mg/dL, triglyceride level >150 mg/dL, or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL (17). CAG was performed using the femoral approach. Non-ionic, low osmolality [Omnipaque (Ioheksol); GE Healthcare, Cork, Ireland] contrast agent was used in all patients. All patients included in the study provided informed consent. Ethical board approval was obtained from local ethics committee.

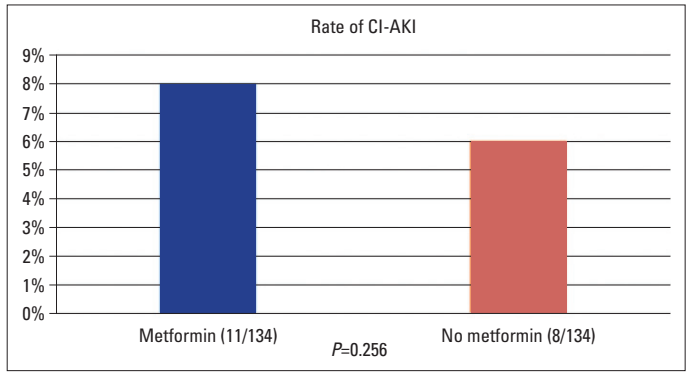

Figure 1. Rate of development of contrast-induced acute kidney injury (CI-AKI) in both groups after CAG

Statistical analysis

Statistical Package for the Social Sciences software (SPSS, version 21, SPSS Inc, Chicago, IL, USA) was used for all statistical calculations. All data were expressed as mean±SD or median (minimum–maximum) for continuous variables and as percentage for categorical variables. Kolmogorov–Smirnov test was used to identify distribution of variables normally. Student's t-test or Mann–Whitney U test was used to compare continuous variables, and chi-square test was used to compare categorical data. The Wilcoxon signed-ranked test was used for comparing levels of continuous variables changing over time in the same groups. Univariate and multiple logistic regression was performed for determining independent predictors of CIN. For all tests, p value of <0.05 was considered statistically significant.

Results

Of the 268 patients enrolled in our study, 134 patients were randomized to the metformin continued group (mean age, 59.4±7.7 years; 59.8% male), whereas 134 patients were randomized to the metformin discontinued group (mean age, 61.4±6.5 years; 51.3% male). The baseline clinical and biochemical characteristics of the two groups are provided in Table 1. Although the rate of prior myocardial infarction was lower in the metformin continued group than in the metformin discontinued group, the difference was not statistically significant (14/134, 10% vs. 26/134, 19%; p=0.130). When preprocedural medications of both groups were evaluated, use of acetylsalicylic acid (100/134, 74% vs. 128/134, 95%; p=0.016) and insulin (20/134; 14% vs. 52/134; 38% p=0.004) was lower in the metformin continued patient group. The risk of preprocedural CIN calculated by the Mehran score [2 (0.7–8) vs. 3 (0.6–8.8); p=0.165] was similar between the groups. eGFR. In a subgroup of 196 patients (metformin continued, n=76 and metformin discontinued, n=120) with mildly impaired renal functions, baseline eGFR was similar for both groups (75±9 vs. 79±8 mL/min,

Table 1. Baseline characteristics of the study population mean±SD or median (minimum–maximum) or n (%)

	Metformin (continued) n=134	Metformin (discontinued) n=134	*P*
Demographic features			
Age, years	59.4±7.7	61.4±6.5	0.113
Gender, female	40 (40.2%)	65 (48.5%)	0.288
BMI, kg/m^2	30.8±3.5	29.9±5	0.182
Hypertension	114 (85%)	111 (83%)	0.751
Hyperlipidemia	86 (64%)	83 (61%)	0.788
Current smoking	38 (28%)	39 (29%)	0.875
Prior myocardial infarction	14 (10%)	26 (19%)	0.130
Diabetes duration, years*	8 (5–10)	10 (7–13)	0.098
Chronic medications			
Acetylsalicylic acid	100 (74%)	128 (95%)	0.016
Clopidogrel	18 (13%)	10 (7%)	0.214
ACEI/ARB	102 (76%)	111 (83%)	0.308
Beta blockers	122 (91%)	115 (85%)	0.220
Calcium channel blockers	40 (30%)	36 (27%)	0.630
Statins	84 (62%)	73 (%54)	0.355
Diuretics	10 (7%)	18 (13%)	0.212
Insulin	20 (15%)	52 (38%)	0.004
Daily dose of metformin, mg*	700 (500–1550)	1000 (850–2000)	0.242
Laboratory values			
Hematocrit, %	40±5.4	38.6±4.3	0.091
Platelet, 10^3/Ml	250±62	256±76	0.619
WBC, Ml	7.7±1.9	7.7±1.7	0.875
CRP, mg/dL*	2.2 (1–7)	2.7 (0.3–8.1)	0.136
Total cholesterol, mg/dL	183±59	189±45	0.553
LDL-C, mg/dL	120±45	126±40	0.395
HDL-C, mg/dL	42±12	43±11	0.788
Triglyceride, mg/dL*	136 (53–477)	140 (55–467)	0.401
Fasting blood glucose, mg/dL*	131 (87–271)	150 (90–328)	0.177
HbA1c, %*	7 (5.6–13)	7.3 (5.5–12.9)	0.162
LV ejection fraction, %	54±8	53±7	0.812
Post CAG lactate level, mmol/L	1.42±0.84	1.53±0.95	0.909
Baseline eGFR, mL/min	86±18	81±9	0.066
Post CAG eGFR, mL/min	82±19	74±12	0.059
Baseline creatinine, mg/dL	0.84±0.18	0.84±0.13	0.885
Post CAG creatinine, mg/dL	0.89±0.22	0.92±0.16	0.490
BMBP, mm Hg	103±14	100±13	0.494
P CAG MBP, mm Hg	98±12	96±13	0.681
CIN, %	11(8)	8 (6)	0.265
Mehran risk score*	5.5 (3.7–11)	6.7 (3.6–11.8)	0.165
Contrast volume, mL*	100 (70–250)	100 (60–350)	0.237

(*) Mann–Whitney U test was used for non-normally distributed variables and expressed by median (minimum–maximum). ACEI - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BMBP - baseline mean blood pressure; BMI - body mass index; CABG - coronary artery bypass graft; CAG - coronary angiography CIN - contrast-induced nephropathy; CRP - C-reactive protein; eGFR - estimated glomerular filtration rate; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; LV - left ventricule; P CAG MBP - Post CAG mean blood pressure; PCI - percutaneous coronary intervention; WBC - white blood cell

Table 2. Comparison of baseline and post CAG eGFR levels in the two groups (**)

Groups	Baseline eGFR	Post CAG eGFR	*P*
Metformin	86±18	82±19	0.078
No metformin	81±9	74±12	0.001

CAG - coronary angiography; eGFR - estimated glomerular filtration rate. (**) Wilcoxon signed-ranks test was used to compare baseline and post CAG eGFR levels in the two groups

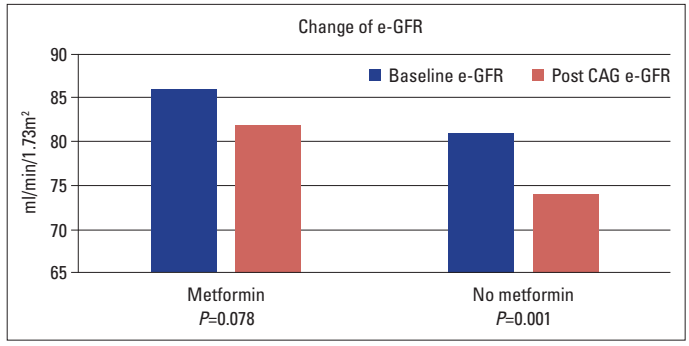

Figure 2. Comparison of eGFR changes in the two groups

p=0.103). There was no difference between both groups in terms of the rate of developing CIN (11/134, 8% vs. 8/134, 6%; p=0.265) (Fig. 1). In patients under metformin treatment, the rate of eGFR reduction after CAG was significantly lower than in that in those not under metformin treatment (86±18 vs. 82±19, p=0.078; 81±9 vs. 74±12 p=0.001) (Table 2) (Fig. 2). Metformin associated LA did not develop in both of the patient groups. In logistic regression analysis, the ejection fraction [OR: 0.760, 95% CI (0.590–0.970); p=0.029] and contrast volume [OR: 0.022, 95% CI (0.010–0.490); p=0.016] were independent predictors of CIN (Table 3).

Discussion

In our study, we have shown that the use of peri-procedural metformin in patients with normal or mildly impaired renal functions (eGFR >60 mL/min/1.73 m^2), who are using metformin for T2DM treatment, and who were scheduled for elective CAG is reliable with respect to the development of CIN and LA. In addition, in patients who continued metformin treatment, eGFR values 48 h after CAG were better than those in patients who discontinued metformin treatment; this may be explained by the renoprotective effect of metformin in the setting of contrast exposure (18). We also found that the left ventricular ejection fraction and contrast volume were independent predictors of acute contrast nephropathy after CAG. To the best of our knowledge, our study is the first randomized study in the literature investigating the reliability of the use of metformin in this patient population.

Currently, whether metformin treatment during contrast-enhanced imaging procedures in patients with T2DM under metformin treatment with normal or mildly impaired normal renal functions (eGFR >60 mL/min/1.73 m^2) should be discontinued and when to restart the treatment are commonly dis-

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Table 3. Logistic regression analysis for contrast-induced acute kidney injury

Variable	Univariate/OR (95% CI)	*P*	Multivariate/OR (95% CI)	*P*
Age	0.98 (0.88–1)	0.775	1.04 (0.88–1.22)	0.635
BMI	0.95 (0.79–1.14)	0.584	1.012 (0.74–1.3)	0.940
Baseline creatinine	0.35 (0.04–2.6)	0.105	0.24 (0.03–1.9)	0.263
CAD	0.51 (0.11–2.3)	0.39	0.53 (0.04–6.4)	0.625
Contrast volume	0.14 (0.02–0.78)	0.025	0.022 (0.00–0.49)	0.016
Ejection fraction	0.9 (0.79–1.02)	0.11	0.76 (0.59–0.97)	0.029
Fasting glucose	0.99 (0.98–1)	0.637	1 (0.97–1.04)	0.516
Gender, female	2.1 (0.39–11)	0.382	0.351 (0.01–9)	0.527
HbA1c	0.79 (0.44–1.4)	0.427	0.49 (0.1–2.2)	0.365
Hemoglobin	0.94 (0.6–1.45)	0.783	1.08 (0.33–3.45)	0.896
Hypertension	0.87 (0.1–7.6)	0.902	0.64 (0.02–16)	0.258
Mehran score	0.98 (0.64–1.4)	0.932	1.1 (0.37–3.38)	0.842
Metformin	0.35 (0.06–1.9)	0.231	0.199 (0.016–2.44)	0.207
Statin usage	0.55 (0.1–2.9)	0.488	0.24 (0.01–3.3)	0.287

BMI - body mass index; CAD - coronary artery disease

cussed. However, such discussions are mainly based on expert opinions or case reports rather than randomized studies. In the literature, Naidu et al. (19) suggested that metformin treatment should be discontinued for 48 h in patients scheduled for CAG, independent of their eGFR value. Kern et al. (20) suggested that metformin treatment should be discontinued preprocedurally because of the risk of LA in patients under metformin treatment and serum creatinine levels should be checked at 48–72 h postoperatively to restart metformin after making sure that there is no renal dysfunction. The 2015 ESC Guideline for the management of acute coronary syndromes in patients without persistent ST-segment elevation stated that data supporting discontinuation of metformin treatment for 24–48 h in all patients prior to angiography are inadequate, and thus, it is suggested that renal functions of patients under metformin treatment and who are undergoing PCI should be monitored. In case of the development of renal dysfunction in patients who underwent CAG or PCI, it was suggested to discontinue metformin treatment for 48 h or until the renal functions restores to baseline levels (21). Andersen (22) suggested that renal functions should be controlled for 48 h after the administration of a contrast agent in patients with T2DM under metformin treatment and metformin should be restarted if no impairment in eGFR is observed. Mijailovic et al. (23) reported that metformin treatment should be discontinued before percutaneous coronary interventions in patients with renal failure to avoid LA, and it should be reinstituted after the procedure only when normal serum creatinine levels are checked.

In our study, the incidence of CIN after CAG was slightly lower than that reported in other studies with more heterogeneous patient population (24). Possibly, this result is related with the exclusion of patients with pre-existing moderate and severe renal impairment, depressed left ventricular function, and using only serum creatinine levels to identify CIN development. Moreover, we observed that the development of CIN after CAG was similar in patients under or not under metformin treatment, but the rate of eGFR reduction after CAG in patients under metformin treatment were significantly lower than that in patients not under metformin treatment. Zeller et al. (25) reported that chronic metformin treatment prior to primary PCI had no significant impact on CIN, and there was a protective effect of metformin against CIN consistent with our results. In the GIPS III trial including 379 patients without diabetes and renal dysfunction, metformin treatment started shortly after primary PCI had no deleterious effect on renal functions, supporting the hypothesis of safe use of metformin in this patient population (26). The doses of metformin administered to both groups in our study were relatively low; thus, the unadaptation to the drug dosage to renal functions might influence renal outcomes. Recent real-life data of a large cohort of elderly patients showed that most patients (75%) had their metformin dosage adapted and unadapted dosage was not associated with worse outcomes (27).

Our findings may have important clinical implications. According to our results, no deleterious impact of metformin treatment was observed in terms of acute contrast nephropathy and LA during elective CAG in patients with normal and mild renal functions. Additionally, we also showed the protective effect of metformin continuation on renal functions in our study population which needs to be verified by further randomized clinical trials. We believe that in clinical practice during elective CAG, metformin treatment can be continued safely in patients with mild and normal renal functions, and metformin treatment prior to elective CAG may play a preventive role for renal functions in this patient population.

Study limitations

Our study has several limitations. First, although appropriately powered, only 268 patients were included from a single institution and the study was not blinded. Second, the risk of preprocedural contrast nephropathy validated by the Mehran score in our study was moderate. Third, renal functions were assessed based only on the creatinine levels. Finally, long-term follow-up data of patients who have developed contrast nephropathy are not available.

Conclusion

Metformin can safely be used during elective CAG in patients having preserved left ventricular ejection fraction (>40%) with normal or mildly impaired renal function (eGFR >60 mL/min/1.73 m^2) and who are under metformin treatment for T2DM.

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Firuz Kanatlı, Ph.D. (Hon.)

1932-2017

We are deeply sorry about the sad loss of Firuz Kanatlı, Ph.D. (Hon.), who was an unconditional supporter of The Anatolian Journal of Cardiology. He made a great psychological and financial contribution to the achievement of having our journal climb in the international rankings, and was a role model to us.

May the mercy of God be bestowed upon him. We send our sincere condolences to all of his friends and family.

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