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Safety of Metformin Continuation During Peri-Procedural Period of Coronary Angiography in Type 2 Diabetic Patients

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Abstract

Background The safety of maintaining metformin therapy in patients undergoing coronary angiography is a topic of ongoing debate. The present study aims to examine patients with type 2 diabetes who continued to use metformin while undergoing coronary angiography for the development of contrast-induced nephropathy and lactic acidosis.

Patients and Methods This investigation was a cross-sectional study that was carried out in Sulaimani Cardiac Hospital between January 2023 to June 2023 that enrolled 100 patients with type 2 diabetes and baseline creatinine clearance more than 45 ml/min for whom elective coronary angiography was performed. Monitoring of renal function and clinical signs of lactic acidosis were observed.

Results The majority of cases (57%) received less than 50 cc of contrast, followed by 50-150 cc in 32 cases. Only one patient, a 70-year-old woman with a baseline impaired creatinine level (1.4 mg/dL), developed contrast-induced nephropathy, and there was no statistically significant change in creatinine level. With vigilant monitoring and proper hydration, her renal function returned to baseline levels within 7 days after the angiogram. Furthermore, there was no lactic acidosis in any of the participants.

Conclusion It appears to be safe to continue metformin therapy during coronary angiography for type 2 diabetic patients whose baseline creatinine clearance above 45 ml/min.

Keywords: Angiography, Acute kidney injury, Contrast-induced nephropathy, Lactic acidosis, Renal failure

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Introduction

Diabetes mellitus is a common predisposing factor for contrast-induced nephropathy (CIN). Contrast-induced nephropathy in diabetic patients receiving metformin may lead to accumulation of the drug and development of lactic acidosis. Contrast-induced nephropathy is one of the iatrogenic factors contributing to the onset of acute kidney injury (AKI), often accompanied by elevated morbidity and mortality rates. It is characterized by a serum creatinine increase of over 25% or ≥0.5 mg/dl (44 μmol/l) compared to the baseline within 1-3 days after the administration of contrast agents when no other causes of AKI are evident. Its peak occurs between 3-5 days after exposure, followed by spontaneous resolution within 14 days.[1,2] Contrast-induced nephropathy is the third most prevalent cause of hospital-acquired AKI. Its incidence is less than 1% in the general population, but it can escalate to as high as 24% in individuals with risk factors, particularly following emergency percutaneous coronary intervention (PCI).[2,3] The mechanisms involved in the underlying pathogenesis include medullary hypoxia resulting from renal vasoconstriction, direct toxic effects caused by the contrast media, and apoptosis.[4] Numerous risk factors elevate the likelihood of developing CIN. Among the most prevalent patient-related factors are preexisting renal insufficiency (characterized by an estimated glomerular filtration rate (GFR) below 60 ml/min) and diabetes mellitus (DM). Additional risk factors encompass advanced age, anemia, heart failure, and hypotension. Procedure-related factors, such as the use of high-contrast volume, high osmolality or viscosity of the contrast agents, and repeated exposure to contrast material within a 72-hour period, also contribute to the risk.[2,5] Diabetes mellitus is a common condition associated with a wide range of cardiovascular diseases that often require radiological procedures involving contrast administration for both diagnostic and therapeutic purposes.[6] Regardless of the baseline GFR, DM doubles the risk of CIN, with the incidence reaching nearly 30%. This risk escalates significantly in patients who already have underlying kidney disease.[5] Metformin, a standard medication for type 2 DM, raises concerns because diabetic patients may develop AKI after receiving contrast, potentially leading to the accumulation of metformin and an increased risk of lactic acidosis (LA).[7] The safety of maintaining metformin therapy in patients undergoing coronary angiography and PCI is a topic of ongoing debate. There is no universal consensus on whether it should be discontinued, resulting in significant variation in daily clinical practice.[6] The present study aimed to observe and assess patients with type 2 DM who continued to use metformin while undergoing coronary angiography for the development of contrast-induced nephropathy and lactic acidosis.

Patients and methods

This investigation was a cross-sectional study that enrolled 100 patients with type 2 DM who underwent elective coronary angiography in Sulaimani Cardiac Hospital (SCH) over a six-month period (January 2023-June 2023). Informed consent was obtained from the patients for their participation and the publication of any related data in this study. Approval (number 102) was granted by the Committee of Ethics of the College of Medicine/University of Sulaimani, Iraq. After taking consent, the data were collected from the patient's profiles at the center. Prior to coronary angiography, vitals including blood pressure were checked, and a blood sample for baseline renal function tests, including blood urea and serum creatinine, was sent to the lab. These tests were repeated 2-3 days after the angiogram. Patients were advised to continue their regular metformin dosage including their overnight and morning dose of

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Metformin at the day of the procedure, and clinical signs of LA were monitored. They were also encouraged to take at least 1 L of water in 6-8 hours after the procedure. In addition, patients underwent further assessments, including hemoglobin levels and an evaluation of left ventricular function by echocardiography. The contrast used in our catheterization laboratory was of low osmolality. The data were initially organized using Microsoft Excel (2019), followed by qualitative analysis (descriptive statistics) using the Statistical Package for Social Sciences (SPSS version 25).

Results

The study included 100 patients diagnosed with type 2 DM, with ages ranging from 40 to 75 years and a mean of 60.46±6.2 year. There were 52 (52%) males and 48 (48%) females. Patients' Characteristics, co-morbidities and concomitant drugs used are shown in Table (1).

Table (1): Patients' Characteristics, co-morbidities and concomitant drugs used by the patients

Patients' Characteristics			
Age (years)	Number, %	Age (years)	Number, %
41-50	16, 16%	61-70	40, 40%
51-60	34, 34%	> 70	10, 10%
Patients' Co-morbidities			
Hypertension	67, 67%	Hyperlipidemia	73, 73%
Ischemic Heart Disease (IHD)	45, 45%	Impaired LV function	22, 22%
Atrial Fibrillation (AF)	11, 11%	Anemia	3, 3%
Concomitant Drugs Utilized by the Patients			
ACE inhibitors# and ARB@	73, 73%	Beta-blockers	37, 37%
Statins	78, 78%	SGLT2 inhibitors*	41, 41%
Anticoagulants	1, 1%	Sulphonylurea	17, 17%
Diuretics	45, 45%	PPIs**	79, 79%

#ACE: angiotensin-converting enzyme @ Angiotensin receptor blockers
*SGLT2: Sodium-glucose co-transporter-2 **PPIs: protein pump inhibitors

Almost three quarters (n=74, 74%) of the patients were in the 6th and 7th decades of life. Most of the participants had a history of DM for at least 5 years (63%). Moreover, hyperlipidemia, hypertension, ischemic heart disease (IHD), and atrial fibrillation (AF) were observed in 73%, 67%, 45% and 11% of the patients respectively. However, none of the patients had hypotension (defined as systolic BP less than 90 mm Hg). Furthermore, 22 patients were found to have impaired left ventricular function, and three had anemia. Almost all (95%) of the patients, received 1-2 gm metformin daily. Besides metformin, some patients used other anti-diabetic medications such as SGLT2 inhibitors (41%) and Sulphonylureas (17%). Additionally, almost three quarters of patients received statins, ACE, ARB, and PPIs as well. Patients' pharmacy also included diuretics (45%) and Beta-blockers (37%) while only one patient was on anticoagulant therapy. Regarding the dose of contrast agents, more than half of patients (57%) received less than 50 cc of contrast, while 32 patients received 50-150 cc. Notably, there was no statistically significant change in creatinine level after exposure to contrast agent table (2), apart from one patient developed CIN. The affected patient

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was a lady of 70 with good left ventricular function and a hemoglobin level of 12.2 g/dL and received just 50 cc of contrast. However, she had a slightly impaired baseline serum creatinine level (1.4 mg/dL) which could explain the occurrence of CIN in her case. Fortunately, the patient responded very well to good hydration in the form of daily 2 L N/S administered intra-venously for 2 days and her renal function returned to the baseline levels 7 days after angiography. None of the patients in this series showed clinical evidence of LA.

Table (2) comparison between baseline and post-procedure serum creatinine level

	Serum Creatinine level		P value *
	Baseline	Post- procedure	
Mean	0.79	0.81	0.14
Standard deviation	0.20	0.19	
Median	0.80	0.81	

*Performed by Wilcoxon sign rank test

It is worthy to mention that creatinine level didn't change significantly in relation to dose of metformin received, amount of contrast agent used and baseline left ventricular systolic function table (3).

Table (3) change in creatinine level in relation to dose of metformin, contrast volume and LV systolic function

	Change in creatinine			P value
	Frequency	Mean ± SD	Median	
Dose of metformin				
≤ 1 Gram	31	0.036 ± 0.18	0.030	0.76 *
1.1 - 1.9 grams	28	0.019 ± 0.14	0.010	
2 - 2.5 grams	40	0.012 ± 0.14	0.050	
Dose of Contrast				
35 - 90 ml	65	0.012 ± 0.15	0.010	0.57 **
100 - 220 ml	34	0.039 ± 0.14	0.030	
LV function				
Impaired or fair	9	0.029 ± 0.11	0.100	0.94 **
Good	90	0.021 ± 0.15	0.020	
Total	99	0.022 ± 0.15	0.030	

*Performed by Kruskal Wallis test
**Performed by Mann - Whitney test

Discussion

Over the past decades, the global prevalence of DM has markedly risen, with projections indicating that by 2035, approximately 592 million individuals will be afflicted by DM. Metformin stands as the most commonly prescribed hypoglycemic medication worldwide for diabetic patients, however, it may have the ability to induce metformin-associated lactic acidosis (MALA).[6] As emphasized in the 2021 scientific statement on evidence-based practices in the cardiac catheterization laboratory, the decision to either continue or discontinue metformin remains a common practice in clinical care, lacking a universally agreed-upon approach.[8,9] Consequently, the safety of maintaining metformin therapy in patients undergoing coronary angiography and PCI remains a subject of debate, leading to significant variability in daily clinical practice. It has been reported that discontinuing metformin could potentially result in delays in coronary angiography, leading to suboptimal glycemic control and an increased risk of cardiovascular events and contrast-associated AKI.[6] Contrast-induced nephropathy remains a significant

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concern due to the large number of patients undergoing procedures that involve contrast injection. The exact incidence of CIN varies depending on several factors, including the specific radiological procedure performed, the dosage and osmolality of the contrast agent administered, the patients' risk factors, and the duration of patient follow-up.[10,11] According to previous studies, the incidence of CIN can vary widely, falling within a range of 0% to 50%.[10,11] In this study, only 1% of the patients developed CIN. Impaired baseline renal function stands out as a primary risk factor for CIN, with occurrences being rare in patients with a baseline GFR above 45 ml/min.[12] Consistent with this, our patient exhibited impaired baseline creatinine levels. DM and left ventricular dysfunction are known to increase the risk of CIN.[11,13] In the current study, despite left ventricular systolic dysfunction in 22 cases, only one of them ultimately developed CIN. Moreover, an additional study investigated the continued use of metformin in diabetic patients with a GFR greater than 60 ml/min per 1.73 m² undergoing coronary angiography. The study suggested that maintaining metformin in diabetic patients with a GFR exceeding 60 ml/min per 1.73 m² during coronary angiography does not increase the risk of MALA development.[14] However, in our cases, the GFR was below 60 ml/min, and yet MALA did not occur. It indicates that continuing metformin in patients with a GFR of <60 ml/min still may be safe, while it is important to highlight that none of our cases had a GFR lower than 45 ml/min. The intravascular administration of iodinated contrast media to patients concurrently taking metformin can potentially lead to LA. However, this rare complication only arises if the contrast medium induces renal failure and the patient persists in metformin use despite renal impairment. Given that metformin is primarily excreted via the kidneys, continued metformin intake following the onset of renal failure can result in toxic drug accumulation and subsequent LA.[6] It is worth noting that the incidence of LA may be higher with high-dose metformin administration compared to low-dose administration.[15] Nevertheless, in this study, none of the patients with different metformin uptake exhibited clinical evidence of LA, likely attributable to diligent hydration practices.[16] Additionally, none of our patients who continued metformin therapy with a creatinine clearance above 45 ml/min experienced CIN. Volume supplementation has played a crucial role in preventing CIN and, consequently, LA. A study conducted by Trivedi et al. compared two hydration strategies, intravenous fluids and oral hydration. They discovered that patients who received a higher volume of fluids for 12 hours both before and after the procedure had a significantly lower incidence of CIN compared to those who underwent oral hydration.[16] Conversely, an oral hydration protocol, administered by the patients themselves, has been reported to be just as effective as the in-hospital intravenous hydration protocol in safeguarding the renal function of individuals at risk of CIN during elective coronary interventions.[17] The 2018 European Society of Cardiology Guidelines on myocardial revascularization recommended discontinuing metformin only in patients with deteriorating renal function, and the recommendation was supported by other authors as well.[18,19] Furthermore, a recent single-arm trial conducted by Chiarito et al. has demonstrated that in diabetic patients undergoing invasive coronary angiography, the continuation of metformin throughout the periprocedural period does not lead to elevated lactate levels and does not contribute to any decline in renal function.[6] This study is supported by peer-reviewed literature, however it has several significant limitations, including a study design that does not provide robust evidence,

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a small sample size, and a lack of statistical analysis or a comparison group. [20] As a result, further research is necessary to strengthen and confirm the findings of this study, despite the existing body of research on the topic.

Conclusion

It appears to be safe to continue metformin therapy in type 2 diabetic patients with a baseline creatinine clearance above 45 ml/min who are undergoing coronary angiography, as there were no observed complications like contrast-induced nephropathy or metformin associated lactic acidosis.

Conflict of interest:

the authors declare that they have no conflict of interest.

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