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Original article

Is it necessary to discontinue metformin in diabetic patients with GFR > 60 ml/min per 1.73 m^2 undergoing coronary angiography: A controversy still exists?

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Summary. *Background:* Although metformin is not directly nephrotoxic, it has been postulated that it can impair gluconeogenesis from lactate, which may lead lactate to be accumulated under circumstances such as contrast-induced nephropathy. The present study aims to assess the role of metformin in lactate production in a group of diabetic patients with GFR > 60 ml/min per 1.73 m^{2}undergoing coronary angiography. *Methods:* In the present randomized clinical trial, 162 metformin-treated diabetic patients were enrolled. The enlisted patients were scheduled to undergo coronary angiography at Modarres Hospital from Feb 2012 to Nov 2012. Patients were randomly allocated to continue metformin during peri-angiography period (M (+) group) or to stop the medication 24 hours prior the procedure (M (-) group). All the patients had glomerular filtration rate of >60 mL/min per 1.73 m^2. Iodixanol was the only contrast media which in all patients. Metformin-associated lactic acidosis (MALA) was defined as an arterial pH <7.35 and plasma lactate concentration >5 mmol/L. *Results:* 162 patients, including79 (48.7%) male and 83 (51.3%) female patients were enrolled in the study. The average of GFR was comparable in both groups (76 ml/min per 1.73 m^2 in the M (+) group versus 79 ml/min per 1.73 m^2 in the M (-) group, p=0.53). No significant difference was observed in the mean dose of metformin before the study between the 2 groups (2.18 tablets per day in M (+) group vs. 2.21 tablets per day in M(-) group, p=0.62).No lactic acidosis was observed in the studied groups. *Conclusion:* In conclusion, the results of the present study indicate that metformin continuation in diabetic patients with a GFR of more than 60 ml/min per 1.73 m^2 undergoing coronary angiography does not enhance the risk of MALA development. (www.actabiomedica.it)

Key words: metformin, diabetes, coronary angiography

Introduction

Metformin as a member of biguanide family is the most commonly prescribed oral agent in diabetic patients (1, 2). Metformin decreases hepatic gluconeogenesis and glycogenolysis; and also decreases insulin resistance by increasing skeletal muscle glucose uptake (3, 4) and was shown previously that is associated with a reduction in cardiovascular morbidity and mortality (5). Ninety percent of metformin was eliminated via renal excretion, with a half-life of about 4-8 hours in the setting of normal kidney function (6, 7).

Phenformin, as another member of biguanides that preceded metformin, was demonstrated to be associated with a conspicuous risk of lactic acidosis (8, 9). This led to manifestation of withdrawal symptoms

of phenformin from clinical practice since 1978. Lactic acidosis is a serious life-threatening agent with an estimated mortality rate exceeding 50% (10).

Although metformin is not directly nephrotoxic (11) it has been postulated that it can impair gluconeogenesis from lactate, and lead to lactate accumulation under circumstances such as acute renal failure (12). In diabetic patients receiving metformin, this condition can be observed in the setting of acute renal failure following contrast media administration during coronary angiography, i.e., contrast-induced nephropathy. Consequently, it has been developed to become a part of routine clinical practice to discontinue metformin before angiography to prevent metformin-associated lactic acidosis (MALA). However, there is no general consensus regarding the incidence of MALA and evidences for such intervention are inadequate. On the other hand, discontinuation of metformin can be associated with detrimental effects on glycemic control and thereby may increase cardiovascular risk in diabetic patients undergoing percutaneous coronary interventions (13). Consequently, questions have been raised recently regarding the routine discontinuation of metformin in low-risk patients undergoing coronary angiography.

The present study was developed to assess the role of metformin in lactate production in a group of diabetic patients with normal renal function; and furthermore, to address the questions regarding the significance of routine discontinuation of metformin in low risk patients undergoing coronary angiography.

Methods

In the present randomized clinical trial, 166 metformin-treated diabetic patients were enrolled. The enrolled patients were scheduled to undergo coronary angiography at Modarres Hospital during Feb 2012 and Nov 2012 were enrolled. Patients were randomly allocated to continue metformin during peri-angiography period (M (+) group) or to stop the medication24 hours prior the procedure (M (-) group). All patients had normal kidney function with a glomerular filtration rate of >60 mL/min per 1.73 m^2. Patients who had contraindication for metformin administration, such as decompensated heart failure; severe liver disease; severe hypoxemia and GFR<60 mL/min per 1.73 m^2 were excluded from the study. Furthermore, four patients in the M (-) group did not complete the study protocol and were excluded from the study. Finally data of 162 patients was included in the final analysis. Iodixanol was the only contrast media used in all patients, due to its low nephrotoxicity. Serum creatinine as well as arterial blood gases and lactate concentration were evaluated prior to angiography. The evaluations were repeated within 48 hours of the procedure. Glomerular filtration rate (GFR) was calculated using Cockcroft-Gault formula:

$$\{GFR= \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{P Cr} \times 72}\ 0.85 \text{ (for women)}\}.$$

Serum creatinine was measured via photometric assay; and arterial blood gases and lactate concentration were gauged via blood gas analyzer. Contrast-induced acute kidney injury was defined as a 25-50% or 0.3-0.5 mg/dl increase in creatinine concentration compared to the baseline values within 48 hours of contrast administration. Metformin-associated lactic acidosis (MALA) was defined as an arterial pH <7.35 and plasma lactate concentration >5 mmol/L. In the M (-) group metformin was re-started 48 hours after angiography in the absence of evidence of lactic acidosis and GFR of >60 mL/min per 1.73 m^2.

A written informed consent was taken from all participants and institutional review board approved the trial.

Results

One hundred-sixty two patients including 79 (48.7%) male and 83 (51.3%) female were enrolled in the study. No significant difference was observed regarding the gender of the patients between the 2 groups (p=0.53). The mean age was 61.5 years in the M (+) group and 60.1 in the M (-) group, which was not significantly different (p=0.43).

The mean dosage of contrast media was 220 cc in the M (+) group and 182 cc in the M(-) group (p=0.18).

All the patients had a left ventricular ejection fraction (LVEF) of more than 30%. The mean LVEF in both groups was 50.0%, which was not significantly different between the 2 groups (p=0.29).The average of GFR was comparable in both groups (79.0±3.4 ml/min per 1.73 m^2 in the M (+) group versus 76.0±2.1 ml/min per 1.73 m^2 in the M (-) group, p=0.53). No significant difference was seen in the mean dose of metformin before the study between the 2 groups (2.18 tablets per day in M (+) group vs. 2.21 tablets per day in M (-) group, p=0.62); (All metformin tablets were 500 mg). No lactic acidosis was seen in the studied groups. Table 1 summarizes demographic, clinical and laboratory data in the study population, according to metformin withdrawal or not before angiography. Table 2 demonstrates creatinine level, GFR and lactate level in the study groups, before and after angiography.

Discussion

In the present clinical trial, 162 patients were included to be studied to determine whether the continuation of metformin administration during peri-angiographic study would increase the risk of metformin-associated lactic acidosis in diabetic patients with GFR of more than 60 ml/min per 1.73 m^2. According to results of this study no cases of MALA was observed in the 2 studied groups.

It was shown previously that metformin may not be the only culprit in the development of lactic acidosis in patients with type 2 diabetes mellitus. In other words, the incidence of lactic acidosis in patients with type 2 diabetes mellitus patients taking metformin is not higher than patients using other oral anti-diabetic agents (14-18). Moreover, it should be mentioned that not all cases of lactic acidosis in diabetic patients re-

Table 1. Demographic, clinical and laboratory data in the study population, according to metformin withdrawal or not before angiography

Groups/Variables	Metformin (+) Group N=83	Metformin (-) Group N=79	P-Value
Age(year)	61.5	60.1	0.43
Gender	Male: 40 (48.1%) Female: 43 (51.9%)	Male: 39 (49.4%) Female: 40 (50.6%)	0.53
Contrast Media Dosage(cc)	220 cc	182 cc	0.18
Metformin Dosage (tablet per day)	2.18	2.21	0.62
Ejection fraction (%)	50.0%	50.0%	0.29

Table 2. Demonstrates creatinine level, GFR and lactate level in the study groups, before and after angiography

Groups/Variables	Metformin (+) Group N=83	Metformin (-) Group N=79	P-Value
Creatinine level before angiography (mg/dL)	1.03±0.07	1.08±0.04	0.24
Creatinine level After angiography (mg/dL)	1.05±0.09	1.1±0.03	0.18
GFR before angiography (cc/min per 1.73 m^2)	79.0±3.4	76.0±2.1	0.53
GFR after angiography (cc/min per 1.73 m^2)	77.2±3.7	74.9±1.6	0.42
Lactate level before angiography (mmol L)	1.42±0.12	1.37±0.10	0.22
Lactate level after angiography (mmol/L)	1.56±0.11	1.47±0.14	0.26

ceiving contrast media during coronary angiography should be considered as MALA; since concomitant risk factors for lactic acidosis and other comorbidities may contribute to development of lactic acidosis irrespective of the metformin effects (16, 19-21). For example, renal failure is a commonly encountered comorbidity in patients with diabetes mellitus, and is a major predisposing factor to lactic acidosis even in the absence of metformin (22).

It should be noted that metformin accumulation due to acute renal failure or metformin overdose has resulted in lactic acidosis in numerous cases which did not have pre-existing risk factors for lactic acidosis or medical comorbidities (23-32). So, lactic acidosis may not necessarily develop in diabetic patients taking metformin, or even in patients with high serum metformin concentration (33).

Concerns regarding the risk of development of MALA in diabetic patients undergoing coronary angiography rose from some case reports (34, 35). It has been suggested that in patients developing contrast-induced nephropathy (CIN) after coronary angiography i.e., acute deterioration in renal function following contrast administration and potential risk of accumulation of metformin results in lactic acidosis. However, there is not enough evidence to support this hypothesis at the present time.

It should be emphasized that, although CIN occurs in 2-25% of patients receiving contrast media undergoing coronary angiography (36), MALA does not occur in all the metformin-treated patients developing CIN (11). Moreover, the majority of reported cases of lactic acidosis in this situation have occurred in patients with severe comorbid conditions, including renal failure, septicemia, hepatic failure and acute decompensated left ventricular failure (37-40).

A meta-analysis of 347 prospective comparative trials and observational cohort studies found no cases of lactic acidosis in 70,490 patient-years of metformin use group or 55,451 patient-years in the non-metformin group (35).

A multicenter randomized controlled trial did not find any lactic acidosis in either groups of patients receiving or discontinuing metformin (41).

Among the first one million patients who received metformin in the United States, 47 cases of lactic acidosis were reported. Among these cases, only four of them did not have other apparent risk factors for lactic acidosis; 13 cases had pre-existing renal failure; and 30 patients had pre-existing cardiac diseases, of whom 18 cases had congestive cardiac failure; 3 patients had chronic pulmonary disease and hypoxia; and 8 cases were older than 80 years (40). On the other hand, in diabetic patients suffering from concomitant underlying diseases, such as acute left heart failure with obvious tissue hypoxia, lactic acidosis was developed in the absence of metformin use (42).

Despite the findings of the mentioned studies above (35, 41), concerns regarding MALA have led to the development of guidelines on the management of diabetic patients taking metformin who are scheduled to undergo coronary angiography. These guidelines aim to reduce the risk of MALA in such patients. Several guidelines have been published recently by several related professional organizations and committees (43-49).

Taking all the discussed issues into consideration, it seems to some extent logical that some clinicians find the risk of MALA not high enough to make the patients discontinue metformin administration prior coronary angiography. This may be the main reason preventing clinicians to adhere rigorously to the present guidelines on metformin cessation in diabetic patients with a GFR of more than 60 ml/min per 1.73 m^2undergoing coronary angiography.

Limitations

First, it is undeniable that the number of the patients enrolled in our clinical trial was relatively small. Future studies with large sample size are recommended for revealing new consequences. Second, the financial resources were inadequate for applying this study to a larger population. Finally, in this clinical trial, we only focused on diabetic patients with a GFR of more than 60 ml/min per 1.73 m^2 undergoing coronary angiography. Detailed assessment of diabetic patients based on different levels of GFR is suggested for the future investigations.

Conclusion

The results of the present study indicate that metformin continuation in diabetic patients, with normal renal function and a GFR of more than 60 ml/min per 1.73 m^2, undergoing coronary angiography, does not carry excess risk for development of MALA. It may be necessary to revise the present recommendations regarding the routine discontinuation of metformin in this group of patients.

Nevertheless, detailed information about the current topic is relatively limited and this clinical trial with such a relatively small sample size cannot adequately respond to all the remaining questions. This study, however, can serve as a trigger for future research examining metformin continuation in wide spectrum of patients undergoing coronary angiography and thus developing new therapeutic approaches.

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