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Metformin Treatment for Patients with Diabetes and Chronic Kidney Disease: A Korean Diabetes Association and Korean Society of Nephrology Consensus Statement

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The safety of metformin use for patients with type 2 diabetes mellitus (T2DM) and advanced kidney disease is controversial, and more recent guidelines have suggested that metformin be used cautiously in this group until more definitive evidence concerning its safety is available. The Korean Diabetes Association and the Korean Society of Nephrology have agreed on consensus statements concerning metformin use for patients with T2DM and renal dysfunction, particularly when these patients undergo imaging studies using iodinated contrast media (ICM). Metformin can be used safely when the estimated glomerular filtration rate (eGFR) is ≥ 45 mL/min/1.73 m^2. If the eGFR is between 30 and 44 mL/min/1.73 m^2, metformin treatment should not be started. If metformin is already in use, a daily dose of $\leq 1,000$ mg is recommended. Metformin is contraindicated when the eGFR is < 30 mL/min/1.73 m^2. Renal function should be evaluated prior to any ICM-related procedures. During procedures involving intravenous administration of ICM, metformin should be discontinued starting the day of the procedures and up to 48 hours post-procedures if the eGFR is < 60 mL/min/1.73 m^2.

Keywords: Contrast media; Diabetes mellitus; Metformin; Renal insufficiency

INTRODUCTION

Chronic kidney disease (CKD) is a global public health prob- lem, and its prevalence is gradually increasing, mainly due to an increase in the number of patients with type 2 diabetes mel- litus (T2DM) [1-4]. CKD develops in approximately 35% of

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patients with T2DM and is associated with increased mortality [1-4]. CKD stages are defined as follows [5]: CKD stage 1 (an estimated glomerular filtration rate [eGFR] ≥90 mL/min/1.73 m², normal or high), stage 2 (eGFR 60–89 mL/min/1.73 m², mildly decreased), stage 3a (eGFR 45–59 mL/min/1.73 m², mildly to moderately decreased), stage 3b (eGFR 30–44 mL/min/1.73 m², moderately to severely decreased), stage 4 (eGFR 15–29 mL/min/1.73 m², severely decreased), and stage 5 (eGFR <15 mL/min/1.73 m², kidney failure). According to a study conducted among elderly Canadian patients with diabetes mellitus (DM) [6], metformin continues to be prescribed to patients with advanced CKD stages 4 to 5, although many guidelines and recommendations have suggested that metformin therapy be avoided because of its potential association with lactic acidosis and all-cause mortality in patients with CKD stage 5 [7]. The safety of metformin in advanced kidney disease is controversial, and more recent guidelines have suggested cautious use in this patient group until more definitive evidence concerning its safety is made available [6,7]. For several decades, one of the most important limitations imposed by regulatory authorities on metformin use was related to renal function, for which a creatinine limit at 1.4 mg/dL for women and 1.5 mg/dL for men was established to contraindicate its use. In subsequent years, clinical studies and reviews were published that justified extending the use of metformin to patients with CKD stage 3 (i.e., an eGFR between 30 and 59 mL/min/1.73 m²) [8]. In 2016, the U.S. Food and Drug Administration (FDA) revised metformin's indication for use in patients with CKD stage 3 [9], whereas the indications for metformin use set by the Korean Ministry of Food and Drug Safety remain unchanged. In this report, we present the opinions of experts on the use of metformin according to renal function. The Korean Diabetes Association (KDA) and the Korean Society of Nephrology (KSN) have agreed on consensus statements for the use of metformin for patients with T2DM and renal dysfunction or patients undergoing imaging studies using iodinated contrast media (ICM).

CURRENT STATUS OF METFORMIN USE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS IN KOREA

We investigated trends in the prescription of antidiabetic medications for patients with T2DM, focusing on renal function. Retrospective data involving patients with T2DM aged ≥30

years were analyzed using information from the National Health Information Database as collected by the National Health Insurance Service in Korea, from January 2009 to December 2015. This study was approved by the Institutional Review Board of Catholic University of Korea (No. SC19ZC-SI0094). Anonymized and de-identified information was used
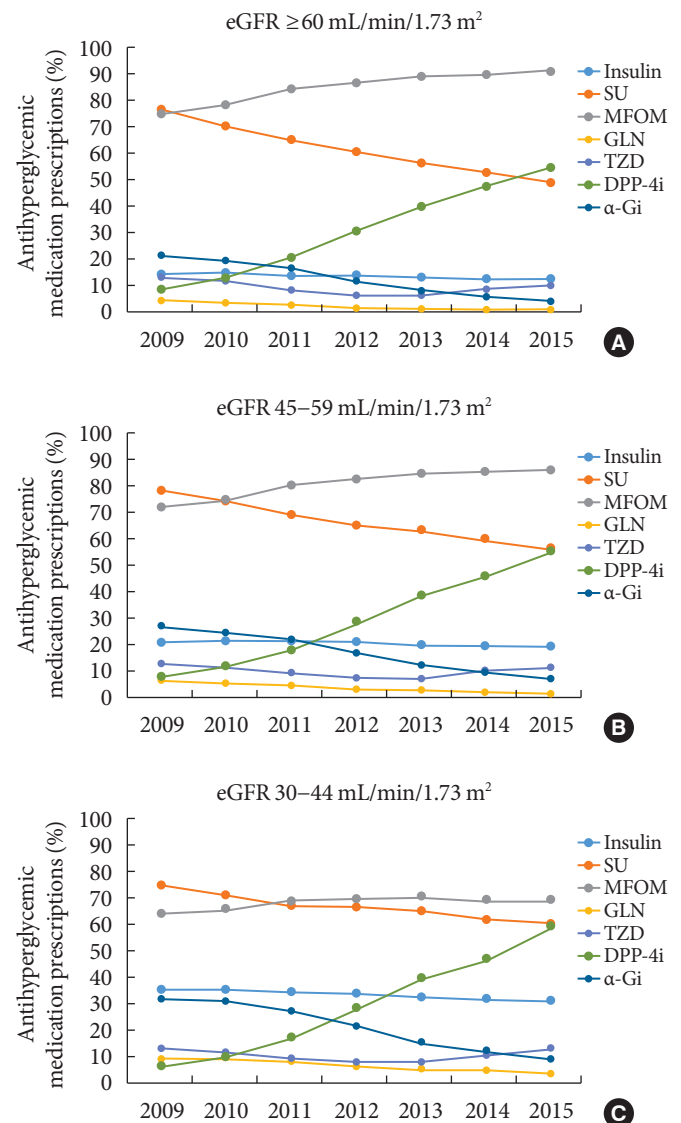
Fig. 1. Secular trends in antidiabetic medication prescriptions in adults with type 2 diabetes mellitus, according to kidney function: (A) in patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m², (B) in patients with eGFR between 45 and 59 mL/min/1.73 m², and (C) in patients with an eGFR between 30 and 44 mL/min/1.73 m². SU, sulfonylurea; MFOM, metformin; GLN, glinide; TZD, thiazolidinedione; DPP-4i, dipeptidyl peptidase-4 inhibitor; α-Gi, α-glucosidase inhibitor.

for analyses and, therefore, informed consent was waived. We identified patients with T2DM who had at least one service claim in each year during the study period. Among antidiabetic medications in 2009, sulfonylurea (SU) was the most commonly used agent (75.9%), followed by metformin (74.7%). However, in 2015, the use of metformin increased to 90.3% of all antidiabetic prescriptions (Fig. 1). The use of the dipeptidyl peptidase-4 (DPP-4) inhibitor began immediately after its release late in 2008 and dramatically increased to 54.3% in 2015. In contrast, the use of SU declined dramatically from 75.9% in 2009 to 48.4% in 2015. Among patients with an eGFR between 30 and 45 mL/min/1.73 m^2, metformin was the most commonly used agent (68.6%) in 2015, SU was the second-most commonly used agent (59.7%), and DPP-4 inhibitor was the third-most commonly used agent (58.6%). Therefore, we found that even among patients classified with CKD stage 3b, the use of metformin was relatively common in a real-world clinical setting.

Because of the potential risk of fatal lactic acidosis, metformin has long been under-prescribed, especially for patients with heart failure (HF) [10]. This situation has changed considerably following recent epidemiological studies that showed the risk of lactic acidosis associated with metformin use was not greater than that of other antidiabetic medications, and that metformin use in patients with DM and HF did not necessarily increase the risk of lactic acidosis [11,12]. We also found that the use of metformin was not associated with an increased incidence of HF in a case-control study of patients with T2DM who were first diagnosed with HF between 2013 and 2015 (Supplementary Table 1). We analyzed retrospective data on patients with T2DM from January 2013 to December 2015. We excluded those with a history of HF before the index year. Between 2013 and 2015, there were 97,178 incident HF cases in patients with T2DM. Potential case subjects were identified by International Classification of Diseases, 10th Revision (ICD-10) code I50 (HF). Control subjects were matched to each case subject according to age (±3 years) and sex. The index date for the control corresponded to the incidence date of the matched HF subject. The use of metformin was associated with a lower risk of HF (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.87 to 0.97), but the use of insulin was associated with an increased risk of HF (OR, 3.60; 95% CI, 3.33 to 3.89). Similar results were obtained when the analysis was performed on a subset consisting of those who had received ≥2 prescriptions of antidiabetic medication (Supplementary Table 1). A

recent population-based retrospective cohort study in Taiwan reported a reduced risk of HF associated with metformin use in patients with T2DM [13].

LACTIC ACIDOSIS ASSOCIATED WITH METFORMIN THERAPY

Lactic acidosis, a well-known complication of biguanide therapy that usually occurs when lactic acid production exceeds lactic acid clearance, is generally defined as a blood pH <7.35 and a blood lactate level >45.0 mg/dL or >5 mmol/L. Lactic acidosis is a rare but potentially life-threatening complication, with a reported mortality risk approaching 50% when the serum lactate level is >23 mg/dL [14].

Phenformin induces conversion of glucose to lactate through the intestinal mucosa, enhances anaerobic metabolism, suppresses hepatic gluconeogenesis, and impairs renal excretion of lactate [14,15]. Since metformin is a type of biguanide with a chemical structure similar to that of phenformin, concerns have been raised regarding lactic acidosis. However, in contrast to phenformin, metformin does not inhibit glucose oxidation or interfere with lactate turnover or hydroxylation polymorphism and is not metabolized and excreted in the urine. Since the underlying mechanisms of these two drugs are different, the incidence of lactic acidosis in metformin therapy is theoretically considered to be lower than in phenformin therapy. Lactic acidosis is a rare event, with an estimated incidence of 4.3 cases per 100,000 person-years among metformin users [16]. Furthermore, evidence indicating that metformin increases the risk of lactic acidosis is lacking, and the frequency of lactic acidosis due to metformin is lower than expected. Most cases of lactic acidosis among metformin users were reported to have occurred when metformin was used inappropriately, such as in patients with severely decreased renal function [17,18].

The term metformin-associated lactic acidosis (MALA) has been used to describe almost all cases of lactic acidosis observed in a metformin-treated patient. However, use of the word 'associated' is ambiguous. It is difficult to distinguish between lactic acidosis due to metformin accumulation (i.e., acute kidney injury [AKI] and voluntary intoxication) and systemic conditions (sepsis, cardiac failure, and bleeding) in patients taking metformin. One recent review article [19] emphasized that metformin therapy does not necessarily induce metformin accumulation, just as metformin accumulation

does not necessarily induce hyperlactatemia, and hyperlactatemia does not necessarily induce lactic acidosis. Therefore, it is important to distinguish between metformin-unrelated lactic acidosis (MULA) and metformin-induced lactic acidosis (MILA). True MALA, which falls between MULA and MILA, is very rare [19].

RECENT RECOMMENDATIONS ON THE USE OF METFORMIN IN CHRONIC KIDNEY DISEASE

In 2016, the FDA [9] and the European Medicines Agency (EMA) [20] removed the contraindications concerning the use of metformin in patients with CKD stages 3a and 3b (eGFR 30–44 and 45–59 mL/min/1.73 m^2, respectively). The FDA recommends metformin use in patients with T2DM and CKD as follows:

(1) Before starting metformin, obtain the patient's eGFR.
(2) Metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2.
(3) Starting metformin in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended.
(4) Obtain an eGFR at least annually in all patients taking metformin.
(5) For patients at increased risk for the development of renal impairment, such as elderly patients, renal function should be assessed more frequently.
(6) For patients taking metformin whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefits and risks of continuing treatment.
(7) Discontinue metformin if a patient's eGFR later falls below 30 mL/min/1.73 m^2.

In addition, the EMA recommends dose reduction for patients with a moderate reduction in kidney function. Lalau et al. [21] recently published three complementary studies concerning the use of metformin for patients with T2DM and CKD stages 3a, 3b, or 4, namely, a dose-finding study, a chronic metformin treatment study, and a pharmacokinetic study. On the basis of the dose-finding study results, they selected a chronic dosage regimen of 1,500 mg/day for patients with T2DM and CKD stage 3a, 1,000 mg/day for patients with T2DM and CKD stage 3b, and 500 mg/day for patients with T2DM and CKD stage 4 (off-label use) [21].

The Korean Ministry of Food and Drug Safety continues to contraindicate the use of metformin for patients with T2DM and CKD stage 3b (creatinine clearance <45 mL/min or an eGFR <45 mL/min/1.73 m^2). However, in 2019, the KDA revised its recommendations as follows [22]: Metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2; Metformin can be used cautiously in patients with an eGFR between 30 and 45 mL/min/1.73 m^2.

IODINATED CONTRAST MEDIA-ASSOCIATED RENAL DAMAGE

When ICM is used for patients with T2DM-related CKD, a patient's renal function should be considered based on CKD staging, the eGFR, and the risk of AKI [23,24]. The FDA has suggested the following risk factors that may warrant renal function assessment prior to contrast procedures: age >60 years, history of renal disease including dialysis, kidney transplantation, single kidney, renal cancer, renal surgery, history of hypertension requiring medical therapy, history of DM, and metformin or metformin-containing drug combinations [25,26].

Post-contrast AKI (PC-AKI) is a general term used to describe a sudden decline in renal function that occurs within 48 hours following intravascular administration of ICM; therefore, PC-AKI is a correlative diagnosis. However, contrast-induced nephropathy (CIN) is a more specific and causative diagnostic term in cases of sudden renal function decline due to the intravascular administration of ICM [27-32].

The exact pathophysiologic mechanism of CIN is not fully understood; however, some etiologic factors have been suggested, such as renal hemodynamic changes, direct tubular toxicity, or agent-specific chemotoxicity [33-36].

In Korea, contrast media was listed third among the most common causes of adverse drug reactions in 2018, following anticancer and nonsteroidal anti-inflammatory drugs. Moreover, 25 fatal cases have been reported in the past 5 years [37]. Therefore, the appropriate management for adverse reactions involving ICM is of growing importance; however, its current institutional management has not been assessed.

IODINATED CONTRAST MEDIA-ASSOCIATED RENAL DAMAGE WHEN USING METFORMIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS-RELATED CHRONIC KIDNEY DISEASE

Many concerns have been raised about MALA following ICM

exposure, especially regarding patients who develop AKI while taking metformin. However, metformin does not confer an increased risk of CIN, and there have been no documented cases among properly selected patients [19,38,39]. The American College of Radiology (ACR) and the European Society of Urogenital Radiology (ESUR) have proposed more relaxed guidelines in recent years [40,41]. However, 57.1% (32/56) of Korean hospitals and 53.3% (8/15) of hospitals outside Korea have been reported to discontinue metformin prior to contrast-enhanced computed tomography (CT) scans, regardless of a patient's renal function, and have failed to take into account up-to-date guidelines [42]. The median cut-off eGFR for stopping metformin prior to contrast-enhanced CT scans has been reported to be 60 mL/min/1.73 m^2 in Korean hospitals, which was significantly higher than that reported in hospitals outside Korea (30 or 44 mL/min/1.73 m^2) [42]. The KSN conducted a simple survey on metformin use in 35 Korean university hospitals. The survey results indicated that metformin was usually stopped prior to contrast exposure, regardless of the patient's eGFR.

Metformin inhibits pyruvate carboxylase and induces excessive lactate production, inhibits the mitochondrial electron transport chain, and blocks the entry of pyruvate into the tricarboxylic acid cycle [43]. As mentioned earlier, MALA is very rare, and in almost all cases, lactic acidosis was reported to have occurred because of overlooked contraindications and several comorbid factors, such as cardiovascular, hepatic, or renal diseases [19,39].

RECENT RECOMMENDATIONS REGARDING METFORMIN DISCONTINU-ATION PRIOR TO CONTRAST PROCEDURES

In 2016, the FDA issued the following revised recommendation concerning the use of metformin for certain patients with reduced renal function:

(1) Discontinue metformin at the time of or prior to an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism, or HF; or in patients who will be administered intra-arterial ICM.

(2) Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable [9].

In contrast, the ACR proposed more specific guidelines in 2018. The ACR guidelines recommend that patients taking

metformin be classified into one of two categories, based on a patient's renal function, measured by the eGFR, as follows:

(1) Category I: In patients with no evidence of AKI and with an eGFR ≥30 mL/min/1.73 m^2, there is no need to discontinue metformin either prior to or following intravenous administration of ICM, nor is there an obligatory need to reassess the patient's renal function following the test or procedure.

(2) Category II: In patients with AKI or severe CKD (stage 4 or 5; eGFR <30 mL/min/1.73 m^2) or patients who are undergoing intra-arterial contrast studies, metformin should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours and reinstituted only after renal function has been re-evaluated and found to be normal [40].

The ESUR also focused on patients with an eGFR <30 mL/min/1.73 m^2, intra-arterial administration, and AKI. They distinguished between the risks of first or second pass renal exposure in intra-arterial administration. Patients with an eGFR >30 mL/min/1.73 m^2 and no evidence of AKI, receiving either intravenous ICM or intra-arterial ICM with second pass renal exposure, could continue taking metformin [41].

However, according to the Korean Ministry of Food and Drug Safety, even patients with an eGFR >60 mL/min/1.73 m^2 should discontinue metformin at the time of or prior to a contrast procedure. Moreover, patients with an eGFR between 45 and 60 mL/min/1.73 m^2 should discontinue metformin 48 hours prior to and after the procedure, for a total of 96 hours [44].

In 2019, the KDA revised its recommendation that patients with an eGFR <60 mL/min/1.73 m^2 should discontinue metformin on the day of the procedure for up to 48 hours, and reinstituted metformin therapy if renal function has not declined following the procedures [22].

KOREAN DIABETES ASSOCIATION AND KOREAN SOCIETY OF NEPHROLOGY JOINT CONSENSUS STATEMENTS ON THE USE OF METFORMIN IN DIABETES

(1) Metformin can be used when the eGFR is ≥45 mL/min/1.73 m^2.
(2) If the eGFR is 30–44 mL/min/1.73 m^2, do not start metformin treatment. If metformin is already in use, administer a daily dose of ≤1,000 mg.
(3) Metformin is contraindicated when the eGFR is <30 mL/min/1.73 m^2.

(4) Evaluate renal function before any procedures involving the use of ICM.

(5) Any decision to use ICM and whether to stop metformin should be based on renal function test results.

(6) During procedures involving intra-arterial administration of ICM, metformin should be discontinued starting the day of the procedures and up to 48 hours after the procedures.

(7) During procedures involving intravenous administration of ICM, metformin should be discontinued starting the day of the procedures and up to 48 hours after the procedures if eGFR is <60 mL/min/1.73 m^2.

(8) Re-evaluate renal function after procedures involving the use of ICM, and re-administer metformin if renal function has not declined after the procedures.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2020.0004.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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