Journal of Clinical Case Reports and Medical Research

Commentary
Article Id: JCCRMR-20-05

Safer Use of Metformin for Chronic Kidney Disease (CKD) and/or Diabetic Kidney Disease (DKD) with Beneficial Efficacy

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Received: *26 June 2020*
Accepted: *10 July 2020*
Published: *14 July 2020*

Citation:
Bando H, Iwatsuki N, Sakamoto K, Ogawa T. Safer Use of Metformin for Chronic Kidney Disease (CKD) and/or Diabetic Kidney Disease (DKD) with Beneficial Efficacy. J Clin Case Rep Med Res 2020;1:05

Abstract

Diabetes has been a prevalent disease worldwide, and metformin has been used widely as an oral hypoglycemic agent (OHA) for type 2 diabetes mellitus (T2DM). Its benefits include low cost, weight neutrality, general effect and positive efficacy for cardiovascular system. American Diabetes Association (ADA) has proposed diabetic guidelines-2020 and evaluated metformin as predominant agent. They include i) the preferred initial pharmacologic agent for T2DM, ii) once starting of metformin, it should be continued as long as tolerated without contraindication. Furthermore, recent studies showed safer effect for impaired renal function. We cannot exclude such results and will contribute the prevention of atherosclerotic cardiovascular disease (ASCVD).

Keywords: American diabetes association, estimated glomerular filtration rate, atherosclerotic cardiovascular disease, chronic kidney disease, diabetic kidney disease

Abbreviation: ADA: American Diabetes Association; eGFR: Estimated Glomerular filtration Rate; ASCVD: Atherosclerotic Cardiovascular Disease; CKD: Chronic Kidney Disease; DKD: Diabetic Kidney Disease

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Diabetes has been one of the most prevalent diseases in the world (1). Adequate treatment for diabetes has been crucial in comprehensive manner including pharmacotherapy (2). For long years, metformin has been the firstly provided oral hypoglycemic agent (OHA) for type 2 diabetes mellitus (T2DM) (3). Diabetologist or primary care physicians have given T2DM patients metformin as a fundamental OHA. It has several beneficial points, such as low cost, weight neutrality and generally positive efficacy for cardiovascular system (3,4).

On the other hand, metformin has not been recommended to administer patients with chronic kidney disease (CKD) and/or diabetic kidney disease (DKD), because of the possible risk of lactic acidosis (5). Lots of diabetologists including the authors, have come to judge according to this recommendation and there was some tendency of withdrawal of biguanide medicine. Diabetes has been the leading cause of CKD, leading to DKD. Then, there have been various investigations for mutual relationships among diabetes, renal dysfunction and effect of metformin (3-5).

Several studies showed the lack of the evidence that metformin would increase lactic acidosis in patients with CKD (6). There are detail data concerning the value of estimated glomerular filtration rate (eGFR) in the following (7,8). From global outcomes for CKD, continuation of metformin is recommended for patients with eGFR>45mL/min/1.73m^2 (eGFR categories G1–G3a) and patients with eGFR 30-45 mL/min/1.73m^2 (G3b). The discontinuation is recommended for patients with an eGFR less than 30 mL/min/1.73m^2 (G4– G5) (7,8). Furthermore, FDA in US has allowed metformin use for patients with eGFR of 45mL/min/1.73m^2, but still restricted metformin for patients with 30 mL/min/1.73m^2 (7). Consequently, metformin usage with eGFR 30-45 mL/min/1.73m^2 has been controversial (7,8).

As to a recent report, no difference was observed regarding to lactic acidosis events among metformin and other OHAs (6). A few papers showed the beneficial effects of long-term use of metformin, with controversial results (9-11). Consequently, there are some trials associated with the hypothesis that metformin use for CKD would be beneficial in the light of incidence of lactic acidosis, mortality and prevalence of end-stage renal disease (ESRD).

From several reports mentioned above until 2019, perspectives for metformin have been developed with evidences. In 2020, ADA proposed the official comment in the standard of medical care in diabetes (12). Among them, comprehensive approaches are observed from various points of view. ADA proposes patient-centered collaborative care and recommends diabetes care by a multidisciplinary team with subspecialty physicians, primary care physicians, nurse practitioners, and other hygiene professionals (12). The goal of diabetic therapy would be to optimize Quality of Life (QOL) and to delay diabetic complications. Furthermore, therapeutic plan needs to include patient-based values and preferences (12). The principle of diabetic treatment has three factors, which are nutrition, exercise and references.

Regarding pharmacologic approaches, the preferred initial pharmacologic agent for long period is metformin (level A) (13). ADA guideline shows that once starting of metformin, it should be continued as long as it can be tolerated without contraindication. If needed, other agents and insulin would be added to fundamental

prescription of metformin (level A). In some patients, early combination treatment can be considered at the initiation of OHA (level A).

Among these, patient-centered care has to be applied to decided which pharmacologic agents to be chosen (13). They include various factors, such as cost, influence on weight, risk for adverse effects, hypoglycemia risk and cardiovascular comorbidities (13,14). In particular, important perspectives are possible development of atherosclerotic cardiovascular disease (ASCVD) and indicators of high ASCVD risk, CKD, and heart failure (HF) (15).

As first line diabetic agent consists, metformin has been safe, effective and inexpensive agent, and may reduce cardiovascular events and mortality. It can be useful for immediate release form for once or twice administration daily. When compared with sulfonylurea agents, it has beneficial efficacy on weight, HbA1c and cardiovascular outcomes (16). Except metformin, there has been little systematic result for other OHAs available for initial treatment of T2DM.

As to the reverse effects of metformin, gastrointestinal tract symptoms such as abdominal discomfort, diarrhea and bloating have been observed. Metformin in the blood is cleared through renal filtration, and elevated circulating levels may cause lactic acidosis. It has been known before, but this situation has been found to be rather rare (17). Consequently, metformin is now evaluated to be safe even in patients with lower GFR. From these situations, FDA has revised the label of metformin that it is safe to provide patients with eGFR $\geq$30 mL/min/1.73m^2.

There was a recent randomized trial with confirmation of previous data that metformin may cause vitamin B12 deficiency with exacerbation of neuropathy (17). This result was consistent with a report from diabetes prevention program outcomes study (DPPOS), which recommends examination of vitamin B12 concentration (17,18).

Since T2DM is usually progressive, monotherapy of metformin can be possible for a few years. After that, combination treatment would be necessary in order to add stepwise medications. This approach is recently revealed to be superior to sequential addition of other medications for primary and secondary development (19). Based on a comparative meta-analysis report, additional therapy to initial metformin administration shows reduction of HbA1c about 0.7-1.0% (20). When HbA1c target will not be achieved for 3 months, metformin plus other agent can be started with any of following six options. They are dipeptidyl peptidase‐4 (DPP‐4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) Inhibitors, sulfonylurea, thiazolidinedione, glucagon-like peptide-1 receptor agonists (GLP-1 Ras) and basal insulin (13).

Among these six options, GLP-1 Ras have been highly evaluated for the efficacy for T2DM. When T2DM patient needs greater blood glucose lowering, GLP-1Ras are recommended for preference to insulin if it is possible (level B). (13). Furthermore, recent reports can support clinical efficacy of GLP-1 Ras. Most GLP-1 Ras are injectable, but a new oral formulation of semaglutide is available at present (21). In contrast, some reports investigating the efficacy between GLP-1 RAs and insulin have showed similar results (22,23).

From economic diabetic treatment point of view, cost for diabetes has been increased for two decades (24). Medication cost may become major stress for diabetic patients influencing adherence with regular medication (25). Then, metformin has been very economic for long years with benefit for patients. From this point, metformin is a useful OHA.

In summary, metformin has been one of the most useful OHA for long. Recent investigation showed the beneficial and safe effect for patients with impaired renal function. This will be expected to become a reference for diabetic practice and research.

Conflict of Interest: None.

Funding: None.

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