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Current topics of possible pharmacotherapy for chronic kidney disease (CKD) and diabetes

Abstract

The authors and colleagues have been involved in Non-Communicable Diseases (NCDs), especially including diabetes, chronic kidney disease (CKD) and hemodialysis. Some topics are described as possible therapy for CKD. (i) Metformin has inhibitory effect on cardiovascular events, and has an evidence for safe administration in mild to moderate renal impairment. (ii) Canagliflozin reduced moderately cardiovascular and renal outcomes across the primary and secondary prevention groups, from mega studies of CANVAS and CREDENCE. (iii) erythropoiesis stimulating agent (ESA) has been effective for improving anemia in HD for years. Some hypoxia-inducible factor (HIF) seems to be applied for clinical practice soon.

Keywords: chronic kidney disease (CKD), Metformin, Canagliflozin, erythropoiesis stimulating agent (ESA), hypoxia-inducible factor (HIF)

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Abbreviations: ESA, erythropoiesis stimulating agent; CKD, chronic kidney disease; CANVAS, Canagliflozin cardiovascular assessment study; CREDENCE, Canagliflozin and renal rvents in diabetes with established nephropathy clinical evaluation; ESRD, end-stage renal disease; HIF, hypoxia-inducible factor

Text

Currently, Non-Communicable Diseases (NCDs) have been increasing in the world. Among them, the crucial issues in focus would be the clinical management of diabetes and chronic kidney disease (CKD).[1] The authors and colleagues have been involved in the practice of diabetes for years.[2] Particularly, we have continued clinical and research studies on low carbohydrate diet (LCD). For actual nutritional therapy, three kinds of LCDs were developed and educated, which are super-, standard- and petite-LCDs. Furthermore, we have treated many patients with CKD and hemodialysis (HD) in our hospital.[3] From the circumstances mentioned above, there are recent beneficial topics concerning DM and CKD. These were 1) relaxed restrictions on metformin use for CKD, which is partly from using estimated glomerular filtration rate (eGFR) and pathophysiological research accumulation, 2) improvement of combined renal outcomes with SGLT2 inhibitor and 3) adequate administration of erythropoiesis stimulating agent (ESA) on dialysis patients. These three topics will be introduced in this article as possible pharmacotherapy for CKD and diabetes.

Firstly, metformin (dimethylbiguanide) has been first-line oral hyperglycemic agent (OHA) to type 2 diabetes mellitus (T2DM).[4] It has the ability to counter insulin resistance and to decrease blood glucose without increased weight or risk of hypoglycemia, which is beneficial for clinical practice. It was proved to have long-term cardiovascular benefits according to UK Prospective Diabetes Study (UKPDS).[5] These data had provided a new rationale to give metformin for initial therapy to T2DM.

Among many OHAs, metformin had been previously the only one that had shown an inhibitory effect on cardiovascular events.[6] Formerly, the clinical use of metformin was restricted for patients with CKD. Its reason included the concerns over metformin-associated lactic acidosis. There are several data to suggest that metformin may bring lower risk of stroke, myocardial infarction and all-cause mortality in T2DM and CKD.[7] After that, several results concerning metformin and CKD were conflicting, and there were some reports with safer prescribing of metformin at different stages of CKD. A recent large-scale cohort study showed the evidence for safe use of metformin in mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30–60 mL/min/1.73m^2). However, administration of metformin to severe level (eGFR< 30) remains a controversial issue.[7]

There was a retrospective observational cohort study for 10,426 patients with type 2 diabetic kidney disease (DKD).[8] As a result, metformin usage has decreased the risk of all-cause mortality and incident end-stage renal disease (ESRD). However, further randomized controlled trials (RCTs) will be necessary to change the administration of metformin worldwide.[8]

Secondly, several SGLT2 inhibitors were investigated in the light of renal function. There have been several mega studies for administrating of SGLT2 inhibitors.[9] They include i) Canagliflozin cardiovascular Assessment Study (CANVAS), ii) Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), iii) Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) study, iv) Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58.

The CANVAS Program randomly assigned 10,142 participants with T2DM to canagliflozin or placebo.[10] In the total cohort, the primary end point was reduced with canagliflozin compared with placebo (hazard ratio [HR] 0.86). Renal outcome was reduced (HR, 0.59) and heart failure hospitalization was also reduced (HR, 0.68). Thus, Canagliflozin reduced moderately cardiovascular and renal outcomes across the primary and secondary prevention groups.[10] Successively, a series of CANVAS study revealed a beneficial efficacy on cardiovascular and also renal outcomes in T2DM.[11] In contrast, the data revealed rather elevated risk ratio for the amputation of lower extremities.[12]

Based on CANVAS results, further investigation was conducted with canagliflozin-based cardio-renal events as primary outcomes.[13] This study has been the CREDENCE Clinical Trials, which was a double-blind, randomized trial concerning canagliflozin as SGLT2 inhibitor.[13] Assigned subjects were T2DM patients with albuminuric CKD, who were provided canagliflozin. Their average age was 63 years old (n=4401). The protocol included two groups, which were canagliflozin group and control group.

As a result, relative risk of primary outcome showed 30% lower in canagliflozin group (HR 0.70).The time period for doubling level of serum creatinine was reduced from control by 40% (HR 0.60).The death from renal cause was reduced from control by 34% (HR 0.66). Furthermore, relative risk of ESKD was reduced by 32% (HR 0.68). Consequently, canagliflozin group revealed a reduced risk ratio of stroke, cardiovascular death and myocardial infarct (HR 0.80), and a reduced risk ratio of hospitalization from heart failure (HR 0.61). On the other hand, there was no significant differences in adverse events (HR 0.87), or in the occurrence of the amputation (HR 1.11) and fracture (HR 0.98).[13]

Regarding the effect of SGLT2 inhibitors in renal failure, there was a systematic review and meta-analysis of randomized, controlled, cardiovascular or kidney outcome trials.[14] The study covered canagliflozin (CANVAS Program and CREDENCE),[11] empagliflozin (EMPA-REG OUTCOME),[15,16] and dapagliflozin (DECLARE-TIMI 58)[17,18] with 38,723 subjects and 335 ESKD. The risk had reduced as ESKD (HR 0.65) and acute renal failure (HR 0.75). Thus, SGLT2 inhibitors reduced the risk of dialysis and renal impairment, suggesting the preventing major kidney outcomes in T2DM.

Furthermore, there was a systematic review and meta-analysis for effect of SGLT2 inhibitor for T2DM and CKD from 7363 participants in 27 studies.[19] The risk was reduced by SGLT inhibitors in heart failure (RR 0.61), cardiovascular death, nonfatal myocardial infarction or nonfatal stroke (RR 0.81), and composite renal outcome (HR0.71). Thus, SGLT2 inhibitors are effective for reducing the risk of cardiovascular and renal exacerbation in T2DM and CKD.

From statistic point of view, there is a recent report from the United States Renal Data System (USRDS).[20] It showed that approximately 40% of CKD patients also have concomitant diabetes.[20,21] As association of DM and CKD may increase mortality and morbidity, effective interventional strategy would be needed for protecting renal impairment, albuminuria, cardiovascular events.[21] For the perspectives in the future, propensity score analysis method may be useful (Leyrat-2017).[22] It can estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict receiving the treatment.

Thirdly, erythropoiesis stimulating agent (ESA) will be described. ESA has been effective for improving anemia in HD for years.[23] As recombinant human erythropoietin is given, the target Hb level would be important. When comparing the level at 13.5g/dL vs 11.3g/dL, the former showed increased risk and no incremental improvement in the quality of life.[23] When comparing short-acting ESAs vs long-acting ESAs, the latter users revealed 13% higher rate of deaths.[24] There have been discussion concerning the target level and ESA type. As oral anti-anemic agents, a few kinds of hypoxia-inducible factor (HIF) will be planned to be introduced in the clinical practice in 2020.[1] Further research development would be expected.

In summary, recent topics of metformin, SGLT2 inhibitor and ESA were summarized in this article. These factors are possible therapy for CKD. We hope that this description will help future medical practice and research.

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Conflicts of interest

The authors declare no conflict of interest.

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