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Commentary
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Clinical Development of Treatment Direction for Diabetic Nephropathy as Diet and Pharmacotherapy

Koji Ebe[1,2], Hiroshi Bando[1,3iD*], Michael Wood[1]
[1]*Japan Low Carbohydrate Diet Promotion Association (JLCDPA), Kyoto, Japan*
[2]*Takao Hospital, Kyoto, Japan*
[3]*Medical Research/Tokushima University, Tokushima, Japan*

Corresponding Author: **Hiroshi Bando** ORCID iD
Address: Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan; Email: pianomed@bronze.ocn.ne.jp

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Abstract

The American Diabetes Association (ADA) announced the Standard of Care (SoC)-2025 in January 2025. It included useful information about the low-carbohydrate diet (LCD), chronic kidney disease (CKD), and Metformin. Historically, the ADA has re-evaluated LCD in 2008, 2011, 2013, and 2019. Authors have developed LCD medically and socially through the Japan LCD Promotion Association (JLCDPA). From the latest report of post hoc analysis, Metformin may have a beneficial effect on CKD cases with an eGFR of less than 30 ml/min/1.73 m^2. For diabetic nephropathy (DN), impressive findings have been observed for major adverse cardiovascular events (MACE) and major adverse kidney events (MAKE).

Keywords

Low-Carbohydrate Diet, Chronic Kidney Disease, Metformin, Diabetic Nephropathy, Major Adverse Cardiovascular Events, Major Adverse Kidney Events

Abbreviations

ADA: American Diabetes Association; SoC: Standard of Care; LCD: Low-Carbohydrate Diet; CKD: Chronic Kidney Disease; JLCDPA: Japan LCD Promotion Association; eGFR: Estimated Glomerular Filtration Rate; DN: Diabetic Nephropathy; MACE: Major Adverse Cardiovascular Events; MAKE: Major Adverse Kidney Events

Commentary

The American Diabetes Association (ADA) has announced the guideline of Standard of Care (SoC)-2025 in January 2025 [1]. It has been revised every year, associated with novel information concerning diet therapy, pharmacotherapy, and others. Furthermore, recent topics include the controversies about chronic kidney disease (CKD) and diabetic kidney disease (DKD) in light of adequate meal content and the first-line agent, Metformin. In this article, some perspectives will be described.

Authors and collaborators have continued clinical research and practice regarding the low-carbohydrate diet (LCD) for a long time [2]. We have developed LCD medically and socially through the activities of the Japan

LCD Promotion Association (JLCDPA) [3]. In Japan, three practical types of LCD have been described, which are super-, standard-, and petite LCD, including carbohydrate contents of 12%, 26%, and 40%, respectively [4]. In the United States, historical changes in the evaluation of LCD have been observed for two decades. The ADA did not recommend LCD until 2007 in their guidelines.

In 2008, the "Statement on Dietary Therapy 2008" stated that "low calorie (fat) diet or LCD is recommended for diabetic patients wishing to lose weight," recognizing the effectiveness of LCD for a one-year period [5]. In 2011, the effectiveness of LCD was approved for obese diabetic patients for a limited period of two years [6]. In 2013, the "Statement on Dietary Therapy 2013" approved LCD without any time limit or restrictions [7]. In 2019, a consensus recommendation stated that LCD is one of the most researched dietary therapies [8]. The same consensus recommendation has been continued from 2020 until now.

Regarding diabetic nephropathy (DN), the ADA has shown gradual weaning off protein restriction rather than salt restriction. During the previous period, when LCD was not recommended, the ADA gradually came to recommend LCD (or high-protein diets). Consequently, in the "Statement on Dietary Therapy 2013," the ADA accepted LCD without time limits or restrictions, which remains the same situation until now. At this point, the ADA announced with a rank A that “protein restriction is not recommended for diabetic nephropathy.”

Recent topics of pharmacotherapy for diabetic nephropathy will be described. Metformin has long been the first-line treatment for T2D patients. Currently, emerging evidence has shown that Metformin may have reno-protective efficacy and that Metformin dose and treatment duration may be related to renal outcomes for T2D. A total of 302 T2D cases with an HbA1c of 7.7% were followed for an average of 11.4 years [9]. Metformin doses significantly impact the eGFR, suggesting that dosage plays a certain role in renal function.

The following comments are found in the ADA SoC-2025 [10]. The FDA revised its guidance for the use of Metformin in CKD in 2016 [11], recommending the use of eGFR instead of serum creatinine to guide treatment and expanding the pool of people with kidney disease for whom Metformin treatment should be considered. The revised FDA guidance states that 1) Metformin is contraindicated in individuals with an eGFR <30 mL/min/1.73 m^2, 2) eGFR should be monitored while taking Metformin, 3) the benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m^2 [12,13], 4) Metformin should not be initiated for individuals with an eGFR <45 mL/min/1.73 m^2, and 5) Metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in individuals with eGFR 30-60 mL/min/1.73 m^2.

The discussion has continued regarding the reno-protective efficacy of Metformin. The latest report showed the clinical effect of Metformin for cases of DKD with highly decreased renal function [14]. The protocol included 316,693 T2D cases from seven hospitals as a retrospective observational multi-center cohort study. The analysis was conducted for 13,096 cases with Metformin and 13,096 cases without Metformin. As a result, the Metformin group showed better renal outcomes, with a lower incidence of doubling time of Cre (Hazard ratio 0.71), eGFR ≤ 15 mL/min/1.73 m^2 (HR 0.61), and end-stage kidney disease (ESKD) (HR 0.55). The analyzed subgroup showed consistent reno-protective efficacy. Moreover, after adjusting for sex, age, comorbidities, and medication, the Metformin participants consistently showed slower decreasing renal function in nearly all subgroups.

A recent retrospective multi-center study reported outcomes from Metformin use [15]. A cohort formed the Metformin group within run-in periods and with at least one additional agent. Another cohort formed the control group with oral hypoglycemic agents (OHAs) other than Metformin or never received Metformin. Regarding the cases without DN, the outcomes showed some events of DN, major adverse cardiovascular events (MACE), and major adverse kidney events (MAKE). By 1:1 propensity matching, two cohorts (Metformin vs. control) were compared. The incidence rate ratios (IRR) for DN, MACE, and MAKE were 1.06, 0.76, and 0.45, respectively. Regarding three levels of renal function for

CKD stages 3A, 3B, and 4, IRRs of (MACE vs. MAKE) were 0.70 vs. 0.39 for CKD 3A, 0.83 vs. 0.44 for CKD 3B, and 0.71 vs. 0.45 for CKD 4. As mentioned above, Metformin continuation for T2D cases across renal functions can correlate consistently with decreased risk of DN, MACE, and MAKE.

From the post hoc analysis, the CKD-FIX population with T2D and stage 3 CKD was analyzed (n=97) [16]. CKD-FIX stands for the Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase. Among them, 51 took Metformin and 46 did not, forming two comparative groups. In addition, a subpopulation (n=80) completed follow-up for two years. The changes in eGFR for the two groups were analyzed, and there was no significant difference of 0.011 ml/min/1.73 m^2 per week. The results were as follows. The Metformin group (n=51) showed eGFR reduction for 18 (35%) as 30% and 7 (14%) as 40%, respectively. The non-Metformin group (n=46) showed eGFR reduction for 14 (30%) as 30% and 9 (20%) as 40%, respectively (**Fig-1**). The group differences were not significant. Concerning serious adverse events or hospitalizations, both groups showed similar results.

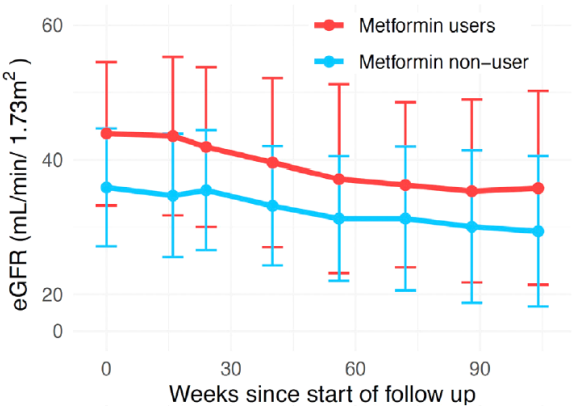

Fig-1:

Mean eGFR (with SD) over time in participants included in post hoc analysis, by metformin status. (modified from Stanley et al.2024)

In summary, various recent topics for 2024-2025 have been introduced concerning LCD, CKD, DKD, and Metformin, as well as the latest ADA SoC-2025 guidelines. Metformin has been the first-line agent for T2D, and it has been re-evaluated for clinical efficacy for DN with possible decreased eGFR.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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References

[1] American Diabetes Association Professional Practice Committee. Introduction and Methodology: Standards of Care in Diabetes-2025. Diabetes Care. 2025 Jan 1;48(1 Suppl 1):S1-S5. [**PMID**: 39651982]

[2] Ebe K, Bando H. New era of diet therapy and research including Low Carbohydrate Diet (LCD). Asp Biomed Clin Case Rep. 2018;2(s1):1-3.

[3] Muneta T, Hayashi M, Nagai Y, Matsumoto M, Bando H, Ebe K, Watanabe H, Watanabe S. Ketone Bodies in the Fetus and Newborn During Gestational Diabetes and Normal Delivery. Int J Diabetes. 2023; 5(1):157-63.

[4] Bando H, Ebe K. Beneficial and Convenient Method of Low Carbohydrate Diet (LCD) as Petite, Standard and Super LCD. Asp Biomed Clin Case Rep. 2023 Nov 04;7(1):1-4.

[5] American Diabetes Association; Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2008 Jan;31 Suppl 1:S61-78. [**PMID**: 18165339]

[6] American Diabetes Association. Standards of medical care in diabetes--2011. Diabetes Care. 2011 Jan;34 Suppl 1(Suppl 1):S11-61. [**PMID**: 21193625]

[7] Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, Neumiller JJ, Nwankwo R, Verdi CL, Urbanski P, Yancy WS Jr. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care. 2014 Jan;37 Suppl 1:S120-43. [**PMID**: 24357208]

[8] Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, Mitri J, Pereira RF, Rawlings K, Robinson S, Saslow L, Uelmen S, Urbanski PB, Yancy WS Jr. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. Diabetes Care. 2019 May;42(5):731-54. [**PMID**: 31000505]

[9] Hadiia GM, Albarasi H, Abdalrehman S, Alasbily HM, Elawamy HA, Alfituri AM, Gaber S, Nefa MA. Metformin dosage and renal protection in type 2 diabetes mellitus: impact on estimated glomerular filtration rate. Mediterr J Pharm Pharm Sci. 2024;4(3):7-14.

[10] American Diabetes Association Professional Practice Committee. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes-2025. Diabetes Care. 2025 Jan 1;48(Supplement_1):S239-51. [**PMID**: 39651975]

[11] U.S. Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. United States: U.S. Food and Drug Administration; 2017 [cited: 2024 Aug 25]. Available from: https://www.fda.gov/media/96771/download

[12] Lalau JD, Kajbaf F, Bennis Y, Hurtel-Lemaire AS, Belpaire F, De Broe ME. Metformin Treatment in Patients With Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4. Diabetes Care. 2018 Mar;41(3):547-53. [**PMID**: 29305402]

[13] Chu PY, Hackstadt AJ, Chipman J, Griffin MR, Hung AM, Greevy RA Jr, Grijalva CG, Elasy T, Roumie CL. Hospitalization for Lactic Acidosis Among Patients With Reduced Kidney Function Treated With Metformin or Sulfonylureas. Diabetes Care. 2020 Jul;43(7):1462-70. [**PMID**: 32327421]

[14] Wang HH, Lin SH, Hung SY, Chiou YY, Hsu WC, Chang CM, Liou HH, Chang MY, Ho LC, Wu CF, Lee YC. Renal protective effect of metformin in type 2 diabetes patients. J Clin Endocrinol Metab. 2024 Jul 11:dgae477. [**PMID**: 38986038]

[15] Yi Y, Kwon EJ, Yun G, Park S, Jeong JC, Na KY, Chin HJ, Yoo S, Kim S, Oh TJ, Kim S, Jung CH, Lee H. Impact of metformin on cardiovascular and kidney outcome based on kidney function status in type 2 diabetic patients: a multicentric, retrospective cohort study. Sci Rep. 2024 Jan 24;14(1):2081. Erratum in: Sci Rep. 2024 May 29;14(1):12337. [**PMID**: 38267451]

[16] Stanley IK, Mallett AJ, Viecelli AK, Hawley CM, Staatz CE, Johnson DW, Milanzi E. A Post Hoc Analysis of the CKD-FIX Study Analyzing the Association Between Metformin Usage and Estimated GFR Decline. Kidney Int Rep. 2024 Feb 9;9(5):1525-27. [**PMID**: 38707797]

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