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Maintained Renal Function by Blood Pressure Control in Patient with Diabetic Kidney Disease (DKD)

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Abstract

The case involves a 74-year-old male with type 2 diabetes (T2D), hypertension, dyslipidemia, and diabetic kidney disease (DKD) at nephropathy stage G3b. He has been receiving treatment with insulin and anti-hypertensive agents (AHAs). In July 2021, his HbA1c was elevated to 7.9%. As a result, the extent of his low carbohydrate diet (LCD) was increased, and insulin doses were raised. The AHAs were changed from Olmesartan to Valsartan/Amlodipine, and Irbesartan/Amlodipine until 2023. By January 2023, his HbA1c had decreased to 6.8%, and his eGFR (CKD-EPI) had remained stable at 34-48 mL/min/1.73/m^2 for 4 years. A recent study demonstrated clinical improvement in renal function through continuous LCD in patients with DKD.

Keywords

Type 2 Diabetes, Anti-Hypertensive Agents, Low Carbohydrate Diet, Chronic Kidney Disease Epidemiology Collaboration, Estimated Glomerular Filtration Rate

Abbreviations

T2D: Type 2 Diabetes, AHAs: Anti-Hypertensive Agents, LCD: Low Carbohydrate Diet, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, eGFR: Estimated Glomerular Filtration Rate

Introduction

For several decades, atherosclerotic cardiovascular disease (ASCVD) has emerged as a significant global health concern [1]. Among the various diseases associated with ASCVD, hypertension (HTN), type 2 diabetes (T2D), chronic kidney disease (CKD), and diabetic kidney disease (DKD) have garnered attention for effective management [2]. These conditions can lead to the deterioration of multiple organ functions, including cerebral vascular accidents (CVA), ischemic heart disease (IHD), and peripheral artery disease (PAD).

In the case of patients with CKD and DKD, numerous interventions have been explored, including lifestyle modifications, calorie restriction (CR), low carbohydrate diets (LCD), and appropriate medications to delay the progression of renal function decline [3]. Weight reduction has shown clinical benefits in obese patients [4]. Additionally, other dietary approaches,

such as low-protein diets (LPD), the Mediterranean diet (Med), the alternate Mediterranean (aMed) diet, and the Alternative Healthy Eating index (AHEI), have been associated with improved outcomes in CKD and DKD [5]. Studies on aMed diet and AHEI have demonstrated a decreased risk of CKD progression [6]. Consistent adherence to a low-sodium diet has also been linked to a longer doubling time for increasing creatinine levels. However, the current clinical efficacy of these interventions in terms of estimated glomerular filtration rate (eGFR), proteinuria, and all-cause mortality remains inconclusive, necessitating further research [7].

The authors and their colleagues have dedicated years to clinical research and practice related to T2D, CKD, DKD, hemodialysis, ASCVD, and other relevant areas [8,9]. Moreover, they have developed LCD approaches from both medical and social perspectives through the Japanese LCD Promotion Association (JLCDPA) [10,11]. Notably, three types of LCD have gained popularity among patients: super-LCD, standard-LCD, and petite-LCD, with carbohydrate contents of 12%, 26%, and 40%, respectively [12]. Recently, the clinical team encountered a male patient with DKD who successfully maintained his renal function through continuous control of blood glucose and blood pressure. This report will detail the patient's clinical progress and provide a discussion of his case.

Case Presentation

History & Physicals:

The patient is a 74-year-old male with a diagnosis of type 2 diabetes (T2D) and diabetic nephrosis at stage G3b [13]. He was initially diagnosed with T2D, hypertension, and dyslipidemia at around 60 years old and was initially treated with oral hypoglycemic agents (OHAs) and anti-hypertensive agents (AHAs). At the age of 67 in 2016, he transitioned to insulin treatment. From 2016 to 2018, his overall diabetic condition remained stable, with HbA1c levels ranging from 5.8% to 6.4%. He reported experiencing some numbness in his hands and feet due to neuropathy. In terms of nephropathy, his creatinine levels ranged from 1.3 to 1.4 mg/dL, with an estimated glomerular filtration rate (eGFR) of 54-59 mL/min/1.73m^2 (using the Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI formula). There were no apparent signs of macroangiopathy, such as cerebral vascular accidents (CVA), ischemic heart disease (IHD), or peripheral artery disease (PAD).

During a physical examination in the spring of 2019, the following observations were made: The patient was conscious and exhibited normal communication during the outpatient visit. Vital signs, including pulse rate, blood pressure, body temperature, respiration rate, and SpO_2, were within normal ranges. No notable abnormalities were found in the head, heart, lungs, or abdomen. Neurological findings revealed slight numbness in the patient's hands and feet. His physical measurements indicated a height of 163 cm, a weight of 67 kg, and a body mass index (BMI) of 25.2 kg/m^2.

Laboratory Tests:

The results of laboratory exams in Spring 2019 were in the following. HbA1c 5.9%, post-prandial blood glucose 201 mg/dL, TP 6.4 g/dL, Alb3.9 g/dL, AST 11 U/L, ALT 13 U/L, GGT 17 U/L (7-74), Uric acid 8.7 mg/dL, BUN 45 mg/dL, Cre 1.94 mg/dL, eGFR 34.1 mL/min/1.73m^2 (CKD-EPI), Na 142 mEq/L, Cl 108 mEq/L, K 4.6 mEq/L, HDL 45 mg/dL, LDL 103 mg/dL, TG 133 mg/dL, T-Cho 175 mg/dL, CRP 0.37 mg/dL, WBC 6600/μL, RBC 3.63 x 10^6 /μL, Hb 11.7 g/dL, Ht 34.9 %, MCV 96.0 fL (80-98), MCH 32.2 pg (27-33), MCHC 33.5 g/dL (31-36), Plt 17.8 x 10^4 /μL. Urinalysis: glucose (+), protein (++), urobilinogen (+/-), pH 6.0, ketone bodies (-).

Clinical Course:

His clinical progress from 2019 to 2023 has been closely monitored, as depicted in **Fig-1**. HbA1c values initially increased to 7.9% in July 2021 but subsequently decreased to 6.8% in January 2023. Regarding renal function, the levels of creatinine and eGFR (calculated using both the CKD-EPI and JSNP formulas) were tracked. These parameters remained relatively stable over the course of more than four years, with creatinine levels ranging from 1.6 to 1.8 mg/dL and eGFR ranging from 34 to 39 mL/min/1.73m^2. Throughout this period, meticulous management was applied to address blood glucose variability, blood pressure control, and renal function related to uric acid and creatinine. This involved the

administration of necessary oral hypoglycemic agents (OHA), anti-hypertensive agents (AHA), and insulin as needed. To regulate HbA1c levels, Novolin 30R was administered twice a day in the morning and evening, with dosages ranging from 14/8 units to 18/10 units. By March 2023, pre-prandial blood glucose levels in the morning and evening had stabilized at an ideal range (refer to **Table-1**). Regarding blood pressure management, there were successive changes in AHAs, including Olmesartan, Valsartan/Amlodipine, and Irbesartan/Amlodipine, until 2023 (see **Fig-1**). Additionally, calcium polystyrene sulfonate was administered to control serum potassium levels. Careful monitoring of these biomarkers and the implementation of appropriate interventions have contributed to the maintenance of his renal function over the years.

Table-1: Profile of Glucose Variability

Date	pre-prandial Breakfast	pre-prandial Supper
1	116	116
2		98
3	127	
4	130	131
5	116	126
6		131
7	118	121
8	119	
9		116
10	136	125
11	135	
12	126	136
13		119
14	137	
15	129	121

The data are from March 1-15, 2023
Rapid insulin is given 13/8 units twice

Other Exams:

A chest X-ray was performed, and the results showed no abnormal findings. The electrocardiogram (ECG) revealed ordinary sinus rhythm (OSR) with a normal axis and a pulse rate of 72 beats per minute, without significant ST-T changes. In June 2021, the patient underwent mechanocardiogram and sphygmogram examinations. The ankle brachial index (ABI) was measured, resulting in values of 1.14/1.10 for the right and left sides, respectively. The cardio-ankle vascular index (CAVI) was also assessed and found to be 11.2/12.5 for the right and left sides, respectively. The same examinations were repeated in May 2022, and the results showed slightly improved or similar findings. The ABI values were 1.15/1.16, and the CAVI values were 9.8/10.5 (refer to **Fig-2**). These results suggest a relatively stable cardiovascular status with no significant abnormalities.

Ethical Standards

This case study adhered to the standard ethical guidelines outlined in the former Declaration of Helsinki, which provides ethical principles for medical research involving human subjects. Additionally, measures were taken to protect the privacy and confidentiality of personal information in accordance with regulatory requirements. The research followed ethical rules and guidelines applicable to clinical research and practice involving human participants. These guidelines were provided by the Ministry of Health, Labor, and Welfare, Japan, as well as the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The authors and researchers established an ethical committee specific to this research, which was located at Sakamoto Hospital in Higashi-Kagawa, Japan. The committee comprised various professionals, including the hospital director, physicians, registered pharmacist, head nurse, registered dietitian, and legal professionals. Full discussions were held among all committee members regarding the case, and a research protocol was agreed upon. Informed consent was obtained from the individual involved in the case, documented in written form, ensuring their understanding and agreement to participate in the research.

Discussion

The current case study concerned a 74-year-old male who has been treated for type 2 diabetes (T2D), hypertension, dyslipidemia, and diabetic nephropathy stage G3b. These diseases have shown mutual influences and relationships in the light of arteriosclerosis [14]. He has been able to control adequate levels of blood glucose, blood pressure, and renal function for years in relation to T2D, hypertension, creatinine (Cre), and estimated glomerular filtration rate (eGFR). For 4.5 years, he has managed his renal function, which seems to be highly evaluated by maintaining his stable regular daily life.

Case Report

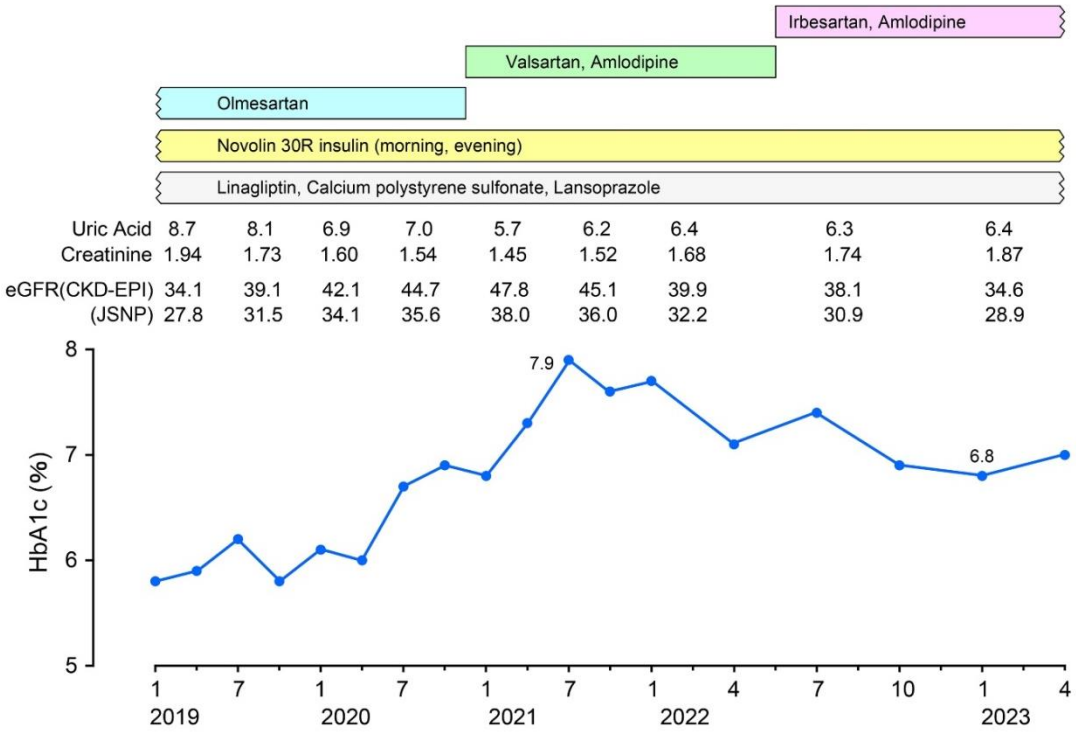

Fig-1:

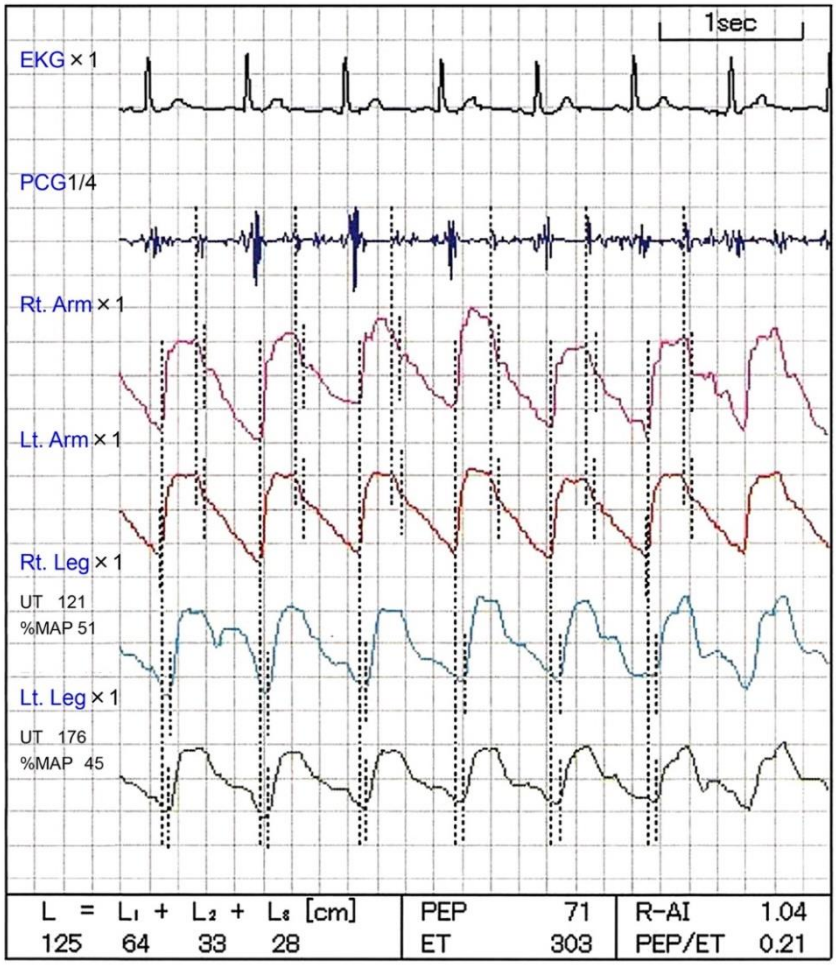

Fig-2:

This article will describe some perspectives concerning i) glucose control, ii) blood pressure control, and iii) an adequate diet for diabetic kidney disease (DKD) [14].

First, the current case has been able to maintain renal function for several years, which may be attributed to maintaining glucose variability to a certain degree. The basic principle of treatment for T2D is adequate diet therapy, which involves restricting carbohydrate intake. The current case has adhered to a satisfactory low carbohydrate diet (LCD) for a long time. His stable daily life with adequate meals, exercise, and medication has continued for an extended period. Through the Japan LCD Promotion Association (JLCDPA) [11], the authors and others have continued to develop and promote LCD medically and socially. For a practical LCD method, we recommend three types of LCD that are easy to understand: petite-LCD, standard-LCD, and super-LCD, which have carbohydrate ratios of 40%, 26%, and 12%, respectively [12]. When diabetic patients adopt the super-LCD, significant improvements in glucose control and rapid weight reduction have been observed [15]. LCD has been recognized as a simple and useful dietary method for weight reduction in ideal situations. In this case, insulin administration has been provided for a long time, and the patient has successfully maintained satisfactory daily glucose variability (**Table-1**). His pre-prandial glucose has been ideal, and his post-prandial glucose values appear to be in the normal range because he always understands the amount of carbohydrates.

Second, the case was able to maintain stable blood pressure by adjusting antihypertensive medications from mild to strong pharmacological effects. When evaluating blood pressure, both home and office blood pressure measurements are required [16]. The KAMOGAWA-HBP study, a prospective cohort study conducted since 2008, investigated blood pressure in patients with type 2 diabetes (T2D) [17]. This study found that elevated risk of progressing to diabetic nephropathy (DN) within 2 years was associated with morning systolic blood pressure (SBP). The data were compared to the odds ratio (OR) of the group with SBP < 120 mmHg. The results showed an OR of 2.725 for SBP 120-129 mmHg, an OR of 3.703 for 130-139 mmHg, and an OR of 2.994 for ≥140 mmHg [18]. A retrospective cohort study of 165 T2D cases with nephropathy was conducted over 10 years [19]. By comparing four groups based on morning home systolic blood pressure ≥125 mmHg, the status of nephropathy 10 years later showed improvement in 5.5%, no change in 72.1%, and exacerbation in 22.4%. The odds ratio (OR) was 10.41 when comparing the continuously high blood pressure group with the well-controlled group. Consequently, chronic home blood pressure monitoring would be significant for the progression of diabetic nephropathy.

In order to suppress the development of diabetic nephropathy (DN), the standard treatment aims for an A1c level below 7% and blood pressure below 130/80 mmHg [20]. For cases of diabetic kidney disease (DKD), a multifactorial intervention was investigated in two groups. The intensive group had an HbA1c level below 6.2%, blood pressure below 120/75 mmHg, and LDL-C level below 80 mg/dL, while the standard group had an HbA1c level below 6.9%, blood pressure below 130/80 mmHg, and LDL-C level below 120 mg/dL. The study, which lasted an average of 8.5 years, showed a significant 32% decrease in kidney events in the intensive group [21].

To protect the heart and kidneys of DKD patients, nonsteroidal mineralocorticoid receptor antagonists (MRAs) have emerged as novel agents. Finerenone was the first nonsteroidal MRA used for DKD patients. Two randomized clinical trials (RCTs), namely FIDELIO-DKD and FIGARO-DKD, along with the FIDELITY analysis, demonstrated the beneficial efficacy of MRA finerenone on the heart and kidneys in 13,000 DKD cases [22]. Among these trials, FIDELIO-DKD stands for Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease.

Third, there have been ongoing debates about the appropriate diet for patients with diabetic kidney disease (DKD). In the past, the focus was primarily on indicators of renal function such as creatinine (Cre) and blood urea nitrogen (BUN), leading to recommendations to restrict protein and salt intake. However, in recent years, there has been a shift towards carbohydrate restriction as a common treatment approach, supported by accumulating data.

The case mentioned in the study was diagnosed with nephropathy stage G3b [23], which indicates overt nephropathy with persistent proteinuria and an estimated glomerular filtration rate (eGFR) greater than 30 mL/min/1.73m^2 [13]. This classification is a result of the revised classification of diabetic nephropathy by The Joint Committee on Diabetic Nephropathy [24].

To investigate the relationship between low-carbohydrate diet (LCD) score and the incidence of type 2 diabetes (T2D), data from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) were analyzed, involving a sample size of 19,084 individuals [25]. During a 5-year period, 490 adults developed T2D. After adjusting for confounding factors, the highest vs lowest quintiles of LCD intake groups showed some overall odds ratio (OR) of 0.64 in men and 0.78 in women. These results may suggest a protective effect of a usual diet with lower carbohydrate intake against the development of T2D.

For DKD patients (n=30), comparative study was conducted in very low carbohydrate diet (VLCBD) and low protein diet (LPD) groups for 12 weeks [26]. Both groups had daily carbo amount 27g vs 89g, and daily protein amount 44g vs 30 g, respectively, with same lipid amount. The result after 122 weeks showed that HbA1c decreased as 1.3% vs 0.7%, fasting blood glucose decreased by 1.5 vs 1.3 mmol/L, associated with no exacerbation of serum creatinine. Both interventions showed well-accepted without any adverse events reported. Formerly, DKD patients were recommended to lower protein consumption, in which protein intake is less than 0.8 g/kg of body weight/day for non-dialysis dependent CKD [27]. Recent discussion includes the comparison of LCD and calorie-restriction (CR) for DKD cases. As recent report by Bruci et al., safe and effective very-low-calorie ketogenic diet (VLCKD) was found for DKD cases [28]. Patients with mild kidney failure (n=38) showed significant improvement of weight and metabolism parameters. Further, 27.7% of the cases showed GFR normalization after dietary intervention. Consequently, VLCKD may become effective and safe method for weight reduction for patients affected mild kidney failure.

Certain limitation exists in this report. The case presented improvement or maintenance of renal function, associated with LCD continuation and weight reduction. Simultaneously, his blood pressure has elevated, which was controlled by strengthening AHAs. All of related clinical factors were not studied so far, and then future follow-up will be necessary.

In summary, this case of 74-year-old male with T2D and DKD stage G3b was shown. Recent perspective and discussion were described concerning several involved factors of T2D, DKD, LCD, blood pressure control. It is expected that current article will be useful data for future DKD and LCD research.

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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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