Short Communication

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The Protective Effect of a Low-Protein Diet against Tubulo-Interstitial Damage in Diabetic Kidneys

Munehiro Kitada*, Yoshio Ogura and Daisuke Koya

Department of Diabetology and Endocrinology, Kanazawa Medical University, Uchinada, Ishikawa, Japan

***Corresponding author:** Munehiro Kitada, Department of Diabetology and Endocrinology, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa, Japan, Tel: +81-76-286-2211; E-mail: kitta@kanazawa-med.ac.jp

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Clinically, the efficacy of a low-protein diet (LPD) on diabetic nephropathy is controversial. Our study clearly showed that a very-low-protein diet (VLPD) intervention improved advanced diabetic nephropathy, particularly tubulo-interstitial injuries by restoring autophagy through the suppression of the mammalian target of rapamycin complex 1 (mTORC1) pathway, in a rat model of type 2 diabetes and obesity. Therefore, a VLPD should be expected as a clinically relevant means of suppressing the decline in renal function that occurs during advanced diabetic nephropathy. However, a severe pan-amino acid restriction should be avoided because of its resulting nutritional issues in patients. Further studies to elucidate which amino acids should be restricted for the greatest renoprotection are necessary for developing replacements for a VLPD to treat the advanced stages of diabetic nephropathy.

Diabetic nephropathy develops in 40% of patients with diabetes and remains the leading cause of end-stage kidney disease (ESKD) worldwide. Diabetic patients with nephropathy have a high risk of cardiovascular disease, which contributes to their high mortality rate [1]. Multifactorial management, including diet therapy, optimal glycemic control, blood pressure control using renin-angiotensin receptor system inhibitors and lipid control using statins or fibrates, is recommended for suppressing the progression of diabetic nephropathy [2]. However, some patients with particularly advanced diabetic nephropathy rapidly progress to ESKD despite having received adequate multifactorial treatment. Therefore, a novel treatment for advanced diabetic nephropathy should be developed. With regards to diet therapy, a low-protein diet (LPD) has been considered for the preservation of renal function during chronic kidney disease, including diabetic nephropathy. Data from previous animal experiments have shown that the primary effects of an LPD might prevent the onset of diabetic nephropathy by improving abnormal metabolic factors and hemodynamics through multiple mechanisms, including improvements in glomerular hypertension, glomerular capillary resistance and glomerular hypertrophy [3-7]. Because the degree of tubulo-interstitial damage (rather than glomerular damage) is predictive of decline in renal function [8-10], protecting the renal tubular cells against diabetes-induced tubular damage will preserve renal function. Does an LPD have a protective effect for the renal tubular cells and glomeruli and glomerular cells in diabetic kidneys? Additionally, does an interventional LPD improve advanced diabetes-induced renal injuries such as the tubulo-interstitial damage? Our study clearly showed that an LPD intervention improved advanced diabetic nephropathy, particularly tubulo-interstitial injuries such as fibrosis, tubular cell damage, inflammation and apoptosis, in Wistar fatty (fa/fa) rats (WFRs), which are animal models of type 2 diabetes and obesity [11]. We also investigated the detailed mechanism by which an LPD improved advanced tubulo-interstitial damage in diabetes, and we focused on the autophagy and the mammalian target of rapamycin complex 1 (mTORC1) pathway. Autophagy has a crucial role in maintaining mitochondrial quality through lysosomal degradation of damaged mitochondria under various stress conditions [12-14]. Therefore, impaired autophagy contributes to the accumulation of damaged mitochondria, resulting in increased mitochondrial oxidative stress, inflammation and apoptosis. Although basal autophagy activity in renal tubular cells is less than that of other renal cells, such as glomerular podocytes [15], autophagy in renal tubular cells is induced through cellular stresses, including hypoxia and proteinuria, and the activation of autophagy protects tubular cells from cellular dysfunction and apoptosis [16-18]. The mTORC1 pathway is recognized as an autophagy regulatory factor, and over nutrition-induced activation of the mTORC1 pathway suppresses autophagy [12]. Because amino acids are recognized as mTORC1 activators [19], an LPD that involves amino acid restriction should suppress the mTORC1 pathway and induce autophagy. We showed that fragmented mitochondria accumulated in diabetic proximal tubular cells (PTCs) because of impaired autophagy, which may have been implicated in increased oxidative stress, inflammation and apoptosis [11]. An LPD intervention decreased the level of abnormal mitochondria in diabetic PTCs by restoring autophagy through the suppression of the mTORC1 pathway, which led to improvements in diabetic nephropathy [11]. In addition, a very LPD (VLPD) is important for renoprotection because a 5.77% LPD, but not an 11.46% LPD, is needed to suppress the mTORC1 pathway and to induce autophagy in the kidneys [11].

In the current clinical situation, the efficacy of an LPD for advanced diabetic nephropathy remains controversial. Some previous clinical studies have not consistently shown the beneficial effects of an LPD for the preservation of renal function in diabetic nephropathy, whereas other studies have shown that an LPD has beneficial effects in that it slows the progressive decline in renal function [20,21]. Nezu et al. showed that an LPD for diabetic nephropathy improves the estimated glomerular filtration rate when patients adhere to a protein-restricted diet [21]. However, adherence to LPDs is often poor, which has contributed to the controversial results of previous clinical studies. In addition, the amount of protein restriction would be expected to be important for renoprotection. A previous report shows that a VLPD consisting of less than 0.5 g/kg/day in the absence of malnutrition significantly suppressed renal dysfunction in patients with chronic glomerular nephritis who had serum creatinine levels of more than 6.0 mg/dl [22]. Thus, an LPD, particularly a VLPD without malnutrition, should have beneficial effects on advanced diabetic nephropathy, as well as on chronic glomerular nephritis, and should be further considered as a clinically relevant means of suppressing the decline in renal function that occurs during advanced diabetic nephropathy. However, there may be some nutritional issues associated with a VLPD in patients over the long term, including sarcopenia, frailty or protein-energy wasting, as well as issues associated with patient adherence to a VLPD. As such, a severe pan-amino acid restriction should be avoided because of its resulting nutritional issues in patients. Therefore, further studies to elucidate which amino acids should be restricted for the greatest renoprotection are necessary for developing replacements for a VLPD to treat the advanced stages of diabetic nephropathy.

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