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## **Methionine restriction diet modulates renal injury in chronic kidney disease animal model**

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### **Objectives:**

Despite the protective effects of protein-restricted diets against metabolic diseases, aging and cancer, it is not clear whether certain nutrients mediate the effects of protein restriction. Recently, methionine restriction (MR) has been reported to improve glucose homeostasis and prolong the lifespan, but studies on the direct effect of MR on kidneys are lacking. We investigated the effects of MR diets on renal injury in animal models of chronic kidney disease (CKD), especially whether the beneficial effect of MR diets may be mediated via intestinal microbiome.

**Methods:** To make CKD, four weeks old C57L/B6 was administered 0.025% adenine chow mixed with the R3 diet for 4 weeks. For the MR diet group, the same adenine but methionine/choline deficient diet was administered. The renal function, renal histology, intestinal permeability and fecal short-chain fatty acid (SCFA) were compared in both groups.

**Results:** The principal coordinates analysis of the microbiome showed the two groups have distinctive component features. The stool SCFA, especially butyrate was increased in the MR diet group. However, gut permeability using FITC-dextran showed no significant difference between the two groups. Interestingly, the infiltrations of neutrophils and macrophages were attenuated in the MR diet compared to adenine alone diet. Renal macrophages from the MR diet group showed more anti-inflammatory M2 subtypes. The improved renal inflammation was associated with better renal function, lower  $\alpha$ -SMA expression and reduced fibrosis, suggesting that dietary methionine restriction modulates renal response and attenuates kidney injury in CKD.

**Conclusions:** In conclusion, MR diet increased butyrate production and decreased renal inflammation resulting in renoprotection in CKD. This study suggests that new therapeutic strategies through specific diet modulation may improve the prognosis of CKD.