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Ketogenic Diet Delays the Progression of Diabetic Nephropathy in db/db Mice

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Objectives: This study aimed to evaluate the efficacy of ketogenic diet (KD) for progression of DN in DN mice models.

Methods: *In vivo*, 5-week-old C57 BLKS/J lar-Lepr^{db}/Lepr^{db} mice (n=28) were divided into the three groups as follows: normal chow diet (NCD) group (n=7), high fat diet (HFD) group (n=9) and KD group (n=12). Weekly measurement of fasting glucose and body weight were performed, and 24 h urine collections excretion and energy expenditure analysis were executed using metabolic cage. Mice were sacrificed at 25 weeks of age, and blood and tissues were harvested. *In vitro*, we determined the effect of 3-β-hydroxybutyric acid (3-OHB) in human renal proximal tubule HK-2 cells by western blot, polymerase chain reaction, and immunofluorescence analyses.

Results: Body weights were significantly lower in the KD group in comparison with those in NCD and HFD groups, but no significant differences in fasting blood glucose levels among three groups were observed. Urinary albumin/creatinine ratio was significantly lower in the KD group compared to other groups. Histologic, electron microscopy, and quantitative analyses revealed less thickened glomerular basement membrane and smaller mesangial area in the KD group compared with NCD and HFD groups, which implicates that KD delayed the progression of DN. KD group showed more energy expenditure and increased renal autophagy via increased p62 and LC3 expressions. *In vitro* mechanistic study showed 3-OHB treatment stimulated autophagy in HK-2 cells evidenced by increased LC3II/I ratio and nuclear factor erythroid 2-related factor 2 (Nrf2). Finally, we validated in vitro results *in vivo* mice model. We observed increased LC3 and Nrf2 expressions. We also found decreased production of reactive oxygen species and inflammatory markers in KD group.

Conclusions: This study showed both *in vitro* and *in vivo* that KD might exert its protective effects by augmenting autophagy leading to inhibition of oxidative stress and inflammation.