Abstract Type : Oral presentation
Abstract Submission No.: A-0135
Abstract Topic : Basic Research

Calorie Restriction Alleviates Kidney Fibrosis: Unraveling Metabolic and Fibrotic Mechanisms

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Objectives : Kidney fibrosis, a hallmark of chronic kidney disease (CKD), is characterized by excessive deposition of extracellular matrix proteins, leading to impaired kidney function. Calorie restriction (CR) has been shown to exert beneficial effects in various age-related and metabolic diseases, but its role in kidney fibrosis remains underexplored. This study aims to investigate the impact of CR on the development and progression of kidney fibrosis, focusing on the modulation of metabolic and fibrotic pathways.
Methods : A murine model of kidney fibrosis was induced using unilateral ureteral obstruction (UUO). Mice were subjected to a 30% calorie-restricted diet (n=6) or a controlled diet (n=6) for four weeks. Kidney tissues were collected and analyzed for histopathological changes by Masson's trichome staining for fibrotic markers (Type-1 collagen, α-SMA, fibronectin) and epithelial marker (E-cadherin). Real time PCR for pro-fibrotic (COL6A1, COL4A1, COL1A1, COL8A1, COL3A1, ITGA, HSPG2, ACTA2, CTGF ,FN1, TGFB1, MMP 9, MMP 10, MMP2, TIMP1) expression was performed from the tissue lysate. Levels of cytokines IFN-g, IL-4, IL-17, IL-1β, IL-6, TNF-a (proinflammatory) and IL-10 (anti-inflammatory) in blood samples of mice were determined by ELISA. Type-1 collagen, α-SMA, fibronectin protein, and key metabolic regulators (AMPK, SIRT1, and mTOR) were examined by flow cytometry and immunoblotting.
Results : Mice on the calorie-restricted diet exhibited significantly reduced kidney fibrosis compared to the control group, as evidenced by downregulation of pro-fibrotic genes (table 1), decreased collagen deposition, lower expression of fibrotic markers, restoration of E-Cadherin, and decreased production of proinflammatory cytokines levels indicating an anti-inflammatory effect. CR was associated with the activation of AMPK and SIRT1 ($p<0.001$), along with the downregulation of mTOR ($p<0.001$), suggesting a shift towards a catabolic state that may protect against fibrogenesis.
Conclusions : The findings suggest that dietary interventions such as CR could serve as a non-pharmacological strategy to mitigate kidney fibrosis and slow the progression of CKD.

Table 1.png

Table 1. Effect of Calorie Restriction against Controlled Diet in Murine Model of Kidney Fibrosis

	Controlled Diet (Fold change in comparison to media + cells only)	**Calorie Restriction (Fold change in comparison to Controlled Diet)**
**COL1A1*	Reference (5.3 fold increase)	(1.5 fold decrease)
**COL1A2*	Reference (4.1 fold increase)	(1.1 fold decrease)
**ACTA2*	Reference (4.7 fold increase)	(2.2 fold decrease)
**CTGF*	Reference (8.9 fold increase)	(4.3 fold decrease)
**FN1*	Reference (5.4 fold increase)	(1.1 fold decrease)
**COL6A1*	Reference (5.3 fold increase)	(3.2 fold decrease)
**COL4A1*	Reference (4.1 fold increase)	(2.2 fold decrease)
**COL1A1*	Reference (4.7 fold increase)	(3.9 fold decrease)
**COL8A1*	Reference (8.9 fold increase)	(6.6 fold decrease)
**COL3A1*	Reference (5.4 fold increase)	(3.0 fold decrease)
**ITGA*	Reference (3.9 fold increase)	(2.6 fold decrease)
**HSPG2*	Reference (1.4 fold increase)	(1.0 fold decrease)
**MMP2*	Reference (0.4 fold decrease)	(0.6 fold increase)
**MMP9*	Reference (0.3 fold decrease)	(0.5 fold increase)
**MMP10*	Reference (0.6 fold decrease)	(0.7 fold increase)
**TIMP1*	Reference (3.1 fold increase)	(1.3 fold decrease)
* MMP2/TIMP1	Reference (0.3 fold decrease)	(0.5 fold increase)
*Type 1 collagen protein	Reference (3.4 fold increase)	(1.5 fold decrease)
*α-SMA protein	Reference (2.8 fold increase)	(1.2 fold decrease)
*Fibronectin	Reference (3.4 fold increase)	(2.0 fold decrease)
*mTOR	Reference (2.8 fold increase)	(2.1 fold decrease)
*AMPK	Reference (1.3 fold decrease)	(2.0 fold increase)
*SIRT1	Reference (1.1 fold decrease)	(1.9 fold increase)

Experiments were performed in (n=5) independent series. Significance was determined by paired student's t test.

*Values marked with asterix indicate those attaining statistical significance ($p<0.05$)