Title: Bone disease in chronic kidney disease: the role of local GH-IGF system and its modulation by Non-pharmacologic approaches.

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Background: Linear growth retardation with reduced muscle mass is a major problem in children and adults with chronic kidney disease (CKD) and has been ascribed to growth hormone (GH) insensitivity. Treatment with exogenous GH has been accepted as standard therapy in children with CKD and short stature. This resistant state has been attributed to impaired GH signaling through the JAK2/STAT5 pathway in liver and skeletal muscle leading to reduced Insulin like Growth Factor (IGF-I).

Research Hypothesis: bone GHR signaling pathway of young growth retarded CKD rats is impaired.

Aims: Since there is no information on the impact of CKD on GH signaling in bone, we set out to investigate whether alterations in GH signaling might contribute to CKD induced linear growth retardation.

Methods: Partially nephrectomized (CKD) and pair-fed control 20 day old rats were followed for 2 weeks. Serum GH and IGF-I, as well as tibial epiphyseal growth plate (EGP) histomorphology, IGF-I, GH receptor (GHR) and its signaling molecules were measured upon euthanasia.

Results: Longitudinal growth attenuation was seen in CKD rats. Serum GH did not change, yet serum IGF-I levels were decreased, implying GH resistance. The EGP hypertrophic zone was wider and vascularization at the primary ossification center was decreased in CKD. Also EGP VEGF mRNA and protein, as well as immunostainable IGF-I were reduced. EGP GHR and STAT5 protein levels were unchanged, while JAK2 was reduced. Despite comparable GH and GHR levels in CKD and controls, relative STAT5 phosphorylation was significantly depressed in CKD. Of note, the mRNA of SOCS2, an inhibitor of GH signaling, was increased in CKD.

Discussion and Conclusions: Young rats with moderate CKD develop significant growth retardation. The decrease in JAK2 mRNA and p-STAT5 and the increase in SOCS2 mRNA in the EGP in spite of unchanged GHR suggest a bone GHR signaling impairment in CKD as an additional mechanism of CKD mediated growth retardation. This may explain the relative insensitivity of bone tissue to the growth promoting effects of physiological GH on bone and potential adverse effects to the kidney of exogenous GH in CKD patients.

Key words: Chronic kidney disease; Growth hormone; IGF-I; Growth plate; Receptor, somatotropin; STAT5.
Publications associated with the project: