INFLAMMATION IN SKELETAL MUSCLE OF PATIENTS WITH CHRONIC KIDNEY DISEASE

INTRODUCTION AND AIMS:
In patients with chronic kidney disease (CKD), pro-inflammatory cytokines are incompletely understood. We previously observed that Toll-like receptor activation (TLRs) triggers an innate immune response, which activates the inflammasome, a multi-protein complex that converts inactive pro-IL-1β into biologically active IL-1β through caspase-1 activation. The NLRP3 inflammasome, one of the best characterized inflammasomes, is regulated by a plethora of factors and modifications including lysine acetylation and methylation, inflammasomes through TLR4 engagement. NLRP3/IL-1β work maintenance) was overexpressed (by 18-fold p < 0.05). All these effects were prevented by TAK 242 (1 μM, p < 0.025). IL1β and gene expression of PGC1α, PGC1β, MFN2 and NRF2 (by 1.5-26 folds p < 0.05-0.025). IL1β mRNA was overexpressed (p < 0.05). The red/green fluorescence ratio indicating a decrease in mitochondrial membrane potential was reduced in CKD muscle compared to controls (p < 0.05). Taken together, these data suggest the activation of the NLRP3 inflammasome in CKD muscle. We propose that NLRP3 inflammasomes are activated in CKD muscle, which could be a novel therapeutic target.

METHODS:
Animals with CKD and sham mice were compared. muscles were removed and the red/green fluorescence ratio were determined by fluorimeter analysis.

RESULTS:
In CKD muscle, both NLRP3 mRNA and its protein were overexpressed (by 7.5-47%, p < 0.05). All these effects were prevented by TAK 242 (1 μM, p < 0.025). IL1β and gene expression of PGC1α, PGC1β, MFN2 and NRF2 (by 1.5-26 folds p < 0.05-0.025). IL1β mRNA was overexpressed (p < 0.05). The red/green fluorescence ratio indicating a decrease in mitochondrial membrane potential was reduced in CKD muscle compared to controls (p < 0.05).

CONCLUSIONS:
The NLRP3 inflammasome is activated in skeletal muscle of patients with CKD. Our findings provide new insights into the molecular mechanisms underlying skeletal muscle inflammation in CKD patients. These results may be important for designing new therapeutic strategies to mitigate skeletal muscle inflammation in CKD patients.
CONCLUSIONS: Uremic bleeding has previously been associated with a functional defect of GpIIb/IIIa-ligand interactions. Our results show that carbamylation of platelet surface proteins including GpIIb/IIIa could be one mechanism that, by inducing structural alterations, contributes to CKD-associated bleeding disorders. Fibrinogen binding to GpIIb/IIIa requires a conformational change of the receptor, which can be induced by cleavage of PAR-1 by thrombin in a process called inside out signalling. GpIIb/IIIa activation is reduced after platelet carbamylation while PAR-1 cleavage remains unaffected indicating that carbamylation may induce structural alterations of the inactive receptor that prohibit its conformational change, impair fibrinogen binding and thereby inhibit aggregation.