Posttranslational regulation of IL-1ß in CKD5-D patients compared to individuals with inflammation and normal renal function

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Introduction

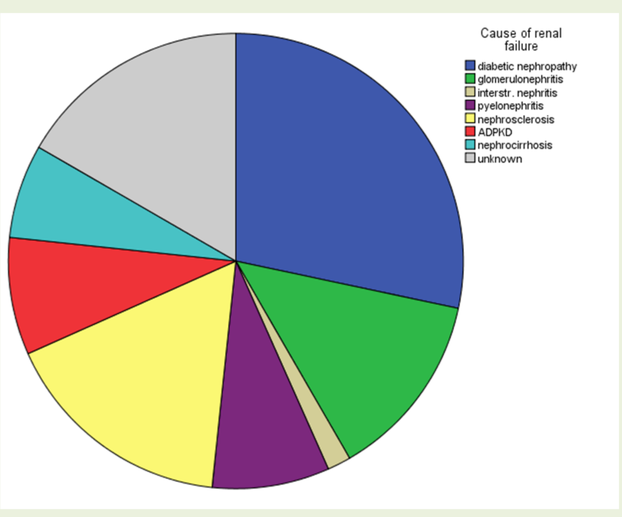
Background: Inflammation in dialysis patients (CKD-5D) is a major driver of morbidity and mortality. Chronic inflammation may be associated with the activity of pattern recognition receptors that respond to certain pathogen related molecular patterns and are part of the innate immune system. Activation of the so called "NLRP3 inflammasome" which is important for the posttranscriptional regulation and release of proinflammatory IL-1ß from the cell might be a relevant cause for chronic inflammation in CKD patients, since this is hallmarked by elevation of cytokines like IL1-ß, IL-6, and TNF-α. The inflammasome consists of pro-IL-1ß and its regulator procaspase I-complex (NLRP3, ASC, Casp1). Activation of this dual pathway finally generates active IL-1ß.

Subjects and methods

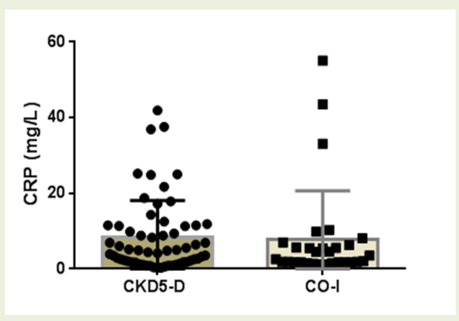
The cross-sectional study enrolled sixty CKD-5D patients (age: 62.3±15.5 years) and a control group (CO) with intact renal function (N=29, age: 61.0 ± 12.8, creatinine: 67±14 µmol/l). The control group had signs of non-infectious inflammation early after surgical procedures. These patients were chosen to elucidate proinflammatory mechanisms specific to chronic renal failure. IL1-ß was measured from plasma samples by ELISA technique, RNA was processed from PAX gene tube™ samples. qPCR was normalized to housekeeping gene and related to an internal standard (x-fold expression).

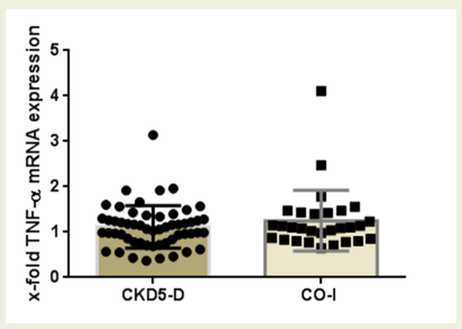
Results

	CKD5-D (N=60)	CO-I (N=29)	p-value
Age (years)	62.3±15.5	61.0±12.8	0.9
Gender (female, %)	38.3	82.8	0.001
BMI (kg/m²)	26.1±5.0	27.7±5.0	0.4
CRP (mg/l)	8.8±9.6	7.7±13.0	0.8
Creatinine (µmol/l)	783±275	67.0±14.5	0.001
Urea (mmol/l)	22.0±7.0	4.2±1.4	0.001
Albumin(g/dl)	3.9±0.5	3.9±0.5	0.9
Total Protein (g/l)	65.6±5.8	67.6±5.9	0.3
HbA1c (mmol/mol)	39.8±9.1	41.0±6.7	0.8
Total-C (mmol/l)	4.4±1.1	6.1±1.1	0.001
Triglyceride (mmol/l)	2.1±1.3	1.9±1.1	0.8
HDL-C (mmol/l)	1.3±0.6	1.6±0.4	0.1
LDL-C(mmol/l)	2.4±0.9	3.8±0.9	0.001
Phosphate (mmol/l)	1.8±0.6	1.1±0.3	0.001
Calcium (mmol/l)	2.2±0.3	2.3±0.1	0.2
Diabetes (%)	35.0	24.1	0.3
Ever Smoker (%)	63.4	34.5	0.04
BP (arm, mm HG)	126±28	133±20	0.5
BP (leg, mm HG)	159±66	147±20	0.6



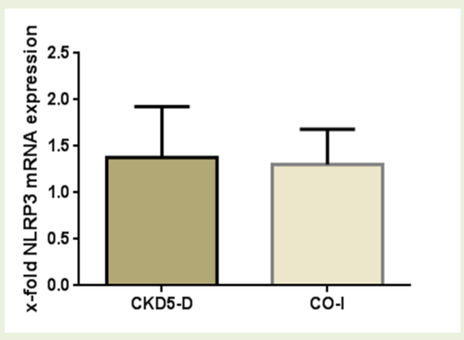
CRP level and TNF-α mRNA expression are not different between CKD5-D and controls

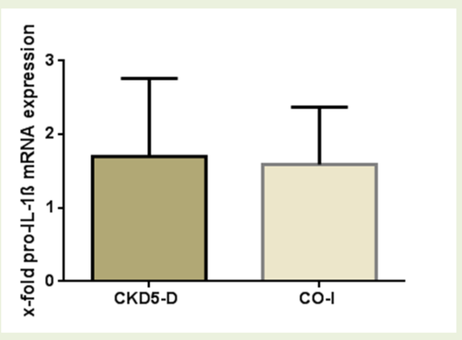




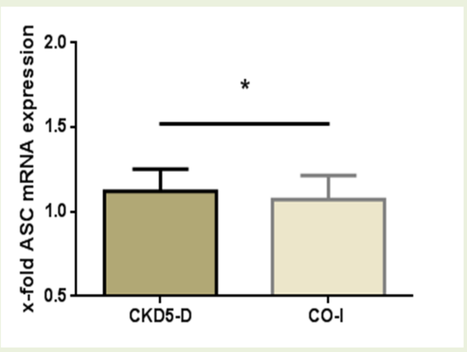
Inflammasomal components partly differ between CKD5-D and controls

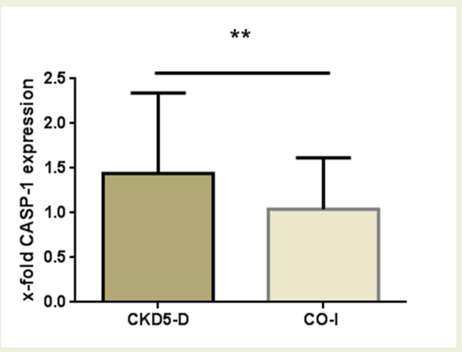
NLRP3 priming step 1





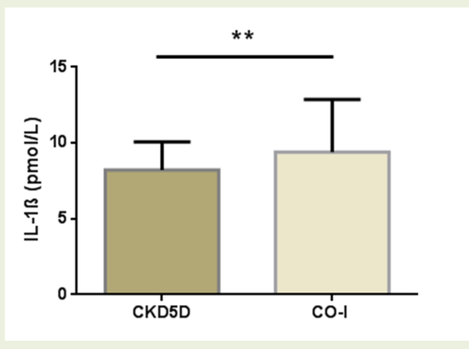
NLRP3 Inflammasome





???????active caspase-1??????

NLRP3 assembly



IL-1ß release

Conclusions

The NLRP3 inflammasome is differently regulated in CKD5-D and individuals with inflammation but intact renal functions. Although some inflammasomal NLRP3 components are upregulated in CKD5-D, IL1-ß plasma levels are higher in controls. This points to a defective NLRP3 inflammasome assembly in CKD5-D. The role of Caspase-1 activity in both cohorts has to be examined. Thus, posttranscriptional regulation of IL-1ß secretion in chronic renal failure seems not different from inflammatory conditions in patients with normal renal function.

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