ENDOTHELIAL DYSFUNCTION IN EXPERIMENTAL CHRONIC KIDNEY DISEASE IS CAUSED BY FGF23

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Introduction

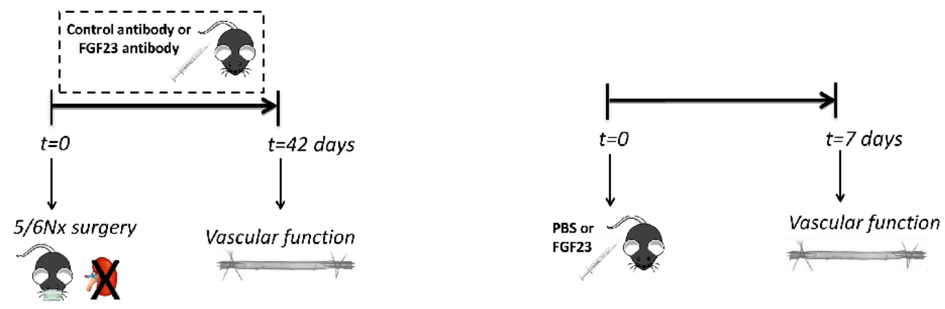
- Cardiovascular causes account for approximately 50% of mortality in patients with chronic kidney disease (CKD).
- FGF23, a phosphate-lowering protein and elevated in CKD, is independently associated with cardiovascular mortality and endothelial dysfunction.

Hypothesis

- **We hypothesized that CKD impairs vascular function and that this impairment can be attributed to FGF23.**

Methods

- Seven weeks old male wild type C57Bl/6J mice were subjected to partial nephrectomy (5/6Nx) or sham-surgery and were kept in the study for six weeks.
- A second non-CKD group received either PBS or FGF23 i.p. injections for 7 consecutive days twice daily.
- A third group received FGF23 antibodies by i.p. injections, in combination with a low phosphate diet, following 5/6Nx surgery. A control group received control antibodies and a normal diet.
- Resistance arteries were isolated and subjected to a pressure myograph setup to test *ex vivo* vascular function.
- Myocardial perfusion before and after vasodilation was assessed by myocardial contrast echocardiography (MCE).



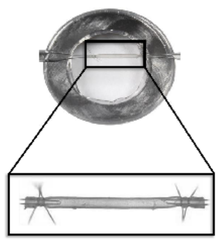
Results

Table 1. 5/6Nx impairs kidney function and increases plasma FGF23 levels.

	Sham	5/6Nx	p-value
Plasma urea (mmol/L)	12.7 ± 0.3	22.1 ± 1.1	**<0.001**
Plasma creatinine (µmol/L)	15.0 ± 1.5	28.3 ± 1.6	**<0.001**
Urinary creatinine (µmol/24h)	2.62 ± 0.23	3.33 ± 0.15	**0.021**
Creatinine clearance (µl/min)	137.1 ± 20.4	92.8 ± 6.0	0.060
Plasma Pi (mmol/L)	3.37 ± 0.19	2.93 ± 0.12	0.088
Urinary Pi (µmol/24h)	19.2 ± 2.8	115.0 ± 18.4	**<0.001**
Fractional excretion phosphate (FEP) (%)	2.95 ± 0.92	17.01 ± 2.87	**0.003**
Plasma c-term FGF23 (pg/ml)	210.2 ± 13.1	315.2 ± 27.6	**0.002**
Renal KLOTHO mRNA expression (fold change)	1.01 ± 0.04	0.69 ± 0.06	**<0.001**
Plasma PTH (pg/ml)	255.6 ± 51.8	555.4 ± 83.8	**0.014**
Plasma 1,25-dihydroxyvitamin D_3 (pmol/L)	226.8 ± 10.2	252.6 ± 23.5	0.317

Data are mean ± SEM

Figure 1. 5/6Nx impairs endothelial but not vascular smooth muscle cell (VSMC) function, which is mimicked by increasing circulating FGF23 levels.



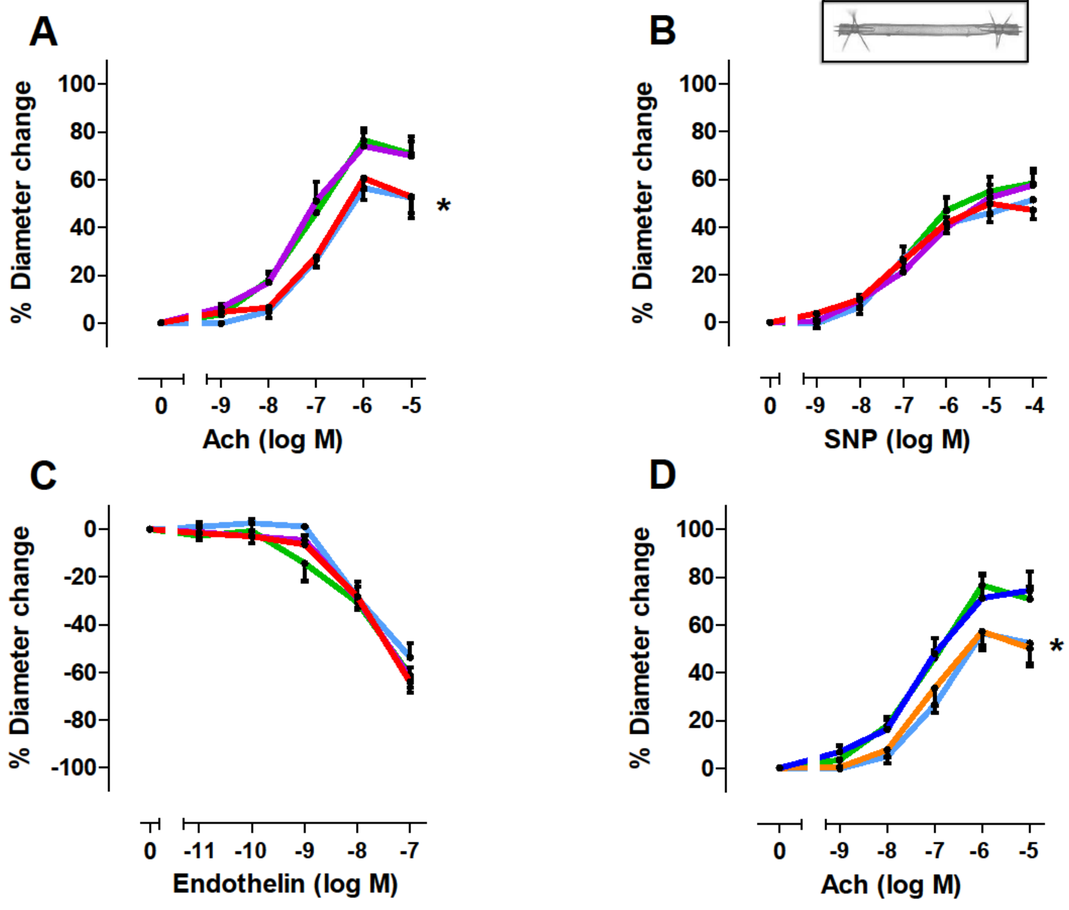
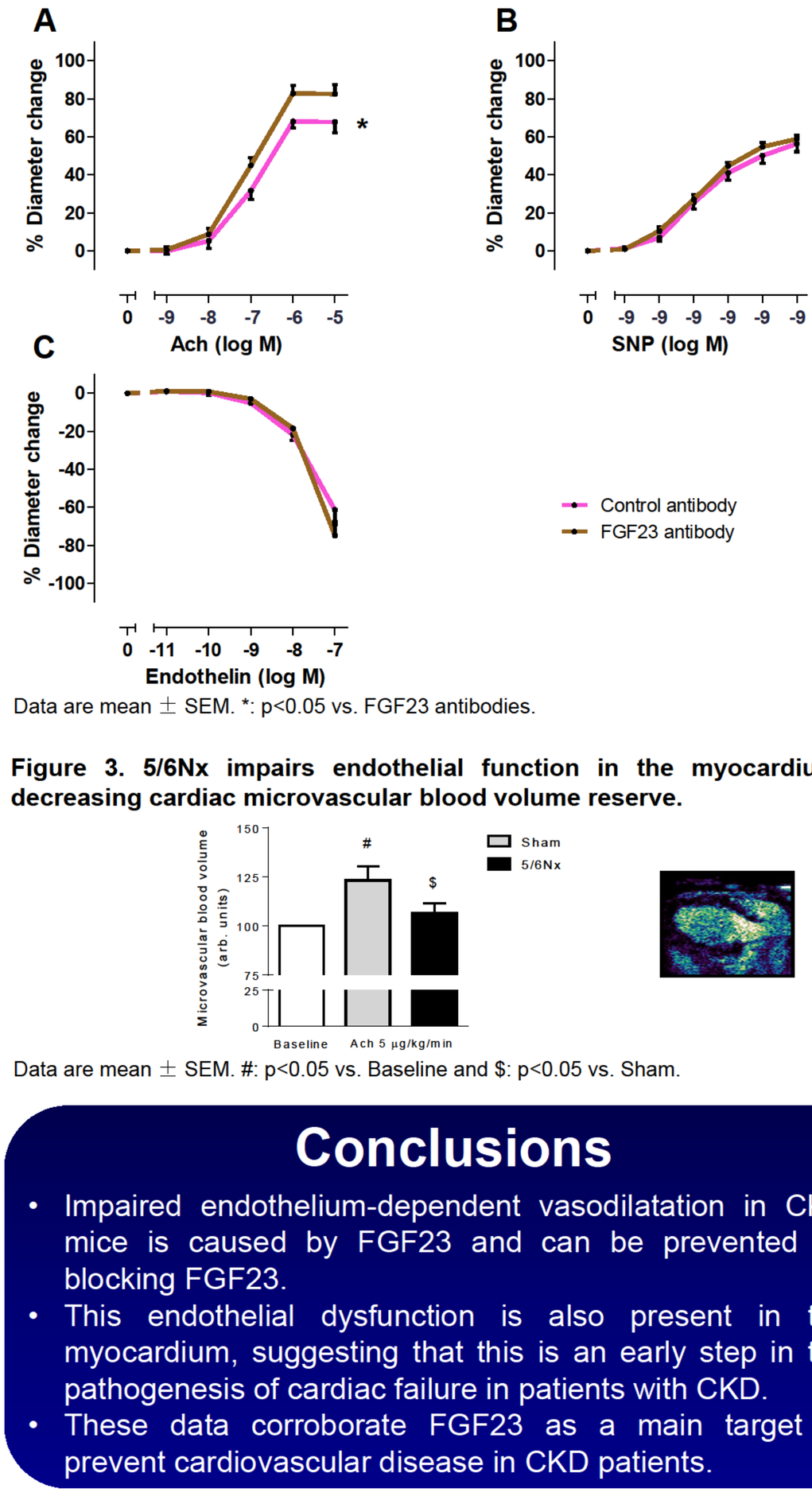


Figure 1. (A) Endothelial function. (B+C) VSMC function. (D) Endothelial function of arterioles from sham and 5/6Nx mice incubated for one hour with recombinant FGF23 (10ng/ml).
Data are mean ± SEM. *: p<0.05 vs. sham or PBS.

- Sham surgery
- 5/6Nx surgery
- PBS i.p. injections
- FGF23 i.p. injections
- 5/6Nx and ex vivo FGF23
- Sham and ex vivo FGF23

Figure 2. FGF23 blockade improves endothelial function in 5/6Nx mice (A), but does not change VSMC responses (B+C).



Data are mean ± SEM. *: p<0.05 vs. FGF23 antibodies.

Figure 3. 5/6Nx impairs endothelial function in the myocardium, decreasing cardiac microvascular blood volume reserve.

Data are mean ± SEM. #: p<0.05 vs. Baseline and $: p<0.05 vs. Sham.

Conclusions

- Impaired endothelium-dependent vasodilatation in CKD mice is caused by FGF23 and can be prevented by blocking FGF23.
- This endothelial dysfunction is also present in the myocardium, suggesting that this is an early step in the pathogenesis of cardiac failure in patients with CKD.
- These data corroborate FGF23 as a main target to prevent cardiovascular disease in CKD patients.

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