Aldosterone and Kidney Disease

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Aldosterone and kidney: a rapidly moving frontier (an update)

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Keywords:

NDT (2013) e-pub Nov.4th
Aldosterone beyond the classical concept

The postclassical concept

Treatment targets beyond epithelial issues and synthesis beyond adrenal gland

- **Heart** (LV hypertrophy, fibrosis in right and left ventricle)
- **Brain** (hypothalamus - hypertension, salt appetite)
- **Vessel wall**
- **Kidney**: structures beyond distal tubulus → glomerulus, interstitium, epithelial tubular cells

**Treatment targets**

**Synthesis**

- **Aldosterone - Synthesis**
  
  # adrenal gland (endocrine)
  # local synthesis in gut, skin, CNS, heart, renal cortex ...
Subtotal Nephrectomy *(SNX)*
Aldosterone overcomes the effect of RAS blockade *(ACEi+ARB)*

<table>
<thead>
<tr>
<th></th>
<th>p-Aldosterone (pg/ml)</th>
<th>Heartweight (g)</th>
<th>Proteinuria (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-op</td>
<td>50±12</td>
<td>1.03±0.05</td>
<td>19±6</td>
</tr>
<tr>
<td>SNX</td>
<td>526±250</td>
<td>1.33±0.19</td>
<td>203±103</td>
</tr>
<tr>
<td>SNX + ACEi+ARB</td>
<td>181±124</td>
<td>0.88±0.11</td>
<td>30±15</td>
</tr>
<tr>
<td>SNX + ACEi+ARB + Aldosterone</td>
<td>487±114</td>
<td>1.28±0.12</td>
<td>217±71</td>
</tr>
</tbody>
</table>


true for exogenous and endogenous aldosterone
Spironolactone:
in the rat model after subtotal nephrectomy: regression of established glomerulosclerosis

“High salt” antagonizes the beneficial effect of aldosterone blockade on the development of:

- thrombotic and/or proliferative lesions in glomeruli
- lesions of renal vessels

Rocha, Endocrinology (2000) 141:3871
Beyond synthesis of aldosterone in the adrenal gland, local (!) synthesis of aldosterone occurs in damaged organs e.g. the kidney in diabetes.

Because there is local synthesis of aldosterone:
the plasma concentration of aldosterone is not necessarily the only relevant indication for aldosterone blockade.

Aldosterone synthase (CYP11B2)
in the renal cortex of adrenalectomised diabetic rats
local production of aldosterone

Xue, Hypertension (2005) 46:584
In adrenalectomised diabetic rats, local production of Aldosterone restricted to the renal cortex, but not does not occur in the renal medulla.

Aldosterone-Synthase (CYP11B2)

Xue, Hypertension (2005) 46:584
Spironolactone mitigates glomerular damage from hyperglycemia: i.e. podocyte damage, mesangial expansion and glomerulomegaly.

Spironolactone reduces podocyte damage caused by hyperglycemia:

Spironolactone thus lowers **proteinuria** in diabetic rats

Proteinuria (mg/day)

weeks after injection of Streptozotocin

Aldosterone synthesised by podocytes in vitro

stimulated by:
# ANG II
# high glucose concentration

reduced by:
Angiotensin-receptor-blocker

In humans:

**Aldosterone predicts incident CKD and microalbuminuria**
*(Framingham offspring study)*

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incident CKD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>entire panel</td>
<td>0.0005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>specific markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>homocysteine</td>
<td>&lt;0.0001</td>
<td>1.41</td>
<td>1.20 to 1.65</td>
</tr>
<tr>
<td><strong>Aldosterone</strong></td>
<td>0.047</td>
<td>1.17</td>
<td>1.002 to 1.36</td>
</tr>
<tr>
<td><strong>Incident microalbuminuria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>entire panel</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>specific markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aldosterone</strong></td>
<td>0.017</td>
<td>1.23</td>
<td>1.04 to 1.46</td>
</tr>
<tr>
<td>BNP</td>
<td>0.0037</td>
<td>1.30</td>
<td>1.09 to 1.54</td>
</tr>
<tr>
<td>homocysteine</td>
<td>0.04</td>
<td>1.20</td>
<td>1.01 to 1.42</td>
</tr>
</tbody>
</table>

*Fox, J.Am.Soc.Nephrol.(2010) 21: 2143*
In rats spironolactone prevents secondary **chronic** renal insufficiency after recovery from ischemic **acute** renal failure.
[Na$^+$] causes stiffening of human vascular endothelial cells in vitro

 endothelial cell stiffness

\[
\begin{align*}
\text{stiffening by Aldosterone} & \quad \bigcirc \\
\text{no stiffening by Eplerenone} & \quad \bullet 
\end{align*}
\]

presumably also relevant for renal vessels!

Human endothelial cells: high $[\text{Na}^+]$ concentration plus aldosterone: inhibition of nitrite (dilatory) synthesis (permissive effect)

Hyperfiltration in **primary hyperaldosteronism**

beneficial renal effect of Spironolacton/Eplerenon

prospective multicentric study in Germany:

# 29 patients with *newly* diagnosed hyperaldosteronism
# overall cohort of 119 patients

1° aldosteronism:

# increased GFR and increased albumin/creatinin ratio
# after start of treatment with Spironolactone/Eplerenone

→ GFR and albuminuria declined

*Aldosterone causes glomerular hyperfiltration and albuminuria*

*Patients treated with well regulated blood pressure*

→ renal parameters not altered

*Fourkiotis, Europ.J.Endocrinol.(2013)169:75*

*Arbeit macht kaputt* (work kills)

*Karl Marx*

~ hyperfiltration damages the glomerulus
CKD patients
Serum aldosterone concentration and renal findings

Renal biopsy in CKD patients with pronounced proteinuria at different creatinine clearances

at decreased creatinine clearance:

# MCP1 mRNA in kidney ↓
# serum aldosterone ↑
# renal fibrosis no (significant) correlation ~

Quinkler, Circulation (2005) 112:1435
Are only plasma aldosterone values relevant? They may underestimate the role of local aldosterone synthesis and the therapeutic potential of aldosterone blockade.

Potential role of local aldosterone synthesis:


Xue, Hypertension (2005) 46:584
Diabetic Nephropathy

Aldosterone blockade effective even after maximal inhibition of ACE:

**Additional** inhibition by mineralocorticoid antagonist:

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Angiotensinreceptor blocker</th>
<th>Mineralocorticoid-antagonist</th>
</tr>
</thead>
</table>

**Mineralocorticoid-blockade**

Additional renoprotection (albuminuria ↓) despite no further decrease of blood pressure

Nephrotic patients treated with ACEi plus ARB: when Spironolactone (but not Furosemide) is added, further decrease of proteinuria unrelated to blood pressure.

"benefit from Spironolactone not explained by its diuretic effect, but by abrogation of mineralocorticoid effect."

Doppel-blind randomised placebo-controlled cross-over study
21 type 1 diabetics with microalbuminuria
Spironolactone 25 mg/day or Placebo for 60 days

**Rx Spironolactone:**

- **# albuminuria ↓**: from 90 mg/day to 35 mg/day (*p* = 0.01)
- **# GFR ↓**: from 78 ± 6 to 72 ± 6 mL/min/1.73m² (*p* = 0.003) *(reversal of hyperfiltration?)*
- **# blood pressure**: unchanged

well tolerated, but in 2 patients S-K⁺ rose to 5.7 mmol/L

*Nielsen, Diabet.Med.(2012) 29:e184*
In *healthy* individuals the serum-aldosterone concentration *predicts* future *microalbuminuria* and *GFR* decrease

**Framingham population**

- 2345 individuals
- 9.5 years follow-up
- **Endpoints:** eGFR < 60 ml/min/1.73m²
  - urine albumin/creatinin > 25 (♀) or 17 (♂) mg/g creatinin

**Predictors:**

- *microalbuminuria*: log serum *aldosterone*, BNP, homocystein
- **GFR** < 60 ml/min/1.73m²: serum *aldosterone* and homocystein

Spironolactone (25mg/day) — in CKD patients: progressive lowering of proteinuria and eGFR

Δ proteinuria

Δ eGFR

Bianchi, Kidn.Internat.(2006) 70:2116

early: GFR decrease (reversal of hyperfiltration)
late: less eGFR loss
Spironolactone (25mg/d) on top of RAS blockade –
again added benefit: progressive reduction of proteinuria
by 61% (43-77%)

% reduction of proteinuria

CKD: Spironolactone beyond the kidney: less cardiovascular/cerebrovascular morbidity/mortality in hemodialysed patients

Matsumoto, JACC (2014) 63:528

3 year randomized trial 309 oligoanuric HD patients
25 mg/d Spironolactone vs placebo

12.5% in controls
HR p <0.404 (95% 0.202-0.809)
p=0.017

5.7%
HR p<0.379 (95% 0.173-0.832)
p=0.016
Limitation of RAS Blockade

Aldosterone “escape”

first communication

Patients with renal failure (n=10) and treated with Captopril

p-Aldosterone (pg/ml)

before Captopril 266 ± 30
Captopril 6 months 105 ± 16
Captopril 12 months 234 ± 31

"Aldosteron escape" - half of the patients with diabetic nephropathy secondary increase of serum - aldosterone during RAS blockade

63 type 1 diabetic patients, Losartan 100 mg/day 36 months follow-up

<table>
<thead>
<tr>
<th>Escape</th>
<th>No Escape</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=26</td>
<td>n=37</td>
</tr>
<tr>
<td>start</td>
<td>start</td>
</tr>
<tr>
<td>2 months</td>
<td>2 months</td>
</tr>
<tr>
<td>end of study</td>
<td>end of study</td>
</tr>
<tr>
<td>p-aldosterone (pg/ml)</td>
<td>p-aldosterone (pg/ml)</td>
</tr>
<tr>
<td>88 62-125</td>
<td>70 54-92</td>
</tr>
<tr>
<td>57 43-76</td>
<td>83 69-102</td>
</tr>
<tr>
<td>102 78-134</td>
<td>49 40-60</td>
</tr>
</tbody>
</table>

GFR-decrease

5 ml/min/year
0.4 - 15.9

2.4 ml/min/year
-1.6 - 11.0

Escape : more rapid loss of GFR

Why do we see **less progression** with *aldosterone blockade* even in (a proportion of) CKD *patients without elevated p-aldosterone*?

⇒ **Local synthesis of aldosterone in kidney cortex?**

*e.g. high salt, diabetes ...*

---

*Xue, Hypertension (2005) 46:584*
Aldosterone and allograft function

153 transplant recipients
5 year follow-up; yearly s-aldosterone

**Higher serum plasma aldosterone** ➔
significantly **higher risk of ESRD**
**HR 1.01** (95% CI 1.00-1.02)

even though systemic aldosterone
does not reflect the intrarenal system

Issa, Kidn.Internat.(2014) 85:404
Serum K$^+$ of CKD patients on ACE inhibitors with or without Spironolactone

Why had we been in the past so hesitant to use RAS plus aldosterone blockade in advanced CKD? Justified concern of hyperkalemia!

Out-patients serum K$^+$ (mmol/L)

Lisinopril + Spironolactone

~Δ 0.45 mmol/L
*but wide scatter!!*

Lisinopril + Placebo

Preston, Hypertension (2009) 53:754
Type 2 diabetic patients with nephropathy: increased risk of endstage renal disease or doubling of S-creatinine even at serum-K⁺ values in the highnormal range (RENAAL study).

Risk increased at S-K⁺ at 5 mmol/L, conventional definition of hyperkalemia >5.5 mmol/L. Causal relation??
K+ handling in CKD patients treated with ARB blockade plus Aldosterone blockade

**safety?**

randomized cross-over 4 week trial
40 mg Lisinopril + 25mg Spironolactone vs placebo
18 participants GFR 25.7 ml/min

at 4 week (study end) 35 mmol oral K+ challenge:
S-K+ 4.87 mmol/l (L/S) vs 4.37 (controls); p<0.001

after oral K+:
only modest 0.44 mmol/h increase of K+ excretion,
but 0.67 mmol/L increase in serum K+

Preston, Hypertension (2009) 53:754
Beneficial effect and safety of Spironolactone added on top of recommended antihypertensive treatment in diabetic nephropathy

22 patients type 2 diabetes with nephropathy randomized double-masked cross-over study in randomized order:
Spironolactone 25 mg/d vs matched placebo for 8 weeks during addition of Spironolactone:

- albuminuria - 33%
- 24h ambulatory BP: - 6 mmHg systolic; - 4 mmHg diastolic

only 1/22 patients had to be excluded because of hyperkalemia

Rossing, Diabetes Care (2005) 28:2106
Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial

Bertram Pitt, Stefan D. Anker, David A. Bushinsky, Dalane W. Kitzman, Faiez Zannad, and I-Zu Huang, on behalf of the PEARL-HF Investigators

K⁺ bound in the gut by RLY5016

50 mg Spironolactone lowers blood pressure even in anuric (!) hemodialysis patients without significant change of S-K⁺

Blood pressure:
- Spironolactone: 142→131 mmHg
- Placebo: 146→142 mmHg

Spironolactone 50mg 3x / week: impact on predialytic S-K⁺ in hemodialysed patients

Vukusich, CJASN (2010) 5:1380
Proposal appears rational:
but in view of experimental and scarce controlled clinical data
better documentation of safety is still necessary
Aldosteron

in renal patients:
primary treatment target

**kidney**

but in renal patients
also treatment targets of Aldosterone

**beyond the kidney**
Patients with modest reduction of eGFR: cardiovascular mortality correlated to plasma aldosterone (LURIC study)

3,153 patients, age 62.7 ± 10.6 years, no primary kidney disease follow-up 7.75 years

Pat. with eGFR < 60 ml/min/1.73m²

**cardiovascular mortality**

HR 1.08
(95%CI 1.02-1.13)
p = 0.004

*“sudden death”*

HR 1.18
(95%CI 1.08-1.29)
p = 0.001

higher aldosterone: CV events not significantly higher

Tomaschitz, AJKD (2011) 57:403
Spironolacton: less thickening of carotid-intima/media in hemodialysis-patients
randomised doubleblind Placebo-controlled study

\[ \Delta \text{IMT (mm)} \]
after 2 years

\begin{align*}
\text{Placebo (n=23)} & & \text{Spironolacton 50 mg 3xweek (n=30)} \\
A & B & C & D & E & F & A & B & C & D & E & F
\end{align*}

Vukusich, CJASN (2010) 5:1380

A-F: different vessels
Spironolactone reduces LVM in patients with CKD 2-3

112 pat. CKD 2,3 and ABPM < 130/85 mmHg on RAS blockade
Spironolactone 25 mg/day or Placebo

LV mass

LV mass index

Spironolactone reduces LVM in patients with CKD 2-3 – in all quartiles of central blood pressure changes

112 pat. CKD 2,3 and daytime ABPM < 130/85 mmHg on RAS blockade addition of Spironolactone 25 mg/day or Placebo

Quartiles of reduction of central blood pressure

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Reduction in mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>&gt;-18</td>
</tr>
<tr>
<td>Q2</td>
<td>-17 bis -7</td>
</tr>
<tr>
<td>Q3</td>
<td>-6 bis -2</td>
</tr>
<tr>
<td>Q4</td>
<td>&lt;-2</td>
</tr>
</tbody>
</table>

Plasma aldosterone plus cortisol

Interaction:
increased risk of sudden death in type 2 diabetics on hemodialysis
(4D study)

Aldosterone (pg/ml)

<table>
<thead>
<tr>
<th>Group</th>
<th>Aldosterone (pg/ml)</th>
<th>Cortisol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>group 1</td>
<td>&lt;15</td>
<td>&lt;13.2</td>
</tr>
<tr>
<td>group 2</td>
<td>&gt;200</td>
<td>&gt;21.1 μg/dL</td>
</tr>
</tbody>
</table>

high Aldosterone plus high Cortisol particularly high CV risk
**Aldosterone** *(in the normal range)*

one of the factors **predicting** 1 year mortality

*(4D study, hemodialysed diabetic patients)*

- Hämoglobin, Leukozyten, LDL-Cholesterin, Glukose, HbA1c, Phosphat, Alkalische Phosphatase, Kreatinkinase, ALAT, ASAT, Kalium
- CRP, BNP, Troponine, Vitamin D
- Lp-PLA2, Fetuin, Transthyretin, Homoarginin
- ST2, carbamylisiertes Albumin
- Aldosteron, Cortisol, Copeptin, Osteoprotegerin

AUC 0.88  
AUC 0.87  
AUC 0.86

courtesy Prof. Maerz
Spironolactone: Prevention of \textit{vascular calcification} in early renal failure?

in smooth muscle cells of the human aorta:

\textbf{Aldosterone increases}:

phosphate transporter PiT-1, as well as TnF\textgreek{a}, Cbfa1/Runx2, alkal.phosphatase

\rightarrow vascular calcification

\textbf{this is prevented by}:

\textbf{Spironolactone}

\textit{Voelkl et al},
Spironolactone ameliorates PIT1-dependent vascular osteoinduction in klotho -/- mice

\textit{Lang,Ritz,Voelkl,Alesutan}
\textit{Vascular calcification – is aldosterone the culprit?}
Aldosterone synthase inhibition in humans

Michel Azizi¹,²,³, Laurence Amar¹,²,³ and Joël Menard¹,²,³

Inhibition of Aldosterone effects:

# not only with Spironolactone,
  but also with
# aldosterone synthase inhibitors
or
# nonsteroidal receptor antagonists
Discovery of BAY 94-8862: A Nonsteroidal Antagonist of the Mineralocorticoid Receptor for the Treatment of Cardiorenal Diseases

Safety ($S-K^+$) and tolerability ($\Delta eGFR$) of the novel nonsteroidal mineralocorticoid receptor antagonist (BAY94-8862) in patients with heart failure

*note: also more moderate reduction of eGFR (perhaps reversal of hyperfiltration)*

What did he say?

new insights into the role of aldosterone in kidney damage:

# renal damage caused not only via systemic aldosterone, but also via local aldosterone production

# aldosterone: crucial role in the "escape phenomenon" of kidney disease (incl. secondary increase of proteinuria)

# aldosterone induced tissue damage is aggravated by salt

# novel role of aldosterone in vascular calcification

# novel drugs to block aldosterone effects (nonsteroidal mineralocorticoid antagonists; mineralocorticoid receptor blockers)
The aldosterone/kidney interaction has become a new frontier in nephrology.

Thank you for your attention.

Old bridge in Heidelberg
Aldosteron "escape" during RAS Blockade

Higher risk of progression (loss of GFR)

63 hypertensive patients; type 1 diabetes and diabetic nephropathy

Losartan 100 mg/day, 35 months follow-up

p- Aldosterone concentration

Increasing 26 Pat. (57 → 102 pg/ml) – "escape"

Decreasing 37 Pat. (83 → 49 pg/ml)

Decrease of GFR

Aldosterone escape 5.0 ml/min/year (0.4-15.9)

No aldosterone escape 2.4 ml/min/year (-2-11.0)

Correlation: the higher aldosterone – the greater GFR loss

Δ plasma-aldosterone ↑ / Δ GFR- decrease ↓

Losartan increases serum- $K^+$ in Type 2 diabetic patients with reduced renal function
(RENAAL study)

**Limiting side effect:** increased plasma $K^+$ in patients with RAS blockade plus Aldosterone blockade

Losartan increases serum $K^+$ in patients with RAS blockade plus Aldosterone blockade.

High serum $K^+$ accelerates eGFR-decrease.

**Graph:**
- **Y-axis:** Serum potassium (mmol/l)
- **X-axis:** Time of study (months)
- **Legend:**
  - Losartan
  - Placebo

Miao, Diabetologia (2011) 54:44
Spironolactone in mild to moderate chronic kidney disease: safety and tolerability

115 patients with non-diabetic early stage CKD (eGFR 30-89 ml/min/1.73m²)

Spironolactone 25 mg/day for 4 weeks, subsequently randomization to:
# placebo or # continuing treatment for 36 weeks

serious hyperkalemia (>6mmol/L) was < 1% 
S-K⁺ 5.5-5.9 mmol/L in 9 pat on Spironolactone

Spironolactone reasonably tolerated in selected patients with early stage CKD

Plasma-Renin-Activity (PRA) and Aldosteron-Renin Ratio (ARR) : both correlated with new onset CKD

Ohasama study

689 participants in Japanese population, mean age 58 years, no medication at start; of study; duration of study 9.1 years : 118 participants with new onset of CKD

Kaplan-Meier survival-function for cumulative onset of CKD in tertiles of PRA and ARR

Terata, J.Hypertens. (2012) 30:1632
In renal biopsies, mineralocorticoid receptor mRNA was correlated with sgk-1 and with mRNA of mediators of kidney injury (MCP-1; TGFβ1; interleukin 6).

Quinkler, Circulation (2005) 112:1435
Spironolactone in mild to moderate chronic kidney disease on top of ACEi or ARB

**Serum K⁺**

![Graph showing serum potassium levels over weeks of treatment.](image)

- Randomized to:
  - Spironolactone (red square)
  - Placebo (blue square)

**Weeks of treatment:** W0, W1, W2, W4, W8, W16, W28, W40

Spironolactone in mild to moderate chronic kidney disease on top of ACEi or ARB

eGFR

randomized to:
- Spironolactone open label
- Placebo

Weeks of treatment

Spironolactone in mild to moderate chronic kidney disease

change in S-K⁺ according to baseline S-K⁺

Acute kidney injury prevented by Spironolactone in rats

Barrera-Chimal, Kidn.Internat.(2013) 83:93
**Spironolactone (25 mg/day)**

Renoprotection in 87 patients with proteinuric kidney disease (>1g/day) follow-up 25 months

the higher the initial eGFR fall, the better longterm evolution of eGFR

Longterm GFR as a function of acute $\Delta$ GFR

Morales, NDT (2013) 28:405
Spironolactone (25 mg/day)
Renoprotection in 87 patients with proteinuric kidney disease (>1 g/day) follow-up 25 months
Proteinuria – 61% (43-77%)
The role of Rho-kinase pathway for profibrotic differentiation of renal epithelial cells by EMT (epithelial-mesenchymal transition)
The role of Rho-kinase pathway for profibrotic differentiation of renal epithelial cells by EMT (epithelial-mesenchymal transition)

The novel non-steroidal mineral receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild/moderate CKD

The novel non-steroidal mineral receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild/moderate CKD

Δ eGFR

Spironolactone + ACE inhibitors or ARB in chronic glomerular disease

221 patients with chronic glomerular disease
Spironolactone 20 mg/day on top of ACEi or ARB
proteinuria, S-creatinine, S-K⁺, plasma aldosterone, BP
4 weekly for 16 weeks:
significant reduction of proteinuria,
no significant differences:
eGFR, S-K⁺, plasma aldosterone and BP

S-K\(^+\) with RAS blockade and with Spironolactone in diabetic nephropathy

Blinded, 3 arm, placebo controlled clinical trial
80 participants with diabetic nephropathy randomized to:
Spironolactone (25mg/d), to Losartan (100mg/d) or Placebo
VII 2003-XII 2006

S-K\(^+\) (mEq/L)
on Spironolactone 5.0;
on Losartan 4.7;
on Placebo 4.5
despite similar renal Na\(^+\) and K\(^+\) excretion
\(\rightarrow\) Role of extrarenal K\(^+\) homeostasis

van Buren, CJASN (2014) 9:205
Safety of Mineralocorticoid Receptor Antagonists in Patients Receiving Hemodialysis

- In studies with spironolactone doses ranging from 25mg 3 times/week after dialysis to 300 mg/day … have shown little increases in serum K⁺ particularly with the lower doses.

- The literature base is limited by methodological weaknesses, low patient numbers, short follow-up and lack of blinded control group.

- Mineralocorticoid receptor antagonists may be used safely in patients with ESRD receiving hemodialysis, although additional large controlled trials are needed before definitive treatment recommendations can be made.

Beneficial impact of Spironolactone on nephrotic range proteinuria in diabetic nephropathy

20 Caucasian diabetic patients with nephrotic range proteinuria (>2500 mg/d) despite recommended antihypertensive treatment (incl. ACEi or ARB)

in random order on top of Rx:
Spironolactone 25 mg/day or placebo for 2 months
Spironolactone: reduction of albuminuria 32% (CI 21-42%) from 3718 (2910-4749) mg/24h on placebo

Schjoedt, Kidn.Internat.(2006) 70:536
Spironolactone diminishes albuminuria in type 1 diabetics with microalbuminuria (double-blind, randomized placebo-controlled crossover trial)

21 type 1 diabetic patients with microalbuminuria
25 mg or placebo once daily for 60 days on top of standard antihypertensive Rx

Spironolactone treatment:
# albuminuria reduced 60% (range 21-80%) p=0.01
# no change in blood pressure
# GFR decrease from 78 to 71 ml/min/1.73m² p=0.003

Rx well tolerated, but 2 patients S-K 5.7 mmol/L

In CKD (but not in primary hypertension):
urinary-sodium-excretion determines excretion of mineralocorticoid-metabolites:

**Thaldo (tetrahydroaldosterone)**  **THDOC (tetrahydrocorticosterone)**

McQuarrie, Nephrol.Dial.Transplant.(2013) 29:1526