Disclosure of Interests

None
When/who do we need to treat?

OBJECTIVES

The major aim of treating potassium and/or magnesium depletion is to increase blood levels in order to avoid consequences related to potassium or magnesium depletion, including rhabdomyolysis or life-threatening ventricular ectopy and to prevent chondrocalcinosis (long-term).

- Children: catch up the growth
- Adults: improve quality of life

- Most often, no direct proof in GS: indirect evidence from patients taking TZD
When/who do we need to treat?
Link between K, Mg and cardiovascular risk in the general population:

5,135 subjects of the Framingham Offspring Study (1979-1983)

- presence of major structural heart disease (detied later)
- use of β blockers, digoxin, or antiarrhythmic medications;
- presence of atrial fibrillation
age <20 years

3,373 subjects of the Framingham Offspring Study

- electrocardiograms
- M-mode echocardiograms
- Serum K, Mg,

When/who do we need to treat?
Link between K, Mg and cardiovascular risk in the general population:

1 SD decrement in serum K (0.46 mEq/L) or in Mg (0.15 mEq/L) was associated with a
- 27% greater odds of ventricular premature complexes (VPC)
- And 20% greater frequency of VPC

When/who do we need to treat?
Link between K, Mg and cardiovascular risk in hypertensives treated by TZD

233 HTN men, 35-70 yrs
90<DBP<105 mmHg

K 40 mmol/d
400 mg Mg

one month

two months

50 mg/d of hydrochlorothiazide (HCTZ)

50 mg/d HCTZ + 40 mmol/d of KCl

50 mg/d HCTZ + 40 mmol/d KCl + 400 mg/d Mg

50 mg/d HCTZ + 100 mg/d of triamterene

50 mg/d of chlorthalidone

Placebo

When/who do we need to treat?
Link between K, Mg and cardiovascular risk in hypertensives treated by TZD

two-fold increase in ventricular arrhythmias (Holter monitoring) in patients in whom the serum potassium concentration fell below 3.0 meq/L or

<table>
<thead>
<tr>
<th>SEVERITY GRADE</th>
<th>DEFINITION</th>
<th>INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GRADE 1</strong></td>
<td>Mild Transient or mild discomfort (&lt; 48 hours)</td>
<td>no medical intervention/therapy required</td>
</tr>
<tr>
<td><strong>GRADE 2</strong></td>
<td>Moderate Mild to moderate limitation in activity</td>
<td>some assistance may be needed; no or minimal medical intervention/therapy required</td>
</tr>
<tr>
<td><strong>GRADE 3</strong></td>
<td>Severe Marked limitation in activity,</td>
<td>some assistance usually required; medical intervention/therapy required, hospitalizations possible</td>
</tr>
<tr>
<td><strong>GRADE 4</strong></td>
<td>Life-threatening Extreme limitation in activity,</td>
<td>significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable</td>
</tr>
</tbody>
</table>

**WHO Toxicity Grading Scale for Determining The Severity of Adverse Events**
### WHICH TARGET?

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypokalemia</strong></td>
<td>3.0 - 3.4 mmol/L</td>
<td>2.5 - 2.9 mmol/L</td>
<td>2.0 - 2.4 mmol/L Or intensive replacement therapy or hospitalization required</td>
<td>&lt; 2.0 mmol/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia</td>
</tr>
<tr>
<td><strong>Hypomagnesemia</strong></td>
<td>0.60 - 0.70 mmol/L</td>
<td>0.45 - 0.55 mmol/L</td>
<td>0.30 - 0.40 mmol/L</td>
<td>&lt; 0.30 mmol/L or abnormal Mg with life-threatening arrhythmia or tetany</td>
</tr>
</tbody>
</table>

*Grade of hypokalemia and hypomagnesemia according to the WHO Toxicity Grading Scale for Determining The Severity of Adverse Events*
Any patients with moderate or severe hypokalemia and/or hypomagnesemia (grade 2 or higher)

or any patient with mild (grade 1) hypokalemia and/or hypomagnesemia AND related manifestations should be treated.

The hypokalemia should be confirmed by at least two analyses (TO DISCUSS)

Patients should be aware of the risk of aggravation of hypokalemia and hypomagnesemia in peculiar cases, including gastroenteritis, diarrhea and the use of certain medications such as corticosteroids, acetazolamide, or other drugs that may induce hypokalemia.
Potassium supplements
Which one? Optimal dose? Precautions? Side-effects?

Slow release potassium has been recommended in hypertensive patients at a dose ranging from 40 to 60 meq/day (3 to 5 g KCl/day) to reverse hypokalemia observed under therapy (> 2 months) with 100 mg hydrochlorothiazide: starting dose

Avoid diarrhea

In case of low dose/efficiency ratio, it is useful to monitor urinary potassium excretion to detect poor intestinal absorption due to intestinal potassium secretion and/or poor observance.

Patients likely to have delayed intestinal transit (e.g. the elderly, immobile, taking a low-volume diet or with hypokalemia induced intestinal paresia) should be given any necessary potassium supplementation in a well-diluted liquid form with or after food.
Intravenous Infusion

When? How?

When hypokalemia worsens and the patient cannot take its tablets (gastroenteritis..)

When the potassium deficit is very severe and is acutely causing severe complications (grade 4): cardiac arrhythmias, quadriplegia, respiratory failure, or rhabdomyolysis

Intravenous Infusion

When? How?

KCl should be given in a non-dextrose-containing solution, usually in a concentration of 40 mmol/l.

No more than 50 mmol/l (4 g KCl/L) should be given through a peripheral vein at a maximum rate of 10 mmol/hour.

Placing a sleeve for heating the forearm infused may limit the pain and rinse the vein at the end of infusion with isotonic saline could be helpful to prevent sclerosis of the vein used.

For central venous line the maximum concentration of 80 mmol/L and a maximum rate of 20 mmol / hour (depending hypokalemia, ECG monitoring). Beyond 10 mmol/hr, the patient should be in intensive care.
Magnesium supplements
Which one? Optimal dose? Precautions? Side-effects?

Very important: to improve potassium repletion, to improve growth, to prevent chondrocalcinosis.

Poor bioavailability (50%) (magnesium lactate and magnesium aspartate better?). Could be impaired by Proton Pomp inhibitors

Recommended starting dose is 300 mg/day of magnesium element (5 mg/kg in children), as slow release tablets when possible. It should be then adapted accounting of intestinal tolerance, divided into two to four doses.

Utility of sequential ambulatory infusion?
In case of acute tetany, 20% MgCl2 should be administered intravenously (0.1 mmol Mg/kg per dose) and can be repeated every 6 hours.

When decrease?

In case of diarrhea induced by supplementation, it could be more efficient to decrease to dose to the maximal tolerated dose (TO DISCUSS)
Salt intake

Table III. Levels of serum sodium (mmol/l) and potassium (mmol/l), plasma renin concentration (ng/ml/h) and plasma aldosterone (ng/100 ml) before treatment, during sodium restriction and during hydrochlorothiazide with and without sodium restriction

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Without HCT</th>
<th>During HCT (50 mg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium intake (mmol)</td>
<td>Sodium intake (mmol)</td>
<td>Sodium intake (mmol)</td>
</tr>
<tr>
<td>150–200⁴</td>
<td>50</td>
<td>150–200</td>
</tr>
<tr>
<td>Na</td>
<td>K</td>
<td>Na</td>
</tr>
<tr>
<td>1</td>
<td>141</td>
<td>4.0</td>
</tr>
<tr>
<td>2</td>
<td>141</td>
<td>4.5</td>
</tr>
<tr>
<td>3</td>
<td>143</td>
<td>4.0</td>
</tr>
<tr>
<td>4</td>
<td>144</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>141</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>141</td>
<td>3.8</td>
</tr>
<tr>
<td>7</td>
<td>139</td>
<td>4.0</td>
</tr>
<tr>
<td>8</td>
<td>140</td>
<td>3.8</td>
</tr>
<tr>
<td>9</td>
<td>140</td>
<td>3.9</td>
</tr>
<tr>
<td>Mean</td>
<td>141</td>
<td>4.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nutriments</th>
<th>K content (mg/g)</th>
<th>Weight (g)</th>
<th>glucose (g)</th>
<th>Kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCl salt</td>
<td>47300</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dry apricot</td>
<td>1162</td>
<td>86 (n=10)</td>
<td>54</td>
<td>207</td>
</tr>
<tr>
<td>strawberry</td>
<td>153</td>
<td>654</td>
<td>50</td>
<td>216</td>
</tr>
<tr>
<td>banana</td>
<td>358</td>
<td>279</td>
<td>64</td>
<td>249</td>
</tr>
<tr>
<td>Orange juice</td>
<td>184</td>
<td>543</td>
<td>65</td>
<td>255</td>
</tr>
<tr>
<td>lentils</td>
<td>369</td>
<td>271</td>
<td>54</td>
<td>314</td>
</tr>
<tr>
<td>Roasted soya beans</td>
<td>1468</td>
<td>68</td>
<td>23</td>
<td>322</td>
</tr>
<tr>
<td>Green beans</td>
<td>370</td>
<td>270</td>
<td>65</td>
<td>349</td>
</tr>
<tr>
<td>Fig confit</td>
<td>640</td>
<td>156</td>
<td>116</td>
<td>389</td>
</tr>
<tr>
<td>Apple juice</td>
<td>101</td>
<td>990</td>
<td>109</td>
<td>455</td>
</tr>
<tr>
<td>Chocolate Flan</td>
<td>184</td>
<td>543</td>
<td>125</td>
<td>772</td>
</tr>
<tr>
<td>Hazel/nuts</td>
<td>755</td>
<td>132</td>
<td>24</td>
<td>856</td>
</tr>
<tr>
<td>Coco nuts</td>
<td>356</td>
<td>281</td>
<td>42</td>
<td>994</td>
</tr>
<tr>
<td>Dark chocolate</td>
<td>342</td>
<td>292</td>
<td>175</td>
<td>1579</td>
</tr>
</tbody>
</table>

*Oral glucose test consists in acute absorption of 75 g glucose
OUR RECOMMENDATION (to discuss)

We recommend not to restrain salt intake but rather to encourage the patients to follow their appetite for salty food. In addition, any clinical extracellular dehydration should be treated.

For potassium rich food, we recommend to take into account not only the potassium content by nutriments but also the energy and glucose provided by and the amount required for a net intake of 1 g potassium.
RAAS INHIBITORS

Angiotensinogen

- Renin inhibitor

Renin

- ACE inhibitor

Angiotensin I

- ARB

Angiotensin II

Aldosterone

- Aldosterone blocker

K sparing diuretics

Majoration of renal Na wasting

Suppression of the residual protective mechanism against hypotension
### How to scale up treatment

**Role of amiloride, eplerenone, indomethacin**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Chronoindocid</th>
<th>Eplerenone</th>
<th>Amiloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>69.2 ± 13.1</td>
<td>70.3 ± 13.4$^1$</td>
<td>66.9±12.9</td>
<td>67.1±13.0$^2$</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>117±10</td>
<td>117±11</td>
<td>112±11$^1$</td>
<td>112±10$^{1,2}$</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>72.5±9.6</td>
<td>72.9±7.5</td>
<td>75.8±8.0</td>
<td>75.0±9.2</td>
</tr>
<tr>
<td>Plasma K, mmol/L</td>
<td>2.8±0.4</td>
<td>3.2±0.4</td>
<td>3.0±0.4</td>
<td>3.0±0.5</td>
</tr>
<tr>
<td>Plasma Mg, mmol/L</td>
<td>0.55±0.07</td>
<td>0.56±0.07</td>
<td>0.56±0.12</td>
<td>0.58±0.08$^1$</td>
</tr>
<tr>
<td>Plasma Na, mmol/L</td>
<td>139.0±1.5</td>
<td>139.3±1.5</td>
<td>138.5±1.8$^{1,2}$</td>
<td>138.6±1.5$^{1,2}$</td>
</tr>
<tr>
<td>eGFR (MDRD)</td>
<td>124±30</td>
<td>115±26$^1$</td>
<td>126±28$^3$</td>
<td>121±31</td>
</tr>
<tr>
<td>Plasma renin, mUI/L</td>
<td>78</td>
<td>46$^1$</td>
<td>107$^{1,2}$</td>
<td>122$^{1,2}$</td>
</tr>
<tr>
<td>Plasma aldo., pg/ml</td>
<td>48</td>
<td>42</td>
<td>140$^{1,2}$</td>
<td>167$^{1,2}$</td>
</tr>
<tr>
<td>UV Na, mmol/24h</td>
<td>195</td>
<td>187</td>
<td>186</td>
<td>201</td>
</tr>
<tr>
<td>UV K, mmol/24h</td>
<td>105</td>
<td>123</td>
<td>102</td>
<td>104</td>
</tr>
</tbody>
</table>

Data are mean ± SD or Geometric mean [IC95%]. Paired test between pre treatment (-) and post treatment (+) values: p<0.05 with corresponding control ($^1$); or eplerenone or amiloride and indomethacin ($^2$); or between eplerenone and modamide ($^3$)

**Blanchard, A et al "Indomethacin, amiloride, or eplerenone for treating hypokalemia in Gitelman syndrome." J Am Soc Nephrol 26(2): 468-75.**
How to scale up treatment
Role of amiloride, eplerenone, indomethacin?

We recommend to discuss potassium sparing inhibitors in case of symptomatic grade 2 or grade 3 to 5 hypokalemia refractory to supplementations. They should be started cautiously to avoid hypotension (amiloride 5 or 10 MG, spironolactone 25 MG or eplerenone 75 MG).

We do not recommend the use of indomethacin in first intention for the only indication of hypokalemia refractory to supplementations.

We do not recommend the use of renin inhibitors, ARB or ACE inhibitor at least until specific trial have been done in this indication.

We recommend to wean these drugs in pregnant women or preventively if pregnancy is expected.
Furosemide can worsen salt and potassium wasting but is rarely indicated in these patients.

Prescription of acetazolamide for ophthalmic indication such as treatment of glaucoma or abruption of retina can be challenging. It generally dramatically worsens hypokalemia.

QT-prolonging medications should be used with caution.

Dehydration in these patients can favor kidney toxicity of NSAID and of lithium salt.

Proton pump inhibitor can worsen hypomagnesemia by decreasing intestinal absorption of magnesium.
During pregnancy, hypokalemia worsens and the use of renin-angiotensin II–aldosterone axis and prostaglandin synthetase inhibitors has been rarely reported.

It is however not recommended because of the relatively high teratogenicity.

The potassium-sparing diuretic amiloride has been proposed in case of severe hypokalemia despite supplementation, but increases the risk of oligohydramnios.

Both oral nonsteroidal anti-inflammatory drugs (NSAID) and low-dose oral colchicine are effective systemic treatment for acute CPP.

Intra-articular corticosteroids may be considered in patients in whom other drugs may be contraindicated or not tolerated or few joints are involved.

Basic treatment includes Mg administration combined with NSAID or colchicine that can result in an improvement or to a complete remission.

The methotrexate (MTX), which works not only as an immunosuppressant, but also as a potent anti-inflammatory agent, has been proposed as an alternative therapeutic option for patients with severe CPDD who fails to respond to standard therapy with nonsteroidal anti-inflammatory drugs and/or glucocorticoids.

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