COMPLICATIONS OF REFEEDING SYNDROME

N. Vink (NL)
Complications of refeeding syndrome

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I have no conflict of interest
Learning objectives

• Acquire knowledge of severe metabolic disturbances which can occur as a result of the Refeeding Syndrome, and how they are handled in practice
Refeeding syndrome

• Potentially fatal shifts in fluids and electrolytes that may occur in malnourished patients receiving artificial refeeding

• Hormonal and metabolic changes -> serious clinical complications

• Hypophosphatemia

• Hypokalemia
• Hypomagnesemia
• Thiamine deficiency
• Abnormal sodium and fluid balance
• Changes in:
  • glucose metabolism
  • protein metabolism
  • fat metabolism
**Hypophosphatemia**

- Phosphate is an intracellular mineral, essential for ALL intracellular processes and for the structural integrity of cell membranes
- Many enzymes and second messengers are activated by phosphate binding
- Required for energy storage as ATP (Adenosine TriPhosphate), conversion of adenosine diphosphate to adenosine triphosphate
- Regulates affinity of haemoglobin for oxygen (production of 2,3-diphosphoglycerate↓)
  
  Decline in 2,3 DPG -> increasing red blood cell’s affinity for oxygen
  Delivery of oxygen to tissue↓ → tissue hypoxie

- RBC dysfunction: alterations in cell shape, survival, physiologic capacity
- WBC dysfunction: depressed chemotactic, phagocytic, bacterial activity of granulocytes and ATP content ↓
- Renal acid-base buffer system
Hypophosphatemia

• Refeeding syndrome -> total body depletion of phosphate

• Insulin surge -> phosphate uptake ↑ and use ↑ in the cells

• Dysfunction of cellular processes affecting almost every physiological system
Hypophosphatemia complications

Cardiovascular:
- Arrhythmias
- Congestive heart failure
- Cardiomyopathy
- Decreased cardiac contractility
- Sudden death

Respiratory:
- Impaired respiratory muscle function -> respiratory failure or ventilator dependency

Muscular:
- Weakness
- Myalgia
- Rhabdomyolysis

Bone
- Osteomalacie
Hypophosphatemia complications

Neurological:
- Weakness
- Paresthesia
- Altered mental state
- Paralysis
- Seizures
- Acute encephalopathy

Hematological:
- Platelet dysfunction
- Haemolytic anaemia
- Leukocyte dysfunction
- Thrombocytopenia
- Altered morphology of red blood cells
- Reduced oxygen release from hyperbaric oxygen
Hypokalemia

• Potassium, major intracellular cation

• Refeeding syndrome:

  - Insulin secretion -> increase in volume and number of cells
  - Derangements in the electrochemical membrane potential
  - Uptake potassium in the cell↑
  - Severe hypokalemia
Hypokalemia, complications

Cardiovascular:
- Arrhythmias
- Cardiac arrest
- Hypotension
- Digoxin toxicity
- Sudden death

Respiratory:
- Pulmonary oedema
- Retention of carbon dioxide (hypoventilation)

Muscular:
- Weakness
- Myalgia
- Rhabdomyolysis

Renal:
- Decreased ability of het renal tubulus to concentrate urine
Hypokalemia, complications

Neurological:
- Weakness
- Altered mental state
- Paralysis

Metabolic:
- Alkalosis (treatment KCl)
- Glucose intolerance
- Hyperglycaemia
- Hypernatraemia
- Ketoacidosis
- Metabolic acidosis (treatment KHCO₃)

Gastrointestinal:
- Constipation
- Paralytic ileus
Hypomagnesemia

- Magnesium, predominantly intracellular cation
- Cofactor in most enzyme systems, e.g. oxidative phosphotylation and ATP production
- Necessary for the structural integrity of DNA, RNA and ribosomes
- Affects membrane potential

Refeeding syndrome:

Insulin stimulates glycogen, fat and protein synthesis -> requires magnesium and phosphate

Intake Mg in the cells ↑

Mg depletion
Hypomagnesemia, complications

Cardiovascular:
- Arrhythmias
- Hypertension
- Tachycardia
- Sudden death

Neurological:
- Weakness
- Paraesthesia
- Altered mental state
- Ataxia
- Tremor
- Vertigo
- Tetany
- Seizures
Hypomagneseemia, complications

Haematological
• Anaemia

Gastrointestinal
• Constipation
• Abdominal pain
• Diarrhea
• Anorexia

Electrolyte
• Hypocalcemia (treat hypomagneseemia first)
• Hypokalemia
Thiamine deficiency

- Thiamine, essential coenzyme in carbohydrate metabolism
- Insulin stimulates glycogen, fat and protein synthesis -> requires magnesium and phosphate and thiamine as cofactor -> deficiency thiamine

Deficiency leads to
- Wernicke’s encephalopathy
- Korsakoff’s syndrome
- Hartfaliure (muscle weakness)
- Inadequate glucose metabolism resulting in accumulation of pyruvaat and lactate (lactateacidosis) -> vasodilatation and oedema
Abnormal sodium and fluid balance

- Carbohydrate introduction in diet leads to:
  - Renal excretion of sodium and water ↓
  - Fluid repletion (maintain normal urine output) → fluid overload

Complications:
- Cardiovascular
  - Arrhythmia
  - Congestive cardiac failure
  - Sudden death

- Respiratory
  - Pulmonary oedema
Glucose metabolism

Release of insulin → Gluconeogenesis ↓

- Hyperglyceamia:
  - Osmotic diuresis
  - Dehydration
  - Metabolic acidosis
  - Ketoacidosis

Release of insulin → lipogenesis

- Fatty liver
- Increased carbon dioxide production
- Hypercapnoea
- Respiratory failure
Treatment complications of refeeding syndrome

- Intravenous supplementation of electrolytes, carefully
- Caution needed in patients with existing renal impairment, hypocalcaemia (may worsen) or hypercalcaemia can lead to metastatic calcification
- Check serum concentrations of phosphate, potassium, magnesium and glucose
- Administer electrolyte supplementations separately

- Oral supplementation of phosphate can lead to diarrhea
- Oral supplementation of magnesium is poorly absorbed and lead to gastrointestinal upset
## Electrolyte supplementation (deficiency)

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Concentration</th>
<th>Supplementation*</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td>Mild to moderate (0.3-0.8 mmol/l)</td>
<td>15-30 mmol/day iv or oral</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>Severe (&lt;0.3 mmol/l)</td>
<td>0.25-1.0 mmol/kg in 8-12 h iv</td>
<td>Every 6 hours</td>
</tr>
<tr>
<td>Potassium</td>
<td>Mild to moderate (3.0-3.4 mmol/l)</td>
<td>30-80 mmol/day iv or oral</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>Severe (&lt;3.0 mmol/l)</td>
<td>2-4 mmol/kg/day iv or 120-240 mmol/day iv</td>
<td>Every 6 hours</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Mild to moderate (0.5-0.7 mmol/l)</td>
<td>13-34 mmol/day oral or 10-15 mmol/day iv</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>Severe (&lt;0.5 mmol/l)</td>
<td>1.5-3 mmol/h iv or in very severe cases 4mmol/h iv</td>
<td>Every 6 hours</td>
</tr>
</tbody>
</table>

*Adjustment needed in case of renal failure

Phosphate: decrease of >0.3 mmol/l/d or life threatening: 4.5 mmol/h in 3 h iv, followed by 2-3.5 mmol/h iv, max 90 mmol/d

*Guidelines according to the NVO, dutch consultation of nutrition teams*
Treatment complications of refeeding syndrome

• Fluid repletion, carefully to avoid fluid overload
  • Monitor pulse rate
  • Monitor fluid balance

• Monitoring cardiac function (ECG)

• Stabilise the patient clinically

• Supplementation of thiamine, risk of providing high doses are small and the benefits potentially lifesaving (200mg)
Take home messages

Refeeding syndrome is a potential lethal condition with various presentations. The most common complications are:

- Hypophosphatemia
- Thiamine deficiency
- Hypokalemia
- Hypomagnesemia
- Abnormal sodium and fluid balance

Leading to:

- Cardiac dysfunction
- Neuromuscular dysfunction
- Hematologic-RBC and WBC dysfunction
- Respiratory dysfunction
Take home messages

• Be aware of the fact that electrolyte deficiency/alterations in blood glucose can be caused by medicines as well:

• Hypophosphatemia: digoxine, phosphate binders, colchicine, antiepileptics, corticosteroids, aluminium or magnesium salts, bile acid-binding resins

• Drugs contributing to diarrhea e.g. antibiotics, motility agents, laxatives, liquids containing sorbitol

• Insulin, oral hypoglycemic agents, corticosteroids
Hope to see you next year in the Hague at Espen 2017