Citrate, Calcium and Magnesium metabolism and related toxicities

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Blood and Beyond

Disclosure of Relevant Financial Relationships

- Hans None
- Marleen None

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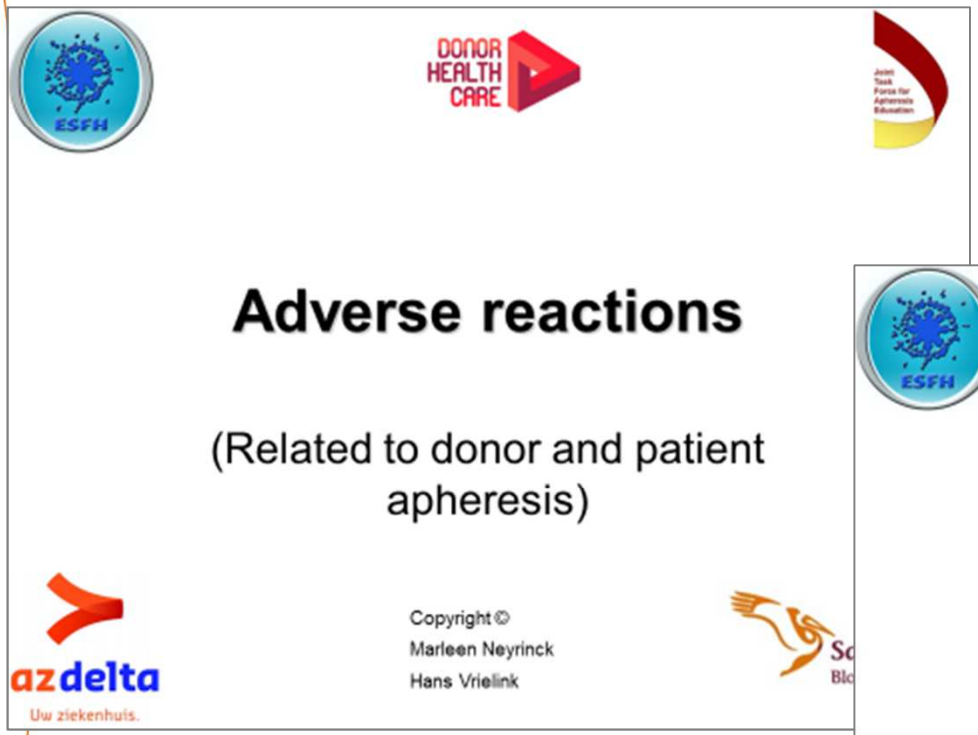

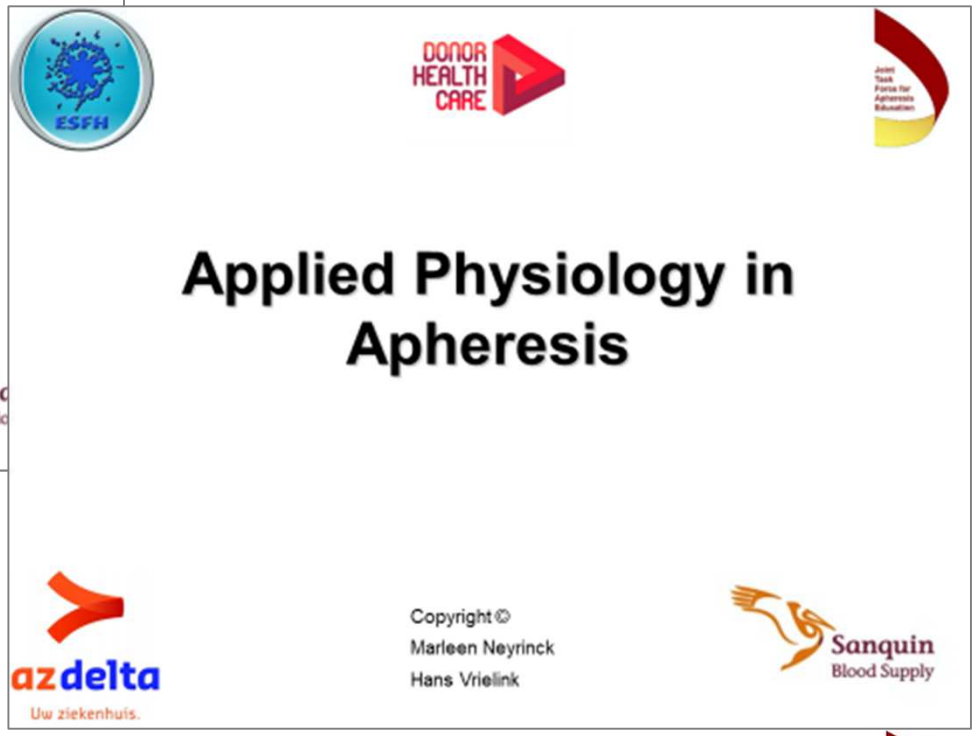

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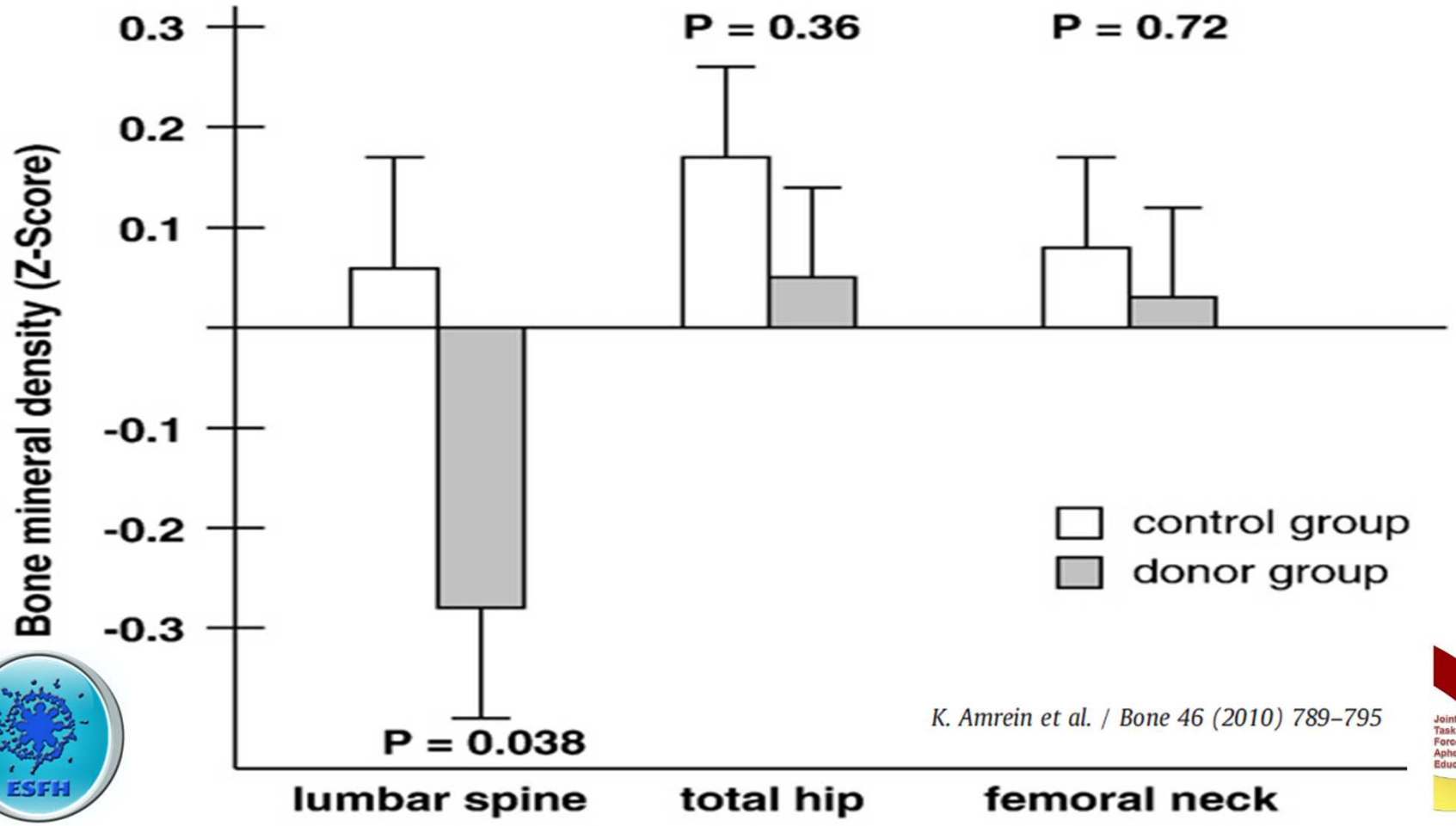
Long term effects of apheresis procedures

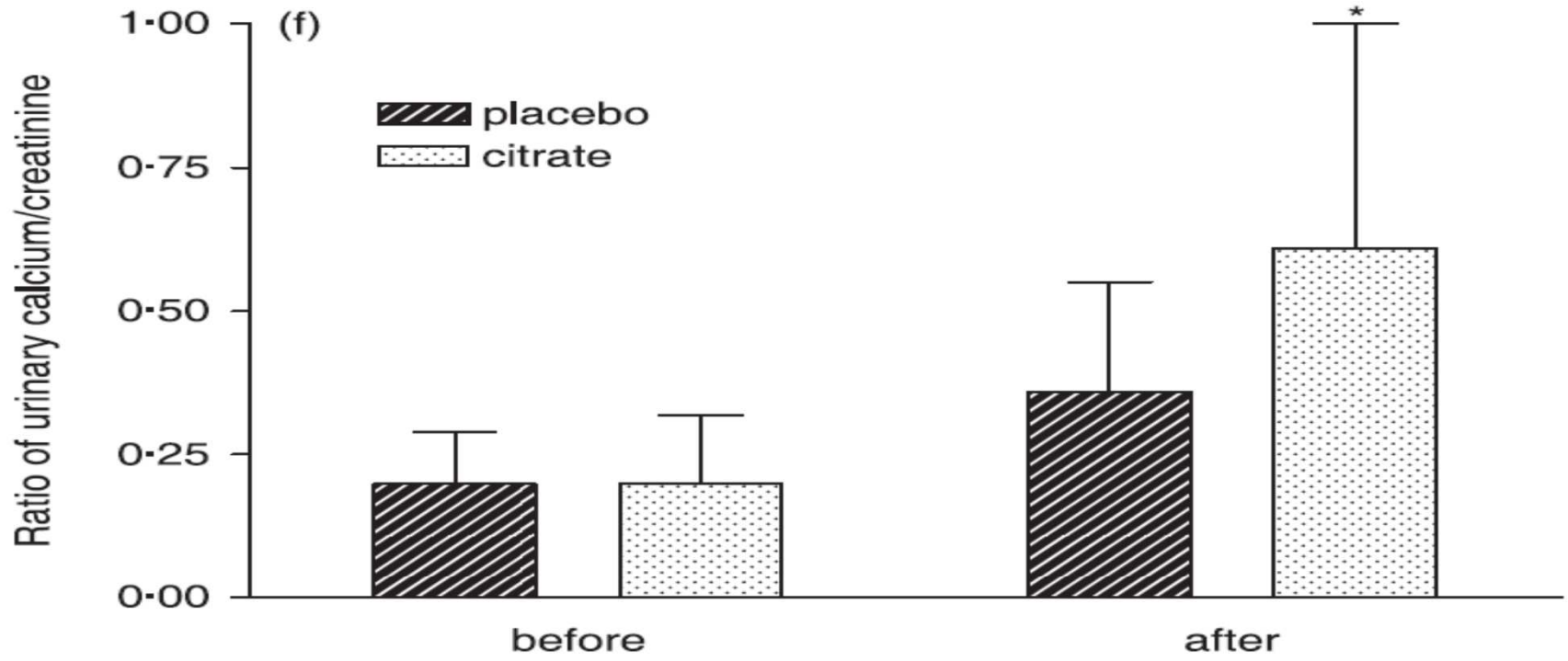
- Comparison bone density of 45 donors >100 PLT-apheresis with 40 donors <50 procedures.
- 35% of >100 procedures donors showed significant osteoporosis.

Dettke J. Clin Apheresis 2003

Long term effects in frequent plt donors?



Calcium in urine

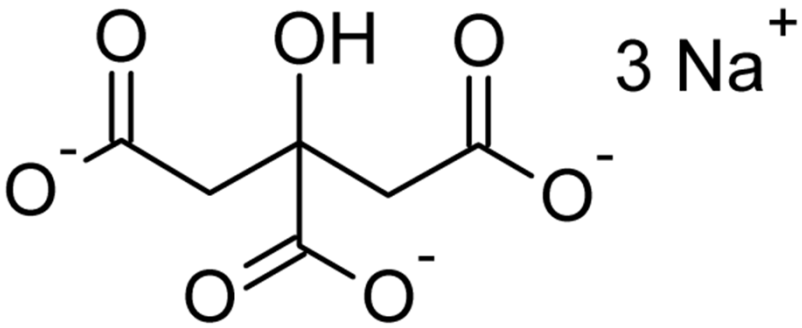


Comparison of urinary calcium excretion

Excretion of urinary calcium increase after citrate intervention. *$P = 0{\cdot}034$

Y. Chen *et al.* *Vox Sanguinis* (2009) **97**, 324–329

Tri-sodiumcitrate and calcium



Vhttp://4.bp.blogspot.com/-69-2fUgntos/T9UE0fnWxTI/AAAAAAAAMPQ/XwbSSOWjNZs/s1600/Calcium.jpg

Calcium

- 99% in the bones → calcium phosphate (± 24,500 mmol)

Extra cellular fluid: 22.5 mmol → 9 mmol in plasma (2.2 – 2.6 mmol/L)

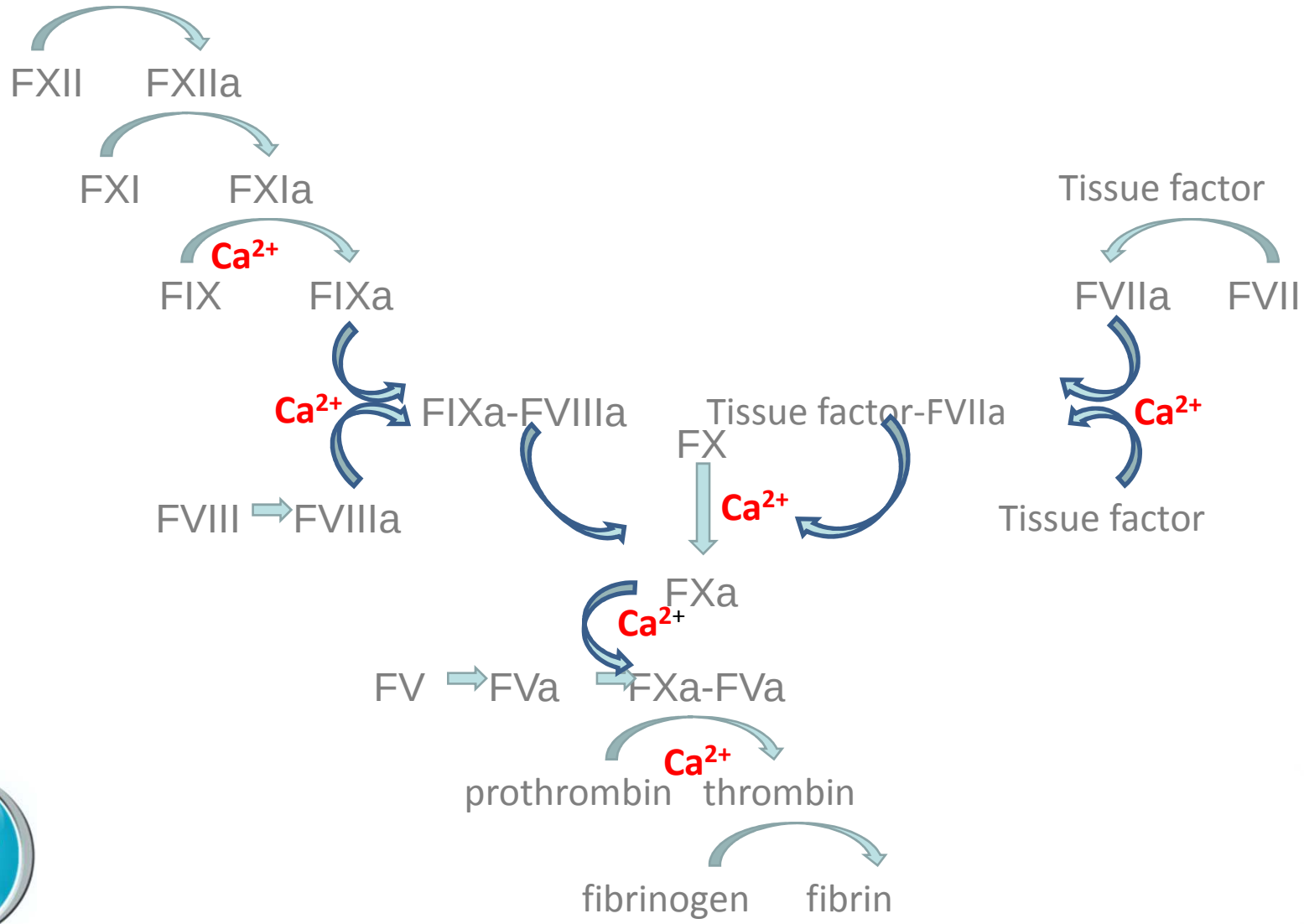
Plasma calcium

Total calcium 2.2 – 2.6 mmol/L (9 - 10.5 mg/dL)

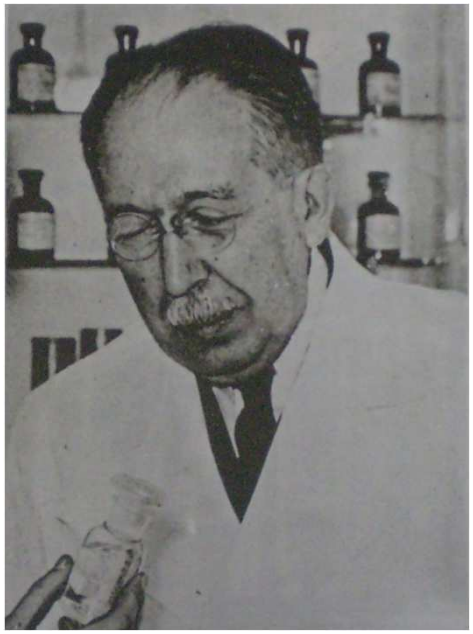
- Ionized (free) calcium 1.1 – 1.4 mmol/L (4.5 – 5.6 mg/dL)
- Remainder bound mainly to albumen (± 50%)

Function of Calcium

- Structural function → bones
- Signaling function → messenger for some hormones
- Enzymatic function → co-enzyme for clotting factors
- Function in transmission of nerve impulse
- Function in the contraction of muscles
- Stabilization of cellular membranes


FXII
FXIIa
FXI
FXIa
Ca2+
FIX
FIXa
Tissue factor
FVIIa
FVII
Ca2+
FIXa-FVIIIa
Tissue factor-FVIIa
Ca2+
FX
Ca2+
FVIII
FVIIIa
Tissue factor
FXa
Ca2+
FV
FVa
FXa-FVa
Ca2+
prothrombin
thrombin
fibrinogen
fibrin

Prevention of blood clotting by citrate

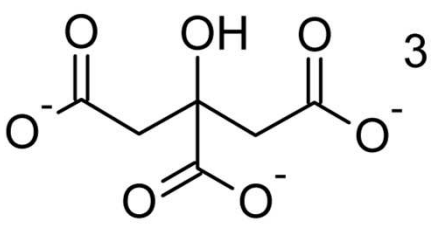


Luis Agote

1914

Albert Hustin

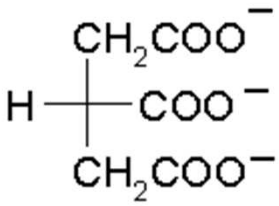
Citrate



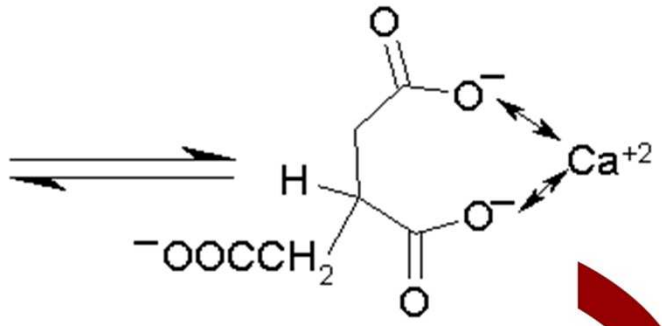
- Trisodiumcitrate
  - Prevention of blood clotting in disposable / machine
  - Flavoring and buffering agent in drinks / food (E330)
  - Laxative
  - WHO “oral rehydration solution”

Citrate handling during apheresis procedures

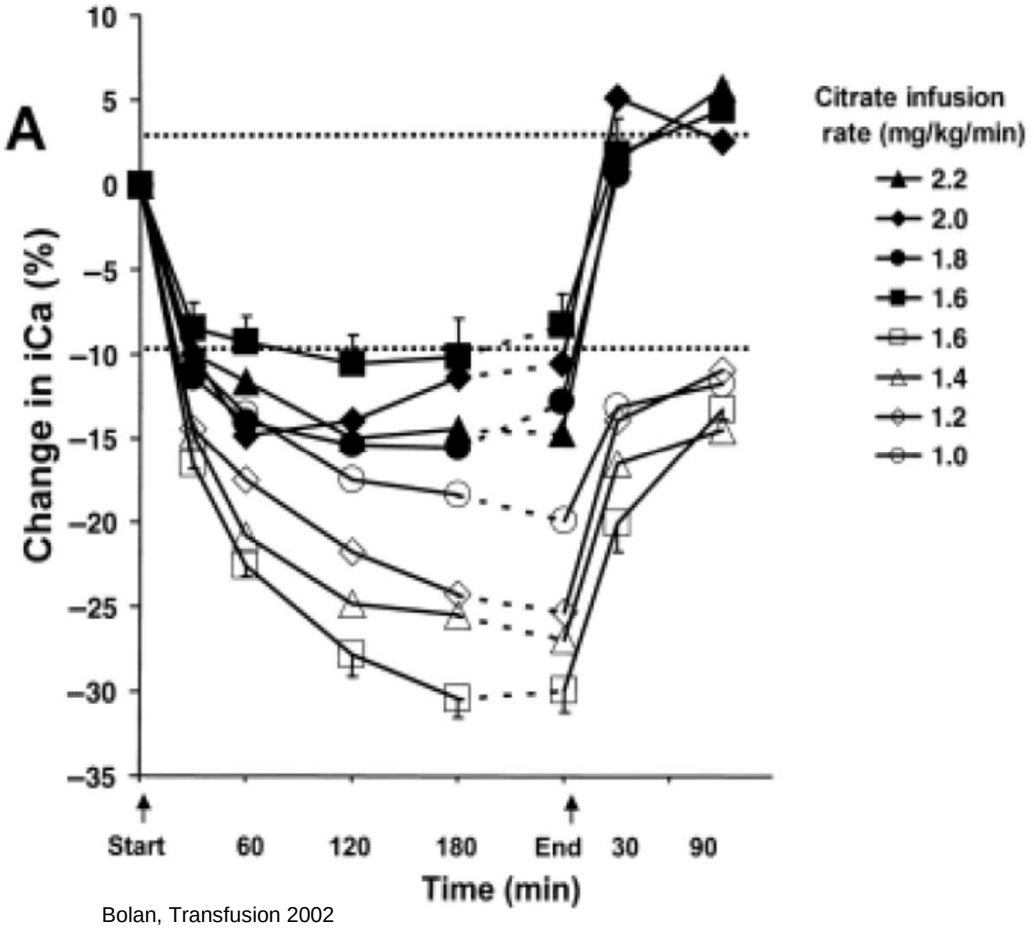
- Tri-sodiumcitrate is added to whole blood in procedure specific ratio
- Citrate resolves completely in plasma
- Citrate chelates free Calcium and Magnesium
- Citrate returns to donor with plasma containing components



sodium citrate

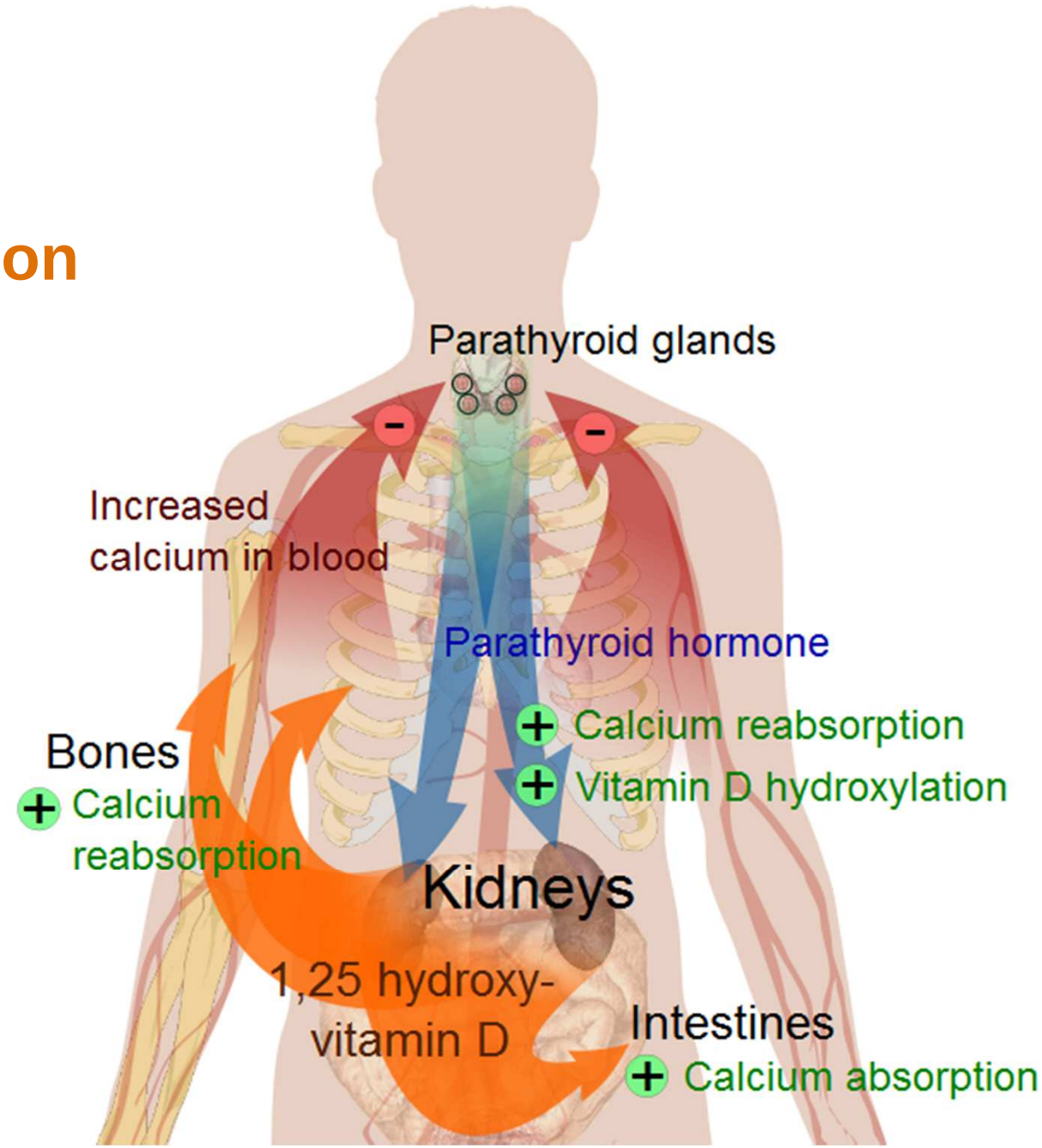


Serum calcium & citrate infusion



Bolan, Transfusion 2002

Calcium regulation



http://www.en.wikipedia.org

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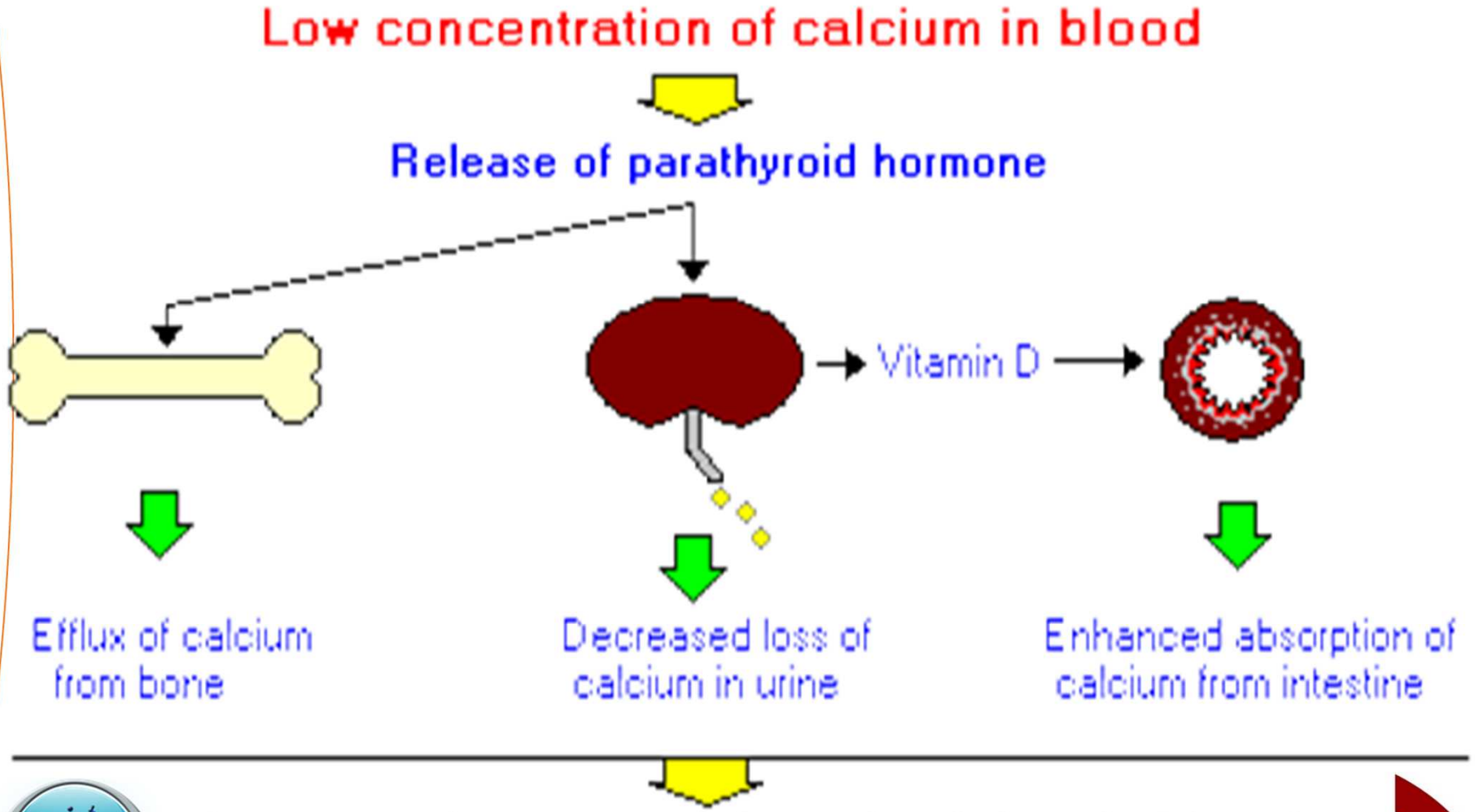

http://www.en.wikipedia.org

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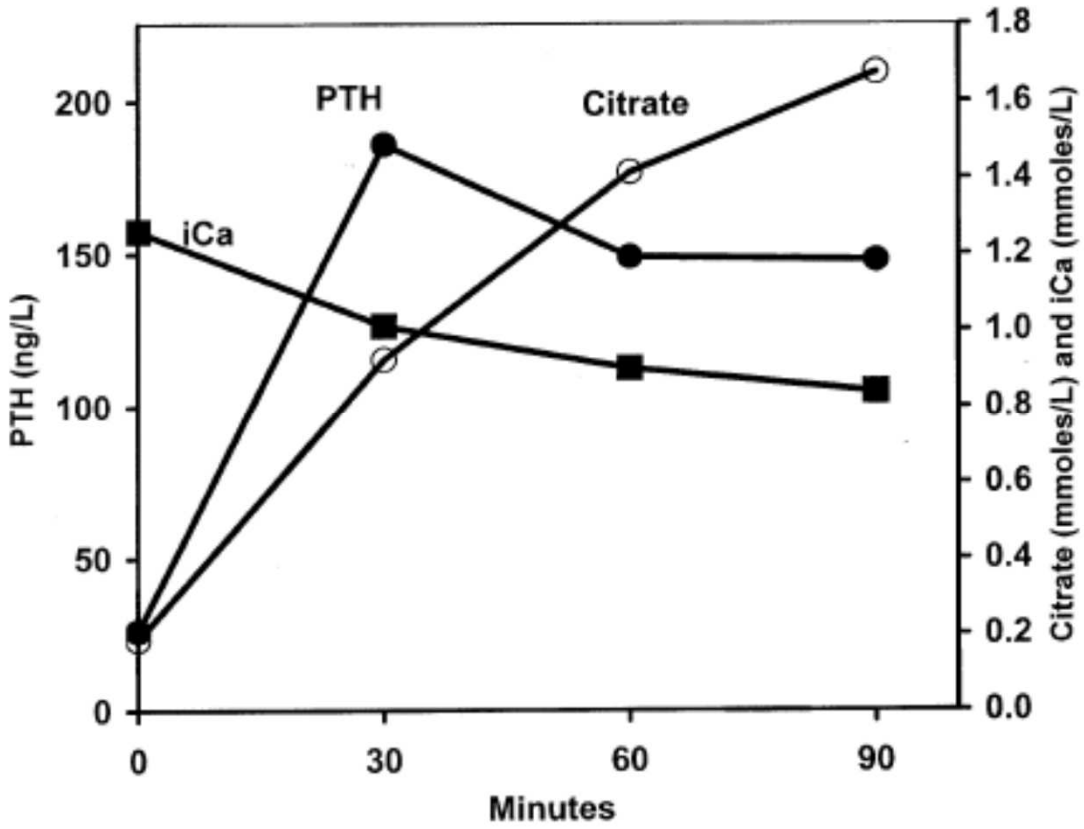
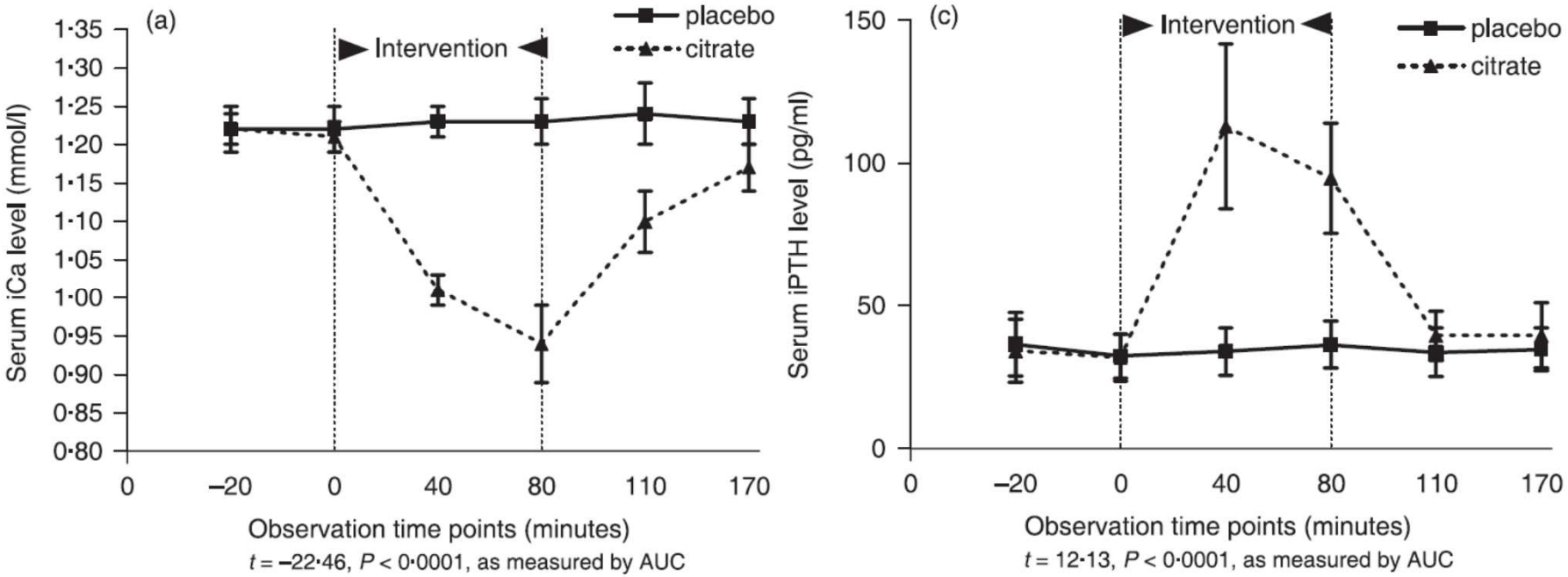
Serum PTH, iCa and Citrate during plt apheresis



McLeod BC, Szczepiorkowski ZM, Weinstein R, Winters JL, eds; *Apheresis: Principles and Practi*
3rd edition; Bethesda, MD: AABB Press, 2010

Serum PTH and Calcium



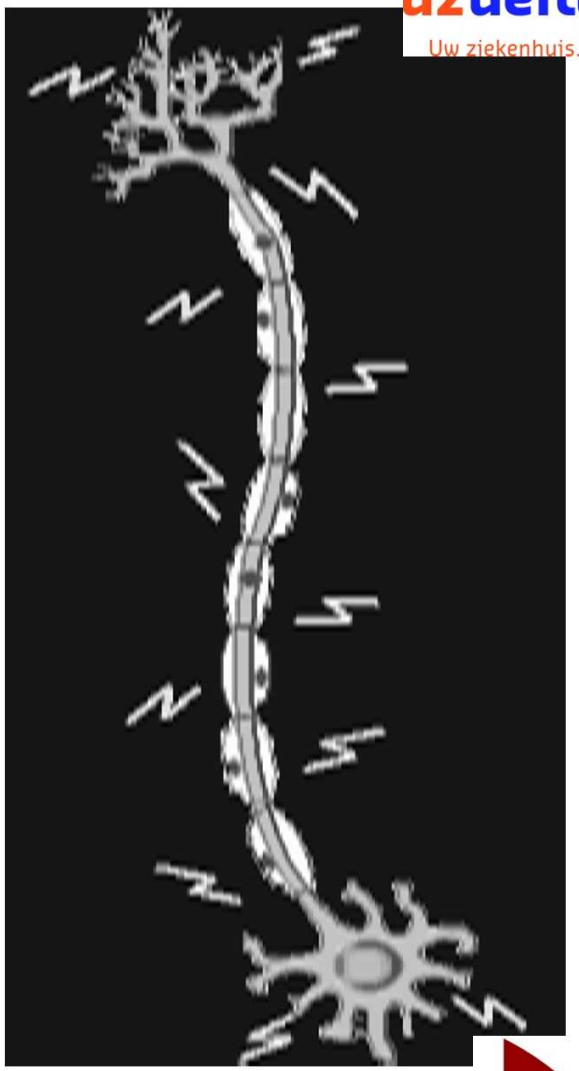
Y. Chen *et al.* *Vox Sanguinis* (2009) **97**, 324–32

Function of Calcium

- Structural function → bones
- Signaling function → messenger for some hormones
- Enzymatic function → co-enzyme for clotting factors
- Function in transmission of nerve impulse
- Function in the contraction of muscles

Hypocalcemia

- Decrease in ionized calcium results in increased excitability of neurons to the point of spontaneous depolarization.



Function of Calcium

- Structural function → bones
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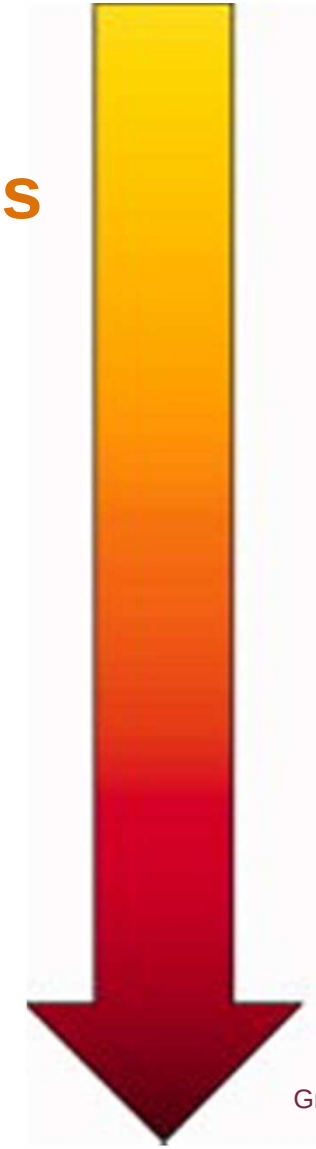
Symptoms of citrate reactions



Mild

Perioral or acral paresthesias
Sneezing
Lightheadedness
Flushing
Shivering
Headaches

Moderate

Nausea and vomiting
Nervousness and irritability
Abdominal cramping
Involuntary muscle contraction: carpopedal spasm, tetany
Tremors
Hypotension

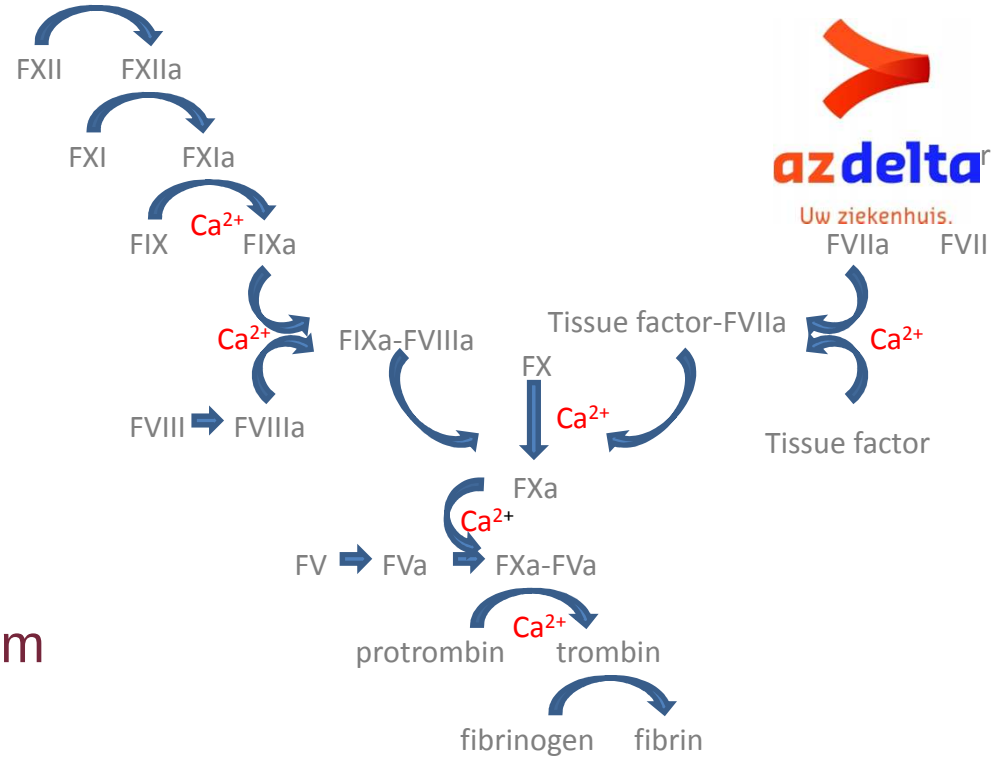
Severe

Cardiac arrhythmias
Seizures

Grace Lee & Gowthami M. Arepally; J Clin Apheresis 2012

Citrate

- Completely dissolved in plasma
- No binding to cells
- Chelates calcium and Magnesium
- Prevents coagulation



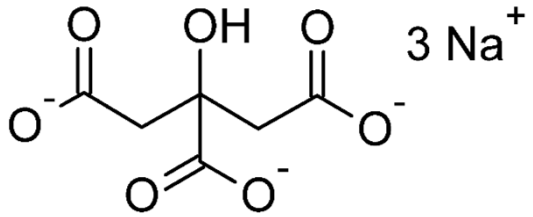
Neutralized by:

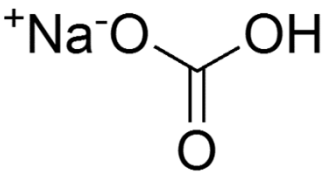
- Distribution throughout extra cellular fluid
- Excretion by the kidneys
- Rapid metabolism by the kidneys, liver and skeletal muscle

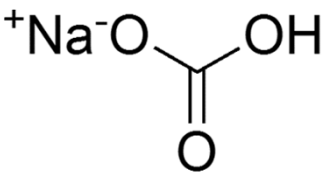
Citrate → Metabolic Alkalosis

Additional factors to consider

- Presence of citrate in replacement fluids (e.g. FFP for TTP)
- Large volume PBSC collections (average drop Ca^{2+} of 11.3±7%)
- Citrate → Bi-carbonate → Alkalosis

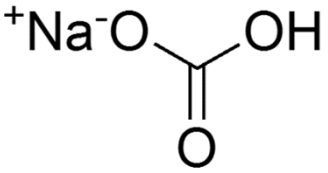






Ca2+

Mg2+



Citrate → Metabolic Alkalosis & Hypokalemia

Additional factors to consider

- Presence of citrate in replacement fluids (e.g. FFP for TTP)
- Large volume PBSC collections (average drop Ca^{2+} of 11.3±7%)
- Citrate → Bi-carbonate → Alkalosis → excretion citrate ↑
- Renal disease preventing the excretion of bicarbonate and citrate
  → symptoms of hypocalcemia ↑, suppression of respiratory rate
  → Metabolic alkalosis
- Metabolic alkalosis results in potassium uptake in cells → hypokalemia
  Decrease in potassium and cardiac arrhythmia

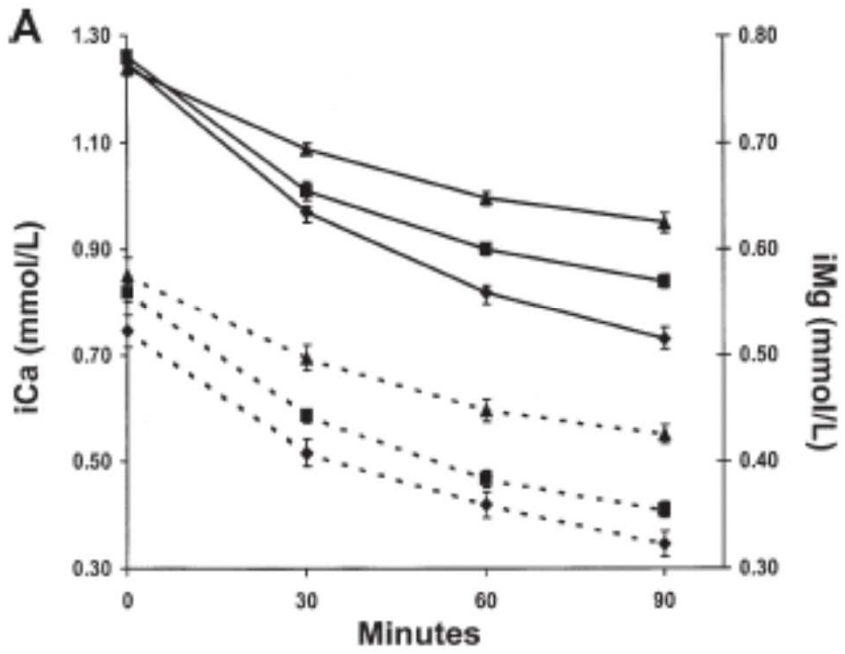
Citrate

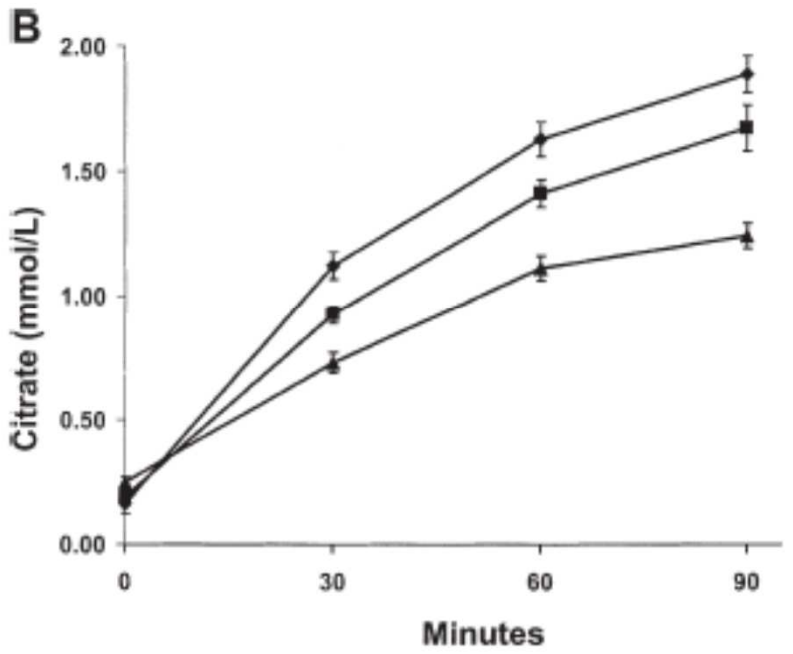
- Chelates calcium and Magnesium

Citrate → Hypomagnesemia

- Mg^{2+} also bound by citrate
- During plateletapheresis: 30% drop in magnesium levels

Serum magnesium during plateletapheresis





Bolan, et al. Transfusion 2001;41:1165-1171

Plasma magnesium

Total magnesium 0.7 – 1.1 mmol/L (1.5 – 2.5 mg/dL)

- Ionized (free) magnesium 0.5 – 0.7 mmol/L (1.1 – 1.5 mg/dL)
- Remainder bound mainly to Albumen and globulins

Magnesium

Involved in:

- Synthesis of nucleic acids
- Synthesis of proteins
- Intermediary metabolism
- Specific actions in
  - Neuromuscular systems
  - Cardiovascular systems

Mg^{2+} competes with Ca^{2+} for binding sides on proteins and membranes

Competitively inhibition of calcium

Magnesium

Affects:

- Muscular contraction and relaxation including the heart and vascular muscles.
- Electrical activity of myocardial cells
- Stabilization of the axon
- The release of neurotransmitters

Hypomagnesaemia

Caused by

- Redistribution of Mg
- Gastrointestinal
- Renal loss
- Renal disease
- Endocrinal
- Diabetes mellitus
- Alcoholism
- Miscellaneous
- Drugs
  - Diuretics
  - Cytotoxic drugs
  - Antibiotics
  - B adrenergic agents
  - Others

Hypomagnesaemia

Citrate and hypocalcaemia

Electrolyte disturbance
Hypokalaemia
Hypocalcaemia
Neuromuscular and central nervous system
Carpopedal spasm
Convulsations
Muscle cramps
Muscle weakness, fasciculations, tremors
Vertigo
Nystagmus
Depression, psychosis
Athetoid movements & choreform movements
Cardiovascular
Atrial tachycardias, fibrillation
Supraventricular arrhythmias
Ventricular arrhythmias
Torsade de pointes
Digoxin sensitivity
Complications of magnesium deficiency
Altered glucose homeostasis
Atherosclerotic vascular disease
Hypertension
Myocardial infarction
Osteoporosis
Miscellaneous
Migraine
Asthma
Chronic fatigue syndrome
Impaired athletic performance

Citrate → Hypomagnesemia

- Mg^{2+} also bound by citrate
- During plateletapheresis: 30% drop in magnesium levels
- Steeper decrease and recovers more slowly than calcium
- Muscle spasms & weakness
- Decreased vascular tonus (blood pressure) + abnormal cardiac contractility
- Interference with potassium and calcium homeostasis
- If suspected 8 mmol Mg^{2+} i.v. in 1 minute

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In Summary

- For apheresis procedures we use citrate solutions
- Citrate is binding calcium and magnesium
- Citrate is returned to the donor
- Hypocalcemia and hypomagnesemia → effects
- Direct (side) effects of citrate

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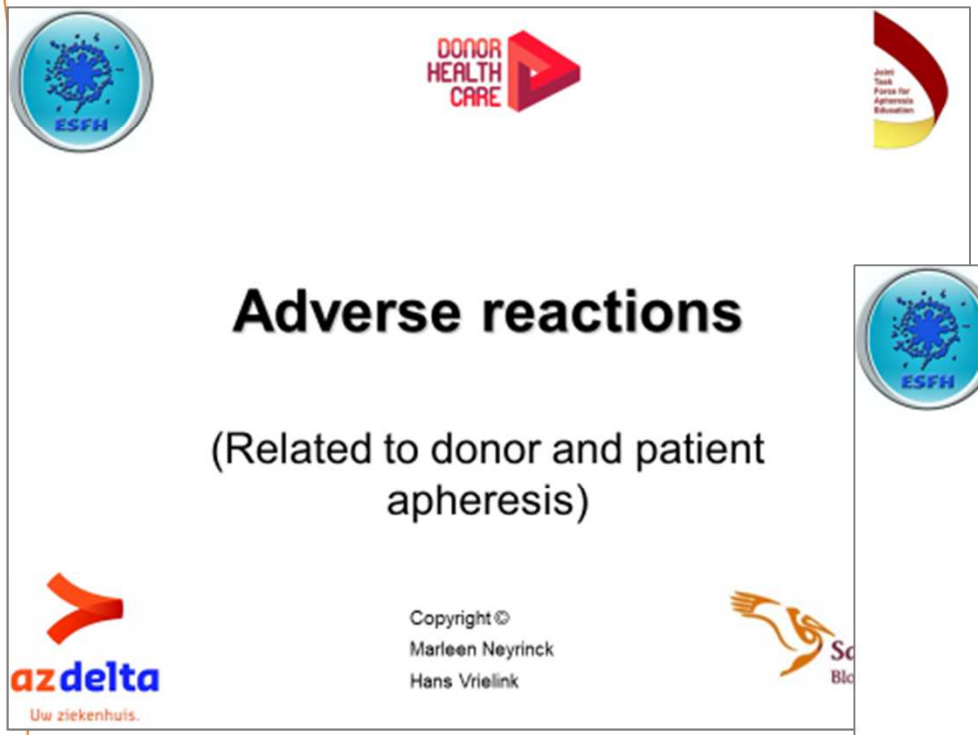

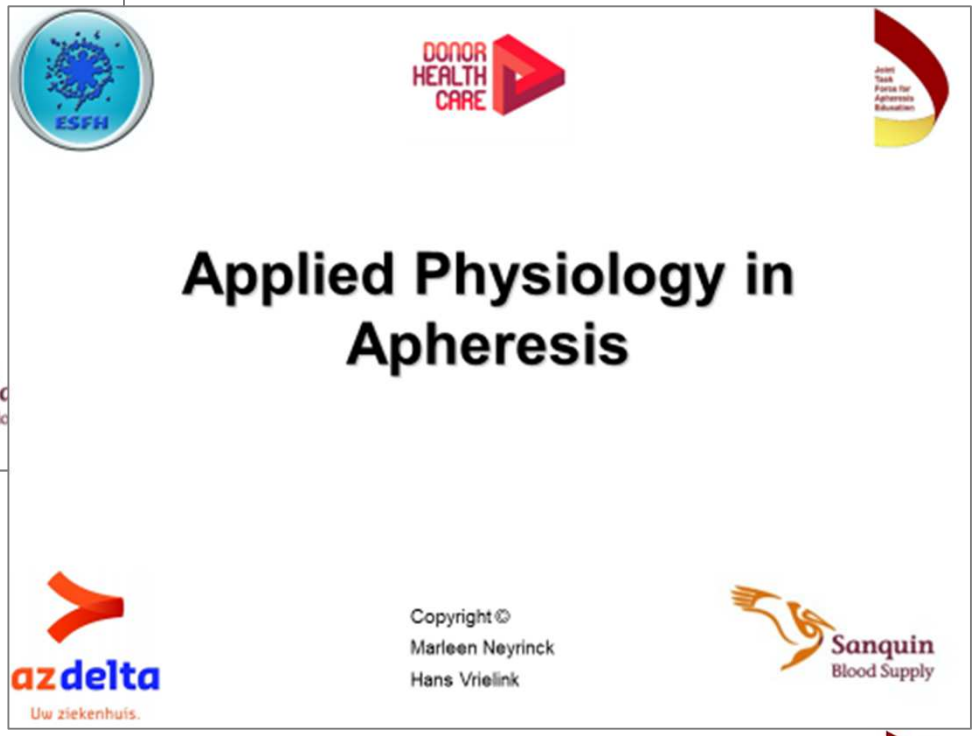

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For information

http://www.sanquin.nl/en/products-services/consulting-services

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