

EUROPEAN SOCIETY
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MEDICINE



Phosphate:

From Understanding to Improved Outcome

Timothy G. Buchman, Ph.D., M.D.

Edison Professor of Surgery

Professor, Anesthesiology and Medicine,
Washington University School of Medicine,
USA

Disclosures

- No product or service will be discussed in this presentation
- Presenter has not served on any pharmaceutical advisory board or consultancy for the past 3 years
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Outline for this talk

- Fast facts about phosphate
- A snapshot of phosphate regulation
- Low phosphate
 - Causes, fixes and prevention by protocol
- High phosphate
 - Causes, fixes

Fast Facts—Discovery

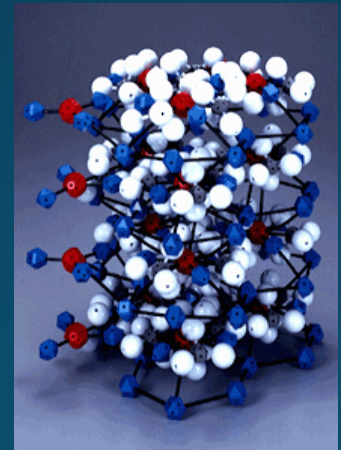
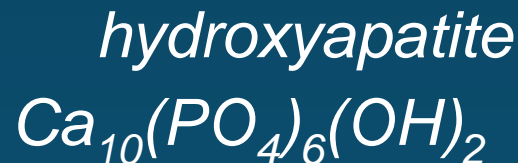
- Phosphorus (Gk. *Phosphoros*, ancient name for planet Venus)
 - discovered in 1669 by Hennig Brand (Ger.) through a preparation of urine
 - an alchemist trying to make gold
 - attempted to distill salts by evaporating urine, produced a white material that glowed in the dark—“phosphorescence”

Fast Facts—Intake and Measure

- WHO prescribes a maximum tolerable daily intake of phosphate = 70 mg/kg/day
- Typical adult diet is <10% of this
- “Phosphate” is a measure of all phosphorus-containing anions

Fast Facts--Storage

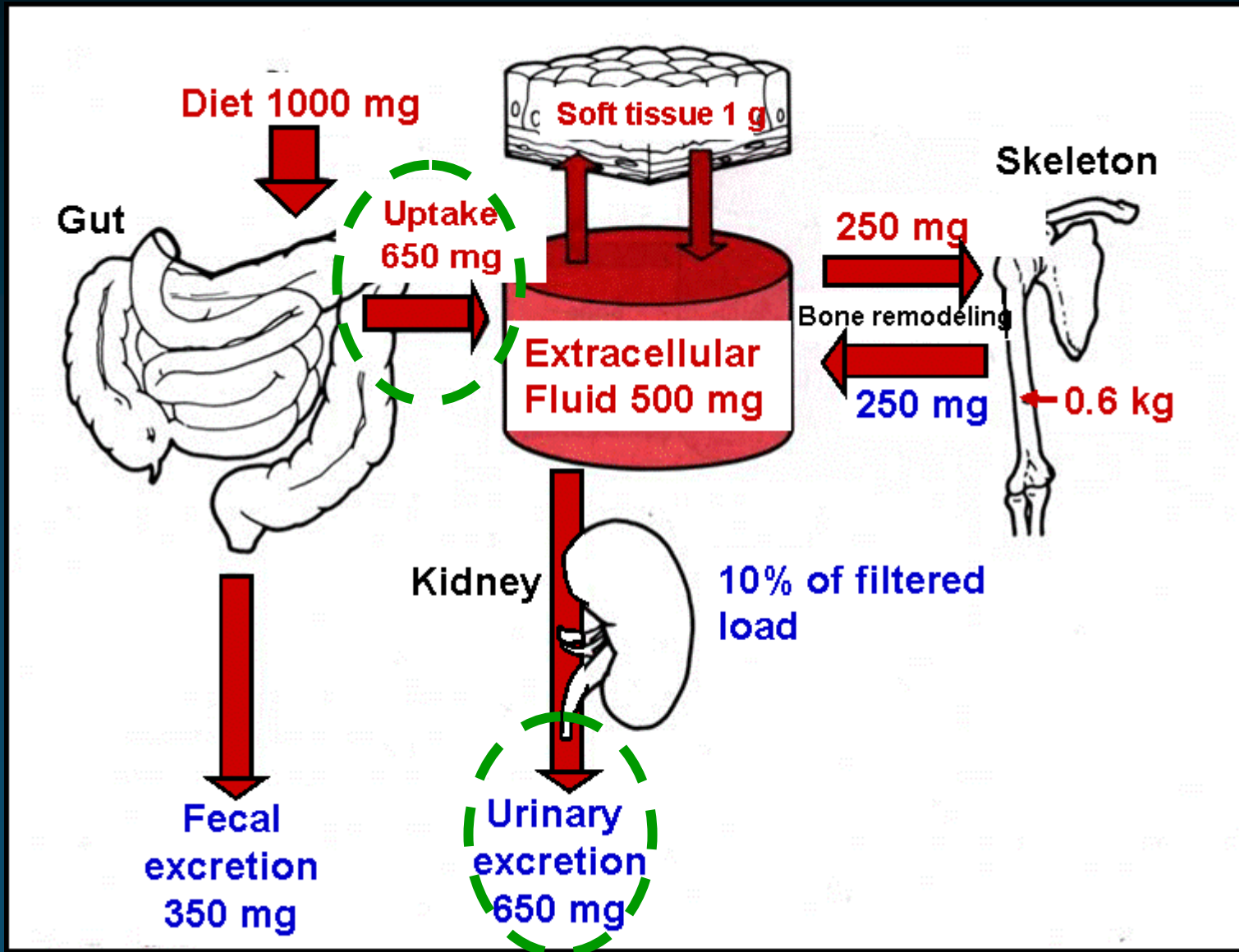
- Hydroxyapatite (bone/teeth)—85%
- Major intracellular anion
 - Shifts between intracellular and extracellular compartments common



Fast Facts--Role

- ◆ High energy phosphate bonds: ATP --> muscle contraction, neuronal transmission, electrolyte transport.
- ◆ Intracellular messenger: cAMP, cGMP.
- ◆ Structural integrity of cell membranes: phospholipids.
- ◆ Genetic material: RNA, DNA and nucleoproteins.
- ◆ Regulates enzymes and cofactors.
- ◆ 2,3-diphosphoglycerate: O₂ unloading.
- ◆ Buffer in serum: $\text{H}^+ + \text{HPO}_4^{-2} \rightleftharpoons \text{H}_2\text{PO}_4^-$
- ◆ Immune and coagulation cascade.
- ◆ Bone matrix.

Overview of Phosphate (and Ca) Flux



The Regulation of Phosphate

- ◆ Internal regulation

Kidneys: filtration, reabsorption - **PTH regulated**
increased excretion with acidosis,
volume expansion, hypokalemia.

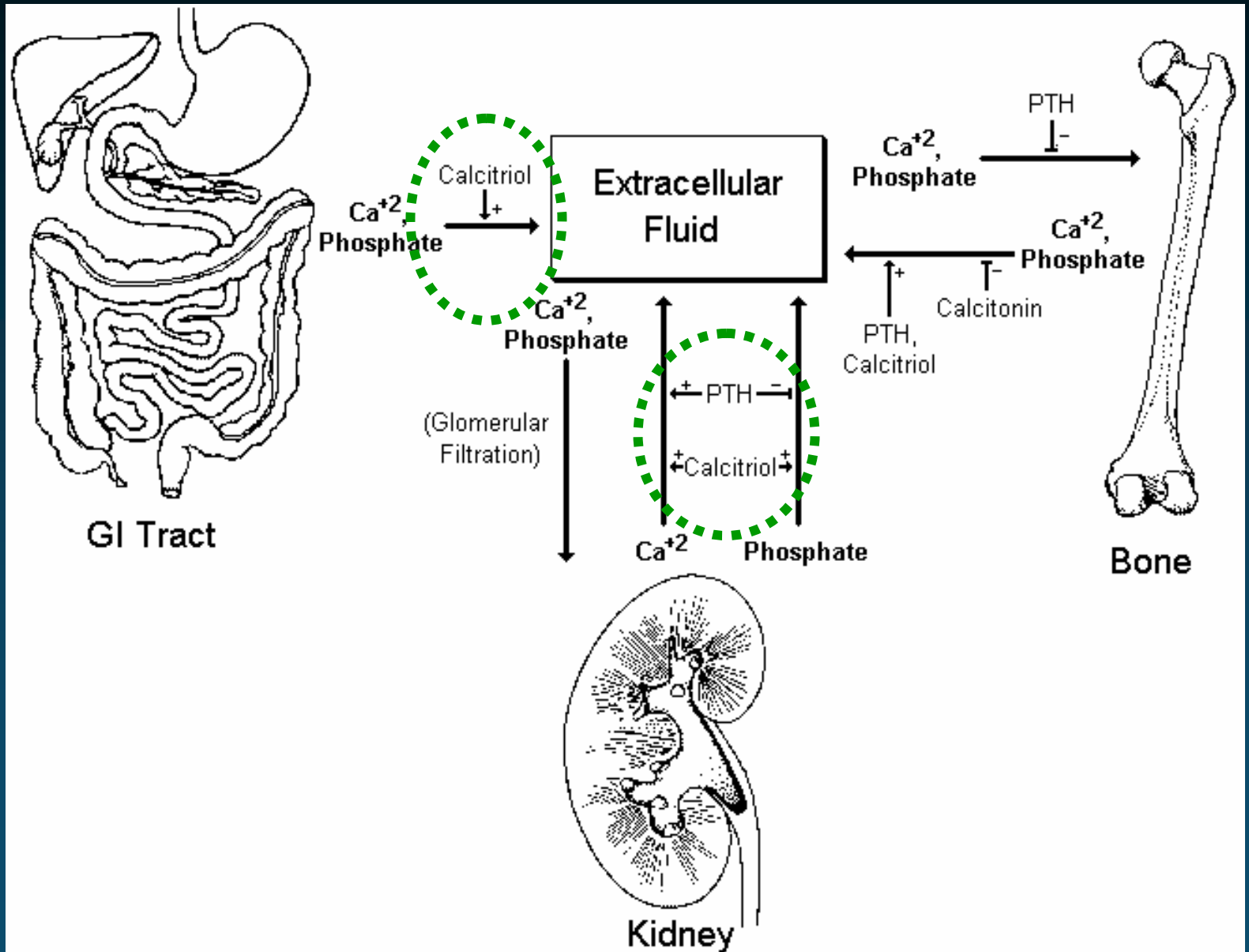
Intestines: 70% passive absorption, 30% active
absorption

Vit D and PTH dependent.

Bone: uptake and release according to serum
calcium. **PTH regulated.**

- ◆ Sources: ubiquitous in fruit, vegetables, meats, dairy

Overview of Phosphate (and Ca) Flux



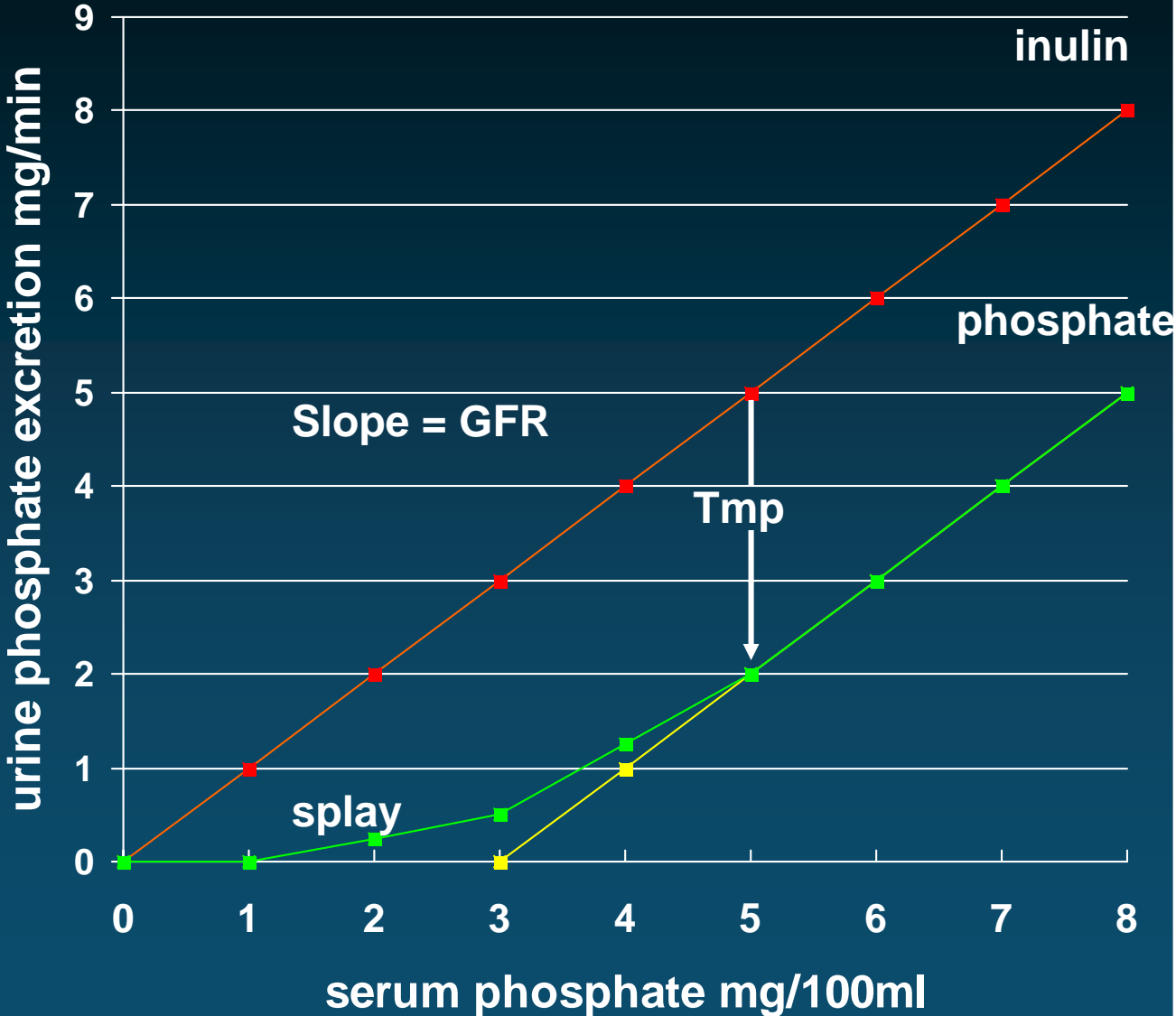
Kidneys and Transport Maximums

- A transport maximum (T_m)
 - you reabsorb as much as you can as long as there are transporters there to do it.
- Transporters can only work so fast
 - they can be overwhelmed
 - when you overwhelm them you urinate out whatever was overwhelming it
- For most substances, the transport maximum is so high that that it does not figure in regulation...but ...

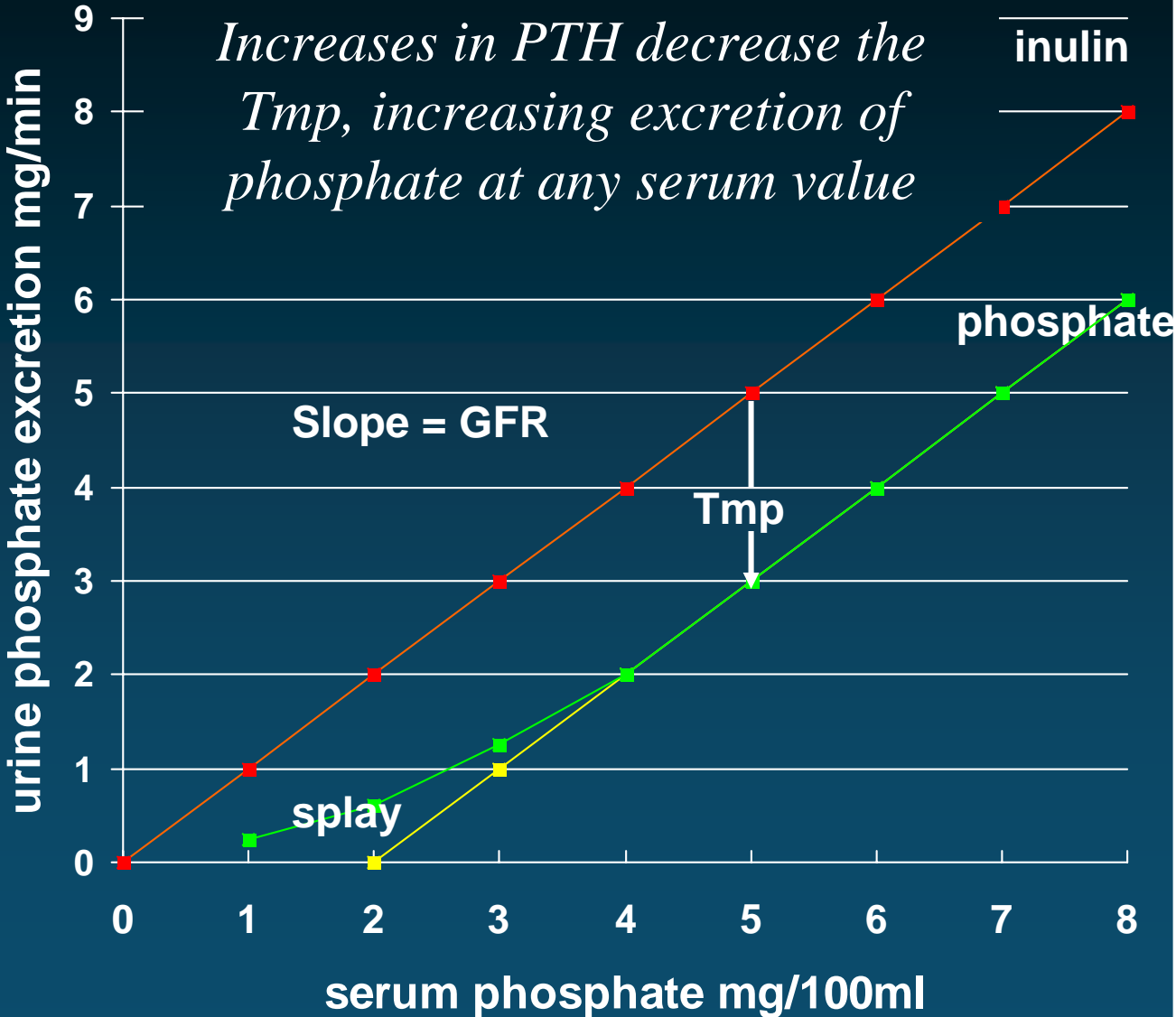
T_m and P (Phosphate)

- The kidney does **regulate** some substances **by means of the T_m mechanism**, including (sulfate and) **phosphate** ions.
- T_m is set at a level whereby the **normal [plasma] causes saturation** so any ↑ above the normal level will be excreted, therefore achieving its plasma regulation.
- Again, phosphate is also subject to PTH regulation, PTH increases lead to ↓ reabsorption.

renal phosphate excretion



renal phosphate excretion



Low Phosphate

- Far more common in the ICU than high phosphate
 - Definition
 - Causes
 - Approach to treatment

Definitions

- Hypophosphatemia—low serum phosphate concentration
 - Mild 2.5-3 mg/dl (.8-.96 mmol/l)
 - Moderate 1-2.5 mg/dl (.32-.8 mmol/l)
 - Severe <1 mg/dl (.32 mmol/l)
- Phosphate depletion—low total body phosphorus

Who gets into trouble?

Increased losses

- Renal: Diuretics (thiazides, loop diuretics)
Renal tubular dysfunction, ARF
Peritoneal dialysis
Hyperosmolar states w/ osmotic diuresis:
DKA (12 to 24h), HHNC
Hyperparathyroidism (high PTH
increases renal phosphate excretion)
Malignancy (high Ca with phosphaturia)
Aldosteronism
Glucocorticoid administration
Associated with ↓K and ↓Mg

Who gets into trouble? Decreased absorption

- GI:

Decreased dietary intake: malnutrition,
EtOH, anorexia nervosa

Phosphate binding antacids

Vitamin D deficiency

Chronic diarrhea

Nasogastric suctioning

Crohn's, radiation enteritis, other malabsorptive
states

Who gets into trouble?

Transcellular shifts

- Transcellular shifts from extracellular to intracellular (follows K^+):

Respiratory alkalosis 2^o....

sepsis, heat stroke, ASA toxicity, NMS,
hepatic encephalopathy, EtOH with-
drawal, HCO_3 administration

Refeeding syndrome

Insulin administration

Beta agonists, catecholamines, HCO_3

Glucose infusion (glucose phosphorylation)

Why hypophosphatemia is bad

- Respiratory
 - Acute failure and ventilator dependence
- Musculoskeletal
 - Muscle weakness, Rhabdomyolysis, Bone demineralization
- Hematologic
 - Hemolysis, failure of phagocytosis & chemotaxis
- Neurologic
 - Δ MS, paresthesias
- Cardiovascular
 - Cardiomyopathy, \downarrow inotropy

Management and Prevention of hypophosphatemia by standing orders

Taylor BE, Huey WY, Buchman TG, Boyle WA, Coopersmith CM.

Treatment of hypophosphatemia using a protocol based on patient weight and serum phosphorus level in a surgical intensive care unit.

J Am Coll Surg. 2004 Feb;198(2):198-204.

Algorithm is available at the
www.medal.org
medical algorithm website
(critical care section)

Hypophosphatemia in hospitalized patients

- Occurs in 2-5% of hospitalized patients
- Incidence rises to 29% in SICU patients
- Association: mortality rates of 20-30%

Baseline data

- 484 patients had phosphorus levels drawn
- 86 patients had serum levels less than 2.2 mg/dl
- Prevalence of hypophosphatemia 18%

Baseline data

- Retrospective review of patients in SICU from January to June, 2001
 - Phosphorus level normal, no supplementation given – 347 patients (no obvious problem, appropriate behavior)
 - Phosphorus level low, phosphorus repleted
 - 64 patients (potential problem number one if repletion inadequate)

Baseline data

- Of 64 patients that received repletion, 47 patients analyzed for efficacy of phosphorus repletion
- 22 (47%) reached normal range after a single dose
- Only 53% success rate in moderate hypophosphatemia
- Only 27% success rate in severe hypophosphatemia
- **More than half the patients examined STILL had abnormal levels after repletion, in keeping with the published literature.**

Baseline data

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 - Phosphorus level low, phosphorus repleted – 47% success rate overall, 27% success rate in severe hypophosphatemia (problem #1)
 - Phosphorus level low, no supplementation given – 22/86 patients with low levels were not given any supplementation (problem #2)

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 - Phosphorus level low, no supplementation given – 22/86 patients with low levels were not given any supplementation (problem #2)
 - **Phosphorus level normal, phosphorus repleted anyway** – 51 patients (51 patients with normal levels repleted, 64 patients with low levels repleted, **problem #3**)

Baseline problems- summary

- More than half of hypophosphatemic patients repleted with a single dose of phosphorus still had low levels 24 hours later
- More than one out of four patients with low levels received no supplementation
- Nearly as many patients with *normal* phosphorus levels received supplementation as those with low levels

Phosphorus repletion grid

Phosphorus level	Weight 40-60 kg	Weight 61-80 kg	Weight 81-120 kg
< 1.0 mg/dl <.32mmol/l	30 mmol Phos IV	40 mmol Phos IV	50 mmol Phos IV
1.0 – 1.7 mg/dl	20 mmol Phos IV	30 mmol Phos IV	40 mmol Phos IV
1.8 – 2.2 mg/dl	10 mmol Phos IV	15 mmol Phos IV	20 mmol Phos IV

If the patient's potassium is < 4.0 use Potassium Phosphate

If the patient's potassium is > 4.0 use Sodium Phosphate

Exclusion criteria

- **Calculated creatinine clearance < 25 ml/min**
- **Serum creatinine >4.0 mg/dl**
- Urine output <30 ml/hr 2 hours before supplementation
- Corrected calcium <7.5 mg/dl
- Corrected calcium x phosphorus > 60 mg/dl
- Receiving phosphorus containing parenteral nutrition
- Actual body weight >120 kg or < 40 kg

Phosphorus repletion protocol -- timeline

- Retrospective group – January, 2001 - June, 2001
- Comprehensive multidisciplinary education program aimed at physicians, nurses, pharmacists
- Prospective group – September, 2001 – February, 2002 (125 patients with serum levels <2.2 mg/dl)
- Post-repletion levels drawn 18-24 hours after supplementation

Patient characteristics

	Age (years)	Gender (M/F)	BMI (kg/m ²)
Retrospective (n=47)	59.3 ±18.6	25/22	25.8 ± 5.9
Prospective (n=111)	54.9 ±17.6	57/56	27.4 ± 4.9
p value	.16	.75	.08

Admitting Diagnoses

Diagnosis	Retrospective (%) n=47	Prospective (%) n=111
Trauma	17 (36%)	44 (40%)
Small/large bowel resection	3 (6%)	6 (5%)
Liver resection or transplant	5 (11%)	1 (1%)
Sepsis	0 (0%)	8 (7%)
Abdominal aortic aneurysm	5 (11%)	10 (9%)
Thermal injury	1 (2%)	7 (6%)
Spinal Fusion	0 (0%)	6 (5%)
Pancreatitis	0 (0%)	1 (1%)
Tumor/mass	9 (19%)	13 (12%)
General surgery	7 (15%)	15 (14%)

Key elements to a successful repletion protocol

- Identify the problem
 - Does current standard of care adequately fix hypophosphatemia?
 - Are low phosphorus levels ignored?
 - Are normal phosphorus levels treated?
- Does the protocol work?

Results

Pre-supplementation serum phosphorus level (total number of patients)	Levels repleted with a single intravenous dose (%)
<1.5 mg/dl (16)	10 (63%)
1.5 – 2.2 mg/dl (95)	74 (78%)

Effect of protocol

	Retrospective success (%)	Prospective success (%)
<1.5 mg/dl	27	63
1.5-2.2 mg/dl	53	78
Overall	47	76

P<0.005 all groups

Effect of BMI and successful repletion

BMI range (total # patients in this range)	Successfully repleted with one dose N (%)
< 18.5 (3)	2 (67%)
18.5 – 24.9 (31)	23 (74%)
25.0 – 29.9 (45)	33 (73%)
30 – 40 (32)	26 (81%)

Effect of protocol on inaction

- Retrospective group -- 22/86 patients with low levels not given any supplementation (26%)
- Prospective group – 14/125 patients with low levels not given any supplementation (11%)
- $P=0.008$

Effect of protocol on inappropriate action

- Retrospective group – 51 patients given supplementation for normal phosphorus levels
 - Four of these developed hyperphosphatemia 8%
 - Two required treatment
- Prospective group – 16 patients given supplementation for normal phosphorus levels
 - None required treatment 0%

Summary

- An aggressive repletion protocol based upon patient weight and serum phosphorus level successfully treats both moderate and severe hypophosphatemia
- The repletion protocol **prevents inaction** (failure to replete low levels)
- The repletion protocol **prevents inappropriate action** (repletion of normal levels)

High Phosphate

- Hyperphosphatemia much less common than hypophosphatemia
- Generally requires two states
 - Renal dysfunction or outright failure; AND
 - Phosphate source in excess of normal dietary intake (endogenous or exogenous)
- Hyperphosphatemia defined as >4.5 mg/dl (1.45 mmol/l), and becomes clinically significant around 5 mg/dl (1.62 mmol/l)

The frequent causes of hyperphosphatemia

- Renal
 - Failure
 - Increased resorption (low PTH, thyrotoxicosis)
- Endogenous phosphate release
 - Rhabdomyolysis, tumor lysis, hemolysis
- Exogenous source
 - Phosphate enemas as laxatives (we see this...)
 - Bisphosphonate therapy

Hyperphosphatemia presents as hypocalcemia

- Ca x P precipitation
- Interference with PTH-mediated resorption of bone
- Decreases Vitamin D levels

Thus the presentation of hyperphosphatemia typically includes that of hypocalcemia:

- Muscle cramps, tetany, hyperreflexia, seizures, arrhythmias...

When you encounter a patient in the ICU with hyperphosphatemia...

- If life-threatening, immediate dialysis
- If there is some renal function,
 - Saline and acetazolamide (proximal tubule effect)
- If not life threatening, oral phosphate binders, especially sevelamer (Renagel™)

Conclusions

- [Phosphate]: balance between source and renal function
- Low phosphate common in the ICU and can be addressed by standing protocol
 - “Two kidneys + one excellent nurse can compensate for many doctors’ orders”
 - Failure to create standing protocol may prolong ICU care
- High phosphate less common, presents as hypocalcemia, and may require immediate treatment

Thank you!