



**LIFE-THREATENING HYPOCALCAEMIA FOLLOWING FIRST  
ZOLEDRONIC ACID TREATMENT FOR OSTEOPOROSIS**

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## Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

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- An emerging potent bisphosphonate for treating osteoporosis
- Increasing use in osteoporosis management for high risk patients with contraindication, intolerance or treatment failure to oral bisphosphonates
- Rare severe adverse events which are not well established to date for its use in osteoporosis

# A case report

- 91 year old female
- Residential care respite
- Background of mild cognitive impairment, hypothyroidism, IHD, hypertension, pernicious anaemia and macular degeneration
- Medications
  - Risperidone 0.5 mg/d, thyroxine 150 µg/d, aspirin 100 mg/d, diltiazem 60 mg bd, ramipril 5 mg/d, simvastatin 10 mg/nocte, vitamin B12 injections

## Admission 3 weeks earlier

- Fractures of right pubic rami following a fall at home
- Intercurrent urosepsis
- Poor functional and mobility recovery
- Poor oral intake
- Zoledronic acid 4 mg IV given before discharge to nursing home respite (2 weeks prior to representation)

## Current admission

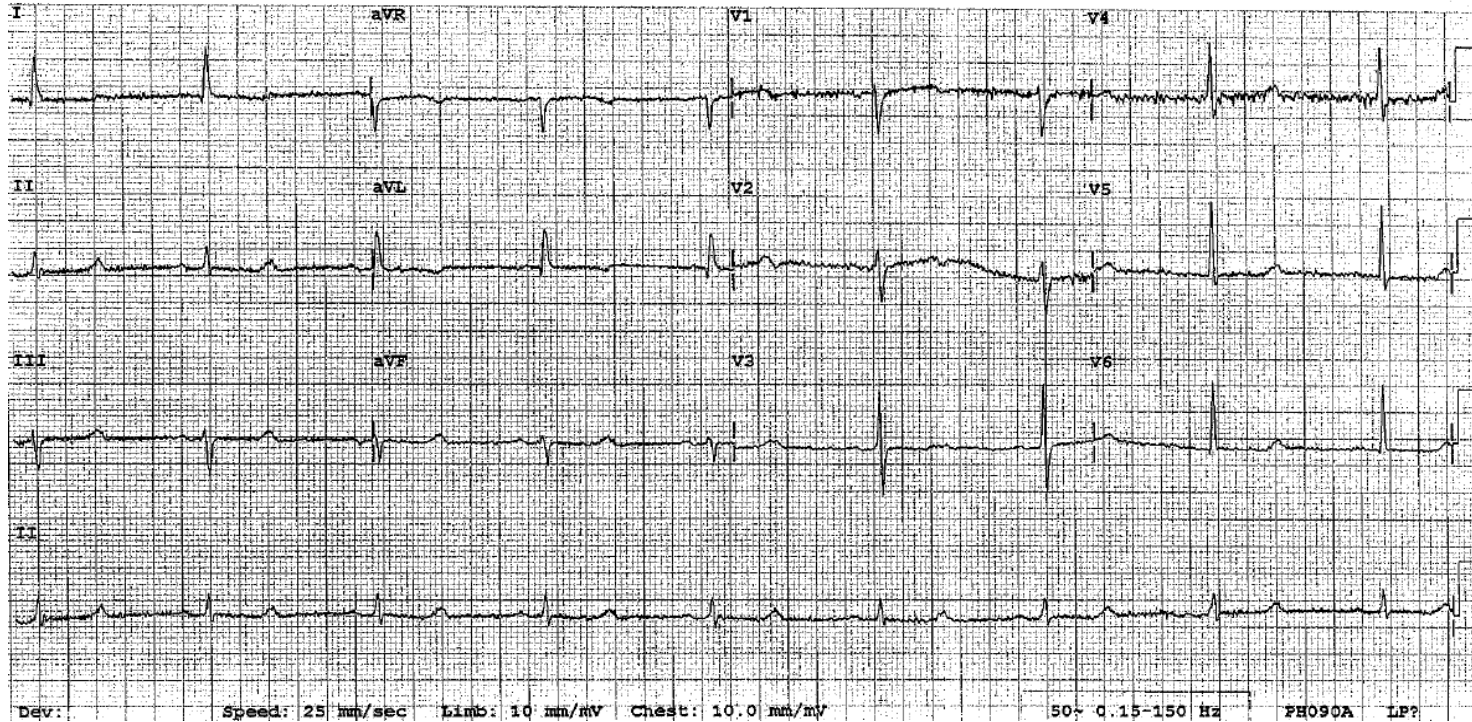
- Found by nursing home staff with reduced level of consciousness, unwell prior few days
- On arrival of paramedics, systolic BP 70 mmHg, HR 25/ minute and GCS 3
- Fluid resuscitation and chronotropic support with IV atropine and adrenaline boluses and isoprenaline infusion
- Early restoration of sinus rhythm, heart rate and blood pressure





Rate 52 . AGE IS NOT ENTERED, ASSUMED TO BE 50 YEARS OLD FOR PURPOSE OF ECG INTERPRETATION  
. SINUS RHYTHM  
PR 180 . BORDERLINE T ABNORMALITIES, ANT-LAT LEADS  
QRSD 100  
QT 504  
QTc 469

--AXIS--  
P 23  
QRS -14  
T 115

Unconfirmed Diagnosis



- 
- Corrected serum calcium 1.7 mmol/L (2.19 3 weeks earlier)
  - Examination limited by confusion
    - General examination unremarkable
    - Laryngospasm but no tetany elsewhere
  - IV calcium chloride, 2 ampoules, in Emergency Department, further 1 ampoule on day 2
  - Oral calcium carbonate 1200mg bd  
Calcitriol titrated to 0.5µg bd
  - Diltiazem ceased

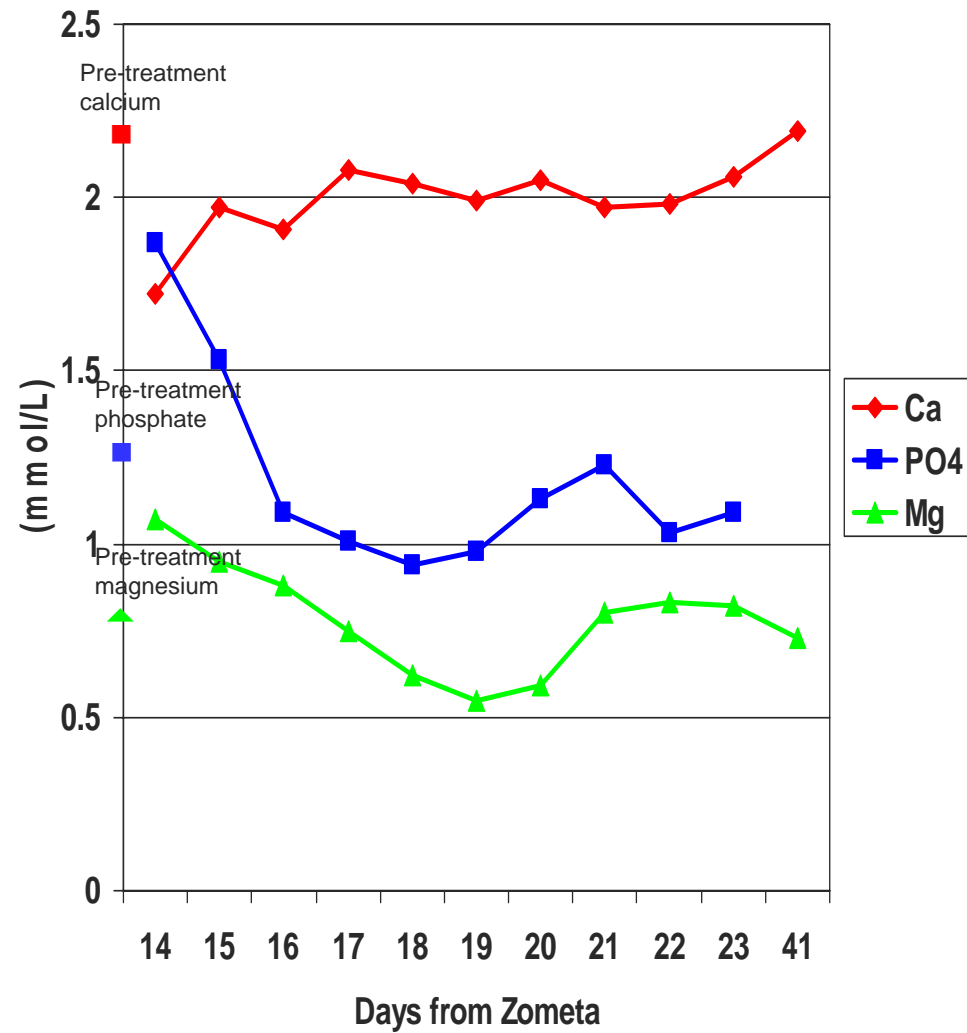


Corrected serum calcium	1.7 mmol/L (2.25-2.58)
Serum phosphate	1.87 mmol/L (0.8-1.5)
Serum magnesium	1.07 mmol/L (0.74-1.03)
PTH	12.6 pmol/L (0.5-5)
25(OH)Vitamin D	22 nmol/L (>50)
ALP	151 U/L (38-126)
Serum creatinine	92 µmol/L (eGFR 53)
Urine calcium/creatinine	<0.1 (<0.8)

## Differential diagnoses of severe hypocalcaemia

- Bisphosphonate side effect
- Vitamin D deficiency
- Poor dietary calcium
- Hyperphosphataemia
- ? Reduced PTH response

# Time course of changes in serum calcium, phosphate and magnesium following Zometa treatment



## Further treatment and assessment

- Renal function normalized with rehydration during admission
- Intercurrent urosepsis, delirium
- Coeliac disease excluded serologically
- Serum protein EPG and immunofixation and common malignancy markers negative



- Discharge 10 days later
  
- At clinic review 3 weeks later
  - Calcitriol weaned
  
  - Ergocalciferol commenced at 2000 IU/d
  
  - Calcium carbonate continued at 1200 mg/d

Corrected serum calcium	2.19 mmol/L (2.25-2.58)
Serum phosphate	1.21 mmol/L (0.8-1.5)
Serum magnesium	0.73 mmol/L (0.74-1.03)
PTH	7.7 pmol/L (0.5-5)
ALP	112
Serum creatinine	70 µmol/L

## Conclusion

- Severe hypocalcaemia following first zoledronic acid treatment
- Highly effective therapy for osteoporosis
- A common clinical setting

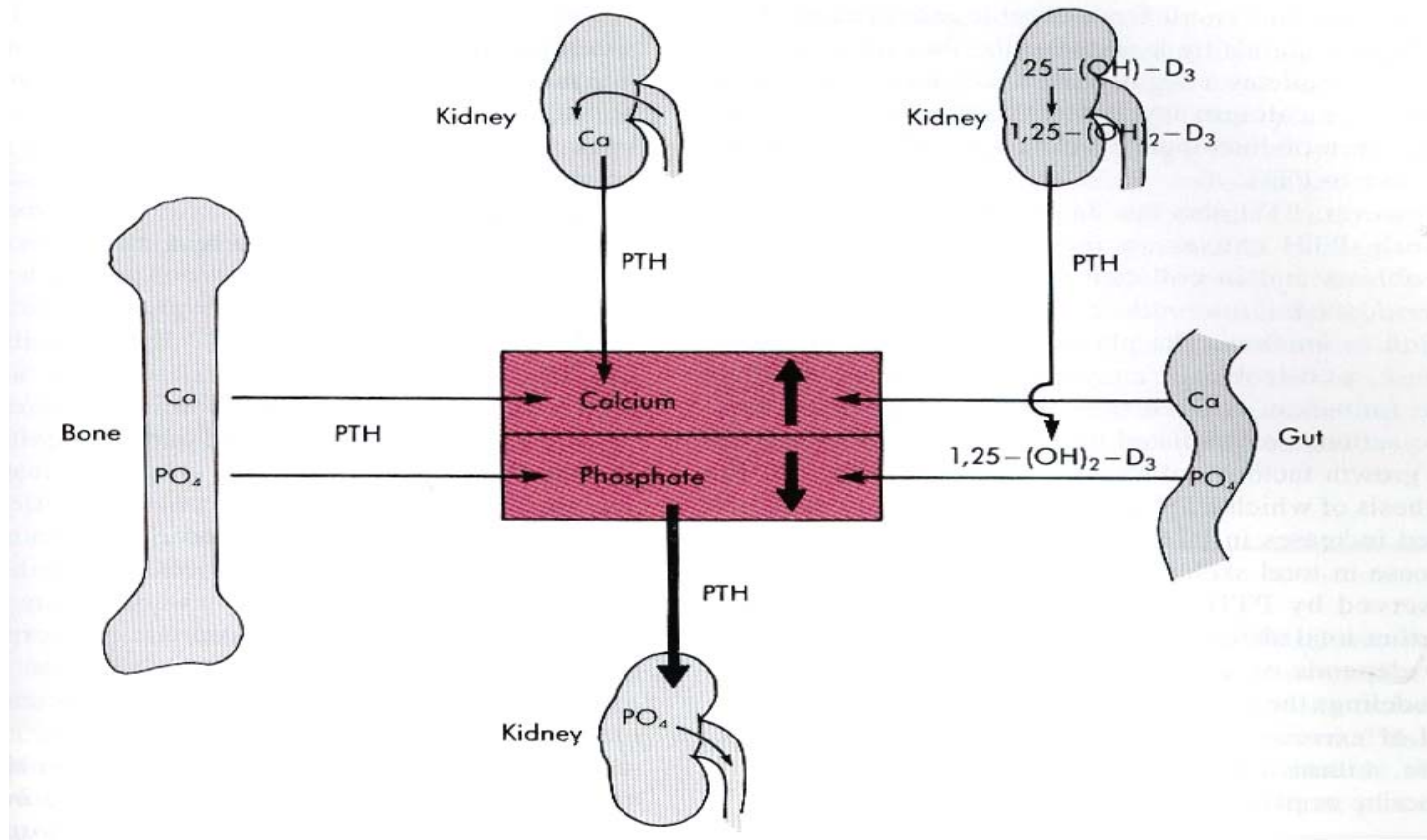
# Issues

- What are the mechanisms of bisphosphonate-induced hypocalcaemia?
- What is the incidence of hypocalcaemia associated with zoledronic acid treatment for osteoporosis and the possible risk factors of severe hypocalcaemia in this setting?
- What measures should have been instituted in this case to minimize the risk of severe hypocalcaemia associated with IV bisphosphonate treatment?

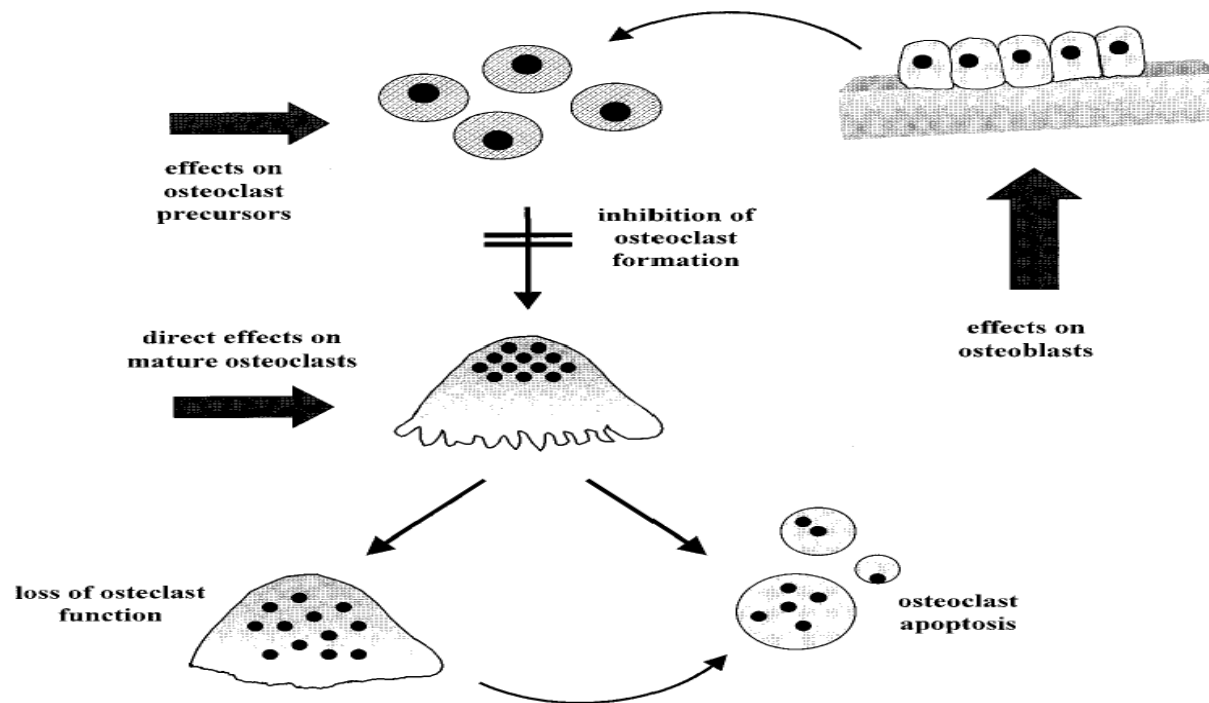


## **Mechanisms of bisphosphonate-induced hypocalcaemia**

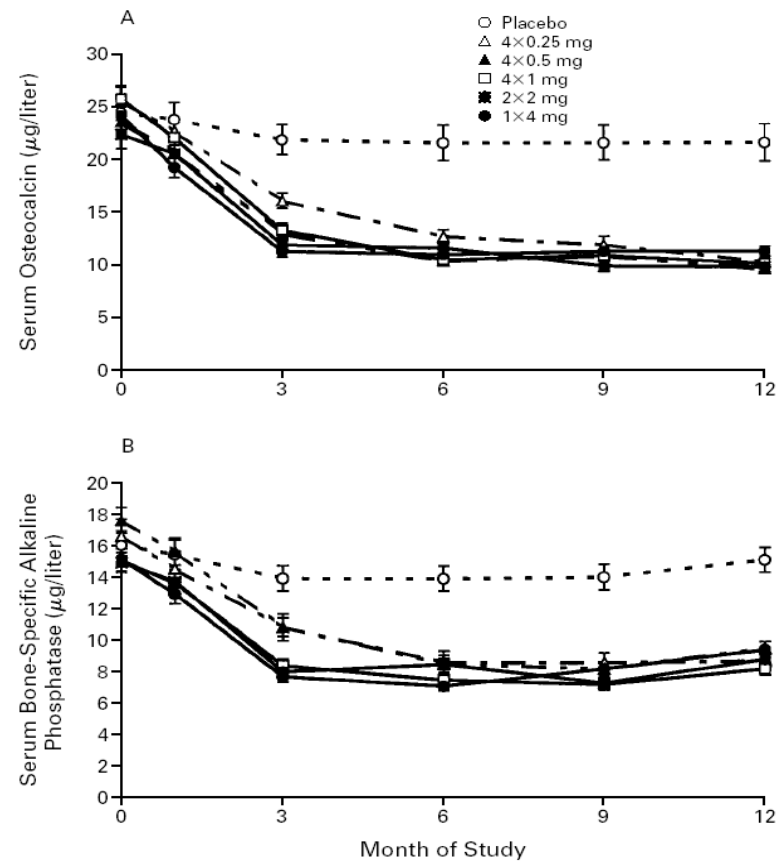
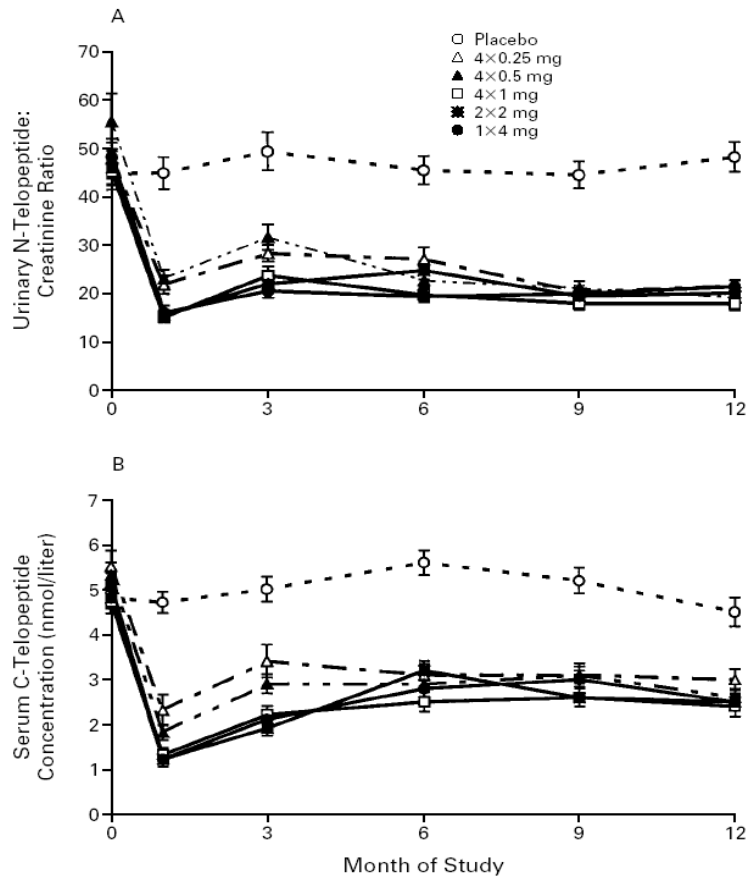
# Calcium homeostasis



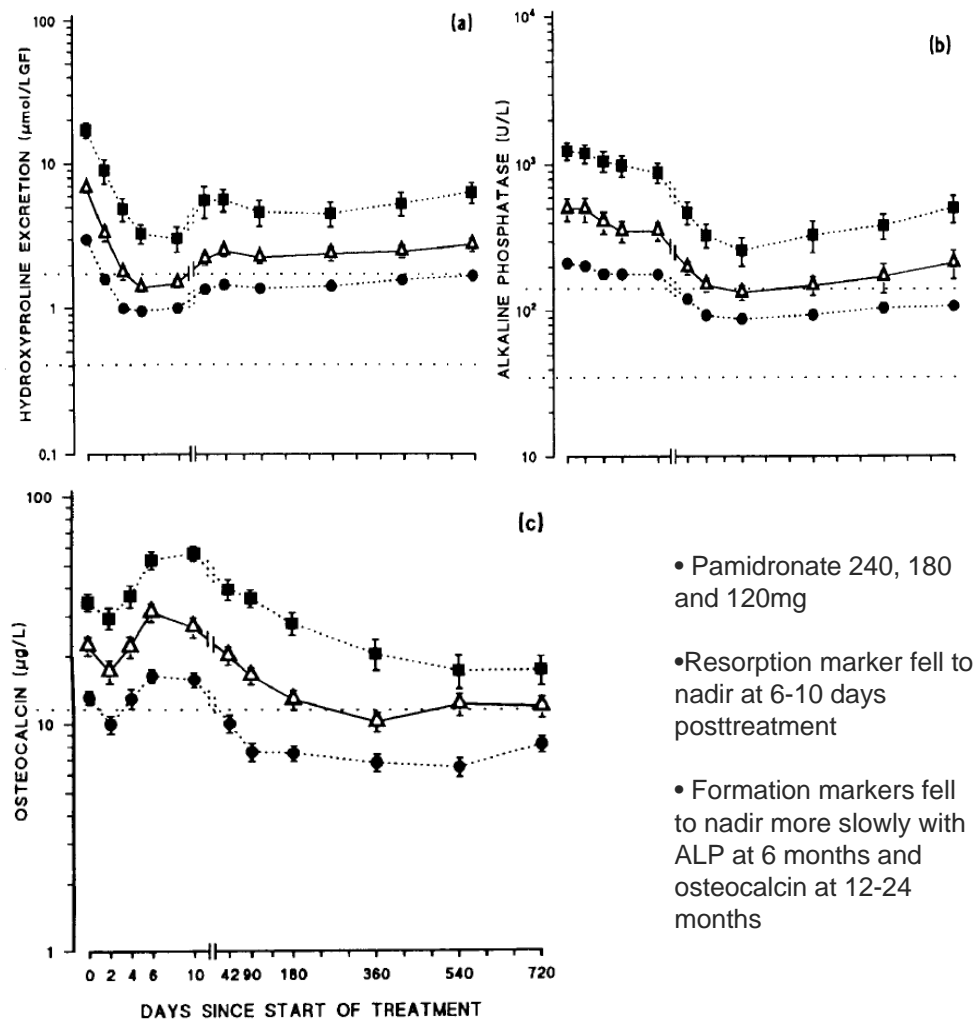
# Bisphosphonates: mechanisms of action (1)



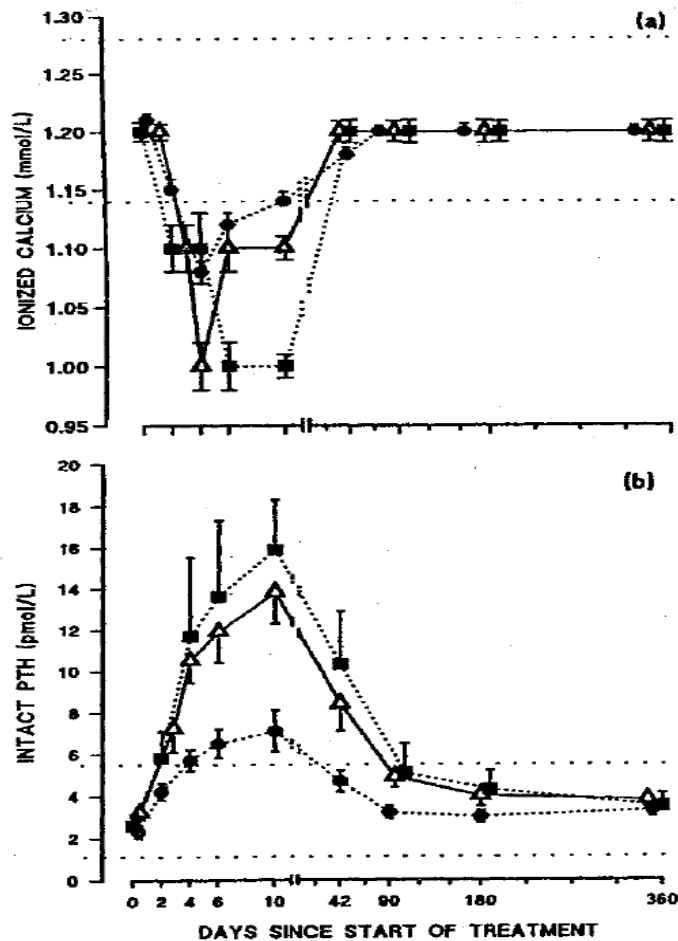
# Zoledronic acid: biochemical changes



# Pamidronate: biochemical changes

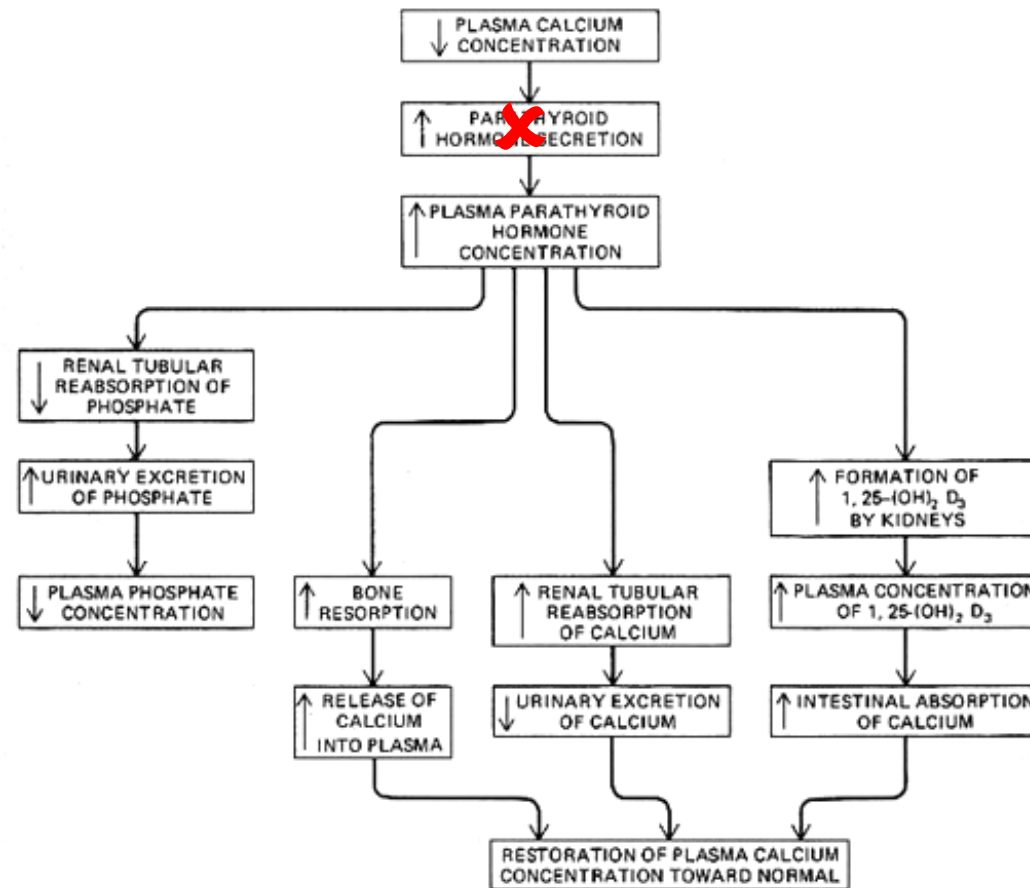


# Bisphosphonates: calcium homeostasis

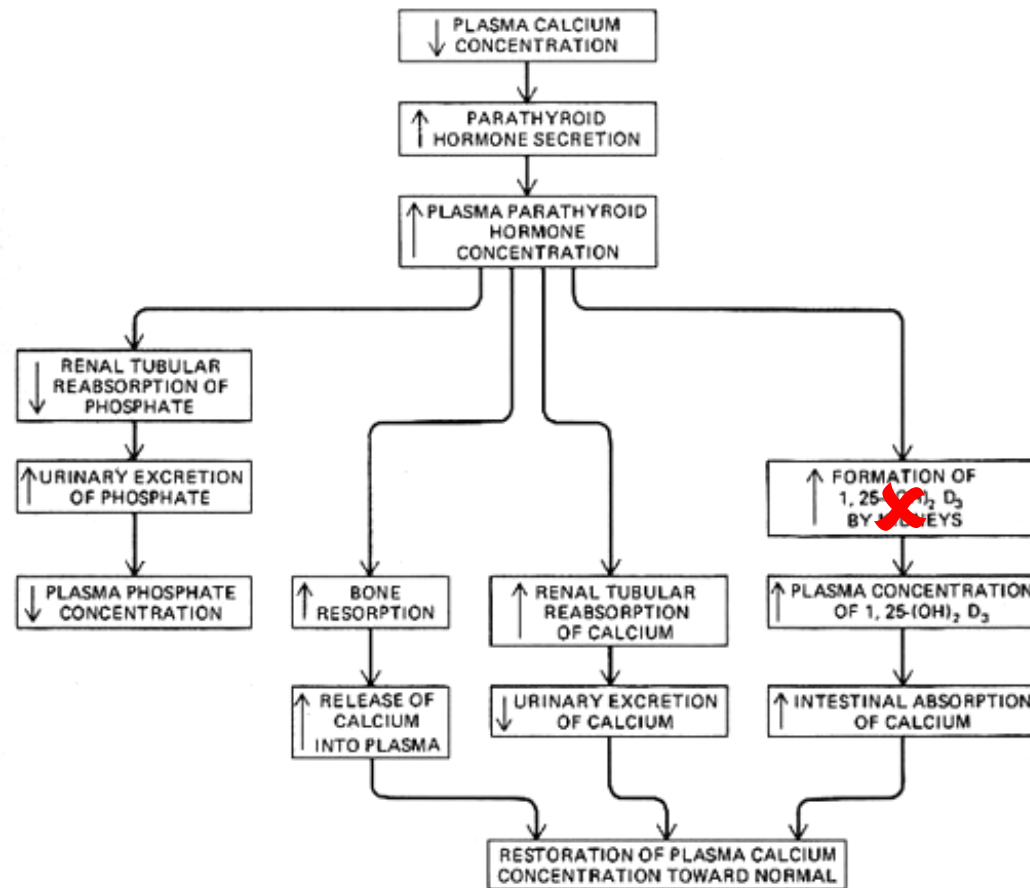


- Significant decrease in ionized calcium from pretreatment value to nadir at day 4-10 for all groups (240mg, 180, and 120)
- Greater fall with higher pamidronate doses (240mg or 180mg vs 120mg,  $p < 0.05$ )
- Return to pretreatment values before week 6 posttreatment for 180mg and 240mg pamidronate dose, and before 3 months for 120mg dose
  
- Significant increase in PTH peaking at day 10 posttreatment for all pamidronate doses
- Significant correlation between change in PTH and change in serum calcium in the first 6 months

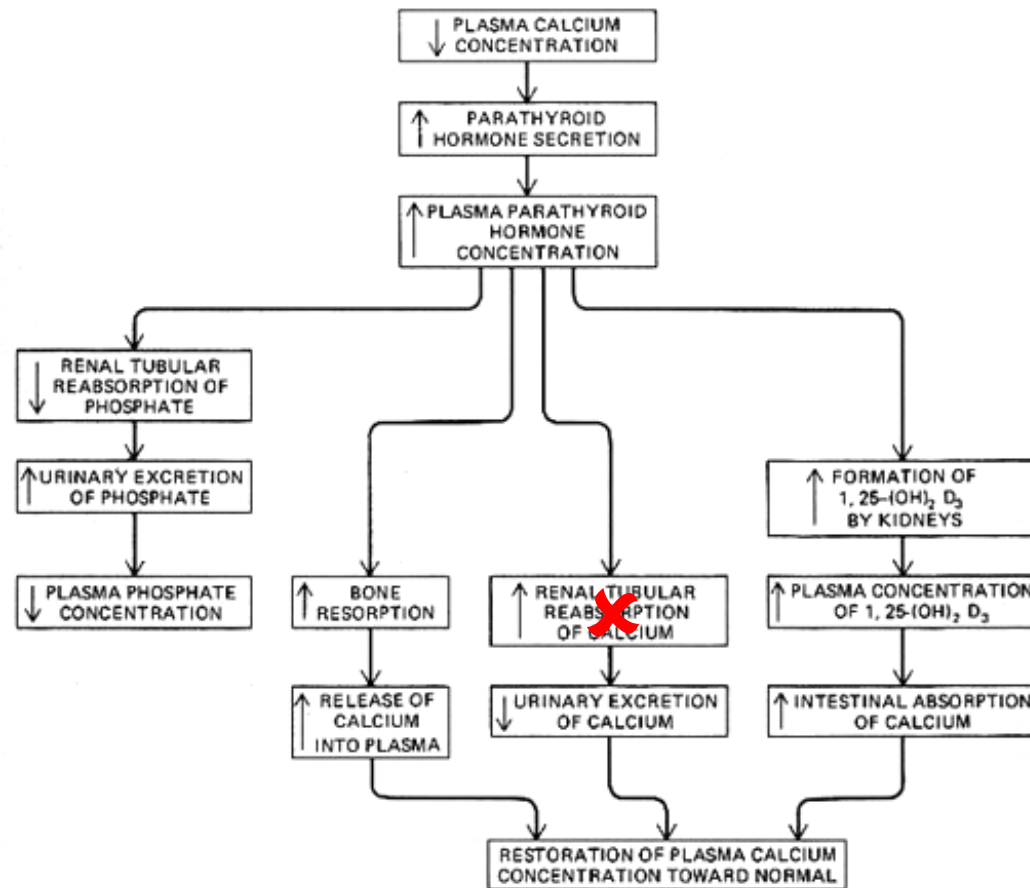
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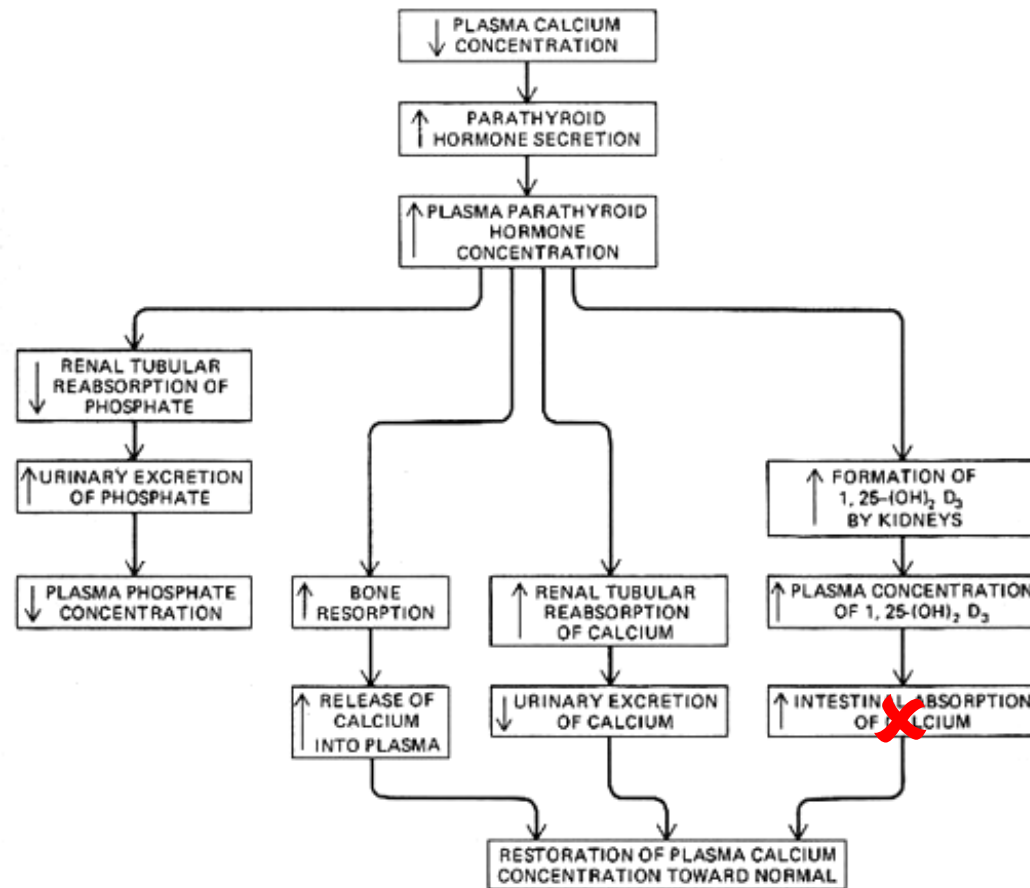
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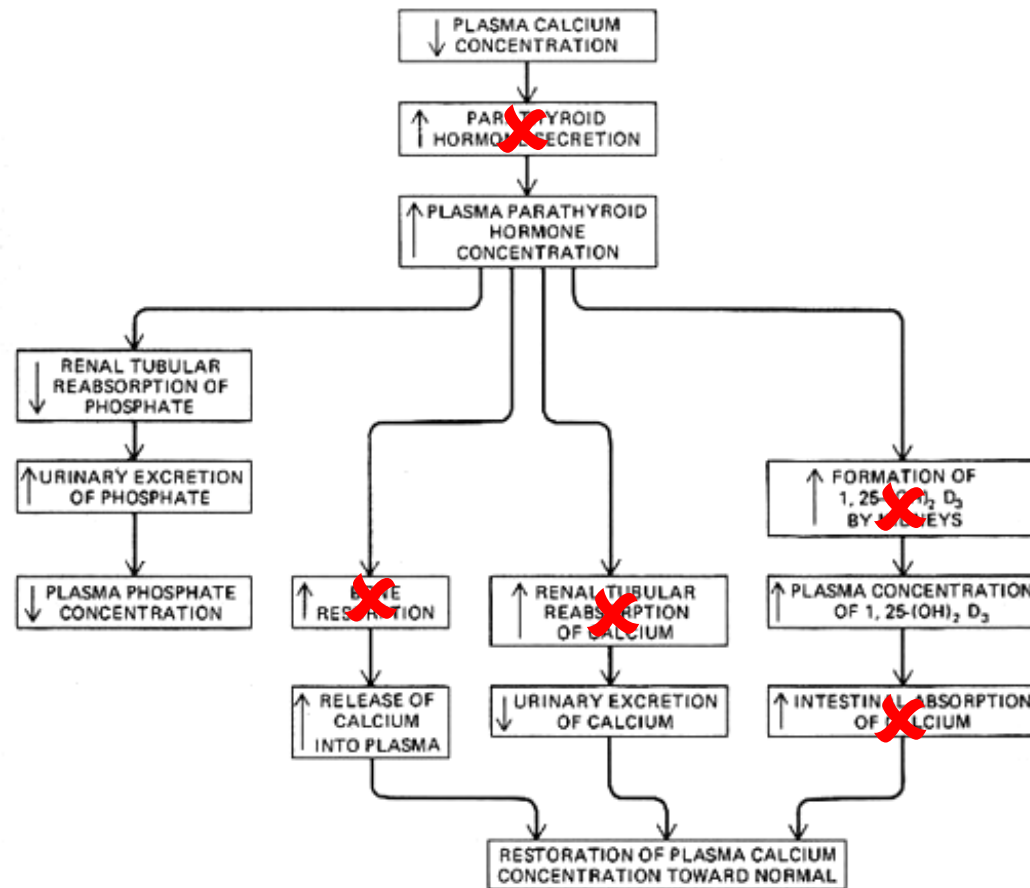
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# Mechanisms of bisphosphonate-induced hypocalcaemia





## **Incidence and Risk Factors**

## Osteoporosis and Bisphosphonate-induced Hypocalcaemia

- In recent large interventional trials of zoledronic acid in osteoporosis, the incidence of hypocalcaemia varies 0.3-1.3%
  - Reported change in mean serum calcium level ranges 0.05 – 0.08 mmol/L in the first month post-treatment
- Symptomatic bisphosphonate-induced hypocalcaemia in osteoporosis appears rare

## Osteoporosis and Severe Bisphosphonate-induced Hypocalcaemia

Author	Age	Bisphosphonate	Baseline calcium (mmol/l)	Lowest calcium (mmol/l)	Recovered calcium (mmol/l)	Magnesium	PTH	25(OH)vitD	Renal function
Hoang et al 2008	91	Zoledronic acid	2.2	1.7	2.2	0.6 mmol/l	12 pmol/l (0.5-5)	22 nmol/l (>50)	Cr 97µmol/l
Maalouf et al 2006	75	Alendronate 10 mg/d	2.2	1.3 at 3 months	2.0 at 4 months	0.6 mmol/l (1.3-1.9)	94 pg/ml (10-65)	3 ng/ml (20-60)	Cr 0.7 mg/dl
Richmond et al 2005	67	Risedronate	2.5	1.5 at day 1	Discharge at day 8 post-op		44 pg/dl at 6 weeks post-op		
Dogru et al 2005	21	Risedronate 35mg/w	2.2	1.5 at day 3		0.71 mmol/l	139 pg/ml (10-65)		Cr normal
Rosen et al 2003	52	Pamidronate 60mg	Normal baseline	1.2 at week 3	1.98 at 6 months		300 pg/ml (10-65)	7 ng/ml (9-55)	
Maclsaac et al 2002	92	Alendronate 70 mg/w		1.82 at week 6	2.3 at week 3	Normal	48.2pmol/l (1.1-6.8)	16 nmol/l (30-110)	Cr normal
Kashyap et al 2000	68	Alendronate 5 mg/d		Ionized calcium 0.8 (1.1-1.4) at day 10	Ionized calcium 1.0 at discharge		14 pg/ml (10-65)	Normal	
Schussheim et al 1999	70	Alendronate 5 mg/d		0.98 at week 2	1.8 at discharge	1.5 mg/dl (1.5-2.3)	15 pg/ml (10-65)		
Campisi et al 1999	24	Alendronate 10 mg/d	Ionized calcium 1.3 (1.2-1.3)	Ionized calcium 1.03 at 6 hours post-op	Ionized calcium 1.21 at day 4 post-op	0.54 mmol/l (0.75-1.05)	25.2 pmol/l (1.1-6.9)	22 nmol/l (20-200)	

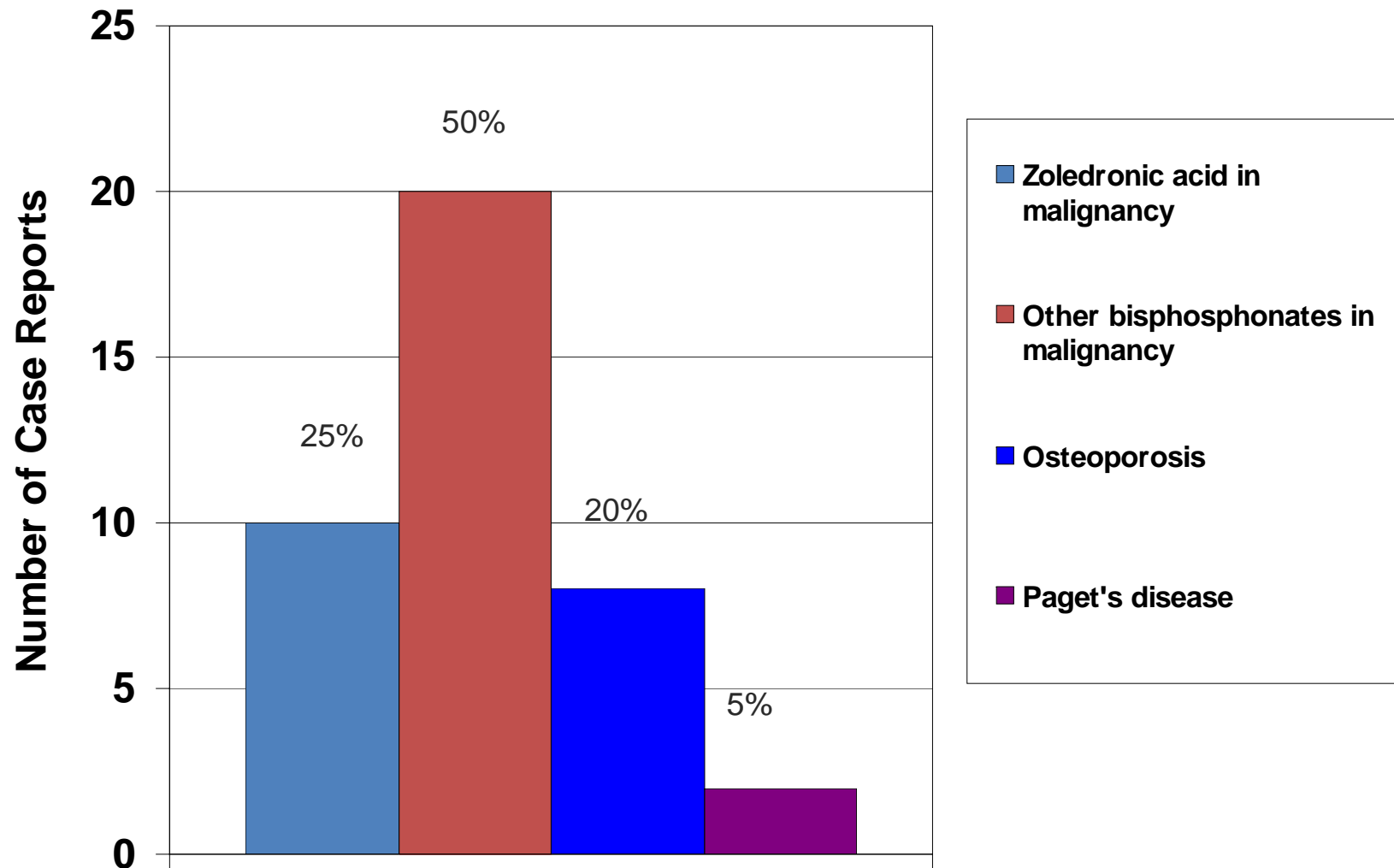
## Malignancy and Severe Bisphosphonate-induced Hypocalcaemia

- In the setting of malignancy, the incidence of hypocalcaemia associated with zoledronic acid is reported to be 5-10%
  - Incidence of grade 3 hypocalcaemia (1.5-1.75 mmol/L) is 1%
  - No reported grade 4 (< 1.5 mmol/L) hypocalcaemia

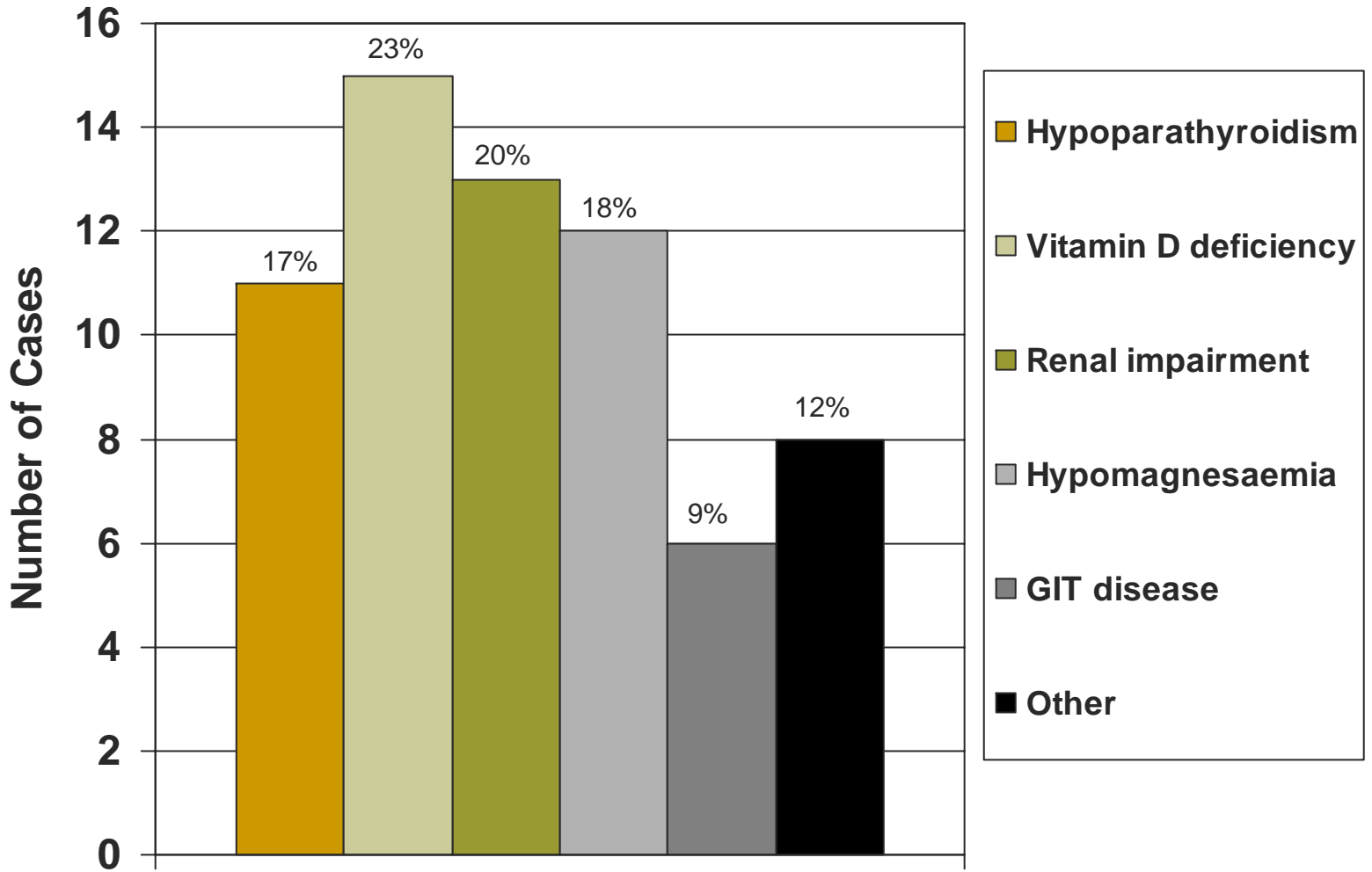
## A literature review of case reports of severe bisphosphonate-associated hypocalcaemia

- 40 of case reports in Medline and Pubmed databases
- Earliest case report by Jodrell DI et al in Lancet 1987
- In 32 of 40 cases (80%), one or more defects of calcium homeostasis were identified
- In 20 of 28 cases (70%) in which IV bisphosphonate was used, severe hypocalcaemia occurred after a first treatment

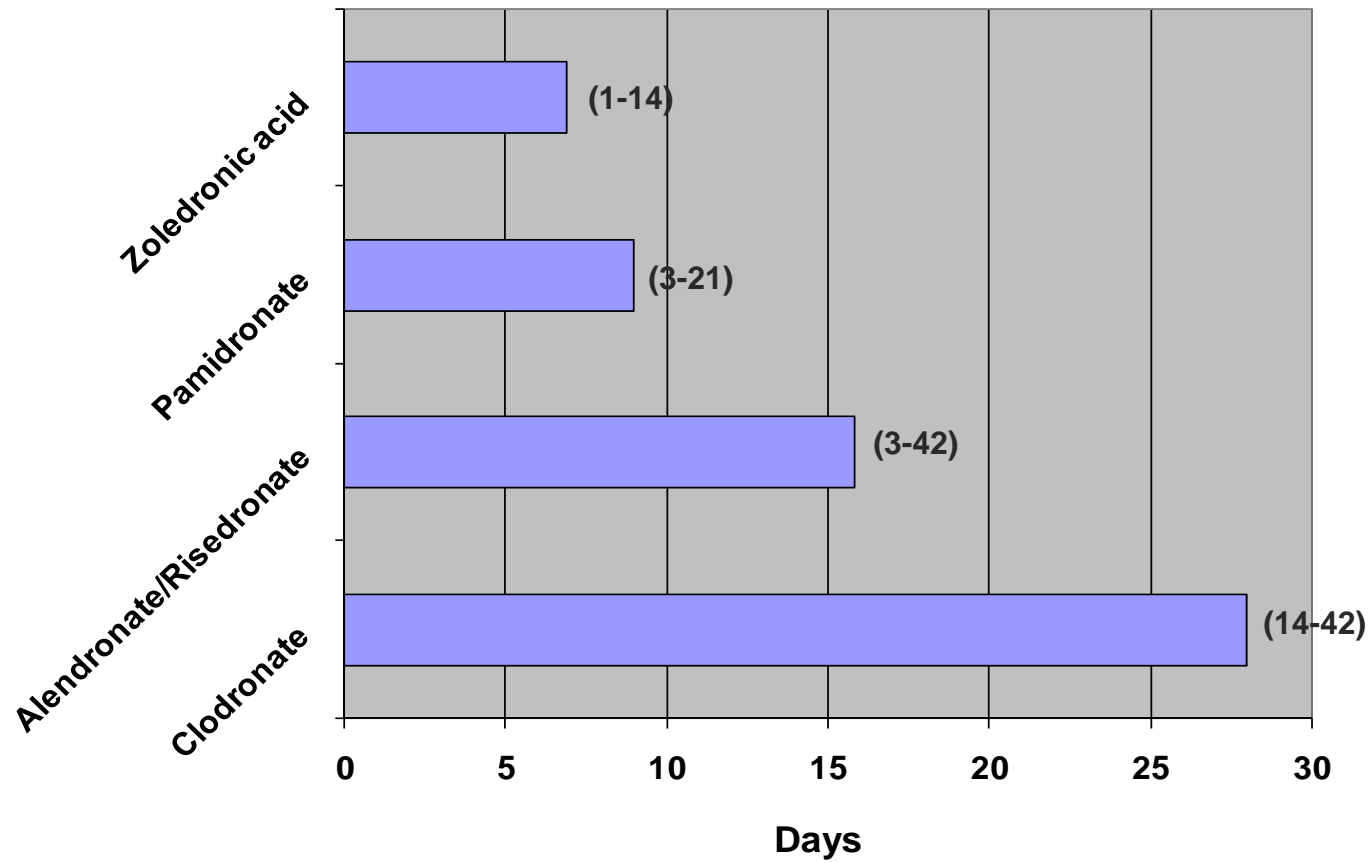
## Underlying Disease



# Compensatory defect



Mean time to trough serum calcium level after commencement of bisphosphonate



## A suggested strategy to minimize the risk of hypocalcaemia following zoledronic acid for osteoporosis – lessons from case reports

- Assess calcium homeostasis before each treatment
  - Corrected serum calcium, phosphate, magnesium, PTH, 25(OH)vitamin D, and creatinine
- Correct vitamin D deficiency before bisphosphonate treatment and continue calcium and vitamin D supplementation during treatment
- In high risk patients (eg. hypoparathyroidism, renal impairment), reassess serum calcium in the first week post-treatment and further as required

## Finally returning to our patient...

- What can we offer this patient for ongoing osteoporosis management ?
  - ? Rechallenge with IV bisphosphonate once vitamin D replete
  - ? Oral bisphosphonate
  - ? Strontium renalate (Protos)
  - Multidisciplinary fall prevention strategies
  - (?Hip protectors)