

Minicorso 3

Emergenze endocrine: ipocalcemia e ipercalcemia

Real clinical practice

E. Solaroli

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni non ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

Real clinical practice

agosto 2011

Roberto, 45 anni
ricoverato in chirurgia
maxillo-facciale in
attesa di asportazione
di granuloma riparativo
a cellule giganti della
mascella



Real clinical practice

PTH 1524 pg/ml



Real clinical practice

PTH 1524 pg/ml

calcio	18.4 mg/dl
fosforo	2.3 mg/dl
creatinina	2.7 mg/dl

Real clinical practice

- collaborante
- riferisce → astenia
poliuria
nausea
dolori ossei



Real clinical practice

- collaborante
- riferisce → astenia
poliuria
nausea
dolori ossei
- non ha parenti di 1° viventi
- madre deceduta a 61 anni per ca mammella
- padre deceduto a 65 anni per ca renale



Real clinical practice

- in età giovanile ha praticato il ciclismo a livello agonistico
- tonsillectomia
- appendicectomia
- nel 2010 comparsa di ascesso dentale
- nel 2011 espansione della lesione con sublussazione degli elementi dell'arcata dentale superiore

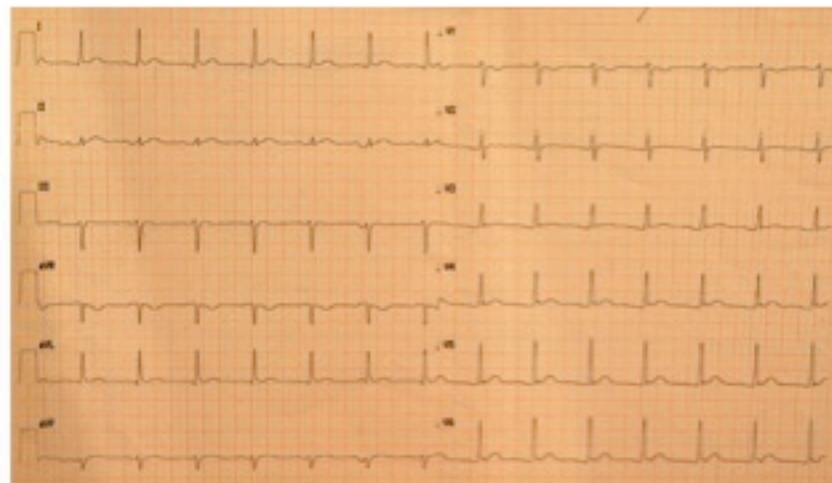


Real clinical practice

- cute pallida
- mucose asciutte
- toni cardiaci validi e ritmici
- Fc 84 bpm, PA 140/90 mmHg
- addome teso, trattabile
- MV normotrasmesso

Real clinical practice

- cute pallida
- mucose asciutte
- toni cardiaci validi e ritmici
- Fc 84 bpm, PA 140/90 mmHg
- addome teso
- MV normotrasmesso



- ritmo sinusale
- alterazioni aspecifiche della RV

Real clinical practice

- posizionato catetere vescicale
- accesso venoso periferico con fisiologica in continuo 200 cc/h, mantenendo una diuresi di 100-150 ml/h
- calcitonina 4 UI/kg peso corporeo im ogni 12 ore

Real clinical practice

- posizionato catetere vescicale
- accesso venoso periferico con fisiologica in continuo 200 cc/h, mantenendo una diuresi di 100-150 ml/h
- calcitonina 4UI/kg peso corporeo im ogni 12 ore
- bisfosfonati?

Real clinical practice

Acido zoledronico: scheda tecnica

Osteonecrosi

Osteonecrosi della mandibola/mascella

L'osteonecrosi della mandibola/mascella è stata riportata come evento non comune negli studi clinici e nel periodo post-marketing in pazienti in trattamento con Zometa.

L'inizio del trattamento o di un nuovo ciclo di trattamento deve essere rimandato in pazienti con lesioni aperte non rimarginate dei tessuti molli del cavo orale, eccetto nelle situazioni di emergenza medica. Prima di iniziare il trattamento con bisfosfonati in pazienti con fattori di rischio concomitanti, si raccomanda un esame odontoiatrico con le appropriate procedure odontoiatriche preventive ed una valutazione del beneficio-rischio individuale.

Real clinical practice

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- accesso venoso periferico con fisiologica in continuo 200 cc/h, mantenendo una diuresi di 100-150 ml/h
- calcitonina 4 UI/kg peso corporeo im ogni 12 ore

Real clinical practice

- posizionato catetere vescicale
- accesso venoso periferico con fisiologica in continuo 200 cc/h, mantenendo una diuresi di 100-150 ml/h
- calcitonina 4 UI/kg peso corporeo im ogni 12 ore
- steroidi?

Real clinical practice

- posizionato catetere vescicale
- accesso venoso periferico con fisiologica in continuo 200 cc/h, mantenendo una diuresi di 100-150 ml/h
- calcitonina 4UI/kg peso corporeo im ogni 12 ore
- prednisone 25 mg/die

Real clinical practice

- posizionato catetere vescicale
- accesso venoso periferico con fisiologica in continuo 200 cc/h, mantenendo una diuresi di 100-150 ml/h
- calcitonina 4UI/kg peso corporeo im ogni 12 ore
- prednisone 25 mg/die
- cinacalcet?

Real clinical practice

- posizionato catetere vescicale
- accesso venoso periferico con fisiologica in continuo 200 cc/h, mantenendo una diuresi di 100-150 ml/h
- calcitonina 4UI/kg peso corporeo im ogni 12 ore

- prednisone 25 mg/die
- mimpara 30 mg 2 cpr/die

Real clinical practice

Ritenete corretto il trattamento effettuato?

Ipercalcemia e disidratazione (Un circolo vizioso)

IPERCALCEMIA

Bilancio idrico negativo

- Anoressia, nausea
- Vomito, diarrea
- Alterazione dello stato di coscienza

Terapia concomitante

- **Diuretici**

**Insensibilità renale all'ADH
(Diabete insipido renale)**

- **Per ridotta espressione di acquaporina-2**

IPOVOLEMIA

↓ VFG

↑ Riassorbimento
prossimale e distale di
Na e Ca

IPERCALCEMIA LIEVE

10,2/10,4 – 12 mg/dL

Ipercalcemia asintomatica o lieve
(calcemia < 12 mg/dL)

- Non richiede trattamento immediato.
- Evitare fattori che possano aggravare l'ipercalcemia
- Diuretici tiazidici, carbonato di litio, deplezione di volume, prolungato allettamento
- Idratazione adeguata (almeno dai 6 agli 8 bicchieri di acqua al giorno) per minimizzare il rischio di nefrolitiasi.

IPERCALCEMIA MODERATA

12 – 14 mg/dL

Ipercalcemia cronica moderata asintomatica o lievemente sintomatica

(calcemia compresa tra 12 e 14 mg/dL)

- potrebbe non richiedere un trattamento immediato
- stesse precauzioni descritte per l'ipercalcemia lieve

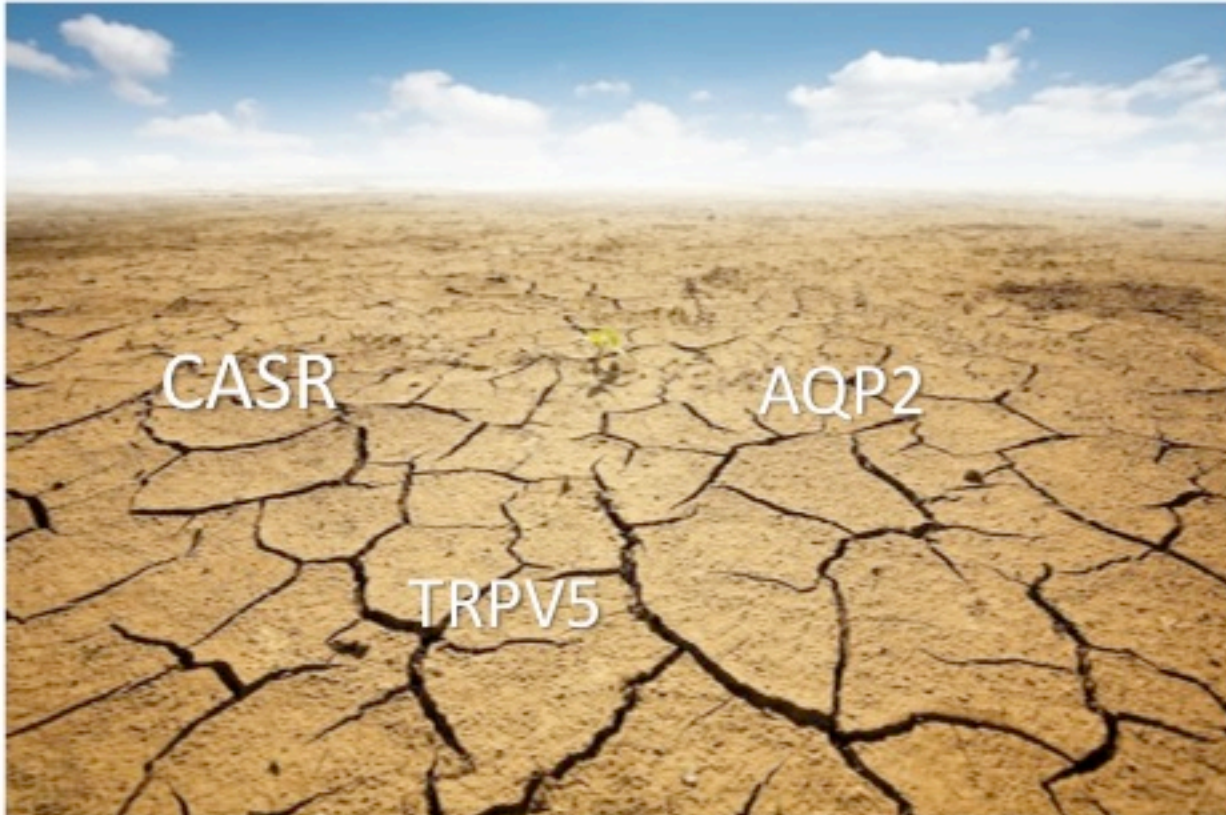
Aumento acuto della calcemia

- potrebbe causare un'alterazione del sensorio e potrebbe richiedere una terapia più aggressiva simile all'ipercalcemia grave
- trattamento con soluzione fisiologica e bisfosfonati come nell'ipercalcemia grave

IPERCALCEMIA GRAVE

> 14 mg/dL


- Disidratazione progressiva;
- Sintomatologia ingravescente.



Intervention	Mode of action	Onset of action	Duration of action
Isotonic saline hydration	Restoration of intravascular volume Increases urinary calcium excretion	Hours	During infusion
Calcitonin	Inhibits bone resorption via interference with osteoclast function Promotes urinary calcium excretion	4 to 6 hours	48 hours
Bisphosphonates	Inhibit bone resorption via interference with osteoclast recruitment and function	24 to 72 hours	2 to 4 weeks
Loop diuretics*	Increase urinary calcium excretion via inhibition of calcium reabsorption in the loop of Henle	Hours	During therapy
Glucocorticoids	Decrease intestinal calcium absorption Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells in patients with granulomatous diseases or lymphoma	2 to 5 days	Days to weeks
Denosumab	Inhibits bone resorption via inhibition of RANKL	4 to 10 days	4 to 15 weeks
Calcimimetics	Calcium sensing receptor agonist, reduces PTH (parathyroid carcinoma, secondary hyperparathyroidism in CKD)	2 to 3 days	During therapy
Dialysis	Low or no calcium dialysate	Hours	During treatment

Intervention	Mode of action	Onset of action	Duration of action
Isotonic saline hydration	Restoration of intravascular volume Increases urinary calcium excretion	Hours	During infusion

- grado di ipercalcemia;
- età e comorbidità (patologia cardiaca e renale)

- | | | |
|---|---|--|
| <ul style="list-style-type: none"> - 200-500 mL/h - 3-4 L nelle prime 24 h - 2-3 L/die |  | <ul style="list-style-type: none"> - 500-1000 mL nella prima ora - 2-6 L nelle prime 24 h - 3 L/die |
|---|---|--|

- diuresi 100-150 mL/h (2-2,5 L/die)

Intervention	Mode of action	Onset of action	Duration of action
Loop diuretics*	Increase urinary calcium excretion via inhibition of calcium reabsorption in the loop of Henle	Hours	During therapy

[Ann Intern Med.](#) 2008 Aug 19;149(4):259-63.

Narrative review: furosemide for hypercalcemia: an unproven yet common practice.

[LeGrand SB¹](#), [Leskuski D](#), [Zama I](#).

- alterazioni elettrolitiche;
- disidratazione



Intervention	Mode of action	Onset of action	Duration of action
Calcitonin	Inhibits bone resorption via interference with osteoclast function Promotes urinary calcium excretion	4 to 6 hours	48 hours

- 4 IU/kg i.m./s.c. ogni 12 h
- 
- 6-8 IU/kg i.m./s.c. ogni 6 h



tachifilassi (48 h)



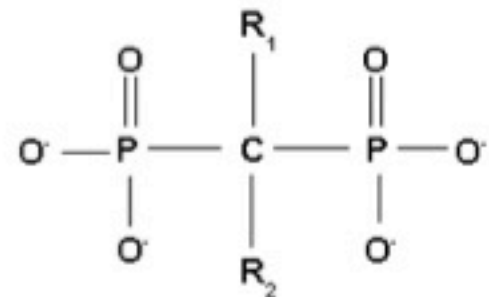
Intervention	Mode of action	Onset of action	Duration of action
Glucocorticoids	Decrease intestinal calcium absorption Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells in patients with granulomatous diseases or lymphoma	2 to 5 days	Days to weeks

- idrocortisone 100-300 mg/die i.v. x 3-5 giorni
- prednisone 40-60 mg/die

- in combinazione con calcitonina può ritardare lo sviluppo di tachifilassi per up-regulation e sintesi de novo dei recettori della calcitonina.

Intervention	Mode of action	Onset of action	Duration of action
Bisphosphonates	Inhibit bone resorption via interference with osteoclast recruitment and function	24 to 72 hours	2 to 4 weeks

- zoledronato 4 mg i.v. in 15 minuti
- pamidronato 60-90 mg i.v. in 2-6 h
- ibandronato 2-6 mg i.v. in 2 h
- clodronato 60-90 mg i.v. in 2-6 h
- ibandronato 2-6 mg i.v. in 2 h



Filtrato glomerulare

< 30 ml/min

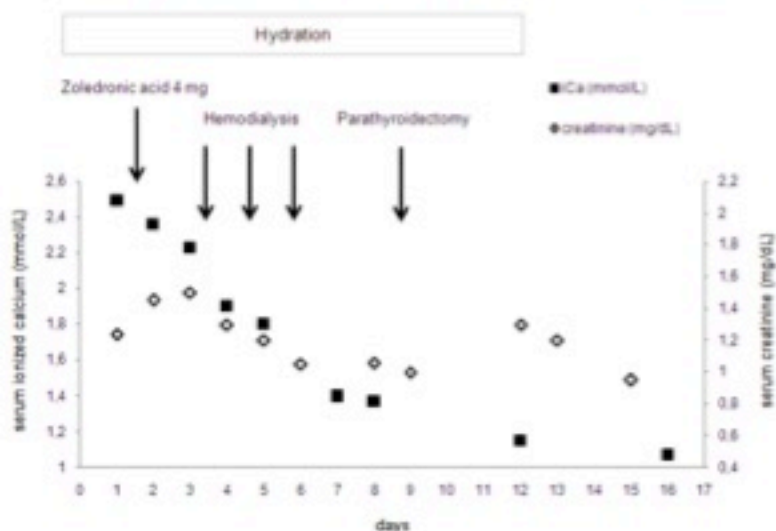


DENOSUMAB?

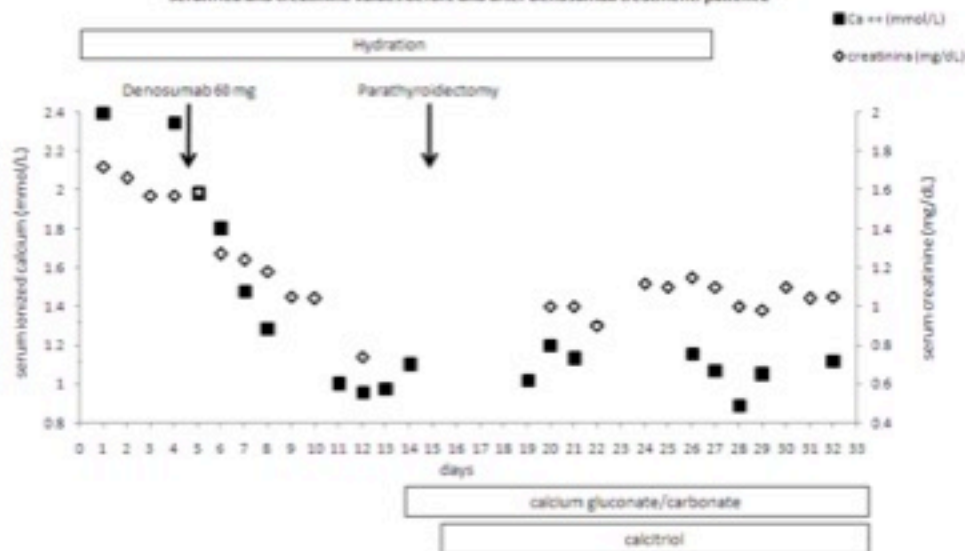
Intervention	Mode of action	Onset of action	Duration of action
Denosumab	Inhibits bone resorption via inhibition of RANKL	4 to 10 days	4 to 15 weeks

- 60 mg una tantum
- 120 mg ogni 4 settimane

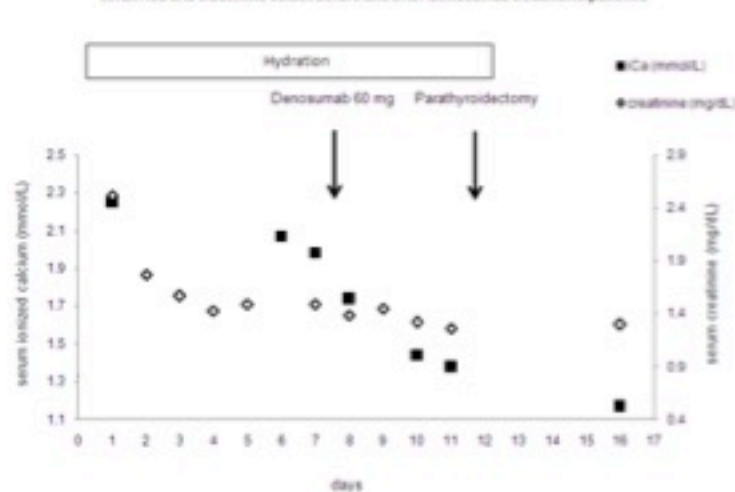
Serum iCa and creatinine values before and after Zoledronic acid and hemodialysis therapy



Serum iCa and creatinine values before and after Denosumab treatment: patient 2

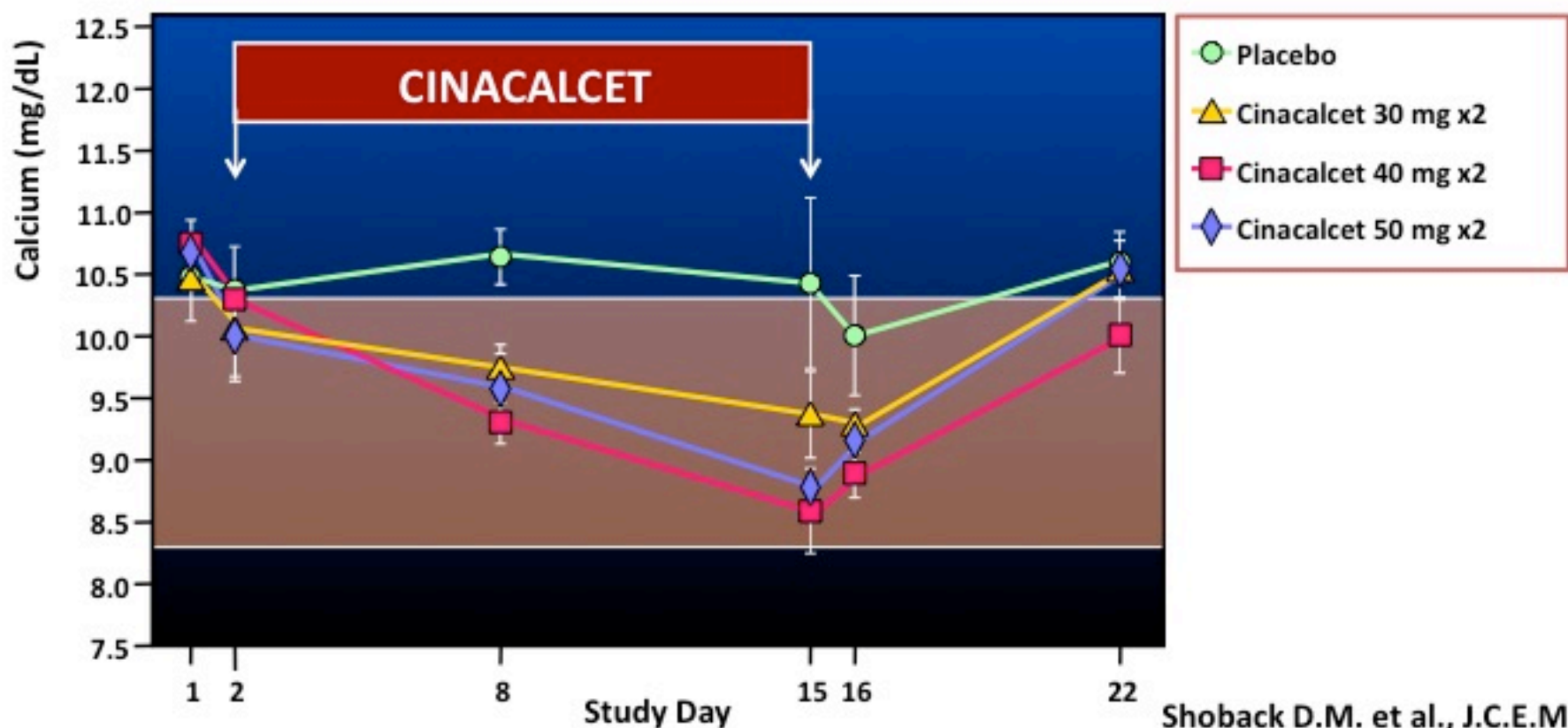


Serum iCa and creatinine values before and after Denosumab treatment: patient 1



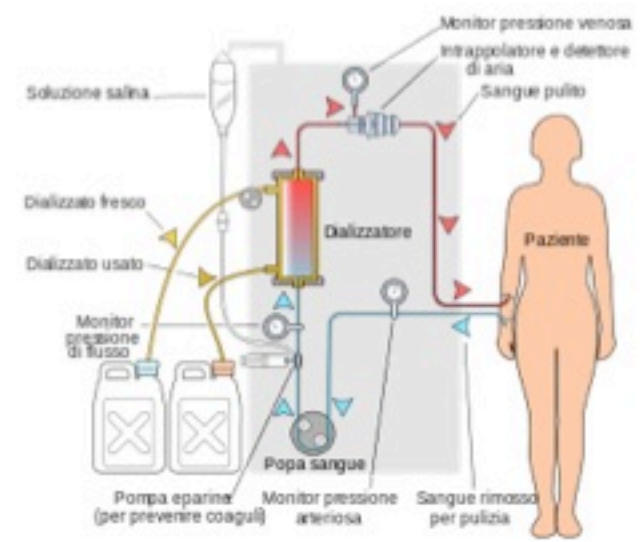
Intervention	Mode of action	Onset of action	Duration of action
Calcimimetics	Calcium sensing receptor agonist, reduces PTH (parathyroid carcinoma, secondary hyperparathyroidism in CKD)	2 to 3 days	During therapy

CHANGES IN SERUM CALCIUM FOLLOWING CINACALCET IN PHPT



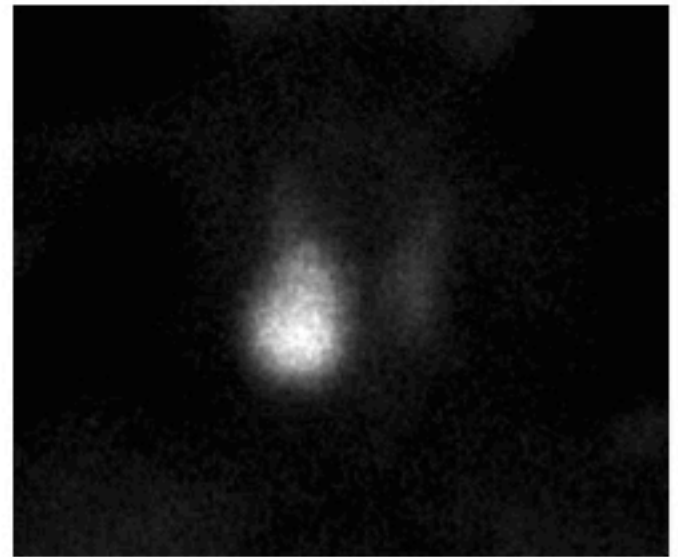
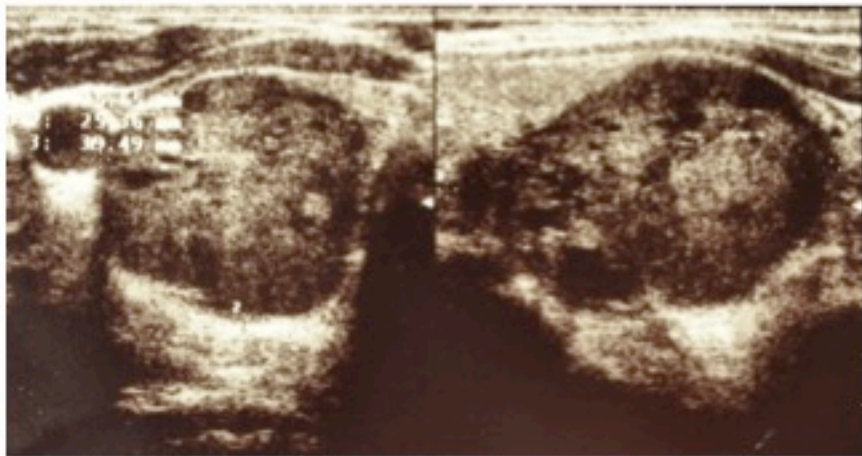
Intervention	Mode of action	Onset of action	Duration of action
Dialysis	Low or no calcium dialysate	Hours	During treatment

- pazienti con grave ipercalcemia, insufficienza renale o scompenso cardiaco



Real clinical practice

formazione ipoecogena, disomogenea intensamente vascolarizzata di 25.6 x 25.3 x 39.4 mm adesa al polo inferiore del lobo tiroideo destro, captante il sestaMIBI



Real clinical practice

formazione nodulare solida,
diametro 30 mm che
impronta la trachea, non
dissociabile dal polo inferiore
del lobo tiroideo destro



Real clinical practice

Eco addome inferiore

reni di normali dimensioni
spessore parenchimale
conservato iperecogeno
non segni di idronefrosi
multipli millimetrici spots
iperecogeni

RX addome diretto

non livelli idroaerei, non
falde di aria libera
ombra renale dx regolare
ombra renale sx mal
valutabile per la presenza
di meteorismo intestinale

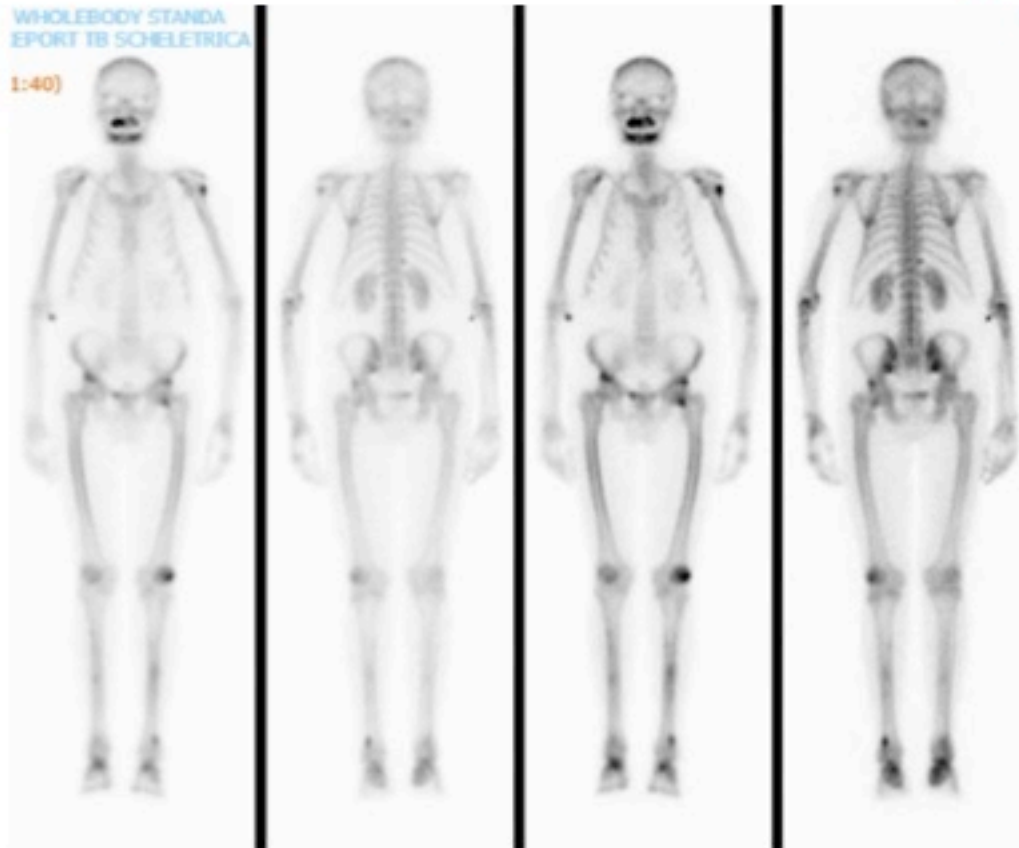
Real clinical practice

TC bacino senza mdc

multiple aree osteolitiche a carico delle ali iliache e delle teste femorali



Real clinical practice



Scintigrafia scheletrica

sedi di accumulo del tracciante

- testa omero sx
- XI costa destra
- tetti acetabolari
- metafisi tibia dx e sx
- diafisi tibiale sx
- teca cranica
- osso mascellare
- osso mandibolare

Real clinical practice

dopo 24 ore

- calcio 15.5 mg/dl
- fosforo 3 mg/dl
- magnesio 1.4 mg/dl
- creatinina 2.2 mg/dl
- proteine totali 6.5 g/dl

dopo 48 ore

- calcio 16.5 mg/dl
- fosforo 2.8 mg/dl
- magnesio 1.6 mg/dl
- creatinina 2.1 mg/dl
- proteine totali 6.5 g/dl

Real clinical practice

- gli inadeguati valori di calcemia rendono necessaria l'emodialisi
- praticate quattro sedute dialitiche
- ultima seduta immediatamente prima dell'intervento

- il pz entra in sala con calcemia 12.8 mg/dl

Real clinical practice

- uomo
- 45 anni
- familiarità positiva per ca renale
- PTH 1524 pg/ml
- calcio 18.4 mg/dl
- formazione di 40 mm



carcinoma della paratiroide

1% dei casi di iperparatiroidismo

Real clinical practice

- taglio orizzontale, isolata emitiroide destra che risulta adesa alla voluminosa neoformazione paratiroidea, con ultracision eseguita emitiroidectomia in monoblocco con la neoformazione paratiroidea
- durata intervento 60 minuti

Real clinical practice

- **macroscopia:** nodulo capsulato di 2.2 cm di asse maggiore
- **microscopia:** proliferazione di cellule principali aggregate principalmente in nidi
- attività mitotica inferiore a 1 per 10 HPF
- attività citoproliferativa misurata con anticorpo Ki67 (1%)
- non bande fibrose, non infiltrazione vascolare
- quadro morfologico di **adenoma paratiroideo** a cellule principali

Real clinical practice

- severa ipercalcemia
- livelli di PTH
- livelli di fosfatasi alcalina
- dimensioni dell'adenoma
- osteite fibroso cistica



hungry bone

Real clinical practice

Pre-intervento

- calcio 12.8 mg/dl
- fosforo 1.8 mg/dl
- magnesio 1.4 mg/dl
- creatinina 2.2 mg/dl
- proteine totali 6.5 g/dl
- PTH 1584 pg/ml
- fosfatasi alcalina 711 U/L

Post-intervento

- calcio 9.3 mg/dl
- fosforo 1.9 mg/dl
- magnesio 1.6 mg/dl
- creatinina 2.1 mg/dl
- proteine totali 7 g/dl
- PTH 225 pg/ml
- fosfatasi alcalina 704 U/L

Real clinical practice

Pre-intervento

- calcio 12.8 mg/dl
- fosforo 1.8 mg/dl
- magnesio 1.4 mg/dl
- creatinina 2.2 mg/dl
- proteine totali 6.5 g/dl
- PTH 1584 pg/ml
- fosfatasi alcalina 711 UI/L

Post-intervento

- calcio 9.3 mg/dl
- fosforo 1.0 mg/dl
- magnesio 1.1 mg/dl
- creatinina 2.1 mg/dl
- proteine totali 7 g/dl
- PTH 225 pg/ml
- fosfatasi alcalina 704 U/L

no hungry bone

Real clinical practice

Quali potrebbero essere i motivi della mancata hungry bone syndrome?

Real clinical practice

- IGA transglutaminasi negative → no celiachia
- nella norma gastrina e cromogranina → no MEN1
- nella norma tropine ipofisarie
- negativa calcitonina → no MEN2
- negative metanefrine e catecolamine ur/24h
- negativa ricerca mutazioni gene HRPT2 → no jaw tumor syndrome

Real clinical practice

- calcio 2 g/die
- calcitriolo 1 mcg/die
- allopurinolo 300 mg/die
- riabilitazione motoria



Real clinical practice

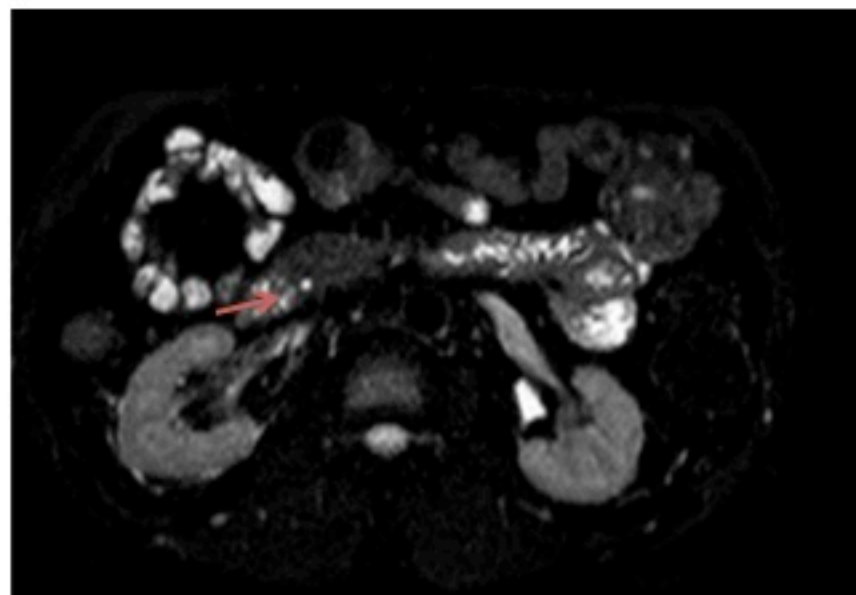
- marzo 2012 asportazione del tumore bruno mascellare superiore con resezione parziale della premaxilla e parcellare del mascellare
- 2012-2013 plurimi interventi per chiusura di fistola oro-nasale
- 2014 impianto zigomatico e pterigoideo
- 2015 riabilitazione implanto-protesica

Real clinical practice

aprile 2017 caduta dalla bicicletta

TC addome con mdc

lesione di 6 mm tenuemente
iperintensa nelle sequenze
post-contrastografiche
compatibile con lesione
neuroendocrina al processo
uncinato del pancreas

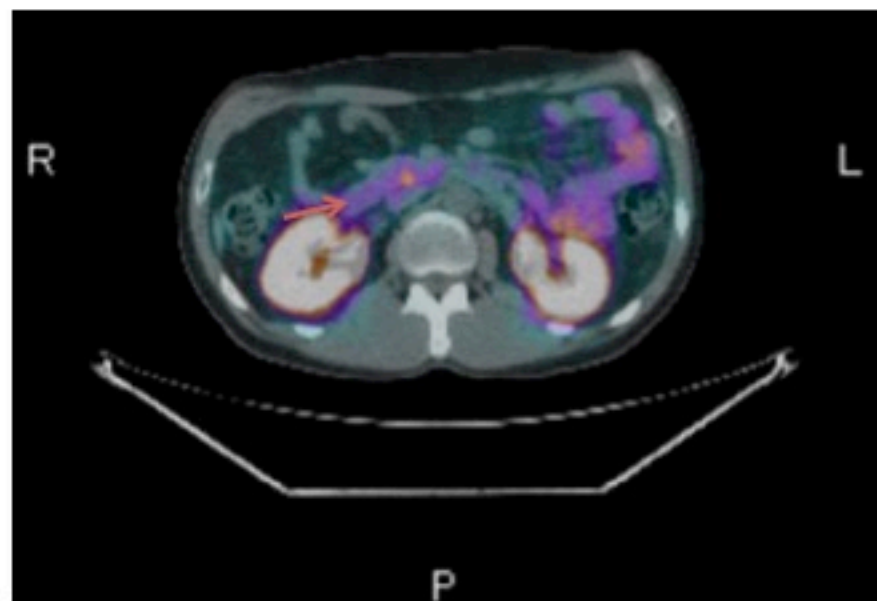


Real clinical practice

Ecoendoscopia conferma la presenza della lesione, FNA preleva solo materiale proteinaceo acellulato

PET con DOTANOC

ipercaptazione a livello del processo uncinato del pancreas, in assenza di aree di sicuro e patologico iperaccumulo del tracciante



Real clinical practice

- nella norma tropine ipofisarie
- nella norma cromogranina, gastrina, NSE, CEA, Ca 19.9
- mutazione: nonsense Gln450Stop, esone 9 del gene MEN1

PORTATORE di mutazione nel gene MEN1

Real clinical practice

- RMN ipofisi negativa
- NET pancreatico non funzionante
- pregresso iperparatiroidismo primitivo
- portatore di mutazione nel gene MEN1

discusso il caso al meeting multidisciplinare,
si opta per mantenere il pz in follow-up

Real clinical practice

C'erano degli elementi che potevano farci
sospettare la presenza di mutazione del gene
MEN1?

Real clinical practice

ottobre 2017

- calcio 10.3
- fosforo 3.7 mg/dl
- magnesio 2 mg/dl
- calcio ur/24h 250 mg/die
- creatinina 1.4 mg/dl
- proteine totali 6.8 gr/dl
- PTH 34 pg/ml
- fosfatasi alcalina 87 UI/L



calcio 500 mg/die
calcitriolo 0.5 mcg/die
allopurinolo 150 mg/die

Real clinical practice

DEXA ottobre 2011

regione	T-score	Z-score
L1-L4	-2.6	-2.2
femore sx	-4.1	-3.4
femore dx	-5.2	-4.5

DEXA ottobre 2017

regione	T-score	Z-score
L1-L4	-2.7	-2.1
femore sx	-1.6	-0.8
femore dx	-2.6	-1.8



Roberto continua la sua corsa

Ipercalcemia



Calcio sierico > **10.2–10.4 mg/dL** o **2.55–2.60 mmol/l**

lieve

moderata

grave

Ca < 12 mg/dL

12 mg/dL < Ca < 14 mg/dL

Ca > 14 mg/dL

Clinical manifestations of hypercalcemia

Renal

Polyuria
Polydipsia
Nephrolithiasis
Nephrocalcinosis
Distal renal tubular acidosis
Nephrogenic diabetes insipidus
Acute and chronic renal insufficiency

Gastrointestinal

Anorexia, nausea, vomiting
Bowel hypomotility and constipation
Pancreatitis
Peptic ulcer disease

Musculoskeletal

Muscle weakness
Bone pain
Osteopenia/osteoporosis

Neurologic

Decreased concentration
Confusion
Fatigue
Stupor, coma

Cardiovascular

Shortening of the QT interval
Bradycardia
Hypertension

ipercalcemia lieve (Ca 10.2- 12 mg/dL)

- asintomatica
- sintomi aspecifici (stipsi, astenia, depressione)

ipercalcemia moderata (Ca 12-14 mg/dL)

- paucisintomatica se cronica
- sintomatologia importante se acuta (poliuria, polidipsia, disidratazione, anoressia, nausea, affaticamento muscolare, alterazioni nel sensorio)

ipercalcemia grave (Ca > 14 mg/dL)

- sintomatologia ingravescente

CAUSE DI IPERCALCEMIA

Parathyroid hormone

- Primary hyperparathyroidism
 - Sporadic, familial, multiple endocrine neoplasia I or IIA
- Tertiary hyperparathyroidism
- Coexisting malignancy and primary hyperparathyroidism
- Ectopic PTH in malignancy (very rare)

Cancer

- Humoral hypercalcemia of malignancy
 - Parathyroid hormone-related protein (PTHrP)
- Local osteolysis
 - Cytokines, chemokines, PTHrP

Vitamin D

- Granulomatous disease (1,25[OH]₂D)
 - Sarcoidosis, tuberculosis, berylliosis, coccidioidomycosis
- Vitamin D intoxication
 - Vitamin D supplements, vitamin D metabolites or analogs
- Lymphoma (1,25[OH]₂D)

Renal Failure

- Chronic renal failure with treatment with calcium and 1,25[OH]₂D or vitamin D analogs
- Rhabdomyolysis and acute renal failure
- Renal transplant

Other Endocrine

- Thyrotoxicosis
- Adrenal insufficiency
- Pheochromocytoma

Medications

- Thiazide diuretics
- Lithium
- Milk-alkali syndrome (calcium and antacids)
- Vitamin A

Other

- Immobilization
- Familial hypocalciuric hypercalcemia

Le Ipercalcemie - Cause

Cause comuni (> 90%)

- Iperparatiroidismo primitivo

- Neoplasie



 - Secernenti PTHrp, TNF, PGE₂ (ca. a cellule squamose, renale, ovarico)

 - Metastasi ossee (ca. mammario)

 - Mieloma multiplo

Cause infrequenti (5-10%)

- Farmaci - vitamina D, litio, diuretici tiazidici

- Sarcoidosi

- Tireotossicosi

Cause rare (1-2%)

- Ipercalcemia ipocalciurica familiare

- Malattie granulomatose

- LNH B, LH, leucemie

AN APPROACH TO THE PATIENT WITH HYPERCALCEMIA

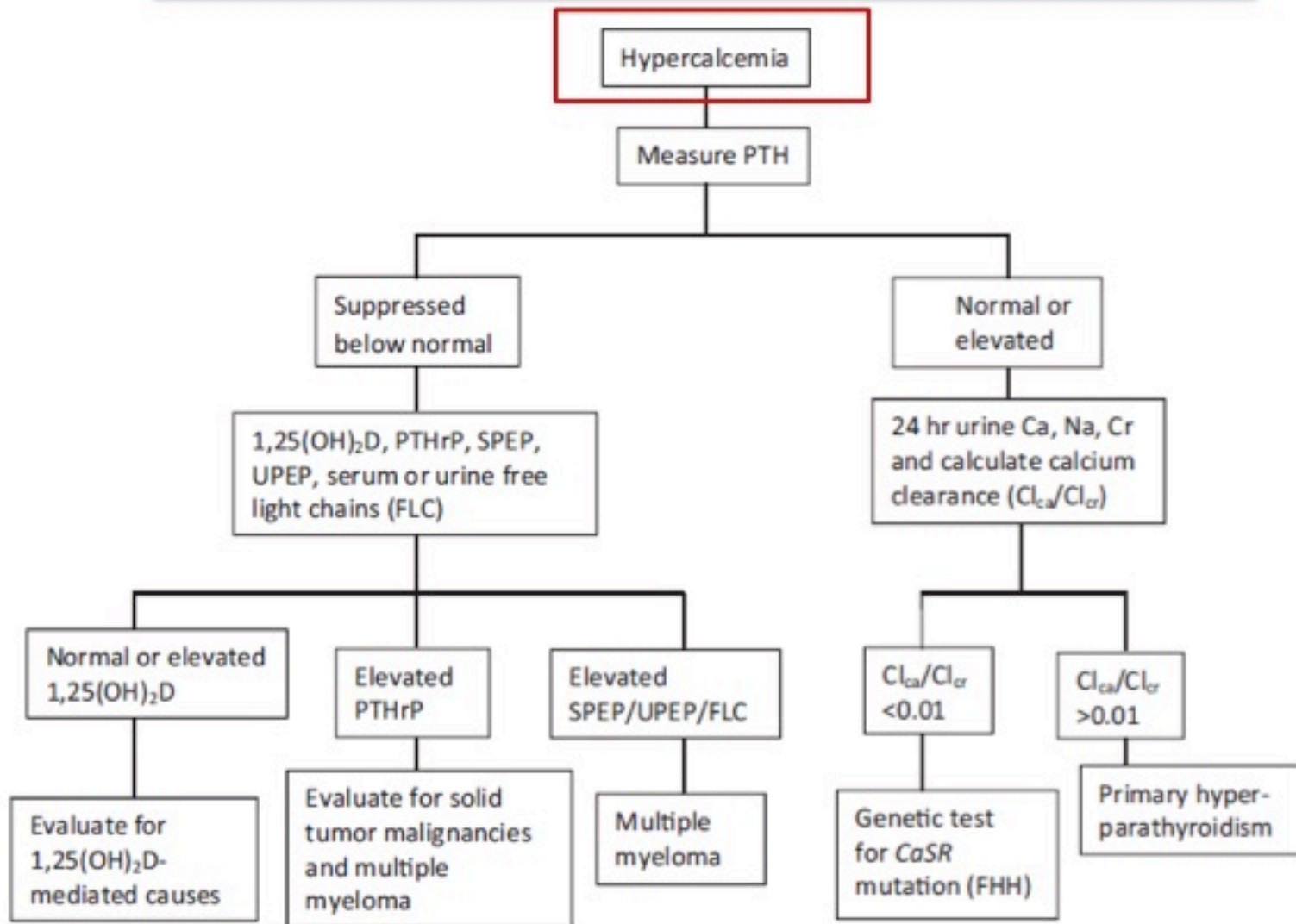


FIGURE 41.1 Outpatient evaluation of hypercalcemia.

Conferma ipercalcemia

- **calcio corretto per albumina**
 - **calcio ionizzato**

If a disorder of calcium metabolism is suspected, **ionized calcium** can provide increased sensitivity and specificity when compared with total calcium. Ionized calcium is more sensitive for the detection of hypercalcemia in primary hyperparathyroid and malignancy [4,15,16,42–49]. Ionized calcium has been reported to be more frequently elevated in patients with primary hyperparathyroidism including those with normal or intermittent total hypercalcemia.

AN APPROACH TO THE PATIENT WITH HYPERCALCEMIA

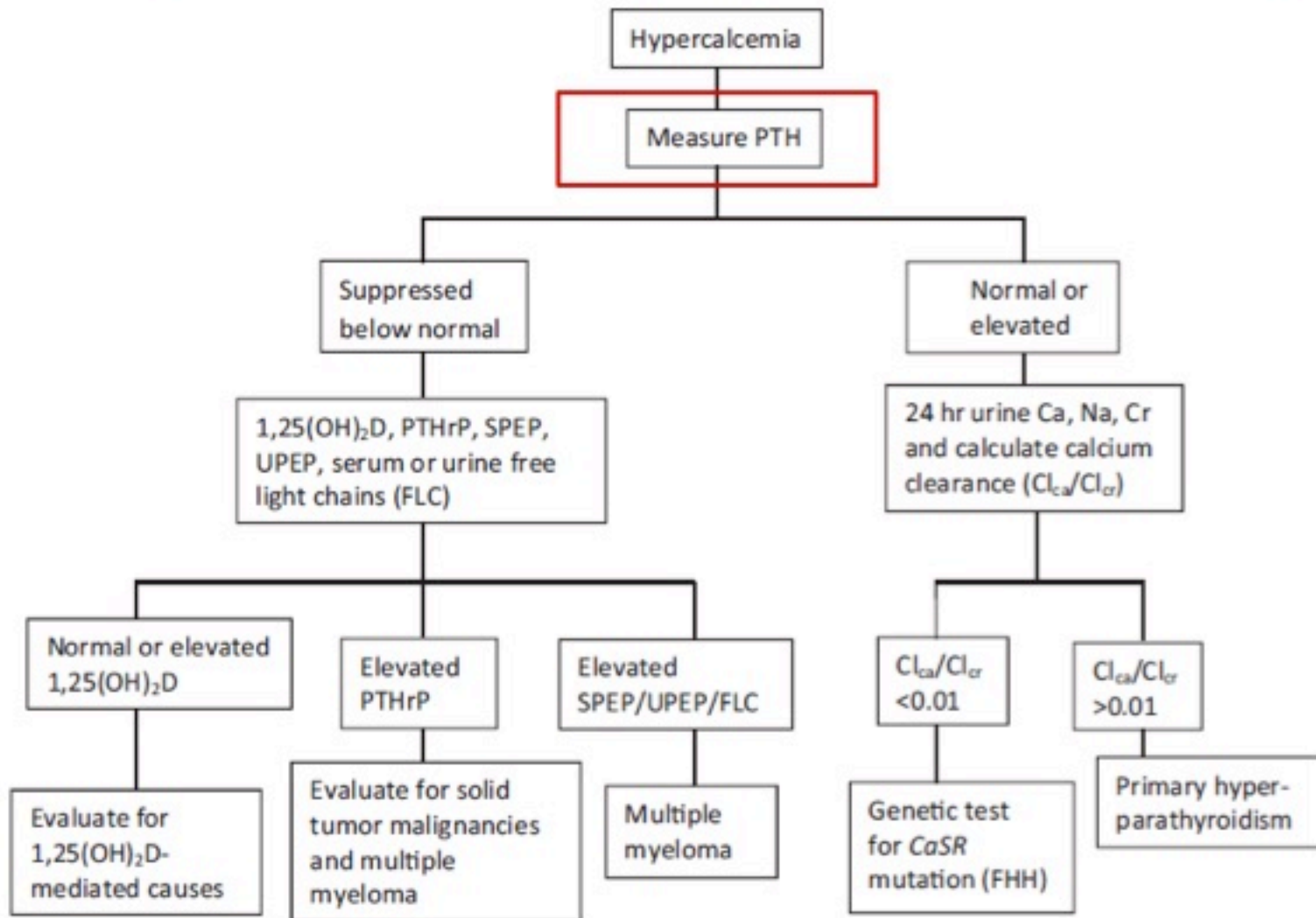
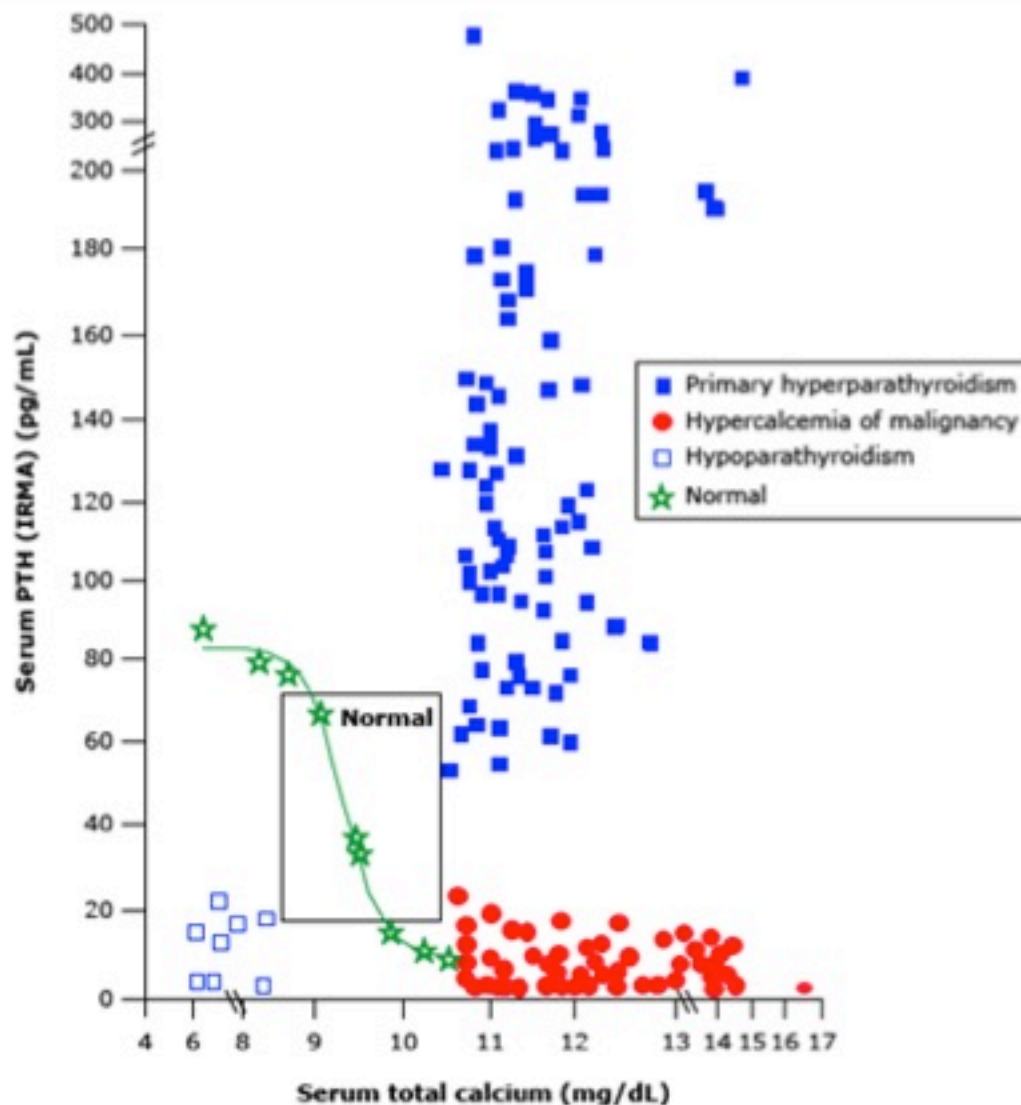


FIGURE 41.1 Outpatient evaluation of hypercalcemia.

Serum parathyroid hormone (PTH) concentrations in hypercalcemia and hypocalcemia



AN APPROACH TO THE PATIENT WITH HYPERCALCEMIA

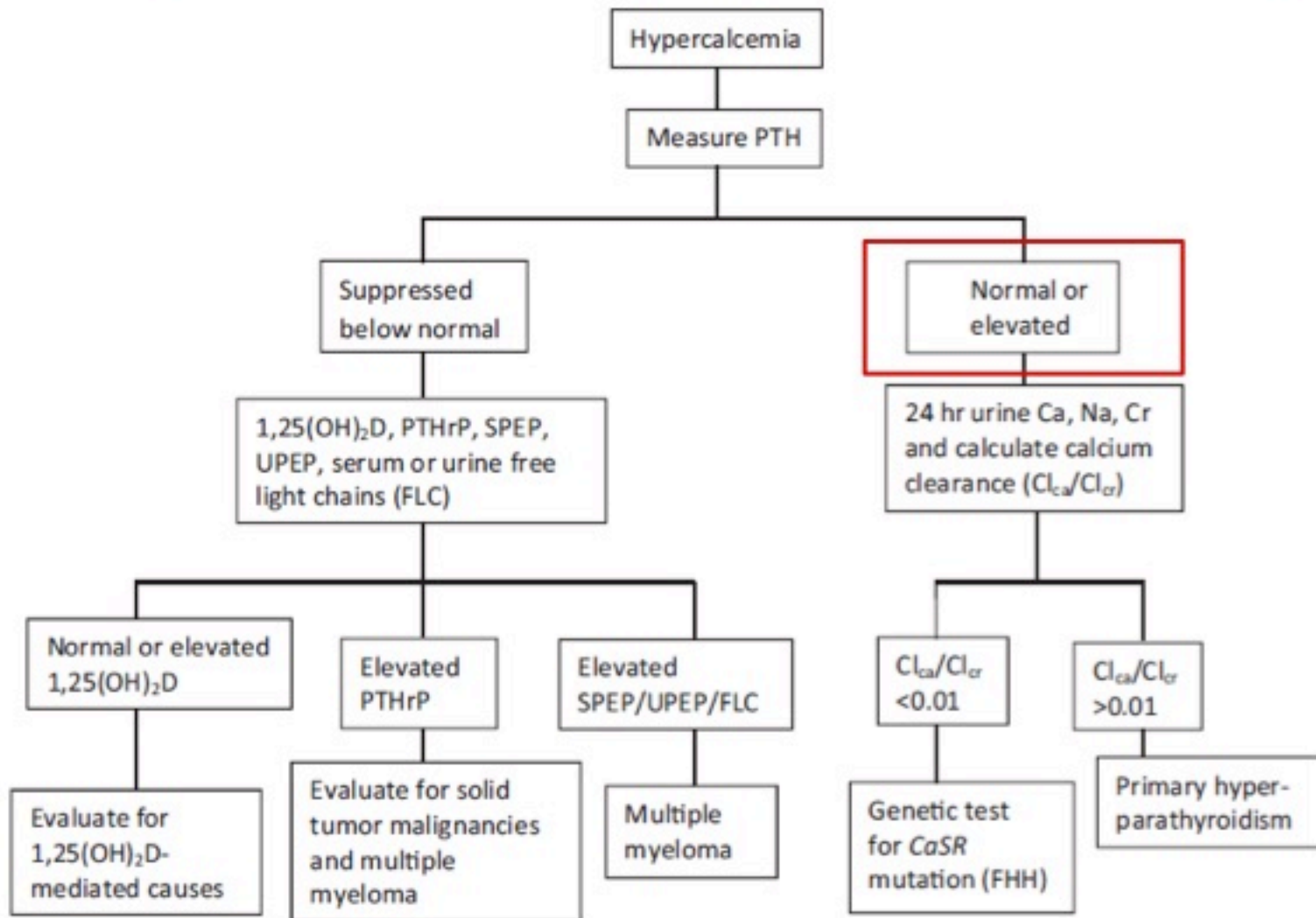


FIGURE 41.1 Outpatient evaluation of hypercalcemia.

Iperparatiroidismo primario

Aumentata secrezione di PTH
per patologia ghiandolare paratiroidea.
Livelli di PTH elevati o inappropriatamente normali
rispetto ai livelli di calcemia

**Senza manifestazioni
cliniche apprezzabili**

Biochimico asintomatico

Con manifestazioni cliniche

Renali

- Litiasi calcica: più frequentemente bilaterale, recidivante
- Nefrocalcinosi
- Danni funzionali: acidosi tubulare prossimale e distale, aminoaciduria, perdita di potassio, riduzione della capacità di concentrazione delle urine

Scheletriche

- Dolori ossei
- Fratture spontanee
- Segni radiologici: erosioni sotto-periostee, cisti, osteoclastomi
- Rilievo densitometrico di osteoporosi

Neuromuscolari

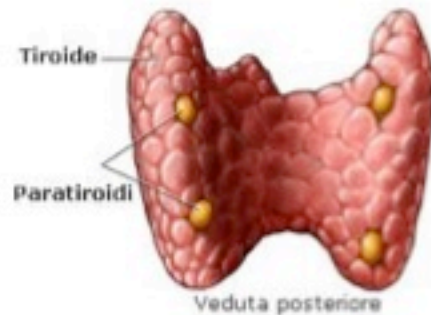
Neuropsichiche

Gastrointestinali

Articolari

Cardiovascolari

Sporadico



Familiare

Iperparatiroidismo
Primitivo

Familial Isolated
HyperParathyroidism
(**FIHP**)

Multiple Endocrine
Neoplasia Type-1
(**MEN1**)

Multiple Endocrine
Neoplasia Type-2A
(**MEN2A**)

Familial Hypocalciuric
Hypercalcemia
(**FHH**)

ANAMNESI

ESAMI

GENETICA

Hyperparathyroidism-
Jaw Tumor
(**HPT-JT**)

Genetics of Hyperparathyroidism, Including Parathyroid Cancer

William F. Simonds, MD

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Table 1
Genes implicated in syndromic and sporadic parathyroid tumorigenesis, and related syndromes

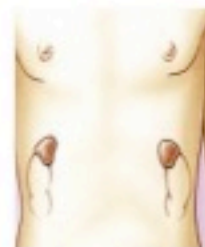
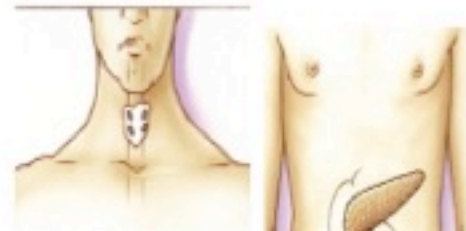
Gene	Protein Encoded	Associated Hyperparathyroid Syndrome: Main Syndromic Manifestations	Features of Syndromic Parathyroid Tumors	Defect in Sporadic Parathyroid Tumors
<i>MEN1</i>	Menin	MEN1: anterior pituitary, parathyroid, enteropancreatic, foregut carcinoid tumors	Multiple, asymmetric tumors typical (>99% benign)	Inactivation in ~25%–35% of benign tumors; mutation exceedingly rare in cancer
<i>CDC73/HRPT2</i>	Parafibromin	HPT–jaw tumor syndrome: fibro-osseous jaw, parathyroid, uterine tumors; renal cysts	Single tumor common (~15% malignant)	Inactivation in ~70% of cancers; mutation rare in sporadic adenomas
<i>CDKN1B</i>	P27(Kip1)	MEN4: anterior pituitary, other involvement varies	Single to multiple glands (benign in reports to date); can be recurrent	Loss-of-function mutation in ~5% of sporadic adenomas; including germline mutation in sporadic presentation
<i>CASR</i>	Calcium-sensing receptor	FHH1 with heterozygous inactivation; NSHPT with homozygous inactivation	FHH1: near-normal size and surgical pathology; altered serum calcium set-point for PTH release NSHPT: marked enlargement of multiple glands by polyclonal (nonneoplastic) mechanism	Decreased expression common; mutation exceedingly rare
<i>GNA11</i>	G protein $\alpha 11$ subunit	FHH2	ND	ND
<i>AP2S1</i>	Adaptor protein-2 sigma subunit	FHH3: hypercalcemia more severe than in FHH1	ND	ND
<i>RET</i>	c-Ret	MEN2A: medullary thyroid cancer, pheochromocytoma, parathyroid tumors	Single tumor common (>99% benign)	Mutation exceedingly rare
<i>CCND1/PRAD1</i>	Cyclin D1	NA	NA	Overexpression results from DNA rearrangement involving PTH gene

Abbreviations: MEN1, multiple endocrine neoplasia type 1; MEN4, multiple endocrine neoplasia type 4; NA, not applicable; ND, not determined (lack of relevant published studies); NSHPT, neonatal severe hyperparathyroidism; PTH, parathyroid hormone.

MEN 1

1. Multiple parathyroid tumors (>90%)

2. NET of pancreas and duodenum
3. pituitary tumors
4. NET thymus, lung and stomach
5. adrenal tumors
6. breast cancer



Italian Society of Endocrinology Consensus Statement: definition, evaluation and management of patients with mild primary hyperparathyroidism

C. Marcocci · M. L. Brandi · A. Scillitani · S. Corbetta ·
A. Faggiano · L. Gianotti · S. Migliaccio · S. Minisola

- **11. We recommend** against routine genetic screening for mutations of the susceptibility genes of parathyroid tumorigenesis (1 ØØØØ).
- **12. We suggest** a complete workout investigating family history and syndrome-related clinical and biochemical features in young (less than 45 years of age) mild PHPT patients (2 ØØØØ).

Sporadic and MEN1-Related Primary Hyperparathyroidism: Differences in Clinical Expression and Severity

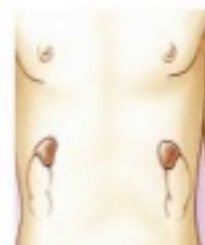
Cristina Eller-Vainicher,¹ Iacopo Chiodini,¹ Claudia Battista,² Raffaella Viti,² Maria Lucia Mascia,³
Sara Massironi,⁴ Maddalena Peracchi,⁴ Leonardo D'Agruma,⁵ Salvatore Minisola,³ Sabrina Corbetta,⁶
David E. C. Cole,⁷ Anna Spada,¹ and Alfredo Scillitani²

ABSTRACT: Primary hyperparathyroidism (PHPT) is a common endocrine disease that is associated with multiple endocrine neoplasia type 1 (MEN1) in ~2% of PHPT cases. Lack of a family history and other specific expressions may lead to underestimated MEN1 prevalence in PHPT. The aim of this study was to identify clinical or biochemical features predictive of MEN1 and to compare the severity of the disease in MEN1-related versus sporadic PHPT (sPHPT). We performed a 36-mo cross-sectional observational study in three tertiary referral centers on an outpatient basis on 469 consecutive patients with sporadic PHPT and 64 with MEN1-related PHPT. Serum calcium, phosphate, PTH, 25(OH)D₃, and creatinine clearance were measured, and ultrasound examination of the urinary tract/urography was performed in all patients. In 432 patients, BMD was measured at the lumbar spine (LS) and femoral neck (FN). MEN1 patients showed lower BMD Z-scores at the LS (-1.33 ± 1.23 versus -0.74 ± 1.4 , $p = 0.008$) and FN (-1.13 ± 0.96 versus -0.6 ± 1.07 , $p = 0.002$) and lower phosphate (2.38 ± 0.52 versus 2.56 ± 0.45 mg/dl, $p = 0.003$) and PTH (113.8 ± 69.5 versus 173.7 ± 135 pg/ml, $p = 0.001$) levels than sPHPT patients. Considering probands only, the presence of MEN1 was more frequently associated with PTH values in the normal range (OR, 3.01; 95% CI, 1.07–8.50; $p = 0.037$) and younger age (OR, 1.61; 95% CI, 1.28–2.02; $p = 0.0001$). A combination of PTH values in the normal range plus age <50 yr was strongly associated with MEN1 presence (OR, 13.51; 95% CI, 3.62–50.00; $p = 0.0001$). In conclusion, MEN1-related PHPT patients show more severe bone but similar kidney involvement despite a milder biochemical presentation compared with their sPHPT counterparts. Normal PTH levels and young age are associated with MEN1 presence.

MEN 1

1. Multiple parathyroid tumors (>90%)

2. NET of pancreas en duodenum
3. pituitary tumors
4. NET thymus, lung and stomach
5. adrenal tumors
6. breast cancer



Breast-cancer predisposition in multiple endocrine neoplasia type 1.

Dreijerink KM¹, Goudet P, Burgess JR, Valk GD; International Breast Cancer in MEN1 Study Group.

Table 1

Characteristics of 10 Patients with Confirmed *MEN1* Germline Mutations and Breast Cancer*

Patient No.	Age at Diagnosis yr	Histologic Analysis	Tumor–Node–Metastasis (TNM) Stage	Estrogen Receptor	Progesterone Receptor	HER2	Menin Expression	Loss of Heterozygosity at <i>MEN1</i> Locus
1	55	Ductal	T1N1M0	+	–	–	–	–
2	38	Ductal	T3N1M0	+	+	+	–	–
3	44	Ductal	T1N0M0	–	–	–	+	–
4	61	Ductal	T1N1M0	+	–	–	–	–
5	52	Lobular	T1N0M0	+	+	+	–	–
6	53	Ductal	T1N0M0	+	+	–	–	+
7	45	Micropapillary	T1N1M0	+	–	–	–	+
8	42	Ductal [†]	T1N0M0	–	+	–	–	+
9	33	Ductal	T1N1M0	+	+	+	+	–
10	46	Ductal	T1N0M0	+	+	–	–	ND

* A plus sign indicates positivity, and a minus sign negativity. HER2 denotes human epidermal growth factor receptor 2, and ND not determined.

[†] This patient had a tumor in each breast.

In conclusion, female patients with MEN1 are at increased risk for breast cancer. Loss of menin expression and loss of heterozygosity at the *MEN1* locus in a subgroup of patients suggest a mammary-cell autonomous effect in MEN1-related breast cancer. Our observations indicate that *MEN1* mutations are involved in human breast carcinogenesis. Further research will clarify the relevance of *MEN1* function for patients with nonfamilial breast cancer. Intensified breast-cancer screening at a relatively young age should be considered in female patients with MEN1.

[Clin Endocrinol \(Oxf\)](#). 2015 Mar;82(3):327-229. doi: 10.1111/cen.12614. Epub 2014 Nov 5.

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Upregulation of RPA2 promotes NF- κ B activation in breast cancer by relieving the antagonistic function of menin on NF- κ B-regulated transcription.

[Chen CC](#)¹, [Juan CW](#)^{2,3}, [Chen KY](#)⁴, [Chang YC](#)⁵, [Lee JC](#)⁵, [Chang MC](#)⁶.

[Cell Rep](#). 2017 Mar 7;18(10):2359-2372. doi: 10.1016/j.celrep.2017.02.025.

Enhancer-Mediated Oncogenic Function of the Menin Tumor Suppressor in Breast Cancer.

[Dreijerink KMA](#)¹, [Groner AC](#)¹, [Vos ESM](#)², [Font-Tello A](#)¹, [Gu L](#)³, [Chi D](#)¹, [Reyes J](#)⁴, [Cook J](#)¹, [Lim E](#)¹, [Lin CY](#)⁴, [de Laat W](#)², [Rao PK](#)¹, [Long HW](#)¹, [Brown M](#)⁵.

[J Clin Endocrinol Metab](#). 2017 Jun 1;102(6):2083-2090. doi: 10.1210/jc.2016-3690.

MEN1-Dependent Breast Cancer: Indication for Early Screening? Results From the Dutch MEN1 Study Group.

[van Leeuwen RS](#)¹, [Dreijerink KM](#)¹, [Ausems MG](#)², [Beijers HJ](#)³, [Dekkers OM](#)^{4,5}, [de Herder WW](#)⁶, [van der Horst-Schrivers AN](#)⁷, [Drent ML](#)⁸, [Bisschop PH](#)⁹, [Havekes B](#)¹⁰, [Peeters PHM](#)¹¹, [Pijnappel RM](#)¹², [Vriens MR](#)¹³, [Valk GD](#)¹.

HPT-JT

CDC73 mutations

- **Hyperparathyroidism** (100%)
(Parathyroid carcinoma)

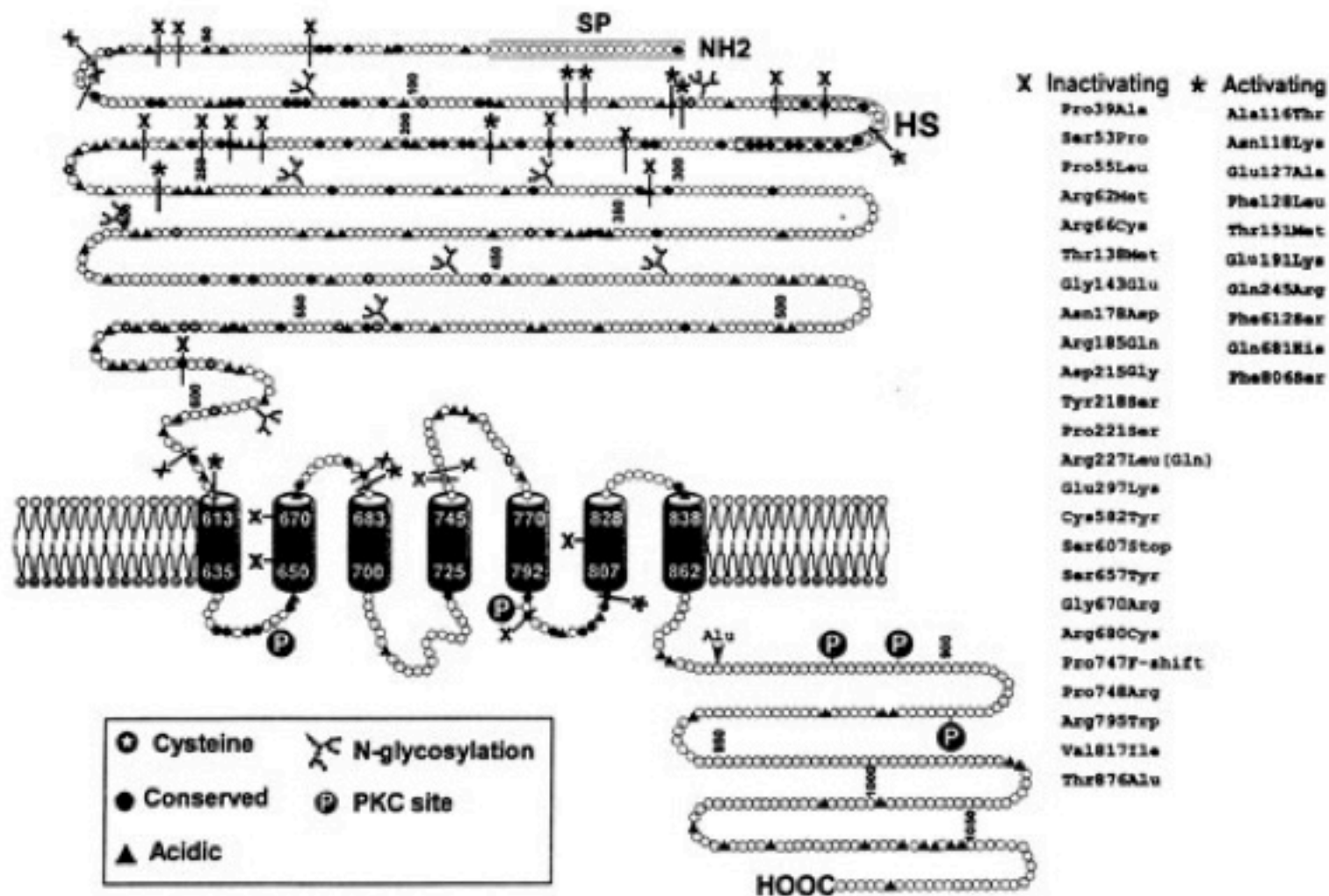
- **Jaw-Tumor** (10-25%)

Associated Tumors:

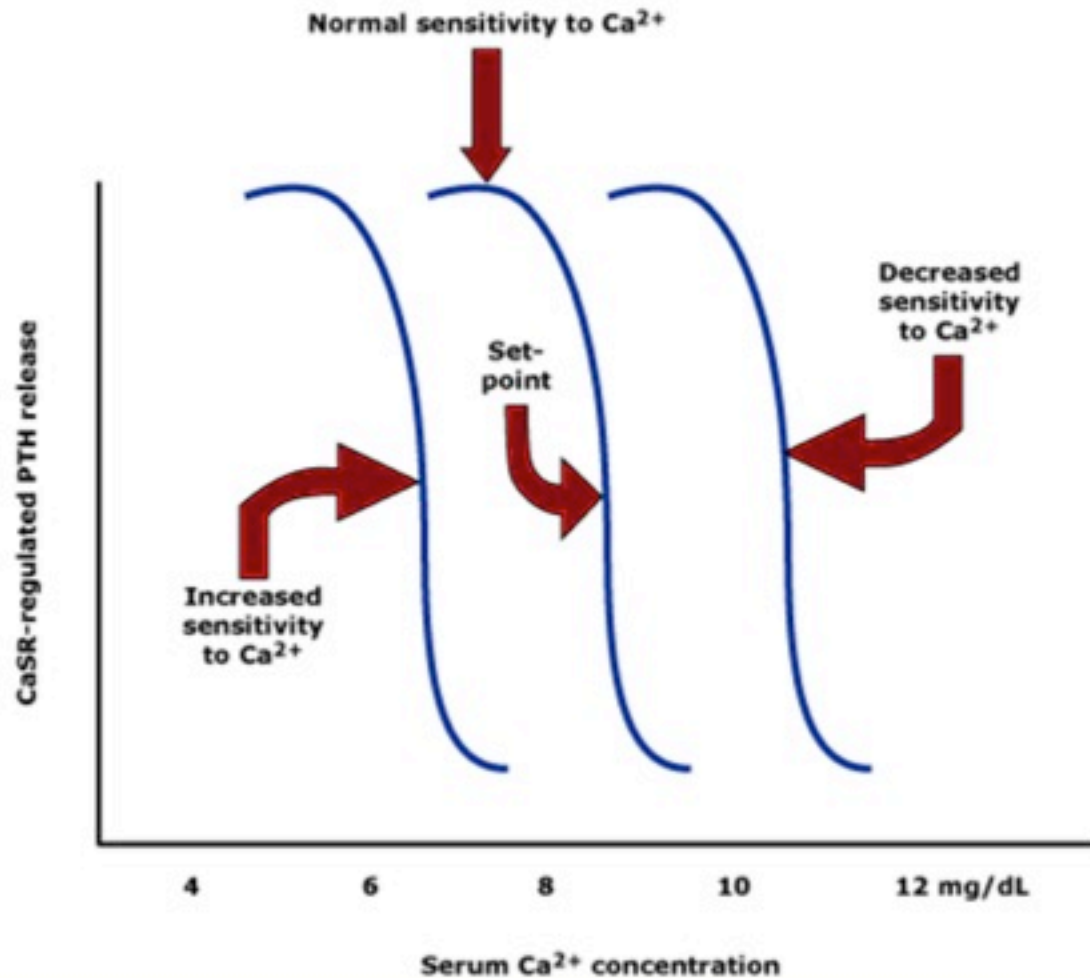
- **Renal** (0-70%)
- **Uterine** (>50%)
- ...

Familial hypocalciuric hypercalcemia (FHH)

CaSR

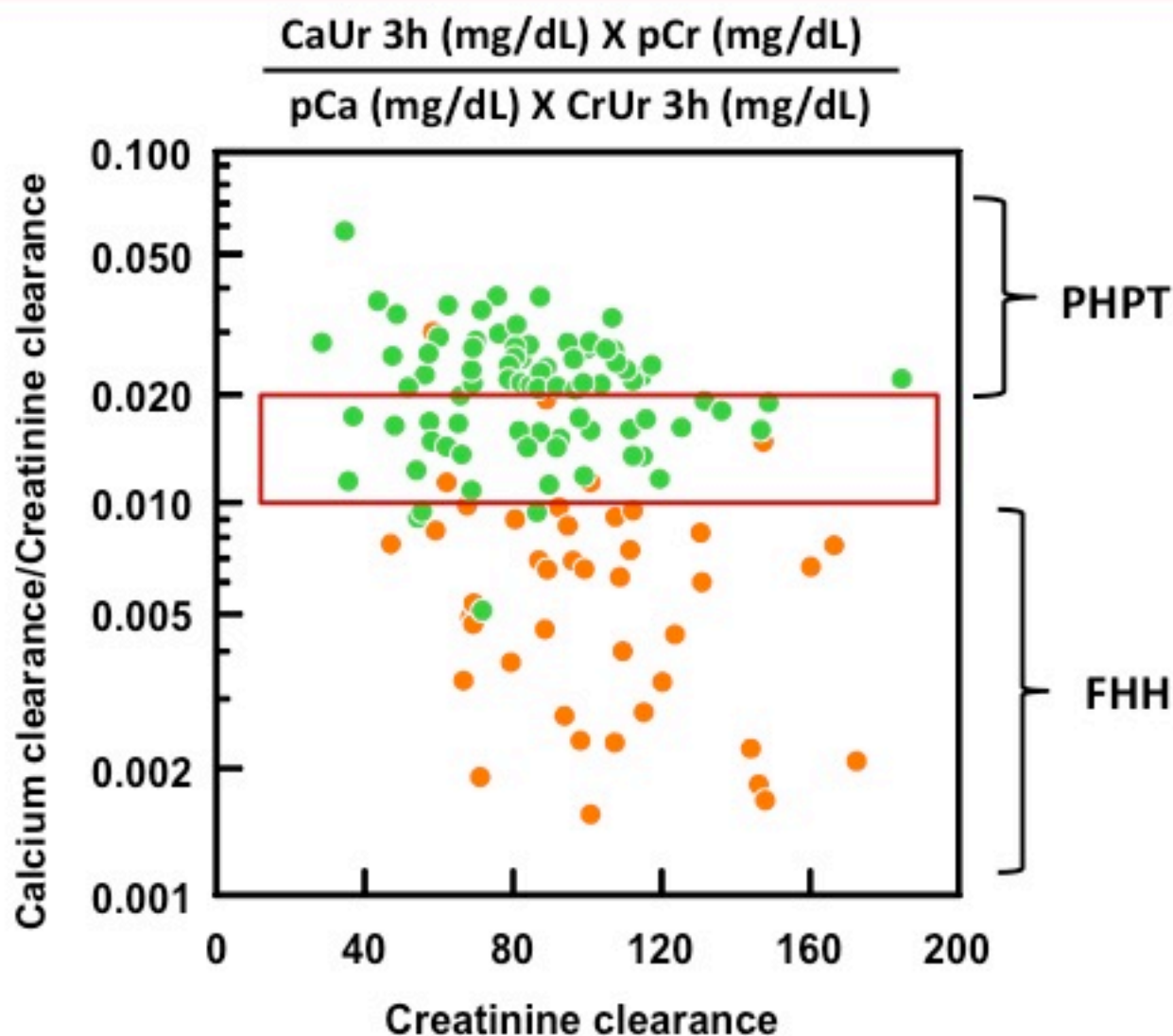


Schematic illustration of impact of changes in Ca^{2+} -sensitivity on set-point



Ca^{2+} : calcium ion; CaSR: calcium-sensing receptor; PTH: parathyroid hormone.

Urinary calcium to creatinine clearance ratio in FHH (●) expressed as a function of total serum calcium concentration relative to the values for patients with PHPT (●)



AN APPROACH TO THE PATIENT WITH HYPERCALCEMIA

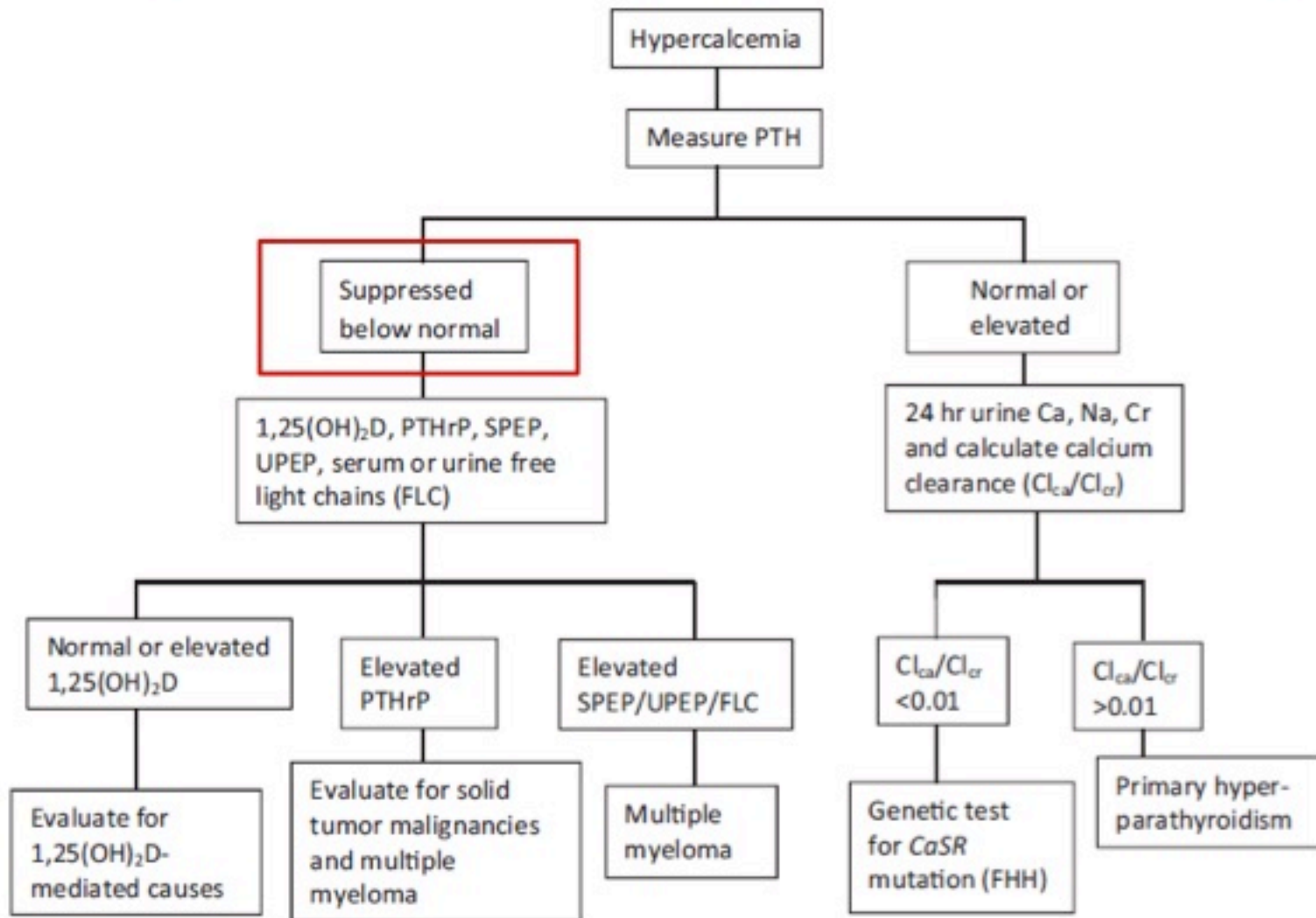


FIGURE 41.1 Outpatient evaluation of hypercalcemia.

Ipercalcemia PTH-indipendente

- Associata a tumori maligni
 - Metastasi osteolitiche
 - Paraneoplastica
- Vit D-dipendente
 - Intossicazione da Vit D
 - Produzione ectopica di 1-25Vit D (granulomi, linfomi)
- Endocrinopatie varie (ipercalcemia di lieve entità)
 - Ipertiroidismo
 - Insufficienza surrenalica
- Aumentato turnover osseo (m. di Paget)
- “Milk-alkali syndrome”
- Insufficienza renale cronica

Neoplasie maligne associate a ipercalcemia

Malignancy	Frequency (%)
Lung	35
Breast	25
Haematologic	14
Head and neck	6
Renal	3
Prostate	3
Unknown primary	7
Others	7

Le Ipercalcemie - Diagnosi differenziale

	PHPT	FHH	HHM	Metastasi	MM	Sarcoidosi
Ca	↑	↑	↑	↑	↑	↑
P	N/↓	N/↓	N/↑	N/↑	N/↑	N/↑
PTH	↑	↑	↓	↓	↓	↓
PTHrp	ind	ind	↑	ind	ind	ind
1-25D	↑	N/↑	↓	↓	↓	↑
Ca _u	↑	↓	↑	↑	↑	↑

PHPT = iperparatiroidismo primitivo; FHH = ipercalcemia ipocalciurica familiare; HHM = humoral hypercalcemia of malignancy; MM = mieloma multiplo