

CORSO DI AGGIORNAMENTO

NUOVE TRAIETTORIE NELLA CURA DELL'IPOPARATIROIDISMO

**IRCCS OSPEDALE SAN RAFFAELE
UNIVERSITÀ VITA E SALUTE
SAN RAFFAELE MILANO
Aula Pinta**

3 luglio 2025

PROGRAMMA

- 8.30 Registrazione partecipanti
- 9.00 Presentazione del corso
A. Giustina, G. Vezzoli

I SESSIONE - EZIOLOGIA DELL'IPOPARATIROIDISMO

Moderatori: *M. Bussi, G. Vezzoli*

- 9.15 Post-chirurgico
F. Perticone
- 9.30 Autoimmune
M. L. Brandi
- 9.45 Genetico
E. Sala
- 10.00 Discussione

II SESSIONE - DIAGNOSI E CLINICA

DELL'IPOPARATIROIDISMO

Moderatore: *A. Giustina*

- 10.15 Fisiopatologia e diagnosi
J. Chodini
- 10.30 Complicanze ossee
L. Di Filippo
- 10.45 Complicanze renali
N. Foligno
- 11.00 Discussione
- 11.15 Coffee break

COME SOSTITUIRE IL PTH NELL'IPOPARATIROIDISMO

Moderatore: *M. Cozzolino*

- 11.30 Palopegteriparatide
G. Vezzoli
- 11.45 Teriparatide e PTH1-84
A. Allora
- 12.00 Eneboparatide e Calciolitici
S. Mora
- 12.15 Discussione

ESPERIENZE TERAPEUTICHE NELL'IPOPARATIROIDISMO

Moderatore: *N. Napoli*

- 12.30 Trattare l'ipoparatiroidismo nella pratica clinica 1
A. Palermo
- 12.45 Trattare l'ipoparatiroidismo nella pratica clinica 2
E. De Menis
- 13.00 Discussione
- 13.15 Conclusioni
- 13.30 Conclusione dei lavori e compilazione questionari ECM

PRESIDENTI DEL CORSO

Andrea Giustina, Giuseppe Vezzoli

RESPONSABILE SCIENTIFICO PER ECM

Giuseppe Vezzoli, U.O. Nefrologia, RCCS Ospedale San Raffaele di Milano, UniSR, Milano

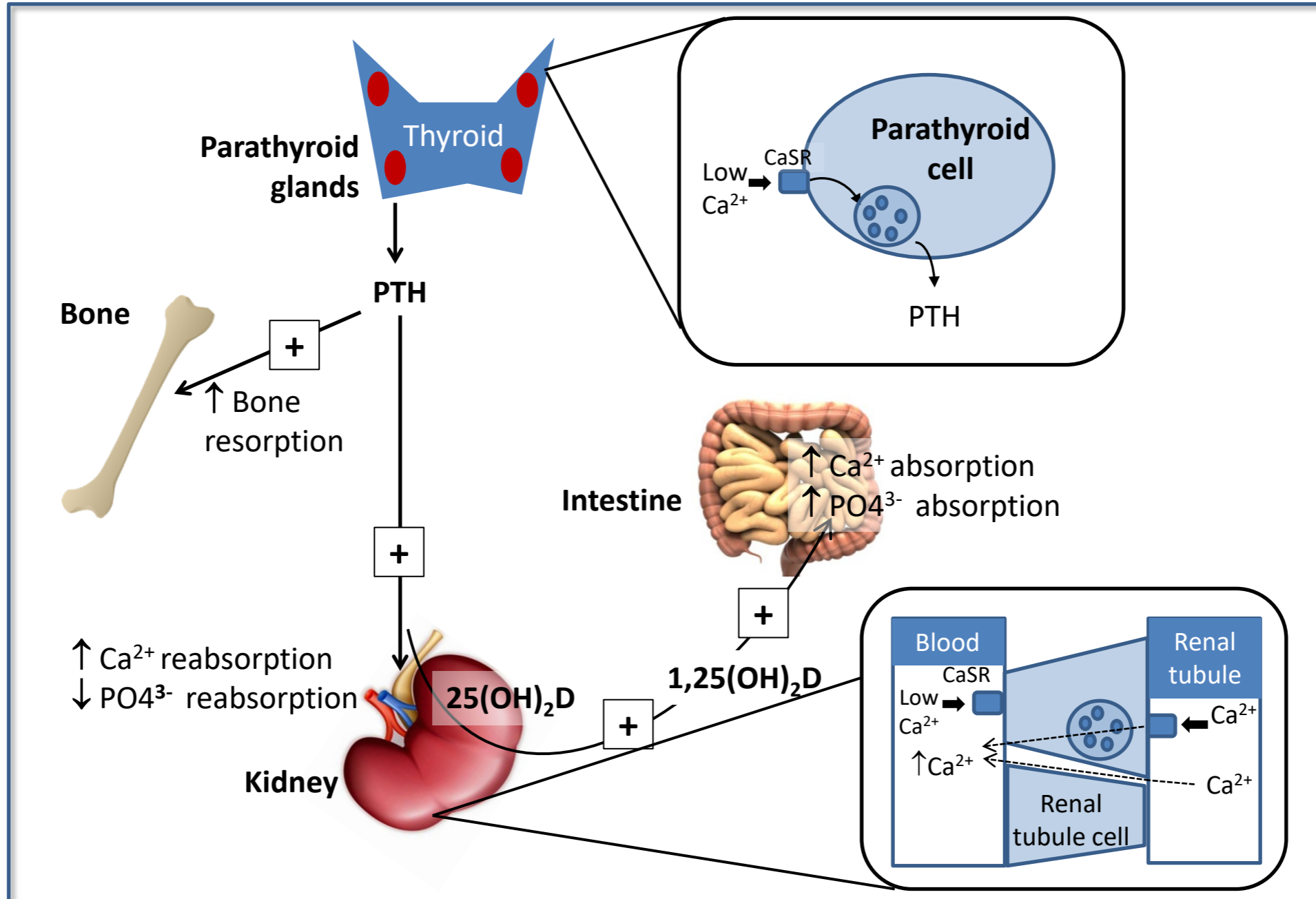
MODERATORI E RELATORI

Agnese Allora, U.O. Endocrinologia, IRCCS Ospedale San Raffaele di Milano
Maria Luisa Brandi, U.O. Endocrinologia, Fondazione Firmo di Firenze, IRCCS Osp. San Raffaele di Milano
Mario Bussi, U.O. Otorinolaringoiatria, IRCCS Ospedale San Raffaele di Milano, UniSR, Milano
Jacopo Chiodini, U.O. Endocrinologia, ASST Grande Osp. Metropolitano di Niguarda, Univ. degli Studi di Milano
Mario Gennaro Cozzolino, U.O. Nefrologia, ASST SS Paolo e Carlo, Ospedale San Paolo, Univ. degli Studi di Milano
Ernesto De Menis, U.O. Medicina Interna, AULSS2 Veneto, P.O. Treviso
Luigi Di Filippo, U.O. Endocrinologia, IRCCS Ospedale San Raffaele di Milano, UniSR, Milano
Nadia Foligno, U.O. Nefrologia, IRCCS Ospedale San Raffaele di Milano
Andrea Giustina, Direttore dell'Istituto di Scienze Endocrine e Metaboliche dell'Università Vita e Salute di Milano San Raffaele, U.O. Endocrinologia

AGENDA: Hypoparathyroidism

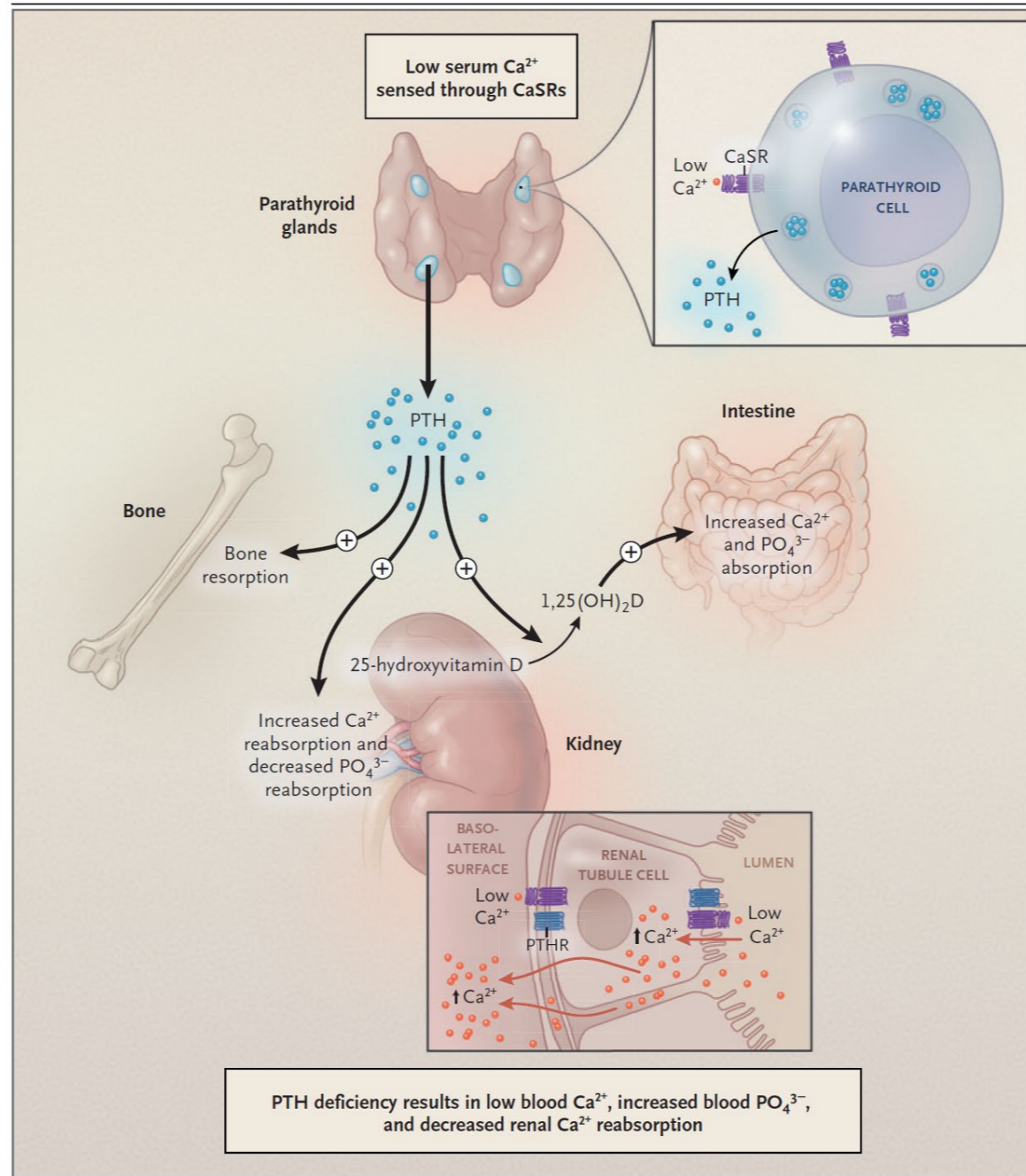
- **pathophysiology**
- **diagnosis**

PTH ACTIONS



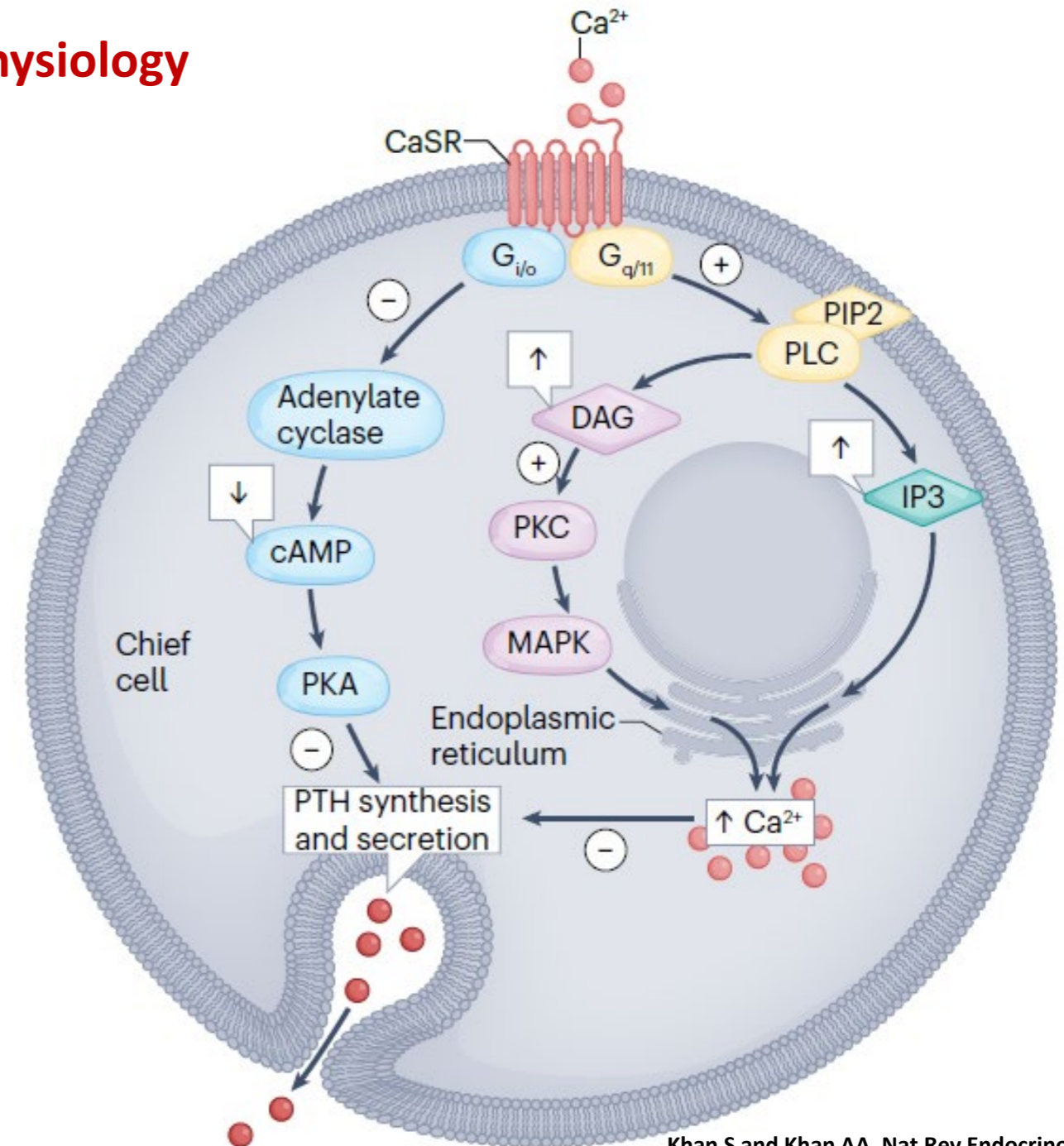
Palermo A et al, Handbook of Endocrinology and Metabolism 2020

CONTROL OF MINERAL HOMEOSTASIS BY PARATHYROID HORMONE AND THE CALCIUM-SENSING RECEPTOR



Parathyroid chief cell physiology

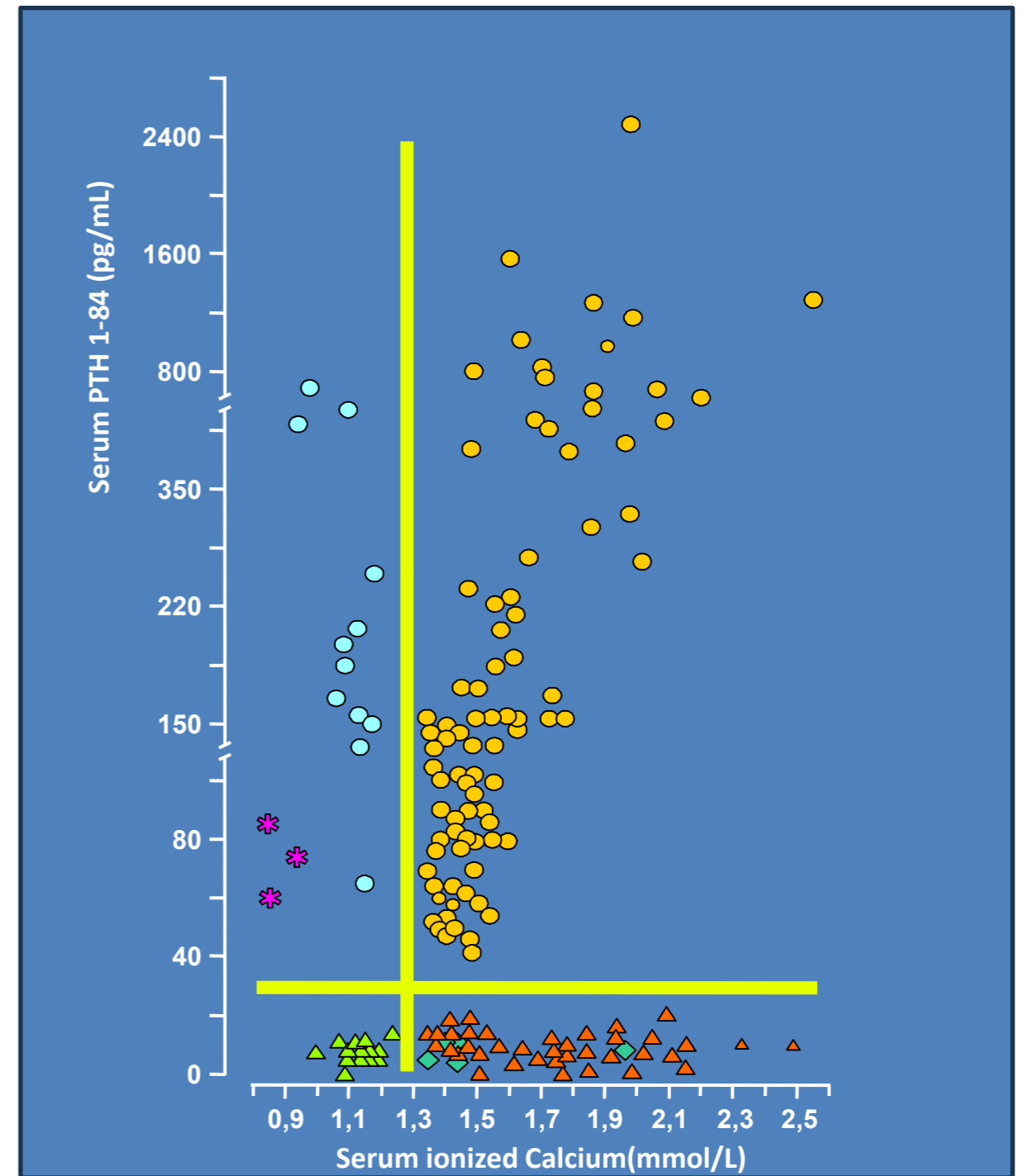
- Calcium binds to the calcium-sensing receptor (CaSR, G-protein-coupled receptor)
- Calcium bound to CaSR activates $G_{i/o}$, which leads to inhibition of adenylate cyclase, which decreases cAMP production and prevents activation of protein kinase A (PKA), leading to reduced parathyroid hormone (PTH) synthesis and secretion.
- Activation of CaSR also activates $G_{q/11}$, through which phospholipase C (PLC) cleaves phosphatidylinositol 4,5-bisphosphate (PIP₂) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP₃).
- IP₃ binds to receptors on the endoplasmic reticulum and increases intracellular calcium concentrations, which subsequently inhibit PTH synthesis and secretion
- DAG activates protein kinase C (PKC), which leads to activation of the mitogen-activated protein kinases (MAPK) signalling pathways, which, in turn, results in increased intracellular concentrations of calcium and inhibition of PTH synthesis and secretion



Khan S and Khan AA, Nat Rev Endocrinol 2025

RELATION BETWEEN CALCIUM AND PTH IN PARATHYROID DISORDERS

- Primary Hyperparathyroidism, n=85
- Osteomalacia, n=12
- ▲ Malignant hypercalcemia, n=38
- ◆ Iatrogenic hypercalcemia, n=5
- ▲ Hypoparathyroidism n=15
- * Pseudo-hypoparathyroidism, n=3



CAUSES OF HYPOCALCEMIA WITH LOW PTH

LOW PTH LEVELS (HYPOPARATHYROIDISM)
Parathyroid destruction
Surgery
Autoimmune disorders (autoimmune polyglandular syndromes type 1)
Storage/infiltrative diseases (Metastatic cancer, Wilson disease, Hemochromatosis, granulomas diseases)
Cervical Irradiation
Acquired Reduced parathyroid function
Hypo/hypermagnesemia
Genetic Reduced parathyroid function
Familiar Isolated Hypoparathyroidism
Autosomal Dominant Hypocalcemia (ADH 1 and 2)
Parathyroid agenesis
DiGeorge Syndrome
Mitochondrial neuropathies
Kenny-caffey Syndrome type 1 and 2

Palermo A et al, Handbook of Endocrinology and Metabolism 2020

POST-SURGICAL HYPOPARATHYROIDISM

Risk factors for postsurgical hypoparathyroidism¹

Patient factors

- Obesity
- BMI >40
- Vitamin D deficiency
- Paediatric patients

Disease factors

- Graves disease
- Malignancy
- Concomitant thyroid and/or parathyroid surgery

Operative factors

- Central lymph node level VI dissection
- Reoperative surgery
- Trans-oral approach
- Surgical time >3h
- Low surgical volume
- Incidental parathyroidectomy.

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APS1 (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy, APECED)

- The cardinal features of APS1 include **adrenal insufficiency, hypoparathyroidism and mucocutaneous candidiasis**. At least 80% of patients with APS1 have hypoparathyroidism.
- In APS1, antibodies against the parathyroid-expressed antigen NALP5 (NACHT leucine-rich-repeat protein 5) are present and are associated with hypoparathyroidism. **Autoantibodies to type I interferons, namely IFN ω and IFN α** subtypes, are present in almost all patients.
- **If interferon testing is unavailable**, then clinicians should proceed with **genetic testing**. **AIRE gene sequencing** confirming biallelic mutations indicates APS1, and a dominant negative mutation indicates non-classic APS1.
- Genetic testing for mutations in the **AIRE gene is recommended if patients exhibit at least two cardinal features of APS1: chronic mucocutaneous candidiasis, adrenal insufficiency or hypoparathyroidism**.
- **Patients with type I interferon antibodies but no evidence of an AIRE gene mutation require imaging to exclude thymomas** and gene sequencing for potential **RAG** mutations as these conditions are also associated with the presence of these antibodies. Patients negative for both antibodies and **AIRE** mutations are classified as having an 'APS1-like' syndrome.

AGENDA: Hypoparathyroidism

- pathophysiology
- diagnosis

HYPOPARATHYROIDISM

Diagnosis

- Hypocalcemia and hyperphosphatemia
- PTH N/↓
- Urinary phosphorous ↓
- Urinary calcium: N/↑

Differential diagnosis of hypocalcemia

- Familial hypercalciuric hypocalcemia (activant CaSR mutation): PTH N and hypercalciuria
- Hypomagnesiemia;
- PTH ↑: pseudohypoparathyroidism, CKD, malabsorption, acute pancreatitis, severe vitamin D deficiency

HYPOCALCEMIA: SYMPTOMS

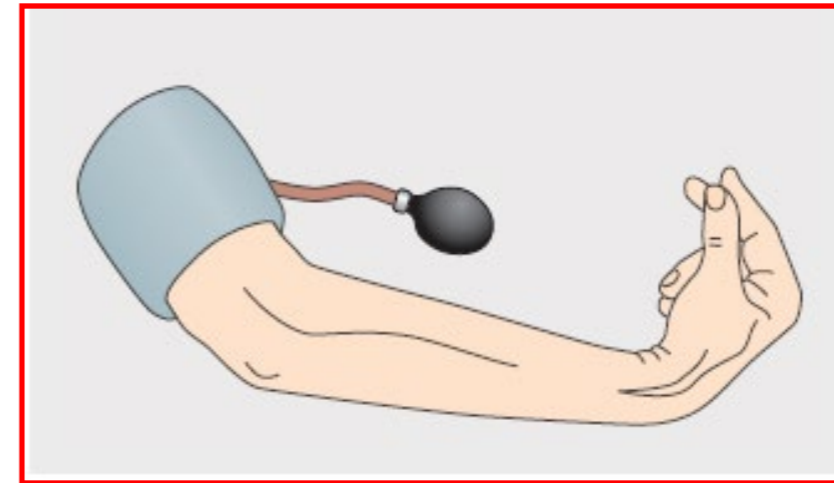
Acute Hypocalcaemia
Paresthesias (peri-oral, extremities)
Muscle spasm
Laryngospasm
Bronchospasm
Seizures
Prolonged QT interval
Arrhythmia
Hypotension
Papilledema
Chronic Hypocalcaemia
Dry skin
Basal ganglia and other ectopic calcifications
Subcapsular cataracts
Dental Abnormalities
Dementia
Parkinsonism and extrapyramidal signs

Palermo A et al, Handbook of Endocrinology and Metabolism 2020, in press

A latent tetany may be disclosed by the Chvostek and Trousseau signs



Positive in up to 10% of normal individuals
Negative in up to 29% of hypocalcemic patients



Positive in only 1% of normal individuals
Negative in only 6% of hypocalcemic patients

POST-SURGICAL HYPOPARATHYROIDISM DEFINITIONS

- Most patients (70-80%) with postsurgical hypoparathyroidism will recover.
- Patients are considered to have immediate **postsurgical hypoparathyroidism** if their total serum levels of **calcium adjusted for albumin and levels of PTH recover within 1 month** after surgery
- Patients who require supplementation for ongoing **hypocalcaemia beyond 1 month** are considered to have **protracted hypoparathyroidism**.
- **Chronic hypoparathyroidism** is diagnosed if the **hypocalcaemia persists beyond 1 year** after surgery.

Khan, A. A. et al. Evaluation and management of hypoparathyroidism summary Statement and guidelines from the second international workshop. *J. Bone Miner. Res.* 37, 2568–2585 (2022).

DIAGNOSIS

- Hypoparathyroidism is diagnosed based on the confirmation of **hypocalcaemia on two separate occasions** at least 2 weeks apart in association with an undetectable, **low or inappropriately normal PTH** levels
- Patients presenting with **severe symptoms of hypoparathyroidism** that require emergency treatment (for example, seizures or cardiac arrhythmias), in association with hypocalcaemia and low levels of PTH, **should be treated for presumed hypoparathyroidism**.
- Once the patient has stabilized, serum levels of calcium and PTH can be **tested again on two separate occasions at least 2 weeks apart** to confirm the diagnosis.

Khan, A. A. et al. Evaluation and management of hypoparathyroidism summary Statement and guidelines from the second international workshop. *J. Bone Miner. Res.* 37, 2568–2585 (2022).

POST-SURGICAL HYPOPARATHYROIDISM

- **Most frequent form**
- **After thyroid or parathyroid surgery, due to**
 - ✓ **parathyroids removal**
 - ✓ **accidental blood supply interruption**
- **Incidence related to the surgeon experience rather than to the type of surgical operations**
- **May be transient (even with severe hypocalcemia), if it is due to tissutal edema or intraglandular hemorrhagia**
- **Differential diagnosis with «hungry bone syndrome»**

HYPOPARATHYROIDISM

Diagnosis in post-surgical hypoparathyroidism

- **Measuring serum levels of PTH 12–24 h after total thyroidectomy provides higher sensitivity and specificity than measuring serum levels of calcium in predicting permanent hypoparathyroidism.**
- **A serum level of PTH >10 pg/ml (1.05 pmol/l) almost certainly excludes the risk of developing permanent hypoparathyroidism**
- **A serum level of PTH <10 pg/ml (1.05 pmol/l) is associated with a higher likelihood of permanent hypoparathyroidism, although this risk is still lower than 50%**
- **Patients who have hypoparathyroidism 1 month after surgery have protracted postsurgical but their chance of parathyroid function recovery at 1 year after surgery is 75%.**
- **The likelihood of parathyroid function recovery 1-year point is 10–15%**

Khan S and Khan AA, Nat Rev Endocrinol 2025

Monitoring

For patients with relatively stable chronic hypoparathyroidism every 3–12 months:

- serum creatinine
- GFR
- calcium (ionized or calcium corrected for albumin),
- magnesium
- phosphate.

For patients with relatively stable chronic hypoparathyroidism every 6–12/24 months:

- 25-hydroxyvitamin
- Calcium 24-h urine

For patients with unstable disease (symptomatic hypocalcaemia and/or hypercalcaemia) more frequent monitoring of these tests is recommended, varying laboratory values and treatment regimens)

Imaging studies: baseline assessment for the presence of nephrolithiasis and/or nephrocalcinosis

Khan S and Khan AA, Nat Rev Endocrinol 2025

Key points

- Hypoparathyroidism is a complex disease characterized by inadequate secretion or action of parathyroid hormone (PTH), which leads to hypocalcaemia and can lead to hyperphosphataemia and hypercalciuria.

- Hypoparathyroidism is a biochemical diagnosis based on the confirmation of hypocalcaemia in association with a low or inappropriately normal PTH level.

- The aetiology of hypoparathyroidism can be divided into surgical causes (75–80% of cases) and non-surgical causes (20–25% of cases).

- Hypoparathyroidism affects multiple organ systems, including the renal, skeletal, cardiovascular, ophthalmological and neurological systems.

THANK YOU

