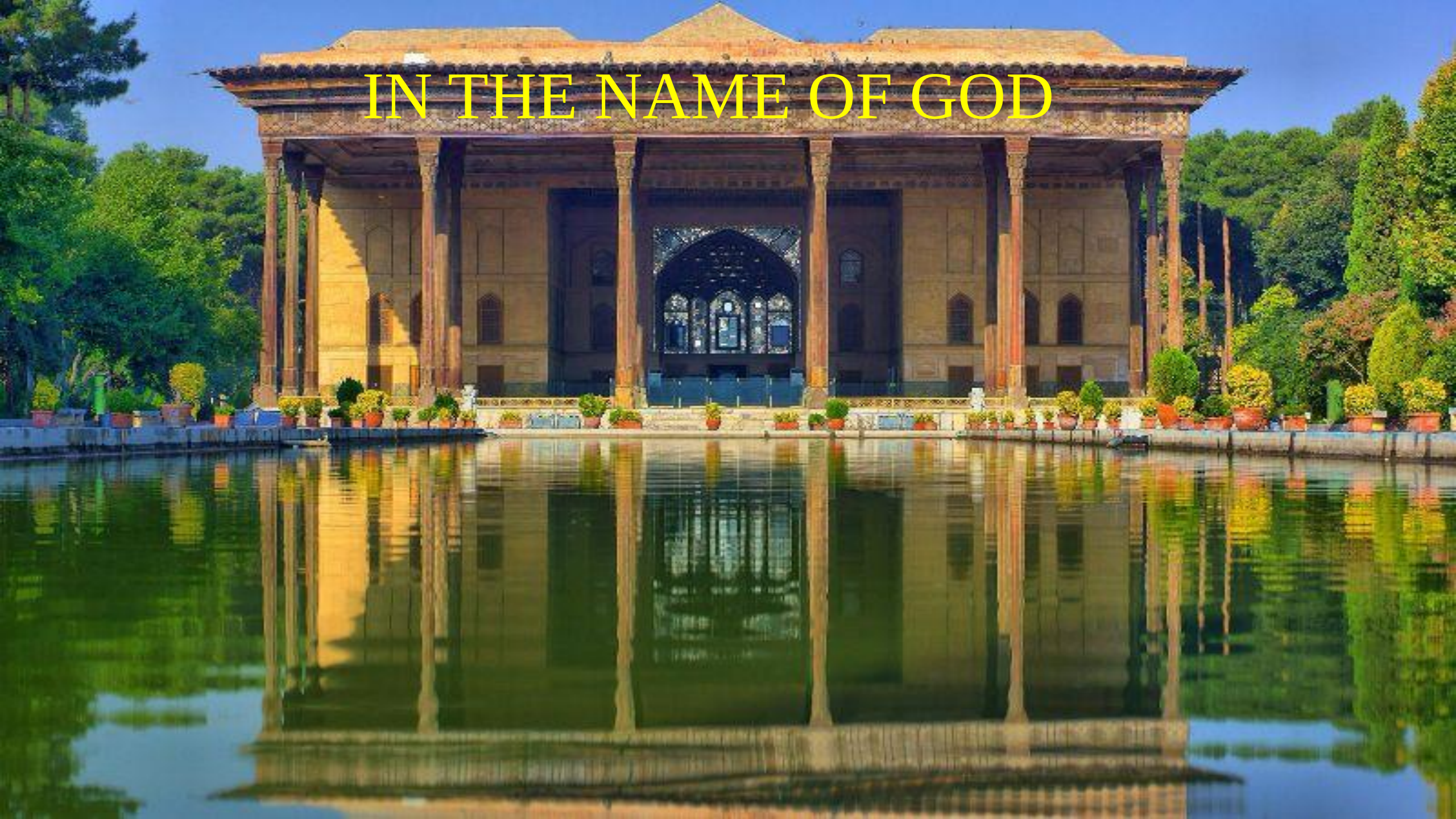
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Vice Chancellery for Research

6th International and 8th Iranian Congress of Endocrinology & Metabolism Updates

21st – 23rd May 2025 Isfahan, Iran

HYPOPITUITARISM

DR. MOZHGAN KARIMIFAR

ششمین همایش بین المللی و هشتمین همایش سراسری

تازه های غدد و متابولیسم

۳۱ اردیبهشت الی ۲ خرداد ۱۴۰۴، اصفهان، هتل بزرگ عباسی

6th International & 8th Iranian Congress of Endocrinology & Metabolism Updates

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محور های همایش

- دیابت و پرده دیابت
- اختلالات لیپید، چاقی و سندرم متابولیک
- بیماریهای تیروئید
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مجتمع آموزشی پژوهشی و درمانی حضرت نرجس (س)

مرکز تحقیقات غدد و متابولیسم دانشگاه علوم پزشکی اصفهان

دارای امتیاز بازآموزی

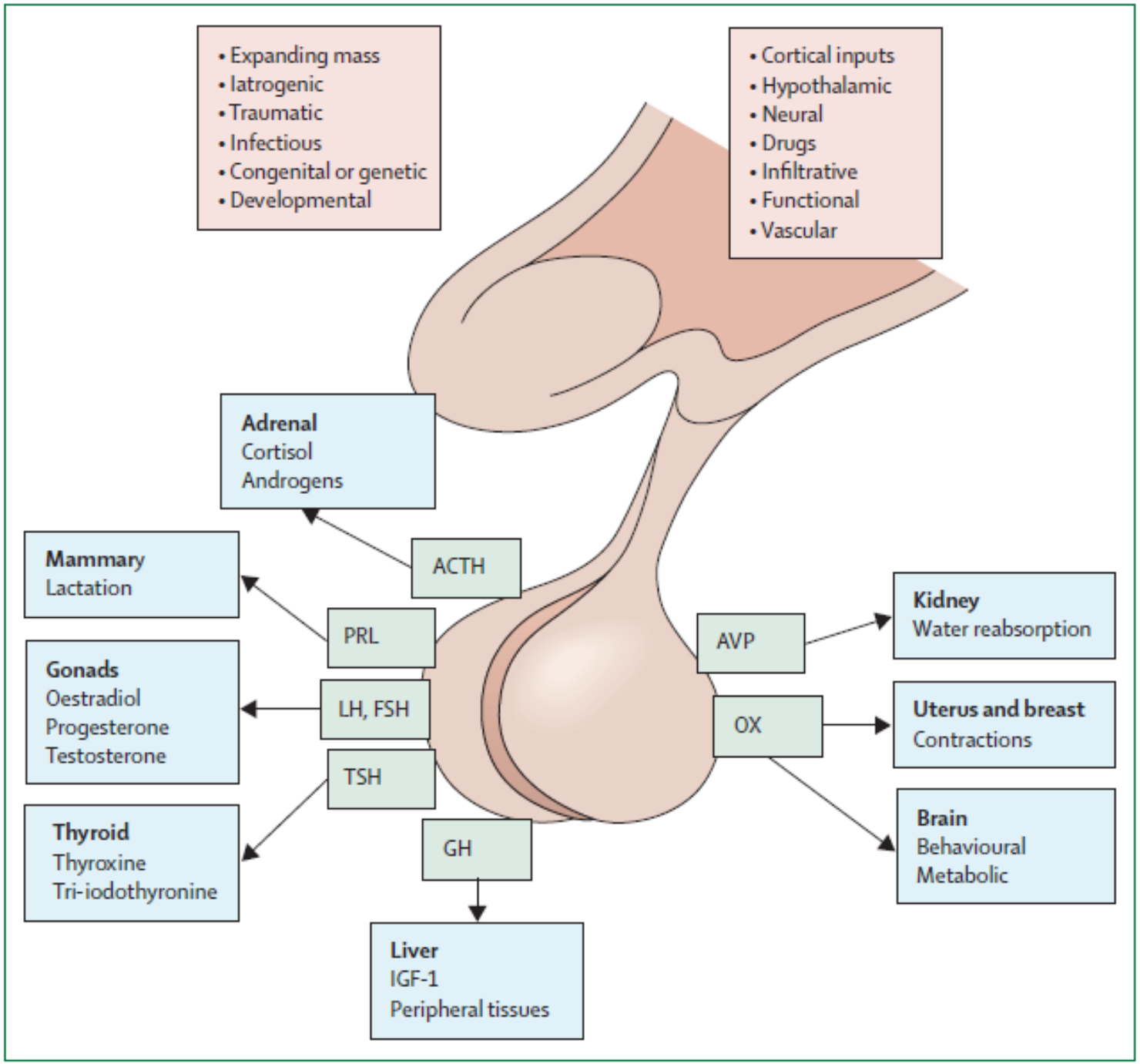
AGENDA

- **Definition of Hypopituitarism**
- **Epidemiology & Main cause of hypopituitarism**
- **Immune checkpoint inhibitors**
- **Traumatic brain injury**
- **Gene-editing therapies**

Introduction

- **Hypopituitarism**, defined as partial or complete deficiency of anterior or posterior pituitary hormones.

- Fleseriu M, Christ-Crain M, Langlois F, Gadelha M, Melmed S. Hypopituitarism. Lancet. 2024 Jun 15;403(10444):2632-2648. doi: 10.1016/S0140-6736(24)00342-8. Epub 2024 May 9. PMID: 38735295.



Fleseriu M, Christ-Crain M, Langlois F, Gadelha M, Melmed S. Hypopituitarism. Lancet. 2024 Jun 15;403(10444):2632-2648. doi: 10.1016/S0140-6736(24)00342-8. Epub 2024 May 9. PMID: 38735295.

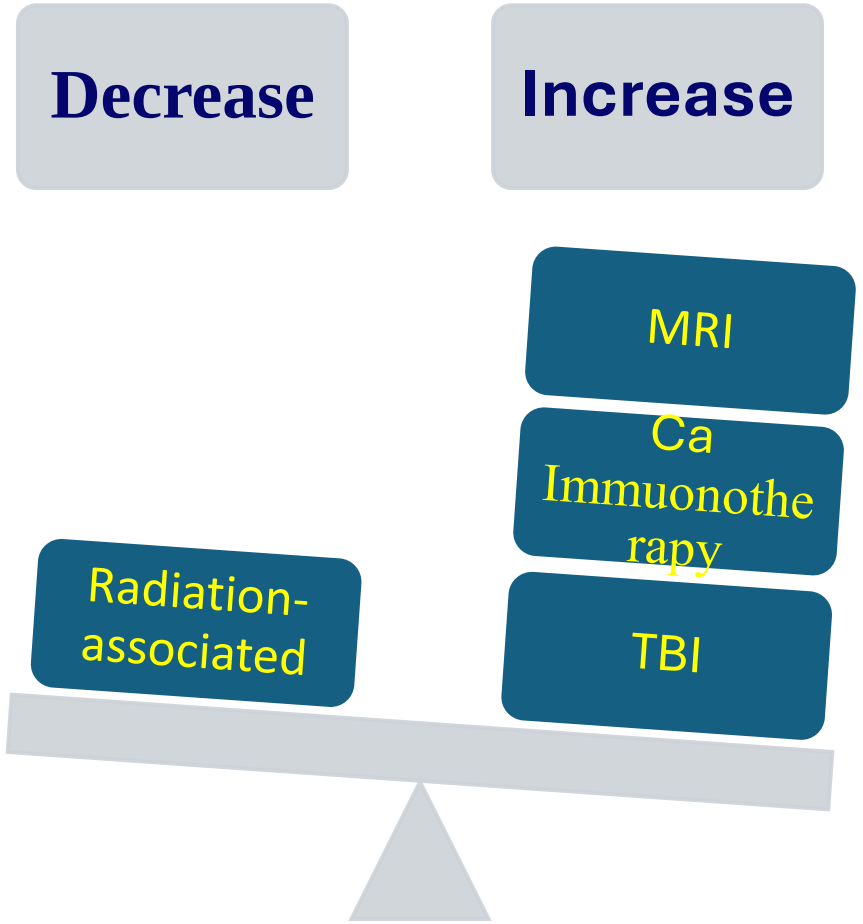
Epidemiology of Hypopituitarism

- A Spanish population-based study reported a prevalence of approximately 45.5 cases of hypopituitarism per 100 000 adults, with similar rates between females and males, and an annual incidence of 4.21 per 100 000 adults.

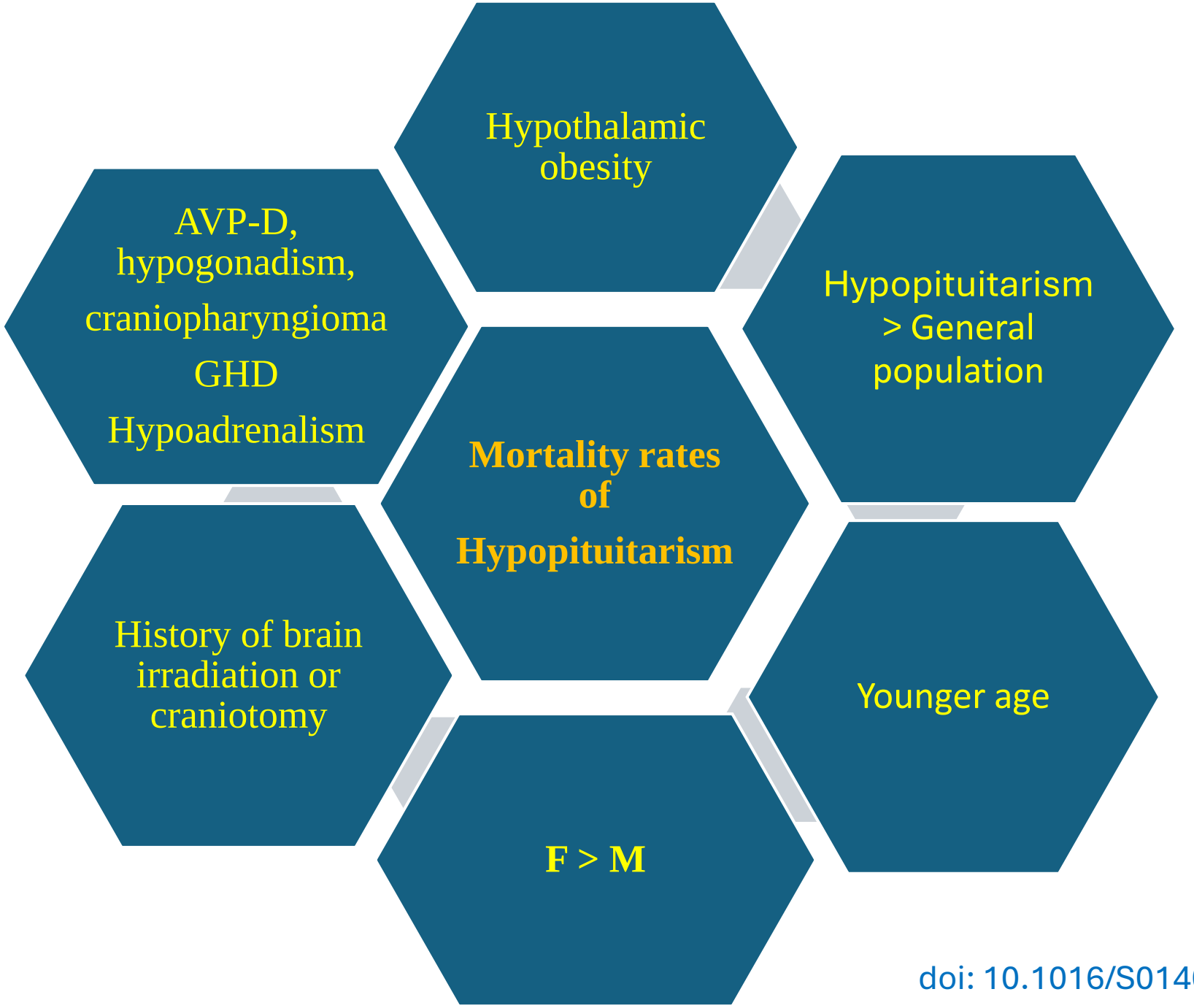
- Congenital hypopituitarism incidence is estimated at one in 4000 to one in 10 000 livebirths per year.

- Fleseriu M, Christ-Crain M, Langlois F, Gadelha M, Melmed S. Hypopituitarism. Lancet. 2024 Jun 15;403(10444):2632-2648. doi: 10.1016/S0140-6736(24)00342-8. Epub 2024 May 9. PMID: 38735295.
- Iwama S, Kobayashi T, Arima H. Management, biomarkers and prognosis in people developing endocrinopathies associated with immune checkpoint inhibitors. Nat Rev Endocrinol. 2025 May;21(5):289-300. doi: 10.1038/s41574-024-01077-6. Epub 2025 Jan 9. PMID: 39779950.

Epidemiology



doi: 10.1016/S0140-6736(24)00342-8



doi: 10.1016/S0140-6736(24)00342-8

	Cause	Underlying cause
Medication-induced or endogenous hormonal excess	Suppression of specific axis, possibly reversible with medication discontinuation	High-dose glucocorticoid treatment (oral, injectable, inhaled, topical, or intranasal) or long-standing endogenous Cushing's syndrome; medications including opiates, drugs causing hyperprolactinaemia, androgens, thyroid hormones, somatostatin receptor ligands, intravenous dopamine, interferon, ribavirin, or other
Functional	Reversible isolated or combined deficiency due to systemic disorder	Acute or chronic severe illness, anorexia nervosa, extreme exercise, obesity or malnutrition, or pseudotumour cerebri
Mass effect and treatment-related effects	Compressive sellar or suprasellar lesion; treatment to the sellar area, basal brain, or nasopharynx	Pituitary adenoma (functioning or non-functioning), pituitary cysts (Rathke, arachnoid, epidermoid, or dermoid), craniopharyngioma, germinoma, metastasis (breast, lung, or other), meningioma, glioma, ependymoma, or other; surgery and radiation therapy to the sellar area
Inflammatory	Hypophysitis or inflammatory process, or both, in the anterior or posterior pituitary, stalk, or hypothalamus	Lymphocytic, granulomatous, IgG4 related, peritumoural, secondary to immunotherapy (anti-CTLA-4, anti-PD-1, or anti-PD-L1), granulomatosis with polyangiitis, giant cell granuloma, secondary to other vasculitis or connective tissue disorders, xanthomatous, necrosis, or paraneoplastic syndromes (anti-POMC or anti-PIT1)
Infiltrative	Pituitary or stalk infiltration, or both, often systemic	Haemochromatosis, sarcoidosis, amyloidosis, or histiocytosis (Langerhans cell or Erdheim-Chester disease)
Infectious or toxic	Mostly in immunosuppressed or endemic populations	COVID-19; tuberculosis; viral, bacterial, fungal, or parasitic infection; syphilis; AIDS; or snakebite venom
Vascular	Infarction or haemorrhage	Pituitary apoplexy, pituitary haemorrhage, Sheehan syndrome, cavernous carotid artery aneurysm, cavernous sinus thrombosis, or subarachnoid haemorrhage
Traumatic	Mechanical or vascular injury to the sellar area	Head injury or contact sports (eg, boxing, kickboxing, or American football)
Developmental	Syndromic or non-syndromic genetic alterations in pituitary development	Septo-optic dysplasia, absent pituitary gland, hypoplastic pituitary gland, empty sella, or stalk interruption (table 2; appendix p 2)
Other	Unknown	Idiopathic

This is a non-exhuastive list of hypopituitarism causes. Genetic causes of hypopituitarism are discussed in table 2. CTLA-4=cytotoxic T-lymphocyte associated protein 4. PD-1=programmed death 1. PD-L1=programmed death ligand 1. PIT1=pituitary-specific transcription factor 1. POMC=pro-opiomelanocortin.

Table 1: **Causes of hypopituitarism by category**

Fleseriu M, Christ-Crain M, Langlois F, Gadelha M, Melmed S. Hypopituitarism. Lancet. 2024 Jun 15;403(10444):2632-2648. doi: 10.1016/S0140-6736(24)00342-8. Epub 2024 May 9. PMID: 38735295.

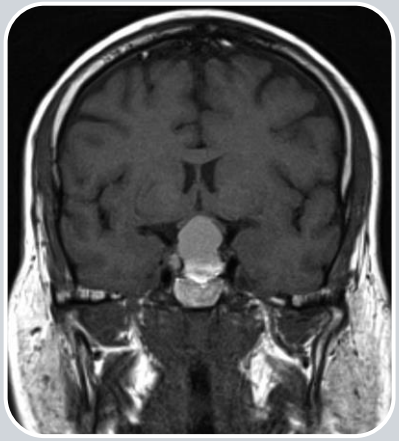
Main cause of hypopituitarism in adults

Adenoma of pituitary

- 17% of all intracranial lesions in adults
- 3% of paediatric brain tumours

Prevalence of clinically apparent adenomas

- Low
- MRI
- Anterior hypopituitarism can be seen in 34–89% of adults with compressive non-functioning pituitary adenomas



Pituitary Adenoma

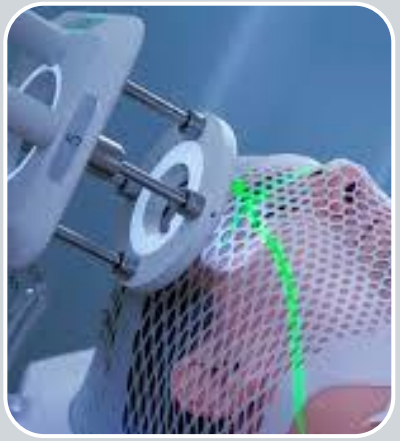
Gonad(80%)

GH

TSH

ACTH

AVP-D (extremely rare)



Radiotherapy

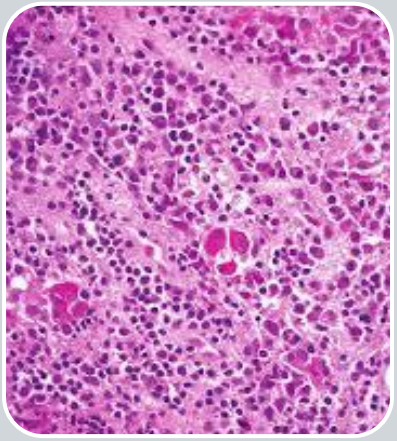
GH (45%)

Gonad (30%)

TSH (25%)

ACTH

(22%)



Lymphocytic hypophysitis

ACTH (60-80%)

AVP-D (50%)

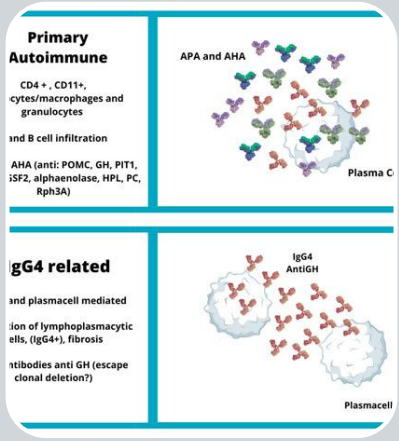
Thyroid and gonadal axes (30–60%)

GH (14–37%)

Pregnancy-related hypophysitis

late pregnancy or the postpartum period

lower AVP-D rate



IgG4-related hypophysitis

Panhypopituitarism(40%)

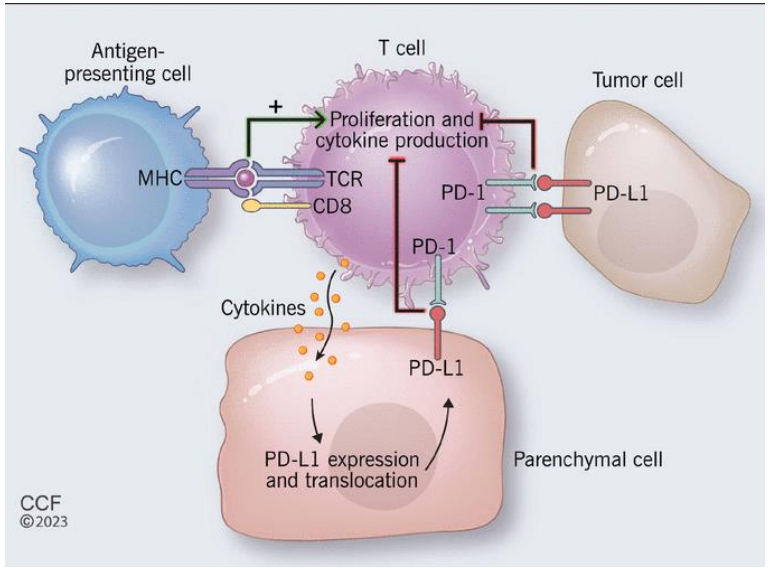
Pituitary metastases

- **AVP-D** is extremely rare in patients with pituitary adenomas, but it may be seen in as many as 50% at presentation in patients with pituitary metastases.

- Fleseriu M, Christ-Crain M, Langlois F, Gadelha M, Melmed S. Hypopituitarism. Lancet. 2024 Jun 15;403(10444):2632-2648. doi: 10.1016/S0140-6736(24)00342-8. Epub 2024 May 9. PMID: 38735295

Immune checkpoint inhibitors

- Diagnoses of hypophysitis have increased in the past decade with increased use of cancer immunotherapies, specifically CTLA-4, PD-1, and PD-L1 inhibitors.



doi:10.3949/ccjm.90a.22032

Endocrinopathy associated ICI

- Thyroid
- Hypophysitis
- Type 1 diabetes mellitus
- Primary adrenal insufficiency
- Hypoparathyroidism

Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775

Immune checkpoint inhibitors by mechanism

Drug mechanism	Drug name
Anti-PD-1	Nivolumab Pembrolizumab Cemiplimab Dostarlimab Retifanlimab Toripalimab Tislelizumab
Anti-PD-L1	Atezolizumab Avelumab Cosibelimab Durvalumab
Anti-CTLA-4	Ipilimumab Tremelimumab
Anti-LAG-3/anti-PD-1	Relatlimab and nivolumab

Uptodate 2025

Epidemiology of Pituitary irAEs

CTLA-4 ICI as monotherapy or in combination with a PD-1 ICI (14%)

- PD-1/PD-L1 ICI monotherapy (1.5%)

Incidence of pituitary irAEs

anti-CTLA4 antibody (24%)

- anti-PD1 antibody (6%)

Another prospective study

anti-CTLA4 plus anti-PD1 antibodies (19%)

https://doi.org/10.1016/j.eprac.2024.03.023
doi: 10.1038/s41574-024-01077-6. Epub 2025 Jan 9. PMID: 39779950.

Pathophysiology of Pituitary irAEs

- Lymphocytic infiltration by T cells accompanied by macrophages and complement deposition
- T cell-mediated cytotoxicity and complement activation

- https://doi.org/10.1038/s41574-024-01077-6

Pathophysiology of Pituitary irAEs

Combined pituitary hormone deficiency	•Necrotic lesions •Fibrosis
Isolated ACTH deficiency	• Necrotic lesions and fibrosis **are not** observed

Pathophysiology of ICI Hypophysitis

doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775

Onset of pituitary irAEs

- The **shortest duration** from the initiation of ICI treatment to the onset of pituitary irAEs was **23 days**, while the *longest duration* was *523* days.

- Iwama S, Kobayashi T, Arima H. Management, biomarkers and prognosis in people developing endocrinopathies associated with immune checkpoint inhibitors. Nat Rev Endocrinol. 2025 May;21(5):289-300. doi: 10.1038/s41574-024-01077-6. Epub 2025 Jan 9. PMID: 39779950.

Table 1

Features That Distinguish Immune Checkpoint Inhibitor-Associated Endocrinopathies Form Other Immune Related Adverse Events

Features	Characteristics of ICI-associated endocrinopathies
Epidemiology	Higher frequency in cohort studies than in trials due to better detection and characterization.
Presentation	Non-specific and subtle clinical features highlight the role of clinical suspicion and biochemical screening.
High-dose glucocorticoids for management	Limited role, mostly reserved for unrelenting pituitary mass effects.
Change in ICI regimen	Usually not necessary for mild dysfunction; can be resumed after control of symptoms and stable hormone replacement.
Long-term management	Hormone deficiency is permanent in most cases, necessitating continuity of care and patient engagement.
Link with cancer outcomes	Survival advantage is strongest with ICI-thyroiditis and not different with other ICI-associated endocrinopathies.

Abbreviation: ICI = immune checkpoint inhibitor.

Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775.

Table 2

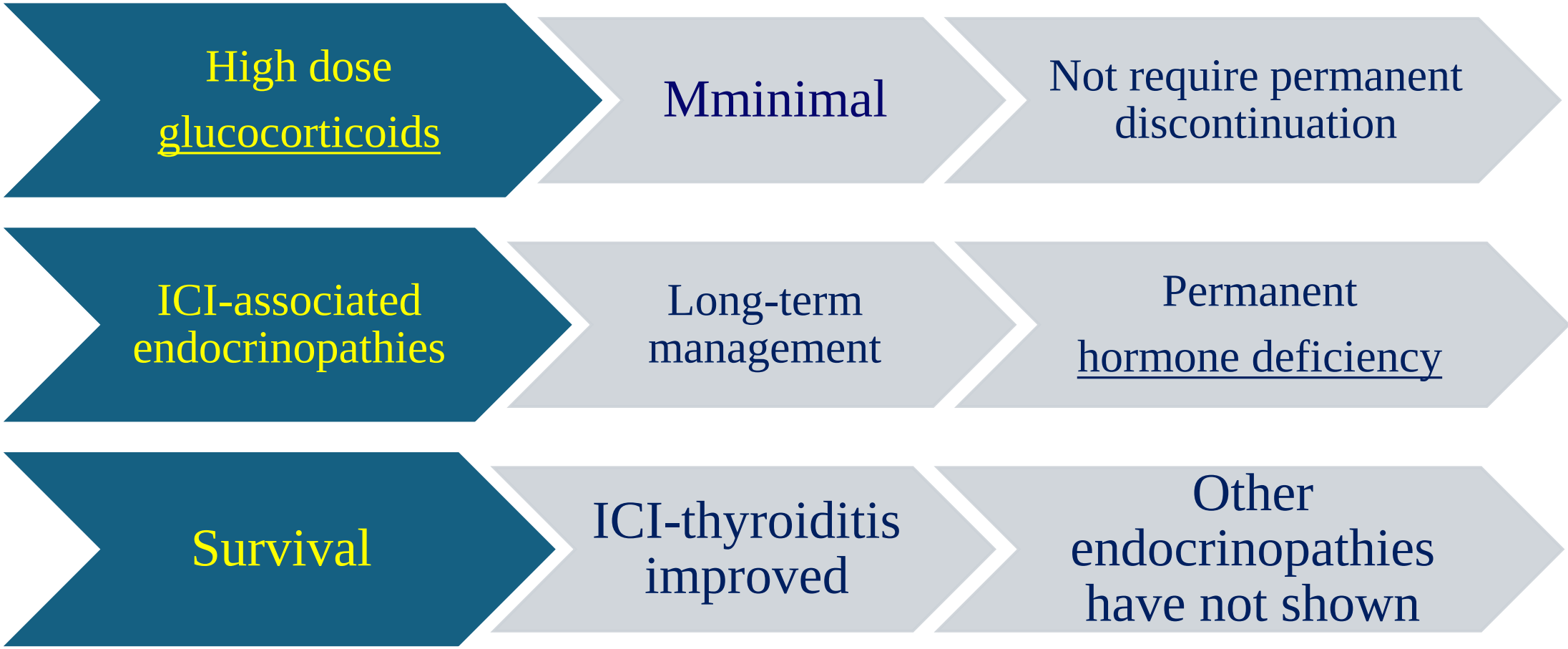
Differences in Immune Checkpoint Inhibitor-Hypophysitis Phenotype Based on Immune Checkpoint Inhibitor Regimens

Characteristics of pituitary dysfunction depending on immune checkpoint inhibitor regimen	CTLA-4 inhibitor monotherapy or combination with PD-1/PD-L1 inhibitor	PD-1/PD-L1 inhibitor monotherapy
Frequency	6-14%	0-1.5% (least with PD-L1)
Time to onset	6-12 wk	16-26 wk
Pituitary enlargement	More likely (approximately 70%)	Less likely (approximately 20%)
Mass effects	More likely	Less likely
Hypopituitarism	Multiple hormone deficiencies (ACTH and TSH most commonly)	Isolated ACTH deficiency

Abbreviations: ACTH = adrenocorticotropic hormone; CTLA-4 = cytotoxic T lymphocyte associated antigen-4; PD-1 = programmed death protein-1; PD-L1 = programmed death protein-ligand 1; TSH = thyroid stimulating hormone.

Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775.

Hypophysitis



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Presentation of ICI Hypophysitis

- The presentation depends on the extent of pituitary enlargement causing mass effects, with:
- headache
- diplopia
- visual field deficits
- and the occurrence of anterior hypopituitarism.
- The posterior pituitary is usually spared, making arginine vasopressin deficiency uncommon except in the setting of a large mass effect at a case-report level.

- Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775

Evaluation	PD-1/PD-L1 ICI	CTLA-4 combination ICI therapy
Asymptomatic screening	Not rec	in the first 6 months[1]
ESMO Guidelines	prior to treatment initiation	prior[2] to treatment initiation
Evaluation includes	ACTH, AM **cortisol**, **TSH, FT4**, electrolytes. repeat testing in 3 months FSH,LH, estrogen or testosterone	
	prolactin and IGF-1 do not impact management, Their low levels may help when differentiating from glucocorticoid induced AI	
ESMO Guidelines (European Society for Medical Oncology)		

1-Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775

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Sickness vs Permanent Hypogonadism

- Measuring **FSH**, **LH**, and **estrogen** or **testosterone** in women or men, respectively, can be performed **3 months later** since initial reduction may be due to sickness, and replacement in the short-term is not crucial.

- Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775

Pituitary MRI

- Especially if:
  - uncertain diagnosis
  - mass effects
  - concern for metastatic disease

- ICI-hypophysitis is confirmed if the patient has evidence of secondary hypothyroidism or AI and/or MRI findings, noting that MRI pituitary enlargement is usually absent after PD-1/PD-L1 ICI

- Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775

Dosage of steroids for the treatment of hypopituitarism

Adrenal crisis

- High-dose hydrocortisone
- 50–100 mg every 6–8 hours
- Alert cards or bracelets

Severe pituitary enlargement

- accompanied
  by headaches and/or visual field disturbances
- prednisolone
- 0.5–1.0 mg/kg–daily

However, previous studies have reported that high-dose steroids were ineffective at restoring pituitary function and were associated with shortened survival compared with low-dose steroids
https://doi.org/10.1038/s41574-024-01077-6

Management

- Hydrocortisone/ prednisone
- Hydrocortisone replacement must be started before initiating levothyroxine replacement
- Medicalert identifier
- Gonadal hormone replacement (persistent and confirmed)
- GH(Not Recommended in setting of active malignancy)

High-dose glucocorticoids

- worse oncologic outcomes

Prednisone 0.8-1 mg/kg/d

- unrelenting mass effects given for the shortest duration necessary (3-4 weeks)

Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775

Pituitary enlargement

- Resolves within 12 weeks

Persistence

- Alternative etiologies
- metastasis to pituitary gland

Recovery

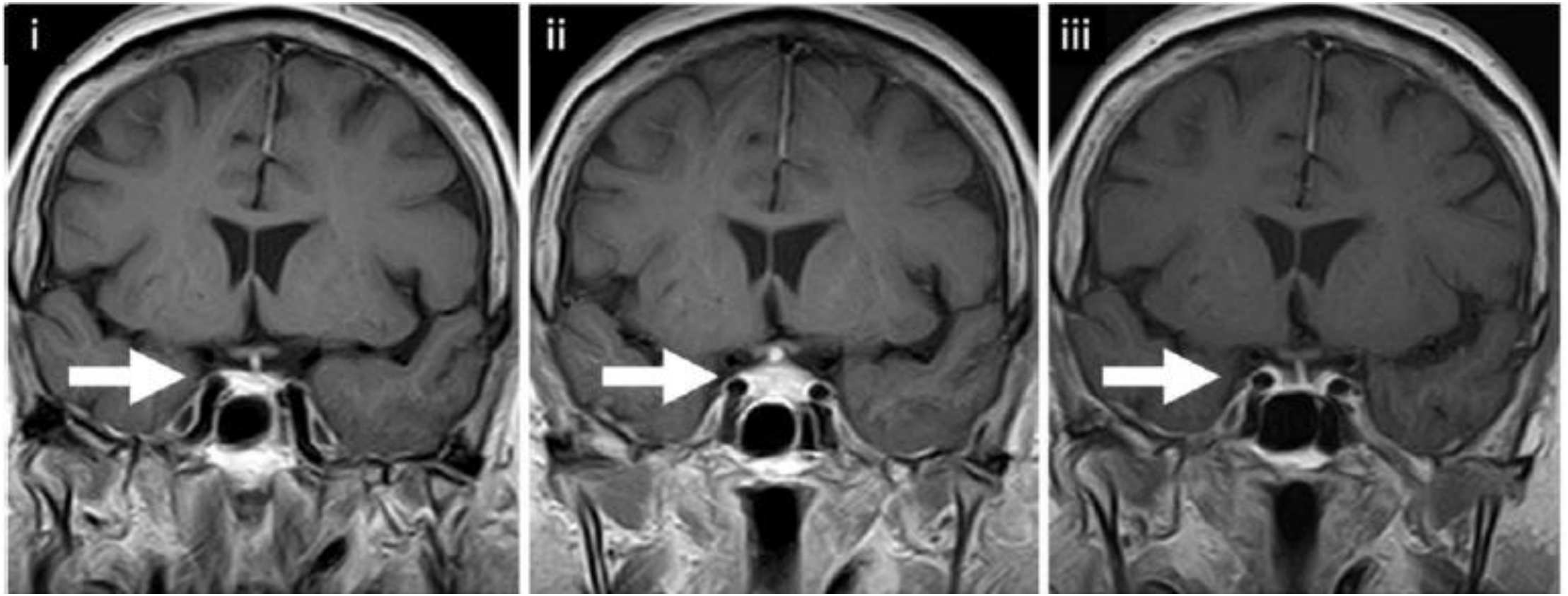
- Recovery of secondary hypothyroidism and hypogonadism in up to 50%.
- Secondary AI is permanent in most cases recovery of ACTH deficiency in a young male

Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775

Recovery of hypopituitarism

- Hence, recovery of hypopituitarism could be tested **every 3 to 6 months** for the **first year** and **every 6 to 12 months thereafter**, especially for the first **2 years** or for those where initial diagnosis was uncertain due to exogenous glucocorticoids

- Kotwal A, Kennedy R, Kikani N, Thosani S, Goldner W, Shariff A. Endocrinopathies Associated With Immune Checkpoint Inhibitor Use. Endocr Pract. 2024 Jun;30(6):584-591. doi: 10.1016/j.eprac.2024.03.023. Epub 2024 Mar 28. PMID: 38554775



Representative imaging changes seen with immune checkpoint inhibitor–induced hypophysitis. (A) Representative changes in the MRI appearance in a subset of 6 subjects within this cohort relative to CPI initiation and hypophysitis diagnosis. The clinical course in the subject highlighted in (B) is outlined by the dashed line. (B) Serial coronal T1 post-contrast MRIs demonstrate a normal appearing pituitary gland and infundibulum (i), followed by an enlarged pituitary gland and thickened infundibulum (ii), and ultimately a partially empty sella (iii).

Quandt Z, Kim S, Villanueva-Meyer J, Coupe C, Young A, Kang JH, Yazdany J, Schmajuk G, Rush S, Ziv E, Perdigoto AL, Herold K, Lechner MG, Su MA, Tyrrell JB, Bluestone J, Anderson M, Masharani U. Spectrum of Clinical Presentations, Imaging Findings, and HLA Types in Immune Checkpoint Inhibitor-Induced Hypophysitis. J Endocr Soc. 2023 Feb 6;7(4):bvad012. doi: 10.1210/jendso/bvad012. PMID: 36860908; PMCID: PMC9969737.

Which Patients treated with ICI are at risk for endocrine irAEs ?

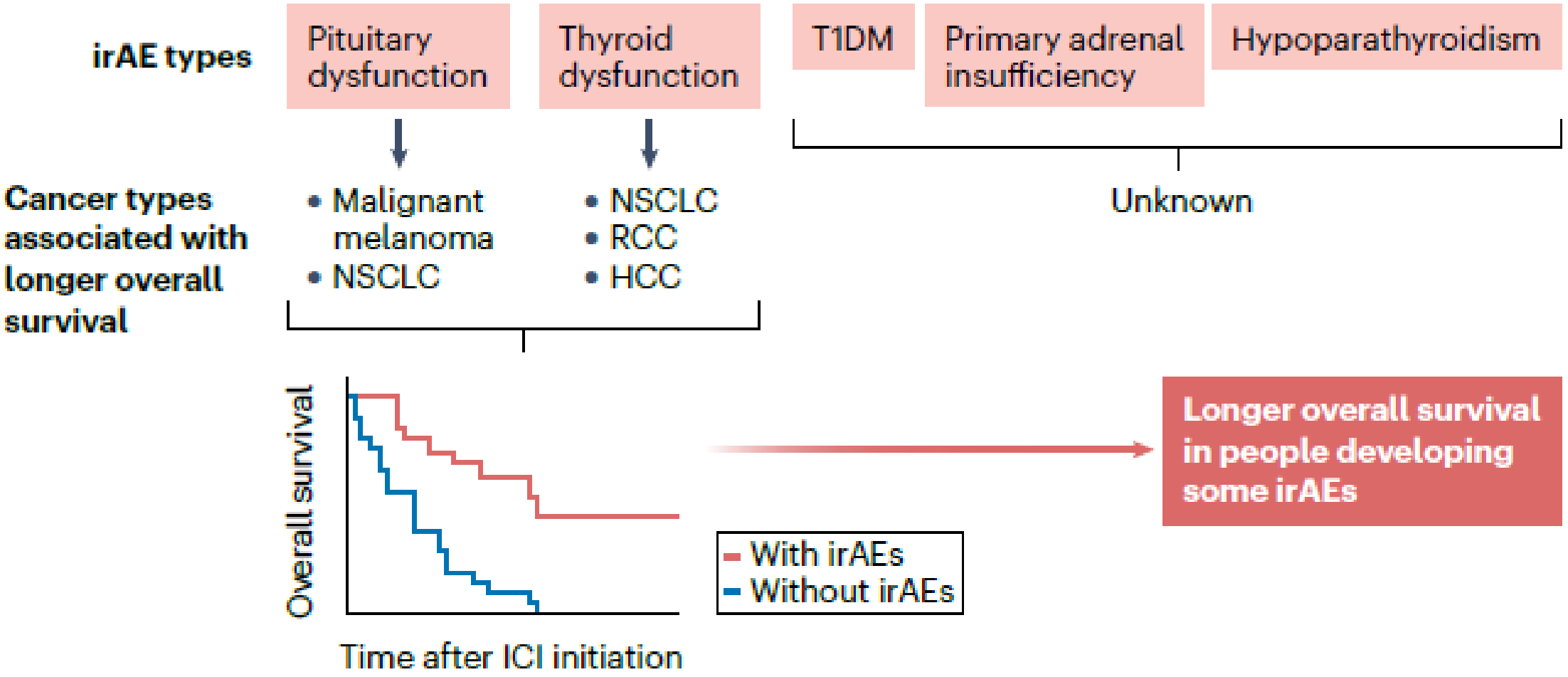
- **Anti-pituitary antibodies** and thyroid **autoantibodies** have been identified as potential biomarkers for the development of pituitary and thyroid irAEs, respectively.

- Iwama S, Kobayashi T, Arima H. Management, biomarkers and prognosis in people developing endocrinopathies associated with immune checkpoint inhibitors. Nat Rev Endocrinol. 2025 May;21(5):289-300. doi: 10.1038/s41574-024-01077-6. Epub 2025 Jan 9. PMID: 39779950.

Prolonged overall survival, after ICI treatment

- However, pituitary and thyroid irAEs have been reported to be associated with favourable clinical outcomes, including prolonged overall survival, after ICI treatment in certain types of cancer after appropriate therapy has been given for the endocrine irAE.

- Iwama S, Kobayashi T, Arima H. Management, biomarkers and prognosis in people developing endocrinopathies associated with immune checkpoint inhibitors. Nat Rev Endocrinol. 2025 May;21(5):289-300. doi: 10.1038/s41574-024-01077-6. Epub 2025 Jan 9. PMID: 39779950.



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Traumatic brain injury (TBI)

- In **traumatic brain injury (TBI)**, **advanced neuroimaging** (MRI) and **machine learning algorithms** now predict pituitary damage with >90% accuracy, enabling preemptive hormone screening.
- Longitudinal data reveal **GH deficiency** persists in 30% of TBI survivors at 5-year follow-up, correlating with poor neurocognitive recovery, spurring advocacy for mandatory endocrine monitoring in TBI guidelines.

- Badjatia N, Podell J, Felix RB, Chen LK, Dalton K, Wang TI, Yang S, Hu P. Machine Learning Approaches to Prognostication in Traumatic Brain Injury. Curr Neurol Neurosci Rep. 2025 Feb 19;25(1):19. doi: 10.1007/s11910-025-01405-x. PMID: 39969697.

Gene-editing therapies

- Gene-editing therapies** show promise in preclinical models: CRISPR-Cas9 targeting *PROP1* mutations restored pituitary function in congenital cases . Meanwhile, **stem cell-derived pituitary organoids** are entering Phase I trials, aiming to regenerate hormone-secreting cells.

- Garcia, M., et al. (2025). *Personalized Hormone Replacement via CRISPR-Edited Stem Cells*. *The Lancet Diabetes & Endocrinology*, 13(5), 345-357. DOI:10.1016/S2213-8587(25)00012-9

Personalized hormone replacement

- Clinically, **personalized hormone replacement** is gaining traction.
- For adrenal insufficiency, dual-release hydrocortisone formulations mimic physiological cortisol rhythms, reducing cardiovascular risks.

- Fleseriu M, Christ-Crain M, Langlois F, Gadelha M, Melmed S. Hypopituitarism. Lancet. 2024 Jun 15;403(10444):2632-2648. doi: 10.1016/S0140-6736(24)00342-8. Epub 2024 May 9. PMID: 38735295.

Oxytocin deficiency

- Oxytocin:
- increased **pro-social** and **empathic behaviour** and **decreased anxiety** typical of methylenedioxymethamphetamine (MDMA)
- Although oxytocin deficiency seems to be a new disease entity shown in patients with AVP-D, the role of oxytocin substitution therapy requires further investigation.

- Fleseriu M, Christ-Crain M, Langlois F, Gadelha M, Melmed S. Hypopituitarism. Lancet. 2024 Jun 15;403(10444):2632-2648. doi: 10.1016/S0140-6736(24)00342-8. Epub 2024 May 9. PMID: 38735295

Gut-pituitary axis

- Finally, the **gut-pituitary axis** has emerged as a research frontier. Dysbiosis-linked inflammation exacerbates pituitary dysfunction in animal models, prompting trials of probiotics and fecal transplants to augment traditional therapies.

- O'Riordan KJ, Moloney GM, Keane L, Clarke G, Cryan JF. The gut microbiota-immune-brain axis: Therapeutic implications. Cell Rep Med. 2025 Mar 18;6(3):101982. doi: 10.1016/j.xcrm.2025.101982. Epub 2025 Mar 6. PMID: 40054458; PMCID: PMC11970326.

Take home massage

- Hypopituitarism in adults most frequently occurs in the setting of a pituitary adenoma and treatments affecting the pituitary or hypothalamus.
- Diagnoses of hypophysitis have increased in the past decade with increased use of cancer immunotherapies, specifically CTLA-4, PD-1, and PD-L1 inhibitors.
- Before ICI treatment: Baseline assessment for serum levels of cortisol, thyroid-stimulating hormone (TSH) and free thyroxine (fT4).
- Personalized hormone replacement
- Gene-editing therapies: CRISPR-Cas9 targeting *PROP1* mutations restored pituitary function in congenital cases
- Oxytocin: increased pro-social and empathic behaviour


THANKS FOR YOUR
ATTENTION