Common Pitfalls in the interpretation of Endocrine Tests

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LACTOTROPH AXIS

Which Tests Must Be Ordered?

- Serum PRL is recommended for diagnosis. A single PRL level is usually adequate to diagnose hyperprolactinemia.

- Nonetheless, when the diagnosis is unclear, the test must be ***repeated***.

PRL

- An elevated PRL level is diagnostic as long as the venous sample was obtained without excessive stress.

- **but drug-induced hyperprolactinemia must be excluded**

- **Falsely Normal Values (Hook Effect)**

When a large pituitary adenoma is associated with a slightly elevated PRL levels in immunoassays, a 1:100 serum dilution is recommended in order to exclude the Hook effect

Falsely Elevated Values
PRL

- PRL circulates in the blood in three molecular forms, a) small PRL of 23 kilodaltons (kDa) (90% of serum PRL), b) big PRL of 45-50 kDa, and c) big-big PRL of > 100 kDa (<1% of serum PRL).

- **Big-big PRL is responsible for macroprolactinemia when large molecular weight PRL is the predominant form in the serum (5).**

Macroprolactinemia

- Macroprolactinemia must be considered especially when no hyperprolactinemia symptoms such as : galactorrhea, oligomenorrhea/amenorrhea, headache, or visual impairment are present.
- However, it is important to note that the presence of these symptoms - galactorrhea, menstrual disorders, or infertility have been reported in up to **45%** patients with macroprolactinemia, hence should not exclude this diagnosis .
- Approximately 10% of monomeric hyperprolactinemia patients may be asymptomatic.
- In cases with symptoms and a confirmed macroprolactinemia, pituitary mass must be ruled out

Table 4. Usual prolactin (PRL) levels in patients with hyperprolactinemia due to different etiologies

Etiology	Usual PRL levels, ng/mL	Comments
Microprolactinomas	100–250	PRL <100 ng/mL in up to 25% of cases; PRL >250 ng/mL in ~10% of cases
Macroprolactinomas (MAC)	200–1,000	PRL <100 ng/mL only in cases of cystic MAC or due to the hook effect; PRL >1,000 ng/mL is often found in patients with giant prolactinomas (>4 cm)
Non-functioning pituitary adenomas (NFPAs)	25–100	PRL between 100 and 250 ng/mL in up to 20% of cases; no report of PRL >250 ng/mL in subjects with immunohistochemically confirmed NFPAs without macroprolactinemia
Drugs	25–100	PRL between 100 and 250 ng/mL in ~30% of cases; PRL between >250 ng/mL in ~5% of cases (particularly with antipsychotics or prokinetics); PRL >500 ng/mL is very rare
Primary hypothyroidism	25–100	PRL between 100 and 250 ng/mL in up to 15% of cases; PRL between 250 and 300 ng/mL in 1–2% of cases
Macroprolactinemia	25–100	PRL >250 ng/mL in 5% of cases; PRL >500 ng/mL is exceedingly rare and usually restricted to patients with concomitant monomeric hyperprolactinemia

Adapted from references [1, 7, 8, 21, 25, 82–84].

Physiologic
Pregnancy; lactation; stress; sleep; coitus; exercise, etc.
Pathologic
Systemic diseases – primary hypothyroidism; adrenal insufficiency; polycystic ovary syndrome (?); renal insufficiency; cirrhosis; pseudocyesis; epileptic seizures
Hypothalamic diseases – tumors (craniopharyngiomas, dysgerminomas, meningiomas, etc.); infiltrative disorders (histiocytosis, sarcoidosis, etc.) metastasis; cranial radiation; Rathke's cleft cysts, etc.
Pituitary diseases – prolactinomas; acromegaly; thyrotropinomas; Cushing's disease; infiltrative disorders; metastasis; hypophysitis; empty sella syndrome, etc.
Stalk disorders – inflammatory (hypophysitis; granulomatosis with polyangiitis (Wegener's), sarcoidosis, Langerhans cell histiocytosis) and infectious (tuberculosis) lesions; neoplasms (germinomas); traumatic brain injury
Neurogenic – chest wall lesions (burns; breast surgery; thoracotomy; nipple rings; herpes zoster; etc.); spinal cord injury (cervical ependymoma; tabes dorsalis; extrinsic tumors; etc.), breast stimulation, etc.
Idiopathic
Ectopic prolactin production – renal cell carcinoma; ovarian teratomas; gonadoblastoma; non-Hodgkin lymphoma; uterine cervical carcinoma; colorectal adenocarcinoma, etc.
Macroprolactinemia

Table 2. Causes of drug-induced hyperprolactinemia

Antipsychotics
Typical – haloperidol, chlorpromazine thioridazine, thiothixene, flupentixol
Atypical – risperidone; paliperidone; molindone; amisulpride; quetiapine; olanzapine; aripiprazole (rarely)
Antidepressants
Tricyclic – clomipramine; amoxapine; amitriptyline; desipramine
SSRIs – fluoxetine; fluvoxamine; paroxetine; citalopram; escitalopram; sertraline
SNRIs – venlafaxine; duloxetine; reboxetine
MOA-I – pargyline; clorgyline
Antihypertensive drugs
Verapamil; α-methyldopa; reserpine; labetalol (intravenous)
Prokinetic agents
Metoclopramide; domperidone
H2-receptor blocker agents
Cimetidine (?); ranitidine (?)
Others
Estrogens; anesthetics; opiates; methadone; morphine; alprazolam; apomorphine; heroin; cocaine; marijuana; alcohol abuse; etc.

SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and noradrenaline reuptake inhibitors; MOA-I, monoamine oxidase inhibitors. Adapted from references [1, 7, 8, 19, 21].

Macroprolactin

- **Gel filtration chromatography (GFC) is the gold standard test to differentiate between different molecular weight prolactins (6), however, this method is both time and labor-intensive.**

  Therefore, an alternate technique **(PEG precipitation test)** has become the most used one (9).

- **In PEG precipitation test*, macroprolactin* is precipitated and monomeric prolactin is left in the supernatant. Macroprolactinemia is usually suspected when precipitable prolactin with PEG exceeds 60% of the total prolactin or when monomeric prolactin in the supernatant is less than 40% of total prolactin**

Functional Hyperprolactinemia in PCOS

The elevation of PRL in ***PCOS*** is explained due to the presence of macroprolactin, it is therefore essential to screen it.

CORTICOTROPIC AXIS

Hypofunction Suspicion

- It should be considered in patients with persistent asthenia and hypoglycemia trends.

  AI is a disease with slow onset and usually manifests within physical stress or concomitant to severe diseases.

- Clinical presentation includes asthenia, anorexia,gastrointestinal symptoms (nausea, vomiting, abdominal pain)

Hyperfunction Suspicion

- Cushing's syndrome must be suspected in young adults with osteoporosis and/or hypertension, difficult-to-control diabetes, pediatric patients with growth delay, weight gain, and adrenal incidentalomas.

According to European criteria, Cushing's syndrome work-up should be performed in the following cases:

1. weight loss with central obesity.
2. uncommon signs or symptoms for the respective age such as osteoporosis and arterial hypertension.
3. multiple signs or symptoms suggestive of Cushing's syndrome.
4. overweight children with short height
5. adrenal incidentaloma

Hypofunction

- ACTH Stimulation test:

The common mistake is that this test with high ACTH analog doses , does not rule out primary AI or central AI. Therefore, in these scenarios, ***a low dose tetracosactide (Synacthen ®)*** stimulation test (1µg/IV) should be conducted, since better diagnostic performance has been demonstrated to confirm central AI .

Hyperfunction

- It is interesting to note that some conditions such as anticonvulsant treatment, depression, etc. can cause false positives in the LDDST.

Therefore, in such cases, a dose of oral loperamide 0.15-0.20 mg/kg (16mg maximum) could be administered to prevent a false positive.

Main mistakes in the Interpretation and Recommendations to Avoid Mistakes

Hyperfunction

- **In pregnancy, 24-hour urinary cortisol or late-night salivary cortisol is preferred.**
- In ***adrenal incidentaloma***, a 1 mg dexamethasone test is preferred.
- In ***cyclical Cushing's syndrome*** hypercortisolism episodes alternate with normal ones, so urinary cortisol and late-night salivary cortisol should be conducted during the dexamethasone suppression test.
- If the initial test is normal and clinical suspicion persists, tests should be repeated during follow up.

- In patients with **chronic kidney disease** with glomerular filtration rate less than 30 ml/minute, 1 mg dexamethasone suppression test is recommended over urinary cortisol .

- In patients with **epilepsy,** urinary cortisol or salivary cortisol is recommended, as many anticonvulsants increase dexamethasone clearance .

CBG

- The main protein involved in cortisol transport is the cortisol binding globulin (CBG).
- Methods used for cortisol measurement do not distinguish protein-bound cortisol (90%) from free cortisol (10%). Therefore, plasmatic cortisol values should be interpreted carefully in situations that could alter CBG concentrations.
- This way, if a reduction in CBG synthesis occurs (liver disease, hypothyroidism, sepsis) or if renal losses are increased (nephrotic syndrome), a falsely low cortisol level may be found.

CBG

- Conversely, cortisol levels will be falsely elevated when an increase in CBG synthesis occurs (hyperthyroidism, pregnancy, estrogen treatment).
- **This artifact may be avoided if salivary cortisol is measured, as it presents an adequate correlation with serum cortisol levels and isn't modified by CBG concentration.**

- **Night serum cortisol is recommended to be drawn in the first two inpatient days to avoid an elevation related to hospitalization-induced stress.**

- **A low-dose dexamethasone suppression test should not be performed in pregnant patients or conditions in whom abnormal CBG concentrations may be found such as estrogen intake (increases CBG) or liver disease (decreases CBG) .**

- **In the case of estrogen intake, it should be suspended, and a new measurement should be performed in four to six weeks.**

- ***False positives*** **such as physiological hypercortisolism (also known as pseudo-Cushing) could occur, as this rarely elevates cortisol levels above the cutoff for diagnosis.**

- **Dynamic tests such as low dose dexamethasone suppression test allow to rule out the excessive endogenous liberation of cortisol.**

- **False-positives in measurement of UFC levels may be observed :**
  - in diuresis greater than 3 liters,
  - pregnancy,
  - glomerular filtration rate less than 30 ml/min, and
  - women with significant weight loss after bariatric surgery.

A single normal result cannot rule out the diagnosis, specifically in patients with intermittent (cyclical) hypercortisolism.

Additional tests should be performed to confirm the diagnosis .

TABLE 2 | Pitfalls in the interpretation of the dexamethasone suppression test and 24-hour urinary free-cortisol excretion.

Dexamethasone suppression test
False-positive tests (i.e., lack of suppression)
Non-Cushing hypercortisolemia
- Obesity
- Stress
- Alcoholism
- Psychiatric illness (anorexia nervosa, depression, mania)
- Elevated cortisol binding globulin (estrogen, pregnancy, hyperthyroidism)
- Glucocorticoid resistance
Test-related artifacts
- Laboratory error, assay interference
Insufficient dexamethasone delivery into the circulation
- Non compliance
- Decreased absorption: for instance, bowel resection
- Increased metabolism (drugs): phenobarbital, phenytoin, carbamazepine, topiramate; Nifedipine; among others.
- Decreased metabolism (drugs): itraconazole, ritonavir, fluoxetine, diltiazem, among others.
False-negative tests
- Chronic renal failure (creatinine clearance < 15 mL/min)
- Hypometabolism of dexamethasone (e.g., liver failure)

HPLC, high-pressure liquid chromatography.

24-hour UFC excretion

Drugs/conditions that increase UFC (False - Positive)

- Exercise/stress
- Proteinuria
- Carbamazepine (if measured by HPLC)
- Fenofibrate (if measured by HPLC)
- Some synthetic glucocorticoids (immunoassays)

Conditions that decrease UFC (False – Negative)

- Incomplete collection
- Low glomerular filtration rate
- Urinary tract infection

CIRCI

Evaluation in critical patients : Inadequate cortisol levels in the context of acute stress may be observed in what is known as critical illness-related corticosteroid insufficiency **(CIRCI).**

Whenever CIRCI is suspected, cortisol levels must be evaluated, and ACTH measurement should be requested before glucocorticoid therapy is initiated.

A frequent mistake when this condition is suspected is that glucocorticoid therapy is started without a cortisol measurement .

CIRCI

A cortisol level < 10ug/dL is highly suggestive of CIRCI and no further studies are needed to confirm the diagnosis.

In cases of doubt due to cortisol level > 10 µg/dL, a dynamic test is recommended and a 30-minute delta cortisol post-ACTH should be calculated, however, this possibility is limited.

Additionally, whenever the doubt exists due to cortisol values of > 10 µg/dL, therapy should be individualized and a new evaluation should be performed after the critical state is overcome to rule in or rule out AI.

When the patient is under prednisolone treatment for any reason, the cross-reactivity of the active molecule with cortisol immunoassays must be considered.

This is the reason **liquid chromatography-mass spectrometry (LC-MS)** has become such a popular technique for such cases, as it provides an accurate measurement of steroidal hormones to overcome the cross - reactivity previously mentioned.

The medication could be swapped to synthetic steroids that do not have crossreaction such as dexamethasone.

SOMATOTROPIC AXIS

Acromegaly

In case of acromegaly confirmation without a pituitary adenoma or pituitary hyperplasia, plasma growth hormone releasing hormone (GHRH) must be requested to rule out a secreting neuroendocrine tumor.

Additionally, a contrasted thorax and abdominal computed tomography and a somatostatin receptor scintigraphy must be performed to locate the source.

Main Mistakes in the Interpretation and Recommendations to Avoid Mistakes

The challenges of biochemical determination of IGF-1 are related to factors such as :

- binding to transport proteins,
- use of different reference values,
- age variations, gender,
- estrogen effects (mainly peroral intake), and
- the number of persons involved to establish the reference values.

GH

To measure IGF-1 it's necessary to separate it from the binding proteins.

Separation methods for these proteins include acidification followed by solid-phase chromatography with size exclusion, or ethanol-acid extraction.

In patients with diabetes mellitus, a frequent comorbidity in acromegaly, IGF-1 would be affected due to the higher proteolysis of IGF-1 binding protein 3 (IGFBP-3), one of the main binding proteins.

At the same time, diabetes mellitus may lead to IGF-I glycosylation, and therefore being unrecognizable by monoclonal antibodies used in some assays.

GH

- In cirrhotic patients, there is a decrease in liver GH receptors, therefore a decrease in serum levels of IGF-I and IGFBP-3 (31), which could lead to errors in the interpretation of these tests.

- Another scenario is when seric IGF-1 increases are disproportionate to GH increase, which could be related to two reasons: GH secretion fluctuates more, and GH stimulates the secretion of both IGF-1 and IGFBP-3. In these cases where GH is disproportionate to IGF-1 levels, IGFBP-3 levels could be requested to further clarify this diagnostic challenge

GONADOTROPIN AXIS

Testosterone

- Total testosterone must be requested for male patients with the sample drawn between 8:00 and 10:00 hours , due to circadian variation (which is lower in elderly patients) .

- To confirm the diagnosis, second total testosterone and sexual hormone-binding globulin (SHBG) should be requested to calculate free testosterone.

- Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) must be requested to determine the origin.

- In the case of primary hypogonadism, karyotype must be requested to rule out Klinefelter syndrome.

Main mistakes in the Interpretation and Recommendations to Avoid Mistakes

Conditions that modify SHBG concentration must be taken into account . (Table 3).

TABLE 3 | Conditions that modify SHBG serum concentration.

Increase SHBG	Reduce SHBG
Thyrotoxicosis and hyperthyroidism	Hypothyroidism
Liver disease	Nephrotic syndrome
Estrogen and anticonvulsive drugs	Glucocorticoids, progestogen, androgenic steroids
HIV	Diabetes mellitus
Ageing	Acromegaly
Genetic polymorphism	Genetic polymorphism
Low weight or malnourishment	Obesity

Adapted from Ortiz-Flores et al. F. Assessment protocol of hypogonadism in adult men and the elderly. Medicine. 2020;13(32):1038 (34). HIV, Human immunodeficiency virus.

Prednisone and other **steroidal drugs** interference. When this phenomenon is suspected, liquid chromatography mass spectrometry must be requested for an accurate measurement .

THYROTROPIC AXIS

The American Association of Clinical Endocrinologists (**AACE**) recommends thyroid-stimulating hormone (**TSH**) to be requested in the following scenarios:

- Type 1 diabetes mellitus, adrenal insufficiency, vitiligo
- Pernicious anemia
- First degree relative with autoimmune thyroid disease
- Neck radiation history, or radioactive iodine therapy
- Previous thyroid surgery
- Abnormal thyroid physical examination: nodule or goiter
- Mental disease
- Patients with amiodarone or lithium intake
- Dysmenorrhea, infertility, irregular menses
- Heart failure, hypertension and high cardiovascular risk patients (Type 2 Diabetes mellitus, e.g.).

Main Mistakes in the Interpretation and Recommendations to Avoid Mistakes

I. **TSH may vary up to 40% in the same individual during serial sampling as a *circadian variation* may be up to 50% on the same day. Therefore, the sample for TSH and free T4 must be taken from the same vein puncture.**

II. Levothyroxine therapy response must be monitored with TSH alone.

III. TSH could be requested in a hospitalized patient only when thyroid disease is the cause of the hospitalization. It may be suppressed < 0,01 mUI/L in a critical patient or elevated up to 20 mUI/L after hospitalization in the recovery phase. (SES)

A. Patients with pituitary adenoma and central hypothyroidism may have slightly elevated TSH values (6-7 mUI/L) due to secretion of biologically inactive hormone which is detected, nonetheless.

B. **Biotin interference:** Multiple TSH immunoassays use noncompetitive methods with biotin-streptavidin antibodies. These non-competitive "sandwich" assays suffer from interference when patients consume biotin, as streptavidin binds avidly to exogenous free biotin.

After the wash step is performed and signal emission is evaluated through spectrophotometry, the sites that would bind TSH to form the sandwich will be occupied by biotin, limiting signal production, this lack of signal will be expressed *as a falsely decreased TSH value*

Biotin interference

Exogenous biotin, leading to a falsely elevated free T4 or TRAb.

Therefore, for patients with a hyperthyroidism profile or even in suspected Graves' disease (suppressed TSH, elevated free T4, and positive TRAb), if no correlation between clinical findings and laboratory results, biotin intake (voluntary or involuntary) must be ruled out.

Biotin interference

It is highlighted that the effect and extent of biotin interference are assay dependent, not only in thyroid function tests but also in multiple hormones (43). For this reason, result interpretation should be cautious in both clinical and laboratory setting.

The presence of **heterophile antibodies**, usually human anti - mice antibodies (HAMA), interfere with non-competitive immunoassay through binding of capture and signal antibodies, leading to a false signal which provokes an inappropriately high value (3, 39).

This erroneous TSH elevation may lead to therapy adjustments in case of hypothyroidism; it must be suspected in cases of primary hypothyroidism with adequate adherence to levothyroxine and proper technique of intake, and when no clinical laboratory correlation is observed.


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FREQUENT MISTAKES IN THE EVALUATION OF MISCELLANEOUS ENDOCRINE TESTS

Renin-Angiotensin-Aldosterone System

- Spironolactone and eplerenone must be suspended at least **six weeks** before.

- In patients with hard-to-control hypertension, it is possible to use alpha-blockers (like prazosin) or non-dihydropyridines calcium channel blockers (like verapamil).

- **Estrogen** or **conjugated contraceptives** intake must also be suspended for six weeks before collecting samples, due to elevated renin levels while using these medications .

Catecholamine Measurements and Its Metabolites

Plasma free metanephrines have the best diagnostic performance (sensitivity 96-100%, specificity 89-98%), however, the readiness and time required to obtain a result in our field are complicated, hence,

its recommended to request - in patients with proper renal function - 24-hour urinary fractioned metanephrines, as this study has better performance, with a sensitivity of 86-97% and a specificity of 86-95%. .

TABLE 4 | Situations and drugs and other substances that can interfere in the diagnostic study of pheochromocytoma.

Drugs
Anxiolytics, tricyclic antidepressants, and antipsychotics
Catecholamines and adrenergic agonists (including oxymetazoline: nasal decongestants)
Clonidine discontinuation
Amphetamines
Levodopa
Phenoxybenzamine
Beta-blockers
Buspirone
Hydralazine
Minoxidil
Other substances: Nicotine, caffeine, ethanol, cocaine
Other situations: Stress, advanced age and hypoglycemia

Critically Ill Hypocalcemia

Interventions must be considered only when hypocalcemia is coupled with symptoms,

or ionic calcium less than **0.9 mmol/L** (48).

Glycated Hemoglobin

HbA1c is an accurate and specific test, which correlates with the mean glucose levels in the last 60- 90 days. Nonetheless, this test does not take into account the **glycemic variability**, with the possibility of being normal in the context of high glycemic variability.

When HbA1c is being interpreted, multiple conditions may lead to it being **falsely low.** These include hemoglobinopathies (Hb S, Hb D, methemoglobinemia), hemolysis, chronic lymphocytic leukemia, nitrates, drugs (dapsone, methylene blue, benzene derivates, vitamin C excess), hereditary spherocytosis, hemodialysis, phlebotomy, and posterior to blood transfusion.

HbA1C

Among the conditions associated with **falsely elevated HbA1c** results, hemoglobinopathies of fetal Hb type, Hb D, carbaminohemoglobin, iron deficiency anemia, B9 or B12 vitamin deficiency.

If one of these conditions is present in diabetic patients, it must be considered to avoid erroneous interpretation of HbA1c results

Chromogranin A Levels

Chromogranin A (CgA) is a protein part of the granin family and is stored in the chromaffin granules. CgA blood levels are the universal marker of neuroendocrine tumors (NET).

Higher levels are observed in metastatic carcinoid tumors (55, 56).

CgA quantification is useful both in diagnosis, a follow-up to determine treatment response and recurrence or persistence of the disease.

Immunoradiometric assay : sen=67% ; speci=96%

ELISA : Sen , Speci= 85%

CgA

RIA : Sen=93% ; Speci=85%

The most important challenge with CgA quantification is the lack of specificity, as is observed in Table 5.

TABLE 5 | Factors that modify CgA concentration.

Factor	False-positive causes of CgA
Cardiovascular disease	Hypertension, heart failure, acute coronary syndrome.
Kidney disease	Altered kidney function / chronic kidney disease
Gastrointestinal tract disease	Chronic atrophic gastritis, inflammatory bowel disease, irritable bowel syndrome, pancreatitis, chronic hepatitis, cirrhosis
Non-neuroendocrine malignancies	Prostate cancer, ovarian cancer, breast cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, hematologic malignancies
Inflammatory disease	Rheumatoid arthritis, systemic lupus erythematosus, chronic obstructive pulmonary disease
Endocrine disease	Pheochromocytoma, hyperparathyroidism, hyperthyroidism, medullary thyroid cancer, pituitary tumors (excluding prolactinomas), hypercortisolemia
Drugs	Proton pump inhibitors (PPI), Histamine type 2 receptor antagonists (H2RA)
Other	Food intake or extenuating exercise before the test

Adapted from Gut P, Czarnywojtek A, Fischbach J, et al. Chromogranin A – unspecific neuroendocrine marker. Clinical utility and potential diagnostic pitfalls. Arch Med Sci. 2016 Feb 1; 12 (1): 1–9 (55).

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- Proton pump inhibitors (PPI) therapy may increase CgA levels only five days after the first intake and leads to a CgA level five to10 times higher than the upper reference level.

  To avoid any impact of PPI therapy on CgA measurement, these drugs must be suspended at least seven days before the test.

- H2RA may influence CgA levels as well. It is suggested to suspend these drugs at least 24 hours before the scheduled CgA test (56).


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