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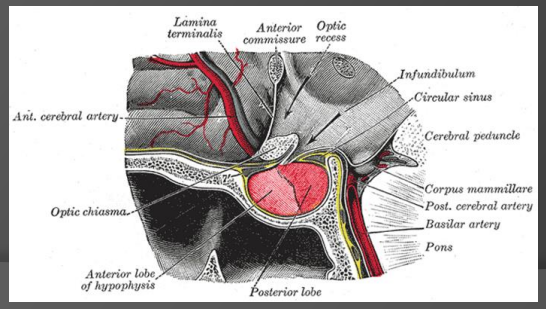
May 26, 2017

HORMOME REPLACEMENT IN HYPOPITUTARISM IN ADULTS:

AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE



J Clin Endocrinol Metab (2016) 101 (11): 3888-3921.

DISCLOSURES

- None.

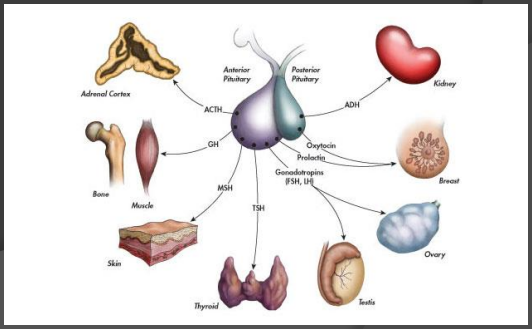
OBJECTIVES

- Understanding clinical issues related to hypopituitarism, including:
  - Biochemical assessment
  - Treatment
    - Avoid hormonal under replacement and over replacement
  - Management during special situations, such as:
    - Pregnancy
    - Pituitary surgeries
    - Stress situations including, trauma and non-pituitary surgery

Introduction

DEFINITION

- Partial or complete deficiency of pituitary hormones due to:
  - Decrease or absence of pituitary secretory function
  - Interference with hypothalamic secretion of pituitary-releasing hormones
- This deficient or absent secretion may result in:
  - Adrenal insufficiency
  - Hypothyroidism
  - Hypogonadism
  - Growth hormone deficiency
  - Diabetes insipidus (less frequently)



Causes of hypopituitarism

- Neoplastic
  - Pituitary adenoma
  - Craniopharyngioma
  - Meningioma
  - Cysts (Rathke's cleft, arachnoid, epidermoid, dermoid)
  - Germinoma
  - Glioma
  - Astrocytoma
  - Ganglioneuroma
  - Paraganglioma
  - Teratoma
  - Chordoma
  - Pituicytoma
  - Ependymoma
  - Pituitary carcinoma
  - Metastases
- Treatment of sellar, parasellar, and hypothalamic diseases
  - Surgery
  - Radiotherapy
- Infiltrative/inflammatory disease
  - Autoimmune (lymphocytic hypophysitis, pituitary and POUF-1 antibodies)
  - Hemochromatosis
  - Granulomatous (granulomatosis with polyangiitis, sarcoidosis)
  - Langerhans cell histiocytosis
  - Giant cell granuloma
  - Xanthomatous hypophysitis
- Infectious
  - Bacterial
  - Fungal
  - Parasites
  - Tuberculosis
  - Syphilis
- Vascular
  - Pituitary tumor apoplexy
  - Sheehan's syndrome
  - Intrasellar carotid artery aneurysm
  - Subarachnoid hemorrhage
- Traumatic
  - Head injury
- Medications
  - Opiates (primarily gonadotropin ACTH, GH)
  - GCs (ACTH only)
  - Megestrol acetate (ACTH only)
  - Somatostatin analogs (GH, ACTH, TSH)
  - CTLA-4 blockers (ACTH, TSH, LH/FSH)
- Empty sella
- Idiopathic

SYMPTOMS AND SIGNS

Symptom/Sign	Pituitary Trophic Hormone Deficiency
General	
Fatigue, weakness	ACTH, TSH, LH/FSH, GH
Weight gain	TSH
Weight loss	ACTH
Decreased exercise capacity	ACTH, TSH, LH/FSH, GH
Impaired sleep quality	TSH, LH/FSH, GH
Depression	TSH, GH, LH/FSH
Cognitive decline	ACTH, TSH, ?GH
Cold intolerance	TSH
Skin	
Pallor	ACTH, LH/FSH
Dry skin	ACTH, TSH
Thinning hair, loss of body hair	ACTH, TSH, LH/FSH
Cardiovascular/metabolic	
Hypertension	TSH, GH
Hypotension, particularly orthostatic	ACTH
Bradycardia	TSH
Decreased lean body mass, increased fat mass	GH
Hyperlipidemia	TSH, GH

Symptom/Sign	Pituitary Trophic Hormone Deficiency
Insulin resistance, impaired glucose tolerance	TSH, GH
Hypoglycemia	ACTH
Impaired cardiac function	ACTH, TSH, GH
Premature atherosclerosis	TSH, GH
Pulmonary	
Shortness of breath, dyspnea on exertion	ACTH, TSH
Gastrointestinal	
Anorexia	ACTH
Nausea/vomiting	ACTH
Diarrhea/loose stools	ACTH
Constipation	TSH
Musculoskeletal	
Muscle weakness	ACTH, TSH, LH/FSH, GH
Osteoporosis, fractures	ACTH, TSH, LH/FSH, GH
Renal	
Increased thirst	ADH
Polyuria, nocturia	ADH
Reproductive	
Oligo/amenorrhea	ACTH, TSH, LH/FSH
Erectile dysfunction	LH/FSH
Low libido	LH/FSH
Hot flashes	LH/FSH
Infertility	LH/FSH
Vaginal dryness	LH/FSH

GUIDELINES DEVELOPMENT

- **Task Force**
  - Two systematic reviews:
    - First review: Panhypopituitarism and Mortality:
      - Meta-analysis, 12 observational studies, 26 017 patients
      - Increased mortality (RR, 1.55; 95% confidence interval [CI], 1.14–2.11)
      - Factors associated:
        - Female gender
        - Younger age at diagnosis
        - Craniopharyngioma or aggressive tumor
        - Presence of DI
        - Prior treatment with surgery or radiotherapy
      - Most common causes of death:
        - Malignancies
        - Cardiovascular disease
        - Cerebrovascular disease.
    - Second review: GH replacement and risk of pituitary tumor recurrence, secondary malignancy, or stroke.
      - Meta-analysis, 7 studies, 22 654 patients.
        - No association between GH replacement and pituitary tumor recurrence (RR, 0.87; 95% CI, 0.56–1.33)
        - No increased risk of secondary malignancies (RR, 1.24; 95% CI, 0.65–2.33).
        - There were no data on the outcome of stroke.

J Clin Endocrinol Metab (2016) 101 (11): 3888-3921.

EPIDEMIOLOGY, MORBIDITY AN MORTALITY OF HYPOPITUITARISM

- Prevalence:
  - 45 cases per 100,000
- Incidence
  - Four cases per 100,000

Clin Endocrinol (Oxf) . 2001;55:735–740.

EPIDEMIOLOGY, MORBIDITY AN MORTALITY OF HYPOPITUITARISM

Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain.
Regal M1, Páramo C, Sierra SM, Garcia-Mayor RV.

- OBJECTIVE:
  - To determine the prevalence and incidence of hypopituitarism in the general population.
- POPULATION:
  - 146,000 adult inhabitants in South Galicia (northwestern Spain).
  - The Medical Register of the General Hospital of Vigo
  - Only patients residing in the study area
  - Diagnosis established with baseline hormone levels and hormonal dynamic tests.
- DESIGN:
  - Two cross-sectional surveys:
    - January to December 1992
    - January to December 1999
  - Longitudinal survey performed between January 1993 and December 1999.

Clin Endocrinol (Oxf) . 2001;55:735–740.

EPIDEMIOLOGY, MORBIDITY AND MORTALITY OF HYPOPITUITARISM

- **First survey**:
  - Prevalence:
    - 29/100,000 (CI, 19.88-37.72)
    - No sex differences
- **Second survey**
  - Prevalence:
    - 45.5/100,000 (CI, 34.92-56.08)
  - Causes of hypopituitarism
    - 61% - Pituitary tumor
    - 9% - Non pituitary-tumor
    - 30% - Non-tumor cause
  - Hormonal deficiencies
    - 50% w/ three or more hormonal deficiencies
    - Most prevalent deficiency: LH/FSH
    - GH deficiency more common in patients with pituitary tumors
- **Longitudinal study**
  - 1,020,764 people-years of observation
  - Average annual incidence rate:
    - 4.21 cases/100,000 (CI, 2.95-5.47)
    - Incidence similar for both sexes.

Clin Endocrinol (Oxf) . 2001;55:735–740.

EPIDEMIOLOGY, MORBIDITY AND MORTALITY OF HYPOPITUITARISM

- High mortality
  - Bates AS, et al. ***The effect of hypopituitarism on life expectancy***
    - 172 patients with hypopituitarism (dx 1967-1994)
    - Ages 1-78 yrs, 102 men, 70 women
    - Ratio of observed/expected deaths compared to an age-sex matched population, 1.73; 95% confidence interval, 1.28-2.28; P < 0.01
    - Small but nonsignificant increase in the number of deaths due to vascular disease (ratio of observed/expected deaths, 1.35; 95% confidence interval, 0.84-2.07; P = 0.11).
    - Significant independent predictive factors for survival were age at diagnosis and hypogonadism

J Clin Endocrinol Metab (1996) 81 (3): 1169-1172.

EPIDEMIOLOGY, MORBIDITY AND MORTALITY OF HYPOPITUITARISM

- ***Premature mortality due to cardiovascular disease in hypopituitarism***

  - Retrospective Study
    - 333 patients with hypopituitarism (DX from 1956 – 1987)
      - Given routine replacement therapy
      - Overall mortality higher than in an age and sex matched population
      - Significant increase in deaths from vascular disorders compared to age and sex matched population:
        - (60 [40 male, 20 female] versus 30·8 expected [23·5, 7·4 female])
        - Hazard function for vascular death was independent of age at diagnosis, time after diagnosis, calendar year of diagnosis, gender, degree of pituitary insufficiency, hypertension, and diabetes mellitus.
        - Mortality risk was raised irrespective of whether hypopituitarism was due to pituitary adenoma or secondary to other diseases.
        - Growth-hormone deficiency could be a factor in this increased mortality from cardiovascular disease.

Lancet. 1990;336:285–288.

EPIDEMIOLOGY, MORBIDITY AND MORTALITY OF HYPOPITUITARISM

- Increased incapacitation
- Increased sick days
- Lower health status
- Higher cost of care
- Working capacity lower than the general population despite replacement

Central Adrenal Insufficiency

Central Adrenal Insufficiency

- Inadequate cortisol secretion:
  - Secondary – ACTH deficiency
  - Tertiary – Decreased hypothalamic CRH
- Prevalence
  - Almost 1/3 of patients with pituitary failure
  - 90% of patients after craniopharingioma surgery
  - High prevalence on patients after cranial radiation
    - Usually presents a few years after radiation

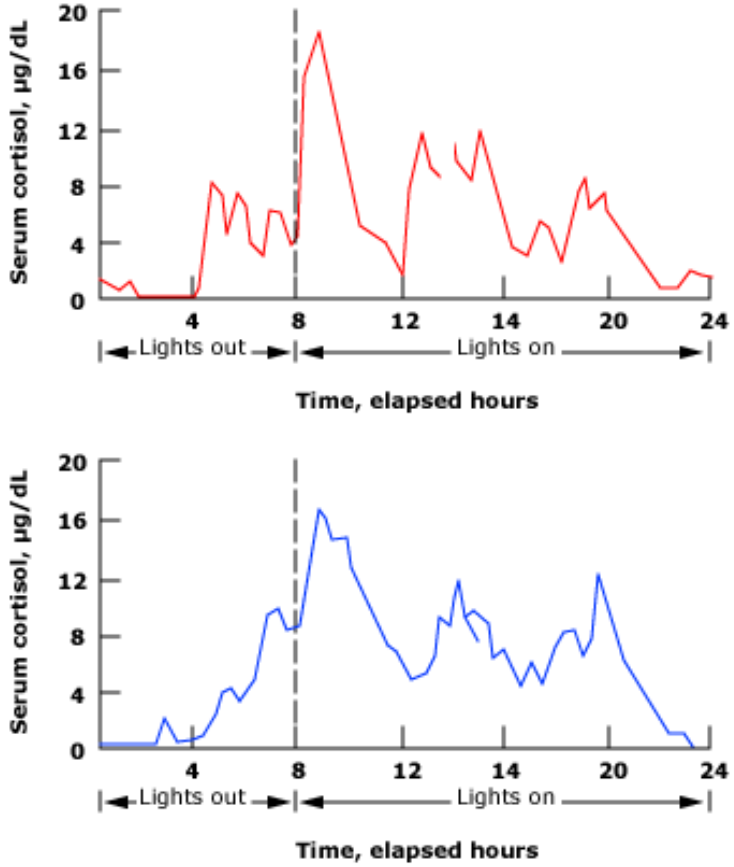
Central Adrenal Insufficiency

- Mortality
  - Failure to treat may cause adrenal crisis and death
  - Mild ACTH deficiency may also result in adrenal crisis in patients during surgery or stress

Central Adrenal Insufficiency

- Diagnoses:
  - **First line test** suggested:
    - Serum **cortisol levels at 8-9 am**
    - Criteria suggested for diagnosis:
      - Cortisol <3 ug/dL = Adrenal insufficiency
      - Cortisol > 15 ug/dL, rules out disease
  - If **morning cortisol between 3-15 ug/dL**, then guidelines suggest performing a **corticotropin stimulation test**
    - Peak cortisol less than 18.1 ug/dL at 30-60 min confirms AI
  - Recommendation against random cortisol for diagnoses
  - Tests should be done 18-24 hours after last hydrocortisone dose.

Circadian rhythm in serum cortisol



Circadian rhythm in serum cortisol concentrations in two normal subjects. Blood samples were drawn every 20 to 30 minutes. The shaded areas indicate the hours of the day during which the lights were turned out. To convert serum cortisol values to nmol/L, multiply by 27.6.

Data from: Weitzman ED, Fukushima DK, Nogeire C, et al. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab. 1971; 33:14.

Comparison of representative glucocorticoid preparations

	Equivalent doses* (mg)	Relative anti-inflammatory activity	Relative mineralocorticoid activity	Duration of action (hours)
Hydrocortisone (cortisol)	20	1	1	8 to 12
Cortisone acetate	25	0.8	0.8	8 to 12
Prednisone	5	4	0.8	12 to 36
Prednisolone	5	4	0.8	12 to 36
Methylprednisolone	4	5	0.5	12 to 36
Triamcinolone	4	5	0	12 to 36
Fludrocortisone	Not used for an anti-inflammatory effect	10	125¶	12 to 36
Dexamethasone	0.75	30	0	36 to 72

Prednisone and prednisolone are potent glucocorticoids and weak mineralocorticoids. Dexamethasone has no mineralocorticoid effect.

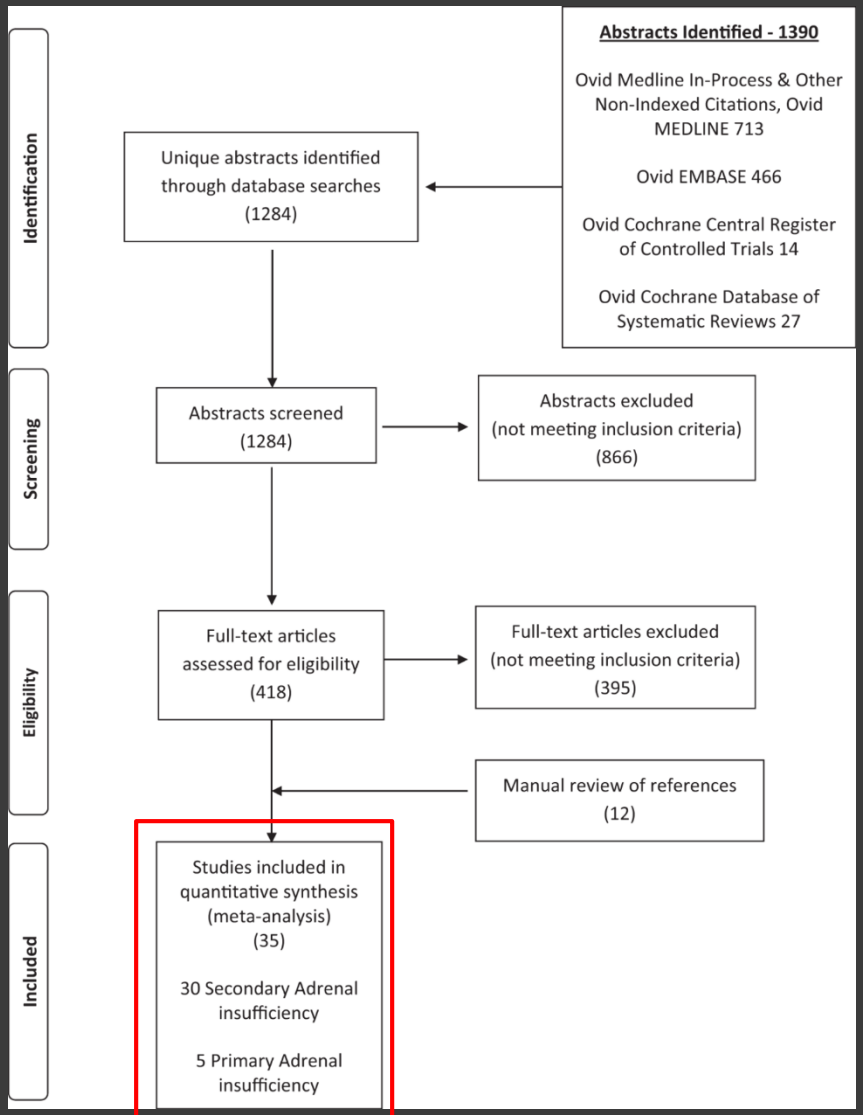
* Equivalent anti-inflammatory dose shown is for oral or intravenous (IV) administration. Relative potency for intra-articular or intramuscular administration may vary considerably.
¶ Glucocorticoid doses which provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone are prednisone or prednisolone 50 mg or hydrocortisone 20 mg.

Data from:

1. *Schimmer BP, Parker KL. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: The Pharmacological Basis of Therapeutics, 11th ed, Brunton LL, Lazo JS, Parker KL (Eds), McGraw Hill, NY. p.1587. Copyright © 2006.*
2. *Donohoue PA. The adrenal gland and its disorders. Kappy MS, Allen DB, Geffner ME (Eds), Charles C Thomas, Springfield, IL. p.403. Copyright © 2005 Charles C Thomas, Publisher, Ltd.*

Central Adrenal Insufficiency

ACTH	Procedure	Normal Response
Insulin tolerance	Administer insulin, 0.05–0.15 U/kg iv.	Glucose should drop <40 mg/dL (2.2 mmol/L).
	Sample blood at −30, 0, 30, 60, and 120 min for cortisol and glucose.	Peak cortisol should be >500–550 nmol/L (>18.1–20 µg/dL) depending on assay.
Corticotropin standard dose (250 µg)	Administer ACTH 1–24 (cosyntropin), 250 µg im or iv. Sample blood at 0, 30, and 60 min for cortisol.	Cortisol should be at 30 or 60 min >500–550 nmol/L (>18.1–20 µg/dL) depending on assay.
Corticotropin low dose (1 µg)	Administer ACTH 1–24 (cosyntropin), 1 µg iv. Sample blood at 0 and 30 min for cortisol.	Cortisol should be at 30 min >500 nmol/L (18.1 µg/dL) depending on assay.



From: ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis

J Clin Endocrinol Metab. 2016;101(2):427-434. doi:10.1210/jc.2015-1700

ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis

- **Naykky Singh Ospina, et al.** Division of Endocrinology, Diabetes, Metabolism, and Nutrition (N.S.O., N.N., I.B.), Mayo Clinic, Rochester, Minnesota
- **Meta-Analysis**: Compared diagnostic accuracy of the high- (250 mcg) and low- (1 mcg) dose ACTH stimulation tests
- Methods:
  - Evaluation of six databases through February 2014
  - Pairs of independent reviewers evaluated selected studies
- 30 studies included of patients with secondary adrenal insufficiency included:
  - Population 1209 adults and 228 children with secondary adrenal insufficiency.

J Clin Endocrinol Metab (2016) 101 (2): 427-434.

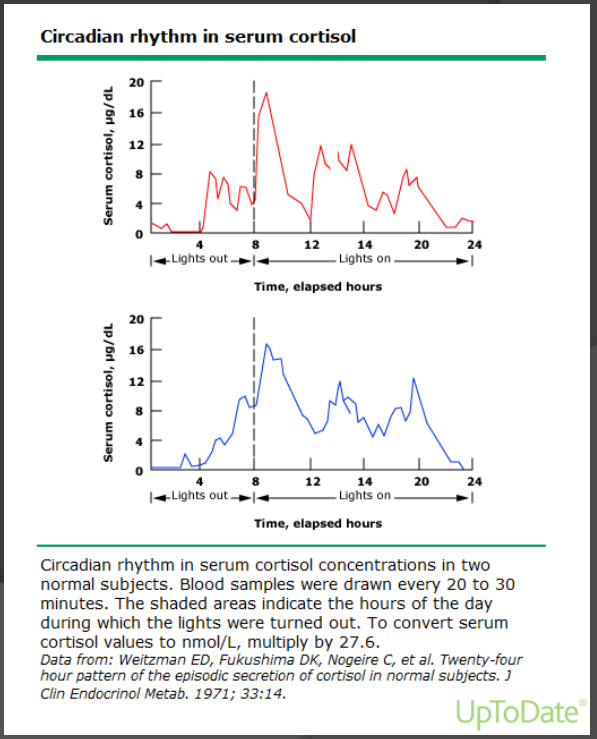
ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis

- **Conclusions:**
  - Both high and low dose Corticotropin stimulation tests have:
    - Low sensitivity and high specificity
    - Similar diagnostic accuracy
    - Adequate to rule in, but not rule out, secondary adrenal insufficiency
    - Data were only available to estimate the sensitivity of high dose ACTH stimulation test (92%; 95% confidence interval, 81–97%).

J Clin Endocrinol Metab (2016) 101 (2): 427-434.

TREATMENT

- 15 to 20 mg of hydrocortisone
  - Single dose
  - Divided doses (two to three doses)
    - Highest dose at awakening
    - Second at lunch
    - Third late afternoon
- Use of fludrocortisone not recommended



TREATMENT

- Use longer acting GCs if:
  - HC not available
  - Poor compliance
  - Convenience

Comparison of representative glucocorticoid preparations

	Equivalent doses* (mg)	Relative anti-inflammatory activity	Relative mineralocorticoid activity	Duration of action (hours)
Hydrocortisone (cortisol)	20	1	1	8 to 12
Cortisone acetate	25	0.8	0.8	8 to 12
Prednisone	5	4	0.8	12 to 36
Prednisolone	5	4	0.8	12 to 36
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2. *Donohoue PA. The adrenal gland and its disorders. Kappy MS, Allen DB, Geffner ME (Eds), Charles C Thomas, Springfield, IL. p.403. Copyright © 2005 Charles C Thomas, Publisher, Ltd.*

TREATMENT

- Teach patients about:
  - Stress dosing
  - Emergency administration of GCs
  - Emergency kit with injectable GC
  - Use of emergency bracelets

Adrenal Crisis

- An immediate parenteral injection of 50-100 mg of HC recommended if adrenal crisis suspected.

CENTRAL HYPOTHYROIDISM

Central Hypothyroidism

- Insufficient TSH stimulation of a normal thyroid gland
  - Inadequate secretion or action of TSH-releasing hormone
  - Decreased or absent secretion of TSH
    - Usually other pituitary hormonal deficiencies coexist.
- Pituitary macroadenomas – 50%
  - 43% of non-functioning pituitary adenomas – before surgery
  - 57% - postoperatively
- Craniopharyngiomas
  - Younger patients mostly
  - Most common extrasellar cause
- Brain irradiation
  - 65 % of patients irradiated for brain tumors
- May occur as a result of traumatic brain injury and post stroke

Central Hypothyroidism

- First line tests recommended by guideline:
  - TSH and free T4
  - Criteria for diagnoses:
    - Free T4 below reference range w/ low, normal or only mildly elevated TSH
- Guidelines suggest starting levothyroxine if patient has a combination of low normal free T4 with symptoms if pituitary disease present and patient not critically ill
  - Another approach is to follow up closely and start treatment if free T4 levels decrease by 20% or more.
- Dynamic testing not recommended

Treatment

- Levothyroxine doses of approximately 1.6 mcg/kg/day recommended
  - Target: Free T4 mid to upper half of reference range
- Other therapies such as: Levotriiodothyronine, thyroid extracts or other formulations, not recommended.
- Use TSH levels to adjust therapy not recommended

GROWTH HORMONE DEFICIENCY

Growth Hormone Deficiency

- Childhood onset and adult onset
- Adult GHD (AGHD)
  - Incidence:
    - ~ 6,000 cases/year
  - Prevalence:
    - ~ 50,000 adults EU

Growth Hormone Deficiency

- Dynamic testing (GH stimulation testing) recommended.
- Controlled body mass index cutoffs should be used to assess peak GH values.
- If the patient has **“clear-cut” features** of GHD and **three other pituitary hormone** deficits, guidelines recommended against testing.

DINAMIC TESTS FOR GROWTH HORMONE DEFICIENCY ASSESSMENT

Hormone Test	Procedure	Interpretation/Expected Normal Response
GH		
Insulin tolerance	Administer insulin, 0.05–0.15 U/kg iv.	Glucose should drop <40 mg/dL, (2.2 mmol/L).
	Sample blood at − 30, 0, 30, 60, 120 min for GH and glucose.	GH should be >3–5 μg/L. Cutoffs for GH response are BMI related.
GHRH[a] + arginine	Administer GHRH, 1 μg/kg (max 100 μg) iv followed by an arginine infusion 0.5 g/kg (max 35 g) over 30 min.	Can give false normal GH response if GHD is due to hypothalamic damage (eg, after radiation).
	Sample blood at 0, 30, 45, 60, 75, 90, 105, and 120 min for GH.	GH >4 μg/L, but cutoffs for GH response should be correlated to BMI. (Obesity may blunt GH response to stimulation.)
Glucagon	Administer glucagon, 1 mg (1.5 mg if weight >90 kg) im. Sample blood at 0, 30, 60, 90, 120, 150, 180, 210, and 240 min for GH and glucose.	GH >3 μg/L, but cutoffs for GH response should be correlated to BMI. (Obesity may blunt GH response to stimulation.)

GROWTH HORMONE REPLACEMENT THERAPY

- **RECCOMMENDATIONS:**
  - Therapy recommended for patients with proven GHD and no contraindications, with initial dosing based on age.
  - Keep IGF-1 below the upper limit of normal
  - Monitor for side effects, adjust dose accordingly

GROWTH HORMONE REPLACEMENT THERAPY

- RECCOMMENDATIONS AGAINST:
  - Use of growth hormone replacement for:
    - Elderly with low age adjusted low IGF-1 levels and no evidence of pituitary disease
    - To enhance athletic performance

GROWTH HORMONE REPLACEMENT THERAPY

Table 5. GH Replacement Therapy for AGHD

Starting dose	
Age <60 y	0.2–0.4 mg/d
Age >60 y	0.1–0.2 mg/d
Dose titration	
Increase by 0.1–0.2 mg/d	6-wk intervals
Dose determinants	
Mid-normal age-adjusted IGF-1 level	

Abbreviation: DXA, dual-energy x-ray absorptiometry. [Derived from S. Melmed: Idiopathic adult growth hormone deficiency. *J Clin Endocrinol Metab*. 2013;98:2187–2197 (167), with permission. ©The Endocrine Society.].

GROWTH HORMONE REPLACEMENT THERAPY

Table 6. Patient Monitoring After Initiating Adult GH Replacement

1. Measure IGF-1 6 weeks after initiating GH replacement, after dose escalations, and every 6 months thereafter.
2. Assess body weight, blood pressure, waist circumference, and BMI every 6 months.
3. Assess thyroid and adrenal function and replace or adjust replacement doses as indicated.
4. Assess metabolic profile including blood sugar and lipids every 6 months.
5. Assess BMD by DXA every 18 months.
6. Periodically assess residual pituitary mass via a pituitary MRI.
7. Assess QOL.

Abbreviation: DXA, dual-energy x-ray absorptiometry. [Derived from S. Melmed: Idiopathic adult growth hormone deficiency. *J Clin Endocrinol Metab*. 2013;98:2187–2197 (167), with permission. ©The Endocrine Society.].

CENTRAL HYPOGONADISM

Central Hypogonadism

- Men
  - Low serum T levels
  - Symptoms of testosterone deficienct
  - Impaired spermatogenesis
- Premenopausal woman:
  - Low estrogens
  - Impaired ovulation
  - Oligomenorrhea or amenorrhea.
- Prevalence:
  - 95%
    - Sellar tumors, post surgery or radiotherapy
  - High prevalence
    - Cranial surgery for non sellar lesions
    - Hyperprolactinemia attributed to tumors or medications

Central Hypogonadism - Men

- Tests recommended if symptoms present:
  - FSH, LH and testosterone levels
  - Perform tests:
    - if no acute or subacute illness
    - Before 10 am
    - After overnight fast

Central Hypogonadism - Men

- TREATMENT SUGGESTION:
  - Testosterone replacement if no contraindications to:
    - Prevent anemia
    - Reduce fat mass
    - Improve bone mineral density
    - Improve libido and sexual function
    - Improve energy levels and sense of well being
    - Improve muscle mass and strenght

Central Hypogonadism - Women

- Premenopausal w/ olygomenorrhea or amenorrhea
  - Test recommended:
    - FSH, LH, estradiol
    - Rule out other causes, such as:
      - Pregnancy
      - Hyperprolactinemia
      - Thyroid disease
      - Hyperandrogenism
  - Dynamic testing, not useful
- Post menopausal woman not on HRT
  - Absence of high FSH, LH is sufficient for diagnoses

Central Hypogonadism - Women

- TREATMENT RECCOMMENDATIONS:
  - Treat premenopausal women, if no contraindication to treatment

CENTRAL DIABETES INSIPIDUS

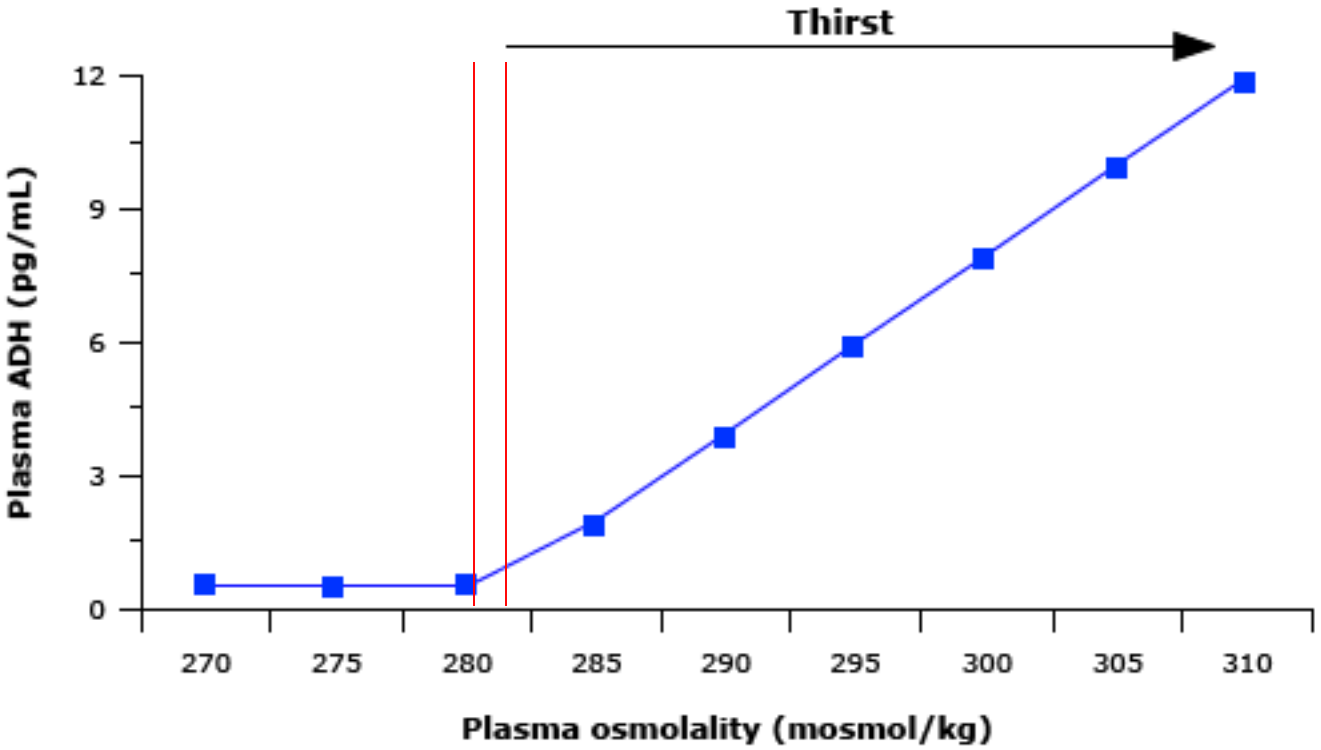
CENTRAL DIABETES INSIPIDUS

- Insufficient secretion of vasopressin by posterior pituitary to allow for adequate urine concentration.
- Prevalence:
  - DI is 7–10 patients per 100 000 inhabitants
- Causes:
  - Congenital
  - Tumors
  - Head trauma
  - Inflammatory
  - Autoimmune
  - Granulomatous
  - Infectious diseases
  - Idiopathic

Central Diabetes Insipidus

- **Simultaneous** serum and urine osmolarity recommended if:
  - Polyuria
    - More than 50/mL/kg body weight in 24 hours
- To rule out DI:
  - Serum osmolarity is > 295 mOsm/L
  - Urine osmolarity ~ 600 mOsm/L
  - Urine/plasma osmolarity ≥ 2
  - Urine dipstick negative for glucose

Osmotic regulation of ADH release and thirst



Relation between plasma antidiuretic hormone (ADH) concentration and plasma osmolality in normal humans in whom the plasma osmolality was changed by varying the state of hydration. The osmotic threshold for thirst is a few mosmol/kg higher than that for ADH.

Data from Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. Am J Med 1982; 72:339.

CENTRAL DIABETES INSIPIDUS

ADH		
Water deprivation test	• **Fluid deprivation for 8h** (starting from 8 am). • **Weigh** patient at beginning of testing • Then, measure **weight and urine volume hourly** during the test. • Measure **plasma and urine osmolality every 2–3 h**. • At **4 pm administer DDAVP 2 µg im** and **allow patient to drink freely.** • Notes: If plasma osmolality **>305 mOsm/kg or if 3% loss of body weight with plasma osmolality >305 mOsm/kg**, proceed to **DDAVP administration earlier**. • If urine output has not decreased and/or urine osmolality/plasma osmolality ratio <2, but the plasma osmolality has not concentrated **to >295 mOsm/kg**, continue water deprivation for a further hour and measure plasma and urine osmolality. **Offer DDAVP after this.** • **Continue measuring urine osmolality hourly for the next 4 h (after DDVAP administration) and measure hourly urine volumes.** Stop test if >3% weight loss occurs.	**Plasma osmolality >295 mOsm/L** with inappropriately hypotonic urine (**urine osmolality/plasma osmolality ratio <2) during the fluid deprivation confirms DI** (test is discontinued). After administering DDVAP: • **Urine concentration >800 mOsm/kg = central DI** • **Urine concentration <300 mOsm/kg = nephrogenic DI**. • **Partial DI or primary polydipsia = urine concentrates partially during the water deprivation test (300–800 mOsm/kg**), (OPTIONS: Prolonged water deprivation test vs. trial with DDVAP therapy).

CENTRAL DIABETES INSIPIDUS

- TREATMENT SUGGESTIONS:
  - (UNGRADED GOOD PRACTICE STATEMENT)
    - Individualize therapy (some pts prefer no treatment)
    - Educate patients regarding overdosing risk
    - Weekly periods of polyuria
- If post-pituitary surgery:
  - Attempt to discontinue therapy with DDAVP to evaluate for pituitary function recovery
    - Weeks/months post Op

CENTRAL DIABETES INSIPIDUS

- TREATMENT SUGGESTIONS
  - If adipsic DI
    - Frequent weighing, Na+ level measuring and fluid intake titration
  - All patients: Wear ID

CENTRAL DIABETES INSIPIDUS

Table 7. Dose Comparisons of Available Desmopressin Formulations

	Melts	Tablets	Spray	Drops	Injections
Bioavailability	0.25% (95% CI, 0.21–0.31%)	0.16 ± 0.17%	6.0 ± 2.29%	Similar to spray?*	NA
Dose equivalence	60 μg	100 μg	2.5 μg	2.5 μg	NA
	120 μg	200 μg	5.0 μg	5.0 μg	<0.5 μg
	240 μg	400 μg	10.0 μg	10.0 μg	<1.0 μg

Abbreviations: *?, unclear; NA, not applicable. [Derived from Y. Oiso et al: Clinical review: treatment of neurohypophyseal diabetes insipidus. *J Clin Endocrinol Metab.* 2013;98:3958–3967 (183), with permission. © Endocrine Society.].

INTERACTIONS BETWEEN REPLACEMENT HORMONES

Glucocorticoids and Growth Hormone Replacement - Suggestions

- Testing of HPA axis before and after starting GHR in patients with apparent normal axis, not receiving GCs suggested.

Glucocorticoids and Thyroid Hormone - Suggestions

- Evaluate patient with central hypothyroidism for adrenal insufficiency before starting therapy with levothyroxine

Glucocorticoids and estrogen - Suggestions

- Consider that total cortisol can be elevated due to estrogen effect when evaluating for AI or assessing adequacy of therapy.

Growth Hormone Replacement and Thyroid Hormones - Recommendations

- Monitor euthyroid patients after starting therapy with GH
- Begin levothyroxine therapy if free T4 below reference range
- If patient on levothyroxine therapy may need increased dose when starting therapy for GHD.

Growth Hormone Replacement and Thyroid Hormones - Suggestions

- Treat central hypothyroidism before assessing for Growth Hormone deficiency

Growth Hormone and Estrogen

- Guidelines suggest higher growth hormone doses for woman on oral estrogen replacement than in eugonadal counterparts.

Glucocorticoids and Diabetes Insipidus

- Monitor for DI after starting glucocorticoid treatment for Adrenal Insufficiency
  - Unmasking of partial DI

Risks of Hormonal Over-Replacement

BONE DISEASE

- Glucocorticoids:
  - Avoid over-replacement to reduce osteoporosis risk
    - Low dose replacement suggested, since may be associated with positive bone-remodeling balance.
  - Evaluate for verterbral fractures (spinal X-rays, VFA) if glucocorticoid over-replacement in men
- Levothyroxine:
  - Avoid over-replacement to reduce risk of fractures.

CARDIOVASCULAR RISKS IN PATIENTS WITH HYPOPITUITARISM ON REPLACEMENT THERAPY

- GLUCOCORTICOIDS:
  - Use the lowest tolerable dose of glucocorticoids to potentially decrease metabolic and cardiovascular risk.
- THYROID HORMONE REPLACEMENT:
  - Avoid under and over-replacement of thyroid hormones to avoid possible long-term cardiovascular risks.

SPECIAL CIRCUMSTANCES

CUSHING'S DISEASE

- Therapy with glucocorticoids recommended after surgical resection of ACTH-secreting tumors
- Retesting thyroid and growth hormone axes before starting therapy after curative surgery is also recommended.

PROLACTINOMAS

- Reassess all pituitary axes after successful treatment with dopamine agonists.

Growth Hormone Replacement after Cured Acromegaly

- Low dose growth hormone therapy suggested after cured acromegaly (if no contraindications to therapy).

PERIOPERATIVE MANAGEMENT OF HYPOPITUITARISM

PITUITARY SURGERY

- If Adrenal Insufficiency:
  - Use stress dose of steroids before surgery if Adrenal Insufficiency
  - Taper doses after surgery before retesting
- If normal preoperative adrenal function
  - Individualize until evaluation of HPA

PITUITARY SURGERY

- If Central Hypothroidism:
  - Use levothyroxine before surgery and during perioperative period
- Other patients:
  - Measure free T4 6-8 weeks post Op

PITUITARY SURGERY

- Diabetes Insipidus
  - Short acting formulations suggested as initial therapy
    - Spontaneous DI resolution expected in most patients
  - Do not use prescheduled DDAVP dosages during first week post Op
    - SIADH risk 7-10 days post Op
  - Discharge instructions:
    - Use oral or intranasal DDAVP, and instruct patients to use ONLY if significant polyuria

PITUITARY SURGERY

- Retest all pituitary axes 6 weeks post Op and then periodically.

NON-PITUITARY SURGERY

- GLUCOCORTICOID ADMINISTRATION
  - Adjust dose according to severity of illness
    - Minor to moderate surgical stress:
      - 25-75 mg HC per 24 hrs – 1-2 days
    - Major surgical stress
      - 100 mg hydrocortisone IV
      - Then, 200 mg HC/ 24 hrs or 50 mg every 6 hrs IV or IM

HYPOPITUITARISM IN PREGNANCY - GLUCOCORTICOIDS

- Hydrocortisone – preferred GC
  - Increase dose bases on clinical course (usually higher doses required in third trimester)
- Closely monitor for clinical symptoms and signs or over and under-replacement
- Dexamethasone not recommended – not inactivated in placenta
- Major surgical stress doses of HC during active labor recommended

HYPOPITUITARISM IN PREGNANCY – THYROID HORMONE REPLACEMENT

- Monitor free T4 (if trimester specific values available) or total T4 (if not available), every 4-6 weeks.

- Increased doses may be required to keep levels within target ranges.

HYPOPITUITARISM IN PREGNANCY – DESMOPRESSIN

- Continue therapy si DDAVP if pre-existing DI
- Dose adjustment may be needed

HYPOPITUITARISM IN PREGNANCY – GROWTH HORMONE

- Discontinuation of therapy suggested:
  - No evidence for efficacy
  - No evidence for safety
  - Placenta produces GH

HYPOPITUITARISM IN PITUITARY APOPLEXY

- Testing for pituitary insufficiency recommended in all patients
- GC therapy until laboratory w/u reveal normal pituitary function
- Monitor patient treated with surgical decompression or conservately for hypopituitarism

HYPOPITUITARISM AND ANTIEPILEPTIC DRUGS (AEDs)

- Patients on non-Dexamethasone therapy who start AEDs
  - Instruct about early symptoms of Adrenal Insufficiency
- Patients on Dexamethasone therapy who start AEDs
  - Increase dexamethasone replacement

HYPOPITUITARISM AND ANTIEPILEPTIC DRUGS (AEDs)

- Patients on Levothyroxine
  - Monitor free T4 in 6 weeks
  - Increase dose if levels decrease below target range
- Patients who start estrogen replacement:
  - Evaluate AED levels and adjust accordingly
- DDAVP
  - Monitor doses and make adjusted as needed.

Hormone Assays

Assays Performance Characteristics

HORMONE ASSAY	ADEQUATE SENSITIVITY	ACCEPTABLE INTRAASSAY VARIABILITY (<20%)	LARGE INTERASSAY VARIABILITY
GH	X	X	X
IGF-1	X	X	
PRL	X	X	
FSH	X	X	
LH	X	X	
TSH	X	X	
FT4	X	X	X
T	X	X	X
E2	X	X	X
Cortisol	X	X	
ACTH	X	X	

Appendix A or Supplemental Table 1: Assay Characteristics of Common Automated Immunoassays

Hormone	Assays Detectable Level	Sample Stability	Remarks	Mean Variability (% Imprecision) at Stated Concentrations	
				Within Method	Between Methods
GH (mcg/liter)	0.002 (b) 0.01 (c) 0.030 (d)	Rfg. <8 h. Frz. >8 h (undetermined duration or about 2 months). Avoid frz.-thawing (activity lost after repeated cycles).	Exhibits adequate assays sensitivity. Some assays (4) indicate detection of both 20 and 22 kDa forms. All assays use IRP 98/574 (lower GH results when compared with earlier standard). Varied conversion factors were applied when converting mIU/liter to ug/liter. All used BMI-related cut-off values. Variability between assays was assessed at 3.4 ng/ml.	6.9%	23.1%
IGF-1 (ng/ml)	20 (c)	Rfg. <24 h. Frz. up to 12 months.	It is preferable to measure IGF-BP-3 on the same sample. Variability between assays was assessed at 75 ng/ml.	13.2%	NA
PRL (ng/ml)	0.6 (a) 0.25 (b) 0.3 (c) 0.047 (d) 1.4 (e)	RT <8 h. If >24 h (remove serum/plasma from gel/cells). Rfg. <48 h (up to 7 days). Frz. up to 12 months. Avoid repeated frz.-thawing.	There is adequate agreement among assays (variability assessed at 7.2 ng/ml).	7.2%	7.1%
FSH (mIU/ml)	0.05 (a) 0.2 (b) 0.3 (c) 0.1 (d) 0.66 (e)		There is variability between assays (variability assessed at 7.9 mIU/liter).	8.1%	8.9%
LH (mIU/ml)	0.5 (a) 0.2 (b) 0.07 (c) 0.1 (d) 0.216 (e)		There is variability between assays (variability assessed at 3.9 mIU/liter).	7.7%	8.9%
TSH (mcIU/ml)	0.0038 (a) 0.015 (b) 0.004 (c) 0.005 (d) 0.015 (e)		There is variability between assays (variability assessed at 0.73 mcIU/ml).	6.1%	8.3%
fT4 (ng/dl)	0.4 (a) 0.25 (b) 0.1 (c) 0.023 (d) 0.07 (e)	RT <8 h. If >24 h remove from gel/cells. Rfg. <48 h (up to 7 days). Frz. >48 h (up to 30 days). Avoid repeated frz.-thawing.	There is variability between assays (variability assessed at 0.73 ng/dl).	12.2%	11.2%
Estradiol (pg/ml)	25 (a) 20.0 (b) 7 (c) 5.0 (d) 6.36 (e)	RT <8 h. If >24 h remove from serum/plasma from gel / cells. Rfg. <48 h (up to 7 days). Frz. (up to 6 months). Avoid more than one freeze-thaw cycle.	There is variable between assays (variability assessed at 141 pg/ml).	16.9%	64.9%
T (ng/dl)	4.33 (a) 10.0 (b) 10 (c) 2.0 (d)	RT <8 h. Remove from gel/cells immediately. Rfg. <48 h (up to 7 days). Frz. (up to 60 days). Avoid more than one freeze-thaw	There is high variability between assays (up to 54%) (variability assessed at 113 ng/dl).	11.4%	15.6%

Appendix A or Supplemental Table 1: Continued

Hormone	Assays Detectable Level	Sample Stability	Remarks	Mean Variability (% Imprecision) at Stated Concentrations: Within Method	Between Methods
ADH			There are limited assays available.	NA	NA
11-deoxycortisol		Rfg. if <7 days. Frz. If <14 days.	An 8 a.m. specimen is preferred.	NA	NA
Cortisol (micg/dl)	1.0 (a)	RT <8 h.	There is adequate assays sensitivity for diagnosis.	9.5%	10.6%
	0.4 (b)	If >8 h, remove serum/plasma from gel/cells.	There is significant and variable cross-reactivity with prednisolone and fludrocortisone.		
	0.2 (c)	Rfg. <48 h (up to 14 days).	There is little or no cross reactivity with dexamethasone.		
	0.1 (d) 0.16 (e)	Frz. >48 h (up to 30 days).	Variability between assays was assessed at 4.1 mcg/liter.		
ACTH (pg/ml)	1.0 (d)	Collect sample in ice-cooled EDTA-tube. Centrifuge immediately in refrigerated centrifuge. Store frozen in plastic container (binds to non-siliconized glass). Stable if frozen for 14 days.	ACTH 1–24 medication causes negative interference. Variability between assays was assessed at 17.4 pg/ml.	19.5%	NA

T, testosterone; PRL, prolactin; IRP, international reference preparation; fT4, free T4; ADH, anti-diuretic hormone; RT, room temperature; Rfg., refrigeration; Frz., freeze; NA, data not available; (a), Abbott Diagnostics, Chicago, IL; (b), Beckman Coulter, Brea, CA, USA; (c), Siemens Healthcare Diagnostics Inc., Tarrytown, NY; (d), Roche Diagnostics, Indianapolis, IN.; (e), Ortho-Clinical Diagnostics, Inc., Rochester, NY; Assay variability (imprecision) was calculated as 100 × (standard deviation/ mean analyte concentration). Only assays with adequate available data are reviewed here. Variability was calculated using available data for the lowest analyte concentration (281).

HORMONE ASSAYS

- Accuracy and reliability are central for diagnosis and monitoring
- Increasing use of liquid chromatography-mass spectrometry assays due to:
  - Improved sensitivity
  - Reduced interference
    - Separation and fragmentation (mass and charge)
      - Less interference with autoantibodies
      - High level of specificity
      - Can measure more than one analyte


Thanks for your attention!
Morovis, PR