



*Better health through  
laboratory medicine.*

## PEARLS OF LABORATORY MEDICINE

# Hypocortisolism

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DOI: 10.15428/CCTC.2017.284950



# Learning Objectives

After participating in this presentation, you will be able to:

- Understand the etiologies and laboratory abnormalities of hypocortisolism
- Discuss the stimulation tests
- Establish diagnostic approach of Addison disease



# Adrenal Insufficiency: Hypocortisolism

## Classification:

- Primary adrenal insufficiency (Addison disease)
- Secondary adrenal insufficiency (pituitary)
- Tertiary adrenal insufficiency (hypothalamic or glucocorticoid administration)

# Hypocortisolism



**Addison disease**, aka **primary adrenal insufficiency** and **hypocortisolism**, is a chronic endocrine disorder in which the adrenal glands fail to produce adequate levels of steroid hormones(cortisol and aldosterone).

It is named after Thomas Addison, who first described the condition in 1855.

Addison disease is adrenocortical insufficiency due to the destruction or dysfunction of the entire adrenal cortex. It affects both glucocorticoid and mineralocorticoid function.

# Addison Disease

## Causes:

- Autoimmune disease (adrenalitis) (80%):
  - Sporadic
  - Autoimmune polyglandular syndrome type 1 (Addison disease, candidiasis, hypoparathyroidism, and primary gonadal failure)
  - Autoimmune polyglandular syndrome type 2 (Addison disease, primary hypothyroidism, primary hypogonadism, type 1 diabetes, and pernicious anemia)

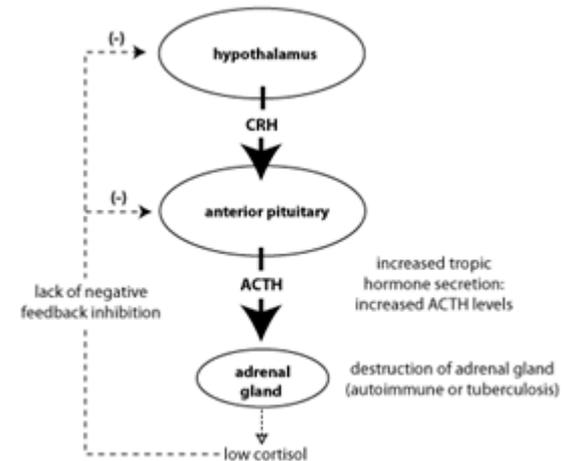
# Addison Disease

- **Other causes (20%)**

- Granulomatous disease: Tuberculosis, histoplasmosis, sarcoidosis
- Infections: HIV, cytomegalovirus, fungus
- Metastatic infiltration: carcinoma of the lung or breast
- Systemic amyloidosis
- Hemochromatosis
- Congenital adrenal hyperplasia
- Hemorrhage (Waterhouse-Friderichsen syndrome)

# Addison Disease

- **Pathogenesis**
  - Destruction of adrenal glands
- **Hormone deficiency**
  - Cortisol
  - Aldosterone
- **Pathophysiology**
  - Deficiency of hormones → characteristic physiological derangements



# Clinical Features of Addison Disease

- Symptoms
  - Progressive weakness & fatigue
  - Non-specific complaints (anorexia, nausea, vomiting, decreased libido, amenorrhea)
- Signs
  - Weight loss, hyperpigmentation (increased ACTH),
- Biochemical changes
  - Hyperkalemia & hyponatremia
  - Hypotension (volume depletion) & dehydration
  - Hypoglycemia
  - Hypercalcemia



# Lab Findings of Addison Disease

- High ACTH
- Hyperkalemia
- Hyponatremia
- Hypoglycemia
- Low serum cortisol
- Low serum aldosterone
- Other laboratory abnormalities:
  - elevated BUN and creatinine
  - hypercalcemia
  - normocytic normochromic anemia

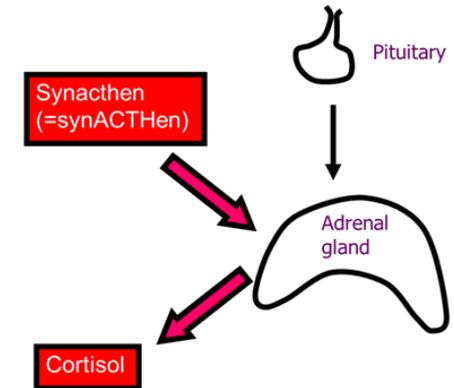


# Diagnosis of Addison Disease

- Early morning basal serum cortisol and plasma ACTH concentrations along with ACTH stimulation test are the primary tests used for the diagnosis of Addison disease.
- Diagnosis of Adrenal Insufficiency:  
Basal levels: ACTH > 150 pg/mL  
Cortisol < 10 µg/dL

# Diagnosis of Addison Disease

## ACTH Stimulation Test



Baseline cortisol may be normal in Addison disease

ACTH Stimulation Test: Cosyntropin, Corticotropin or Synacthen test

- ACTH test: a small amount of synthetic ACTH (1-24AA) is injected, and the amount of cortisol that the adrenals produce in response to ACTH is measured to determine the adrenal insufficiency.

## Rapid ACTH Stimulation Test

### Procedure:

- Baseline serum cortisol
- 250 $\mu$ g ACTH given intramuscularly or IV (1h)
- Samples for serum cortisol 30 and 60 min after injection

### Interpretation:

- Normal response: a rapid rise in serum cortisol with peak concentration  $>20\mu$ g/dL.
- Subnormal response: no or slight change in serum cortisol suggests the diagnosis of adrenal insufficiency

## 1 $\mu\text{g}$ of ACTH Stimulation Test

### Procedure:

- Baseline serum cortisol
- 1 $\mu\text{g}$  ACTH given intramuscularly or intravenously (1h)
- Samples for serum cortisol 30 and 60 min after injection
- This is not a standard test and its use is controversial. Only specifically used for investigation of central causes of adrenal insufficiency.

## Multi-Day ACTH Stimulation Test

- ACTH, 250 $\mu$ g, is injected for 3 days followed by a standard 8-hour infusion of 250 $\mu$ g ACTH.
- Serum and urinary cortisol are measured daily.
- Interpretation:
  - Normal: serum cortisol >20 $\mu$ g/dL
  - Primary adrenal insufficiency: little or no increase in cortisol
  - Secondary or tertiary adrenal insufficiency: a delayed or staircase rise is seen over 2 to 3 days.

## Insulin-Induced Hypoglycemia Stimulation Test

- Baseline blood glucose and cortisol levels
- Regular insulin 0.1 U/kg b.w. is injected intravenously at morning
- Blood for glucose and cortisol measured at 30, 60, 90, and 120 min after insulin injection
- Interpretation:
  - Normal response: blood glucose levels  $<40$  mg/dL and cortisol levels  $>20$   $\mu\text{g/dL}$ .
  - No response or inadequate responses may be due to pituitary or hypothalamic hormone insufficiency.



# References

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# Disclosures/Potential Conflicts of Interest

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- **Employment or Leadership:**
- **Consultant or Advisory Role:**
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