Regulation of ACTH and cortisol secretion:

- Negative feedback control:

CRH→ ↑ ACTH → ↑ cortisol → ↑cortisol or synthetic steroid→ suppress CRH & ACTH secretion.

- Stress:

Stress →↑↑ CRH&ACTH → ↑↑ cortisol

- The diurnal rhythm of plasma cortisol:

highest in the morning (8-9 am) and lowest in the late afternoon and evening(8-9pm)

- In the circulation, glucocorticoids are mainly protein-bound (about 90%), chiefly to cortisol-binding globulin (CBG or transcortin).
- ↑↑ in pregnancy and with estrogen treatment (e.g. oral contraceptives).
- ↓↓ in hypoproteinemic states (e.g. nephrotic syndrome).
- The biologically active fraction of cortisol in plasma is the free (unbound) component.

Investigations Of Suspected Adrenocortical Hyperfunction:

A. Screening Tests (out-patient)

distinguish simple non-endocrine obesity from obesity due to Cushing's syndrome. (clinical diagnosis)

1- Low-dose dexamethasone (DXM) suppression test: Dexamethasone → ↓ CRH → ↓ ACTH → ↓ cortisol.

2-24 hour urinary free cortisol: Cortisol < 250 nmol/day → exclude Cushing's disease

- An **alternative** is to determine the urinary cortisol : creatinine ratio on an early morning specimen.

➢**CAUSES OF elevated serum cortisol concentrations**:

- **Increased cortisol secretion:**

· Exercise , Alcohol abuse ,Obesity Stress, Anxiety, Depression.

· **CUSHING'S SYNDROME**:

○ ACTH – dependent

1.↑ Pituitary ACTH 70% (Cushing's disease).

2. Ectopic ACTH by neoplasms 10%. (Example: Bronchial cancer)

3. ACTH therapy.

○ ACTH – independent

1. Adrenal tumor 20% (adenoma or carcinoma)

2. Glucocorticoid therapy.

- **Increased cortisol binding globulin (CBG):**

· Congenital ,Estrogen therapy, Pregnancy

B. **Confirmatory tests (in-patient)**

- insulin-induced hypoglycemia: (Hypoglycemia →↑ CRH →↑ ACTH →↑ cortisol)

1- To test the integrity of the hypothalamicpituitary-adrenal (HPA) axis.

2- To distinguish true Cushing's syndrome from pseudo-Cushing's syndrome.

Pseudo-Cushing patients= abnormal diurnal rhythm of Serum cortisol, but with Insulin-induced hypoglycemia ,↑ CRH, ACTH and cortisol blood levels

Cushing's syndrome= don't respond normally to insulin-induced hypoglycemia.

no increase in Serum cortisol

C. Tests used to determine the cause

1-Plasma ACTH (Diurnal rhythm)

-Undetectable amount →Functional adrenal tumor

-↑↑ ACTH→ Cushing's disease (pituitary-dependent)

-↑ ↑↑ ↑ ACTH→ Ectopic origin of ACTH (non-endocrine origin)

2- High-dose dexamethasone suppression test

distinguish Cushing's disease from ectopic ACTH secretio

-90% of patients with Cushing's disease show suppression of cortisol output.

-10% of patients with ectopic ACTH production (or with adrenal tumors) also show suppression.

3- CRH stimulation test

- Cushing's disease →↑↑ ACTH & cortisol above basal at 60 min,and 10% of patients fail to response

- Ectopic ACTH & adrenal tumors No response. (False-positive responses are unusual).

4- Radiological tests

-MRI of pituitary gland : Coronal contrast-enhanced MRI of the sella turcica in a patient with recurrent Cushing's disease.

- CT scanning of the adrenal glands or lungs.