Clinical Features of Hypercortisolism

A spectrum of signs and symptoms

Clinical Features Associated With Hypercortisolism and Their Prevalence[1]

Round face	81%-90%
**Plethora*	70%-90%
Hirsutism	56%-75%
Hair loss	31%
Prominent neck fat pad	50%

Recent weight gain	70%-95%
Overweight	21%-48%
Obesity	32%-41%
**Easy bruising*	35%-65%
**Purple striae*	<50%
Thin skin	37%

**Proximal muscle weakness, myopathy*	60%-82%

*Discriminatory features for hypercortisolism; most have low sensitivity.[2]

1. Braun LT, et al. *Front Endocrinol (Lausanne)*. 2019;10:766. 2. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93:1526-1540.

Clinical suspicion is based on a spectrum of clinical features

Accumulation of features should raise clinical suspicion and prompt a biochemical workup

Circulatory[1]
- Hypertension
- Hypokalemia
- Peripheral edema

Endocrine[1]
- Type 2 diabetes
- Incidental adrenal mass

Skeletal[1]
- Vertebral osteoporosis

Dermatologic[1]
- Poor skin healing
- Thin skin

Neuro/Psychiatric[1-6]
- Depression
- Decreased concentration
- Impaired memory
- Insomnia
- Irritability
- Mood changes
- Delusions
- Headache

Gynecologic[1]
- Menstrual abnormalities
- Polycystic ovary syndrome
- Hirsutism or female balding
- Decreased libido

Immune[1]
- Unusual infections

Skin[1]
- Easy bruising
- Facial plethora
- Reddish, purple striae

Muscle[1]
- Proximal myopathy

Renal[1]
- Kidney stones

Metabolic[1,6]
- Obesity
- Prominent neck fat pad
- Facial fullness
- Supraclavicular fullness
- Weight gain
- Increased appetite

New signs, symptoms, and clinical presentations associated with CS diagnosis continue to be recognized

CS=Cushing's syndrome.

1. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540. 2. Martins JM, et al. *J Endocrinol Metab*. 2022;12(1):40-48. 3. Dugandzic MK, et al. *Metabolites*. 2022;12(11):1033. doi:10.3390/metabo12111033 4. Gonzalez A, et al. *World Neurosurg*. 2019;126:331-335. 5. Telbizova T, et al. *J of IMAB*. 2020;26:3443-3448. 6. Alfakhri AS 4th, et al. *Cureus*. 2022;14(6):e25761. doi:10.7759/cureus.25761

Wide spectrum of comorbidities associated with hypercortisolism

Immune System

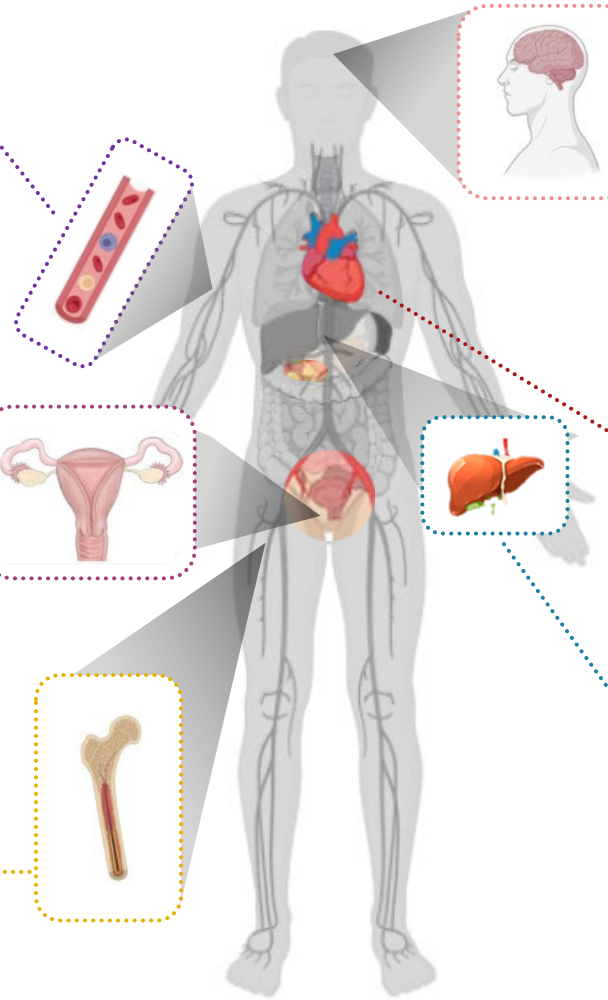
Infections[1-3]	Up to 51%

Reproductive System

Menstrual irregularity[4]	Up to 80%
Sexual dysfunction[5]	78.3% (men) 37.5% (women)
Decreased libido[4]	Up to 80%

Bone

Osteopenia[4]	Up to 80%
Osteoporosis fragility fractures[4]	Up to 80%



Nervous System

Up to 83%	Cognitive impairment[6]
Up to 81%	Major depression[4]
Up to 80%	Lethargy, depression, labile mood[4]
60%	Sleeping disorder, fatigue[4]

Cardiovascular System

Up to 85%	Hypertension[4]
54%	Hypercoagulopathy[4]
Up to 31%	Atherosclerotic changes[4]
Up to 18.2%	Thromboembolism[7,8]

Liver and Adipose

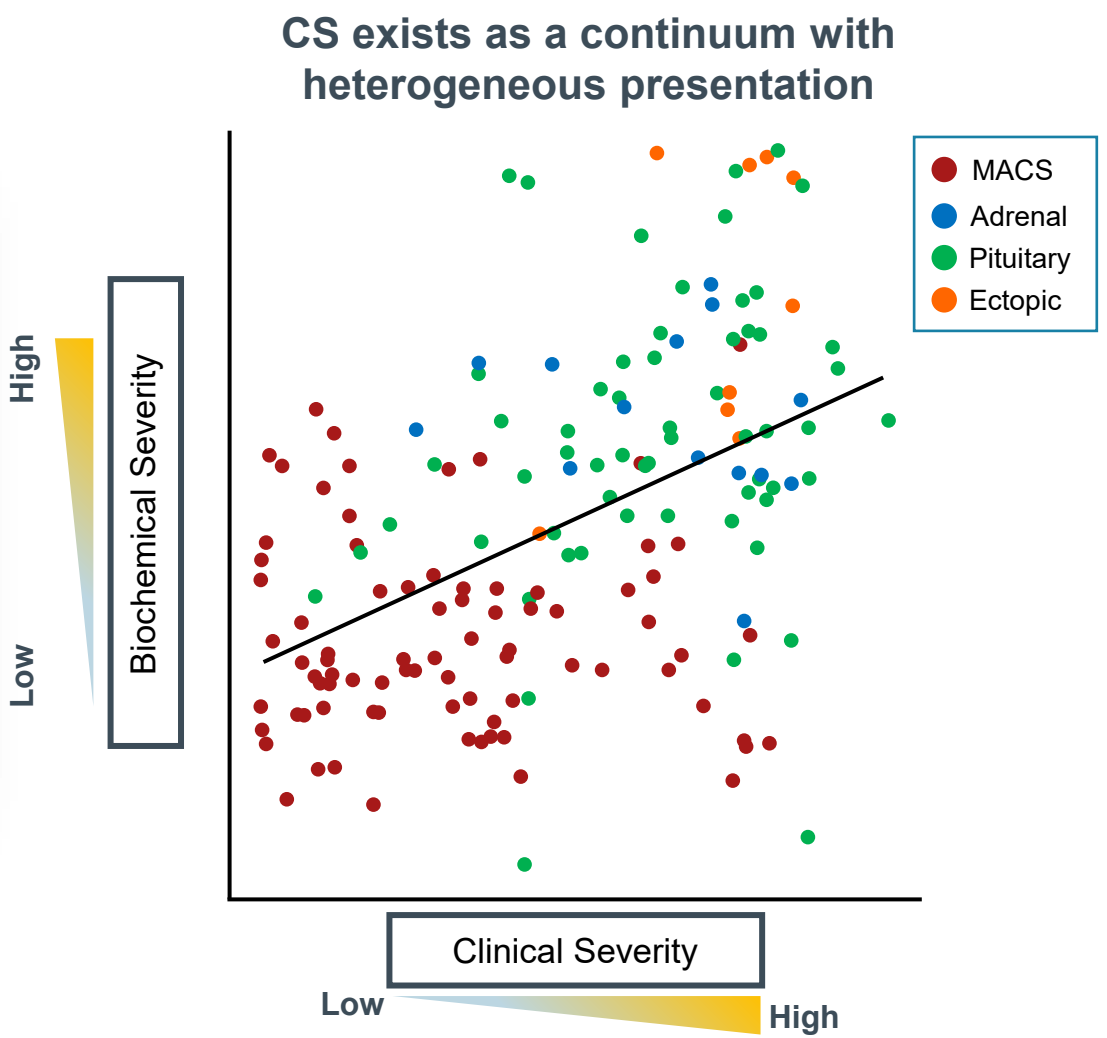
Up to 71%	Dyslipidemia[4]
Up to 64%	Abnormal glucose tolerance[4]
Up to 47%	Diabetes mellitus[4]

1. Ilias I, et al. *J Clin Endocrinol Metab.* 2005;90:4955-4962. 2. Ejas S, et al. *Cancer.* 2011;117:4381-4389. 3. Broder MS, et al. *Pituitary.* 2015;18:796-802. 4. Braun LT, et al. *Front Endocrinol (Lausanne).* 2019;10:766. doi:10.3389/fendo.2019.00766 5. Huan C, et al. *Biomed Mater Eng.* 2014;24(6):3439-3446. 6. De Alcubierre D, et al. *J Endocrinol Invest.* 2023;46(10):1961-1982. 7. Wagner J, et al. *Front Endocrinol (Lausanne).* 2019;9:805. doi:10.3389/fendo.2018.00805 8. Suarez MG, et al. *J Endocr Soc.* 2019;4(2):bvz033. doi:10.1210/jendso/bvz033

Hypercortisolism exists as a continuum

Biochemical severity

- **Presence of hypercortisolism**
  - 24-h UFC
  - DST
  - LNSC
- **ACTH-independence**
  - Baseline ACTH
  - Sex-adjusted DHEA-S levels



Clinical severity

- **Metabolic abnormalities**
  - Hypertension
  - T2DM
  - Decreased bone density
  - VTE
- **Physical findings**
  - Central obesity
  - Supraclavicular and/or dorsocervical fat pads
  - Rounding of face
  - Skin changes
  - Proximal muscle weakness

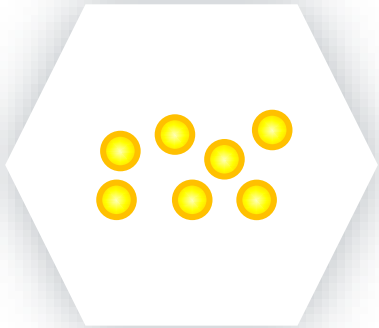
ACTH=adrenocorticotropic hormone; DHEA-S=dehydroepiandrosterone sulfate; DST=dexamethasone suppression test; LNSC=late-night salivary cortisol; MACS=mild autonomous cortisol secretion; T2DM=type 2 diabetes mellitus; UFC=urinary free cortisol; VTE=venous thromboembolism.

Li D, et al. *Eur J Endocrinol*. 2023;188(7):603-612.

Cortisol activity is influenced by cortisol levels and GR sensitivity

Cortisol levels[1,2]

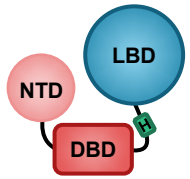
- Cortisol synthesis
- Serum cortisol levels
  - CBG affinity and concentrations
- 11β-HSD 1/2 regulation



Cortisol

GR sensitivity[1,2]

- GR mutations
- GR isoforms/variants
- GR post-translational modifications



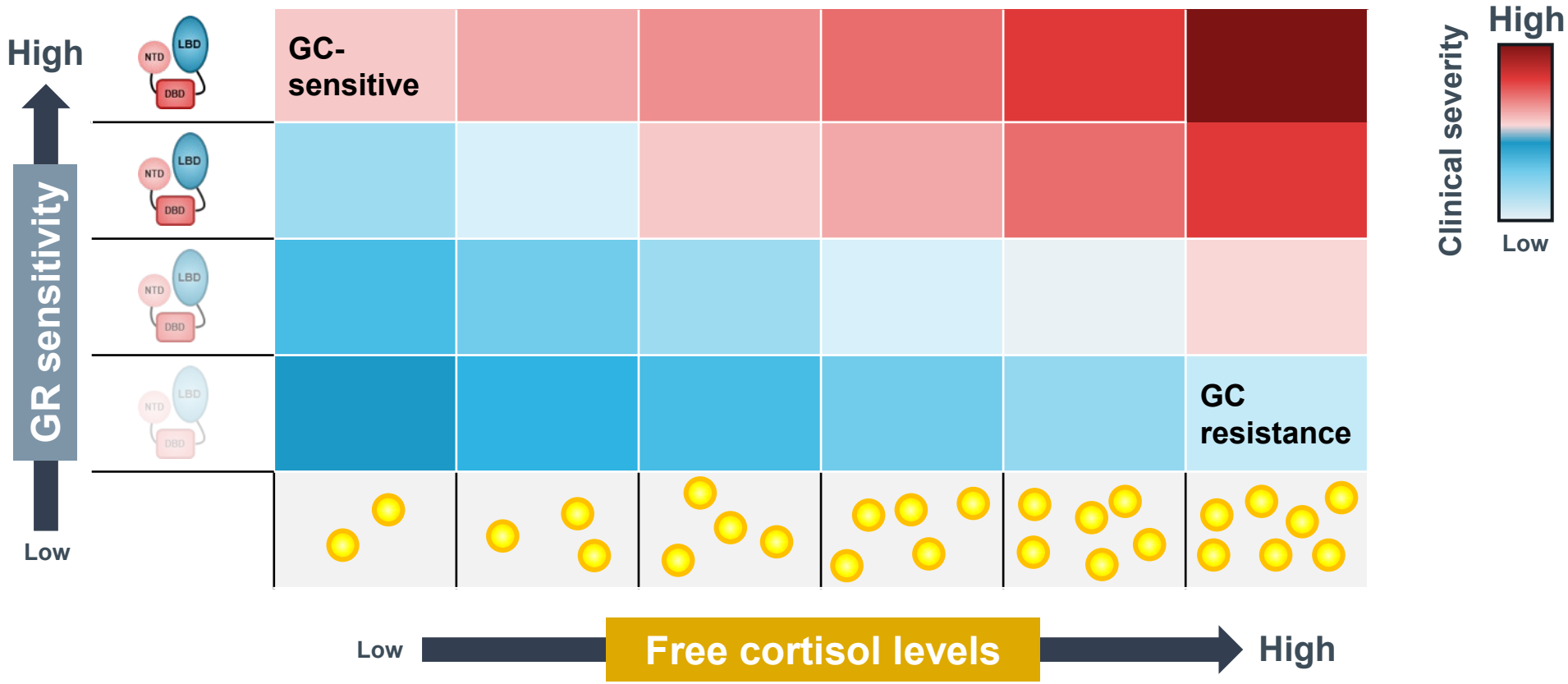
GR

CBG=corticosteroid-binding globulin; DBD=DNA-binding domain; H=hinge region; HSD=hydroxysteroid dehydrogenase; LBD=ligand-binding domain; NTD=N-terminal domain.

1. Timmermans S, et al. *Front Immunol*. 2019;10:1545. doi:10.3389/fimmu.2019.0154 2. Vandevyver S, et al. *Endocr Rev*. 2014;35:671-693.

Spectrum of clinical severity

Cortisol levels and GR sensitivity drive clinical severity in hypercortisolism[1,2]



GC=glucocorticoid.

1. Timmermans S, et al. *Front Immunol*. 2019;10:1545. doi:10.3389/fimmu.2019.01545 2. Vandevyver S, et al. *Endocr Rev*. 2014;35:671-693.