

TEST ID: CORTF

CORTISOL, FREE, SERUM

USEFUL FOR

- ▶ Assessment of cortisol status in cases where there is known or a suspected abnormality in cortisol-binding proteins or albumin
- ▶ Assessment of adrenal function in the critically ill or stressed patient, thus preventing unnecessary use of glucocorticoid therapy

CLINICAL INFORMATION

Cortisol, the main glucocorticoid (representing 75%–95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism (Cushing disease) and hypo-cortisolism (Addison disease) can cause disease. Cortisol is also used to treat skin disease, allergic disorders, respiratory system disease, inflammatory disorders, and nephrotic syndrome.

Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6–8 a.m.) and nadirs (11 p.m.) in plasma ACTH and cortisol levels.

The majority of cortisol circulates bound to corticosteroid-binding globulin (CBG) and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Only free cortisol can access the enzyme transporters in liver, kidney, and other tissues that mediate metabolic and excretory clearance.

Historically, measurements of free cortisol have been achieved from indirect means using a ratio known as the free cortisol index. This measurement takes into account the amount of total cortisol and CBG to give a percentage and ultimately absolute value of free cortisol. These methods do not take into account the possible variations in albumin levels. These calculations also rely on CBG which can be lowered in critically ill patients despite normal adrenal function. Equilibrium dialysis best serves to separate free from bound cortisol without disrupting the bound fraction.

REFERENCE VALUES

6:00–10:30 a.m. Collection
0.121–1.065 mcg/dL

ANALYTIC TIME

2 days

SPECIMEN REQUIRED

Type

Serum

Container/Tube

Red top

Specimen Volume

1.25 mL

INTERPRETATION

Cortisol is converted to cortisone in human kidneys and cortisone is less active toward the mineralcorticoid receptor. The conversion of cortisol to cortisone in the kidney is mediated by 11 β -hydroxysteroid dehydrogenase isoform-2. Also, cortisol renal clearance will be reduced when there is a deficiency in the cytochrome P450 3A5 (CYP3A5) enzyme as well as a deficiency in P-glycoprotein.

Cortisol Binding Globulin (CBG) has a low capacity and high affinity for cortisol, whereas albumin has a high capacity and low affinity for binding cortisol. Variations in CBG and serum albumin due to renal or liver disease may have a major impact on free cortisol.

Based on the study by Bancos,¹ normal ranges of free cortisol found in patients without adrenal insufficiency were:

- ▶ Free cortisol at baseline: median 0.400 mcg/dL (IQR 2.5–97.5% - 0.110–1.425 mcg/dL)
- ▶ Free cortisol at 30 minutes: median 1.355 mcg/dL (IQR 2.5–97.5% - 0.885–2.440 mcg/dL)
- ▶ Free cortisol at 60 minutes: median 1.720 mcg/dL (IQR 2.5–97.5% - 1.230–2.930 mcg/dL)

Based on the study by Bancos,¹ the following cutoffs were calculated for exclusion of adrenal insufficiency:

- ▶ Free cortisol at baseline*: greater than 0.271 mcg/dL (>271 ng/dL, AUC 0.81)
- ▶ Free cortisol at 30 minutes: greater than 0.873 mcg/dL (>873 ng/dL, AUC 0.99)
- ▶ Free cortisol at 60 minutes: greater than 1.190 mcg/dL (>1190 ng/dL, AUC 0.99)

(*please note that baseline free cortisol should not be used to exclude adrenal insufficiency given low performance)

The use of free cortisol in the management of glucocorticoid levels in the stressed patient due to major surgery or trauma requires further studies to establish clinical dosing levels and efficacy.

CLINICAL REFERENCE

1. Bancos I, Erickson D, Bryant S, et al: Performance of free versus total cortisol following Cosyntropin stimulation testing in an outpatient setting. *Endocr Pract* 2015 Dec;21(12):1353-1363. doi: 10.4158/EP15820
2. Hamrahan AH, Oseni TS, Arafah BM: Measurements of Serum Free Cortisol in Critically Ill Patients. *New England Journal of Medicine* 2004;350;16:1629-1638
3. Ho JT, Al-Musalhi H, Chapman MJ, et al: Septic shock and sepsis: a comparison of total and free plasma cortisol levels. *J Clin Endocrinol Metab* 2006;91:105-114
4. Roux CJ, Chapman GA, Kong WM, et al: Free Cortisol Index is Better Than Serum Total Cortisol in Determining Hypothalamic-Pituitary-Adrenal Status in Patients Undergoing Surgery. *Journal of Clinical Endocrinology and Metabolism* 2003;88:2045-2048
5. Huang W, Kalthorn TF, Baillie M, et al: Determination of Free and Total Cortisol in Plasma and Urine by Liquid Chromatography-Tandem Mass Spectrometry. *Ther Drug Monit* 2007;29(2):215-224