

## Total Cortisol Measurement May Not be Reliable in the Diagnosis of Adrenal Insufficiency in Liver Cirrhosis

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### Abstract

Many studies report increased prevalence of adrenal insufficiency (AI) as high as 65% among patients with liver cirrhosis based on measurement of total serum cortisol. However, in liver cirrhosis, the low concentrations of cortisol-binding globulin (CBG) and albumin may underestimate cortisol values leading to a false diagnosis of AI. Measurement of free serum cortisol, the biologically active fraction of cortisol, reflects adrenal function better than total cortisol. Four studies reported that attainment of a free cortisol value of 0.9 µg/dl either at baseline or after corticotropin stimulation rules out AI in patients with liver cirrhosis. Based on these data and until new guidelines are released, the author recommends the measurement of plasma free cortisol in addition to total cortisol to confirm the diagnosis of AI in patients with liver cirrhosis.

**Keywords:** Adrenal Insufficiency; Free Cortisol; Total Cortisol; Corticotropin

### Introduction

Circulating total cortisol consists of 3 components: cortisol bound to CBG (80% of total cortisol), cortisol to albumin (10 - 15% of total cortisol), and free cortisol (5 - 10% of total cortisol) [1]. Only free cortisol represents the biologically active form of cortisol [2]. In liver cirrhosis, levels of CBG and albumin are decreased and thereby may underestimate the plasma levels of total cortisol. Therefore, this finding may lead to an overdiagnosis of AI [3]. This problem becomes more complex as symptoms and signs of liver cirrhosis overlap with those of AI. Thus, hospitalized patients with liver cirrhosis may exhibit weakness, fatigue, abdominal pain from ascites, and hyponatremia. In fact, hyponatremia is the most common electrolyte abnormality in patients with decompensated liver cirrhosis [4]. Furthermore, in the author's experience, hyponatremia is the most common cause for ruling out AI in liver cirrhosis. Indeed, making a correct diagnosis of AI in patients with liver cirrhosis is crucial because a false diagnosis of AI based on a low total cortisol value will lead to lifelong unnecessary treatment with glucocorticoids. These drugs have serious adverse effects such as hyperglycemia, osteoporosis, and increased propensity for infections [5]. The purpose of this article is to present current data showing the limitations of total cortisol for diagnosis of AI in patients with liver cirrhosis, and to propose plasma free cortisol as more accurate alternative for such diagnosis.

### Laboratory diagnosis of adrenal insufficiency

In its latest practice guideline, the American Endocrine Society recommended a short corticotropin test (also called cosyntropin or Synacthen test) as the gold standard diagnostic tool to establish the diagnosis of AI [1]. This test includes blood withdrawal for measurement of baseline total cortisol followed by intravenous injection of 250 mcg of synthetic corticotropin. Then, 2 other serum cortisol values were checked 30 and 60 min after cosyntropin injection. The diagnosis of AI is ruled out if total cortisol level attains 18 µg/dl or more [1]. Unfortunately, the American Endocrine Society did not specify any recommendations regarding diagnosis of AI in various conditions that lower cortisol binding proteins such as liver cirrhosis [1].

### Prevalence of adrenal insufficiency in cirrhosis based on total cortisol measurement

In general, AI is not a common disease [6]. Yet, studies relying on measurement of serum total cortisol levels after standard cosyntropin test for diagnosis of AI reported very high prevalence of AI that far exceeds its prevalence in the general population. In a recent study from Egypt, Naguib, *et al.* [7] reported 65% prevalence of AI among 132 patients with stable liver cirrhosis based on positive cosyntropin test. Using the same diagnostic approach, Park, *et al.* [8] reported a 34.7% prevalence of AI in 55 Korean men with hemodynamically stable liver cirrhosis. Of note, these authors documented that serum albumin levels were significantly lower in patients with AI ( $P < 0.05$ ) [8]. In a third study from Turkey of 108 patients with decompensated cirrhosis, Rakici [9] reported a prevalence of AI of 29.6%.

### Prevalence of adrenal insufficiency in cirrhosis based on free cortisol measurement

The discrepancy between total and free cortisol in the diagnosis of AI in cirrhotic patients is best illustrated in studies that simultaneously measured both cortisol values during the cosyntropin stimulation testing. In these studies, the prevalence of AI is consistently lower when evaluated by free cortisol compared with total cortisol. Using the standard (250 mcg) cosyntropin stimulation testing in 43 patients with severe but stable liver cirrhosis, Tan, *et al.* [10] reported a prevalence of AI of 58% using total cortisol compared with 12% using free cortisol. In a retrospective study of 26 patients with hepatic impairment, Vincent, *et al.* [11] compared the diagnosis of AI based on peak serum total cortisol  $> 19.7$  µg/dl (550 nmol/L) versus free cortisol index. The latter parameter correlates strongly with serum free cortisol (correlation coefficient 0.98) and therefore is considered a surrogate marker for free cortisol [11]. These researchers have shown that when total cortisol alone is used to interpret the standard cosyntropin test in patients with liver impairment, 46% may have been misclassified as having AI [11].

Results of studies using low-dose i.e. 1 mcg of synthetic corticotropin instead of the standard 250 mcg) reached similar conclusions. Thus, in 61 consecutive patients with liver cirrhosis, Theocharidou, *et al.* [12] found that 18% of patients had AI based on total cortisol, whereas no patients fulfilled the diagnosis of AI based on free cortisol measurement. In 79 patients with stable liver cirrhosis, Fede, *et al.* [13] reported a diagnosis of AI in 34% and 28% using total and free cortisol criteria, respectively. Interestingly, CBG concentrations were the main factor explaining the discordance between the 2 cortisol measurements. Thus, patients who were diagnosed as having AI by total cortisol but had normal free cortisol had lower CBG concentrations (21 versus 54 µg/ml,  $P < 0.01$ ) [13].

### Level of serum free cortisol that corresponds to the total cortisol diagnostic cutoff for adrenal insufficiency

To help establish a cutoff value of free cortisol for diagnosis of AI, 4 studies examined the free cortisol levels that corresponded to the total cortisol cutoff of 18 µg/dl (497 nmol/L). In the first study, Dichtel, *et al.* [2] examined the correlation between plasma total and free cortisol values in 3 conditions associated with altered levels of CBG and albumin. These conditions included liver cirrhosis ( $n = 38$ ), patients admitted to intensive care unit ( $n = 26$ ), and women taking estrogen-containing oral contraceptives ( $n = 31$ ). In addition, they included 243 healthy control subjects for comparison [2]. These authors found that a free cortisol level of 0.9 µg/dl (24.8 nmol/L) predicted total cortisol of 18 µg/dl (497 nmol/L) with 98% sensitivity and 91% specificity [2]. Using the standard cosyntropin stimulation test in 3 groups of subjects: healthy volunteers ( $n = 27$ ), patients with known diagnosis of AI ( $n = 44$ ), and patients with mild liver cirrhosis

(n = 15), Rauschecker, *et al.* [14] reached the same value of free cortisol of 0.9 µg/dl corresponding to total cortisol of 18 mcg/dl with a sensitivity of 95% and specificity of 100%. In a relatively large sample of 295 subjects with unknown adrenal status, Bancos., *et al.* [15] measured the free and total cortisol values at 30 min and 60 min during the standard cosyntropin stimulation test. They found that the free cortisol cutoffs for AI were 0.9 and 1.2 ug/dL at 30 and 60 minutes, respectively. Finally, in a small pilot study including 12 patients with AI and 10 healthy control subjects, Peechakar., *et al.* [16] recorded free cortisol cutoffs for diagnosis of AI of 0.9 µg/dL and 1.3 µg/dL at 30 min and 60 min, respectively during the standard dose cosyntropin test. Taken together, there is general agreement between the 4 above studies that reaching a free cortisol of 0.9 µg/dl either at baseline or after cosyntropin stimulation can be used as cutoff to rule out AI.

### Limitations of plasma free cortisol measurement

Despite its superior accuracy in making the diagnosis of AI compared with total cortisol, free cortisol measurement suffers from the following limitations. First, it is expensive, not widely available, and takes time until results come back (approximately 7 days) [3]. Therefore, until more data are available, the author suggests performing the standard corticotropin stimulation test in patients with liver cirrhosis who have symptoms of AI (hypotension, abdominal pain, vomiting, diarrhea, hyponatremia) using both total and free cortisol. If total cortisol values are diagnostic of AI (i.e. all values are < 18 µg/dl), hydrocortisone therapy (10 mg qAM and 5 mg qpm) may be started until free cortisol values become available. If any free cortisol value comes back at 0.9 µg/dl or higher, AI is ruled out and hydrocortisone therapy may be stopped. Meanwhile, if all free cortisol concentrations are below 0.9 µg/dl, the diagnosis of AI is confirmed, and hydrocortisone is continued.

### Conclusion and Current Needs

Liver cirrhosis is characterized by low plasma concentrations of CBG and albumin that may lower circulating total cortisol concentrations leading to overestimation and false diagnosis of AI. This is a common problem encountered in practice given the overlapping symptoms and signs between liver cirrhosis and AI. Thus, measurement of free cortisol, although expensive and has slow turnaround time, is more reliable than total cortisol in diagnosis of AI in cirrhotic patients. Ruling out AI by free cortisol will avoid unnecessary treatment of cirrhotic patients with lifelong hydrocortisone. Therefore, it is worthwhile performing the standard corticotropin stimulation test measuring free cortisol in addition to total cortisol. If any free cortisol value reaches or exceeds 0.9 µg/dl, AI is ruled out. Further studies are needed to validate this threshold value of free cortisol in various patient populations. In addition, studies are needed to evaluate salivary cortisol, a relatively inexpensive surrogate of free plasma cortisol for the diagnosis of AI in cirrhotic patients [17]. The American Endocrine Society should clarify these issues in its upcoming guidelines.

### Conflict of Interest

The author has no conflict of interest to declare.

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