

To Study Adrenal Insufficiency and to Determine Relationship between Serum Albumin and Serum Cortisol Levels in Cirrhotic Patients

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ABSTRACT

Introduction: In patients with cirrhosis, albumin synthesis is decreased because of the loss of hepatic cell mass. Adrenal insufficiency (AI) has been demonstrated in patients with severe liver disease. The percentage of AI in cirrhotic patients varies among different studies and depends on different methods and criteria used to evaluate adrenal function. As both serum albumin and cortisol levels are low in cirrhotic patients we want to determine relationship between serum albumin and cortisol levels. Current research aimed to study adrenal insufficiency in patients of cirrhosis and to determine the relationship between serum albumin and serum cortisol levels.

Material and Methods: Prospective study was done on 50 patients of cirrhosis who were admitted in medicine/gastroenterology ward of DMC & H, Ludhiana. Depending on the levels of cortisol, patients were categorized into 3 groups. Clinically diagnosed patients of cirrhosis were included in our study whereas HIV/Immunodeficiency, Severe chronic heart disease, Chronic obstructive lung disease, Chronic hemodialysis, Severe sepsis, septic shock and patients on steroid therapy were excluded.

Results: The data was analyzed using Microsoft excel and SPSS version 20.0 (IBM SPSS, Chicago, Illinois). Mean and standard deviation were computed for the variables. The comparison between groups were done by Chi square and ANOVA. AI was present in 14 (28%) patients of Cirrhosis. The difference between cortisol levels with respect to Albumin was found to be statistically significant (0.05).

Conclusion: AI forms important part of spectrum of Cirrhosis and these patients should be evaluated for adrenal dysfunction.

Keywords: Adrenal insufficiency, Albumin, Cortisol

INTRODUCTION

Albumin is a protein of 585 aminoacids and 66 kDa of molecular weight that primarily contributes to the plasma oncotic pressure. It is synthesized by the liver, passes into blood circulation and remains in the bloodstream for about 21 days.¹ It helps in the transport and disposal of toxic substances, hormones and drugs to target cells.^{2,3}

Patients with advanced cirrhosis almost always have hypoalbuminemia caused by decreased synthesis by the hepatocytes, water and sodium retention that dilutes the content of albumin in the extracellular space and increased transcapillary transport rate.⁴

Adrenal insufficiency (AI) has been described in all stages of cirrhotic patients.⁵ However, the exact mechanism leading to AI in cirrhotic population is not yet known. It is known that cholesterol is an important substrate for steroid synthesis and

adrenal glands synthesize cortisol whenever is necessary. In cirrhosis, the adrenal glands synthesize the reduced amount of cortisol especially under stress conditions leading to “adrenal exhaustion syndrome” ending to AI.⁶

The mechanism of action of ACTH is through binding to a seven-membrane-spanning G protein-coupled ACTH receptor.⁷

Upon ligand binding, the receptor undergoes conformational changes that stimulate adenylyl cyclase, which further leads to an increase in intracellular cAMP and subsequent activation of protein kinase A. It stimulates lipoprotein uptake into cortical cells. This stimulates transcription of the genes coding for P450_{scc}, steroid 11 β -hydroxylase, and their associated electron transfer proteins.⁸ Current research aimed to study adrenal insufficiency in patients of cirrhosis and to determine the relationship between Serum Albumin and serum cortisol levels.

MATERIAL AND METHODS

Study was done on patients admitted in medicine/gastroenterology ward of DMC & H. 50 consecutive patients of cirrhosis were included in the study.

Inclusion Criteria

Diagnosed patients of cirrhosis based on clinical/ biochemical / radiological/ endoscopy and or liver biopsy.

Exclusion criteria

1. HIV/Immunodeficiency
2. Severe chronic heart disease
3. Chronic obstructive lung disease
4. Chronic hemodialysis
5. Severe sepsis or septic shock.
6. Patients on steroid therapy

Depending upon the levels of cortisol, patients were divided into 3 groups:

Group I Patients having >15 μ g/dl cortisol (Baseline levels) n=31

Group II Patients having 3-15 μ g/dl cortisol (Baseline

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levels) n=11

Group III Patients having <3 µg/dl cortisol (Baseline levels) n=8

In Group II, ACTH Stimulation (SD-SST) was done, then this Group was further divided into II a and II b

II a Patients having >18 µg/dl cortisol levels 30 minutes after ACTH stimulation (n=5)

II b Patients having <18 µg/dl cortisol levels 30 minutes after ACTH stimulation (n=6)

Diagnostic criteria for Adrenal Insufficiency

Levels of serum cortisol at 6-10 am <3µg/dl confirms Adrenal Insufficiency.

Levels of serum cortisol at 6-10 am >15µg/dl rules out Adrenal Insufficiency

Intermediate cortisol levels at 6-10 am are 3-15 µg/dl.

ACTH Stimulation should be performed for intermediate cortisol levels. The diagnosis of adrenal insufficiency will be considered if the serum cortisol level is <18µg/dl, 30 minutes after stimulation.

To assess the severity of liver, CTP scoring system and MELD scoring systems are used.

1.Child-Turcotte-Pugh (CTP) scoring system:

Group A- CTP Score (5-6)

Group B- CTP Score (7-9)

Group C- CTP Score ≥ 10

2.MELD Score: Model for End-Stage Liver Disease.

3.8 (log_e serum bilirubin mg/dl) +11.2 (log_e INR) +9.6 (log_e serum creatinine mg/dl) +6.4.

Serum cortisol

Test method: Electrochemiluminescence Immunoassay

Principle: Elecsys Cortisol assay makes use of competition test principle using a monoclonal antibody which is specifically directed against cortisol.

Endogenous cortisol in the sample which has been liberated from binding proteins with danazol competes with exogenous cortisol derivative in the test which has been labelled with ruthenium complex for the binding sites on biotinylated

antibody.

Serum Albumin

Test Method: Colorimetric assays

Principle: Albumin binds with the dye Bromocresol Green in a buffered medium to form a green colored complex. The intensity of color formed is directly proportional to the amount of albumin present in sample. This test is performed on the cobas c 501 system after running maintenance, QC and calibration schedule as defined in supporting procedure.

STATISTICAL ANALYSIS

The data was analyzed using Microsoft excel and SPSS version 20.0 (IBM SPSS, Chicago, Illinois). Mean and standard deviation were computed for the variables. The comparison between groups were done by Chi square and ANOVA. P value ≤ 0.005 was taken as significant.

RESULTS

Diagnostic criteria for Adrenal Insufficiency

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Intermediate cortisol levels at 6-10 am are 3-15 µg/dl.

ACTH Stimulation should be performed for intermediate cortisol levels. The diagnosis of adrenal insufficiency will be considered if the serum cortisol level is <18µg/dl, 30 minutes after stimulation.

Group II b and Group III consist of patients suffering from adrenal insufficiency.

And Group I and Group II a consists of patients with normal adrenal function.

Distribution of subjects according to adrenal function

Out of 50 patients included in this study, 14 (28%) patients had Adrenal Insufficiency (figure-1)

Distribution of subjects according to Albumin levels

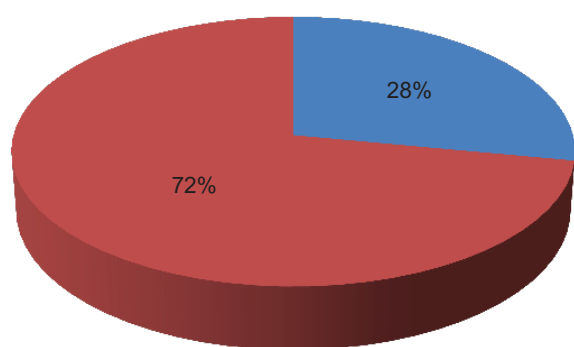
Group II b and Group III patients were suffering from adrenal insufficiency. Mean albumin levels of these patients are

| Factor | Units | 1 | 2 | 3 |
|------------------------|---------|-------------|----------------|------------|
| Serum bilirubin | mg/dl | 1-1.9 | 2-2.9 | >3 |
| Serum albumin | g/dl | >3.5 | 2.8-3.5 | <2.8 |
| Prothrombin time / INR | Seconds | 1-3 <1.7 | 4-6 1.7-2.3 | >6 >2.3 |
| Ascites | | absent | Slight | Moderate |
| Hepatic encephalopathy | grade | none | 1 & 2 | 3 & 4 |

Table-1: CTP Score

| Albumin(g/dl) | Group I | Group II a | Group II b | Group III | P value |
|-------------------|------------|------------|-------------|-------------|---------|
| <2.5 (n=17) | 8(25.8%) | 0(0.00%) | 5(83.33%) | 4(50.00%) | 0.05 |
| 2.5-3.5 (n=26) | 17(54.83%) | 4(80.00%) | 1(16.66%) | 4(50.00%) | |
| 3.5-5.0 (n=7) | 6(19.35%) | 1(20.00%) | 0(0.00%) | 0(0.00%) | |
| Mean ± SD | 2.9 ± 0.61 | 3.1 ± 0.54 | 2.32 ± 0.33 | 2.57 ± 0.42 | |

Table-2: Mean Albumin levels of 3 Groups



■ Adrenal insufficiency ■ Normal adrenal function

Figure-1: Distribution of subjects according to adrenal function

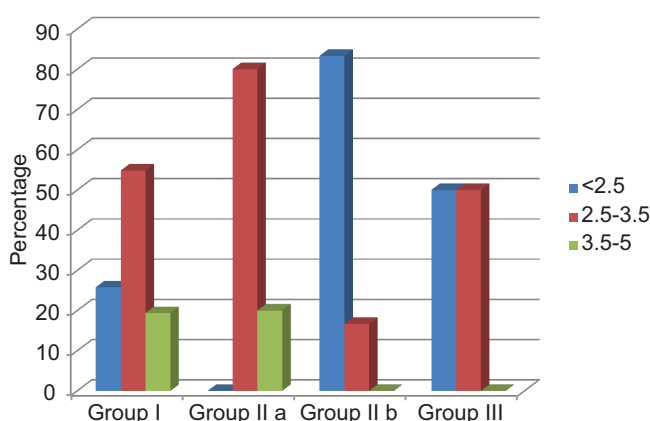


Figure-2: Distribution of subjects according to Albumin levels

lower than group I and Group II a which consist of patients with normal adrenal function (figure-2, table-2).

Out of 50 patients included in this study, All the 14 patients of adrenal insufficiency had albumin levels <3.5 g/dl. A significant relationship was found between cortisol and albumin levels ($p=0.05$)

DISCUSSION

The prevalence of AI in Cirrhosis was 28% in our study. Acevedo et al⁹ reported 26% AI. Galbois et al¹⁰ reported 33% AI prevalence whereas other studies reported higher prevalence of AI.¹¹

Prevalence varies according to choice of subjects in different studies. Higher prevalence of AI was found in studies that included subjects with liver failure, liver transplant recipients and critically ill cirrhotic patients as compared to studies with stable cirrhotic patients. The percentage of AI in cirrhotic patients varies among different studies and depends on the different methods used to estimate adrenal function.

In our study, a significant relationship was observed between cortisol levels and albumin levels which is also consistent with the findings of Fede et al¹² and Kharb et al¹³ but in contrast to findings of Tsai et al.¹⁴

Adrenal insufficiency was related to the degree of liver cirrhosis in our study.

Some authors suggested that low levels of HDL cholesterol may be responsible for the defects in adrenal function in cirrhosis.⁶ Whereas Some authors suggested that patients with acute and chronic liver disease have increased

levels of circulating endotoxin (lipopolysaccharide) and proinflammatory mediators such as tumor necrosis factor which cause reductions in CRH and ACTH release and therefore low levels of cortisol.^{15,16}

In liver failure where albumin and corticosteroid binding globulin (CBG) levels are reduced, total cortisol levels may be low whereas free cortisol levels may be normal or even increased as in serum, as 70% of circulating cortisol exists bound to (CBG), 20% is bound to albumin and 10% exists as biologically active free cortisol.¹⁷

Galbois et al.¹⁰ concluded that using serum total cortisol assays overstate adrenal insufficiency prevalence among cirrhotic patients, mainly because of inaccurate concentrations related to hypoalbuminemia. Therefore Salivary cortisol assays should be preferably used in these patients.

There are many arguments about the best method to assess adrenal function in patients with liver cirrhosis.

CONCLUSION

We concluded that AI forms important part of spectrum of Chronic liver disease and these patients should be evaluated for adrenal dysfunction periodically.

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