ORIGINAL PROF-595

CHRONIC LIVER DISEASE;
ASSESSMENT OF ANTITHROMBIN III LEVELS

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ABSTRACT

This study was designed to estimate AT III levels in patients with chronic liver disease and to correlate it with other coagulation screening tests. In the present study 30 patients of chronic liver disease (cirrhosis) were included. Twenty healthy controls were selected who have no liver disease, not taking any hepatotoxic drug or any anticoagulant. The following tests were performed, AT III levels PT, APTT, Fibrinogen levels and serum albumin. Significantly reduced levels of AT III were recorded in the patient group as compared with the healthy controls. A significant negative correlation was found between AT III and Prothrombin time. The patient showed reduced AT III levels with normal PT. A positive correlation was found between serum albumin and AT III. It is concluded that reduced AT III level is more sensitive indicator of synthetic function of liver and thrombo-embolic phenominon should be suspected in patients of chronic liver disease when AT III levels are reduced.

KEYWORDS: AT (Anti Thrombin)

INTRODUCTION

An excess of circulating AT III has been described in occasional patients with liver disease but studies in the larger group of patients suggest that the level of AT III are usually reduced[1].Reduced level of AT III in decompensated liver cirrhosis was noticed by Robert and Cederbaum(1972)[2], Ito et al (1986)[3]. Reduce level of AT III in liver cirrhosis are also reported by Von Kaulla and Duckert(1973)[4], Al-Mofleh et al(1989)[5], Dumitrascu et al(1991)[6], Langley & William(1992)[7].

AT III activity determination was found to be better value than prothrombin time to determine liver disease[8]. Abnormal AT III are also found in chronic liver disease[9]. Acquired deficiency of AT III, plasminogen and fibrinogen are reported in chronic liver disease by Pasqualetti et al (1997)[10].

In the light of above facts the laboratory measure of AT III is of great importance to assess, diagnose and treat the possible thromboembolic complication of chronic liver disease, so the present study was structured to determine plasma level of AT III in patients with chronic liver disease.

AIMS & OBJECTIVES

1. To determine plasma levels of AT III in patient with chronic disease.

2. To correlate AT III levels with prothrombin time, plasma fibrinogen level and serum albumin.

MATERIALS & METHODS

This study was conducted at Pathology department of PGMI Lahore. A total number of 30 subjects having age range of 40-75 years irrespective of sex, occupation and socioeconomic status were included. Along with 20 subjects served as controls, the controls were age, sex and socioeconomically matched with patient group. Subjects with family history of liver diseases, pregnant females and subject taking anticoagulant were excluded from the control group. The patients were already diagnosed cases of chronic liver disease by histopathology. The subjects were collected from various hospitals of Lahore. Following investigations were performed in these subjects;

PLASMA AT III LEVELS

AT III assay was carried out by single radial immunodiffusion technique or norpartigen plates. The diameter of precipitated rings formed after 48 hours incubation was measured by means of nor-partigen scale and concentration as well as percentage activity was read out from the table provided with the plates.

Other lab procedures carried out included serum albumin and PT by quick one stage method, APTT, Fibrinogen levels were estimated by Clauss's techniques. Serum albumin was estimated by kit provided by lab. System and the estimation was based on the binding of dye to albumin. Dye used was BCG.

RESULTS

Age Distribution

The mean age of control subject was 49.6 ± 8.4 with a range of 40-65 years. The mean age of the apatient with chronic liver disease was 56.6 ± 9.7 with range of 38-73 years.

Sex Distribution

Among 20 controls 15 (75%) were male and 5 (25%) were females. In case of patients 20 (66.6%) were males and 15 (33.3%) were females.

Serum Albumin

In controls the serum albumin was 39.8±3.2 with a range of 35 - 46 g/L. In patient with cirrhosis serum albumin was 27.2±10.5 g/L with a range of 10-49 g/L. This difference was highly significant statistically between patient and control group (P<0.001) Table I.

Prothrombin time

In control subject the prothrombin time was 21.15±6.3 with a range of 14-30 seconds. In patient with cirrhosis P.T was 30.71±8.1 with a range of 21-50 seconds. Statistically this difference was highly significant (P<0.001) (Table-II).

Table-I. Comparison of serum albumin (g/l) in controls and patients.

Group	Serum albumin (g/l)
Controls (n=20)	39.8±3.2 (35-46)
Patients (n=30)	27.2±10.5 (10-49)
P value (Patients vs controls P<0.001)	

Table-II. Comparison of plasma prothrombin time (seconds) in controls and patients.

Group	Plasma prothrombin time(second)
Controls (n=20)	21.15±6.3(14-30)
Patients (n=30)	30.71±8.1 (21-50)
P value (Patients vs controls P<0.001)	

Table-III. Comparison of plasma fibrinogen (g/l) in controls and patients.

Group	Plasma prothrombin time(second)
Controls (n=20)	2.42±0.7(1.47-3.62)
Patients (n=30)	1,72±0.8 (0.98-4.01)
P value (Patients vs controls P<0.001)	

Plasma fibrinogen levels

In the control subjects the plasma fibrinogen level was 2.42±0.7 with a range of 1.47-3.62 g/L. In patient with

cirrhosis, plasma fibrinogen level was 1.72±0.8 with a range of 0.98 - 4.01 g/L. Statistically this difference was highly significant (Table-II).

Plasma Anti-thrombin III Levels

In control subjects, the AT-III level was 0.263±0.034 with a range of 0.23-0.33 g/L. In patient group plasma AT III level was 0.158±0.024 with a range of 0.12 - 0.22 g/l. Statistically the difference was very highly significant (P<0.001) (Table.-III).

Correlation of investigations

In control group there was a negative correlation between AT III and Albumin (R=0.0465) and this was not significant. However in patient with cirrhosis there was a positive correlation (R=0.6204) and this correlation was highly significant (P<0.001) (Table-IV).

Table-IV. Comparison of plasma fibrinogen (g/l) in controls and patients.

Group	Plasma prothrombin time(second)
Controls (n=20)	2.42±0.7(1.47-3.62)
Patients (n=30)	1.72±0.8 (0.98-4.01)
P value (Patients vs controls P<0.001)	

Table-V. Correlation co-efficient of plasma prothrombin time and AT III in controls and patients

Subjects	No of Pts	Plasma prothrobmin time	Plasma AT III	R Value	T Value	P Value
Controls	20	21.15±6.3	0.263±0.034	0.0364	0.1543	>0.05
Patients	30	30.71±8.1	0.158±0.024	-0.4256	-2.4889	<0.02

Table-VI. Correlation co-efficient of plasma Fibrinogen and AT III in controls and patients

Subjects	No of Pts	Plasma Fibrinogen	Plasma AT III	R Value	T Value	P Value
Controls	20	2.42±0.7	0.263±0.034	0.0555	0.2359	>0.05
Patients	30	1.72±0.8	0.158±0.024	0.4038	2.3355	<0.005

Plasma prothrombin & AT III Levels

In control subject there was a positive correlation (R=0.0369) which was not significant. In patient with cirrhosis there was a negative correlation (R=0.4256) and this correlation was statistically significant (P<0.02) (Table-V).

Plasma Fibrinogen & Plasma AT III Levels

In the control group there was a positive correlation (R=0.0555) which was not significant statistically. In patient group there was a positive correlation (R=0.4038) which was statistically significant (P<0.05).

DISCUSSION

General appearance is that AT III is synthesized mainly by liver[8,11,12,13,14,15,16]. In the present study low AT III levels are in accordance with above mentioned studies. Different reasons regarding decreased plasma AT III is due to reduced production of AT III by diseased liver. Scherer et al noted such situation of AT III in the chronic liver disease with thrombin AT III complex[16]. Decrease AT III can be due to increase catabolism of AT III. In patient of cirrhosis Disseminated Intra vascular Coagulation (DIC) can be present without any systemic presentation which is called silent DIC[15,17].

In the present study prolonged prothrombin time and reduced fibrinogen level can be found without any clinical manifestation. It can be due to silent DIC [9,13,15,18,19,20,21].A study of metabolism of AT III in liver cirrhosis was conducted suggesting that there was rapid turn over of protein in these patients and this could be due to accelerated trans-capillary flux[18,20]. Pirssi et al

(1995) noted reduced AT III levels and increased D dimers in chronic liver disease. Acute deficiency in plasma AT III have been reported in many clinical conditions like nephrotic syndrome causing thromboembolism[23].

Plasma Albumin

In the present study very highly significant reduction in albumin level was seen in patient with cirrhosis. This finding is inconsistent with observation of Chan et al, Qureshi & Sheikh, Monreal, Al-Mofleh and Tomiya and Fuji wara[24,25,26]. Hypoalbunemia is due to inability of hepatocytes to synthesized albumin. Determination of serum albumin is not very efficient liver function test because it has a long half life and it does not exhibit changes immediately when hepatic failure occur[2]. However falling concentration indicates poor prognosis[27].

Prothrombin Time

Promthrombin time is commonly prolonged in liver disease because liver is unable to manufacture adequate amount of clotting factors. Prothrombin along with other vitamin K dependent factors e.g. Factor-V, VII & X are produced in liver[12,24]. Since prothrombin is synthesize in liver, PTT is prolonged in chronic liver disease[1,19]. In the present study there was very highly significant prolongation of prothrombin time in patients of cirrhosis as compared to control. Factor VII is a rate limiting factor in the extrinsic pathway and thus has the greatest influence on prothrombin time. Fall of factor VII which has shortest half life has bad prognosis. This finding is compatible with other studies as mentioned above. Prothrombin time correlate well with serum albumin[3].

Plasma Fibrinogen

In the present study, plasma fibrinogen level was very significantly decreased in patient of hepatic cirrhosis as compared to normal control. This finding was the same as reported by Bernardi et al (1984), Saitoh (1986), Al-Mofleh (1989), Tomiya & Fuji won (1981)[12,16,5,26]. Previously it was though that fibrinogen is synthesized by kupffer cells of billiary canaliculi. Now it is proved that fibrinogen is formed in hepatocytes[28].

Correlation of plasma AT III and serum albumin

In the present study a positive correlation was found in patient with cirrhosis. This observation is in agreement with the study done by Ito (1986), Inclair et al (1988) and Dumitrescu et al (1991)[3,13,6].

Correlation of plasma ATY III and Prothrimbin time;

A significant negative correlation was found between AT III and prothrombin time. This finding correlates with the study of Dumontier et al (1992)[15] but no correlation was found by Dumistrescu et al (1991)[16].

Correlation of plasma AT III and plasma fibrinogen

A positive correlation was found in the present study between plasma AT III and plasma fibrinogen.

CONCLUSION

AT III is more sensitive test than PT in cirrhosis to measure the synthetic ability of liver. A larger study with more clinical awareness is needed to detect thromboembolic phenomenon in chronic liver disease associated with low AT III levels. If possible a postmortem study could be conducted.

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