ORIGINAL ARTICLE

Gall Bladder Wall Thickness as a Marker of Portal Hypertension in Patients of Alcoholic Cirrhosis of Liver

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ABSTRACT

BACKGROUND AND OBJECTIVES: One of the major complications of cirrhosis is the occurrence of Portal Hypertension, which can lead to bleeding from Esophageal Varices, Hepatic Encephalopathy, Ascites, Spontanoeus Bacterial Peritonitis, Hepatorenal Syndrome, Hepatopulmonary Syndrome, etc. Early diagnosis and treatment of Portal hypertension is vital to prevent major complications in Cirrhosis of liver. Portal hypertension causes increase in the hydrostatic pressure causing oedema and congestion of Gallbladder also known as Congestive Cholecystopathy. In this study, we have attempted to find the correlation between presence of portal hypertension and increased diffuse Gallbladder Wall Thickness(GBWT). To study the relationship of Portal Hypertension to Diffuse Gallbladder Wall thickness on ultrasonography in patients of Alcoholic Cirrhosis of Liver, without any intrinsic Gallbladder disease. **METHODS:** In the present study, 60 patients of Alcoholic Cirrhosis of Liver admitted in the medical wards of SSGH, Baroda were studied. Data was collected regarding the history, physical examination, laboratory and radiological investigations, especially Gallbladder wall thickness and Upper GI Endoscopy. **RESULTS:** Patients were divided into 2 groups as per the Gall Bladder Wall thickness; Group A with GBWT <4mm, which consisted of 17 patients and Group B with GBWT >4mm, which consisted of 43 patients. Comparison of Serum Albumin levels between the two groups showed. **CONCLUSION:** In patients of Cirrhosis, increased GBWT correlated well with increased Portal Vein diameter, increased incidence of Ascites and presence of Esophageal Varices. Thus, the presence of GBWT on Ultrasonography in patients of cirrhosis without intrinsic gall bladder disease should be considered as an early sign of Portal Hypertension.

Keywords: Alcohol, Gall Bladder Wall Thickness, Cirrhosis, Portal Hypertension

INTRODUCTION

Cirrhosis is a chronic liver disease, characterized by development of fibrosis. The common causes being Alcohol, Chronic Hepatitis C and B infection. In the past, it has been thought that cirrhosis was never reversible; however, it has become apparent that when the underlying insult that has caused the cirrhosis has been removed, there can be reversal of fibrosis [1]. In the early compensated stage of cirrhosis, patients are usually asymptomatic. Diagnosis of Cirrhosis is relatively straightforward during the decompensated stage when the treatment may be problematic, on the contrary, diagnosing Cirrhosis while it is still in compensated stage is more challenging[2]. Compensated Cirrhosis may progress and has two major consequences, Portal hypertension and Hepatic Failure. Portal Hypertension is defined as the elevation of the hepatic venous pressure gradient (HVPG) to > 5mmHg[1].Portal Hypertension is caused by one, increased hepatic resistance to the passage of blood flow through the liver due to regenerative nodules, and second due to increased splanchnic blood flow secondary to vasodilation[1]. Progression of fibrosis parallels the increase in portal pressure and, frequently, patients with severe fibrosis in the pre-cirrhotic stage have a HVPG>5mmHg[2]. Portal hypertension is associated with the most severe complications of cirrhosis including Ascites and Varicealhemorrhage. Variceal bleedingis an immediate life-threatening problem with a 20-30% mortality rate associated with each episode of bleeding. The concept of diagnosis of cirrhosis is

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changing from the documentation of histological fibrosis to the identification of patients truly at risk of developing complications. HVPG is the most robust predictor of clinical decompensation in patients with compensated cirrhosis and portal hypertension without varices[4]. It has been clearly demonstrated that the onset of clinically significant portal hypertension (HVPG>10mmHg) marks the progression to a stage at risk of clinical complications. It is therefore necessary to diagnose clinical decompensation in otherwise compensated cirrhosis patients, so that early treatment can be initiated and thereby increasing the chances of reversal of fibrosis. In this scenario, non-invasive methods able to mirror the hemodynamic threshold play an important role[3].Since a long time ago, simple blood tests were used in the diagnosis and prognostication of patients with advanced liver diseases. The most largely used is a combination of markers of liver synthetic functions(albumin, bilirubin and prothrombin time) that, together with two clinical variables (presence and severity of ascites and encephalopathy), constitute the Child Pugh Score[5]. HVPG is the best surrogate marker in chronic liver disease; however the measurement of HVPG has its limitations, such as its invasiveness[6].Upper GI Endoscopy is recommended for screening of EsophagealVarices, so as to start primary prophylaxis in patients who are at high risk of Variceal Bleeding. Upper Gastrointestinal(GI)Endoscopy , as a screening method for diagnosis of Portal Hypertension is also an invasive and costly method. Predicting the presence of EsophagealVarices by Non Invasive means might increase the compliance and would permit to restrict the performance of endoscopy to those patients with a high probability of having varices.[7] The ideal noninvasive test for diagnosing fibrosis and portal hypertension, should be simple and reproducible, readily available, less expensive than a biopsy, and able to predict a full spectrum of fibrosis and reflect any changes induced by therapy[8]. Gall bladder wall thickness found on ultrasonography can be of two types: Diffuse and Focal. Focal is usually due to intrinsic Gall bladder diseases, while diffuse is associated with many conditions without intrinsic gall bladder disease, like hypoalbuminemia, Right sided heart failure, Cirrhosis of Liver, Chronic Kidney Disease. Gall Bladder wall thicknening in patients with Cirrhosis is mostly due to raised hydrostatic pressure of vasculature of Gall bladder wall. Gall bladder wall thickening is frequently observed and frequently reported in association with portal hypertension[9,10]. Proper diagnosis and management of complications of PHT are vital to improving quality of life and reducing mortality in cirrhotic patients. The present study was undertaken with a view to determine the correlation of GBWT with presence of Hypoalbuminemia, Ascites, Portal Vein Diameter, Upper GI Bleed and presence of EsophagealVarices.

MATERIALS AND METHODS

Study sample

The present study was conducted at Shri Sayaji General Hospital, Vadodara, a tertiary health care institute, from October 2015 to November 2016. This was a cross sectional study where we enrolled 60 patients of Alcoholic Cirrhosis of Liver.

Inclusion Criteria

Patients diagnosed as having Alcoholic Cirrhosis of Liver, with age more than 18 years

Exclusion Criteria

- Patients with history of Gall Bladder diseases or Cholecystitis
- Patients with Congestive Cardiac Failure
- Patients with Chronic Kidney Disease
- Patients with Serum SGPT levels>400U/L

Method

The patients were explained in detail about the study, following which an informed consent was taken regarding permission for inclusion in the study. Detailed Clinical history was taken and then patients were subjected to a thorough clinical

examination. Blood samples were drawn under complete aseptic precautions after obtaining informed consent. Blood investigations sent included, Complete Hemogram, Liver function tests with enzymes, Total protein and serum Albumin levels, Prothrombin time .Additional blood investigations were sent depending on the need of the patient's clinical condition. All the patients underwent Ultrasonography of Abdomen, for visualisation of hepatic size, liver echotexture, Portal Vein diameter at porta, Flow in portal vein, Collaterals/Varices and Gall Bladder Wall thickness. The patients were subjected to the Ultrasound in the mornings ,after proper overnight fasting of atleast 8 hours . The Ultrasound of all patients was done by a single radiologist. All patients, irrespective of a history suggestive of Gastrointestinal Bleed, were subjected to Upper GastroIntestinal Endoscopy. The lower end of Esophagus was assessed for presence of varices, stomach for congestive gastropathy and peptic ulcer. The Varices were classified as:

- Grade I - Small, straight varices
- Grade II – Enlarged, tortuous varices that occupy less than one-third of the lumen
- Grade III- Large, coil-shaped varices that occupy more than one third of the lumen

Data Analysis

On the basis of ultrasonographic findings, patients were divided into two groups

Group A- gall bladder wall thickness <= 4mm

Group B- gall bladder wall thickness >= 4mm

Statistical analysis was done using chi square test and two sample t test on MedCalc. A p value of <0.05 was considered as statistically significant. The results were tabulated and represented using Microsoft Office for windows 2010.

OBSERVATIONS

The 60 patients were divided into two groups, depending on the Gall bladder Wall thickness, those who had GBWT<4mm were in Group A, While those with GBWT >= 4mm were in Group B. There were 17 patients in Group A, while Group B had 43 patients. Comparison amongst both groups was made with respect to Serum Albumin levels, Portal Vein diameter, presence of Ascites, history suggesting Upper GI bleed,and presence of esophagealvariceson Upper GI endoscopy .

Table 1: Correlation of GBWT with Serum Albumin Levels

Sr. Albumin levels (gm/dl)	Group A		Group B	
	No. of patients	% of patients	No. of patients	% of patients
<2.4	3	17.64	20	46.51
2.5 to 2.9	5	29.41	15	34.88
>3	9	52.94	8	18.60

The above table shows the percentage of patients having different albumin levels. On comparing the percentage of patients having serum albumin levels less than 3 gm/dl in Group A (47.05%) with that in Group B(81.39%),p value was 0.04, which suggests significant correlation. The mean of serum albumin levels in group B was 2.52+_0.455 while mean of group A was 2.87+_0.485, the p value is 0.01, which again confirms a significant correlation between GBWT and serum albumin levels.

Table 2: Correlation of GBWT with Portal Vein Diameter

Portal vein diameter (mm)	Group A		Group B	
	No. of Patients	% of Patients	No. of Patients	% of Patients
<11.9	8	47.05	4	9.30
12-15.9	5	29.41	16	37.20
>16	4	23.52	23	53.48

The above table shows the percentage of patients having different portal vein diameters. The mean of the Portal vein diameter in group A is 13.11+_2.37 while mean of that in group B is 14.67+_2.01 ,which shows that the difference is significant, the p value being 0.012.

Table 3: Correlation of GBWT with Ascites and G.I. Bleeding

The following table shows the correlation of GBWT with ascites andupper gastrointestinalbleeding,i.e. history of hematemesis or malena

GBWT	ASCITES		G.I BLEEDING	
	No: of Patients	% of Patients	No: of Patients	% of Patients
GROUP A (<4mm)	9	52.94%	2	11.76%
GROUP B(>=4mm)	36	83.72%	9	20.93%

It was observed that 9 patients i.e. 52.94% in Group A had ascites as compared to 36 patients i.e. 83.71 % in Group B, with p=0.013, which suggests significant correlation between GBWT and presence of Ascites. While 20.93 % of patients in Group B i.e. 9 patients had evidence of gastrointestinal bleeding clinically as compared to only 11.76 % i.e. 2 patients in Group A, with p=0.412, which is not significant.

Table 4: Correlation of GBWT with GI Bleed and Upper GI Scopy

GBWT	GI BLEED		UPPER GI SCOPY	
	No: of patients	% of patients	No: of patients	% of patients
GROUP A(<4mm)	2	11.76%	5	8.3%
GROUP B(>=4mm)	9	20.93%	38	88.37%

The above table shows the correlation of GBWT with clinical evidence of upper GI Bleed and evidence of esophagealvarices on Upper GI scopy. Group B had only9patients(20.93%) who had clinical evidence of Upper GI Bleed, but Upper GI scopy revealed presence of varices in 38 (88.37%) patients as compared to Group A wherein only 2 patients(11.76%) had clinical evidence of Upper GI Bleed, but presence of varices was seen in 5(8.3%) patients. On comparing the Group A(8.3%) and B(88.37%) patients for presence of Esophagealvarices, significant correlation(p<0.0001) was found between GBWT and presence of varices on endoscopy.

DISCUSSION

Increased gallbladder wall thickness could be due to different etiologies other than gallbladder diseases such as liver diseases, hypoalbuminemia, ascites, hepatitis, congestive heart failure, kidney disease, AIDS, malignancy and sepsis[10,11]. GBWT is classified as mild (between 4-7mm), marked (more than 7mm) and in focal and diffuse. As a rule, systemic diseases such as heart, renal or hepatic failure cause diffuse and less marked thickening , contrary to tumor lesions that cause focal or more exuberant thickening, frequently greater than 10mm[12].Increase gall bladder wall thickness in cirrhotic patients is due to ascites, decreased peripheral vascular resistance and portal hypertension which shows that GBWT could be multifactorial[13] .Liver disease as the cause for Gall Bladder wall thickening is suggested by the absence of gallstones or signs of gall bladder inflammation in the presence of cirrhotic liver morphology and stigmata of portal venous hypertension, such as splenomegaly, varices and reversal of hepatopedal flow. In our study it is observed that compared to patients with a normal gall bladder wall(i.e Group A), patients in Group B had a significantly lower serum Albumin levels (2.87+_0.485Vs 2.52+_0.455gm/dl; p<0.05).This is in agreement to a study carried out by T F Wang et al[9]who observed that compared to patients with normal gall bladder wall, patients with gall bladder wall thickening had significantly lower serum albumin levels(3.6+-.6 vs 2.9+-.7gm/dl;p<0.05) . These findings in our study of hypoalbuminemia being a significant finding in cirrhotic patients with increased GBWT is not supported by a few studies by Colli et al[14] and Saverymuttu et al[15] where there was no significant correlation between GBWT and hypoalbuminemia. Hypoalbuminemia causing oedema can lead to GBWT, but as this findings is not supported by quite a few studies , it is possible that other factors like presence of ascites and portal hypertension may also contribute to the increased GBWT.[16] The normal Portal Vein diameter can vary between 7 to 15 mm while normal portal vein pressure lies between 5-10 mmHg(14 cm H2O)[17].A portal vein diameter greater than 13mm is assumed to be the cutoff point for Portal Hypertension in appropriate clinical settings[18]. The diameter of Portal Vein is a reflection of the degree of the resistance it faces in the liver and the velocity of blood flow within the portal vein.The normal

portal vein diameter is 10mm[19]. Studies have shown that this value increases with the advancement of liver fibrosis and subsequently with development of cirrhosis, where the mean Portal vein diameter is reported to be around 14mm(18-20).In our study, it was observed that compared to the patients with a normal cirrhosis and found that compared to patients with normal Gall bladder wall, those with increased GBWT had higher hepatic Venous pressure gradient (13.9+-4.5 vs 17.1+-4.1 resp. p<0.01). Another study by Saverymuttu et al[15] where they studied 40 patients of cirrhosis , they found that GBWT was more in 27 patients who had evidence of portal hypertension. Ascites is a major complication of cirrhosis,[21] occurring in 50% of patients over 10 years of follow up[22]. The development of ascites is an important landmark in the natural history of cirrhosis as it is associated with a 50% mortality over two years[22,23,24,25] and signifies the need to consider liver transplantation as a therapeutic option.Portal hypertension increases the hydrostatic pressure within the hepatic sinusoids and favours transudation of fluid into the peritoneal cavity. Portal hypertension is critical to the development of ascites, and ascites rarely develops in patients with a wedged hepatic venous portal gradient of <12 mm Hg. In our study we observed that the presence of Ascites was significantly (p<0.05)more in patients of groupB as compared to the patients of Group A. This was in agreement to the positive correlation between gall bladder wall thickness and presence of ascites (p<0.05) as observed by Galipet al[13].Similar observations were made by Wang et al[9] on studying 77 cirrhotic patients,presence of ascites in patients with normal GBWT was 8% as against 50% in those with increased GBWT[9]. These observations are supported by several other studies on comparing GBWT in patients of ascites due to cirrhosis with ascites due to noncirrhotic causes.In a study by Colli et al[14] , where 47 patients of ascites were studied,it was gall bladder wall thickening, those with gall bladder wall thickening, i.e. Group B patients had a higher portal vein diameter (13.11+_2.37vs 14.67+_2.01;p<0.05) which is suggestive of increased portal venous pressure in Group B. This is similar to the observations by T F Wang et al[9] where they studied 77 patients of concluded that finding of Ascites and GBWT should be considered a valuable sign of transudative ascites and of portal hypertension whatever its cause.A study by Brogna et al[26]showed GBWT to be more in patients of ascites with cirrhosis(6.7+-2.1mm)as compared to ascites due to non cirrhotic cause(2.5+-1.6mm) and these findings are supported by similar observations made byGeorgiv et al[27]and A Mohammdi et al[28].In patients with cirrhosis as a result of pathologic changes due to Portal hypetension in the liver, there is a stasis of blood in the viscera and gall bladder veins , which leads to congestion and oedema of the GBW, that is more in cirrhotics as compared to non cirrhotics[28]. On correlating the GBWT with evidence of upper GI bleed in our study, we did not find significant correlation(p =0.412)between the two. But significant correlation was found (p<0.001) between presence of esophageal varices on upper GI scopy in patients of Group B as against in patients of Group A. This finding is in consistency with the findings in a study by Shamsi Ara Begum et al[29]where they observed that the mean GBWT was significantly increased (p<0.05)in Chronic liver disease with Grade 3 and 4 varices (6.1+-.8mm)as against in Grade 1and 2 varices (3.9+-.7mm). Supporting these findings is a study by K R Yousaf et al[32] which concludes that congestive cholecystopathy is an important early sonographic sign of evoloving esophagealvarices and portal hypertension in liver cirrhosis[30].Esophagealvarices are the major complication of portal hypertension. It is detected in about 50% of cirrhosis patients, and approximately 5–15% of cirrhosis patients show newly

formed varices or worsening of varices each year. As a result any increase in portal venous pressure will lead to development of esophagealvarices ,bleeding from which is the most important complication of liver cirrhosis and a major cause of death. Therefore, identifying the non invasive markers to predict esophagealvariceal bleeding during the follow up may be an important tool for a better management of cirrhotic patients[31].

CONCLUSION

In the patients of Cirrhosis of liver, here we had enrolled patients of Alcoholic Cirrhosis, the presence of Hypoalbuminemia, increased Portal vein diameter, presence of Ascites and presence of esophagealvarices, which are parameters suggesting portal hypertension, were significantly more in those cirrhotic patients who had increased diffuse Gall Bladder wall thickness. Hence, the presence of Diffuse GBWT on Ultrasonography in patients without intrinsic gall bladder disease should be considered as a sign of Portal Hypertension.

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