ORIGINAL ARTICLE

HEPATITIS C–A RISK FACTOR FOR GALLSTONE DISEASE

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Background: There is increasing evidence that chronic liver disease is one of the risk factors for gallstone disease. A few published studies have documented the link between Hepatitis C Virus (HCV) related chronic liver disease and increased incidence of gallstones but these studies did not exclude subjects with other risk factors like cirrhosis. This study aimed to establish an association between HCV infection and gallstones by excluding subjects with all other risk factors for gallstones. **Methods:** This cross sectional study was carried out at four hospitals of Rawalpindi, Pakistan, over a period of 18 months. It included all cases referred for ultrasound scan of abdomen. A total of 2000 cases, were included in the study by consecutive, non-probability sampling. Anti-HCV antibody test was carried out in all subjects by ELISA and sonography was done to determine presence or absence of gallstones. **Results:** Patients suffering from HCV had a significantly high percentage of gallstones as compared to seronegative subjects (p=0.001). In seropositive group, more males had gallstones (p=<0.001) and prevalence of gallstones was significantly high in younger population with age at or below 40 years (p=<0.001). **Conclusion:** Risk of gallstone disease is increased in patients suffering from HCV infection. This association is more pronounced in males.

Keywords: Hepatitis C, Gallstones, Cholelithiasis.

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INTRODUCTION

HCV is globally distributed and it is estimated that up to 170 million people (3% of the world's population) are infected worldwide.[1] In Pakistan, about 4.7% of the population is HCV positive. This ranks as the second highest percentage after Egypt (15.5%).[2] In recent years more and more males have been diagnosed with symptomatic gallstones and their complications including choledocholithiasis, gallstone pancreatitis and cholangitis. A significant proportion of these patients have been observed to be seropositive for HCV.

Association of gallstones with chronic liver disease is documented in medical literature[1,3,4] but no such study has been carried out in Pakistan or the subcontinent despite the fact that HCV is endemic in this region. Risk factors described for gallstones include hyperlipidemia[5], obesity[6,7], high serum levels of female sex hormones[8], sickle cell disease, and thalassaemia[9] among others. Cirrhosis of liver is a known risk factor for gallstones[10,11] but very little is known about gallstone disease in individuals with HCV infection without cirrhosis.[1,4] None of the studies previously conducted have investigated HCV infection as a solitary risk factor for gallstones.

Some findings of these studies have a significant bearing on the health economy. It has been found that HCV positive subjects develop gallstone disease at a younger age[3] and are more likely to have gallstones in bile ducts (0.4%) as compared to normal population (0.1%).[12] It was also found that males with HCV infection were more likely to need surgery for gallstone disease compared to women.[5] Keeping in view that HCV infection is endemic in Pakistan, the demographics of the affected population and the burden on the hospitals for gallstone related complications would lead to a significant financial burden. A common observation was made in our institution that there was a clear difference in gall stones occurrence in patients with and without HCV infection. Our hypothesis was that HCV infection is a risk factor for gallstone disease.

The objective of this study was to compare the frequency of gallstones in patients who have hepatitis C virus infection, with seronegative subjects.

MATERIAL AND METHODS

This cross-sectional study was carried out from November, 2011 to April, 2013 at the Fauji Foundation Hospital and the Combined Military Hospital at Rawalpindi. Patients from Military Hospital and Al-Ihsan Hospital were also included. In order to maintain the same standard in sonography, all the scans were performed by the same radiologist. The study included all cases referred for ultrasound scan of abdomen. Patients in this study were sampled by consecutive non-probability sampling technique. Data was collected using a structured *pro forma*. Anti-HCV antibody was tested by ELISA on all subjects. An equal number of patients with and without HCV infection were chosen and presence of any gallstones was observed in both groups. Ultrasound scan of abdomen was done on all subjects and special note was made of gallstones in the gallbladder or the bile ducts and presence or absence of cirrhosis.

Patients diagnosed as suffering from hepatitis C were included in Group-1 while those without Hepatitis C were included in Group-2. Patients of either gender, between and including the ages of 18 years and

70 years, were included. An equal number of HCV positives and HCV negative patients were included without taking into account their gender. Patients who were excluded from study were those with: deranged LFTs due to any cause other than hepatitis C; deranged lipid profile; BMI in obese range; acute or fulminant hepatitis and/or cirrhosis; pregnancy; sickle cell disease; malignancy; thalassemia; and history of abdominal surgery or birth control measures. Anti-HCV antibody detected positive by ELISA at least three months before the ultrasound examination was considered as suffering from HCV infection. Gallstones were considered present if they were detected on ultrasound.

Data was analyzed by SPSS-18. Chi-square test was used to determine the association of HCV infection with gallstones by comparing the frequency of gallstones in the two groups. *p-value* of <0.05 was considered significant. Odds Ratios with 95% confidence intervals (CI) were also calculated.

RESULTS

A total of 2000 patients were included in the study, 1000 subjects were HCV negative and while the other 1000 subjects were HCV positive. Of the total 2000 participants in the study, 1066 (53.3%) individuals were males while 934 (46.7%) were females. The age of subjects ranged between 19 and 66 years with a mean of 41.66±10.11 years. As far the age groups are concerned, 63.2% of the HCV positive subjects aged 40 years or below, while 60.4% of HCV negative group were above 40 years of age. Males and females with Hepatitis C antibodies were 575 (57.5%) and 425 (42.5%) respectively.

Overall presence of gallstones in both groups was a total of 514 subjects (25.7%). In HCV negative males, gallstones were found in only 0.9% as compared to 13.9% in females. Frequency of gallstones in both groups and their comparison is shown in Table-1.

Gender distribution of gallstones in both groups is detailed in Table-2 whereas Figure-1 shows age distribution. The odds ratio for exposure of HCV and effect of gall stones with 95% confidence interval was 3.39 (95% CI 3.1 to 4.8). The results are statistically significant with a risk range given in the CI for those exposed compared to non-exposed. Distribution of gall stones in either gender showed that frequency of gallstones is high in HCV positive males (p=.001) but decreases in HCV positive females.

Quantity of stones in gallbladder was labeled as single, multiple or no stones. Cross-tabulation of number of stones with study group revealed a significant association between multiple gallstones and HCV infection (p=<.001) as shown in Table-3.

Presence of gallstones in the common bile duct was evaluated between the two groups. There were more cases of CBD gallstones in HCV positive group (2.5%) as compared to HCV negative group (0.9%). The difference is statistically significant (p=<0.001).

Table-1: Presence of gallstones in study groups (p= .001)

Study Group	Gallbladder Stones		Total	*p*-value
	Present	Absent		
(HCV Positive)	373	627	1000	
% of Total	18.65	31.35	50	
(HCV Negative)	133	867	1000	
% of Total	6.65	43.35	50	
Total	506	1494	2000	
%	25.3	74.7	100	0.001

Table 2: Gender distribution of subjects

Study Group	Gender		Total	*p*-value
	Male	Female		
(HCV+)	575	425	1000	
% of Total	28.8	21.2	50	
(HCV-)	491	509	1000	
% of Total	24.6	25.4	50	
Total	1066	934	2000	
%	53.3	46.7	100	0.001

Table 3: Distribution of stones in the both the groups (p=<.001)

Study Group		Number of Stones			Total
		None	Single	Multiple	
(HCV+)	Male	268	50	257	575
	Female	359	0	66	425
	Total	627	50	323	1000
(HCV-)	Male	481	2	8	491
	Female	386	24	99	509
	Total	867	26	107	1000

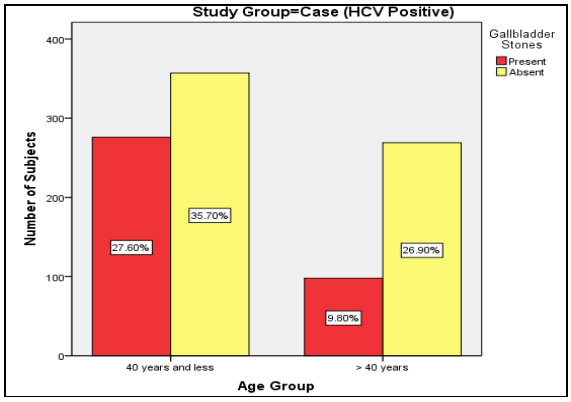

Figure-1: Gallstone disease is more prevalent in young HCV positive subjects (p=<.001)

DISCUSSION

Cholelithiasis has been traditionally associated with middle aged females. Gall stones are of various types but the commonly found calculi are cholesterol stones. Risk factors described for cholesterol stones, in addition to those described above, include rapid weight loss[13,14],

female sex hormones[8,15,16], multiparity and diabetes mellitus.[17]

Cirrhosis has long been known to be a risk factor for gallstones.[10,11,18] Stroffolini *et al*, reported in 2007 that gallstone prevalence was significantly higher in patients with HCV-related cirrhosis than in those with HBV-related or alcoholic cirrhosis.[18] Formation of gallstones in cirrhosis is due to many factors such as reduced secretion of bile acids, reduced gallbladder motility[19] and reduced synthesis of cholesterol. Although high estrogen levels have been suggested as a possible mechanism of increased gallstone formation in cirrhotic patients, Li *et al* did not find any significant differences in plasma levels of sex hormones between cirrhotic with and without gallstones.[20]

In contrast to the abundance of literature on cirrhosis and its association with gallstones, very little is known about gallbladder disease in individuals with HCV infection in the absence of cirrhosis. There are only three published studies on this subject so far.[1,3,4] Probably the first study to establish the link between HCV infection and gallstone disease was carried out in 2000 at Taiwan. In this study by Chang *et al*[3], the prevalence of gallstones in HCV positive subjects was found to be significantly higher (11.7%) than the control subjects (6%). Bini *et al*[4] examined the data of more than 13000 subjects who participated in a United States national survey for health and nutrition, in 2005, and discovered that 12.5% of those with HCV infection had gallstone disease, most of whom were males. They also discovered that the relative odds of gallstone disease among persons with HCV infection increased with the severity of liver disease as assessed by serum total bilirubin levels, serum albumin levels, and platelet counts. This was construed as demonstrating a direct link between liver disease and gallstone formation. A 2009 Romanian study by Acalovschi *et al*[1], reported 19% incidence of gallstones in HCV positive patients.

In our study, we found that a total of 37.4% of HCV positive individuals had gallstones as compared to 14% in HCV negative group. The significant difference between the two groups (p=.001) clearly establishes an association between HCV infection and gallstone disease, keeping in view the fact that we excluded subjects with all other known risk factors for gallstone disease. As compared to previous studies, the prevalence in this study is higher in both groups. It may be argued that this extraordinarily high prevalence in our results is due to the peculiar sampling technique, but the study of Acalovschi *et al* used a similar technique with comparable sample size and revealed lower overall prevalence.[1] Therefore, results of our study may partly reflect an actual rise in the incidence of gallstone disease in Pakistani population.

Bini *et al* found that HCV infection was a strong risk factor for gallstone disease in men but not in women.[4] The reason for this difference is not cited except for the likelihood that the pathophysiology of and risk factors for gallstone formation differ among men and women. This study corroborates this observation as our results that show that 28.2% of HCV positive males had gallstone disease whereas prevalence in HCV positive females was only 8.5%. This difference becomes more significant because only 0.1% HCV negative males in our study had gallstone disease whereas 19.2% HCV negative females had the disease. This means that HCV infection may actually be protective to women against gallstone disease. In contrast, males revealed a strong association (p=.001) between HCV infection and gallstones.

Our results revealed that younger males are more prone to acquire gallstones if they are HCV positive. This age association is statistically significant in males (p=<.001). These results are in conformity with those of Acalovschi *et al* and Chang *et al.*[1,3] Younger age group was also found to have a predilection for acquiring multiple gallstones.

There is also a significant association (p=<.001) between HCV infection and development of multiple, as opposed to single gallstones. HCV infection appears to make the patients more prone to suffer from choledocholithiasis.

Various reasons have been postulated for HCV infection causing gallstones. Sluggish function of the liver in synthesizing bile acids has been cited.[21] Direct infection of the gallbladder by HCV[22] and gallbladder hypomotility[19] has been demonstrated. This direct effect is more probable because an infection by Hepatitis B virus does not increase the risk of gallstone disease[4] despite having a similar effect on liver function. Some studies have even suggested a protective effect of hepatitis B in developing gallstones.[23] This direct effect seems to spare the gallbladders in females.

The findings of this study significantly bear on the health economy. As established, males less than 40 years are more prone to develop gallstones if they are HCV positive. These stones are usually multiple with more likelihood of causing obstructive jaundice. These patients are more likely to need surgery for gall stone disease[4] and morbidity may be high because of compromised liver function. In economic terms, the breadwinner of the family is disabled, workplace gets affected and hospitals have to allocate more resources for HCV positive patients undergoing surgery.

The strength of our study is in the fact that this is the first attempt to describe association of gallstones with HCV not only in Pakistan but in the entire South Asian region. Secondly, we have been scrupulous in the selection of subjects by excluding those HCV positive individuals who had any other risk factor of gallstone disease. The limitation of this study is that the study sample is not representative of the general population.

Subjects were selected from patients coming for treatment to four large hospitals of Rawalpindi.

CONCLUSION

There is a strong association between HCV infection and gallstones. HCV infection is definitely a risk factor for gallstone disease particularly in young males. By invalidating young subjects and rendering them as potential candidates for surgery, this association has a profound effect on health economy. There is a predilection for HCV positive patients to acquire multiple gallstones. Further studies are needed to evaluate the precise cause for this association.

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