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Hepatitis C virus infection: A risk factor for gallstone disease

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Abstract
Background and Objectives: In India, approximately 1.8% - 2.5% of the population is currently infected by HCV and about 20 million people are already infected with HCV. 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. Very few studies were done in India demonstrating association of HCV hepatitis with gallstones, and hence due to paucity of studies we intend to assess the association and risk factors for gallstone disease in patients with HCV hepatitis. This study aimed to establish an association between HCV infection and gallstones by excluding subjects with all other risk factors for gallstones.
Methodology: 50 patients admitted to IP surgical wards with diagnosis of hepatitis c will be selected for the study using purposive sampling technique. However as many patients during study period may be admitted in study. These patients will be evaluated by a detailed history regarding the age, sex, personal history, past history and clinical examination including general physical examination, and systemic examination.
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). Among them the prevalence of gallstone disease in HCV was found to be higher in older age group >50 years, 11 out of 16 positive patients with gallstones. Patients with HCV hepatitis and gallstone disease had a higher percentage of abdominal obesity (BMI >25kg/m^2 plus a greater waist circumference and liver steatosis. No differences were found in the association in the association of arterial hypertension, diabetes mellitus and metabolic syndrome.
Conclusion: The study shows HCV patients have an increased prevalence of gallstones. It is present in older age group and has association with central obesity and liver steatosis and not related to diabetes mellitus, dyslipedemia or metabolic syndrome. This association of HCV infection and gallstone disease is real and appears linked in predisposed individuals namely obese and with liver steatosis.

Keywords: Gallstones, cholecystectomy, hepatitis virus, liver steatosis, body mass index

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].
Gallstone disease (GD) is a common and costly digestive disorder that has been diagnosed in 10–20% of adults in the developed world. The main risk factors for gallstone formation are gender (females have a higher risk), advanced age, obesity, alcohol use, diabetes, and hypertriglyceridemia. Risk factors described for gallstones include hyperlipidemia, obesity high serum levels of female sex hormones, sickle cell disease, and thalassaemia among others. Cirrhosis of liver is a known risk factor for gallstones but very little is known about gallstone disease in individuals with HCV infection without cirrhosis [3, 4, 5].
Determining the potential relationship between the development of gallstones and the etiology of CLD is of great interest, as previous research has suggested that HCV infection is a relevant risk factor for gallstone formation. Recent studies have found that gallstones may occur more frequently in patients infected with HCV than in either patients infected with HBV or alcoholics. It has been found that HCV positive subjects develop gallstone disease at a younger age and are more likely to have gallstones in bile ducts (0.4%) as compared to normal population (0.1%). It was also found that males with HCV infection were more likely to need surgery for gallstone disease compared to women [5].

Thus, the current study was undertaken to specifically analyze the risk factors for the development of gallstones in chronic liver disease CLD patients, as well as the possible relationships between HCV infection and gallstone formation in subsets of chronic liver disease CLD patients, such as those with liver cirrhosis and the elderly.

Aims & objectives

1. To study exclusively the association between Hepatitis c virus and gallstone formation.
2. To study the risk factors for gallstones in HCV hepatitis.

Materials & methods

The data was collected from patients admitted to IP Surgical wards in Shadan Institute of Medical Sciences, Hyderabad. It is a cases series study. Fifty patients admitted to surgical IP wards with diagnosis of hepatitis c are selected for the study.

These patients were evaluated by a detailed history regarding the age, sex, personal history, past history and clinical examination including general physical examination, and systemic examination. Abdominal ultrasonography, HCV–Spot Test, HCV-ELISA, RBS, Serum Triglycerides, Serum Cholesterol, and basic lab investigations to support the diagnosis. Diagnosis of viral c hepatitis is established by liver disease, positivity of anti-HCV, absence of HBSAG and no/low alcohol consumption. Gall stone is diagnosed if gall bladder stones confirmed by ultrasonogram, or in case of previous cholecystectomy for gallstones. Variables to be evaluated are age, gender, gallstone heredity, body mass index, waist circumference, parity, serum lipids, fatty liver, arterial hypertension, diabetes mellitus and metabolic syndrome (International Diabetes Federation criteria).

Inclusion Criteria: All patients diagnosed with hepatitis C infection.

Exclusion Criteria: All patients with gallstones who have aetiology other than hepatitis C likemetabolic syndrome, diabetes, dyslipedemia, arterial hypertension.

Results

In the HCV group of the patients (50), 18 (36%) of them had gallstones. There were 18 men and 3 women (6:1) in HCV infected patients with Gallstone disease (N= 21). There were 26 men and 3 women (8:1) in HCV patients without gallstone disease (N= 29). The mean age of HCV infected patients with Gallstone disease was 52+/-11 years. There were 18 men and 3 women (6:1) in HCV infected patients with Gallstone disease. The mean age of HCV patients without gallstone disease was50+/-14 years. There were 26 men and 3 women (8:1) in HCV patients without gallstone disease. Prevalence of HCV was higher in older age group (>50 years) 25 of 50 patients (50%). Among them the prevalence of gallstone disease in HCV was found to be higher inolder age group >50 years, 12 out of 16 positive patients with gallstones. Patients with HCV hepatitis and gallstone disease had a higher percentage of abdominalobesity (BMI >25kg/m^2 plus a greater waist circumference and liver steatosis. No differences were found in the association in the association of arterial hypertension, diabetes mellitus and metabolic syndrome.

Table 1: Group Statistics

	Outcome		Mean	Std. Deviation
Age	0	34	53.221	10.333
	1	16	56.227	12.111
Weight	0	34	62.789	6.9555
	1	16	73.555	5.6889
Height	0	34	1.689	0.058
	1	16	1.666	0.0533

Table 2: Gender wise outcome

			Outcome		Total
			0	1	
Sex	F	Count	3	3	6
		% within SEX	50.0%	50.0%	100.0%
		% within Outcome	10.4%	14.3%	12.0%
	M	Count	26	18	44
		% within SEX	59.1%	41%	100.0%
		% within Outcome	89.7%	85.7%	88.0%
Total		Count	29	21	50
		% within SEX	58.0%	42.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%

Table 3: Independent Samples Test

		t-test for Equality of Means						
		t	df	Sig. (2- tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
							Lower	Upper
Age	Equal variances assumed	-.822	42	.398	-3.91000	3.4222	-10.1876	4.0376
	Equal variances not assumed	-.800	28.557	.410	-3.91000	3.5822	- 10.2233	4.3033
WT	Equal variances assumed	-5.655	41	.000	-10.5250	2.0333	- 15.6184	- 7.326
	Equal variances not assumed	-5.323	38.39	.000	-10.5250	1.9455	- 15.3403	- 7.3333
HT	Equal variances assumed	-1.222	49	.201	-.01272	.01710	-.04853	.0130
	Equal variances not assumed	-1.300	35.22	.128	-.01272	.01701	-.04788	.0143

Table 4: Liver steatosis

			Outcome		Total
			0	1	
Liver	0	Count	28	4	32
		% within liver	87.5%	12.5%	100.0%
		% within Outcome	82.4%	25.0%	64%
	1	Count	6	12	18
		% within liver	33.3%	66.7%	100.0%
		% within Outcome	17.65%	75.0%	36%
Total		Count	34	16	50
		% within liver	68.0%	32.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%

Table 5: Chi-Square Tests (liver steatosis)

	Value	df	Asymp. Sig. (2-sided)	Exact Sig.(2- sided)	Exact Sig.(1- sided)	Point Probability
Pearson Chi-Square	8.122[a]	1	.0011	.0044	.0042	
Continuity Correction[b]	6.550	1	.008			
Likelihood Ratio	8.922	1	.002	.0044	.0042	
Fisher's Exact Test				.0044	.0042	
Linear-by-Linear Association	8.411[c]	1	.003	.0044	.0044	.0040
N of Valid Cases	42					

a) 0 cells (.0%) have expected count less than 5. The minimum expected count is7.41
b) Computed only for a 2x2 table
c) The standardized statistic is 2.908.

Table 6: Comparison of HCV with gallstones VS HCV without gallstone

	HCV+Gallstone Disease (21)	HCV–Gallstone Disease (29)
Gender Male Female	18	26
	3	3
Age <50 years (18)	8	10
>50 years (32)	18	14
Hypertension	-	-
Dyslipedemia	-	-
Type 2 Diabetes	-	-
BMI >25kg/m^2	15	4
Waist circumference >94cm (male) >80cm (female)	15	4
Liver steatosis	12	6
Metabolic syndrome	-	-

Discussion

We prospectively studied the association of Gallstone disease with HCV infection, excluding cases of viral C cirrhosis to assess whether HCV infection represented a risk factor for gallstones even in the absence of cirrhosis.

We evaluated all patients with HCV hepatitis admitted for a 2 years period. The mean age of HCV patients with gallstone disease was slightly older. This is in accordance with a study done in Chang Gung Memorial Hospital [1] in 2002 which stated prevalence of gall stones in hep C patients were high for age groups 61-70 years. Regarding gender ratio of men: women, it was higher among male HCV patients with gallstone disease. This result is in accordance with study conducted by NHANES III population survey in 2005 which stated gall stone disease occurrence is more in chronic HCV infection. Analyzing the known risk factors for gallstone disease in general population, HCV patients with gallstone disease central obesity and fatty liver disease (steatosis) were the only significant risk factors. Although abdominal ultrasound might not have sufficient sensitivity to detect mild liver steatosis, this method was used in all our subjects.

These results are in conformity with those of Acalovschi *et al.* and Chang *et al.* [1, 2] Younger age group was also found to have a predilection for acquiring multiple gallstones.

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.* [1] used a similar technique with comparable sample size and revealed lower overall prevalence.

Various reasons have been postulated for HCV infection causing gallstones. Sluggish function of the liver in synthesizing bile acids has been cited. Direct infection of the gallbladder by HCV and gallbladder hypomotility has been demonstrated [6, 7]. This direct effect is more probable because an infection by Hepatitis B virus does not increase the risk of gallstone disease4 despite having a similar effect on liver function. Some studies have even suggested a protective effect of hepatitis B in developing gallstones. This direct effect seems to spare the gallbladders in females [8, 9].

Fatty liver accompanies HCV infection. The HCV nonstructural protein NS5A was found to be associated with lipid droplets and apoA1,

suggesting that NS5A, together with the core protein may play a role in the pathogenesis of the derangement of lipid metabolism and contribute to liver steatosis commonly observed in hepatitis C Fatty liver disease was also found to be associated with an increased prevalence of gallstones, because of obesity and

increased insulin resistance.

Bini *et al*. found that HCV infection was a strong risk factor for gallstone disease in men but not in women [3]. 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.

Increased insulin resistance might be a candidate link between HCV infection and gallstone disease, by increasing the bile saturation in cholesterol. Presumably, gallstones are predominantly cholesterol type in patients with chronic HCV hepatitis, but to date no study has evaluated this aspect.

The BMI and waist circumference were increased in HCV patients with gallstone disease. Metabolic disease and its components, (dyslipedemia, diabetes, arterial hypertension) do not appear to increase the risk of developing gallstone disease in HCV patients, which suggests HCV infection might be an independent risk factor for gallstone disease. This result is in accordance with earlier study published in 2009 by M Acalovschi *et al*. which showed similar results of BMI and waist circumference increased in HCV patients with gallstone disease.

Other factors related to HCV infection might favor biliary lithogenesis. Bile duct damage represents a histological characteristic for hepatitis. HCV infection was found to be a risk factor for intrahepatic cholangiocarcinoma and was suggested the HCV core protein could favor the malignant transformation of human biliary epithelial cells.

Permissiveness of gallbladder epithelial cells to infection by HCV virus was demonstrated by HCV infected individuals by detecting HCV – RNA in gallbladder cell cultures, in gallbladder epithelium by immunohistology and in bile in a concentration similar to that in serum. All these facts suggest that HCV infection impairs gallbladder mucosa function, and thus favor gallstone formation.

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 [10].

The study has strengths like one in a few where we attempt to study the risk factors for gallstone disease in Hepatitis C virus infected patients including general physical examination, anthropometric examinations like BMI, waist circumference, investigational modalities including lipid profile, blood sugars, ultrasound abdomen (for gallstone disease as well as liver steatosis) with a long study time period of 18months [11, 12]. Limitations of this study include not including a control population to compare and assess the relative risk for each factor from the general population, viral C etiology was not confirmed by HCV RNA levels. Also study population was done on a purposive sampling basis and hence a selective one comprising patients seeking medical care in a tertiary care hospital. Patients with HCV hepatitis and gallstone disease had a higher percentage of abdominal obesity (BMI >25kg/m^2 plus a greater waist circumference and liver steatosis. No differences were found in the association in the association of arterial hypertension, diabetes mellitus and metabolic syndrome.

Conclusion

The study shows HCV patients have an increased prevalence of gallstones. It is present in older age group and has association with central obesity and liver steatosis and not related to diabetes mellitus, dyslipedemia or metabolic syndrome. This association of HCV infection and gallstone disease is real and appears linked in predisposed individuals namely obese and with liver steatosis.

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