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RESEARCH ARTICLE

METABOLIC SYNDROME AMONG PATIENTS WITH GALLSTONE DISEASE - A STRONG RISK FACTOR FOR POSTOPERATIVE WOUND INFECTION AFTER CHOLECYSTECTOMY, A STUDY FROM NORTHEAST INDIA

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ABSTRACT

Gallstone disease remains one of the most common medical conditions and leading cause of hospital admissions for gastrointestinal problems. The association between gallstone disease and metabolic syndrome has already been proved by previous studies. The aim of this study is to find out the relation between metabolic syndrome and gallstone disease and post operative complications after cholecystectomy in patients with gallstone diseases. We conducted a cross-sectional study among 100 patients with gall stone diseases during the period from october 2012 to September 2014 in the department of Surgery, Regional Institute of Medical Sciences Hospital, Imphal, Manipur, India. We found out that metabolic syndrome was associated with 36% gallstone disease and the patients with metabolic syndrome have higher chance of getting multiple, cholesterol stones and post operative wound infection compared to those who do not have metabolic syndrome. So we recommend that extra care should be given to patients with metabolic syndrome to prevent post operative wound infection or related complications.

INTRODUCTION

Gallstone disease was first described in 1507 by Antonio Benivenius who was a Pathologist (Portincasa *et al.,* 2006). The disease might have existed for more than 35 centuries as multiple gallstones were found in a mummified Egyptian priestess (Gordon and Taylor, 1937). The prevalence of gallstone disease is 10–15% among adults in Europe and USA. Gallstone disease remains one of the most common medical conditions and leading cause of inpatient admissions for gastrointestinal problems (Sandler *et al.,* 2002). The prevalence of gallstone disease varies in different parts of India, more prevalent in north India compared to south India (Tandon and Saraya, 1996). The pathogenesis of cholesterol gallstone disease is multifactorial and it is a major cause of morbidity in most of the developing countries. In these countries, the economic impact of gallstone disease is high (Sampliner *et al.,* 1970). Archard and Thiers first described metabolic syndrome in association with polycystic ovary syndrome in 1921. The features of the metabolic syndrome was described by Vague in 1956 (Vague, 1956). The metabolic syndrome (Syndrome X) include central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperglycemia, and hypertension (Eckel, 2010). Prevalence of the metabolic syndrome varies across the world, reflecting the age and ethnicity of the populations studied and the diagnostic criteria applied. The importance of metabolic syndrome is increasing, especially when associated co-morbidities are considered. The prevalence of metabolic syndrome in China was 13.6% in men and 16.6% in women in 2000 (Gu *et al.,* 2005). By 2009 prevalence of metabolic syndrome had elevated to 31.5% in men and 30.5% in women (Marschall and Einarsson, 2007). According to Gupta *et al.* (2004) metabolic syndrome was present in 31.6% subjects with a prevalence of 22.9% in men and 39.9% in women (Gupta *et al.,* 2009). The highest recorded prevalence worldwide is in native Americans, with nearly 60% of women ages 45-49 years and 45% of men ages 45-49 years. Metabolic syndrome, diabetes and gallstone size were associated with complicated gall stone disease and metabolic syndrome can be regarded as an indication for prophylactic surgery in patients with gallstone disease (Ata *et al.,* 2010). The prevalence of gallstone disease in women who had the five components of metabolic syndrome were five times higher than in those without metabolic syndrome (Li-Ying *et al.,* 2012). The incidence of gallbladder disease has been increasing. The number of gallbladder operations, both open and laparoscopic procedures, has also been increasing correspondingly.

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Identifying modifiable risk factors (i.e., extreme obesity, rapid weight loss, sedentary lifestyle, and key dietary factors) should provide an opportunity to prevent cholelithiasis. Even though the association between metabolic syndrome or its components with gall stone disease is an important topic for discussion nowadays, we have limited data from our country regarding this topic. This prompted us to carry out a cross sectional study to investigate the association between metabolic syndrome or its components with gall stone diseases and postoperative outcome.

MATERIALS AND METHODS

Aim

To study the relation between metabolic syndrome and gallstone disease and post operative complications after cholecystectomy in patients with gallstone diseases.

Methodology

This is a cross-sectional study carried out from October 2012 to September 2014 in the Department of Surgery, Regional Institute of Medical Sciences Hospital, Imphal, Manipur, India. 100 cases of gall stone disease confirmed by clinical evaluation and ultrasonography were included and those patients who are not willing to participate in this study and those who are not having gall stone disease by clinical evaluation and ultrasonography were excluded from this study. Informed and written consent was taken from the participant (if he/she is > 18 yrs) and from parent/guardian along with consent from the participant (if he/she is < 18 yrs). Detailed history of the cases was taken from the patients and final diagnosis was based on clinical features, radiological findings operative findings, and histopathology report. Investigation included blood and urine routine examination, fasting blood sugar, lipid profile, liver and kidney function tests, serum electrolytes, ECG and X-ray chest. Statistical analysis was done by Statistical Package for Social Sciences (SPSS 21) software. Level of significance was determined by calculating P value. It was considered as significant if P value is <0.05.

Diagnostic criteria for metabolic syndrome

National cholesterol Education program/Adult Treatment Panel (NECP/ATPIII) criteria (Heng *et al.,* 2006) was used as the criteria for the diagnosis of metabolic syndrome in this study. Any 3 of the following lead to a diagnosis of metabolic syndrome.

1. Abdominal obesity, defined as a waist circumference in men ≥ 90 cm and in women ≥ 80 cm (for Asians)
2. Serum triglycerides ≥ 150 mg/dL (1.7 mmol/L) or medicinal treatment for elevated triglyceride(TG)
3. Serum HDL cholesterol < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women or medication for low HDL Cholesterol
4. Blood pressure ≥ 130/85 mmHg or medication for high blood pressure
5. Fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L) or medication for elevated blood glucose.

Observation and results

Hundred patient with gallstone disease were studied. The observation is analysed systematically. Out of hundred patients in this study, the maximum incidence 44% is observed in the age group of 21-40 years followed by 41-60 age group with incidence of 40%. The incidence gradually declined after 60 years and it was low below 20 years (9%) (Fig.1).

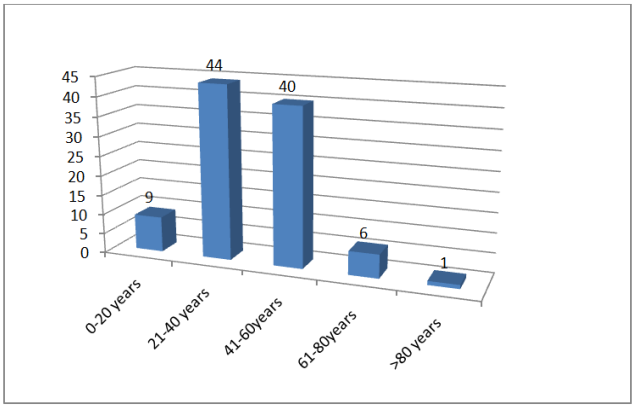

Fig. 1. Bar chart showing age distribution

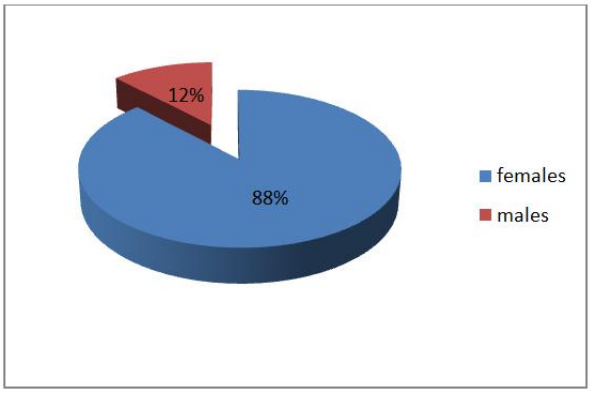

Fig. 2. Pie chart showing sex distribution

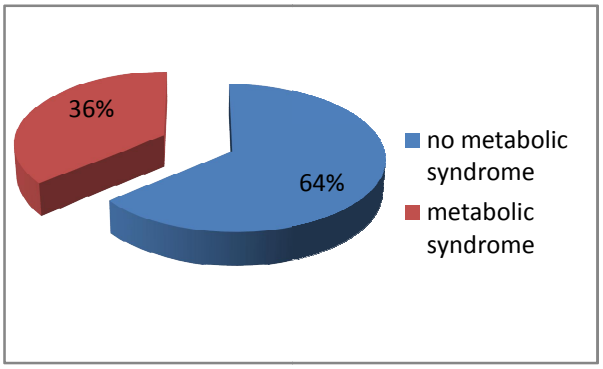

Fig. 3. Pie chart showing frequency of metabolic syndrome

Females were 88% and males were only 12% (Fig.2) and 84% were married. Hindus comprised 79%, while Muslims and Christians were 16% and 5% respectively. In the present study

all except one (99%) experienced pain in right hypochondrium, which was the commonest symptom. Other complaints experienced were nausea (55%), vomiting (31%), fever (18%) and jaundice (7%). In the present study 9% consume alcohol, 9% were smokers, 83% were non-vegetarians. Family history of gallstone disease was present among 50%.

Out of 100 patients studied 36 had metabolic syndrome(Fig. 3). This constitute 36%. All 5 components of metabolic syndrome were studied separately. Most commonly associated component is waist circumference. A waist circumference of 90cms or more among men or 80cms or more among women was observed in 61% of cases. A low serum High-Density Lipoprotein (HDL) <40mg/dl in men and <50mg/dl in women is the next commonly associated component which constituted 36%. Occurrence of high blood pressure ≥130/85 mmHg, Serum triglyceride ≥150 mg/dl and fasting blood sugar > 100 mg/dl were 29%, 26% and 16% respectively in the order of occurrence (Table 1)

Table 1. Presence of Metabolic syndrome and its components

Metabolic syndrome or its components		Frequency	Percentage(%)
Waist circumference	men≥90cms,women≥80cms	61	61%
	men<90cms, women<80cms	39	39%
Blood pressure	≥130/85 mmHg or on treatment	29	29%
	<130/85 mmHg	71	71%
Fasting blood sugar	>100 mg/dl or on treatment	16	16%
	<100 mg/dl	84	84%
Serum TG	≥150 mg/dl or on treatment	26	26%
	<150 mg/dl	74	74%
Serum HDLc	<40 mg/dl in men or <50mg/dl in women or on treatment	36	36%
	>40 mg/dl	64	64%
Metabolic Syndrome	Present (presence of 3 or more above components)	36	36%
	Absent	64	64%

Three components of metabolic syndrome were present in 27% of cases. All 5 components were present in 2% of cases. None of the components were associated in 31% of patients with gallstone disease. Only one patient had bile duct injury during operation which was diagnosed in the first postoperative day. Severe adhesions were noted intaoperatively around the gall bladder and Calot's triangle. Patient later developed cutaneous biliary fistula and went into septic shock. She was managed aggressively and bile duct injury managed conservatively. Later SLE (Systemic Lupus Erethematosus) was diagnosed and revised treatment started. Patient improved and was discharged after 2 months. Nine out of 100 (9%) developed mild or less severe post operative wound infection out of which 8% had metabolic syndrome. This is discussed later in this section. Other complications were 3 patients developed post operative pyrexia which was treated with paracetamol and one patient developed cutaneous biliary fistula which was mentioned earlier. Majority of the patients had multiple stones(65%). Solitary stone were present among 20% and stones were double among 15%. Most common type of stone in our study was mixed type comprising 53%. It is followed by cholesterol stones and pigment stones which constitute 36% and 11% respectively.

Out of 100 patient studied 9 (9%) developed post operative wound infection in which 8 (8%) had metabolic syndrome, which meant 22.1% out of 36% of patients with metabolic syndrome developed postoperative wound infection and out of 64% patients who do not have metabolic syndrome, only 1.6% developed postoperative wound infection. On statistical analysis it has been found that p- Value is 0.001. This showed the strong association between postoperative wound infection and metabolic syndrome among patients with gallstone disease (Table 2).

Table 2. Metabolic syndrome (MS) and Post operative wound Infection (POWI)

Metabolic syndrome (MS) and Post operative wound Infection (POWI)		Post operative wound Infection		Total (%)	p - Value
		Present (%)	Absent (%)		
Metabolic syndrome Present	Count (%)	8 (8%)	28 (28%)	36 (36%)	
	% within MS	22.2%	77.8%		
	% within POWI	88.9%	30.8%		
Metabolic syndrome Absnt	Count(%)	1 (1%)	63 (63%)	64 (64%)	
	% within MS	1.6%	98.4%		
	% within POWI	11.1%	69.2%		
Total (%)		9 (9%)	91 (91%)	100	0.001

Out of 36 (36%) of patients who had metabolic syndrome, cholesterol stones were present among 61.1%, pigment among 8.3% and mixed among 30.6% of cases in contrast to 21.9% of cholesterol 12.5% pigment and 65.5% mixed stones among patients (64% of total cases) who do not have metabolic syndrome. This shows that the patients with metabolic syndrome has got a higher chance of getting cholesterol type of stones compared to other type of stones (Table 3).

Table 3. Metabolic syndrome (MS) and Type of stones

Metabolic syndrome (MS) and Type of stones		Type of stones			Total (%)
		Cholesterol	Pigment	Mixed	
Metabolic syndrome Present	Count	22	3	11	36 (36%)
	% within MS	61.1%	8.3%	30.6%	
	% of total	22%	3%	11%	
Metabolic syndrome Absnt	Count	14	8	42	64 (64%)
	% within MS	21.9%	12.5%	65.6%	
	% of total	14%	8%	42%	
Total (%)		36 (36%)	11(11%)	53 (53%)	100

The incidence of single, double and multiple stones were 2.8% Vs 29.7%, 11.1% Vs 17.2% and 86.1% Vs 53.1% respectively among the patients with metabolic syndrome (36%) Vs the patients without metabolic syndrome (64%). This shows that incidence of multiple stones are higher among patients with metabolic syndrome. This has been found to be statistically significant on statistical analysis (p-value is 002) (Table 4).

Table 4. Metabolic syndrome (MS) and number of stones

Metabolic syndrome (MS) and Type of stones		Number of stones			Total (%)
		Single	Double	Multiple	
Metabolic syndrome Present	Count	1	4	31	36 (36%)
	% within MS	2.8%	11.1%	86.1%	
	% of total	1%	4%	31%	
Metabolic syndrome Absnt	Count	19	11	34	64 (64%)
	% within MS	29.7%	17.2%	53.1%	
	% of total	19%	11%	31%	
Total (%)		20(20%)	15(15%)	65(65%)	100

DISCUSSION

Gallstone diseases represents a significant burden for health care worldwide and is one of the most common disorders among the patients admitted to the emergency rooms with abdominal discomfort, epigastric pain, nausea, vomiting, loss of appetite (Marschall and Einarsson, 2007). It is well known that incidence of gallstone diseases is more among females of forty. The increase in the incidence is observed after 20 years. In our study the maximum incidence, 44% is observed in the age group of 21-40 years followed by 40% in the age group of 41-60 years. The incidence gradually declined after 60 years and it is also low among those who are less than 20 years (9%). The incidence of cholelithiasis is increasing now-a-days in the younger age group also. Guipseppe *et al.* (1989) reported that approximately 4% of cholecystectomies were performed below 20 years.

Females are more commonly affected by gall stone diseases. Our study also supports this fact. In the present study 88 patients were females out of 100 cases studied (88%) with a sex ratio of 1:7.3. The male: female ratio varies according to different authors, that is from 1: 1.2 (Bailey *et al.,* 1989) to 1: 9.1 (Van Beck *et al.,* 1991). Among various religions Hindus comprised 79%, Christians constitute 16% and Muslims constitute 5%. The increased incidence among Hindus may be due to their dietary habits which composed of fats and protein of both animal and vegetable source and also carbohydrate in the form of rice or they may seek prompt medical attention very early or more health conscious compared to other religion, or due to some other factors which is not yet studied. The incidence of gallstone disease in various ethnic groups might be controlled by genetic or other unidentified factors (Oviedo *et al.,* 1977).

Greater incidence of gallstone disease was noted among multiparous females (Honroe, 1980). In the present study 84% were married. The association between gallstone disease and parity may be due to gallbladder relaxation, dilation and stasis that may increase progressively with each pregnancy resulting in increased gallbladder volume or due to increased cholesterol saturation of bile during pregnancy (Kern *et al.,* 1991). Gall stone disease has been reported to show a familial aggregation. In our study 50% of the patients gave positive family history. The exact reason behind this familial association is uncertain. Ethnicity and family traits are recognized as contributing factors (Wittenburg and Lammert, 2007). According to Danzinger *et al.* (1972) it is likely to be due to genetic factors (Danzinger, 1972).

Most of the studies couldn't find out any relationship between gall stone disease and smoking or alcoholism. In our study, smokers constitute 9% and those who consumes alcohol also constitute 9%. According to Kratzer *et al.* (1997) there is no definite relationship between nutritional factors and the consumption of alcohol, tobacco, or caffeine and an increased prevalence of gallbladder stone disease (Kratzer *et al.,* 1997). Another study conducted by Kono *et al.* claims that alcohol confer protection against gallstone formation while smoking is unrelated with gall stone formation (Kono *et al.,* 2002). Gallstone disease usually present with pain in the right hypochondrium. The intensity of pain may varies. In our study almost all except one (99%) have experienced right hypochondrial pain during one or more occasions and it became the most common symptom experienced by the patients. These results are comparable with that Chatterjee *et al.* (1987) who reported that almost all of their patients had complaint of pain in the right hypochondrium. Next common symptom in our study was nausea (55%) followed by vomiting (31%) and History of fever at the onset or at one time during the course of illness was experienced by 18% of patient. Jaundice was present in 7% of cases. The overall complain are comparable with previous studies.

In our study, majority of stones were multiple (65%). Solitary and double stones were found in 20% and 15% of the cases respectively. Stones of mixed type were seen in 53%, followed by cholesterol stones in 36% whereas pigment stones comprised only 11%. In the USA and Europe, 80% are cholesterol or mixed stones, whereas in Asia, 80% are pigment stones (Conlon, 2013). This discrepancy in our study may be due to difference in dietary habits in this part of country or may be due to small sample size

Out of 100 patient studied 36 patients had metabolic syndrome (36%). This result is comparable with that of Nahum *et al.* who reported that the prevalence of metabolic syndrome in gallstone disease is 40% (Mendez-Sanchez *et al.,* 2005). In our study, we found that 61% of the patients have abdominal circumference greater than the cut off value for diagnosis of metabolic syndrome (men≥90cms, women≥80cms) and infarct, it was the component of metabolic syndrome which was most commonly associated with gallstone disease. Chung-Jyi Tsai *et al.* (2004) found out that both a higher waist-to-hip ratio and a higher waist circumference were significantly associated with a higher risk of symptomatic gallstone disease in men. Next commonly associated component in our study was serum HDL cholesterol. 36% of the patients having gallstone diseases have low serum HDL cholesterol value than the cut off (HDL<40 mg/dl or on treatment). A study from Korea demonstrated lower levels of HDL cholesterol in patients with gallstone disease (Kim *et al.,* 2011) Another cross-sectional study from Mexico City described the influence of low HDL cholesterol (OR = 2.32) on developing gallstone disease (Mendez-Sanchez *et al.,* 2005).

High blood pressure (≥130/85 mmHg or on treatment) was observed among 29% of cases in our study. This fact is supported by a study from Taiwan which proved that cholelithiasis in Asian obese patients is significantly associated with increased diastolic blood pressure and blood pressure more than 130/85 mmHg was significantly associated with a higher risk of cholesterol gallstone (Liew *et al.,* 2007). More studies are required to elucidate the mechanisms behind the relationship between blood pressure and gallstone disease. In our study, we observed elevated serum triglyceride among 26% of the patients. Obesity and insulin resistance is often associated with higher triglyceride level in the blood. This may be due to cholesterol supersaturated bile and diminished gallbladder motility seen with hypertriglyceridemia which contributes the formation of gallstone (Smelt, 2010). If the bile is supersaturated with cholesterol, this may leads to phase

separation of cholesterol crystals which is considered the key event in formation of cholesterol gallstone. Taking into account this association, some authors thought of administering lipid-lowering drugs as a therapeutic option for gallstone disease. Ezetimibe, a drug which lowers plasma cholesterol levels by decreasing cholesterol absorption in the small intestine, was shown to have a beneficial effect against cholelithiasis in both animal and humans (Wang *et al.,* 2008). Previous studies indicated that diabetes mellitus was a risk factor for gallstone disease (Nakeeb *et al.,* 2006; Ruhl and Everhart, 2000; Nervi *et al.,* 2006). In our study impaired fasting blood sugar (≥100 mg/dl or on treatment) was noted among 16% of cases. Impaired fasting blood sugar is the least commonly associated component of metabolic syndrome in the present study. This may be due to the inhibition of bile secretion from the liver by hyperglycemia which also disturbs gallbladder contraction and mobility (Nervi *et al.,* 2006) Hyperinsulinemia is considered to be a common factor linking cholesterol gallstone disease, diabetes mellitus and obesity (Nervi *et al.,* 2006). Previous studies showed that Insulin resistance predisposes to cholesterol gallstone formation (Ruhl and Everhart, 2000; Nervi *et al.,* 2006). We also had found out that the patients with metabolic syndrome has got a higher chance of getting cholesterol stones compared to other type of stones and the incidence of multiple stones are more among patients with metabolic syndrome whereas incidence of single or double stones are more among patients without metabolic syndrome.

One of the most important finding in our study is that there is a higher chance of getting postoperative wound infection among the patients with metabolic syndrome. This association is statistically significant (p-value is 0.001). Even though some previous studies (Laurent *et al.,* 2010) have shown that the risk of post operative wound infection is higher among patients with metabolic syndrome, no one studied this association in the setting of gallstone disease. Further studies are required to conform this finding. So we recommends that extra care should be given to all patients with metabolic syndrome to prevent post operative wound infection or related comlications.

CONCLUSION

The association between gallstone disease and metabolic syndrome has already been proved by previous studies. The present study showed that the patients with metabolic syndrome has got higher chance of getting multiple, cholesterol stones. The novel finding in our study is the fact that the chance of getting postoperative wound infection after cholecystectomy is more among those with metabolic syndrome. So we strongly recommend that extra care should be given to all patients with metabolic syndrome who undergo cholecystectomy to prevent post operative wound infection or related complications. Further studies are required to conform this finding.

Ethical issues

The study was carried out after obtaining approval from the Institutional Ethical Committee (IEC), Regional Institute of medical Sciences, Imphal.

Conflicts of interest

None

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