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Original Article

To Find Incidence of Metabolic Syndrome in Patients with Gallstones Admitted in Surgery Department

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Abstract

Background: *Gallstone disease (GD) is a common condition worldwide. Gallstone disease (GSD) is a chronic disease that consumes a lot of economic and medical resources. Because of its high prevalence and elevated health costs, it is an important condition for which further research is needed. The aim of this study is to establish if there is an association between the presence of metabolic syndrome and the development of gallstone disease. If the risk factors of GSD can be identified, more interventions can be introduced earlier to prevent the disease.*

Methods: *A cross sectional study conducted at Indira Gandhi Medical College, Shimla, Himachal Pradesh on a sample size of 100 cases and 100 controls. The Body Mass Index, waist circumference, blood pressure, fasting blood glucose, triglycerides, HDL-Cholesterol levels of the patients were tested. National Cholesterol Education Program-Adult Treatment Panel III criteria modified for Asian subjects, was used for estimating the prevalence of Metabolic Syndrome.*

Results: *27% of the cases and 15% of the controls were found to have Metabolic Syndrome. Out of the cases found to be affected with Metabolic Syndrome 81.42% were females and 18.52% were males.*

Conclusion: *Metabolic Syndrome can be considered to be associated with Gallstone disease and can be used as a predictor of Gallstone disease. It can be used as a screening tool.*

INTRODUCTION

It is estimated that around 20-25 percent of the world's adult population have the metabolic syndrome and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome. In addition, people with metabolic syndrome have a five-fold greater risk of developing type 2 diabetes.[1]

The underlying cause of the metabolic syndrome continues to challenge the experts but both insulin resistance and central obesity are considered significant factors.[2-3]

With the metabolic syndrome driving the twin global epidemics of type 2 diabetes and Cardio-vascular disorders there is an overwhelming moral, medical and economic imperative to identify those individuals with metabolic

syndrome early, so that lifestyle interventions and treatment may prevent the development of diabetes and/or cardiovascular disease.

Gallstone disease (GD) is a common condition worldwide. Gallstone disease (GSD) is a chronic disease that consumes a lot of economic and medical resources.[4] Because of its high prevalence and elevated health costs, it is an important condition for which further research is needed. Cholesterol comprises more than 80% of gallstones, which are associated with older age, pregnancy, obesity, insulin resistance, specific dietary habits, genetic background and ethnicity.[5-7]

The pathogenesis of gallstones is multifactorial and involves environmental and individual factors resulting in three main consequences: bile cholesterol saturation, cholesterol nucleation and gallbladder dysmotility.[8]

While the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, central obesity and insulin resistance are acknowledged as important causative factors.[9-12]

Central (abdominal) obesity, easily assessed using waist circumference and independently associated with each of the other metabolic syndrome components including insulin resistance, is a prerequisite risk factor for the diagnosis of the syndrome in the new definition. Insulin resistance, which is difficult to measure in day-today clinical practice, is not an essential requirement.[13]

Obesity is an increasingly important health problem worldwide including the developing countries. In India, obesity is emerging as an important health problem particularly in urban areas, paradoxically co-existing with undernutrition. Almost 30-65% of adult urban Indians are either overweight or obese or have abdominal obesity.[14]

Obese women are more likely to develop gallstones than are obese men.[15]

The frequently simultaneous presence of obesity, high blood fat, diabetes and hypertension was first reported as the 'plurimetabolic syndrome' in the 1960s, when the high risk of coronary artery disease was described in people with this cluster of metabolic abnormalities.[16]

The importance of metabolic syndrome is increasing, especially when associated co-morbidities are considered. The prevalence of metabolic syndrome varies according to the diagnostic criteria selected. The general prevalence is 23.7%, although the prevalence varies widely in population analyses.[17]

The aim of this study is to establish if there is an association between the presence of metabolic syndrome and the development of gallstone disease. If the risk factors of GSD can be identified, more interventions can be introduced earlier to prevent the disease.

Studies about the association between gallstone disease and Metabolic Syndrome suggested that Metabolic Syndrome is a risk factor for gallstone disease (GSD)[18], and some studies concluded that GSD might be a component of Metabolic Syndrome[18,19] although it needs to be validated by more evidences.

Risk factors associated with cholelithiasis include female gender, age, obesity, diabetes, hyperlipidemia, rapid appetite loss, hepatitis C, cirrhosis, and high caloric intake.[20-22]

The currently recommended cut-offs of waist circumference (>102 cm in men and >88 cm in women) are not be applicable to all the populations due to heterogeneity in the average levels of measurements and different relationship with cardiovascular risk.[23]

National Cholesterol Education Program-Adult Treatment Panel III criteria modified for Asian subjects, was used for estimating the prevalence of MS[24] (The modification is: Waist circumference >90 cm in males and >80 cm in females).

REVIEW OF LITERATURE

A cross-sectional study published in the Bio med central was conducted by I-Ching-Lin *et al* during 2011 ~ 2012 "To investigate the association between metabolic syndrome, including its factors, and gallstone disease (GSD) in a Taiwanese population" in which a total of 12050

subjects who completed a questionnaire and underwent physical examination, laboratory tests and abdominal ultrasonography formed the study population. Physical examination was also performed for the subjects and included body height, body weight, waist circumference, and blood pressure. Age, abdominal obesity, and lower high-density lipoprotein cholesterol were associated with gallstone disease after adjusting for other factors. Metabolic Syndrome was defined as the presence of three or more of the five criteria proposed by the Taiwan National Health Department. The diagnosis of GSD was determined based on the sonographic findings. The prevalences of metabolic syndrome and gallstone disease were 24.09% and 6.16%. Females had a higher odds ratio than males in waist circumference for GSD, whereas males had a lower odds ratio than females in HDL-C for GSD.[26]

In a study by N Ata et al in 2008-2009, 217 patients with gallstones were examined. All patients underwent biliary ultrasonography after a complete medical history and laboratory examination. Data collection for the diagnosis of metabolic syndrome included measurements of waist circumference, blood pressure and lipids, and biochemical tests.

102 consecutive patients with uncomplicated Gallstone Disease (UCGD) and 115 consecutive patients with Cholesterol Gallstone Disease (CGD) were examined in the internal medicine and surgery clinics, and emergency room of the Kecioren Teaching and Research Hospital (Ankara, Turkey). Patients were recruited between January 2008 and April 2009. All subjects underwent biliary ultrasonography after a complete medical history and laboratory examination. Patients who experienced at least one acute cholecystitis attack were defined as having CGD. Data collection included the exploration of risk factors for coronary artery disease, waist circumference measurement (measured at the level of umbilicus with the patient standing), blood pressure measurement, biochemical tests, lipid measurements, life-style habits and medications. Patients receiving statins or fibrates before lipid measurement were excluded because of the possibility of introducing bias in the determination of metabolic syndrome. Results of this study demonstrated that metabolic syndrome, diabetes and gallstone size were associated with Cholesterol Gallstone Disease (CGD). This study was the first to demonstrate metabolic syndrome as an independent risk factor for CGD.[27]

A study published in the World Journal of Gastroenterology-Méndez-Sánchez N et al carried out a cross-sectional study in a check-up unit in a university hospital in Mexico City. They enrolled 245 subjects, comprising 65 subjects with gallstones (36 women, 29 men) and 180 controls (79 women and 101 men without gallstones). Body mass index, waist circumference, blood pressure, plasma insulin, and serum lipids and lipoproteins levels were measured. Insulin resistance was calculated by homeostasis model assessment. Unconditional logistic regression analysis (univariate and multivariate) was used to calculate the risk of gallstone disease associated with the presence of at least three of the criteria (Adult Treatment Panel III). Analyses were adjusted for age and sex.

This study concluded that as in cardiovascular disease and diabetes mellitus, gallstone disease appears to be strongly associated with metabolic syndrome. These results of this study were also consistent with the hypothesis that insulin resistance plays an important role in the pathogenesis of such diseases and that gallstone disease may be a part of metabolic syndrome.[28]

Li-Ying Chen et al conducteda cross-sectional study in 7570 subjects enrolled from the Physical Check-Up Center of the Sir Run Run Shaw Hospital in China. The gallstone cases and controls consisted of a series of consecutive asymptomatic subjects. Exclusion criteria included histories of cholecystectomy, pancre-atitis, sequela of clonorchissinensis infection, gallbladder polyps, gallbladder wall thickening,

chronic kidney disease, pregnancy, and major gastrointestinal surgeries. This study showed an obvious association between Metabolic Syndrome and GSD, and the more the metabolic components of Metabolic Syndrome, the higher the prevalence of the GSD.[29]

A cross-sectional study by *Sreenath et al* carried out from October 2012 to September 2014 in the Department of Surgery, Regional Institute of Medical Sciences Hospital, Imphal, Manipur in which100 cases of gall stone disease confirmed by clinical evaluation and ultrasonography were included and those patients who were not willing to participate in this study and those who were not having gall stone disease by clinical evaluation and ultrasonography were excluded from this study. The study concluded that metabolic syndrome is associated with 36% gallstone disease and the patients with metabolic syndrome have higher chance of getting multiple, cholesterol stones.[30]

Chang et al reported that the prevalence of obesity, abdominal obesity and the metabolic syndrome in subjects with gallstones were higher than in those without.[31]

Shaffer reported obesity as a major risk factor for Gallstone disease.[32]

AIMS AND OBJECTIVES

- To find the correlation between metabolic syndrome and the development of gallstone disease.
- Metabolic syndrome is known to be strongly associated with the lifestyle, and if metabolic syndrome is proved to be related to gallstone, we may reduce the prevalence of gallstones through lifestyle modifications.

MATERIALS AND METHODS

Study Type: The study is a cross sectional study conducted at Indira Gandhi Medical College, Shimla, Himachal Pradesh. It is a case-control study.

Sample Size: The study was conducted on a sample size of 100 cases and 100 controls who fulfilled the inclusion criteria and agreed to be the part of the study, after having completely explained the procedure and obtaining a written informed consent. Local language (Pahari/Hindi) was used if patient requested.

Study Duration: 2 months from 5-July-2015 to 5-September-2015

Inclusion Criteria: Patients admitted to Department of Surgery with Ultrasonography proven diagnosis of gallstone disease and consenting to be the part of the study.

Exclusion Criteria

- Patients not willing to be a part of the study
- Patients suffering from any other comorbidities

Choice of Subjects

Cases- Patients admitted to Department of Surgery with Ultrasonography proven diagnosis of gallstone disease and consenting to be part of the study.

Controls- The attendants of the cases ; random patients whose diagnosis is other than cholelit-hiasis and are non-diabetic, non-hypertensive, non-hypothyroid were considered after obtaining a written informed consent from them.

The study has been carried out after obtaining the clearance and approval of institutional ethical committee of Indira Gandhi Medical College, Shimla after a meeting held on 2-July-2015.

All the cases were subjected to biliary ultrasonography after complete medical and surgical examination, to confirm the diagnosis of gallstone disease.

History of the patients was noted for Diabetes Mellitus, Hypertension, chronic liver disease along with their age and sex.

The Body Mass Index, waist circumference, blood pressure, fasting blood glucose, triglycerides, HDL-Cholesterol levels of the patients were tested.

The Body Mass Index measures the weight status of your body in relation to the fat. It is a simple tool that helps to figure out the amount of excess body fat and the associated risks of carrying this extra weight. It can be applied to both men and women.

BMI is calculated as weight (kg) divided by height (m) squared.

$$BMI = Weight\ (kg)/Height\ (m^2)$$

The weight was measured under 12 hour fasting conditions, with subject wearing minimal clothing, to nearest 0.5kg on standard beam scale, and height was measured to nearest 0.5 cm on standard wall mounted height boards, without wearing any shoes, heels, and heels, buttocks, shoulders touching the vertical wall surface with line-of-sight aligned horizontally.

Waist circumference was measured to the nearest centimetre with a flexible steel tape measure while the subjects was in the standing position at the end of gentle expiration. The following anatomical landmarks were used for measurement of waist circumference: laterally, midway between the lowest portion of the rib cage and iliac crest.

The blood pressure was measured with a mercury sphygmomanometer in left arm in sitting position, with legs relaxed and uncrossed, and feet touching the floor. The arm was supported, with lower edge of the cuff 1 inch above the bend of the elbow. The cuff was inflated rapidly and deflated slowly, allowing the pressure to fall slowly and noting the systolic pressure when sound of blood is first heard and diastolic when the sound disappears.

Mercury sphygmomanometer is considered a gold standard for measurement of blood pressure, by auscultatory method, a non-invasive method for the measurement of blood pressure.

Blood sample to be tested for Fasting blood sugar, triglycerides, and HDL-Cholesterol levels was drawn from antecubital vein from participants after 12 hours or overnight fasting and sent to the laboratory attached to the hospital.

All the laboratory investigations were not charged to the patients unless and until they were undergoing for the same in routine.

National Cholesterol Education Program-Adult Treatment Panel III criteria modified for Asian subjects, was used for estimating the prevalence of MS.[24]

CRITERIA FOR CLINICAL DIAGNOSIS OF METABOLIC SYNDROME[24]

1. Abdominal Obesity ----------1 point

   Male waist ≥ 102 cm, **For Asians, male waist ≥ 90 cm**

   Female waist≥88cm **female waist ≥ 80 cm**

2. Serum Triglycerides ≥ 150 mg/dl

   Or ----------1 point

   On triglycerides lowering drugs

3. Serum HDL-Cholesterol : Male < 40mg/dl

   Female < 50mg/dl

   Or ----------1 point

   On HDL-Cholesterol improvement drugs

4. Blood pressure ≥130/85 mm of Hg

   Or ----------1 point

   On Treatment for High Blood Pressure

5. Fasting blood glucose ≥ 100 mg/dl

   Or ---------- 1 point

   On glucose lowering treatment

Total criteria point count for Metabolic Syndrome will be calculated by adding up the points.
0-2 points- absent
3-5 points- Present

The correlation between metabolic syndrome and gallstone disease data, was assessed using the data obtained, along with appropriate method for statistical analysis using IBM-SPSS v17 software. Further, all the patient records were used after having an informed written consent from the patient or the attendant present.

ALGORITHM

Identify patients fulfilling the inclusion criteria

↓

Explain the patient about the study (attendant if patient is not competent enough)

↓

Have an informed consent (if willing to be a part of study)

↓

Measure their parameters for Metabolic Syndrome

↓

Calculate their Metabolic Syndrome score using AHA/NHLBI Criteria (Modified NCEP ATP-III)

↓

Statistical Analysis

↓

Compile the report

OBSERVATIONS AND RESULTS

Our study included 100 cases and 100 controls. The metabolic syndrome score was calculated after obtaining individual values of Fasting blood glucose , HDL Cholesterol , Triglycerides , Waist Circumference and Blood Pressure for all the candidates and calculating the score according to the defined criteria. The observations are as:

The mean age of the cases included in the study was 47.47±15.089 with Standard error mean of 1.509.

The mean age of the controls included in the study was 43.58±13.887 with a Standard error mean of 1.389.

The mean Fasting Blood Glucose levels in cases came out to be 96.27±28.374 with a Standard error mean of 2.837. The mean Fasting Blood Glucose levels in controls were 90.64±23.623 with a Standard error mean of 2.362.

The mean HDL Cholesterol in cases was 45.88±11.369 with a standard error mean of 1.137 and in controls was 50.66±10.973 with a standard error mean of 1.097.

The mean of Triglycerides in cases was 155.04±79.459 with a standard error mean of 7.946 and in controls was 132.48 ±59.061 with a standard error mean of 5.906.

The mean of Waist circumference in cases was 81.51±8.486 with a standard error mean of 0.849 and in controls was 80.84±7.081 with a standard error mean of 0.708.

The mean value of BMI for cases was 22.94±3.714 with a standard error mean of 0.371

and for controls was 22.93±4.048 with a standard error mean of 0.405.

The mean of systolic and diastolic BP for cases was 127.08±15.022 (SEM=1.502) and 81.09±9.820 (SEM=0.982) respectively. The mean systolic and diastolic BP for controls was 125.37±14.515 (SEM=1.451) and 79.90±8.964 (SEM=0.896) respectively.

Table 1

		t-test for Equality of Means		
		Sig. (2-tailed)	Mean Difference	Std. Error Difference
FBG	Equal variances assumed	.129	-5.630	3.692
	Equal variances not assumed	.129	-5.630	3.692
HDL CHOLESTEROL	Equal variances assumed	.003	4.780	1.580
	Equal variances not assumed	.003	4.780	1.580
TRIGLYCERIDES	Equal variances assumed	.024	-22.560	9.900
	Equal variances not assumed	.024	-22.560	9.900
WAIST CIRCUMFERENCE (	Equal variances assumed	.545	-.670	1.105
	Equal variances not assumed	.545	-.670	1.105
BMI	Equal variances assumed	.980	-.014	.549
	Equal variances not assumed	.980	-.014	.549
BP SYSTOLIC	Equal variances assumed	.414	-1.710	2.089
	Equal variances not assumed	.414	-1.710	2.089
BP DIASTOLIC	Equal variances assumed	.372	-1.190	1.330
	Equal variances not assumed	.372	-1.190	1.330

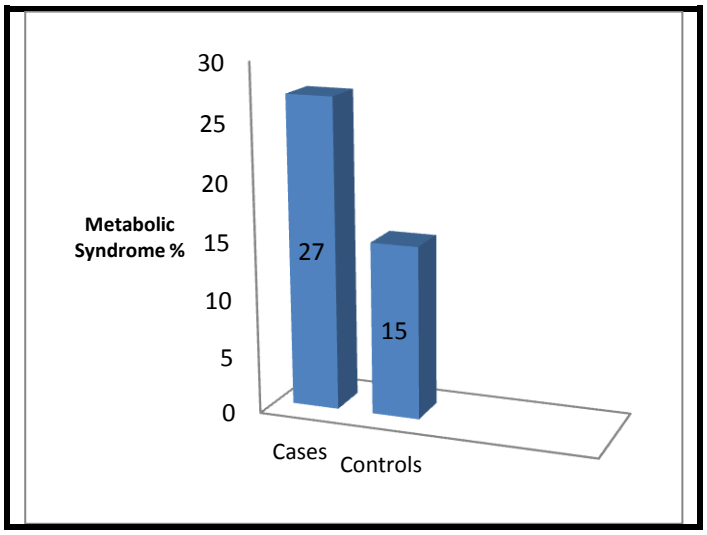
t-Test was used to draw a comparison between cases and controls.

Table 2

		t-test for Equality of Means	
		95% Confidence Interval of the Difference	
		Lower	Upper
FBG	Equal variances assumed	-12.911	1.651
	Equal variances not assumed	-12.912	1.652
HDL CHOLESTEROL	Equal variances assumed	1.664	7.896
	Equal variances not assumed	1.664	7.896
TRIGLYCERIDES	Equal variances assumed	-42.084	-3.036
	Equal variances not assumed	-42.094	-3.026
WAIST CIRCUMFERENCE	Equal variances assumed	-2.849	1.509
	Equal variances not assumed	-2.850	1.510
BMI	Equal variances assumed	-1.097	1.070
	Equal variances not assumed	-1.097	1.070
BP SYSTOLIC	Equal variances assumed	-5.829	2.409
	Equal variances not assumed	-5.829	2.409
BP DIASTOLIC	Equal variances assumed	-3.812	1.432
	Equal variances not assumed	-3.812	1.432

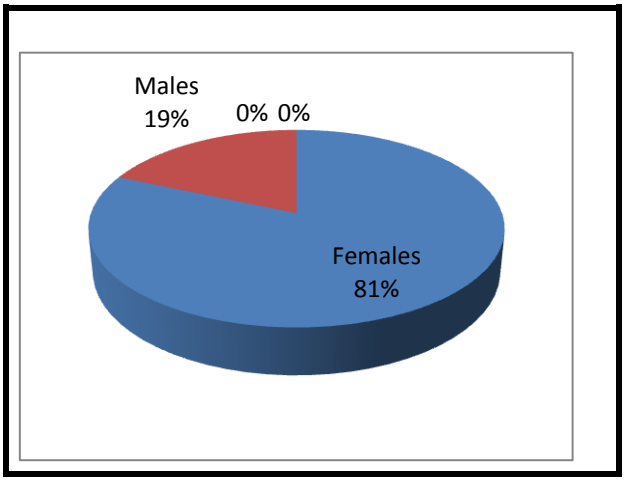
On the basis of the NCEP-ATP-III (AHA) Criteria for Metabolic Syndrome, the following results were obtained:

Figure 1



27% of the cases were found to have Metabolic Syndrome whereas 15% of the controls were found to have Metabolic Syndrome (Table 10 and figure 1)

Figure 2



Pie chart showing sex distribution of Metabolic Syndrome in the cases.

Out of the cases found to be affected with Metabolic Syndrome 81.42% were females and 18.52% were males.

	Controls with Metabolic Syndrome (15)	%
Males	3	20
Females	12	80

Out of the controls found to be affected with Metabolic Syndrome 80% were females and 20% were males.

DISCUSSION

Epidemiological transition in the prevalence of diseases is taking place worldwide and with regional variations. The shift is driven by nutritional, demographic, socioeconomic, industrialization, urbanization and associated changes in lifestyle. In developing countries, communicable diseases continue to be a major cause of death, but non communicable diseases related to inactivity and obesity are also on the rise and projected to increase substantially over the next two decades.[25]

Females are more commonly affected by gall stone diseases.[30]Our study also supports this fact. In our study, out of the cases studied 82% of the subjects were females and 12% were males. This is consistent with another study conducted between 2012 and 2014 in India.[30] However, according to some studies, gender as a risk factor for cholelithiasis still remains controversial. While the majority of studies conducted in the West have concluded that women are more likely to develop cholelithiasis than men[33,34], studies among Asian patients have failed to identify a gender-related difference.[35,36]

Estrogen is the main factor responsible for the difference between males and females in terms of Gall stone formation. One study showed that exogenous estrogens, administered either transdermally or orally, affect physiological markers in a pattern that favors GB stone formation.[37]

Our study concluded that Metabolic Syndrome is found in 27% of the cases suffering from gallstone disease. This is consistent with earlier studies conducted in 2009 [27]and 2012 [30].

The most strongly associated factor with Metabolic Syndrome was found out to be lowered serum HDL Cholesterol followed by Waist circumference, Triglycerides, Blood pressure and Fasting blood glucose.

51out of 100 cases (51%) showed a lowered serum HDL Cholesterol level(HDL<40 mg/dl in males , HDL<50 mg/dl in females or on treatment) . 29 out of 100 controls (29%)showed lowered serum HDL Cholesterol.

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). In our study, we found that 43% of the patients had waist circumference greater than the cut off value for diagnosis of metabolic syndrome (men≥90cms, women≥80cms).43 cases out of 100 (43%) and 37 controls out of 100 (37%) had an increased waist circumference. Not much of a difference was seen in this factor when comparing cases and controls. 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. The results of our study as far as waist circumference is concerned are not consistent with the previous studies. This may be due to the small sample size and subjects restricted to a particular department (Surgery) of the hospital.

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 to the formation of gallstone.

Out of 100 cases, 33 (33%)had raised triglycerides (≥150 mg/dl). This is supported by a study conducted in 2012 in Imphal. 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.[30]

13 controls out of 100 reported raised triglycerides (13%). This clearly shows that raised triglyceride levels is an important indicator of gallstone disease .

High blood pressure (≥130/85 mmHg or on treatment) was observed among 31% 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. 30 out of 100 (30%) controls reported high BP values.

Increased Fasting blood glucose values were observed in 21% of cases and 16% of controls. This is inconsistent with the previous studies which indicated that diabetes mellitus was a risk factor for gallstone disease (Nakeeb*et al.,* 2006; Ruhl and Everhart, 2000; Nervi *etal.,* 2006).

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).[34]

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