JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Prevalence & Risk factors of Cholecystolithiasis: A Review

Dr. IRAM NASEER[1], Dr. ALBINA[2], Prof. TAFSEER ALI[3], Dr. RAHIDA HILAL[2]

[1,2]Assistant Professor, [3]Professor

[1]Department of Jarahat

[1]Rehbar Ayurvedic & Unani Tibbi Medical College Hospital and Research Centre, Punjab, India

ABSTRACT

Cholelithiasis is a Greek word, *chol*→bile, *lith*→stone and *iasis*→process. Cholelithiasis also known as biliary calculi or gallstone disease or cholecystolithiasis, are hardened deposits of cholesterol and biliary pigments that accumulates in gallbladder. Biliary calculi remain one of the most common disease of hepato-biliary apparatus. Gallbladder is a small pear shaped organ situated on the inferior surface of liver, It has 4 parts anatomically. Cholelithiasis has been well known disease all over the World with rising prevalence as evident by documented data. All the continents of the world are affected by cholelithiasis with highest prevalence in Europe and lowest in Africa according to the sonographic studies. Ultrasonography is considered as the Gold standard diagnostic technique for biliary calculi. North Indian are 7 times more at risk than compared to South Indians. The risk factors for cholecystolithiasis are female gender specially of fertile age, Family history, Obesity, Rapid weight loss, Hypertriglyceridemia, High calorie diet, Alcohol, Smoking and Luxurious life style.

KEY WORDS: Gallstone, Prevalence, Risk factors, Female

INTRODUCTION

Cholelithiasis is one of the common pathology of extra hepatic biliary system.[1] Gallstone disease occurs worldwide in about 5-25% of population and also contributes to one of the vital cause of morbidity.[1]

It is evaluated that 20-60 million people have cholelithiasis and about 1 million new cases of gallstone develop each year in India.[2,3] According to numerous epidemiological studies, There is 4% prevalence of gallstone in India which frequently occur in Northern states like Uttar Pradesh, Bihar, Orissa, West Bengal and Assam.[4,5,6,7,8,9,10]

Gallbladder is a part of extra hepatic biliary system, the other structure which comprises the extra hepatic biliary apparatus are right and left hepatic duct, common hepatic duct, cystic duct and common bile duct. Gallbladder is a pear shaped appendage located in the bed of the liver on the junction of right and left lobe of the liver and having average capacity of 50 ml but capable of considerable distension in certain pathological conditions. It measures 10 cm in length and 3 cm in width and divided into four anatomic portions: fundus; corpus or body; infundibulum; and neck. The gallbladder is supplied by the cystic artery, which normally originates from the right hepatic artery behind the cystic duct. Venous return is carried through small veins, which enter directly into the liver from the gallbladder and a large cystic vein, which carries blood back to the right portal vein. Lymphatics of gallbladder drain into several nodes along the surface of portal vein. Nerves from celiac plexus innervate the gallbladder.[11]

The components responsible for the formation of gallstones are female gender, increasing age, genetic factors, obesity, rapid weight loss, hypertriglyceridemia, slow intestinal transit, gallbladder stasis, high calorie diet, highly absorbable sugars, low fibre diet, low vitamin C diet, increased alcohol consumption, smoking and sedentary behaviour.[12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33, 34,35,36,37]

In traditional system, the element responsible for *Hisat-e-Mararah* are *Farbahi* (Obesity) also called *Saman-e-Mufrat*, *Ziabetus Shakri* (Diabetes Mellitus), *Mana-e-Hamal advia* (Contraceptive pills) which turns down the level of *Haamiz-e-safra* (Bile acid) and it aids in the accumulation and genesis of *Hisat*/stone.[34]

LITERATURE REVIEW

PREVALENCE AND GEOGRAPHICAL DISTRIBUTION

There are a large number of published studies which give data on international variations in the prevalence of gallstones. These data are derived from autopsy records, mortality and hospital admission statistics, and from a few special surveys using Cholecystography. The use of Diagnostic Sonography allows determination of the prevalence of gallstones in a representative sample of the general population.[35,36]

The mean prevalence rate of Cholecystolithiasis reported in European populations is 10-12%, whereas it is only 3-4% in Asian populations. For populations in the Americas, Africa, the Near East, and the countries of Eastern Europe and the former Soviet Union, there is a great paucity of Sonographic data.[37]

Europe

The largest number of sonographic studies reporting the prevalence of Cholecystolithiasis has been performed in Western Europe. Using findings from autopsy studies published since 1940, Brett and Barker determined that the median prevalence rate of gallstones in European populations was 15.7% in 1976. This rate substantially exceeds the median prevalence rate of Cholecystolithiasis reported in other sonographic surveys (10.7%; range 5.9-21.0%).The median prevalence rate of gallstones in larger (> 1,000 subjects) sonographic epidemiologic surveys ranged from 5.9% to 21.9%, with the highest rates seen in the populations from Bergen, Norway (21.9%) and Schwedt, Germany (19.7%). Low prevalence rates were reported in surveys from Chianchiano, Italy (5.9%) and Sirmione, Italy (6.9%). All the studies showed an increased prevalence of gallstones with increasing age, obesity, heredity, female sex, and fecundity were associated with an increased prevalence of cholecystolithiasis. The male: female ratio was about 1:1.5. Besides genetic factors that likely also contribute to the high prevalence of cholesterol gallstones in western industrialized nation's nutritional factors probably play a significant role in gallstone prevalence.[38,39,40,41,42,43,44]

North and South America

There has been a marked increase in the incidence of the gallstone in the West during the past century. In the United States, the autopsy series has shown gallstones in at least 20% of women and 8% of men over the age of 40 years. It is estimated that at least 20 million persons in the United States have gallstones and that approximately one million new cases of cholelithiasis developed each year.[45]

Almost all relevant studies from the Americas were conducted on Latin-American populations. Even investigations conducted on populations in the United States dealt exclusively with persons of Hispanic origin. The prevalence rate of cholecystolithiasis in Hispanics (19-40.2%) was higher than the prevalence rates reported for European population and higher than those determined from autopsy studies on non-Hispanic whites in the United States. With the exception of studies focused on the Hispanic population, no large diagnostic sonography study regarding the prevalence of gallstones has been done in the United States.[46,47,48]

The overall male/female ratio found in North American whites is approximately 1 to 2 and in Negroes 1 to 3. The prevalence among whites is approximately twice as high as that among Negroes. Stones in the Americas are mostly of the mixed type, but no type was specified for Panama or Trinidad.[49]

Africa

In Africa, other than South Africa, gallstones are so uncommon that in some parts they were never seen, while elsewhere the recorded prevalence is less than 1 percent and the stones are of the pigmented type. There was no information on regarding sex difference available. In South Africa the recorded prevalence in whites ranges from 14 to 17 per cent and in the Bantu from 2 to 5 per cent. In both ethnic groups females are affected more often than males, and the sex ratio is approximately 1 to 2 in whites and 1 to 4 in the Bantu. Whites have mainly mixed cholesterol stones, while the majority of stones in the Bantu are pigmented.[50,51,52]

Asia

The highest prevalence rate among Asian populations was found in India (6.1%). As observed in Europe, the prevalence of gallstones in Asian populations increased with increasing age, but obesity did not appear to affect the rate, and the male: female ratio was nearer to 1:1. Findings in Asia contrast with those in other areas for the female preponderance is inconstant. Almost all the stones found have been of the pigmented type.[49]

Australia

A study carried out in Brisbane in 1971 showed a prevalence of 31 per cent. In earlier studies in Adelaide and Melbourne lower values of 11, 13 and 15 per cent were found. The male/female ratio was approximately 1 to 2.[53,54]

India

The prevalence of gallbladder stone varies widely in different parts of the world. In India, it is estimated to be around 4%. An epidemiological study restricted to railroad workers showed that North Indians have 7 times higher occurrence of gallstone as compared to South Indians.[2,5,6,7,8,9,10]

It is estimated that 20-60 million persons have gallstone and approximately one million new cases of Gall stone develops each year in India.[55,4]

The prevalence of gallstones in urban Kashmir's adult population was 6-12 percent (men 3-7 percent, women 9-6 percent), it increased with age in both the sexes a peak was observed in the sixth decade of life.[56]

Epidemiological study revealed that gall stone disease is more common in women in the north, north-east and east as compared to other zones in the country.[45,57,58]

North India

Sayeeda Unisa et al. described in their study, that in 6548 persons (2625 males and 3923 females) who underwent USG examination, the prevalence of gall stones was 1.99% in males and 5.59% in females. In all, total gall stones accounted for 4.15%. Females had 2.9 times greater prevalence of gallstones than males in all three districts: female vs. males ratio, in Patna was 5.33% vs. 1.78%, in Varanasi it was 4.29% vs. 1.46% and in Vaishali the ratio was 7.27% vs. 2.49%. The prevalence of gall stones was more in symptomatic individuals (4.72%) than asymptomatic (2.31%). Prevalence of gall stones was 2.3 times more in both males

and females with symptoms than without symptoms: symptomatic vs. asymptomatic in males 2.25% vs.0.99% and in females the ratio was 6.41% vs. 2.87%.[59]

ETIOLOGY OF GALLSTONE DISEASE

Gallstone formation is multifactorial. Both constitutional (unmodifiable) and environmental (modifiable) risk factors are accountable for lithogenesis.

Unmodifiable risk factors for gallstones

- Female gender
- Increasing age
- Genetic factors: ethnicity, family

Modifiable (environmental) risk factors for gallstones

- Obesity
- Rapid weight loss
- Hypertriglyceridemia
- Slow intestinal transit
- Gallbladder stasis
- High calorie diet
- Highly absorbable sugars
- Low fibre diet
- Low vitamin C diet
- Alcohol abstinence
- Smoking
- Sedentary behaviour

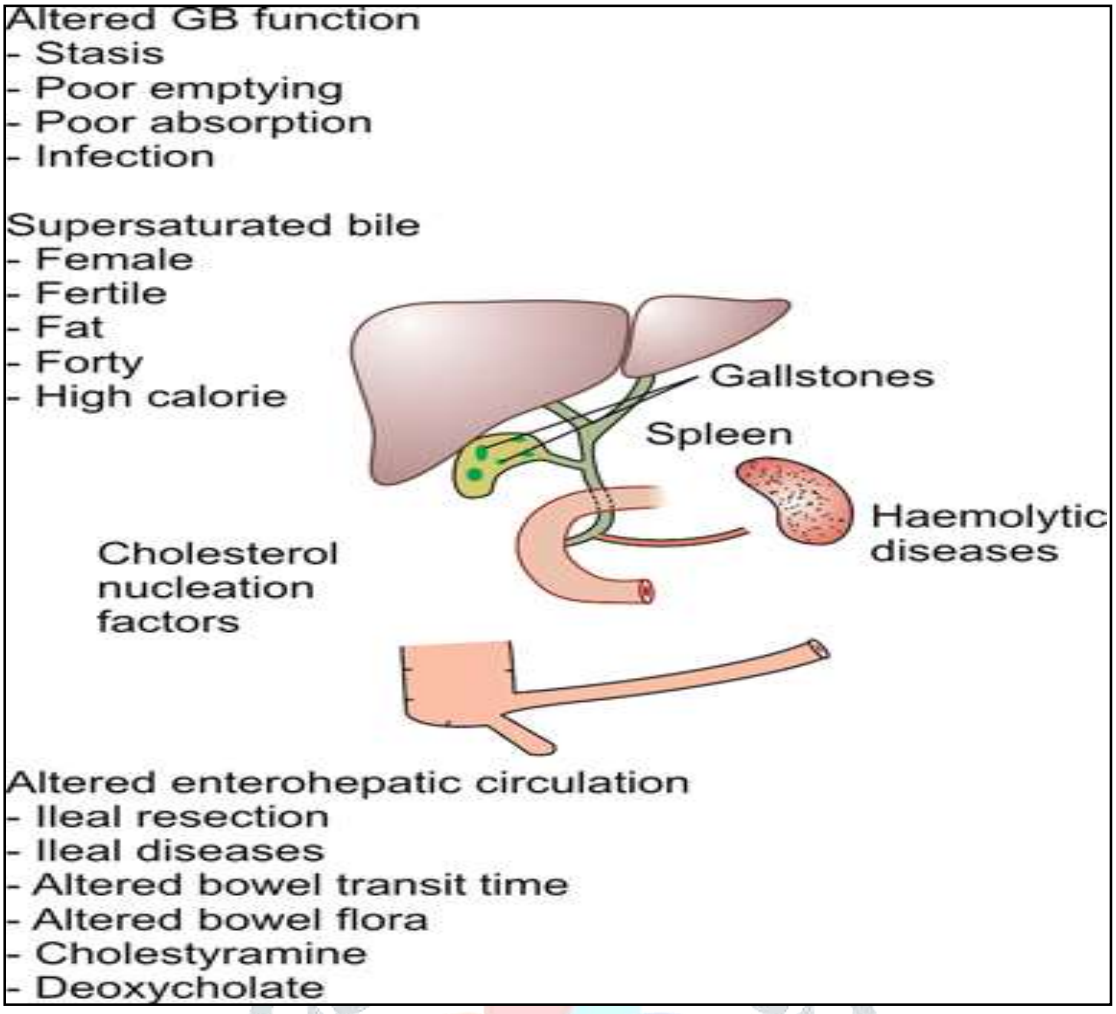

Fig. 1: Diagram showing different causes of gallstone formation.

Gender, Parity and Oral contraceptives

In all populations of the world, regardless of overall gallstone prevalence, women are almost twice as likely as men to experience cholelithiasis. Gender is one of the most powerful influence on gallstones, which are more common in females during their fertile years. This preponderance persists to a lesser extent in the postmenopausal period, but the sex difference narrows with increasing age. Among persons younger than 40yrs, the female/male prevalence ratio varies from 1.2 to 9.9 in Bergen, Norway and among Pima Indians. For ages 60 yrs and older, the female/male ratio varies from 0.96 to 2.9 in Okinawa, Japan and among Mexican Americans in the south western USA. Women with gallstones are more likely to have had a cholecystectomy than men with gallstones.[12,60,61,62]

The influence of the female sex hormones has been studied in normal females, during pregnancy, and in women using oral contraceptives. The risk of gallstones is greater in younger women, and is influenced by parity. A critical review of the literature indicates that parity is associated with gallstones only in younger females. This risk seems to apply to both the number and age of pregnancies. For example, a woman who has four pregnancies before the age of 25year has a four-fold to twelve-fold increased risk of cholesterol gallstones compared to woman of same age and nullipara. Pregnancy favours gallstone formation by hormonal effects on bile composition (increased secretion of biliary cholesterol, decreased and unbalanced supply of bile acids).Oestrogens induce an increased input to the hepatic free cholesterol pool by up-regulating the low density lipoprotein receptor. Decreased gallbladder motility during the third trimester of pregnancy and an altered function of gallbladder mucosa may favour nucleation and growth of stones. Biliary sludge and most gallstones will disappear spontaneously within a few weeks after delivery.[63,64,65]

Several studies have confirmed the link between gallstones and the use of exogenous oestrogens, whether as oral contraceptives, replacement of postmenopausal oestrogen or administration of oestrogen in men. The current evidence indicates that the modern contraceptives, containing a medium/low (less than 50 μg) daily dose of oestrogen, do not increase the risk of forming gallstones, but may accelerate the performance of cholecystectomy. Sex steroids given by other routes, such as transdermal or vaginal, are less lithogenic, probably by avoiding the first pass effect in the liver.[66,67]

Age

The frequency of gallstones increases with age, escalating markedly after the age of 40 yrs to become 4 to 10 times more likely in older individuals. All epidemiological studies showed that increasing age was associated with an increased prevalence of gallstones. Biliary cholesterol saturation increases with age, the rate limiting enzyme for bile acid synthesis, leading to a decrease in cholesterol 7α hydroxylase activity. In the elderly, the synthesis of bile acid is reduced, biliary cholesterol output is increased and bile saturation of cholesterol increases, and that is true in both men and women. The proportion of deoxycholic acid in the bile increases with age by increased 7α dehydroxylation of primary bile acids by the intestinal bacteria. In addition, increasing age allows the cumulative lithogenic action of more risk factors.[13,14]

Obesity and Body fat distribution

Ultrasonographic and cohort studies in selected populations confirmed the clinical impression that gallstones are more common among obese than non-obese individuals. Obesity is an important risk factor for gallstone disease, more so for women than for men. It raises the risk of cholesterol gallstones by increasing biliary secretion of cholesterol, as a result of an increase in HMG CoA reductase activity. Epidemiological studies found that the lithogenic risk of obesity in young women is strongest and that slimming protects against cholelithiasis.[15]

In most studies, obesity in men as expressed by BMI was not related to an increased gallstone formation. A significant stepwise relationship of gallstones with waist/hip circumference ratio was found in men aged 40–69 years, although there was no association between BMI and gallstones in this population. Further studies confirmed that men's chances of having gallstones are increased by having an abdominal distribution of body fat, leading to the conclusion that obesity represents a risk for gallstones both through total body fat mass and through fat regional distribution.[16,17]

Rapid weight loss

Weight reduction in obesity is associated with gallstone formation risk. Different studies in the morbidly obese presenting for gastric bypass surgery or after a very low calorie diet showed the occurrence of sludge and gallstones in 10% to 25% of patients in a few weeks after slimming procedures. During weight loss, bile lithogenicity is further enhanced by increased excretion of cholesterol due to the decrease in the synthesis and bile acids pool size and rapid cholesterol mobilization from adipose tissue stores. In case of severely fat restricted diets, gallstone formation is also favoured by gallbladder stasis. Enhancing gallbladder emptying by inclusion of a small amount of dietary fat inhibits gallstone formation in patients undergoing rapid weight loss.[108] The effect of weight loss on bile lithogenicity is depend on the initial body weight, the calorie and fat content of the diet and the rate of weight loss. A dramatically increasing risk for gallstone formation was found at rates of weight loss above 1.5 kg/week.[18,19,20]

Hypertriglyceridaemia

Some biliary stones are formed from cholesterol; lipoprotein lipids are precursors of biliary lipids; plasma lipoproteins are synthesized, consumed, and degraded in the liver; cholesterol and bile acids in bile is the only way cholesterol can be eliminated from the body. However, no clear association patterns between serum lipids and gallstones were identified even in the largest clinical series, except for a high frequency of gallstones in subjects with hypertriglyceridemia (type IV hyperlipoproteinaemia). Nearly all patients with hypertriglyceridemia have supersaturated gallbladder bile even if they are slim. Most studies found no relationship between plasma cholesterol and gallstones, but suggested that the gallstone risk varies inversely with plasma total HDL or HDL3 cholesterol, attributing to HDL cholesterol, a "protective" effect against gallstone formation.[21,22]

Diabetes mellitus

The gallbladder function impaired in the presence of diabetic neuropathy, and control of hyperglycaemia with insulin tends to increase the lithogenic index, gallstone association with diabetes mellitus remains controversial. Relationships are more complex; only some diabetics are at risk.

Intestinal hypomotility

Intestinal hypomotility may be a primary factor in gallstone development, as demonstrated by the increased concentration of deoxycholate in the bile of sluggish intestinal transit women who are not obese. Acromegaly patients treated with octreotide develop gallbladder and intestinal hypomotility, with a higher proportion of bile deoxycholate, as well as cholesterol supersaturation." Diabetes patients and autonomic neuropathy may run the risk of gallstones being developed by the same mechanism. In addition, gallbladder stasis allows sufficient time for nucleation in these patients.[23]

Diet

One of the main environmental exposures contributing to gallstone formation is the nutritional exposure. The progressive increase in the prevalence rate of gallstones during this century supports the role of lifestyle and dietary factors in gallstone pathogenesis. In Japan, post-war westernisation has provided an example for the interplay between environment and disease. Since the late 40s, the prevalence of gallstones in Tokyo has more than doubled. Moreover, there has been a change from pigment to cholesterol gallstones and the sex ratio has changed in favour of females. This increase in gallstone incidence was associated with an increased fat intake and a decreased fibre content of the diet and consequently was attributed to the westernisation of the Japanese diet. [31,68]

Studies in France have observed a higher caloric intake in subjects with gallstones than in controls. Refined carbohydrates cause obesity, raised plasma triglyceride, fasting plasma insulin level and lower plasma HDL cholesterol. For vegetable fats and protein, an inverse association with gallstones was found in some studies, but not confirmed in others.[24]

A high intake of fibre in the form of wheat bran reduces bile cholesterol saturation. By accelerating intestinal transit and therefore decreasing the deoxycholate in bile, fibers have a protective effect against cholesterol gallstones. An inverse relationship was found between vegetarian diet and the risk of gallstones.[25]

Calcium intake appears to be inversely associated with the prevalence of gallstones. Dietary calcium decreases cholesterol saturation of gallbladder bile by preventing secondary bile acid reabsorption in the colon. Vitamin C influences 7α hydroxylase activity in the bile and it was shown that ascorbic acid might reduce lithogenetic risk in adults. Coffee consumption seems to be inversely correlated with gallstone prevalence, due to an increased enterohepatic circulation of bile acids. [26,27]

Dietary factors are significant independent exposures; however, the current evidence from a recent meta-analysis of all published studies showed only the positive association of sugars and the negative association of fibers and alcohol with cholesterol type of gallstones. Fasting in the short term increases the cholesterol saturation of gallbladder bile and, in the longer term, gallbladder

stasis can lead to sludge and eventually gallstone formation. Younger women with gallstones were shown to be more prone to skip breakfast than controls. A shorter overnight fasting is protective against gallstones in both sexes.[28,29,30]

Alcohol consumption

Certain experimental studies have suggested the alcohol's protective effect against gallstone formation. The consumption of alcohol has been shown to minimize lithogenicity of bile in humans. Alcohol's protective effect can occur through the liver, by increasing cholesterol conversion to bile acids, or by altering the enterohepatic circulation of bile acids, including deoxycholic acid. Moderate alcohol consumption also raises plasma HDL cholesterol concentrations.[30]

Smoking

Data related to smoking as a risk factor for gallstones was inconsistent. Some authors found a linear relationship between amount of smoking and gallstone risk, while other studies found no relation between them. Smoking is linked to low concentrations of plasma HDL cholesterol, a risk factor for gallstones. It also depresses prostaglandin synthesis and mucus production in the gallbladder.[16]

Socio-economic status

Diehl et al. analysed the socioeconomic status in Mexican Americans as compared with non- Hispanic whites and observed that those living in affluent neighbourhoods, with high occupational status, high family incomes, and high educational attainment had lower rates of gallstones than those lower on the social scale. Interestingly, at high levels of socioeconomic status, the ethnic differences in gallbladder disease prevalence narrowed or even reversed. As other studies failed to find an association, the relation between socioeconomic status and gallstone disease is still controversial.[32]

Physical activity

The potential role of physical activity in avoiding the formation of gallstone cholesterol is largely unknown. In addition to facilitating weight control, regular exercise alone or in combination with diet improves several metabolic anomalies related to both obesity and cholesterol gallstones. In a prospective study in 60290 women, increased physical activity was associated with a significant reduction in the risk of cholecystectomy. Not only vigorous physical activities, but also moderate forms of exercise, such as brisk walking, were associated with a reduced risk of cholecystectomy. In contrast, sedentary behaviour, as assessed by time spent sitting, was positively associated with the risk of cholecystectomy.[33]

CONCLUSION

Cholelithiasis is one of the commonest disease in gastroenterology and also contributes to one of the vital cause of morbidity all over the World. Prevalence of cholelithiasis is rising, about 10-15% of world's population affected by the cholelithiasis annually. In India, Epidemiological study revealed that gallstone disease is more common in the north, northeast and east as compared to other zones in the country. Biliary calculi is 2-3 times more common in female as compared to male, this difference assigned to be due to estrogen, which increases the synthesis of biliary cholesterol secretions. Women are more likely to develop gallstones especially during their reproductive life. Patient's Age, Parity, Obesity and Family history significantly increases the risk of developing gallstones. Exhaustive understanding of etiology is necessary because negligence may results in serious complications.

REFERENCES

1. Jain A and IH Khan (2017). Comparison of biliary stenting with T-tube drainage as a method of decompression in cases of open common bile duct exploration: A randomized control trial. IOSR- Journal of Dental and Medical Sciences 16(11). 40-44.
2. Specint MJ. Calots triangle. JAMA; 1967; 200:1186.
3. Choudhuri G, Agarwal DK, Negi TS.Polarizing microscopy of partially dissolved gallstone powder: A simple technique for studying gallstone composition. J Gastroenterol Hepatol 1995; 10:241–5.
4. G.S. Sainani.API Text book of Medicine.6th Edition.Reprinted New India Press, New Delhi; 2001:601.
5. Gordon KC. A comparative anatomical study of the distribution of the cystic artery in man and other species. J Anat 1967; 101:351-359.
6. Mincsev M. Bilocular gallbladder. Orvoskepzes 1967; 42:286-98.
7. McSherry CK. Cholecystectomy: The gold standard. Am J Surg 1989; 158: 174-8.
8. Morgenstern L, Wong L, Berci G. Twelve hundred open cholecystectomies before the laparoscopic era: A standard for comparison. Arch Surg 1992; 127:400-3.
9. Besen EA, Page RE. A practical reappraisal of the anatomy of the extrahepatic bile ducts and arteries. Br J Surg Endosc 1995:1081-4.
10. Rocko JM, Swan KG, Di Gioia JM. Calots triangle revisited. Surg Gynecol Obstet 1981;153:410.
11. Shawartz SI. Principles of Surgery.5thEdition Vol.2nd.Singapore: McGraw-Hill;1988:1381,1390.
12. Everhart JE. Gallstones. In: Everhart JE, ed. Digestive diseases in the United States: epidemiology and impact. (NIH Publication No 94-1447.) 1994: 647-90.

13. Einarsson K, Nilsell K, Leijd B, Angelin B. Influence of age on secretion of cholesterol and synthesis of bile acids by the liver. N Engl J Med 1985; 313:277-282.

14. Bertolotti M, Bertolotti S, Menozzi D, et al. Ageing and bile acid metabolism: studies on 7á hydroxylation of cholesterol in humans. In: Paumgartner G, Gerok W.eds. Trends in bile acid research. Lancaster: Kluwer Academic Publishers;1989: 75-8.

15. Kono S, Shinchi K, Todoroki I, et al. Gallstone disease among Japanese men in relation to obesity, glucose intolerance, exercise, alcohol use and smoking. Scand J Gastroenterol 1995; 30:372-6.

16. Sahi T, PaffenbargerRSJr, Hsieh C, et al. Body mass index, cigarette smoking and other characteristics as predictors of self-reported, physician-diagnosed gallbladder disease in male college alumni. Am J Epidemiol 1998; 147:644-51.

17. Heaton KW, Braddon FEM, Emmett PM, et al. Roles of abdominal fat and hyperinsulinaemia. Eur J Gastroenterology Hepatology.1991; 3:745-51.

18. Yang H, Petersen GM, Roth MP, et al. Risk factors for gallstone formation during rapid loss of weight. Dig Dis Sci.1992; 37:912-8.

19. Gebhard RI, Prigge WE, Ansel HJ, et al. The role of gallbladder emptying in gallstone formation during diet induced rapid weight loss. Hepatology.1996; 24:544-8.

20. Weinsier RL, Wilson LJ, Lee J. Medically safe rate of weight loss for the treatment of obesity: A guideline based on risk of gallstone formation. Am J Med.1995; 98:115-7.

21. Ahlberg J. Serum lipid levels and hyperlipoprotinaemia in gallstone patients. Acta Chir Scand.1979; 145:373-7.

22. Petitti D, Friedman GD, Klatsky AL. Association of a history of gallbladder disease with a reduced concentration of high-density-lipoprotein cholesterol. N Engl J Med 1981; 304:1396-8.

23. Heaton KW, Emmett PM, Symes CL, et al. An explanation for gallstones in normal-weight women: slow intestinal transit. Lancet 1993; 341:8-10.

24. Sarles H, Chabert C, Courcoul MA. Dietary evolution in gallstone patients from 1957 to 1972. Real frequency of gallstone disease. Biological Gastroenterology 1973; 6:162-3.

25. Pixley F, Wilson D, McPherson K, et al. Effect of vegetarianism on development of gallstones in women. BMJ 1985; 291:11-12.

26. Moerman CJ, Smeets FW, Kromhout D. Dietary risk factors for clinically diagnosed gallstones in middle-aged men. A 25-year follow-up study. An Epidemiology 1994; 4:248-54.

27. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of gallbladder disease among US adults. Am J Public Health 1998; 88:1208-12.

28. Tseng M. Dietary intake and gallbladder disease: a review. Public Health Nutrition 1999; 2: 161-72.

29. Capron JP, Delamarre J, Herve MA, et al. Meal frequency and duration of overnight fast: a role in gallstone formation. BMJ 1981; 283:1435.

30. Attili AF, Scafato E, Marchioli R, et al, MICOL group. Diet and gallstones in Italy: the cross-sectional MICOL results. Hepatology 1998; 27:1492-8.

31. Kameda H, Ishihara F, Shibata K, et al. Clinical and nutritional study on gallstone disease in Japan. Japanese Medical Journal 1984; 23:109-13.

32. Diehl AK, Rosenthal M, Hazuda HP, et al. Socioeconomic status and the prevalence of clinical gallbladder disease. J Chronic Dis 1985; 38:1019-26.

33. Leitzmann MF, Rimm EB, Willett WC, et al. Recreational physical activity and the risk of cholecystectomy in women. N Engl J Med 1999; 341:777-84.

34. Sharique K, Mulla G, Farooqui AH, Mukadam M, Ahmed J, Ghawte SA. A Prospective Open Label Randomized Clinical Trial to Evaluate Safety and Efficacy of Olive Oil in Cases of Gall Stone.

35. Heaton, K. W.: The epidemiology of gallstones and suggested etiology. Clinics in Gastroenterology (ed. I.A.D. Bouchier) 2: 67, 1973.

36. Torvik, A. and Hoivik, B. Gallstones in an autopsy series. Ada Chirurgica Scandinavica 120: 168, 1960

37. Kratzer W, Mason RA, Kächele V. Prevalence of gallstones in sonographic surveys worldwide. Journal of clinical ultrasound. 1999 Jan; 27(1):1-7.

38. Barbara L, Sama C, Labate AMM, et al. A population study on the prevalence of gallstone disease: the Sirmione study. Hepatology 1987; 7:913.

39. Attili AF, Carulli N, Roda E, et al. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian study on Cholelithiasis (M.I. - COL.). Am J Epidemiol 1995; 141:158?

40. Heaton KW, Braddon FE, Mountford RA, et al. Symptomatic and silent gallstones in the community. Gut 1991; 32:316.

41. Berndt H, Nurnberg D, Pannwitz H. Prevalence of cholelithiasis: results of an epidemiological sonographic study in the Democratic Republic of Germany [in German]. Z Gastroenterology 1989; 27:662.

42. Glambek I, Kvaale G, Arnesjø B, et al. Prevalence of gallstones in a Norwegian population. Scand J Gastroenterology 1987; 22:1089.

43. Janzon L, Aspelin P, Erikson S, et al. Ultrasonic screening for gallstone disease in middle-aged women. Scand J Gastroenterology 1985; 20:706.

44. Jørgensen T. Prevalence of gallstones in a Danish population. Am J Epidemiology 1987; 126:912?

45. Sharadha B, Srinivas D. Clinical study of cholelithiasis. Int J Sci Stud. 2017 Jun 1; 5(3):210-4.

46. Maurer KR, Everhart JE, Ezzati TM, et al. Risk factors for gallstone disease in the Hispanic population of the United States. Am J Epidemiology 1990; 131:836.

47. Ratner J, Lisbona A, Rosen bloom M, et al. The prevalence of gallstone disease in very old institutionalized persons. J Am Med Assoc 1991; 265:902.

48. Hanis CL, Hewett-Emmett D, Kubrusly LF, et al. An ultrasound survey of gallbladder disease among Mexican Americans in Starr County, Texas: frequency and risk factors. Ethn Dis 1993; 3:32.

49. Brett M, Barker DJ. The world distribution of gallstones. International journal of epidemiology. 1976 Dec 1; 5(4): 335-41.

50. Brebner, I. W. Surgical conditions of the liver, including the gallbladder. South African Medical Journal 8: 867, 1934.

51. Lopis, S. The incidence of cholelithiasis in the Bantu. Clinical Proceedings 6: 338, 1947.

52. Owor, R. Gallstones in the autopsy population at Mulago Hospital, Kampala. East African Medical Journal 41: 251, 1964.

53. Cleland, J. B. Gallstones in 7,000 postmortem examinations. Medical Journal of Australia 2: 488, 1953.

54. Hamilton, I. Gallstones found postmortem. Medical Journal of Australia 1932;2:78.

55. C.R.W. Edward & C. Haslett. Davidson's Principles and Practice of Medicine. 17th Edition. Reprinted in Great Britain: BPC Paulton's Books Limited; 2002:1712.

56. Khuroo MS, Mahajan R, Zargar SA, et al. Prevalence of biliary tract disease in India: a sonographic study in adult population in Kashmir. Gut 1989; 30:201-5.

57. Jayanthi V, Palanivelu C, Prasanthi R, Mathew S, Srinivasan V. Composition of gallstones in Coimbatore district of Tamil Nadu State. Indian J Gastroenterol 1998; 17:134.

58. Cheryl AL. Ethnomedicines used in Trinidad and Tobago for urinary problems and diabetes mellitus. J EthnobiolEthnomed 2006; 2: 45

59. Unisa S, Jagannath P, Dhir V, Khandelwal C, Sarangi L, Roy TK. Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India. Hpb. 2011 Feb 1; 13(2):117-25.

60. Horn G.Observations on the aetiologiy of cholelithiasis.British Medical Journal 1956;732

61. Byakodi K. G, Vikram S, Abhijit Hiregoudar, Vishwas M. R, Vasant Teggimani, Narayan Kabade.Study of clinical profile of cholelithiasis in kims, Hubli. J. Evolution Med. Dent. Sci. 2018;7(21):2604-2608.

62. Alshoabi S. Gallstones: Site, Size, Number, Prevalence and Complications by Ultrasonography. International Journal of Medical Imaging 2016; 4(6): 52-56

63. Barbara L, Sama C, MorselliLabate AM, etal.A population study on the prevalence of gallstone disease: the Sirmione study. Hepatology 1987; 7:913-7.

64. Scragg RKR, McMichael AJ, Seamark RF. Oral contraceptives, pregnancy, and endogenous ostrogen in gallstone disease: a case control study. BMJ 1984; 288:1795-9.

65. Valdivieso V, Covarrubias C, Siegel F, et al. Pregnancy and cholelithiasis: pathogenesis and natural course of gallstones diagnosed in early puerperium. Hepatology 1993; 17:1-4.

66. Royal College of General Practitioners' Oral Contraceptive Study. Oral contraceptives and gallbladder disease. Lancet 1982; ii: 957-60.

67. VanErpecum KJ, VanbergeHenegouwen GP, Verschoor I, et al. Different hepatobiliary effects of oral and transdermal estradiol in postmenopausal women. Gastroenterology 1991; 100:482-8.

68. Castiglioni. A.A: *History of medicine. 2nd ed.* PP: - 34-36; 196; 215; 270-273 *New York*: Alfred A. Knopf 1947.