Journal of The Faculty of Science and Technology (JFST)
http://journal.oiu.edu.sd/index.php/JFST
https://doi.org/10.52981/jfst.vi7.966
ISSN: 1858 - 6007
مجلة العلوم و التقانة – جامعة أم درمان الإسلامية – وزارة التعليم العالي و البحث العلمي - السودان

Research article **JFST Issue No. 7 (2020) 132 - 144**

Biochemical changes in serum liver enzymes and total bilirubin cholelithiasis in hospitals in Khartoum

Ibtisam Bruai Mustafa
Department of Chemistry, Faculty of Science and Technology, Omdurman Islamic University, Omdurman, Sudan.
Email: bsmabio777@gmail.com

Abstract:

Cholelithiasis is one of the most prevalent diseases in gastroenterology, and it is a major public health problem in all developed countries. It has the most common in patient diagnosis among gastrointestinal and liver diseases and it accounts for many hospital admissions and surgical interventions in our local population. Gallstone disease also known to cause liver disease and defragment of its enzymes. Our main objective in the this study was to investigate the biochemical changes in serum liver enzyme and total bilirubin associated with Cholelithiasis. High incidence of cholelithiasis was more prominent among females 127(84.7%) relatives to males 23(15.3%), giving males to females ratio (1:5.5).The most affected age groups were 41-50 years .The majority of patients 62(41.33%) were obese and their body mass index (BMI) 25-30. The most common type of stones was Mixed stones (MS). Serum liver enzymes level of patients was found to be nearly within the same range, whereas their serum total bilirubin significantly increased in comparison with the control group. Furthermore, it is found that there was significant difference between males and females in ALT and AST in patients group. The serum total bilirubin of the patients with pigment stones was significantly elevated. Cholelithiasis is an important cause to significant pathological changes in serum total bilirubin and slight changes in liver enzymes.

Keywords: Gallstone disease, cholecystectomy, liver Enzymes, total bilirubin .

Introduction:

Cholelithiasis or gallstone disease is one of the most common gastrointestinal diseases, It is presence of hardened deposits of digestive fluid that usually formed in the gallbladder (Febyan, 2020; Albert and Groen, 2016), but may also develop in the extra hepatic biliary

tree and occasionally with in intrahepatic duct (Lammert et al., 2016; Boulton et al., 2011). Gallstone is a major public health problem in all developed countries (Acalovschi , 2001) and it is the most common abdominal reason for admission to hospital in these countries (Macsween and Whaley, 1997). It is estimated prevalence of 10% to 15% in Caucasian adult population (Cao and Eslick, 2018) and white adults, leading to significant morbidity, mortality, and considerable health care costs (Stinton et al., 2010; Bouchier, 1989). The highest prevalence was observed in Western Europe and North America ranging from 10–21.9% and the lowest is seen in Asia and sub-Saharan Africa 7-15% (Getachew, 2008; Stinton and Shaffer , 2012). The true prevalence of the disease remains hard to derive as the majority of patients remain asymptomatic (Idris et al., 2013; Cojocaru et al., 2014; Pimpale et al., 2019). Only symptomatic patients should be considered for treatment (Willium et al., 2008). Gallstone disease is one of the major surgical problems in the Sudanese population and it accounts for many hospital admissions and surgical interventions (Helmy et al., 2013). Gallstones are classified into three types according to their chemical composition, cholesterol stones (>50% cholesterol content), mixed stones (20 to 50%cholesterol content), and pigment stones (<20% cholesterol content) (Mullhaupt , 2006). The pathogenic mechanism by which gallstones form is generally agreed to be due to: metabolic factor, alteration in the composition of bile, stasis and infection (David , 1991). Pathology and pathogenesis of gallstones has been the subject of extensive research several years by (Mohammed and Alsaif, 2005; Misty, 1979; Mahdi, 2017; Venneman and Van Erpecum, 2010).

The risk factors which affect the formation of cholesterol gall stones include : demography, sex, advancing age, obesity, diet female sex hormones, pregnancy and contraceptive agents genetic and ethnic influences, ileal disease and resection, diabetes mellitus , clofibrate therapy and smoking ((Bennion and Crundy, 1978; Baig et al., 2002; Stampfer et al., 1992). Gallstone formation is relatively increased with chronic hemolysis syndromes, liver cirrhosis, biliary infection and biliary stasis (Kumar et al., 2007). With the increasing trend of population aging and the change of people's living habits, gallbladder stone is increasingly common around the world (Marschall and Einarsson, 2007; Chenhuia et al., 2018). This study describes the prevalence of different types of gallstone in Sudanese patients and evaluate the relationship between gallstones diseases and increase level of the liver enzymes and total bilirubin.

Materials and Methods:

Study populations:

One hundred and fifty Sudanese patients with gall stones participated in this study They were admitted to Khartoum teaching hospital and Ibn Sina hospital, Khartoum state. During Oct 2009 to Oct 2010. The patients were confirmed by abdominal ultrasound scanner and underwent cholecystectomy which performed on 22 laparoscopically and 128 by open survey. 50 healthy persons matched for age and sex with patients as control group had also participated in this study.

Sampling and Data collections:

Biochemical tests were performed using overnight fasting blood samples from each individual patient and control group. Such tests included serum, alkaline phosphatase (ALP) alanine amino- Transferase (ALT) and aspartate amino- transferase (AST) and total bilirubin . serum ALP was estimated by method reported by (Rosalki et al., 1993) and the method used for the estimation serum ALT and AST was described by (Gella et al., 1985) whereas, Serum total bilirubin was determined by method according to (Burtis and Ashwood, 1994). All parameters were analyzed by spectrophotometric methods, using commercially kits supplied by Bio Systems S.A. company (Spain),which obtained from National Health Laboratory. Gallstones samples recovered from the patients were analyzed physically, noting number, shape, size and texture were noted then they divided into 3 groups depending upon their colors. according as described by (Hadi et al., 2012). Necessary information about subjects i.e. demography sex, age, body weight, number of pregnancies, family history, race social classes, tribe and dietary habits were filled in the questionnaire by direct interview of respondents .

Statistical analysis:

All the experimental data were subjected to analysis of variance in order to determine the changes in the means of the parameters. Student.s t test was used to compare the data between patients and control groups and between the patients distributed in different groups. Also analysis of variance (ANOVA) was used for comparison between the different age groups using Statistical Package for Social Sciences (SPSS) computer package version 20. At 95% confidence level of p. value <0.05 was considered statistically significant

Results:

Table (1): Distribution of the participants according to cholecystectomy type

Hospitals admission	**Ibn Sina hospital**		**Khartoum hospital**		**Total**
Type of cholecystectomy	**No of patients (male)**	**No. of patients (Female)**	**No of patient (male)**	**No. of patients (Female)**	
open surgery	18	87	3	20	**128**
Laparoscopic	2	17	0	3	**22**
Total	**20**	**104**	**3**	**23**	**150**

Table (2): Distribution of the participants according to sex and age

Age group (years)	**No. of patients (Male)**	**No. of patients (Female)**	**Total**	**No of control (male)**	**No of control(female)**	**Total**
< 30	1(0.7%)	21(14%)	**22(14.67%)**	3(6 %)	2(4%)	**5(10 %)**
31-40	2(1.3%)	27(18%)	**29(19.33%)**	2(4 %)	17(34 %)	**19(38 %)***
41-50	8(5.3%)	42(28%)	**50(33.33%)***	3(6%)	8(16 %)	**11(22%)**
51-60	6(4%)	23(15.3%)	**29(19.33%)**	0(0 %)	8(16 %)	**8 (16 %)**
> 60	6(4%)	14(9.3%)	**20(13.33%)**	0(0 %)	7(14%)	**7(14%)**
Total	**23(15.3%)**	**127(84.7%)**	**150(100%)**	**8(16 %)**	**42(84%)**	**50(100%)**

Table (3): Incidence of different types of gallstones in relation to age in patients

Age group (years)	Cholesterol stones (CS)		Mixed stones (MS		Pigment stones (PS)		Total		
	Male	Female	Male	Female	Male	Female	Male	Female	**Total**
< 30	1(0.7%)	7(4.7%)	0(0.0%)	7(4.7%)	0(0.0%)	7(4.7%)	1(0.7%)	21(14%)	**22(14.67%)**
31-40	0(0.0%)	5(3.3%)	1(0.7%)	14(9.3%)	1(0.7%)	8(5.3%)	2(1.3%)	27(18%)	**29(19.33%)**
41-50	3(2 %)	6(4%)	4(2.7%)	21(14%)	1(0.7%)	15(10 %)	8(5.3%)	42(28%)	**50(33.33%)***
51-60	0(0.0%)	5(3.3%)	4(2.7%)	10(6.7%)	2(1.3 %)	8(5.3%)	6(4%)	23(15.3 %)	**29(19.33%)**
>60	0(0.0%)	6(4%)	3(2 %)	3(2 %)	3(2 %)	5(3.3%)	6(4%)	14(9.3%)	**20(13.33%)**
Total	4(2.7%)	29(19.3%)	12(8 %)	55(36.7 %)*	7(4.7%)	43(28.7 %)	23(15.3 %)	127(84.7 %)	150(100%)

Table (4): Mean concentration values of serum liver enzymes parameters and total bilirubin in gallstone patients and control group.

Subject	No.	Alp (i.u./L) [Mean ±SED]	Alt (i.u./L) [Mean ±SED]	Ast (i.u./L) [Mean ±SED]	Total bilirubin (mg/dl) [Mean ±SED]
Patients	150	131.8253±6.76528	30.4607±2.41356	40.4607±3.07575	.8936±.04284**
Control	50	120.9960±6.40177	34.7400±4.03273	41.5440±3.53993	.7440±.02805
Probability		0. 247	0.372	0. 850	0.004

*Significant difference at P< 0.05 **Highly significant difference at P< 0.001

Alp: alkaline phosphatase, **Alt**: alanine amino transferase, **Ast**: aspartate transaminase.

Table (5): Mean concentration values of serum liver enzymes parameters and total bilirubin of the patients (Male and Female).

Group	No.	Alp (i.u./L) [Mean ±SED]	Alt (i.u./L) [Mean ±SED]	Ast (i.u./L) [Mean ±SED	Total bilirubin (mg/dl) [Mean ±SED
Males	23	122.313±17.314	43.517±6.073*	55.030±7.773*	.982±.109
Females	127	133.548±7.368	28.096±2.585*	37.822±3.308*	.878±.047
Probability		0.551	0.021	0.043	0.381

*Significant difference at P< 0.05 **Highly significant difference at P< 0.001

Table (6) : concentration [Mean ±SED] of serum liver enzymes parameters and total bilirubinparameters of the patients with deferent age groups.

Age group	No.	Alp (i.u./L) [Mean ±SED]	Alt (i.u./L) [Mean ±SED]	Ast (i.u./L) [Mean ±SED	Total bilirubin (mg/dl) [Mean ±SED
< 30	22	134.945±17.877A	26.955±6.294A	43.555±8.075A	.980±0.113 A
31-40	29	140.290±15.570A	24.162±5.482A	30.734±7.033A	.951±0.098 A
41-50	50	129.590±11.858A	35.392±4.175A	42.228±5.356 A	.891±0.075 A
51-60	29	126.397±15.570A	34.797±5.482A	42.462±7.033A	.815±0.098 A
> 60	20	129.580±18.749 A	24.835±6.601 A	43.840±8.469A	.837±0.118 A
Total	150	131.8253±6.76528	30.4607±2.41356	40.4607±3.07575	.8936±0.04284

*Significant difference at P< 0.05 **Highly significant difference at P< 0.001

*Mean with the same letter are not significantly different

Table (7) :Mean concentration values of serum liver enzymes parameters and total bilirubin of the three types of patients

Type of patients	No.	Alp (i.u./L) [Mean ±SED]	Alt (i.u./L) [Mean ±SED]	Ast (i.u./L) [Mean ±SED	Total bilirubin (mg/dl) [Mean ±SED
Type one	33	135.324±14.206 AB	29.270±5.177A	41.633±6.550A	.730±0.089* A
Type two	67	147.478±9.970*A	29.885±3.633A	35.591±4.597A	.839±0.062* A
Type three	50	108.542±11.541*B	32.018±4.206A	46.212±5.322A	1.075±0.072*B
Probability		0.040	0.898	0.316	0.006

*Significant difference at P< 0.05 **Highly significant difference at P< 0.001

*Mean with the same letter are not significantly different

This study consisted of 150 patients who underwent cholecystectomy. Predominantly the patients were females (127) accounting for 84.7% whereas males were only 23 constituting 15.3%, their mean age was 46.7years (ranged between 28 to 75 years), Female to male ratio was 5.5:1 (table 2) Our findings are similar to a study in our local population by (Suleiman, 1977) and from , Iraq. By (Hadi et al., 2012) which revealed that, the ratio of female to male were 5.3:1 and 5:1 respectively. The high incidence of gallstone in females may be attributed to female sex hormones, oral contraceptive use, and estrogen replacement therapy, are risk factors for gallstone disease. Female sex hormones adversely influence hepatic bile secretion and gallbladder function. Estrogens increase cholesterol secretion and diminish bile salt secretion. Progestins act by reducing bile salt secretion and impairing gallbladder emptying leading to stasis with gallstones (Stinton et al., 2010) on the other hand Women are also more likely to undergo cholecystectomy than men (Acalovschi, 2001).

The highest percentage of gallstones (33.3%) observed in the age groups (41-50) while the lowest percentage of gallstones (14.7%)and (13.3%) found in the age groups(< 30)and (> 60) years.(table 2). These results were in agreement with (Gopi , 2019) who found that the highest age incidence of cholelithiasis was in the 4th decade, and partial agreement with Sudanese's study conducted by (Saadeldin et al., 2014) who reported that the high incidence of gallstones found in age group31-50 years (64 patients (68.08%)), while it was rare in patients < 30 and elderly patients > 70 years. A possible explanation for the higher prevalence of gallstones in these age groups is that, with increasing age the activity of 7-hydroxlase decreases and activity of HMG CoA reductase increasing ,thus increasing

gallstone formation (Friedman et al., 1966). On the other hand the low incidence of gallstone disease over the age of 60 might be due to partly the fact that old people are poor candidate for surgery and anesthesia in addition to lesser easy access of medical assistance to this age group (Hadi et al., 2012).

Classification of gallstones was carried out according to criteria suggested by (Helmy et al., 2013; Hadi et al., 2012) which based on their colors: Cholesterol stones(CS)were white or yellow, pigment stones(PS) were black or black-brown and mixed Stones(MS) were greenish, red or brownish yellow. (table3) .The physical analysis or visual classification showed that 67(44.7%) of the stones were mixed calculi (MS), 50(33.33%) were pigment calculi (PS) and 33(22%) were cholesterol calculi (CS) indicating the incidence of gallstones in the studied patients as follows: Mixed calculi more than Pigment calculi more than cholesterol calculi . Our findings are similar to a study from Iraq by (Hadi et al., 2012) which revealed that the most common type of stones were mixed type.

The results in study disagree with those by (Saadeldin et al., 2014; Jaraari et al., 2010) Sudanese and Libyan study in which who revealed that the most common type of gallstone in their population were pigment calculi followed by mixed and then cholesterol type.

In the present study the levels of serum alkaline phosphatase (ALP) alanine amino-Transferase (ALT), aspartate amino- transferase (AST) and total bilirubin where measured in patients and control group. Table (4) revealed the Mean concentration values [Mean ±SED] of serum ALP, ALT , AST and total bilirubin.

Comparison of serum liver enzymes between patients and controls groups showed that the levels of serum ALP of the patients was relatively higher than that of control group but there was no significant variation ($p>0.05$) between the patients and controls groups . Furthermore, it is found that the mean level of serum ALT and AST of the patients were slightly lower than that of the controls groups.

Comparison for serum liver enzymes between male and female in patients group as indicated in Table (5) showed significant differences ($p<0.05$) between the two groups in serum ALT and AST .However the mean value of serum ALP was higher in females but the difference was not significant. Within the patients age groups the differences were not significant in the levels of the three liver enzymes table (6).

The present study was agreed with that of (Olokoba et al., 2009) who also did not show any significant role of gallstones in change of liver enzymes concentration . Comparison of serum total bilirubin between gallstone patients and controls showed that the level of total bilirubin in the serum of patients was significantly higher than that of control group.

These results were in agreement with (Abdulameer et al., 2020) who reported that serum total bilirubin was elevated in 20% of patients, but not more than 4mg/dL in acute cholecystitis . Our study also showed a comparable results to that of the study in Nigeria by (Olokoba et al., 2009) who founded that the serum level of total and conjugated bilirubin were higher in patients with gallstones disease than in those without. The possible explanation of this difference is that, direct and indirect level of the serum total bilirubin are elevated when the liver is affected or when there is biliary tract obstruction (Cuschini et al., 1995). No significant difference was reported for the level of the serum total bilirubin between male and female in patients group table(5).

Among age groups patients, there was a no significant variation in serum total bilirubin table (6). No information about the effect of sex and age on serum total bilirubin was available.

The patients with gallstones were classified in to three types according to their type of stone: Type one : patients with CS, Type two: patients with MS and Type three: patients with PS. The Mean concentration values of serum ALP, ALT, AST and total bilirubin in the three types of gallstones patients presented in table (7). Type three: patients with PS, showed the highest concentration values of serum total bilirubin, data also presented significant difference ($p>0.05$) in serum total bilirubin between the three types of patients. The explanation of these result was that the Pathogenesis of pigment stones is due to: hemolysis, e.g. hereditary spherocytosis, sickle cell anemia, thalassemia and malaria, in which bilirubin production is increased, increased bilirubin production is associated with an increased risk of gallstone disease (Abdulameer et al., 2020). Results presented in table (7) showed that there was significant difference ($p>0.05$) in serum ALP between the three types of patients, and also indicated that the highest level of serum ALP was found in type two: patients with MS.

There are no known local study comparing the relationship between type of gallstone and liver enzymes.

Conclusion:

Cholecystitis is the most prevalent biliary disease causes of morbidity and surgical operation in Sudan, Findings of present study considered that the incidence of gallstones diseases among Sudanese was not rare, as indicated of biliary operation in hospitals.

An interesting finding of our study is that MS was the most common type of gallstones, and gallstones disease is an important cause to significant pathological changes in serum total bilirubin and slight changes in liver enzymes.

More studies with respect to the pathogenesis of gallstones with more number of patients has to be done, to further conclude the gallstone analysis and the risk factors .

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