Original Article

The role of bile acids signaling as regulator of cholesterol metabolism in normal and diseased gallbladders

Physiology

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ABSTRACT

Background: Bile acids (BAs) are cholesterol-derived steroid acids and constitute one of the major components of bile. They are known to have a part in assimilation of lipid, cholesterol and fat dissolvable vitamins. Recent researches have revealed that bile acids operate as signaling molecules that regulate the metabolism of bile acids, fatty acids, glucose homeostasis, lipoproteins and energy metabolism via interfering with nuclear and surface receptors.

Objective: to investigate the role of bile acids signaling in farnesoid x receptor (FXR) / fibroblast growth factor(FGF)19 pathway in cholesterol metabolism in normal and gallstone gallbladders.

Methodology: Thirty individuals participated in this study and were separated into 2 groups, each group 15 individuals. Group (i) normal group: adult persons with healthy gallbladder underwent elective cholecystectomy as a part of another procedure as they were living-donor liver transplant, and group(ii) gallstone group (GS): adult persons underwent elective cholecystectomy for gallstone disease. Serum concentration of cholesterol, Fibroblast growth factor 19 (FGF19), Cholesterol 7α-hydroxylase enzyme (CYP7A1) and Sterol 12-hydroxylase (CYP8B1) and bile concentration of Phospholipid, Cholic acid (CA), Deoxycholic acid (DCA) and Chenodeoxycholic acid (CDCA) were determined.

Results: Concentration of cholesterol,CYP7A1 and CYP8B1 in the serum as well as concentration of cholesterol in bile were all significantly higher in gallstone group. While, concentration of FGF19 in serum as well as concentration of phospholipids, CA, DCA and CDCA in bile were all significantly lower in gallstone group.

Conclusion: The bile acids/FXR/FGF19 pathway regulates cholesterol metabolism and prevents gallstone development by reducing the levels.

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INTRODUCTION

Recent studies have shown that bile acids act as signaling molecules that regulate the expression of multiple genes encoding enzymes and proteins involved in synthesis and metabolism of bile acids, fatty acids, glucose homeostasis, lipoproteins as well as energy metabolism. These receptors include FXR, pregnane X receptor, vitamin D receptor, and G protein-coupled receptors (TGR5), muscarinic receptor 2, and sphingosine-1-phosphate receptor(S1PR)2. Among these receptors FXR are involved in cholesterol metabolism [1].

The hepatic synthesis of bile acids accounts for the majority of cholesterol catabolism in the body. In humans, every day 500 mg of cholesterol is converted to bile acids. Being amphipathic molecules, bile acids are also important regulators of cholesterol absorption. Among all the bile acids, CA has the most capability to allow cholesterol absorption [2]. Cholesterol can also enter the liver in the form of high-density lipoprotein (HDL), a process termed reverse cholesterol transport. Classically, reverse cholesterol transport is a process involved in the removal of excess cholesterol that is accumulated in the peripheral tissues (e.g., macrophages in the aortae) by HDL, transporting it to the liver for excretion into the feces via the bile. ATP-binding cassette transporter (ABCA1) is the transporter responsible for the first step in reverse cholesterol transport; it transports cholesterol

from the peripheral tissues to apolipoproteins. Scavenger receptor class B type I (SR-B1) mediates the uptake of cholesteryl esters from HDL into the liver. FXR is known to reduce cholesterol levels via inducing SR-B1 expression to enhance HDL removal from the blood into the liver. Also, the activation of direct FXR target, enterokine FGF15/19 has been shown to stimulate powerful secretion of cholesterol into the intestinal lumen via the sterol-exporting heterodimer adenosine triphosphate (ATP)-binding cassette subfamily G member 5/8 (ABCG5/G8) [1].

Bile acids synthesis takes place in the liver mainly through two pathways, the classical and the alternative pathway. The classical pathway of bile acid synthesis is the major pathway in human and represents about 90% of total bile acid synthesis [2]. In the classical pathway, the initial and rate-limiting step is the 7α-hydroxylation of cholesterol by CYP7A1. 7α-hydroxycholesterol is then converted to 7α-hydroxy-4-cholestene-3-one (C4), which can be converted to CA by CYP8B1. Without 12α-hydroxylation, C4 is converted to CDCA. CYP8B1 is at the branch point for CA and CDCA synthesis and determines the ratio of 12α-hydroxylated bile acids (CA and DCA) to non-12α-hydroxylated bile acids (CDCA and LCA) in the bile acid pool. The enzyme CYP7A1 is largely determining the bile acid pool size whereas CYP8B1 is considered important for the CA/CDCA ratio in the bile acid pool [3]. Bile acid pool in human is consisted mainly of primary BAs 40%CA, 40%CDCA that are formed in the liver, and 20% secondary bile acid, DCA that is formed by the action of bacteria in intestine [3]. Once primary BAs are synthesized, they can undergo conjugation with taurine and glycine and form Na^{2+} salts (bile salts) [2]. Conjugation decreases BA toxicity and facilitates their secretion into the bile.

Conjugated BAs are transfered to the bile to be stored in the gallbladder through the canalicular membrane. Cholecystokinin, a hormone secreted by the duodenum after a meal, increases gallbladder contraction, causing BAs to be released into the gut. The major part of BAs are reabsorbed and delivered back to the liver through portal circulation in the ileum. BAs are expelled in the stool in about 0.5 g per day, or 5% of the total BA pool, with BAs being recycled 4–12 times each day. BA transporters are responsible for continuous moving of BAs during the enterohepatic circulation. Efflux of BAs from the hepatocytes into canaliculi is mainly mediated by the bile salt export pump (BSEP; ABCB11/Abcb11). Reabsorption of BAs in the terminal ileum is mainly mediated by the apical sodium- dependent bile salt transporter (ASBT), intracellular binding to intestinal bile acid-binding protein (IBABP) and basolateral BA efflux by the organic solute transporters (OSTαand OSTβ) heterodimer into the portal circulation[4].

Farnesoid x receptor (FXR) is the most important nuclear receptor to regulate BA homeostasis and hence cholesterol metabolism. FXR is highly expressed in the liver, ileum, kidneys,and adrenal glands. There is a clear role of FXR in the liver and intestine to regulate bile acid synthesis. As shown in Figure 1 :Activation of intestinal FXR plays a major role while activation of liver FXR plays a minor role in the suppression of CYP7A1 and CYP8B1 gene expression through the induction of the intestinal FGF19 and hepatic small heterodimer partner 1 (SHP-1)in humans[5][6]. Moreover, FXR has a critical role in the regulation of the enterohepatic circulation of bile acids through the induction of BSEP, IBABP and OSTα β / genes expression and suppression of ASBT[3].
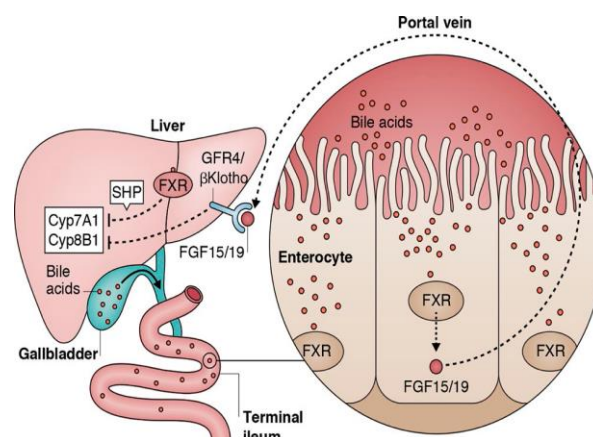
Figure1: Farnesoid X receptor (FXR) regulates bile acid (BA) synthesis. In the intestine, FXR activation induces fibroblast growth factor (FGF)19, which go to the liver and then activate the FGFR4/β-klotho dimer to activate signalling pathways that inhibit the expression of CYP7A1 and CYP8B1 genes in the classical pathway. Activation of hepatic FXR also inhibits BA synthesis but to a lesser extent [21].

However, the physiological role of this signalling pathways under normal physiological conditions in human is still not clear and not completely understood [6]. So, the current study was conducted to investigate the role of bile acids signalling in FXR/ FGF19 pathway in human cholesterol metabolism in normal and gallstone gallbladders.

SUBJECTS and METHODS
I. Study Design
A prospective observational case-control study was designed.

II. Study Methods
- *Population of study and disease condition*
Thirty individuals were used in this study. They were obtained from National Hepatology & Tropical Medicine & Research Institute during March 2019 to December 2019. The ethical committee of National Hepatology & Tropical Medicine & Research Institute approved the

protocol .All candidates signed an informed consent form. They were divided into 2 groups, each group 15 individuals. Group(i) normal group and group(ii) gallstone group (GS).

1. **Normal group:** Subjects in normal group were donors of living donor liver transplant (LDLT), submitted to cholecystectomy as a step in the transplant procedure. All donors were subjected to a pre-transplant assessment by the transplant teams.
2. **Gallstone group:** It includes all patients with chronically diseased gallbladders who diagnosed as chronic calcular cholecystitis and they were subjected to full history taking, clinical examination and investigations, as abdominal ultrasonography to confirm the diagnosis, complete blood picture, liver, kidney functions tests. All patients went for elective cholecystectomy by laparoscopy.

Inclusion criteria
Adult patients with symptomatic gallstone disease submitted to elective cholecystectomy, and donors with healthy gallbladders submitted to living donor liver transplant. **Exclusion criteria**: Patients with a small shrunken and atrophic gallbladder, no bile content at all or the cystic duct was occluded and the gallbladder was hydropic.

Methodology
All the following steps were done for both healthy and gallstone groups: Preoperative investigations as an abdominal ultra-sound and laboratory tests for liver and kidney functions and complete blood count.

-Sample collection
Blood sample: a sample (5 ml) of fasting venous blood was obtained during the operation from each patient and healthy subject and was collected in plain vacutaier tube, after coagulation. The sample centrifuged at 3000×g for 20 min at 4°C (according to the kit instructions) to separate sera for determination of Cholesterol level, FGF19, CYP7A1 and CYP8B1. Samples were stored at -80°C until assayed. Bile sample: during surgery, after removing the gallbladder, 5 cc of gallbladder's bile was aspirated from it with a syringe. After surgery the sample was kept in a sterile tube for determination of Cholesterol level, Phospholipid level, CA, DCA and CDCA. The samples were stored at -80°C until assayed.

III. Biochemical analysis:
Serum and bile cholesterol were determined by Quantitative Colorimetric kit of BioAssay Systems, USA [7].

- Biliary phospholipids level was determined by Quantitative Colorimetric method using EnzyChromTM Phospholipid Assay kit (EPLP-100) of BioAssay, USA [8].
- Bile CA was determined by Competitive ELISA kit of MyBioSource, USA [9].

- Bile CDCA was determined by competitive Eliza kit of CELL BIOLABS, USA [9].
- Bile DCA was determined by ELIZA kit of Cloud-Clone Crop, USA [9].
- Serum FGF19 was assayed by ELISA kit of MyBiosource, USA [10].
- Serum CYP7A1 was determined by ELISA kit of MyBiosource, USA [11].
- Sterol CYP8B1 was determined by ELISA kit of MyBioSource, USA [11].

Statistical analysis
Statistical analysis were carried out using the statistical software SPSS (Statistical Package for Scientific Studies) version 20, quantitative variables were expressed as mean ± standard deviation(SD) and range. Simple comparisons between groups were performed with independent sample t-test. A Pearson correlation test between some parameters was done.
The level of significance were considered at p-value < 0.05"

RESULTS
Demography and clinical characteristics of study Groups:
30 patients were included in this study. 15 (50%) had chronic symptomatic gallstone disease and 15 (50%) had healthy gallbladders. most patients with gallstones were female 12 (80%), 3 (20%) were male and were older than patients with healthy gallbladder where, their mean age 40.6 years ranging from (32-59). Donors with healthy gallbladder were mostly male 12 (80%), 3 (20%) were female and younger than patients with gallstones. Their mean age were 31.9 years ranging from (21-52).

Comparison of cholesterol, biliary phospholipids and bile acids in healthy and gallstone groups.
Both serum and biliary cholesterol levels in gallstone group are significantly elevated in comparison to healthy one, while biliary phospholipids level is significantly decreased in gallstone group compared to healthy one (table 1).

Comparison of biliary bile acids in healthy and gallstone groups
Biliary CA, DCA and CDCA levels show a significant decrease in gallstone group compared to healthy one (table 2).

Comparison of FXR pathway (Serum Fibroblast growth factor 19, cholesterol 7α-hydroxylase enzyme and sterol 12-hydroxylase enzymes) in healthy and gallstone groups.
There is marked decrease in serum FGF19 level of gallstone group compared to healthy one. Whereas, there is significant increase in both serum levels of CYP7A1 and CYP8B1 in gallstone group compared to healthy one (table 3).

Correlation Study Between serum FGF19 and cholesterol 7α-hydroxylase in gallstone group:

Results of the Pearson correlation indicates that there is a significant negative association between serum FGF19 & CYP7A1 levels in patients of gallstone group(r=0.966, n= 15, P< 0.001) (figure 2).

Table (1): Comparison of serum, bile Cholesterol and bile phospholipids levels in normal and gallstone groups

Groups Parameters	Healthy group (n=15)	Gallstone group (n=15)	p-value
Serum cholesterol(mg/dl) Mean± SD (Range)	178.4 ± 20.29 (152-213)	265.9 ± 37.51* (197-317)	0.001
Bile cholesterol(mg/dl) Mean± SD (Range)	206.93 ± 18.49 (176.2 – 232.6)	326.1 ± 56.61* (241.8- 391.5)	0.001
Bile phospholipids(mg/dl) Mean± SD (Range)	64.2 ± 11.38 (51.3 – 64.2)	34.02 ± 9.01* (21.4 - 53.9)	0.001

*: Significant p-value (p< 0.05)

Table (2): Comparison of Biliary bile acids levels CA, DCA and CDCA in normal and gallstone groups.

| Groups Parameters	Healthy group (n=15)	Gallstone group (n=15)	p-value
Bile CA (ng/ml) Mean± SD (Range)	193.5 ± 48.09 (122.7 -273.8)	95.4 ± 26.04* (55.3 -150.7)	0.001
Bile DCA (ng/ml) Mean± SD (Range)	108.64 ± 8.55 (95.4 -127.1)	66.72 ± 14.94* (51.7 - 102.3)	0.001
Bile CDCA (nM/ml) Mean± SD (Range)	7.22 ± 1.83 (4.10 – 9.60)	2.4 ± 0.83* (1.30 – 4.20)	0.001

CA: cholic acid, DCA: deoxycholic acid, CDCA: chenodeoxycholic acid, *: Significant p-value (p< 0.05)

Table (3): Comparison of serum FGF19, CYP7A1 and CYP8B1 levels in normal and gallstone groups

Groups Parameters	Healthy group (n=15)	Gallstone group (n=15)	p-value
Serum FGF19 (pg/mL) Mean± SD (Range)	111.75 ± 12.37 (92.1 -131.9)	48.54 ± 13.85* (33.1 – 75.1)	0.001
Serum CYP7A1 (pg/mL) Mean± SD (Range)	18.5 ± 4.29 (12.4 – 26.20)	87.76 ± 22.9* (55.2 – 125.2)	0.001
Serum CYP8B1 (ng/mL) Mean± SD (Range)	1.07 ± 0.23 (0.93 – 1.9)	2.17±0.77* (1.08 – 4.05)	0.001

FGF19:fibroblast growth factor 19, CYP7A1: cholesterol 7 alpha hydroxylase enzyme, CYP8B1: sterol 12-hydroxylase enzyme *: Significant p-value (P< 0.05)
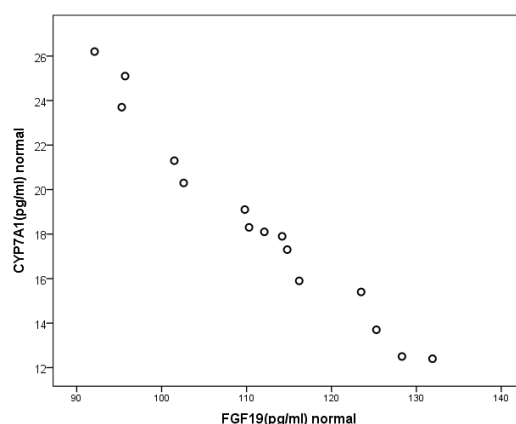
Figure (2): Scatter plot showing negative correlation between serum FGF19 & CYP7A1 in normal group

DISCUSSION

The aim of this study was to determine the involvement of bile acids in cholesterol metabolic process as signaling molecules in the FXR/FGF19 route in healthy people and people with gallstones. In the current study, the serum cholesterol level was significantly higher in the gallstone group compared to normal group. Wang et al. [12] and Sheng et al. [13] supported this result. Whereas, Hayat et al. [14] and Batajoo et al. [15] found no change in serum cholesterol between normal and gallstone bladders in their studies. Although cholesterol saturation in bile plays a role in the pathological process of gallstones, the link between gallstones and higher concentration of serum cholesterol in patients is debatable in the literature and has been explained by a diversity of factors including genetics, geography, social status, and eating habits in the pathologic process of various types of gallstones [14]. In the current study hypercholesterolemia may be attributed to FXR deficiency. As activation of FXR reduces intestinal cholesterol absorption and increases cholesterol excretion in feces by inhibiting hepatic CYP8B1 [15]. CYP8B1 increases CA synthesis which enhances cholesterol absorption. In the current study, biliary cholesterol levels in GS patients were significantly higher than in normal group. This result was supported by a study of Jayanthi et al. [16]. On the other hand, Rudling et al. [17] contradicted it.

In the current study, the gallstone group had significantly lower biliary phospholipid levels compared to normal group. This is in line with the result of Rudling et al.[17]. Reduced phospholipid levels in bile may be caused by reduced expression of the phospholipid transporters ABCB4 due to FXR inactivation [17]. CDCA primarily activates the Farnesoid X receptor (FXR) [18] [19]. FXR stimulation causes the intestinal hormone FGF19 to be released [20].

In the current study, serum FGF19 levels (measured as a marker for FXR) [20] were significantly lower in the gallstone group compared to normal one. The reason for the decreased level of serum FGF19 was attributed to inactivation of FXR in gallstone patient as a consequence of decreased level of CDCA or CA [21] or due to variation of FXR gene [22].

On the other hand, this result was contradicted by Renner et al. [23] and it was explained by ethnicity variation and also serum FGF19 level may be affected by sequence variations in the gene, epigenetic as well as posttranslational factors, and variations in protein degradation [23].

In the current study, both CYP7A1 and CYP8B1 serum levels were significantly higher in the gallstone group when compared to the control group indicating up regulation of bile acid synthesis. There is a consistency between this finding and that reported by Renner et al. [23]. Induction of bile acids in gallstone patients is thought to be a response to increased intestinal bile acid loss in order to compensate for the interruption of enterohepatic bile acid circulation as well as a result of FXR and FGF19 deficiency.

In the current study, there is a strong negative connection between serum FgF19 and CYP7A1 Renner et al. [23] and Li et al. [24] supported this result. Despite the fact that CYP7A1 and CYP8B1 are much higher in the GS group, indicating up regulation of bile acid synthesis, the bile acid pool size (CA, CDCA, and DCA) is much lower. This is in line with the findings of Rudling et al. [17]. Reduced secretion of bile salts and phospholipids in bile was linked to decreased expression of the bile acid and phospholipid transporters, BSEP (abcb11) and Abcb4, respectively, as a result of inactivation of FXR, which plays an essential role in transcription regulation of these genes [17]. Reduced bile acid pool may be also attributed to reduced bile acid reabsorption in the gut and increased bile acid loss in stool owing to reduced function of ASBT, OST-OST, and ileal lipid binding protein (ILBP), all of which are caused by FXR, and thus may participate in gallstone development in non-obese individuals [17].

CONCLUSION

The farnesoid X receptor (FXR)/FGF19 pathway is important for regulation of cholesterol metabolism in

normal individuals and prevention of gallstone. As deficiency of FGF19 in gallstone patients lead to upregulation of CYP8B1 which affects affects CA production. CA lowers cholesterol levels by reducing intestinal cholesterol absorption and increasing faecal cholesterol excretion. In addition, FGF19 deficiency increased bile acid production due to up regulation of CYP7A1. Given the importance of CYP7A1 for bile acid homeostasis, it is probable that intestinal FXR/FGF19 signaling is the primary physiological mechanism for the negative feedback control of bile acid production and the prevention of gallstone formation. Future studies are needed to better understand the molecular mechanism of the FXR/FGF19 pathway in cholesterol metabolism, which can aid in gallstone prevention.

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الملخص العربي

الدور الفسيولوجي للأحماض الصفراوية كمنظم لأيض الكوليسترول في أصحاء ومرضى الحويصلة المرارية

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ملخص البحث

الخلفية: الأحماض الصفراوية هي أحماض ستيرويد مشتقة من الكوليسترول وتشكل أحد المكونات الرئيسية للصفراء. من المعروف أن لها دورًا في هضم وامتصاص الكوليسترول والدهون والفيتامينات التي تذوب في الدهون. أظهرت الدراسات الحديثة أن الأحماض الصفراوية تعمل كجزيئات إشارات تنظم عملية التمثيل الغذائي للأحماض الصفراوية والأحماض الدهنية وأيض الجلوكوز والبروتينات الدهنية وكذلك الطاقة من خلال العمل على المستقبلات النووية والسطحية.

الهدف: دراسة دور الأحماض الصفراوية في مسار مستقبلات الفارنسويد اكس(FXR) و عامل نمو الخلايا الليفية 19(FGF19) كمنظم لأيض الكوليسترول في أصحاء ومرضى الحويصلة المرارية.

الطرق: تم استخدام ثلاثين فردًا في هذه الدراسة. كل مجموعة 15 فرد وتم تقسيمهم إلى مجموعتين: المجموعة (1) مجموعة الأصحاء وهم الأصحاء المتبرعون بالكبد والذين تم استئصال المرارة السليمة أثناء اجراء العملية. والمجموعة (2) مجموعة الحصوات المرارية وهم الذين خضعوا لعملية استئصال المرارة بسبب وجود الحصوات. و تم قياس مستويات الكوليسترول وعامل نمو الخلايا الليفية 19 وأنزيم الكوليسترولهيدروكسيلاز 7 و انزيم ستيرول 12 هيدروكسيلاز في الدم. كما تم قياس مستويات الصفراء من الفوسفوليبيد وحمض الكوليك وحمض الديؤكسي كوليك وحمض الكينوديؤكسي كوليك.

النتائج: تم ارتفاع مستويات الكولسترول وأنزيم الكوليسترول هيدروكسيلاز 7 و انزيم ستيرول 12 هيدروكسيلاز في الدم و مستوى الصفراء من الكوليسترول بشكل ملحوظ في مجموعة حصوات المرارة. بينما انخفض مستوى المصل من عامل نمو الخلايا الليفية 19 ومستويات الصفراء من الفوسفوليبيد وحمض الكوليك وحمض الديؤكسي كوليك حمض الكينوديؤكسي كوليك بشكل ملحوظ في مجموعة حصوات المرارة.

الخلاصة: يلعب مسار الأحماض الصفراوية / في مسار مستقبلات الفارنسويد اكسو عامل نمو الخلايا الليفية19 دورًا مهمًا في تنظيم أيض الكوليسترول ومنع تكوين حصوات المرارية من خلال خفض مستويات انزيمات الكوليسترول هيدروكسيلاز 7 و ستيرول 12 هيدروكسيلاز التي تؤثر على امتصاص الكوليسترول وتخليق حمض الصفراء.

الكلمات المفتاحية: انزيم كوليستيرول هيدروكسيلاز7، انزيم ستيرول 12هيدروكسيلاز، عامل نمو الخلايا، الحصوات المرارية، الكوليستيرول.

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