

the prevalence of biliary stone diseases in patient with thyroid disorder

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الخلاصة:-

الخلفية:-حصاه المرارة هي من بين أهم أمراض الجهاز الهضمي التي تحتاج إلى رقود في المستشفيات ، بصورة عامه اغلب المرضى من متوسطي العمر ، وينسبه ١١ الى ٣٦ بالمائة موجودة في تقارير التشريح لناس أصحاء .

الدراسات السابقة أظهرت أن الخلل في الغدة الدرقية يكون مصاحب إلى :-
١ - تباطؤ في حركة المادة الصفراوية مصاحب إلى انخفاض وظائف الغدة الدرقية في كل من الدراسات على الإنسان وعلى الحيوان.

٢ - تسارع في حركة المادة الصفراوية مصاحب إلى زيادة وظائف الغدة الدرقية في الدراسات على الحيوان .
انخفاض وظائف الغدة الدرقية هو ثاني أهم سبب في زيادة نسبة الكولسترول في الدم. المريض المصاب بنقصان إفراز هرمونات الغدة الدرقية تكون نسبة الكولسترول في الدم لديه أكثر ب ٥٠ بالمائة من الإنسان السليم . و ٩٠ بالمائة من كل مرضى قصور الغدة الدرقية يكون لديهم زيادة في نسبة الكولسترول بالدم وهذا يؤثر في ذوبان الاملاح في المادة الصفراوية.

المرضى وطرق البحث:-هذه الدراسة أجريت في مستشفى الصدر التعليمي في مدينه النجف الاشرف في الفترة بين الأول من شباط من عام ٢٠١٠ ولغاية الأول من نيسان ٢٠١١ .ضمت الدراسة شريحة عشوائية من المرضى المصابين باختلال الغدة الدرقية تتراوح أعمارهم بين ١٠ إلى ٧٠ عام . في البداية شملت الدراسة ٣٠٠ مريض ، منهم ٢٣٦ مريض فقط تمت متابعتهم في مستشفانا بصورة دورية صحيحة، كل مريض منهم قام بزيارة وحده الجراحه مرتين على الأقل وتم إرسال فحص وظائف الغدة الدرقية الى المختبر التابع لمستشفانا مرتين على الأقل وخلال ٣ أشهر بين الفحص والآخر لذلك كانت نتائج الدراسة معتمدة على توثيق مستمر لوظائف الغدة الدرقية .في نفس الوقت تم ارسال كل مريض لفحص البطن والرقبة بالاشعه فوق الصوتيه(السونار) للتحري عن وجود حصاه المرارة ، حصاه القناة الصفراويه او توسعها مرتين على الأقل للتأكد من وجود أو عدم وجود هذه الاختلالات المرضية.

النتائج: الدراسة أظهرت إن ٢٠٠ مريض هم من الإناث و ٣٦ مريض فقط هم من الذكور ، وإن ١٣٤ مريض منهم كانوا لا يعانون من اختلال نسبة هرمونات الغدة الدرقية في الدم، و ٣٨ مريض فقط يعانون من قصور الغدة الدرقية و ٦٤ مريض فقط يعانون من ارتفاع نسبة هرمونات الغدة الدرقية في الدم. الدراسة أظهرت إن اختلال الغدة الدرقية عند النساء هو أكثر منه عند الرجال بغض النظر عن نوع هذا الاختلال .الكشف بالاشعه فوق الصوتية للبطن اظهر إن ٣١ مريض فقط يعانون من وجود حصاه في المرارة أو القنوات الصفراوية و إن ٢٠٥ مريض لا يعانون من وجود حصاه المرارة .كما أن الدراسة أظهرت إن ١٤ مريض فقط يعانون من حصاه المرارة ونسبة هرمونات الغدة الدرقية لديهم سليمة ، و إن ١٥ مريض فقط يعانون من حصاه المرارة ولديهم قصور في الغدة الدرقية .بينما مريضين فقط اللذين يعانون من حصاه المرارة ولديهم ارتفاع نسبة هرمونات الغدة الدرقية.

الاستنتاج: ١-إن حصاه المرارة أكثر حدوثا عند المرضى اللذين يعانون من قصور هرمون الغدة الدرقية اذا ما قورنوا بالمرضى اللذين نسبة هرمونات الغدة الدرقية لديهم سليمة.اما نسبة حدوث حصاه المرارة عند المرضى اللذين يعانون من ارتفاع نسبة هرمون الغدة الدرقية فهي ضئيلة جدا (حتى عند المرضى اللذين أكثر تعرضا لحصاه المرارة). ٢-إن نسبة حدوث حصاه المرارة تزداد مع انخفاض نسبة هرمون الغدة الدرقية.

Abstract

Background:-Gallstones are among the most common gastrointestinal illness requiring hospitalization and frequently occur in young, otherwise healthy people with a prevalence of 11% to 36% in autopsy reports. ^(1,2) Previous studies showed that hypothyroidism is associated with delayed biliary flow in human study.⁽¹⁰⁾ and in animal study. ⁽¹¹⁾ While hyperthyroidism is associated with enhances biliary flow in animal study. ⁽¹¹⁾ Hypothyroidism is the most common secondary cause of hypercholesterolemia, patient with hypothyroidism have serum level of cholesterol approximately 50% higher than level in euthyroid patient, and 90% of all hypothyroid patient have elevated cholesterol level.⁽¹²⁾ this will influence the bile solubility. ⁽¹³⁾ The aims of the study is to evaluate the prevalence of gall stone and common bile duct stone in patient with thyroid disorder and-to evaluate the effects of thyroid function on the biliary stone formation.

Patients and method:-This is a prospective study was done in AL-SADER Teaching hospital in AL-NAJAF city in the period between 1st of February 2010 and 1st April 2011.

A random sample of population aged 10 ---70 years was included in the study. At first 300 patients were included in the study, but finally only 118 patients were followed properly by at least 2 visits to our hospital surgical unit. Every patient sends for thyroid function test (T3, T4, and TSH.) in the laboratory of our hospital for at least two times, 3 months apart. So our results depend on recording persistent thyroid function status. At the same time patients send for ultrasound of the neck and abdomen especially for gall stone and common bile duct stone also for at least two times to be sure about the presence or absence of the biliary stone.

Result:-The study show that 200 patients (84.75%) where female and 36 patients (15.25%) where male .Our study thyroid function test shows that 134 patients (56.78%) euthyroid, 38 patients (16.1%) hypothyroid while 64 patients (27.12%) hyperthyroid. The study also showed that thyroid disorder occurs in female more than male whatever the thyroid status. The ultrasound of the abdomen of our patients showed that only 31 patients (13.14%) have biliary stone, all of them are female patients, while 205 patient (86.86%) did not showed biliary stone .The study show that only 14 patients (10.45%) of those with euthyroid have biliary stone and 15 patients (39.47%) with hypothyroidism have biliary stone while only 2 patients (3.125%) with hyperthyroidism have biliary stone .

Conclusion:-1-The prevalence of biliary stone disease is more common in hypothyroid patients compared to euthyroid patients while the prevalence of biliary stone in hyperthyroidism, even in high risk group for cholelithiasis (female gender,fair, fertile, forty or fifty years old , and others) is very low

2- The prevalence of biliary stone disease increase with the decreasing level of thyroid hormone.

Introduction:-

Gallstones are among the most common gastrointestinal illness requiring hospitalization and frequently occur in young, otherwise healthy people with a prevalence of 11% to 36% in autopsy reports^(1,2). Common bile duct stones are found in 6% to 12% of patients with stones in the gall bladder .Gall stones represent an inability to maintain

certain biliary solutes, primarily cholesterol and calcium salts, in a solubilized state. Gallbladder mucosal and motor function plays a key role in gallstone formation.⁽¹⁾

The pathogenesis of cholesterol gall stones involves three stages:

1-Cholesterol supersaturation in bile.^(1, 3, 4, 5)

2-Crystal nucleation.^(1, 3, 4, 5)

3-Stone growth and bile stasis.^(1, 3)

Risk Factors for Gallstones include: Obesity, Rapid weight loss, Childbearing, Multiparity, Female sex, First-degree relatives. First degree relative of the patient with gall stone have a two fold greater prevalence. Drugs: ceftriaxone, postmenopausal estrogens, total parenteral nutrition, Ethnicity: Native American (Pima Indian), Scandinavian. Ileal disease, resection or bypass and Increasing age. The incidence of gall stone increase with age.⁽³⁾, fatty foods, Crohn's disease, gastric surgery, hereditary spherocytosis, sickle cell disease, and thalassemia. Only first-degree factors for development of symptomatic gallstone disease.^(1,2)

Considerable evidence suggests that mucin glycoproteins play a role as a pronucleating agent for cholesterol crystallization. The concentration of bile may relatives of patients with gallstones and obesity have been identified as strong risk affect the solubility of two important components of gallstones: calcium and cholesterol. As the gallbladder bile becomes concentrated, several changes occur in the capacity of bile to solubilize cholesterol. The net effect of concentrating bile is an increased tendency for cholesterol nucleation. Acidification of bile promotes calcium solubility, thereby preventing its precipitation as calcium salts. Cholecystokinin, the major regulator of gallbladder function. In addition to stimulating gallbladder contractions, cholecystokinin also acts to functionally inhibit the normal phasic motor activity of the sphincter of Oddi.

Sphincter of Oddi is a complex structure that is functionally independent from the duodenal musculature. It creates a high-pressure zone between the bile duct and the duodenum. Both neural and hormonal factors influence the sphincter of Oddi. Sphincter of Oddi activity appears to be coordinated with the partial gallbladder emptying and increases in the bile flow that occur during phase III of the migratory motor complex. This activity may be a preventive mechanism against the accumulation of biliary crystals during fasting.⁽¹⁾ An abdominal ultrasound is the standard diagnostic exam for gallstones, if performed by an experienced operator, given the high specificity (>98%) and sensitivity (>95%) of this test for the diagnosis of cholelithiasis. Dilation of the extrahepatic (>10 mm) or intrahepatic (>4 mm) bile ducts suggests biliary obstruction.

Hypothyroidism: In many underdeveloped countries, lack of sufficient iodine intake explains a large proportion of hypothyroid conditions. In more developed countries, most cases of adult hypothyroidism are caused by Hashimoto's thyroiditis, radioactive iodine therapy, or surgical removal.

Hyperthyroidism: Increased thyroid secretion can be caused by primary alterations within the gland (Graves' disease, toxic nodular goiter, toxic thyroid adenoma) or central nervous system disorders and increased TSH-produced stimulation of the thyroid. Most hyperthyroid states occur because of primary malfunction.⁽¹⁾

Thyroid Function Tests: the ultrasensitive radioimmunoassay TSH assay has become the most sensitive and specific test for the diagnosis of hyper- and hypothyroidism and for optimizing T₄ replacement and suppressive therapy.⁽²⁾ is an important screening test for the diagnosis of thyroid dysfunction⁽¹⁾. This assay is especially important in the delineation of hypothyroid from euthyroid states. Additionally, clinically euthyroid

patients may have suppressed TSH levels (subclinical hyperthyroidism), and the assay can therefore demonstrate hyperthyroidism before it becomes clinically manifested. The sensitivity of the TSH assay is less affected by nonthyroidal disease processes and remains unaffected by changes in thyroid hormone-binding proteins.⁽¹⁾

Accurate evaluation of thyroid function requires measurement of free T₄ levels.⁽¹⁾

The T₃ resin uptake test is one of the most common indirect measurements of the proportion of T₄ that is not protein bound. These measures are not generally used for routine screening but are helpful in the diagnosis of T₃ thyrotoxicosis.⁽¹⁾

The aims of the study is To evaluate the prevalence of gall stone and common bile duct stone in patient with thyroid disorder and to evaluate the effects of thyroid function on the biliary stone formation.

Patient and method:-

This is a prospective study was done in AL-SADER Teaching hospital in AL-NAJAF city in the period between 1st of February 2010 and 1st of April 2011.

A random sample of population aged 10 ---70 years was included in the study. At first 300 patients were included in the study, but finally only 236 patients were followed properly by at least 2 visits to our hospital surgical unit.

The criteria for selection of patients for this study are those with thyroid disorder whether hypothyroidism, hyperthyroidism and euthyroid with thyroid nodule.

Hypothyroid patient include:-post-thyroidectomy , Hashimoto's disease.

Hyperthyroid patient include: - Graves disease, toxic multinodular goiter, and toxic nodule. All patients with history of treated or diagnosed thyroid abnormalities recruited into the study from one hospital.

We exclude from the study patients with smoking, diabetes mellitus, obesity abnormal serum lipid and patients on oral contraceptive pill.

Full history was taken from patients including age, gender, chief complain, thyroid status, past medical history, past surgical history, drug history and smoking.

Physical examination of the patients including examination of neck, pulse rate, and ECG.

Every patient sends for thyroid function test (T₃, T₄, and T.S.H.) in the laboratory of our hospital for at least two times, 3 months apart. So our results depend on recording persistent thyroid function status.

At the same time patients send for ultrasound of the neck to assess thyroid size and ultrasound of abdomen especially for gall stone and common bile duct stone also for at least two times to be sure about the presence or absence of biliary stone disease.

The data of history, physical examination, thyroid function test and ultrasound of those 236 patients were available for this study analysis is written in special paper. Thyroid function test was done at morning, analyzed by immunchemiluminescent procedure in our hospital laboratory..

Normal values of thyroid function test in our hospital laboratory are:-

T₄-----4.2—11.0 ug/100ml

T₃-----0.52---1.6 ug/100ml

TSH-----0.25---5.0 ug/100ml

In order to evaluate independent relation between thyroid function and cholelithiasis and choledocholithiasis, our patients divided to 3 groups according to the result of thyroid function test:-low, high, and normal TSH Levels. (Euthyroid, hypothyroid and hyperthyroid). Statistical analyses were performed using SPSS 12.0 for windows.Inc.

Data were expressed as mean \pm SEM. Analysis of Variance (ANOVA) was used for the multiple comparisons among all groups followed by post-hoc tests using LSD method. The statistical significance of difference was assessed by Mann-Whitney U test was used for the difference between 2 groups. In all tests, $P < 0.05$ was considered to be statistically significant.

Result:-

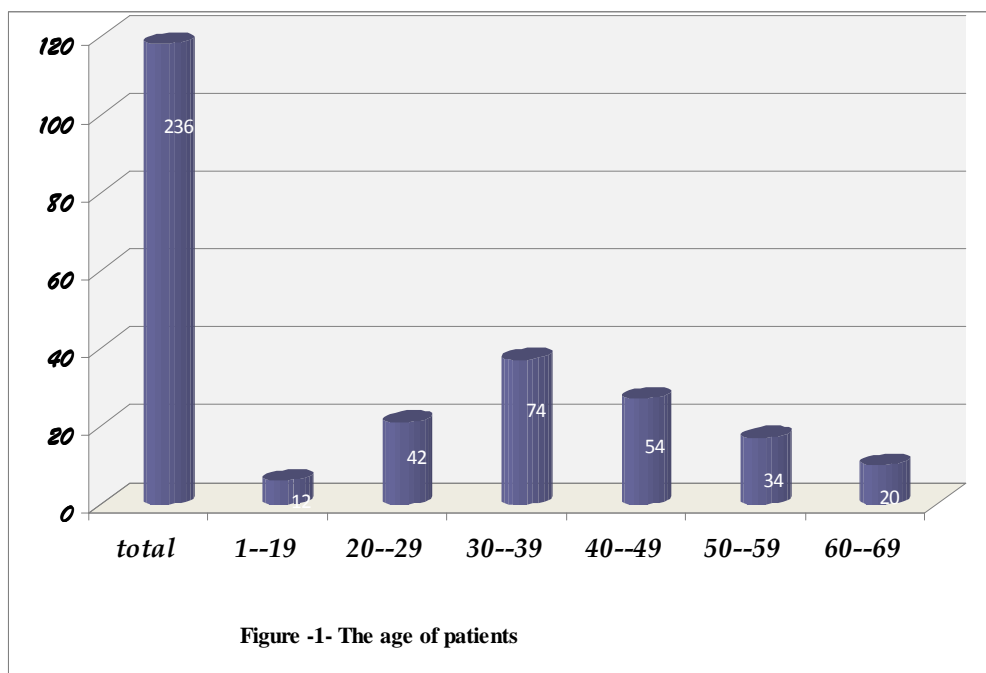
During the study period, firstly 300 patients with thyroid disease were included in the study but finally only 236 patients were followed properly in our study program. Patients' age range from 10 to 70 year old as shown in figure (1), the mean of age of our patients was 38.44 years. All patients with thyroid dysfunction (hypo- or hyperthyroidism) in our study are in the age group range between 20-49 years. Also the study show that all patients with biliary stone are in the same age group.

The study show that 200 patients (84.75%) where female and 36 patients (15.25%) where male as shown in figure (2).

Our study thyroid function test shows that 134 patients (56.78%) euthyroid, 38 patients(16.1%) hypothyroid while 64patients (27.12%) hyperthyroid . As in figure (3) which show the thyroid status with the gender of the patient. This figure also showed that thyroid disorder occurs in female more than male whatever the thyroid status.

The ultrasound of the abdomen of our patients showed that only 31 patients (13.14%) have biliary stone, all of them are female patients, while 205 patients (86.86%) did not showed biliary stone as show in figure (4).

The study show that only 14 patients (10.45%) of those with euthyroid have biliary stone and 15 patients (39.47%) with hypothyroidism have biliary stone while only 2 patients(3.125%) with hyperthyroidism have biliary stone as shown in table (1).



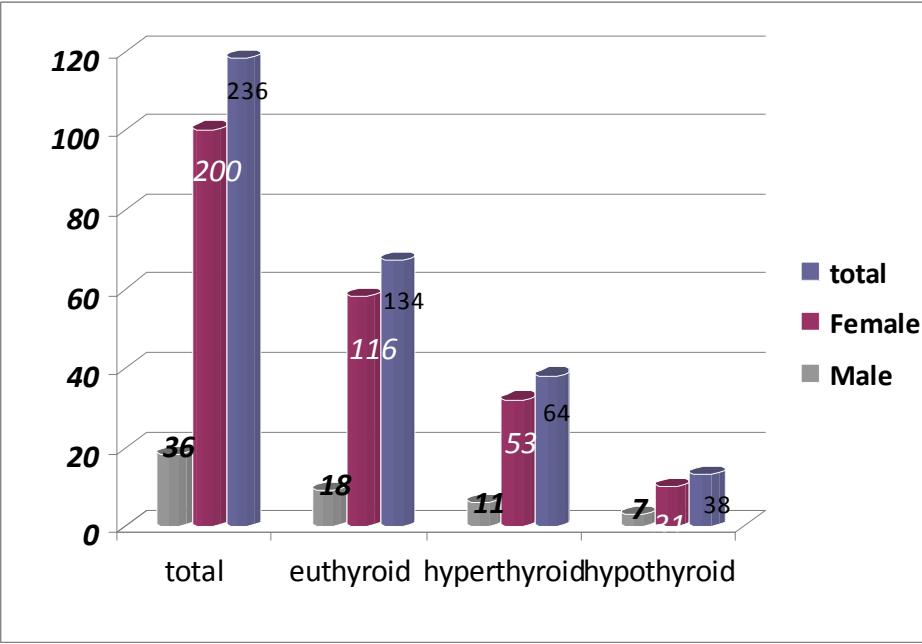
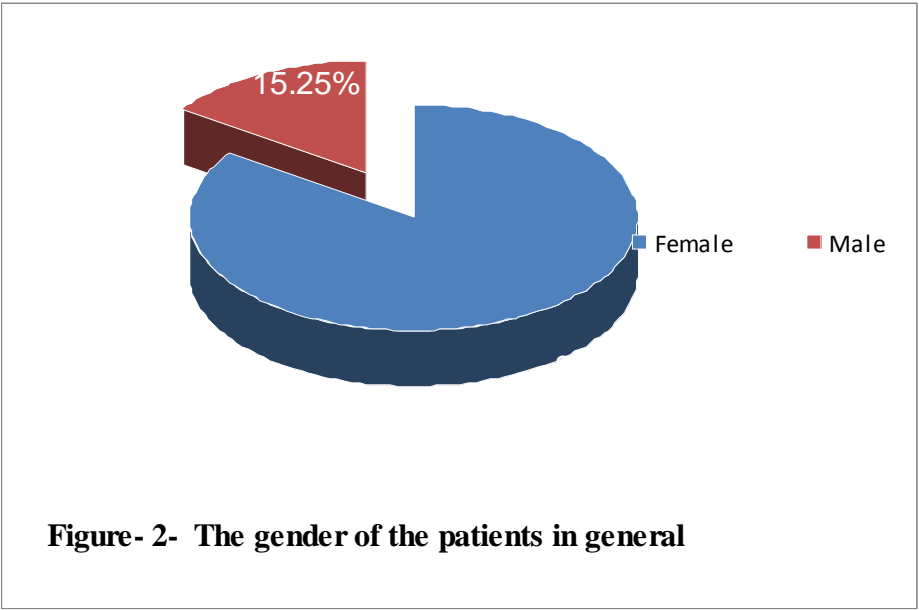


Figure- 3 - The relationship between the gender and thyroid status

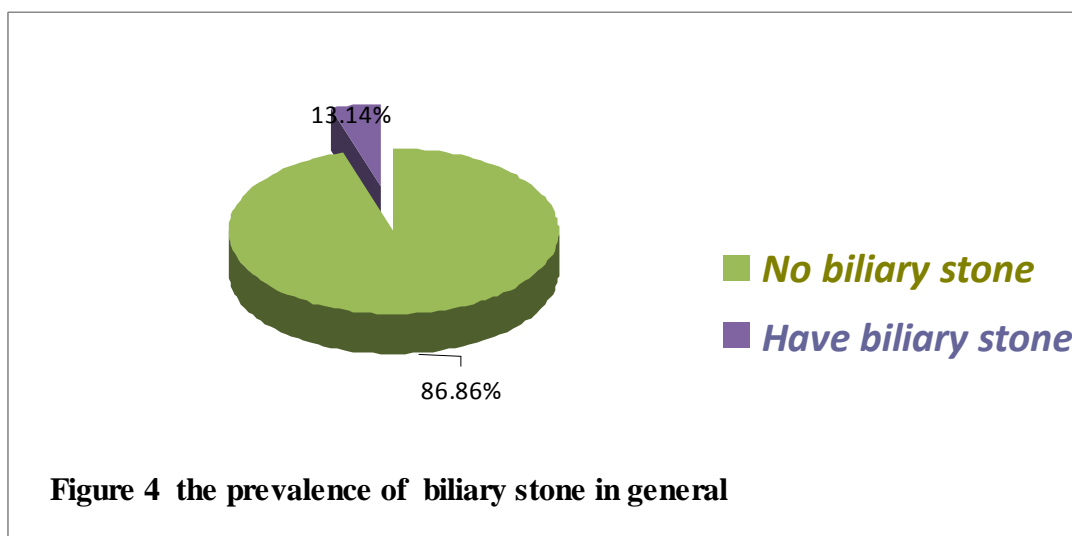


Table -1- Show the prevalence of biliary stone in different thyroid status in patient

THYROID STATUS	NO.OF PATIENT	HAVE STONE	HAVE NO STONE	P Value
EUTHYROID	134 (56.78%)	14 (10.45%)	120 (89.55%)	0.05<P<0.2
HYPOTHYROID	38 (16.1)	15 (39.47%)	23 (60.53%)	P<0.05
HYPERTHYROID	64 (27.2)	2 (3.125%)	62 (96.875%)	P>0.2
total	236 (100%)	31 (13.14%)	205 (86.86%)	P>0.2

Discussion:-

The pathophysiology of gall stone formation includes abnormalities in biliary flow and sphincter of Oddi function.⁽⁶⁾ Biliary stasis due to any cause is an important pathophysiological mechanism for choledocholithiasis.⁽⁷⁾

Defect in motor activity of the gall bladder are thought to play a role in cholesterol nucleation and gall Stone formation gallbladder filling is facilitated by tonic contraction of sphincter of Oddi, which create a pressure gradient between the bile ducts and the gallbladder. In response to a meal, the gallbladder empties by a coordinated motor response of gallbladder contraction with sphincter of Oddi relaxation .Hormonal and neural pathways are involve in the coordination of the gallbladder with the sphincter of Oddi .⁽²⁾

Regarding age factor and thyroid status: All patients with thyroid disorders in our study are in the age group between 20-49 years. This is comparable to what is reported, women between the ages of 20 and 40 years are most commonly affected.⁽¹⁾

Regarding gender factor and thyroid status: our study show that the prevalence of thyroid disorders whether euthyroid, hypothyroid or hyperthyroid is 5 times more in female than in male and this is comparable to the result of other studies.

Our study shows that euthyroid status with thyroid nodule or goiter 6 times more common in female than male.

Also our study reveal that hypothyroid condition 4 times more common in female than male, this is similar to what is reported, In adults, spontaneous hypothyroidism is usually manifested in females (80%) ⁽¹⁾. Other studies show that the prevalence of hypothyroidism (clinical plus subclinical) among women older than 60 years may be as high as 20 % ⁽⁸⁾.

Hyperthyroid status 5 times more common in female than in male in this study, this is comparable to what is reported, Graves' disease, which is the most common cause of hyperthyroidism ^(1,2), accounting for 60 to 80% of cases ⁽²⁾, with female to male ratio (5:1). ⁽²⁾

Regarding biliary stone and thyroid status factor: Our study show that the prevalence of biliary stone disease in general (whether euthyroid, hypothyroid or hyperthyroid) is 13.14%, this prevalence is similar to what is reported, where healthy people have a prevalence of 11% to 36% in autopsy reports. ^(1, 2) All patients with biliary stone in our study are female patients and this is comparable to the result of previous studies which show that women are 3 time more likely to develop gall stone than man. ⁽²⁾

Our study show that the prevalence of biliary stone in euthyroid patients is 10.45% and this is comparable to the result of other studies while the prevalence of biliary stone in hypothyroid patients is 39.47% with P value <0.05 i.e. the prevalence is about 4 times more common in hypothyroid patients compared to euthyroid patients, this result comparable to the result of previous studies which showed that the incidence of cholelithiasis and choledocholithiasis are increased in patient with hypothyroidism. ⁽⁹⁾

This is may be due to two possibilities:

1:-delayed biliary flow that occurs in hypothyroid condition. Previous studies showed that hypothyroidism is associated with delayed biliary flow in both human study ⁽¹⁰⁾ and in animal study. ⁽¹¹⁾ The delayed biliary flow may be attributed to the loss of the pre-relaxation effect of thyroxin on the sphincter of Oddi that occur in hypothyroidism. Thyroid hormones receptors have been shown to be expressed in the sphincter of Oddi and in patient with hypothyroidism the incidence of common bile duct stone increase due to loss of thyroid relaxation action. ⁽¹²⁾ Previous studies showed that hypothyroidism associated with choledocholithiasis relatively more than cholelithiasis ^(7,13) possibly due to dysfunction of sphincter of Oddi rather than change in the lipid metabolism or biliary flow.

2:-The increased prevalence of biliary stone in hypothyroid patients in our study can also be explained by the elevated serum cholesterol level that occur in hypothyroidism, which shown to be a factor that influence the bile solubility. ⁽¹⁴⁾ Cholesterol supersaturation in bile is an important step in the pathogenesis of cholesterol gall stone formation. ^(1,3,4,5). Hypothyroidism is the most common secondary cause of hypercholesterolemia, patients with hypothyroidism have serum level of cholesterol approximately 50% higher than level in euthyroid patient, and 90% of all hypothyroid patient have elevated cholesterol level. ⁽¹⁵⁾ In previous studies a trial was used to dissolve gall stone by using thyroxin. ⁽⁹⁾ however, animal trial showed that thyroxin usage reduce the weight of gall stone but not dissolve it. ⁽¹⁶⁾

Previous study shows a gender specific relation between hypothyroid and cholelithiasis, especially males with gall stones should be further examined for thyroid disorders. ⁽¹⁷⁾

However our study show that all hypothyroid patients with biliary stone are female patients and this is comparable to the result of other studies which show that women are

3 time more likely to develop gall stone than man.⁽²⁾ However the number of patients with hypothyroidism in our study is relatively low which affect the prevalence of biliary stone disease.

Another important result that the ultrasound of abdomen of patients with hyperthyroidism in our study (64 patients) revealed that only 2 patients (3.125%) have biliary stone (low prevalence), although most of patients with hyperthyroidism in our study (53 patients) were females who are more likely to be affected by gall stone disease. This might be explained by the pro-relaxation effect of thyroxine on sphincter of Oddi, which will aid the biliary flow. Previous animal study showed that hyperthyroidism is associated with enhanced biliary flow.⁽¹¹⁾

It is important to note that gall stone disease and thyroid dysfunction are more common in female and both occur in approximately similar age group.

Thyroid hormones are known to have an enterohepatic circulation^(18,19) and estrogen (estradiol, estrone, and estriol) also have enterohepatic circulation⁽³⁾, both hormones are conjugated in the liver and converted to form sulfate and glucuronides conjugates, these conjugates enter the bile, some of these conjugates are reabsorbed.

Previous studies show that the prevalence of hypothyroidism (clinical plus subclinical) among women older than 60 years may be as high as 20%.⁽⁸⁾ The incidence of gall stone increases with age.⁽³⁾ So biliary stone formation might be due to relative changes in the level of thyroid hormone and estrogen during the aging process.

Conclusion:-

1:-The prevalence of biliary stone disease is more common in hypothyroid patients compared to euthyroid patients (4 times) while the prevalence of biliary stone in hyperthyroidism, even in high risk group for cholelithiasis (female gender, fair, fertile, forty or fifty years old, and others) is very low.

2:-The prevalence of biliary stone disease increases with the decreasing level of thyroid hormone.

Recommendation:-

Evaluation of use thyroxine in adjusted physiological doses to prevent occurrence of gallstone disease in high risk group for cholelithiasis (keeping in mind that the process of cholelithiasis starts at early age and needs time to present with gallstone formation).

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