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Association of cholelithiasis with hypothyroidism

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Abstract
Hypothyroidism causes dyslipidemia and stasis of bile and sphincter of oddi dysfunction causing cholelithiasis and choledocholithiasis. Therefore patients with hypothyroidism should be screened for gall stones which can be managed prior to development of complications. A case control study was done comparing 110 cases and 110 controls were sampled. A significant portion of cases were diagnosed with subclinical hypothyroidism. With an odds ratio of 14.3. Female sex, age greater than 50 years, obesity, dyslipidemia, non-vegetarian diet were also significant risk factors for cholelithiasis. The bile leak and need for drain placement was found to be higher in hypothyroid patients as compared to euthyroid patients undergoing laparoscopic cholecystectomy.

Keywords: hypothyroidism, cholelithiasis, pathophysiology, laparoscopic cholecystectomy, case control study

Introduction
The highest incidence rates of cholelithiasis in the world are 21.5/100 000 in females in Delhi [1]. The disease frequently occurs in young to middle aged, otherwise healthy people with a prevalence of 11-36 % on autopsy report. The prevalence of hypothyroidism in India is 10.95%. [2].

Despite a significant percentage of cases being asymptomatic, gallstone disease adds substantially to health care costs and manpower, and its complications are sometimes life threatening.

According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid diseases [3]. The prevalence differs not only between countries but also between ethnic groups. Age and gender also influence the prevalence of gallstone disease.

The aim of this study to evaluate the association of hypothyroidism and cholelithiasis and complications associated with laparoscopic cholecystectomy

Materials and Methods
A case control study was done in JSS hospital Mysuru. It included analysis of 110 cases and 110 controls

Inclusion criteria
Patients between age 18-72 years of age admitted to the department of general surgery

Exclusion criteria
Pregnancy
Known cases of haematological disorders
Patient on drugs causing hypothyroidism: Amiodarone, Lithium, antidepressants, Phenytoin, Interferon, Imatinib
Patient on drugs causing gallstones: Estrogen, Fenofibrate, Gemfibrozil.
Patients who do not give consent to participate in the study

Primary objective
To determine the association between hypothyroidism and cholelithiasis.

Secondary objectives

- Demographic study
- Anthropometric data
- Post-operative complications of laparoscopic cholecystectomy

Case group included 110 patients ultrasound proven cholelithiasis undergoing laparoscopic cholecystectomy, clinically euthyroid / undiagnosed hypothyroidism
Control group -110 Patients with no ultrasonographic evidence of cholelithiasis, clinically euthyroid/undiagnosed hypothyroidism

Measurement of exposure

Hypothyroidism was defined as >10, sublinical hypothyroidism defined as TSH 5-10, euthyroidism TSH < 5.
Study duration: 18 months

Data Analysis

A validated proforma will be filled by the principal investigator which will include demographic and anthropometric data such as diet, BMI and medical history, drug history and hypothyroid symptoms for each participant in the study.
Morning fasting blood samples will be sent to the Department of Biochemistry for Thyroid profile and Lipid profile. The values of the test will be entered into the data sheet.

The collected data will be analyzed by the following statistical methods

Summary statistics - by mean, standard deviation and proportion.
Inferential statistics - by Chi square test, Independent T test, Odds Radio with 95 % confidence interval.
Software used: SPSS 21.0
Study setting and method of collection of data

Results

This case control study compared 110 patients with cholelithiasis and 110 controls without cholelithiasis.
Details were recorded in performas after obtaining due consent and analysis was performed. P value of less than 0.05 was considered significant

Descriptive statistics

Age distribution of the study

- Mean age in the case group was 48 years and mean age in control group was 51 years with standard deviation of 13and 18 respectively
- Maximum age distribution was found to be in 51-60 year age group for cases and 61-70 years age group for controls.

Table 1: Descriptive statistics age as a riskfactor for cholelithiasis and hypothyroidism

		Group			
		Case		Control	
		Count	Column N %	Count	Column N %
Age group in yr	<30	14	12.7%	18	16.4%
	31-40	20	18.2%	15	13.6%
	41-50	23	20.9%	18	16.4%
	51-60	34	30.9%	17	15.5%
	61-70	13	11.8%	24	21.8%
	>71	6	5.5%	18	16.4%
	Total	110	100.0%	110	100.0%

Study of sex distribution in study

Total number of females in case group was 68 (61.8%) and males was 42 (38.2%).
Total number of females in control group was 39 (35.5%) and males was 71 (64.5%).Males were statistically higher in the control group P=0.005

Table 2: Sex distribution in the study

Gender	Group			
	Case		Control	
	Count	Colum N %	Count	Column N %
Female	68	61.8%	39	35.5%
Male	42	38.2%	71	64.5%

P<0.001, Chi square test

Study of BMI Affecting Cholelithiasis

- The mean BMI in cases was 28.1 and in controls was 22.5. Raised BMI was found to be statistically associated with cholelithiasis
- Among the cases, 52 % of the hypothyroid cases were obese and 50 % of euthyroid cases were obese with BMI 25-30
- 66.7 % of the controls had normal BMI
- Among the controls, 8.4 % of hypothyroid cases were and 8.4 % of the euthyroid controls were obese.

Table 3: Association of BMI with of cholelithiasis, hypothyroidism

BMI kg/m2	Group							
	Case				Control			
	Thyroid abnormality				Thyroid abnormality			
	Normal		Hypothyroidism		Normal		Hypothyroidism	
	Count	Column N %	Count	Column N %	Count	Column N %	Count	Column N %
Underweight (<18.5 kg/m2)	0	.0%	0	.0%	17	15.9%	0	.0%
Normal (18.6-23kg/m2)	7	11.7%	2	4.0%	58	54.2%	2	66.7%
overweight (23.1-25 kg.m2)	7	11.7%	6	12.0%	19	17.8%	0	.0%
Obese(25.1-30 kg/m2)	30	50.0%	26	52.0%	9	8.4%	1	33.3%
Morbid obese (>30 kg/m2)	16	26.7%	16	32.0%	4	3.7%	0	.0%
p	0.5				0.5			

Primary Objective: Association of Cholelithiasis and Hypothyroidism

- Mean T3, T4, TSH were 82.12, 6.85, 10.45 among cases and 38.98,7.89 and 1.31 among controls suggesting significant association of cholelithiasis and hypothyroidism
- Among cases, 54.5 % were euthyroid, 21.8 % were subclinical hypothyroidism and 23.4 % were hypothyroid
- Among controls, 97.3 % were euthyroid, 2.7 % had subclinical hypothyroidism and 0 % had clinical hypothyroidism
- Thus with a p value of < 0.0001 there was significant proportion of cases with hypothyroidism compared to controls

Table 4: Distribution of thyroid disease among cases and controls

		Group					
		Case		Control			
		Count	**Column N %**	**Count**	**Column N %**	**OR**	**p**
Thyroid	Normal	60	54.5%	107	97.3%		<0.0001
	Subclinical hypothyroidism	24	21.8%	3	2.7%	14.3(4.1-49.3)	
	Clinical Hypothyroidism	26	23.6%	0	.0%	-	
Thyroid abnormality	Normal	60	54.5%	107	97.3%	29.7(8.9-99.4)	<0.0001
	Hypothyroidism	50	45.5%	3	2.7%		

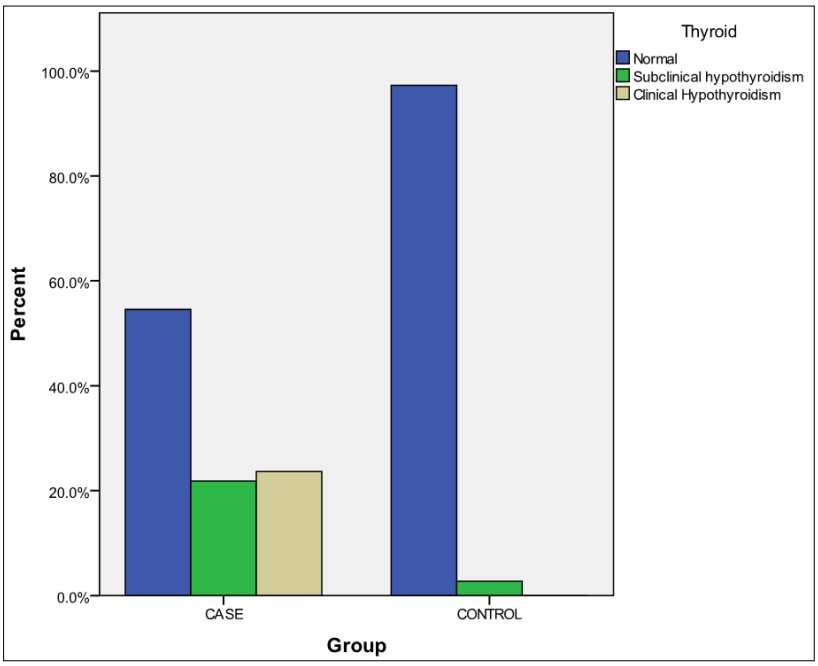

Fig 1: Distribution of Hypothyroidism

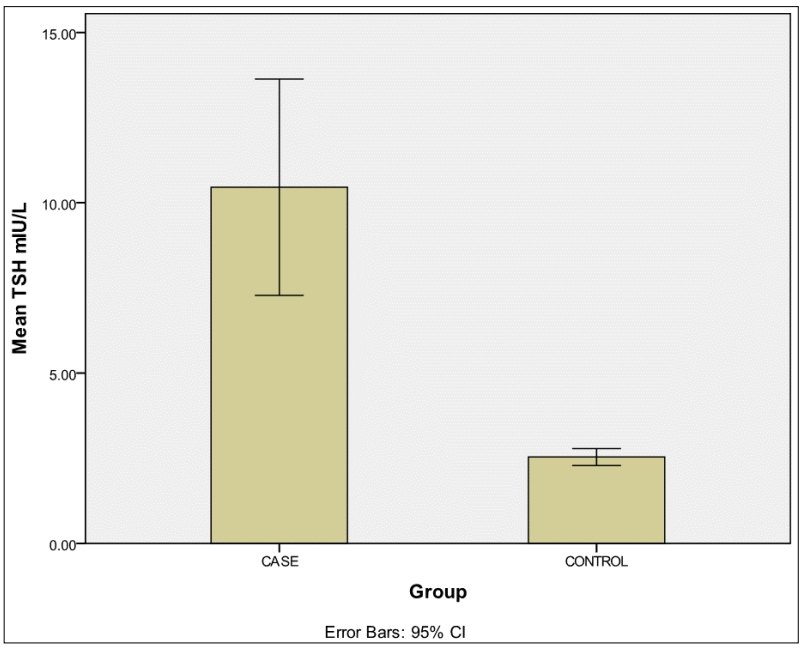

Fig 2: Study of TSH among cases and controls

Study of USG findings in the study

- Among cases 4.5% cases had acute calculous cholecystitis, 64.5 % had cholelithiasis, 22.7 % had chronic calculous cholecystitis, 5% cases had cholelithiasis with choledocholithiasis, 0.9 % cases had choledocholithiasis with chronic calculous cholecystitis, 0.9 % cases had mucocele.

Table 5: USG findings among cases and controls

Diagnosis	Group			
	Case		Control	
	Count	Column N %	Count	Column N %
ascites	0	.0%	13	11.8%
Acute calculous cholecystitis	7	4.5%	0	.0%
Fatty liver	0	.0%	4	3.6%
Blunt trauma abdomen	0	.0%	1	.9%
Cholelithiasis	71	64.5%	0	.0%
Cholelithiasis choledocholithiasis	5	4.5%	0	.0%
Chronic calculous cholecystitis	25	22.7%	0	.0%
Chronic calculous cholecystitis with choledocholithiasis	1	.9%	0	.0%
Subacute intestinal obstruction	0	.0%	1	.9%
Medical renal disease	0	.0%	1	.9%
Polycystic ovarian disease	0	.0%	2	1.8%
Cystitis	0	.0%	1	.9%
Empyema gb	1	.9%	0	.0%
Hepatomegaly	0	.0%	9	8.2%
Hernia	0	.0%	2	1.8%
Splenomegaly	0	.0%	1	.9%
Mucocele + calculous cholecystitis	1	.9%	0	.0%
Normal study	0	.0%	69	62.7%
hepatosplenomegaly	0	.0%	1	.9%
Polycystic kidney disease	0	.0%	3	2.7%
Uterine fibroid	0	.0%	1	.9%
Renal cyst	0	.0%	1	.9%

Study of hospital stay among cases

- 61.8 % cases undergoing laparoscopic cholecystectomy had a mean hospital stay of less than 7 days
- 38.2 % cases had a mean hospital day of > 7 days

Table 6: Duration of hospital stay among cases

		Count	Column N %
Hospital stay	<7 days	68	61.8%
	>7 days	42	38.2%
	Total	110	100.0%

Study of drain placement among cases

- 50.9% patients had a tube drain placed in the gall bladder bed.
- 49.1 % patients did not require drain placement
- Bile leak intraoperatively was documented in 53.6 % cases
- There was no bile leak in 46.4 % cases
- Mucocele was observed intraoperatively in 0.9 % cases.
- Placement of drain in gall bladder bed was required in 62.5% of hypothyroid patients undergoing laparoscopic cholecystectomy as compared to 37.5% of euthyroid cases
- The incidence of bile leak was 37.3% in euthyroid cases as compared to 62.7% cases undergoing laparoscopic cholecystectomy
- The mean hospital stay was not found to differ significantly between cases with hypothyroidism and euthyroidism p value 0.9%

Table 7: Study of drain placement, bile leak, mucocele

		Count	Column N %
Drain	No	54	49.1%
	Yes	56	50.9%
Leak	No	59	53.6%
	Yes	51	46.4%
Mucocele	No	109	99.1%
	Yes	1	.9%

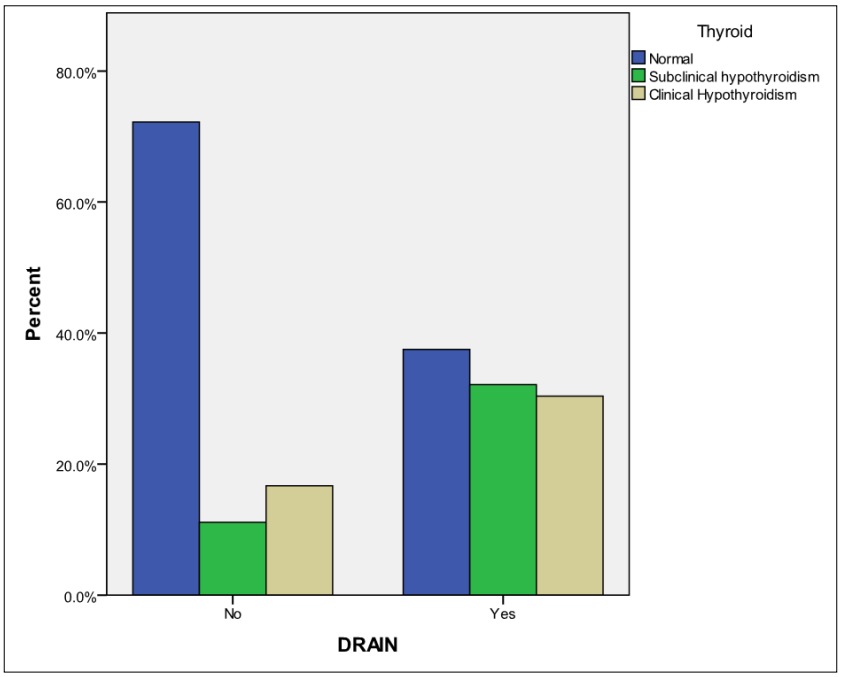

Fig 3: Study of drain placement among cases

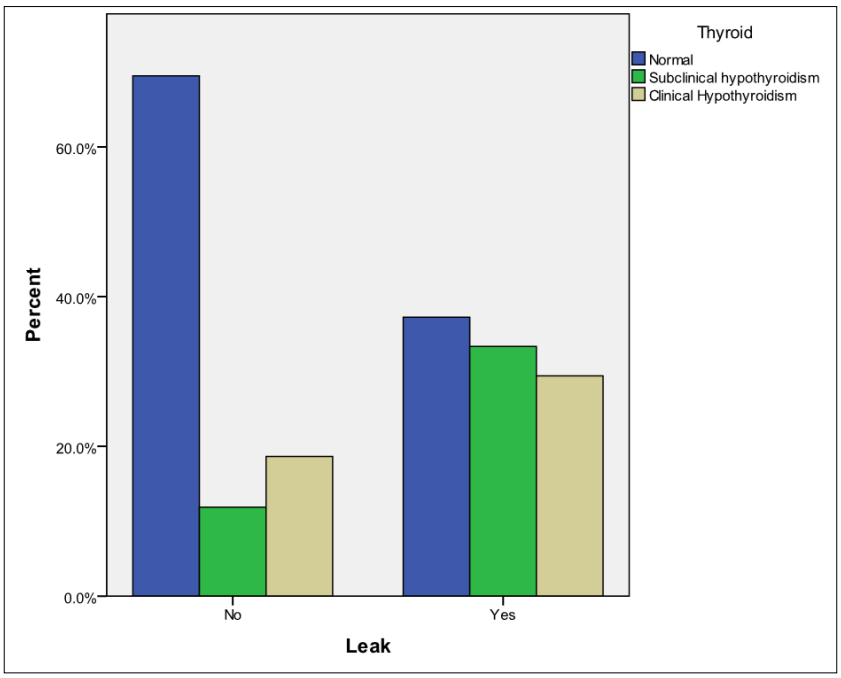

Fig 4: Study of intraoperative bile leak

Table 14: Analysis of drain placement, intraoperative bile leak, number of calculi, hospital in hypothyroid and euthyroid cases undergoing laparoscopic cholecystectomy

		Thyroid						
		Normal		Subclinical hypothyroidism		Clinical Hypothyroidism		
		Count	Row N %	Count	Row N %	Count	Row N %	p
DRAIN	No	39	72.2%	6	11.1%	9	16.7%	0.001
	Yes	21	37.5%	18	32.1%	17	30.4%	
Leak	No	41	69.5%	7	11.9%	11	18.6%	0.002
	Yes	19	37.3%	17	33.3%	15	29.4%	
No calculi	MULTIPLE	47	52.2%	19	21.1%	24	26.7%	0.3
	SINGLE	13	65.0%	5	25.0%	2	10.0%	
Hospital stay	<7 days	37	54.4%	15	22.1%	16	23.5%	0.9
	>7 days	23	54.8%	9	21.4%	10	23.8%	

Study of number of gall bladder calculi on USG

- 81.8 % cases had multiple gall bladder calculi
- 18.2 % cases had solitary calculi on USG

Table 8: Study of number of gall bladder calculi

No of calculi	Count	Column N %
Multiple	90	81.8%
Single	20	18.2%
Total	110	100

Table 9: Study of largest size of gall bladder calculi

		Largest size mm			
		Count	Mean	SD	p
Thyroid abnormality	Normal	60	8.72	3.11	0.2
	Hypothyroidism	50	7.86	2.56	
Thyroid	Normal	60	8.72	3.11	
	Subclinical hypothyroidism	24	7.58	2.69	0.24
	Clinical Hypothyroidism	26	8.12	2.45	

One way ANOVA, independent t test

Study of comorbidities among cases and control

- 17.3 % Cases had hypertension, 15. 5 % cases were diabetic and 0.9 % cases had ischemic heart disease
- Among controls 21.8 % had hypertension, 15. 5 % had type II diabetes mellitus and 2.7 % had ischaemic heart disease

Table 10: Study of combordities in cases and controls

		Group				
		Case		Control		
		Count	Column N %	Count	Column N %	p
IHD	NO	109	99.1%	107	97.3%	0.3
	YES	1	.9%	3	2.7%	
HTN	NO	91	82.7%	86	78.2%	0.4
	YES	19	17.3%	24	21.8%	
DM	NO	93	84.5%	93	84.5%	NA
	YES	17	15.5%	17	15.5%	

Study of diet among cases and controls

- 79.1 % cases were non vegetarian and 20.9 % cases were vegetarian
- 60.4 % controls were non vegetarian and 40 % were vegetarian

Table 11: Study of diet

		Group			
		Case		Control	
		Count	Column N %	Count	Column N %
Diet	NON	87	79.1%	66	60.0%
	VEG	23	20.9%	44	40.0%

P=0.002, OR – 2.52(1.4-4.5)

Study of symptoms of cholelithiasis and hypothyroidism in cases

- The most common symptom of cholelithiasis was biliary colic which was present in 97.3 % cases
- Vomiting was present in 35.5 % of cases, jaundice was present in 3.6 % cases, fever present in 3.6 % cases
- 2.7 % patients had symptoms of hypothyroidism and 1.8 % cases had a goitre at presentation.

Study of prior Ercp/pancreatitis prior to laparoscopic cholecystectomy

- 5.5 % cases underwent ERCP prior to laparoscopic cholecystectomy
- 8.2 % cases had an episode of acute biliary pancreatitis prior to interval laparoscopic cholecystectomy

Table 12: Study of presenting symptoms amongst cases

	Count	Column N %
Pain abdomen	107	97.3%
Vomiting	39	35.5%
Fever	4	3.6%
Jaundice	4	3.6%
Hypothyroid	3	2.7%
Goitre	2	1.8%

Table 13: Ercp / pancreatitis prior to laparoscopic cholecystectomy

		Count	Column N %
ERCP	No	104	94.5%
	Yes	6	5.5%
Pancreatitis	No	101	91.8%

Discussion

This study tests the association of hypothyroidism with cholelithiasis by analysis of cases and controls. In the case group Female gender was a significant risk factor for gall stones. The age group 51-60 years was the most common age of presentation of gall stones.

Obesity (BMI 25-30) was a significant risk factor for gall stones in this study.

Analysis of comorbidities revealed 17.3 % Cases had hypertension, 15. 5 % cases were diabetic and 0.9 % cases had ischemic heart disease. Among controls 21.8 % had hypertension, 15. 5 % had type II diabetes mellitus and 2.7 % had ischaemic heart disease. Thus comorbidities were not found to affect the formation of gallstones.

87 cases consumed a mixed diet while 23 cases consumed a vegetarian diet. In the control arm 66 patients consumed a mixed diet while 44 cases consumed a vegetarian diet. This observation was statistically significant as consumption of a non vegetarian diet leads to higher lipid content in blood and early onset of fatty liver thus causing supersaturation of bile with lipids which would lead to gall bladder sludge and cholelithiasis.

Mean value of T3, T4, TSH were 82.12, 6.85, 10.45 among cases and 38.98,7.89 and 1.31 among controls suggesting significant association of cholelithiasis and hypothyroidism

Among cases, 54.5 % were euthyroid, 21.8 % were subclinical hypothyroidism and 23.4 % were hypothyroid. Among controls, 97.3 % were euthyroid, 2.7 % had subclinical hypothyroidism and 0 % had clinical hypothyroidism. Thus with a p value of < 0.0001 there was significant proportion of cases with hypothyroidism compared to controls. The odds ratio for hypothyroidism 29.7. To conclude, patients with hypothyroidism were 30 times more likely to develop cholelithiasis as compared to the euthyroid population.

Results of a cross sectional study done in Bhadgad [4] in 2015 examined 103 cases of cholelithiasis stated 8 out of 103 that is 7.8% had subclinical hypothyroidism.

Analysis of ultrasonographic findings suggested thre was no correlation between thyroid profile and number or size of stones.

The most common symptom of cholelithiasis was biliary colic which was present in 97.3 % cases. Vomiting was present in 35.5 % of cases, jaundice was present in 3.6 % cases, fever present in 3.6 % cases. 2.7 % patients had symptoms of hypothyroidism and 1.8 % cases had a goitre at presentation.

50.9% patients had a tube drain placed in the gall bladder bed. 49.1 % patients did not require drain placement. Bile leak intraoperatively was documented in 53.6 % cases. There was no bile leak in 46.4 % cases. Mucocele was observed intraoperatively in 0.9 % cases.

Placement of drain in gall bladder bed was required in 62.5% of

hypothyroid patients undergoing laparoscopic cholecystectomy as compared to 37.5% of euthyroid cases. The incidence of bile leak was 37.3% in euthyroid cases as compared to 62.7% cases undergoing laparoscopic cholecystectomy

The mean hospital stay was not found to differ significantly between cases with hypothyroidism and euthyroidism p value 0.9%.

This study concludes that hypothyroidism impacts cholelithiasis with an odds ratio of 29, followed by age, female sex, obesity. The theories that suggest the role of hypothyroidism causing bile stasis and cholelithiasis have been proven. Intraoperative bile leak and need for drain placement was also higher in the hypothyroid group as compared to euthyroid. Thus early detection and treatment of hypothyroidism could prevent cholelithiasis.

Conclusion

The study was aimed at determination of the association between hypothyroidism and cholelithiasis. Results state that subclinical hypothyroid/ hypothyroid patient were 29 times more likely to develop cholelithiasis as compared to euthyroid population. Upon comparison with previous studies, this study reaffirms that hypothyroidism is a significant risk factor for cholelithiasis. Other risk factors determined by the study included female gender, age 51-60, non vegetarian diet, BMI (25-30).

Further prospective studies to determine the role of thyroxine supplementation in subclinical hypothyroid patients and long term follow up to determine formation of gall stones are necessary.

Recommendations from this study in the management of hypothyroidism and cholelithiasis include:

TSH screening for patients admitted with gall stones.

Thyroxine supplementation for subclinical hypothyroidism to prevent gall stones

Obese, female, hypothyroid/subclinical hypothyroid patients, consuming non vegetarian diets should undergo a routine ultrasonogram to rule out cholelithiasis and plan early laparoscopic cholecystectomy.

3.12 References

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