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Low thyroid profile (hypothyroidism) a potential risk factor in a series of cases of gall stone disease

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Abstract

Background: The most common biliary pathology is Gallstones. They are of three types: 1) Cholesterol 2) Pigment (black, brown) 3) Mixed. A lot of studies are done to find out the risk factors for Gallstone disease. Nucleation of cholesterol monohydrate crystals from multilamellar vesicles is a crucial step in Gallstone Formation. (3) There is possibility of relation between hypo thyroidism and GSD as thyroid failure causes disturbances in lipid meta bolisim. If an increased prevalence of thyroid disorders will be found, it might have an effect on the diagnostic and therapeutic workup of patients withGSD.

Methodology: Prior permission and approval from the ethics committee will be obtained and an informed and written consent to participate in the study will be taken from all the patients. Demographic data of each patient will be recorded including relevant clinical examination findings, Blood investigations and findings of radio logical imaging.

Results: In our study it was observed that among cases 83 (70.3%) patients while in controls 111 (94.1%) patients presented with normal thyroid function. Sub clinical hypothyroidism was seen in 27 (22.9%) cases while among controls 4(3.4%) subjects. 8(6.8%) cases and 2 (1.7%) controls presented with overt hypo thyroi dism.

Conclusion: It is evident that subclinical hypothyroidism is associated with Gallstones and is also associated with hyper lipidemia. So, while treating patients with Gall stone disease, clinici ans should be aware of possibility of hypothyroid background and consider examining the thyroid function.

Keywords: GSD, Cholesterol, Gall bladder.

Introduction

Gallstones are closely associated to the spectra of acute biliary diseases and acute cholecystitis, acute cholangitis and biliary colic gallstone pancreatitis, are examples of typical symptomatic gallstone diseases stones are the most prevalent biliary pathology and can be divided into Cholesterol, pigment (black, brown), and mixed stones. The size of the gallstones can range from a pea to a golf ball, and they can appear in any quantity and size. [1]

They are more prevalent in women, the elderly and overweight individuals. Twenty percent of Americans over the age of 65 havegallstones, yet the majority never develop any symptoms. If symptomatic gallstones are left untreated, gallstone consequences can be severe. Gall stones continue to be a global health hazard affecting millions of people.[2]

In the Europe and United States, 80 percent of the gallstones are either mixed or cholesterol stone while in Asian population, in 80 percent of the stones are pigmented. Cholesterol or mixed stones are made up of 51–99% cholesterol together with bile pigment, bile acids, and phospholipids. Gallstones can be multiple or solitary, small or large. They are radiopaque if they include calcium salts. Single stones are unusual, but typically contain mostly cholesterol and form as a result of a disturbance in the physio-chemical equilibrium in bile, which normally keeps cholesterol in micellar form in bile.[3]

During fasting, the gallbladder accumulates and con centrates bile. After gastric emptying, especially after a heavy meal, the gallbladder contracts and the sphincter of Oddi relaxes at the same time, causing concentrated bile to flow out and mix with food in the duodenum. Super saturation of cholesterol in bile, nucleation and growth of crystals in the gallbladder, and gallbladder dysmotility leadingin delayed emptying are important contributors in the formation of cholesterol stones[4].

Gallstones are believed to be caused by a combination of factors such as obesity, heredity, and the motility of gallbladder. Other factors include increasing age, female gender and ethnicity. [5]

In the past decade, the role of thyroid problems in gallstone disease has been a subject of controversy. Hypothyroidism causes an increase in cholesterol production, whereas hyperthyroidism causes a decrease. Some researchers have demo nstrated an increased frequ ency of hypo thyroidism in cholelithiasis, while others have shown contradictory findings. The con nection between thyroid problems and the formation of gall stones remains uncertain.[6]

It is believed that various factors are responsible for the formation of gallstones in hypothyroidism, such as :

- Decreased cholesterol metabolism in the liver.
- Decreased bile secretion by the liver
- Reduced bile flow into the duodenum
- Impaired relaxation of the oddi sphincter[7,8].

Cholesterol metabolism is affected by hypothyroidism at various levels. It is believed to increase the serum cholesterol levels and supersaturates the bile with cholesterol thus leading to reduced contractility, motility, and filling of gall bladder resulting in extended stay of bile.

This leads to retention of cholesterol crystals, giving them enough time to enucleate and mature into gall stones. The clearance ofprecipitates from the gall bladder and biliary system is also impaired by a delayed hilum-duodenum transit time.

Multiple disorders, including sphincter of oddi dys kinesia, strictures and stenosis of the bile duct, can

induce biliary stasis. Thyroxine has a β1 and β2 receptor mediated prorelaxing action on sphincter of oddi motility at physiological levels of serum T4. Therefore, decreasing serum thyroxine levels affect the normal motility of the sphincter of oddi, causing its contractility. Other than biliary stasis, a diminished prorekaxing impact on the sphincter of oddi, an increase in cholesterol burden, and a delay in hepatocyte clearance shift the balance toward gallstone formation.[9]

Material and methods

Following Protocol for patients was followed

Detailed history

1. Complete clinical examination
2. Complete Blood Count, Renal Function Test, Liver FunctionTest, Serum Electrolytes, Random Blood Sugar.
3. Chest Radiograph, ECG.
4. USG abdomen and pelvis.
5. Thyroid Function Test (Free T3, T4, TSH).

Study Design

The study was of Case Control Type. It is a hospital based study where two groups were formed, patients diagnosed as gallstone disease and subjected to elective cholecystectomies (CASES) and patients admitted for other diseases (CONTROL). Subsequent evaluation was done with emphasis on thyroid profile.

Study Site

This study was conducted in Shri Vinoba Bhave Civil Hospital, Silvassa, UT of DNH

Study Population

118 patients with clinically and radiologically proven gallstone disease were included with inclusion and exclusion criteria as mentioned below.

Inclusion criteria

Cases

1) Patients in age group of 18 to 70 years.
2) Patients with clinically and radiologically proven gallstonedisease were included.

Control

The control group was matched for age and sex and consisted of: Patients with no history of cholelithiasis, liver diseases where there was elevation of serum bilirubin or liver enzymes and admitted for other diseases needing USG abdomen and pelvis.

Exclusion criteria

For cases and control

1) Hemolytic Anemia
2) Hormone replacement therapy
3) Diabetes Mellitus
4) Pregnancy
5) Previous Cholecystectomy
6) Thyroidectomy
7) Choledocholithiasis
8) Acute Cholecystitis
9) Liver or renal failure
10) Those prescribed medications known to affect the thyroid function test such as Phenytoin, Carbamazepine, Meto clopromide, Amiodarone and Lithium.

Fasting Blood samples of both Cases and Controls was taken and thyroid function were assessed. Prevalence of Hypothyroidism in both Cases and Controls were assessed and a Case Control Study was done.

Investigations

1) USG abdomen/CECT Abdo pelvis/MRCP
2) Free T3,T4 and TSH.

Results

Table 1 shows the distribution of subjects according to age. The age among cases and control was comparable as no significant difference was seen between both the group. (p>0.88)

Table 1: Distribution of subjects according to age.

Age groups	Cases		Control		Total		Chi square	p- value
	n	%	n	%	n	%		
≤30	9	7.60%	13	11.00%	22	9.30%	1.17	0.88
31-40	40	33.90%	41	34.70%	81	34.30%		
41-50	40	33.90%	39	33.10%	79	33.50%		
51-60	21	17.80%	17	14.40%	38	16.10%		
>60	8	6.80%	8	6.80%	16	6.80%		
Total	118	100.00%	118	100.00%	236	100.00%		

Figure 1: Distribution of subjects according to age.

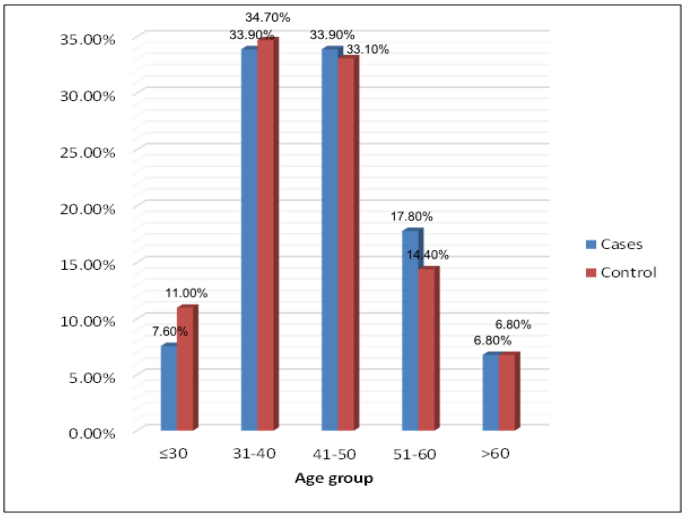


Table 2: Distribution of subjects according to gender

Gender	Cases		Control		Total		Chi square	p-value
	n	%	N	%	n	%		
Female	88	74.6%	84	71.2%	172	72.9%	0.34	0.55
Male	30	25.4%	34	28.8%	64	27.1%		
Total	118	100.0%	118	100.0%	236	100.0%		

Table 2 shows the distribution of subjects according to gender. No significant differences were obtained between two groups.

It was observed that in the study population females predominated then males with males with females being approximately 3 times than the males.

Figure 2: Distribution of subjects according to gender.

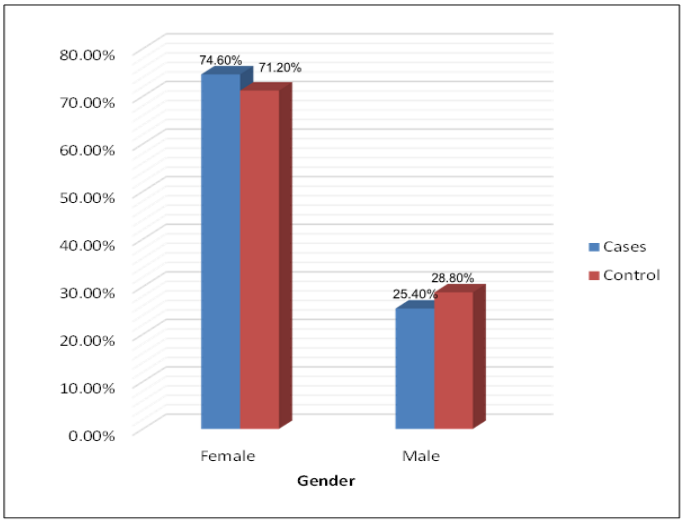


Table 3: Distribution of subjects according to lipid profile.

Variables	Groups	Cases		Control			P-Value
		n	%	n	%	chi square	
Total cholesterol	Normal(≤200mg/dl)	28	23.7%	54	45.8%	12.2%	<.001**
	High(>200mg/dl)	90	76.3%	64	54.2%		
LDL	Normal (<130)	20	16.9%	79	66.9%	60.5	<.001**
	High (≥130)	98	83.1%	39	33.1%		
TGL	Normal (≤150)	67	56.8%	88	74.6%	8.2	0.004*
	High (>150)	51	43.2%	30	25.4%		
HDL	Normal (<=40)	41	34.7%	42	35.6%	0.019	0.89
	High (>40)	77	65.3%	76	64.4%		

** Highly significant, * Significant

Above table shows that total cholesterol, LDL and Triglycerides (TGL) were significantly more in patients with gall bladder stones while no significant difference wasseen in HDL .

Figure 3: Distribution of subjects according to lipid profile.

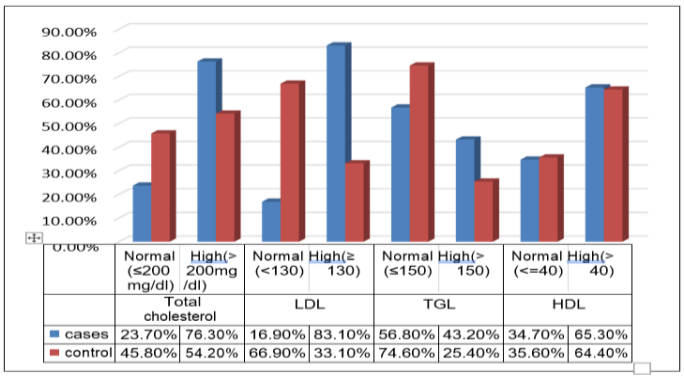


Table 4: Distribution of subjects according to abnormal thyroidfunction.

Thyroidfunction	Cases		Control		Total		Chi square	p- value
	n	%	n	%	n	%		
Normal thyroid function	83	70.30%	111	94.10%	194	82.20%	25.5	<.001
bnormalthyroid function	35	29.70%	7	5.90%	42	17.80%		
Total	118	100.00%	118	100.00%	236	100.00%		

Figure 4: Distribution of subjects according to abnormal thyroidfunction

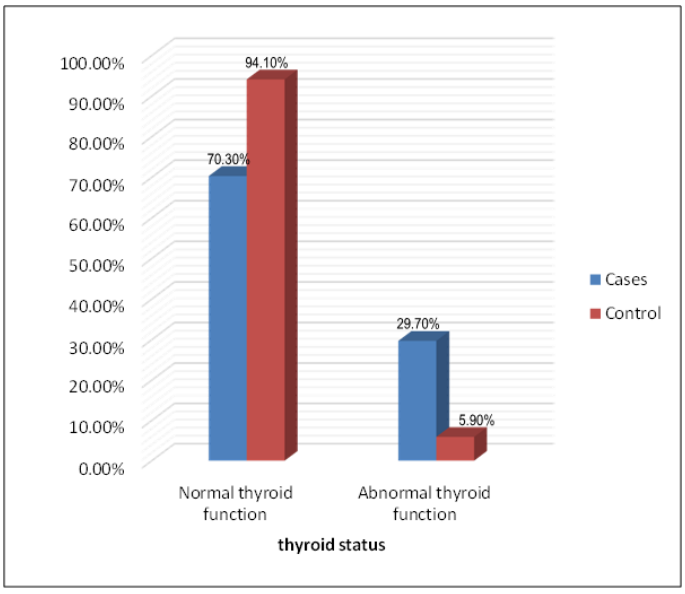


Table 5: Distribution of subjects according to diagnosis

Thyroid function	Cases		Control		Total		Chi square	p-value
	n	%	n	%	n	%		
Euthyroid	83	70.30%	111	94.10%	194	82.20%	25.7	<.001
Subclinical hypothyroidism	27	22.90%	4	3.40%	31	13.10%		
Overt hypothyroidism	8	6.80%	2	1.70%	10	4.20%		
Subclinical hyperthyroidism	0	0.00%	1	0.80%	1	0.40%		
Total	118	100.00%	118	100.00%	236	100.00%		

** Highly significant

Above table shows the distribution of patients according to the thyroid function. It was observed that among cases 83(70.3%) patients while incontrols 111(94.1%) patients presented with normal thyroid function. Subclinical hypothyroidism was seen in 27 (22.9%) cases while among control 4(3.4%) subjects. 8(6.8%) cases and 2 (1.7%) controls presented with overt hypothyroidism respectively. Only one case of hyperthyroidism was seen among control. Thus, more number of patients among

cases presented with abnormal thyroid function than control and this association was statistically significant.

Figure 5: Distribution of subjects according to thyroid function.

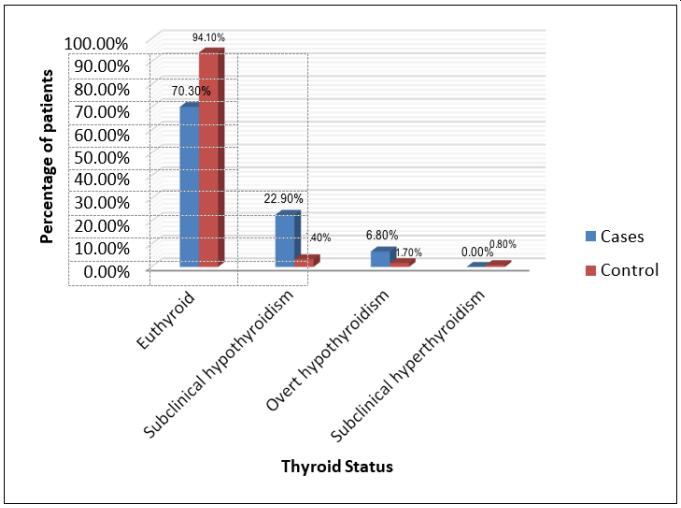


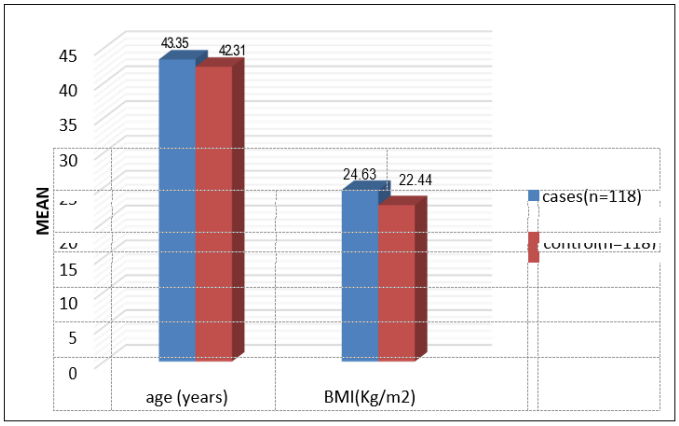
Table 6: Comparing the various grouped variable bet ween casesand control.

	cases(n=118)		control(n=118)		T-value	p-value
	mean	SD	mean	SD		
Age (years)	43.35	10.11	42.31	9.90	0.80	0.42
BMI(Kg/m2)	24.63	1.84	22.44	1.43	10.17	<0.001**
Haemoglobin (g/ dl)	12.66	0.80	13.22	0.98	-4.80	<0.001**
FBS (mg/dl)	86.77	6.89	86.82	6.80	-0.06	0.95
FT3 (pg/ml)	2.37	0.67	2.95	0.75	-6.28	<0.001**
FT4 (ng/dl)	1.19	0.35	1.34	0.29	-3.47	<0.001**
TSH (microIu/mL)	6.59	6.20	3.73	2.86	4.55	<0.001**
Serum Creatinine(mg/dl)	0.85	0.15	0.88	0.15	-1.63	0.10
Na+((meq/l)_	142.17	2.82	142.41	2.98	-0.67	0.5
K+(meq/l)-	4.06	0.28	4.04	0.27	0.52	0.60
CL(meq/l)	94.96	2.49	94.56	2.70	1.18	0.24
Total Cholesterol(mg/dl)	219.81	29.52	200.58	26.24	5.29	<0.001**
LDL (mg/dl)	153.29	24.84	123.38	21.51	9.89	<0.001**
Tgl (mg/dl)	145.13	27.05	134.30	22.77	3.32	<0.001**
hdl (mg/dl)	44.04	6.50	43.10	6.82	1.08	0.28
Serum Bilirubin(mg/dl)	1.04	0.10	0.87	0.09	13.53	<0.001**
SGOT	41.82	4.19	41.40	4.41	0.76	0.45
SGPT	43.53	4.55	43.25	4.96	0.45	0.65
ALP	53.87	7.93	51.94	9.00	1.75	0.08

** Highly significant, * Significant

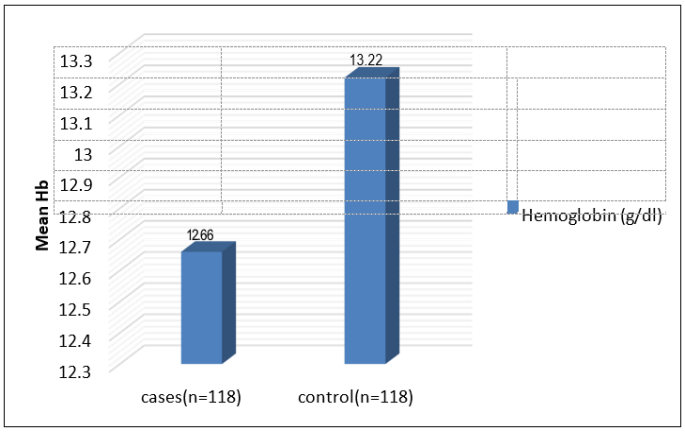
No significant association was observed between Age, FBS, Cl, lipid profile, SGOT, SGPT.ALP, K+, Na+, serum creatinine, while rest variable presented with significant difference which are represented in the figures below

Figure 6: Comparison of age and BMI among both groups.



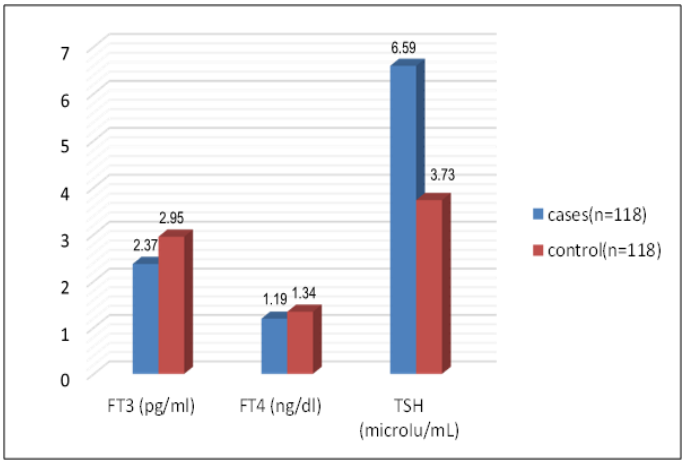
Above figure shows the comparison of grouped variables between cases and control. it was observed that BMI was significantly more among control. while no significant difference was observed among age of the patients.

Figure 7: Comparison of haemoglobin among both groups.



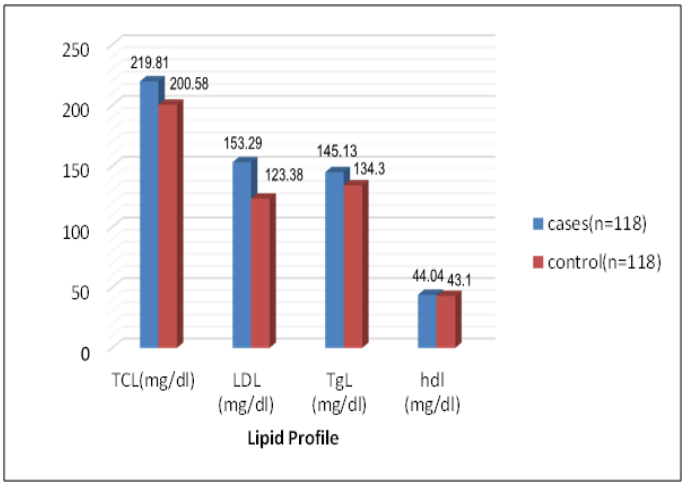
Haemoglobin among cases (12.66±0.80) was significantly less than thecontrol (13.22±0.98).

Figure 8: Comparison of thyroid profile among both groups



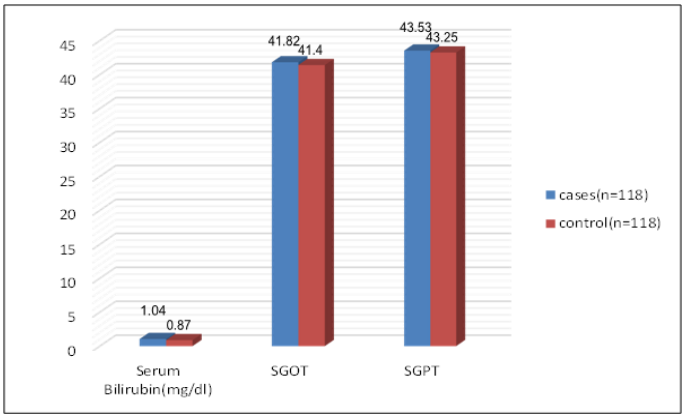
FT3 was significantly less (2.37±0.67 pg/ml) in cases than the control (2.95±0.75 pg/ml). (p<0.001). FT4 was significantly less (1.19±0.35 ng/dl) in cases than the control (1.34±0.29 ng/dl). (p<0.001). TSH was significantly more in cases (6.59±6.20 microIu/mL) in cases than the control (3.73±2.86 microIu/mL). (p<0.001).

Figure 9: Comparison of Lipid profile among both groups



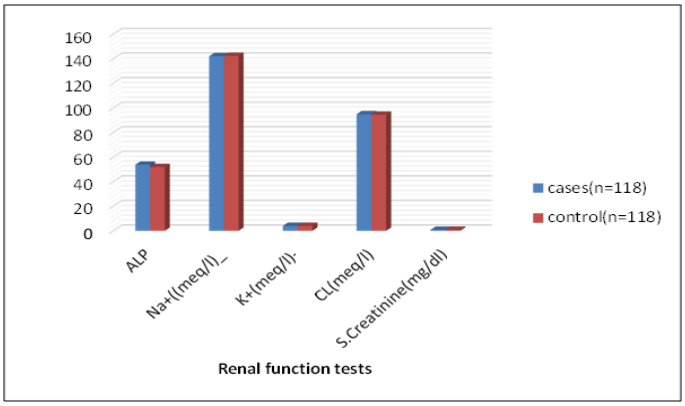
We observed that mean total cholesterol, LDL and TgL (triglycerides)was significantly more in Cases then controls.

igure 10: comparison of liver function tests among both thegroups.



We observed that serum bilirubin was significantly more in control(1.04±0.10mg/dl) then cases (0.87±0.09mg/dl). (p<0.001)

Figure 10: comparison of renal function tests among both thegroups.



No significant differences were observed among renal function tests.

Table 7: Distribution of subjects with cholelithiasis according toUSG findings (cases)

Findings	No. of patients	% age of patients
Single stone	27	22.8
Double stone	16	13.6
Multiple stone	75	63.6
Total	118	100

Maximum patients 75 (63.3%) presented with multiple stone while 27 (22.8%) patients presented with single stone. Double stones were seenin 16 (13.6%) patients.

Figure 11: Distribution of subjects with Cholelithiasis according toUSG findings (cases)

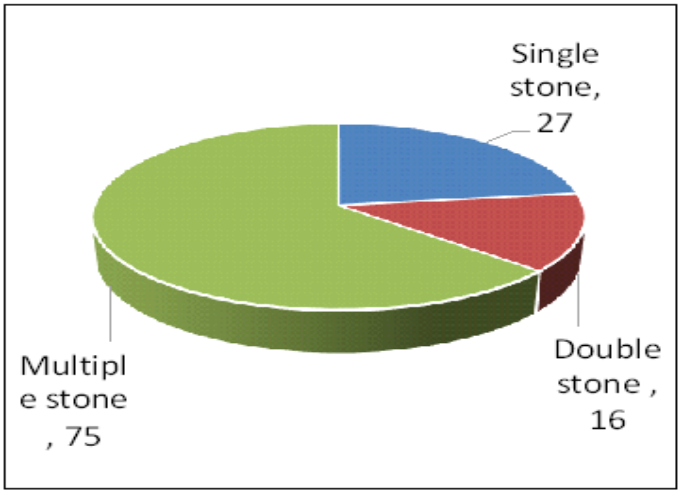


Table 8: Distribution of subjects according to size of stone (largest diameter) in patients with Cholelithiasis

Size of stone	No. of patients	% age of patients
≤10mm	44	37.3%
11-15mm	53	44.9%
16-20mm	19	16.1%
>20mm	2	1.7%
Total	118	100.0%

In majority of patients i.e. 53 (44.9%) the largest diameter of the stone was 11-15mm while in 44 (37.3%) the diameter was <=10mm. in 19 (16.1%) patients the largest diameter of the stone was >20mm.

Figure 12: Distribution of subjects according to size of stone(largest diameter)

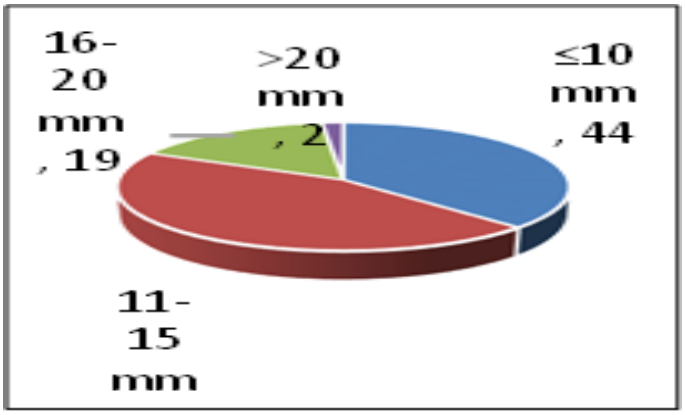


Table 9: Association between thyroid status and gender insubjects with Cholelithiasi.

No. of stone	Euthyroid		Subclinical hypo thyroidis m		Overt hypothyroidis m		Total		Chi-square	p- value
	N	%	n	%	n	%	n	%		
Female	2	70.0	7	23.3%	2	6.7%	30	100.0		
	1	%						%		
Male	6	70.5	20	22.7%	6	6.8%	88	100.0		
	2	%						%	.005	.998
Total	8	70.3	27	22.9%	8	6.8%	11	100.0		
	3	%					8	%		

No significant association was seen among gender and thyroid statusin patients with Cholelithiasis. However the number of females outnumbered men in the study population there was no variation in prevalence of thyroid disorder.

Figure 13: Association between number of the stone and gender insubjects with Cholelithiasis.

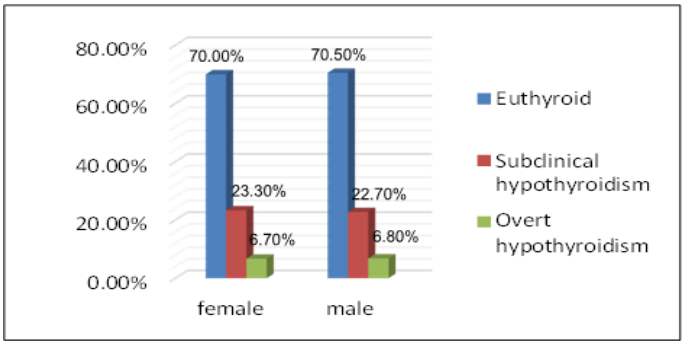


Table 10: Association between number of the stone and age ofsubjects with Cholelithiasis

No. ofstone	Euthyroid		Subclinical hypothyroidism		Overt hypothyroidism		Total		Chi- square	p- value
	N	%	n	%	n	%	n	%		
≤30	6	66.7%	2	22.2%	1	11.1%	9	100.0%		
31-40	29	72.5%	9	22.5%	2	5.0%	40	100.0%		
41-50	28	70.0%	9	22.5%	3	7.5%	40	100.0%		
51-60	17	81.0%	4	19.0%	0	0.0%	21	100.0%	3.7	0.87
>60	3	37.5%	3	37.5%	2	25.0%	8	100.0%		
Total	83	70.3%	27	22.9%	8	6.8%	118	100.0%		

No significant association was observed among age and thyroid status among patients with cholelithiasis (p=0.87). patients were equally distributed among all the age groups.

Figure 14: Association between number of the stone and age ofsubjects with Cholelithiasis.

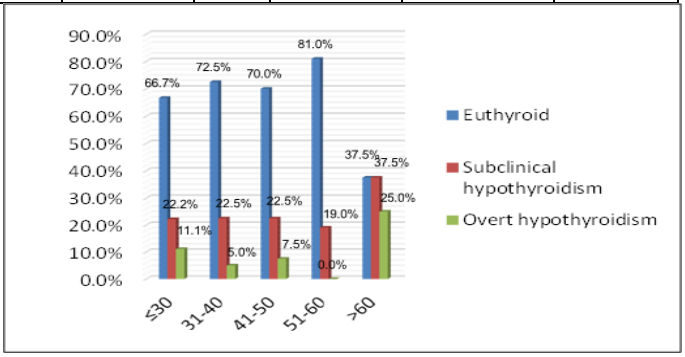


Table 11: Association between the number of stones anddiagnosis in subjects with Cholelithiasis

No. of stone	Euthyroid		Subclinical hypothyroi dism		Overt hypothyroid ism		Total		Chi-square	p- value
	n	%	n	%	n	%	n	%		
Single stone	17	63.0%	8	29.6%	2	7.4%	27	100.0%		
Double stone	14	87.5%	1	6.3%	1	6.3%	16	100.0%		
Multiple stone	52	69.3%	18	24.0%	5	6.7%	75	100.0%		
Total	83	70.3%	27	22.9%	8	6.8%	118	100.0%	3.4	.489

No significant association was seen in patients with respect to number of stones and thyroid function.

Figure 15: Association between the number of stones and diagnosis in subjects with Cholelithiasis

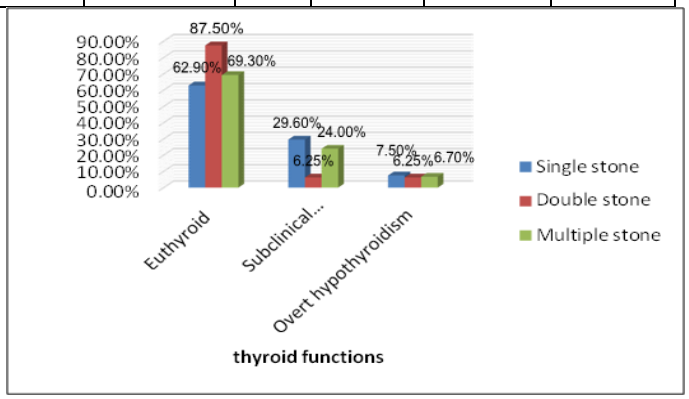


Table 12 : Association between the size of stones and thyroidfunction in subjects with Cholelithiasis.

	Euthyroid		Subclinical hypothyroidism		Overt hypothyroidism		Total		Chi-square	p- value
	n	%	n	%	n	%	n	%		
≤10mm	29	65.90%	13	29.54%	2	4.56%	44	100%		
11- 15mm	40	75.4%	9	16.9%	4	7.70%	53	100%		
16- 20mm	13	68.42%	4	21.05%	2	10.53%	19	100%		
>20mm	1	50%	1	50%	0	0%	2	100%	3.4	0.48
Total	83	70.30%	27	22.90%	8	6.80%	118	100%		

No significant association was seen in patients with respect to size ofstones and thyroid function.

Figure 16: Association between the size of stones and thyroidfunction in subjects with Cholelithiasis.

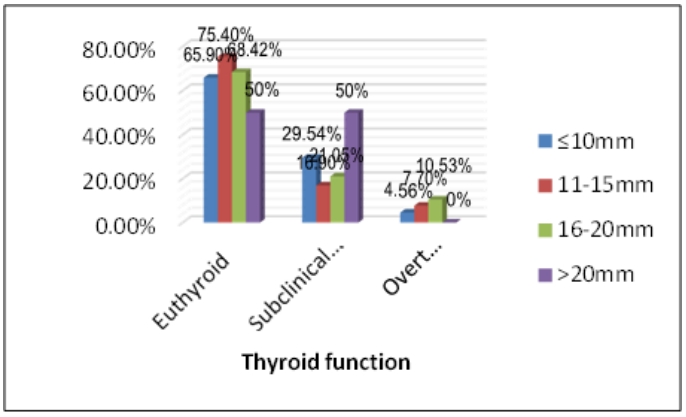


Table 13: Comparison between the thyroid status and various grouped variables in subjects with Cholelithiasis.

	Euthyroid (n=83)		Subclinical hypothyroidism (n=27)		Overt hypo thyroidism (n=8)		Factor	P-value
	Mean	SD	Mean	SD	Mean	SD		
age (years)	43.07	9.77	43.56	10.68	45.50	12.69	0.21	0.81
BMI(Kg/m2)	24.70	1.99	24.60	1.46	24.01	1.42	0.50	0.61
moglobin (g/dl)	12.62	0.84	12.70	0.73	13.01	0.38	0.95	0.39
FBS (mg/dl)	86.57	7.08	87.30	6.98	87.13	4.70	0.12	0.88
FT3 (pg/ml)	2.47	0.62	2.40	0.62	1.26	0.19	14.40	<0.001**
FT4 (ng/dl)	1.26	0.28	1.18	0.36	0.48	0.11	25.62	<0.001**
TSH (microIu/mL)	3.38	1.24	12.48	6.50	20.00	2.38	146.87	<0.001**
Serum Bilirubin (mg/dl)	1.04	0.10	1.02	0.10	1.06	0.07	0.75	0.48
SGOT	41.69	4.25	42.48	4.08	41.00	4.18	0.53	0.59
SGPT	43.67	4.31	43.26	5.41	42.88	4.36	0.17	0.84
ALP	53.93	8.24	54.52	7.62	51.13	5.33	0.57	0.57
size average	12.28	3.37	12.00	3.85	12.50	3.82	0.09	0.91
Na+((meq/l)	141.96	2.81	143.04	2.79	141.13	2.17	2.11	0.13
K+(meq/l)	4.04	0.26	4.15	0.34	4.01	0.17	1.87	0.16
CL (meq/l)	95.10	2.49	94.67	2.30	94.50	3.21	0.45	0.64
Total Cholesterol (mg/dl)	210.13	25.38	235.48	21.93	267.38	24.16	26.92	<0.001**
LDL (mg/dl)	146.99	24.60	164.52	17.37	180.75	16.96	12.31	<0.001**
TGL (mg/dl)	138.24	25.00	155.74	22.63	180.75	23.63	14.38	<0.001**
HDL (mg/dl)	42.49	6.27	46.85	5.69	50.63	4.27	10.42	<0.001**
Serum Creatinine (mg/dl)	0.85	0.15	0.83	0.15	0.89	0.18	0.48	0.62

*significant; ** highly significant

Significant differences were seen in data pertaining to LDL, HDL, total cholesterol and TGL in present study with patients with hypothyroidism having greater lipid levels than normal thyroid levels.

Discussion

The current study was conducted at department of surgery at Shri Vinoba Bhave Civil Hospital, Silvassa, UT of DNH to assess the association between hypo thyroidism and gall bladder disease. It consisted of 236 patients (118 cases and 118 controls). The results of the study are discussed below

The age among cases and control was comparable and insignificant difference was seen between both the group (p>0.88).Maximum patients in both groups were present inn 31-50 years of age (67.8% each). The average age of the patients among cases was 43.35±10.11 years while among controls it was 42.31±9.90 years. The results of the present study were in accordance with the study conducted by Watali et al[20] where in subjects (18-72 years) in case group had a mean age of 45.73±13.86 while in controls a mean was 44.78±13.63. Both the groups were comparable with a p value of 0.625. Prasad et al(2020)[31] conducted a similar kind of study on 200 subjects(100 cases and 100 control) . They reported that the mean age of cases was 43.25 and the mean age of controls was 45.5, with no significant difference between the two groups (P = 0.412). In contrast to the current study, Nake bet al observed that participants with a history of symptomatic gallstones were considerably older than those without a history of gallstones (58.2 ± 10.1 vs. 50.9±14.0 years, P<0.001).[32]

In the present study, there were 72.9% women and 27.1% men. There was no significant difference between the two groups. Among patients, females predominated (74.6%), followed by males (25.4%), with the female population being almost three times that of the male population. Prasad et al. found a female preponderance in their study, with 157 (78.5%) females and 43 (21.5%) males in total. In the cholelithiasis group, there were 82% females and 18% males, representing a 4:1 ratio of females to males.[32] Schirmer et al. reported that chole lithiasis is approximately four times more frequent in females than in males. [33]

This may be related to the hormonal variations between males and females, as well as the differences that may arise due to the co- expression of sex hormone receptors in both sexes' gallbladders. [32]

In present study it was observed that maximum patients presented with multiple stones (63.6%) and in majority of patients i.e. 53(44.9%) the largest diameter of the stone was 11-15mm. the average size of the stone in present study was 12.3mm. In a study conducted by Lodha et al (2020) 81.1% subjects presented with multiple stones and the average diameter was 11.3 mm in single and 6.3mm in multiple stones[34]. 80% of the patients in a study by Misrani et al.[35] had multiple stones, while 20% of the patients had just one stone. According to Jenkins PJ et al. [36] 64.9% of the stones were multiple, whereas 35.1% were single. Sebahattin et al.[37] reported multiple stones in 66.1% of cases and single in 33.9% of cases. According to Aslam et al. [38], 15.4% of patients had single stones, 84.5% had multiple stones. According to Jalali SA et al. [39], there were more multiple stones than single stones (69% vs. 31%). According to Mofti AB et al. [40], 11.56% of the stones were single, and the other 89.44% were numerous. All above study were in accordance to the present study.

The serum cholesterol levels that included total cholesterol (219±29.52mg/dl vs 200.58 ± 26.24 mg/ dl)), LDL (153.29 ± 24.84 vs 123.38 ± 21.51), TGL (145.13 ± 27.05 vs 134.30±22.77) were

significantly more in cases than in the control group. However non-significant differences were observed in HDL levels between both the groups. The results of the present study were in accordance with the study conducted by Watali et al[20] who showed the mean level of serum cholesterol in cholelithiasis group to be 151.01±22.64 mg/dl while I controls it was 144.95±16.99 mg/dl in control group. (p- value=0.0333). The results

of the present study were in accordance with study conducted by Volzke et al where also the total cholesterol, HDL LDL and lipoprotein were significantly more in patients with cholelithiasis than without chole lithiasis [41]. Numerous other investigations have demon strated that hyper triglyceridemia, hyper cholesterolemia, and a low HDL levels are prevalent in cholelithiasis patients.[41,42]

In present study we observed that 94.1% (111) patients in control and 83(70.3%) patients in cases presented with normal thyroid function while 35(29.7%) in cases and 7(5.9%) in control presented with abnormal thyroid function. The difference between both the group was statistically significant (p<0.001). Regarding diagnosis it was observed that subclinical hypothyroidism was seen in 27 (22.9%) cases while among control 4 (3.4%) subjects. 8 (6.8%) cases and 2 (1.7%) controls presented with overt hypothyroidism respectively. Only one case of hyperthyroidism was seen among control. Thus, a greater number of patients among cases presented with abnormal thyroid function than control and this association was statistically significant.

The results of the present study were in accordance with the study conducted by Prasad et al. [31] where 40% of the patients with gall bladder disease while 24% of patients without gall bladder disease were hypothyroid.(P value= <0.001). In their study, the prevalence of sub clinical hypothyroidism among cholelithiasis patients (cases) was 31% while that of overt hypothyroidism was 9%, whereas the prevalence of subclinical hypo thyroidism among controls was 18% and that of overt hypothyroidism was 6%. This was comparable with the present study.

In Kashmir, subclinical hypothyroidism was found to be present in 21.3% of subjects with cholelithiasis and overt hypothyroidism in 9.0%, according to Bashir H et al's study [43]. Ajdarkosh et al. [44] in their analysis of the thyroid function of choledocholithiasis patients showed that there was subclinical hypothyroidism in 30.6% of patients and 22.5% of controls. The prevalence of overt hypothyroidism was 11.3% in patients and 10.0% in controls. According to case-control study, conducted by Jabni et al the prevalence of subclinical hypothyroidism was higher in the cholelithiasis group (case group) with p = 0.029. [45] Gafoor et al. also conducted a case-control research in which 15% of the case group and 9% of the control group had hypoth yroidism. Hypothyroidism was not present in any of the patients in the control group (p = 0.005). [46]

In a cross-sectional study conducted in West Nepal, Ghimire et al. found that 26.7% of 160 patients with gallstone disease had hypothyroidism out of which 5.6% had clinical hypothyroidism and 21.1% had subclinical hypo thyroidism.[47]

All of the aforementioned studies support the idea that hypothyroidism is a risk factor for the development of gallstones, as they found a considerable prevalence of hypothyroidism among cholelithiasis patients recruited for the study.

The results of the present study were in contrast with the study conducted by Watali et al[20] who showed the prevalence of 14% of hypothyroidism in case and 8% in the controls, However, the prevalence was more in cases, statistically the results were non-significant in their study. (p= 0.175). A prospective investigation on the frequency of thyroid abnormalities in patients with gallstone disease in Uttar Pradesh, conducted by Singh et al.[48], revealed that gallstone disease was more pre valent in patients aged 51 to 60 years. Though, no conclusive association was detected between thyroid hor

mones dysfunction and cholelithiasis; hence, they concluded that thyroid dysfunction was not associated with cholelithiasis.

In a study conducted in Iraq, Zaini and Zwain et al. determined that there is no significant association between hypothyroidism and gallstones in both sexes (p=0.12)[14]. Sundar Eshwari et al. did a prospective study which revealed that only 12% of cholelithiasis patients had hypothyroidism, which was not statistically significant (p>0.05). The majority, however, had sub clinical hypothyroidism.[49]

Gallstone formation is a complex process involving multiple mechanisms that alter bile flow and bile composition. Several mechansims have been proposed for the same:

- Relationship between thyroid dysfunction and issues with lipid metabolism that could possibly modify the composition of bile.

[11]

- Decreased bile flow to the duodenum in hypo thyroidism.[12]
- The sphincter of oddi expresses thyroid hormone receptors, and thyroxine directly relaxes the sphincter of oddi.[50]
- Thyroxine is believed to dissolve gallstones and common bileduct stones in certain circumstances. [51]
- In hypothyroidism, the digestive tract is dysmotile.[9]
- Hypothyroidism reduces biliary cholesterol release, leading bile to become supersaturated with cholesterol and cause sludge or gallstone disease. [13]
- Hypothyroidism has been related in certain studies with decreased bilirubin excretion due to decreased UDP glucuronyl transferase activity.[52]

In present study no significant association was seen amonggender and thyroid function among patients with gall bladder disease.In a case-control research conducted by Volzke et al. in Germany, patients with thyroid disease were connected with cholelithiasis more frequently than those without thyroid dysfunction[12]. But in both males and females, there was no connection between gallstone disease and thyroid disease. Similar findings were observed by Watali et al[20] which was in accordance to the present study.

Male hypothyroids were more prevalent than female hypothyroids in gallstone disease, according to Arun et al., who also conducted a study on the frequency of hypothyroidism in identified cholelithiasis patients in Trissur Medical College, Kerala. Given the high prevalence of hypothyroidism in patients with gallstones, he came to the conclusion that these individuals should have their serum TSH levels examined[23].

The above-mentioned studies have shown varying results with respect to incidence of the thyroid dysfunction and cholelithiasis inaccordance to gender.[12,23]

In present study also we observed that there serum lipid levels were more in patients with hypothyroidism as compared to euthyroid among the cases. Total cholesterol were 210± 25.38mg/dl in euthyroid while it was 235.48±21.98 and 267.38±24.16mg/dl in subclinical and overt hypothyroidism respectively. LDL levels were 146±99 in euthyroid while they were 164±17.37 and 180±16.96 mg/dl in subclinical and overt respectively. TgL levels were 138.24 ± 25.00mg/dl in euthyroid while it was 155.74±22.63 and 180.73±23.63 mg/dl in subclinical and overt hypothyroidism respectively. HDL levels also showed the same trends.

Dhoka et al[53] in their study showed that, people with hypothyroidism have significantly greater levels of

dyslipidaemia than those with Euthyroidism (p< 0.001). In their investigation, Marwaha et al.[54] found that serum total cholesterol and LDL levels significantly increased in hypothyroid people. In addition, Hussain et al.[55] foundthat subclinical hypothyroid patients had significantly higher levels of total cholesterol, trigly cerides, and LDL than controls in their study. Similarly, hypothyroidism patients had higher levels of total and LDL cholesterol, according to Pedrelli et al. all these studies were in accordance to the present study.[56]

To the contrary, Ahmmed Hassan Issa et al.[24] found that there was no correlation between hypothyroidism and cholelithiasis in their study of 232 patients, where 175 patients with dyslipidaemia demonstrated that only 25 were hypothyroid (p=0.92).

Ninety percent of hypothyroid individuals had high cholesterol, triglyceride, or both values [57-61]. The treatment of patients with hypothyroidism and concurrent hyperlipidemia will improve serum cholesterol levels [59]. In hypothyroidism, decreased LDL receptor activity results in impaired cholesterol elimination from the serum [62,63], and decreased control of HMG-CoA reductase expression results in decreased cholesterol synthesis . Even while THs inhibit bile salt formation in human hepatocytes , a reduction in biliary bile salt content has been recorded in hypoth yroidism[64-67]. Hypoth yroidism decreases biliary cholesterol secretion in rats, but thyroxine treatment significantly enhances cholesterol secretion in hypothyroid animals [48].

In hypothyroidism, serum hypercholesterolemia can cause bile to be saturated with cholesterol. Reduced motility, decreased contractility, and poor filling of the gallbladder are direct effects of cholesterol-saturated bile, leading to prolonged bile residence in the gallbladder. This may contribute to the preservation of cholesterol crystals, hence enabling ample time for gallstone nucleation and development[11, 68-71].

No significant differences were observed among the liver and renal function tests in present study which was similar to the study by Dhoka et al[53].

Also in present study no significant association was seen among size of stone, number of stone and thyroid function which was in contrast to study conducted by raghuwanhi et al[17]. They showed that in hypoth yroidism patients, all stones were larger than 1 cm, and overall, 58 percent of stones were larger than 1 cm (statically significant). Three of the twelve hypothyroidism patients (or 25%) had a single stone, compared to nine (75%), who had multiple stones (statically significant).

Thus From our study, it is evident that subclinical hypothyroidism is also associated with gall stones and is also associated with hyperlipidaemia. We found no association of gender and age in gall bladder disease with thyroid function. Most importantly, when treating patients with gall stones or microlithiasis, clinicians should be aware of the possible hypothyroid background and consider examining the thyroid function. We propose to conduct multi-centric, large population-based studies in order to provide a higher level of evidence that should include patients with choledocholithiasis, as they were excluded from this study and structural and histopathological examination of the stones so as to assess the types of stones.

Summary and conclusion

The current study was conducted at department of surgery at Shri Vinoba Bhave Civil Hospital, Silvassa, UT of DNH.

Following observations were made during the study:

1) No significant difference was observed in the age distribution among both the groups. Maximum patients in both the groups were seen in age group 31-50 years.

2) It was observed that in the study population females predominated then males with males with females being approximately 3 times than the males. No significant difference was observed in gender distribution among both the groups.

3) Total cholesterol, LDL and Triglycerides (TGL) were significantly more in patients with gall bladder stones while no significant difference was seen in HDL.

4) It was observed that among cases 83 (70.3%) patients while in controls 111 (94.1%) patients presented with normal thyroid function. Subclinical hypoth yroidism was seen in 27 (22.9%) cases while among control 4 (3.4%) subjects. 8 (6.8%) cases and 2 (1.7%) controls presented with overt hypoth yroidism res pectively. Only one case of hyperthyroidism was seen among control. Thus, more number of patients among cases presented with abnormal thyroid function than control and this association was statistically significant.

5) No significant association was observed between Age, FBS, Cl, lipid profile, SGOT, SGPT.ALP, K+, Na+, serum creatinine, while T3. T4, TSH, Total cholesterol, LDL, TGL, HDL, and serum bilirubin were signifi cantly more in cases.

6) Among cases Maximum patients 75 (63.3%) presented with multiple stone while 27 (22.8%) patients presented with single stone. Double stones were seen in 16 (13.6%) patients.

7) In majority of patients i.e. 53 (44.9%) the largest diameter of the stone was 11-15mm while in 44 (37.3%) the diameter was

<=10mm. in 19 (16.1%) patients the largest diameter of thestone was >20mm.

8) No significant association was seen among gender, age, size of stone, number of stone and thyroid status in patients with Cholelithiasis.

9) Total cholesterol, LDL, TGL and HDL were significantly more in patients with hypothyroidism.

Conclusion

Thus from our study, it is evident that subclinical hypothyroidism is associated with gall stones and is also associated with Hyper lipidaemia. We found no associ ation of gender and age in gall bladder disease with thyroid function.

Most importantly, when treating patients with gall stones or micro lithiasis, clinicians should be aware of the possible hypo thyroid back ground and consider examining the thyroid function.

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