Title: Risk factors of cholecystitis among high altitude (Taif City) population .

Abstract (150-250 words)

Abstract to study the risk factors of gallstones diseases in high altitude in (Taif City) population, Saudi Arabia .A cross sectional community based was made of 863 people from Taif city. Questionnaire was distributed on website as electronic questionnaires.

Backgrounds/Aims

Our study aimed at pointing the magnitude of cholecystitis among Taif City population and determining its actual risk factors in order to avoid this health problem in the future.

and to evaluate several co-morbidities, such as hypertension, diabetes mellitus, cardiovascular disease.

Methods

A cross-sectional community-based study using a questionnaire was performed. The questionnaires were distributed among population of Taif city, Saudi Arabia from June 2017 to September 2017. The collected number of questionnaires was 863 through a website as an electronic study.

The questionnaire data were attended to risk factors of cholecystitis.

Results

The research sample consisted of 863 people, the research sample divided into males with percent (46.6%) and female with percent (53.4%), female gender (p=0.038), age group between 30-40 years (p=0.000), intake of contraceptive pills (p=0.049), eating spicy foods (p=0.008), eating fats (p=0.005), diabetes mellitus (p=0.02), hypertension (p=0.03).

Conclusions

The modifiable risk factors must be changed and avoided. , the associating diseases such as diabetes mellitus and hypertension should be controlled. In addition, cholecystitis in females in the fourth decade of age living in high altitude cities should be checked and followed up as well as treated promptly to avoid the complications and to achieve better prognosis.

Keywords: Cholecystitis, Risk factor, Cholecystectomy, diseases of high altitude.

Introduction:

Taif city is located in the Makkah area of western Saudi Arabia on the eastern slopes of the Sarawat Mountains at an altitude of 1700 meters above sea level. The rise is increasing as we move west and south to 2500 meters. It has gained a reputation for tourist, commercial, agricultural and military since ancient times. Taif is one of the governorates of Makkah and one of the largest governorates in the Kingdom. according to the population census in 1431 H, 1,281,613 people, 82.52% of whom are Saudis. The area of Taif province is 87561 square kilometers.

The gall stone diseases it is estimated in American population about 10% to 20% (20 to 25 million Americans). [1]

Acute cholecystitis means acute inflammation of the gall bladder, and the most frequent cause is gallstone. Actually it is one of the most common disorders in the gastrointestinal tract representing about 10% of individuals in Western societies[2][3]. About 80% of all patients are asymptomatic and 1-3% of patients had symptomatic gallstones [4]. The most common cause of biliary diseases are helminthic infection particularly ascariasis in developing countries in Asia, southern Africa, and Latin America [5].

The inflammatory process started when the cystic duct is obstructed causing acute cholecystitis. However, the inflammation may continue leading to perforation or gangrene of gall bladder (in 10% of patients of acute cholecystitis). The perforation usually occurs at the fundus and constituting mortality rate about 30%. Localized perforation is more common than generalized and usually it is combined by abscess formation producing a palpable mass in most of cases. Gangrene of the gall bladder constituted the highest risk in men aged above 50 with history of cardiovascular disease and leukocytosis. Generalized peritonitis in feverish male patient (temperature

>38°C) with serum bilirubin >170 μmol/l is more likely to develop complications [21][22][23].

The most common and classical symptoms of acute cholecystitis are severe right upper quadrant pain, abdominal guarding, fever, and a positive Murphy's sign with leukocytosis. Although the initial diagnostic approach is ultrasonography for patients with suspected acute cholecystitis. To identify the complications, computed tomography and magnetic resonance imaging are performed [6]. The cause of acute cholecystitis is not yet fully understood]1]. The most common cause of cholecystitis is cholecystolithiasis that means gallstones in the gallbladder accounting 90-95% while just 5-10% of cases represent acalculous cholecystitis that means an inflammation of gallbladder without evidence of gallstones or cystic duct obstruction [7][8][9][10][11][12][13] .

In USA there is 10% of population have gallstones without any symptoms and that may lead to acute cholecystitis [3]. The account of acute cholecystitis is 3-10% of all patient with abdominal pain]11- 12]. Additionally, 6.3% of acute cholecystitis cases are encountered in patients under 50 years old whereas 20.9% occur with patients over 50 years old [18].

Obesity is one of risk factors of cholecystitis. The Framingham study confirms that the increase in body weight is related to the increase in its incidence [14] . Also, the hard diet will increase risk of gallstones formation may reach 10% - 12% after 8 – 16 weeks of low- calorie diet [15].

The evidence of cholecystitis among women is common as twice as in men, and pregnancy also related to increase risk of cholelithiasis and the level of estrogen and progesterone are contributed to the formation of gallstones. In pregnant women

the cholecystitis is the second most common cause of acute abdomen after appendicitis [14–19].

Fifth decade is a risk factor according to the Framingham study among 5209 men and women aged 30–62 years who underwent observation for 10 years, the risk was highest in fifth decade, and most of them were diagnosed possessing cholelithiasis [14].

Drugs such as oral contraceptive, fibrate and third-generation cephalosporin may cause cholelithiasis [20].

Diagnosis of acute cholecystitis is done easily by clinical features obtained on history and examination and supported by ultrasound findings that include fluid around the gall bladder, distended gall bladder, thickened gall bladder wall and gallstones formation. Also, plain abdominal X-ray will show radio-opaque gallstones in about 10% of patients of acute cholecystitis. In addition, the gold standard investigation is HIDA (hydroxyl-imino-diacetic acid) scan if the diagnosis is still unclear with ultrasound, we give the patient an intravenous injection of radiolabelled hydroxyiminodiacetic acid, then, scan the abdomen is performed that reveals that gall bladder doesn't take up any radioactive isotope 1-2 hours after injection, thus, the gall bladder doesn't be visible on the scan. [24][25]

The management divides into two sections; first one will be medical and the second one is surgical. Medical management is an immediate measure including an intravenous fluid, oxygen therapy and analgesic such as indomethacin (25mg three time daily) that has a prokinetic action improving postprandial emptying of gall bladder. Also, antibiotics, as second generation of cephalosporin with metronidazole, treat the risk of infection. In the unfit patients to surgery, shockwave lithotripsy can be applied unless being curative [26][27].

The surgical management involves either open cholecystectomy or laparoscopic cholecystectomy. Open cholecystectomy is traditional method and it is performed after six to twelve weeks after beginning an acute episode to give time for the inflammatory process to be resolved before the operation. Nowadays the laparoscopic cholecystectomy is the standard management, if performed efficiently and safely, and is associated with a rapid recovery and a less time of hospitalization. Therefore, the best management of acute cholecystitis patient is resuscitation followed by laparoscopic cholecystectomy as soon as possible [28][29][30][31][32].

Our study aimed at pointing the magnitude of cholecystitis among Taif City population and determining its actual risk factors in order to avoid this health problem in the future.

PATIENTS AND METHODS:

A cross-sectional community-based study using a questionnaire was performed. The questionnaires were distributed among population of Taif city, Saudi Arabia from June 2017 to September 2018. The collected number of questionnaires was 863 through a website as an electronic study.

The questionnaire included questions focused on whether the condition is acute or chronic cholecystitis, the questionnaire data were attended to the following risk factors of cholecystitis related to gender, age (less than 30 years, from 30 to 40 years , more than 40 years), BMI using formula [BMI = weight (kg)/ height (M^2)], physical exercise (once, twice or more per week), hypertension [HPT; its type, duration of treatment and being controlled by antihypertensive medications], diabetes [DM; its type, duration of treatment and being controlled by medications), smoking (its type, duration of intake and quantity per day), any heart disease (its type, duration

of treatment and being controlled by medications) and any performed laboratory or radiological investigations for diagnosis and/or follow-up of the above mentioned associating diseases, any medication other than hypoglycemics or antihypertensives particularly antihyperlipidemics and contraceptive pills (their names, dosage, duration of intake and whether they were continuously and regularly or intermittently and irregularly taken), intake of spicy food (its type and quantity either once, twice or more per week), intake of fat rich meals (once, twice or more per week), family history of cholecystitis, number and frequency of pregnancies and abortions in married women (infertile, primipara or multipara).

STATISTICAL ANALYSIS:

The relationships between the clinical outcomes and patient demographic factors and the co-morbidities and laboratory data were analyzed by performing univariate and multivariate analyses. The data were analyzed by using SPSS version 21.0 (IBM Corp). We assessed statistical significance using person correlation test. A *p*-value less than 0.05 indicated statistical significance.

RESULTS:

The research sample consisted of 863 people with three age groups (**Table 1-1**); less than 30 (39.3%), from 30 to 40 (31.1%) and more than 40 (29.7%). One way Anova test showed a statistical significant result (p=.000) in age group ranged from 30 up to 40 years (**Table 1-2**). In addition, Kruskal-Wallis Test displayed more mean rank (452.70) in that age group than in other groups (**Table 1-3**).

Regarding the gender, our sample was divided (**Table 2-1)** into males (46.6%) and female (53.4%). We used one way Anova test (**Table 2-2)** and Chi-Square test (**Table 2-3)** that showed statistically significant results between males and females

about cholecystitis (*p*=.038) as well as Kruskal-Wallis Test (**Table 2-4)** that revealed more mean rank for females (439.98) than that for male (422.84).

Person Correlation test found a significant correlation between cholecystitis on one hand and either of contraceptive pills' intake (**Table 3;** *p*=.049), eating spicy foods (**Table 4;** *p*=.008), eating fat rich foods (**Table 5;** *p*=.005), associating diabetes mellitus (**Table 6;** *p*=.02) or associating hypertension (**Table 7;** *p*=.030) on the other hand.

Table 1-1: Correlation between incidence of cholecystitis and age groups of patients:

	Group of age	No;	Percent	Valid Percent	Cumulative Percent	P value
Valid	less than 30	339	39.3	39.3	39.3	0.152
	from 30 to 40	268	31.1	31.1	70.3	0.000
	more than 40	256	29.7	29.7	100.0	0.271
	Total	863	100.0	100.0		

Table 1-2: ANOVA correlation between age groups of cholecystitis patients:

cholecystitis					
Age	Sum of Squares	df	Mean Square	F	P value
Between Groups	1.265	2	.633	8.195	0.000
Within Groups	66.389	860	.077		
Total	67.655	862			

Table 1-3: Kruskal-Wallis Test correlation between age groups and cholecystitis patients:

Ranks			
	Age	N	Mean Rank
cholecystitis	less than 30	339	420.45
	from 30 to 40	268	452.70
	more than 40	256	416.75
	Total	863	

Table 2-1: Correlation between incidence of cholecystitis and gender groups of patients:

	Gender	No;	Percent	Valid Percent	Cumulative Percent	P value
Valid	Female	461	53.4	53.4	53.4	0.038
	Male	402	46.6	46.6	100.0	0.118

	Gender	No;	Percent	Valid Percent	Cumulative Percent	P value
Valid	Female	461	53.4	53.4	53.4	0.038
	Male	402	46.6	46.6	100.0	0.118
	Total	863	100.0	100.0		

Table 2-2: ANOVA correlation between gender groups of cholecystitis patients:

cholecystitis					
	Sum of Squares	df	Mean Square	F	P value
Between Groups	0.339	1	.339	4.333	0.038
Within Groups	67.316	861	.078		
Total	67.655	862			

Table 2-3: Statistics analysis between gender groups of patients:

Test Statistics[a,b]	
	cholecystitis
Chi-Square	4.317
df	1
P value	0.038
a. Kruskal Wallis Test	
b. Grouping Variable: gender	

Table 2-4: Kruskal-Wallis Test for correlation gender groups of cholecystitis patients:

Ranks			
	Gender	N	Mean Rank
cholecystitis	Female	461	439.98
	Male	402	422.84
	Total	863	

Table 3: correlation between incidence of cholecystitis and contraceptive pills intake:

		cholecystitis	q9
cholecystitis	Pearson Correlation	1	-.067*
	Sig. (2-tailed)		0.049
	N	863	863
q9	Pearson Correlation	-.067*	1

	Sig. (2-tailed)	.049	
	N	863	863
*. Correlation is significant at the 0.05 level (2-tailed).			

Table 4: correlation between incidence of cholecystitis and eating spicy foods:

		cholecystitis	Spicy food
cholecystitis	Pearson Correlation	1	0.718**
	Sig. (2-tailed)		0.008
	N	863	863
Spicy food	Pearson Correlation	.718**	1
	Sig. (2-tailed)	.008	
	N	863	863

Table 5: correlation between incidence of cholecystitis and eating fats:

		cholecystitis	fats
cholecystitis	Pearson Correlation	1	0.513**
	Sig. (2-tailed)		0.005
	N	863	863
fats	Pearson Correlation	.513**	1
	Sig. (2-tailed)	.005	
	N	863	863

Table 6: correlation between incidence of cholecystitis and diabetes mellitus:

		cholecystitis	DM
cholecystitis	Pearson Correlation	1	.425**
	Sig. (2-tailed)		0.02
	N	863	863
DM	Pearson Correlation	.425**	1
	Sig. (2-tailed)	.02	
	N	863	863

Table 7: correlation between incidence of cholecystitis and hypertension:

		cholecystitis	HTN
cholecystitis	Pearson Correlation	1	0.384**
	Sig. (2-tailed)		0.030
	N	863	863
HTN	Pearson Correlation	.384**	1
	Sig. (2-tailed)	.030	
	N	863	863

DISCUSSION:

The risk factors of cholecystitis differs in all the population of the world depending on

the location and the population of the study. several studies have sought to determine that female sex, race, obesity, diabetes mellitus, ageing, parity, type IV hyperlipidemia, oral contraceptive use , cirrhosis , smoking, and family history of gallstone disease are risk factors for gallstone formation [*33*,*34*,*35*,*36*,*37*].

In our study, female sex ,age from 30 to 40 , taking contraceptive pills , eating spicy and fatty food , presence of diabetes mellitus and hypertension were found to be significant risk factors.

This discrepancy could be referred to the genetic and environmental differences among different communities .

Few studies have research to describe the propagation of gallstones in high altitude populations. Moro et al, [*38*] in their study of gallstone disease in high altitude populations , recorded that high altitude was not a positive risk factor for gallstone disease. But the other study , Spathis et al. [*39*] recorded high rates of gallstones among high altitude villagers of Ladakh, India. They referred this rate to slow intestinal transit time that can produce constipation, increased bilirubin absorption and more bile concentrations in the gallbladder [*38*,*39*]. also , increased blood cell formation and increased hemolysis may augment levels of bilirubin pigments with an enhance risk of pigment gallstones [*40*]. Our city is one of the highest altitude regions in the Middle East .

This may be one of the risk factors participating to the high prevalence in our region.

It is quite a meager description to say that cholecystitis is an inflammatory change in the gallbladder, thereby identifying only the pathologic conditions. Clinically cholecystitis is characterized by symptoms of dyspepsia, right upper quadrant abdominal pain, and fever. Moreover, it is accompanied by changes in laboratory results, reflecting biliary inflammation or cholestasis. Thus, the concept of cholecystitis includes all the above changes in addition to the pathologic changes [41]. Our study revealed that age group ranged from 30-40 years and associating conditions like diabetes mellitus and hypertension were statistically significant risk factors for cholecystitis among Taif city population. In contrast to those mentioned by Sol et al.[41] who found that the old age group (50 years or more) and some clinical features such as fever, leukocytosis and serum total bilirubin levels equal or exceeded 1.2 mg/dl were statistically significant risk factors. This controversial data could be resorted to the differences in both location and wider number scale of our researched cases.

In addition, our research displayed that female gender and intake of contraceptive pills as well as fat rich and spicy foods were statistically significant risk factors for the incidence and prevalence of cholecystitis among Taif city residents. These results were identical to those stated by Chari and Shah [42] who reported that our previously mentioned risk factors in addition to accompanied obesity, multiparity, family history, rapid weight loss and physical inactivity are recognized risk factors for gallbladder stones. Also, they reported that cholecystitis without gallstones is not resorted to cystic duct blockage but lack of blood supply to the gallbladder might cause sluggish bladder motility and biliary stasis with subsequent cholecystitis.

Conclusions

Our study concluded that the modifiable risk factors such as intake of contraceptive pills, ingestion of fat rich and spicy foods must be changed and avoided. Moreover, the associating diseases such as diabetes mellitus and hypertension should be controlled. In addition, cholecystitis in the high risky patients particularly females in the fourth decade of age living in high altitude cities should be checked and followed up as well as treated promptly to avoid the complications and to achieve better prognosis.

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