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Original Article

Gallstone disease as a clue for metabolic syndrome

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Abstract

Background: Nowadays, metabolic syndrome (MetS) is considered a global health concern. Patients with MetS are at 5- and 2-times higher risk of developing type 2 diabetes and gallstones, respectively. Although gallstone disease (GSD) and MetS are common, little is known about their association. This study aimed to compare the frequency of metabolic syndrome criteria between the GSD group and the control group.

Methods: In this case-control study, we enrolled 432 subjects, including 216 with gallstones (184 females, 31 males) and 216 controls (187 females and 29 males without gallstones). Body mass index (BMI), waist and hip circumferences, fasting blood sugar (FBS), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, metabolic score for insulin resistance (METS-IR), and fibrosis score four index (FIB-4), were measured.

Results: Out of 432 participants, 36% of the subjects had MetS documented. There were no significant differences between the case and control groups regarding age and gender (P=0.144 and P=0.674, respectively). The univariate analysis illustrated that individuals with GSD exhibited higher weight, BMI, hip and waist circumferences, waist-to-hip circumference ratio, total cholesterol, TG, LDL, FBS, METS-IR, and hypertension incidence than those without GSD. Conversely, HDL levels were significantly lower in subjects with GSD(P<0.05).

Conclusion: Similar to cardiovascular diseases and type 2 diabetes mellitus, GSD seems strongly associated with MetS. Therefore, it is recommended that GSD patients be investigated and monitored for metabolic syndrome and its potential long-term consequences.

Keywords: Gallstone disease, Metabolic syndrome, Insulin resistance, Obesity.

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Gallstone disease (GSD) is considered a common condition worldwide. The prevalence of GSD has been estimated to be 15% in the USA (1), 9-21% in Europe (2, 3), and 5% in Africa (4). Different rates of GSD have been reported in Iran, including 0.8% in Amol, 2.5% in Birjand (5), and 4.7% in Southern Iran (6). Gallstone formation has multifactorial pathogenesis and involves several environmental and individual factors that result in bile cholesterol hyper-saturation, cholesterol nucleation, and gallbladder dysmotility (7). Cholesterol is the main component of more than 80% of gallstones, which are associated with conditions such as older age, insulin resistance, pregnancy, obesity, dietary habits, genetics, and ethnicity. Cholelithiasis poses a serious health risk, as it is closely associated with the development of gallbladder, pancreatic, and colorectal cancers. Alarmingly, the National Institutes of Health estimates that complications from cholelithiasis and gallbladder disease contribute to nearly 3,000 deaths each year, accounting for 0.12% of all deaths. Awareness and early intervention are crucial for mitigating these risks and saving lives (8). Nowadays, metabolic syndrome (MetS) is considered a global health concern (9).

MetS is usually defined as 3 to 5 quantitatively defined markers including, abdominal obesity, and high blood pressure, elevated fasting glucose level, elevated triglyceride levels, and decreased high-density lipoprotein cholesterol (HDL) (9). Despite variations in different countries, the overall prevalence of MetS has been reported to be 20%. Patients with MetS are 2 to 3 times more prone to the development of acute coronary syndrome and stroke. Also, they are at 5 and 2 times higher risk of developing type 2 diabetes and gallstones, respectively (10). Although GSD and MetS are common conditions, little is known about their association. Therefore, in the current case-control study, we aimed to compare the prevalence of MetS among patients with and without GSD.

Methods

This case-control study was conducted on patients with GSD who were referred to 22 Bahman and Aria hospitals in Mashhad, Iran in 2022. The case group included participants with symptomatic GSD who were scheduled for cholecystectomy. On the other hand, the control group was made up of cross-matched outpatient individuals without GSD (All of them underwent abdominal ultrasounds, confirming that gallstones were absent). To be included in the study, both the case and control groups had to sign the consent form and be between 18 and 70 years old. Patients with porcelain gallbladder and incomplete data were excluded from the study. Additionally, for the control group, individuals with a history of cholecystitis episodes or cholecystectomy surgery were not included.

The sample size was calculated regarding an expected prevalence of MetS among patients with GSD (33.9%) (12) to guide the sample saturation stage to reach a 95% confidence interval. Therefore, 186 patients with GSD were consecutively enrolled. The following equation was used to calculate the sample size:

$$(N = \frac{Z^2 P(1-P)}{d^2} = \frac{(1.96)^2 \times 0.339(1-0.339)}{(0.05)^2} = 186)$$

Although the number of participants in each group was 186, we increased the sample size to 216 to make sure our analysis is strong and reflects the population accurately. Moreover, we enrolled other 216 participants as a control group which was completely matched with the cases group except for GSD.

In this study, MetS was defined according to the NCEP/ATP III criteria, which include blood pressure, waist circumference, high-density lipoprotein cholesterol, triglyceride levels, and fasting blood glucose levels. A person with three or more components was considered to have MetS: Waist circumference greater than 102 cm in men and greater than 88 cm in women, fasting blood glucose (FBG) equal to or greater than 100 mg/dL or receiving drug treatment to lower blood glucose, systolic blood pressure equal to or greater than 130 mmHg or diastolic blood pressure equal to or greater than 85 mmHg or receiving drug treatment for hypertension, Triglycerides equal to or greater than 150 mg/dL or receiving drug therapy for hypertriglyceridemia, HDL less than 40 mg/dL in men and less than 50 mg/dL in women, or receiving drug therapy to increase serum HDL cholesterol (9).

The surgeon has requested pre-operative data on basic metabolic profiles, which include FBG, lipid profile, and HbA1c levels (The Alpha Classic ATT Autoanalyzer and the IRIC kit for glucose, the Biorex Fars kit for cholesterol and triglycerides, and the Ideal Atie kit for HbA1c were used). Additionally, all patients underwent an abdominal ultrasonography before the operation to confirm the diagnosis of cholelithiasis. The medical staff also measured blood pressure, body mass index (BMI is calculated by dividing a person's weight in kilograms by the square of their height in meters), waist circumference, and hip circumference using a sphygmomanometer, a weighing scale, a height scale, and a measuring tape. All of these items were also performed for the control group.

In this study, we utilized the metabolic score for insulin resistance (METS-IR) value which was introduced in 2018 as a novel insulin resistance (IR) value:

$$METS - IR = \frac{(Ln)\{(2 \times FBS) + (Fasting\ TG) \times BMI\}\text{Error! Bookmark not defined.}}{Ln(HDL)}$$

Also, to examine the amount of hepatic fibrosis, Fibrosis-4 index (FIB-4) was used and it was calculated through the following formula:

$$FIB - 4\ index = \frac{Age \times AST}{Platelet\ count \times \sqrt{ALT}}$$

Data were analyzed by using SPSS software Version 23 (IBM, Armonk, NY, USA). We reported descriptive statistics via frequency tables, means, and standard deviations. Also, for interferential analysis, chi-square and logistic regression analysis were used. The significance level of 0.05 was considered.

This research was approved by the Ethics Committee of Mashhad University of Medical Sciences, a member of the IR.MUMS.REC.1401.015. All participants provided written informed consent, and they did not incur any additional costs.

Results

A total of 216 patients diagnosed with GSD were enrolled, with 85.6% of them were females, and their mean BMI was 30.26±6.64. The mean age of the patients was 44.74±13.64 years. The mean size of the stones was measured as 15.35±11.47 millimeters. Regarding the medical history of the participants, 25 patients had known thyroid disease, and 50 patients had hyperlipidemia in their past medical history. Moreover, 23 patients reported opium abuse, while alcohol abuse was reported by 3 of them. The main findings of ultrasonography included increased gallbladder thickness (88%), fluid around the gall bladder (2.8%), and gallbladder polyp (2.3%). Less than 5 percent of the stones were in extrahepatic ducts. No significant differences were observed between the case and control groups regarding age and gender (P>0.05). The univariate analysis illustrated that individuals with GSD exhibited higher weight, BMI, hip and waist circumference, waist-to-hip circumference ratio, triglycerides (TG), low-density lipoprotein (LDL), fasting blood sugar (FBS), atherogenic factor, METS-IR, and hypertension incidence compared to those without GSD. Conversely, HDL levels were significantly lower in subjects with GSD (table 1).

Applying diagnostic criteria for MetS revealed 157 cases of MetS in both groups. Surprisingly, 109 patients of the GSD group had MetS, while only 48 subjects of the control group fulfilled the MetS criteria. A comparative analysis of metabolic indexes between GSD patients with MetS and those without indicated significant differences (table 2).

We observed that the group of GSD patients who also had MetS were older than the other GSD patients and had remarkably elevated levels of LDL, TG, and cholesterol, and decreased levels of HDL. DM and FBS levels were also significantly higher in patients with MetS. Moreover, the calculation of METS-IR showed that MetS patients were more insulin-resistant. The frequency of hypertension, as one of the criteria for MetS, was remarkably greater in patients with MetS (table 2).

Table 1. Comparing the criteria for MetS between the patients with GSD vs. the control group.

Variable	Control (n=216)	Case (n=216)	Total	P-value
Gender n (%) **Male** **Female**	 28 (13.0) 187 (87.0)	 31 (14.4) 184 (85.6)	 59 (13.7) 371 (86.3)	 C 0.674
Age (year)	46.51±11.44	44.74±13.64	45.63±12.61	t 0.144
Weight (kg)	70.55±13.06	74.96±19.43	72.76±16.68	t 0.006**
Height (cm)	157.55±7.03	157.10±9.38	157.33±8.28	t 0.576
BMI (kg/m^2)	28.40±5.05	30.26±6.64	29.33±5.97	t 0.001**
Hip (cm)	105.11±9.86	108.59±14.17	106.86±12.32	t 0.003**
Waist (cm)	70.55±13.06	96.12±14.54	83.31±18.82	t 0.0001**
Waist/Hip Ratio (cm)	0.64±0.14	0.89±0.07	0.77±0.15	t 0.0001**
Cholesterol (mg/dl)	189.13±40.42	173.92±44.87	181.66±43.29	t 0.0001**
Triglyceride (mg/dl)	129.05±70.55	148.72±78.60	138.86±75.23	t 0.007**
HDL (mg/dl)	46.78±10.56	44.23±10.33	45.53±10.51	t 0.013*
LDL (mg/dl)	108.63±37.91	121.00±41.88	114.67±40.33	t 0.002**
FBS (mg/dl)	95.81±39.23	105.00±32.74	100.40±36.38	t 0.009**
Atrogenic Factor	2.43±0.98	2.88±1.17	2.65±1.10	t 0.0001**
METS-IR	42.75±9.02	47.16±11.42	44.91±10.49	t 0.0001**
HTN n (%) **Yes** **No**	 63 (29.2) 153 (70.8)	 86 (39.8) 130 (60.2)	 149 (34.5) 283 (65.5)	 C 0.020*
DM n (%) **Yes** **No**	 30 (13.9) 186 (86.1)	 32 (14.8) 184 (85.2)	 62 (14.4) 370 (85.6)	 C 0.784

For quantitative variables Mean±SD and for qualitative data the Count (%) is reported., t) Student test, C) Chi-Square test, F) Fisher's Exact Test.*) P<0.05, sig., HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FBS: Fasting blood sugar, METS-IR: Metabolic score for insulin resistance, HTN: Hypertension, DM: Diabetes mellitus

Table 2. Comparing the criteria for MetS between the GSD patients with and without MetS

Variable	GSD patients without MetS (n=107)	GSD patients with MetS (n=109)	P-value
Gender n (%)			
Male	15 (14.0)	16 (14.7)	C 0.890
Female	92 (86.0)	93 (85.3)	
Age (year)	41.28±12.81	48.14±13.63	t 0.0001**
Weight (kg)	71.54±16.50	78.33±21.47	t 0.010*
Height (cm)	158.30±9.06	155.93±9.57	t 0.063
BMI (kg/m^2)	28.44±5.62	32.04±7.09	t 0.0001**
Hip (cm)	104.47±12.13	112.61±14.90	t 0.0001**
Waist (cm)	90.80±12.99	101.28±14.14	t 0.0001**
Waist/Hip Ratio (cm)	0.86±0.06	0.89±0.08	t 0.005**
Cholesterol (mg/dl)	161.65±39.70	186.68±46.54	t 0.0001**
Triglyceride (mg/dl)	120.16±51.78	176.75±89.81	t 0.0001**
HDL (mg/dl)	48.46±10.21	40.17±8.72	t 0.0001**
LDL (mg/dl)	114.07±39.29	127.74±43.39	t 0.019*
FBS (mg/dl)	93.10±16.27	116.68±39.96	t 0.0001**
Atrogenic_Factor	2.47±0.95	3.27±1.23	t 0.0001**
METS-IR			t 0.0001**
HTN n (%)			
Yes	22 (20.6)	64 (58.7)	C 0.0001**
No	85 (79.4)	45 (41.3)	
DM n (%)			
Yes	1 (0.9)	31 (28.4)	C 0.0001**
No	106 (99.1)	78 (71.6)	

For quantitative variables Mean±SD and for qualitative data the Count (%) is reported.
t) Student test, C) Chi-Square test, F) Fisher's Exact Test
*) P<0.05, sig.HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FBS: Fasting blood sugar, METS-IR: Metabolic score for insulin resistance, HTN: Hypertension, DM: Diabetes mellitus

Discussion

In the present case-control study, we compared the MetS criteria among patients with GSD and a control group. To the best of our knowledge, this is one of the first studies in Iran to focus on the association between MetS and GSD. Our results revealed that patients with GSD had significantly greater anthropometric values, more disturbed lipid profiles, and higher insulin resistance. A national survey conducted in the USA revealed that the prevalence of cholelithiasis is high, ranging from 13.9% to 26.7% in women and 5.3% to 8.9% in men (1). In Iran, the prevalence of gallstones has been reported to be between 2.4% and 6.3%, and women are at a higher risk for GSD, approximately twice as much as men (11, 12). Our study also confirmed this issue, as 85.6% of the gallstone patients were females. It is widely believed that there is a possible association between sex hormones and cholesterol metabolism (13). Most of the previous investigations have shown female predominance in the prevalence of GSD as well as their higher risk for GSD development (14). In contrast, Liu et al. denied the correlation between gender and GSD (15). The mean age of our participants was 44.74±13.64, following the findings of Lirussi et al. which indicated a significant correlation between age and cholelithiasis, which was more prominent in women. This can be explained by the fact that people of older age have been more exposed to chronic risk factors such as alcohol drinking, hyperlipidemia, and diabetes, leading to decreased motility of the gallbladder (16).We discovered that hyperlipidemia, overweightness, insulin resistance, and diabetes were more common in patients with GSD. Similarly, Chen et al. (13) stated that hyperlipidemia, high BMI, and insulin resistance contribute to GSD pathogenesis by altering the motility of the gallbladder. The first step in

GSD formation is the separation of cholesterol crystals from super-saturated bile. Phospholipids and bile acids make cholesterol more soluble and prevent precipitation. Phospholipid transfer protein (PLTP) transfers lipids from LDL to HDLs. However, in hyperlipidemia, haptoglobin inhibits PLTP, reversing cholesterol transport.

Approximately 12% of our participants had the habit of addiction. Of them, 10% had opium addiction. Despite the results of our study, it shows that the frequency of opiate derivates abuse in different regions of Iran ranges from 1.2% to 8.6% among the general population (17), which highlights the role of opium abuse in the pathogenesis of gallstone bladder. Consistent with this, the results of a previous study represented that 53.6% of patients with gallstones are addicted to opium (18). One of the effects of opium on the bile system is disturbing the function of Oddi's sphincter, which results in delayed emptying of the gallbladder contents. This spasm increases the intra-CBD pressure and causes problems in the discharge of bile into the duodenum. Following the increase in intra-CBD pressure, the dilatation of CBD happens (19-21). Three patients in our study had alcoholism habits. Alcohol consumption is considered a contributing factor for gallstone formation (22). In opposition to this, evidence shows that intake of small to moderate amounts of alcohol reduces the biliary cholesterol saturation index and acts as protective, accordingly (23). In our study, 50.4% of patients with GSD had metabolic syndrome. The association between GSD and MeS has never been explored before 2005. Then, Mendez-Sanchez et al. (24) presented the first article, which showed a strong association between them. Their results were so surprising that the authors concluded that even GSD may be characteristic of MeS. Consequently, their results were confirmed by studies with larger sample sizes (13). In line with this, a study recommended prophylactic surgery for patients with MeS (25).Obesity is an important risk factor for the development of GSD particularly for women. Consistently, it is shown that women with a BMI of 30 or higher are at least 2 times more prone to the formation of gallbladder stones (22, 26-28). Our results illustrated that the mean waist and hip circumferences as well as waist-hip ratio were notably greater in patients with GSD compared with the controls. In line with a similar study (29), our results showed that the mean waist and hip circumference was greater in patients with GSD compared with the controls. Currently, there is an increasing prevalence of obesity, reaching 20.9% of the United States population (30). Following this, in Mexican-American individuals, the frequency of high waist circumference in patients with MetS is higher (62.7%) (31).

Moreover, in the present study, we measured insulin resistance through using METS-IR which we found to be significantly higher in patients with GSD compared with the controls (P = 0.0001). This increased rate of insulin resistance could be due to the presence of obesity, which is a major risk factor for the development of GSD. In obese individuals, because of excessive synthesis of cholesterol, lithogenic bile is produced (32). Additionally, it is reported that the increased levels of plasma insulin in obesity can be a determinant in developing GSD. Scragg et al. (33), showed that insulin concentration of plasma was higher in patients with GSD. They also found that increased plasma insulin levels in patients with obesity elevate the bile cholesterol saturation index. It is demonstrated that an increase in insulin level of 10 µU/mL was correlated with an increased relative risk of developing GSD in women (34). The mechanism by which insulin increases gallstone formation can be explained by increasing the activity of hydroxy-3-methylglutaryl-coenzyme A reductase. Furthermore, insulin has been reported to stimulate the flow of bile acids (35, 36). Reduced levels of HDL are a main characteristic of metabolic syndrome, which is associated with an increased risk of cardiovascular diseases and higher morbidity and mortality (37). Interestingly, it is illustrated that HDL levels are negatively correlated with the bile cholesterol saturation index (38). In this study, we recruited FIB-4 score to evaluate fibrosis degree. We found that the mean score of FIB-4 was 0.81±0.39. Scores of less than 1.45 are illustrative of the absence of advanced liver fibrosis. Unfortunately, we FIB-4 score was not measured in the control group and it was not compared among the groups, accordingly (Due to a lack of access to liver enzymes in the control group). However, the literature has shown that cirrhosis is a well-known risk factor for the formation of gallstones. Liver cirrhosis may lead to gallbladder hypomotility, bile malabsorption, reduced bile synthesis, increased enterohepatic cycling of unconjugated bilirubin, and gallstones (39). Another possible explanation for gallstone formation in liver cirrhosis may be due to steatohepatitis, which acts as a key etiology of advanced hepatic fibrosis, and a hepatic component of metabolic dysfunctions such as representing insulin resistance (40).In line with our study, the PERSIAN Guilan cohort study population demonstrates an association between Metabolic Syndrome and Gallstone Disease. It shows that metabolic syndrome is significantly associated with an increased risk of gallstone disease, and higher BMI, greater waist circumference, and lower HDL levels are the most significant risk factors for gallstone disease (41). Wang et al. demonstrated the relationship between MetS and GSD,

highlighting a complex bidirectional interaction supported by shared biological mechanisms. These mechanisms include insulin resistance, lipid metabolism disorders, obesity, and dysbiosis of gut microbiota. Their thorough review establishes an integrated framework that connects epidemiological observations with mechanistic explanations, providing a solid foundation for improved clinical management strategies. Understanding these connections allows for better risk prediction and targeted interventions. By addressing the components of MetS through lifestyle modifications, appropriate pharmacological treatments, and potential microbiome modulation, it may be possible to simultaneously reduce the risk of GSD, which ultimately leads to better patient outcomes. This integrated approach, bolstered by emerging mechanistic insights, suggests a promising direction for both the prevention and treatment of these increasingly common conditions (42). This study was conducted at a single center, which constitutes a significant limitation due to the restricted sample size. Furthermore, due to the lack of access to liver enzymes in the control group, we could not calculate the FIB-4 index. Similar to cardiovascular diseases and diabetes mellitus, GSD seems to be significantly associated with MetS. These results also confirm the hypothesis that insulin resistance has an important role in the pathogenesis of such diseases and that GSD may be a part of MetS. Ultimately, our findings underscore the importance of routinely conducting MetS assessments in patients diagnosed with GSD, leading to early diagnosis and improved treatment outcomes.

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Ethics approval: This study was conducted by the current (2024) version of the Helsinki Declaration. The patients did not incur any additional costs and the data was only used for generating study findings. This research was approved by the Ethics Committee of Mashhad University of Medical Sciences, a member of the IR.MUMS.REC.1401.015.

Conflict of interests: The authors have no competing interests to declare.

Authors' contribution: Conceptualization: TZ - Methodology and Formal analysis: MM and YR- Investigation, Data curation: VAB, AD, and ARR- Writing- Original draft: VAB - Writing - review & editing: TZ and VAB.

Consent to participate: Written informed consent was obtained from all participants included in the study.

References

1. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999; 117: 632-9.
2. Aerts R, Penninckx F. The burden of gallstone disease in Europe. Aliment Pharmacol Ther 2003; 18: 49-53.
3. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut Liver 2012; 6: 172-87.
4. Miquel JF, Covarrubias C, Villaroel L, et al. Genetic epidemiology of cholesterol cholelithiasis among Chilean Hispanics, Amerindians, and Maoris. Gastroenterology 1998; 115: 937-46.
5. Toosi FS, Ehsanbakhsh AR, Tavakoli MR. Asymptomatic gallstones and related risk factors in Iran. Hepatogastroenterology 2011; 58: 1123-6.
6. Massarrat S. Prevalence of gallstone disease in Iran. J Gastroenterol Hepatol 2001; 16: 564-7.
7. Reshetnyak VI. Concept of the pathogenesis and treatment of cholelithiasis. World J Hepatol 2012; 4: 18.
8. Pak M, Lindseth G. Risk factors for cholelithiasis. Gastroenterol Nurs 2016; 39: 297-309.
9. Expert Panel on Detection E. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001; 285: 2486-97.
10. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006; 23: 469-80.
11. Farzaneh E, Zavvareh HT, Gharadaghi J, Sheikhvatan M. Prevalence and characteristics of gallstone disease in an Iranian population: a study on cadavers. Hepatobiliary Pancreat Dis Int 2007; 6: 509-12.
12. Ansari-Moghaddam A, Khorram A, Miri-Bonjar M, Mohammadi M, Ansari H. The prevalence and risk factors of gallstone among adults in South-East of Iran: A population-based study. Glob J Health Sci 2016; 8: 60.
13. Chen LY, Qiao QH, Zhang SC, et al. Metabolic syndrome and gallstone disease. World J Gastroenterol 2012; 18: 4215.
14. Unisa S, Jagannath P, Dhir V, et al. Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India. HPB (Oxford) 2011; 13: 117-25.
15. Liu CM, Tung TH, Chou P, et al. Clinical correlation of gallstone disease in a Chinese population in Taiwan:

experience at Cheng Hsin General Hospital. World J Gastroenterol 2006; 12: 1281-6.
16. Lirussi F, Nassuato G, Passera D, et al. Gallstone disease in an elderly population: the Silea study. Eur J Gastroenterol Hepatol 1999; 11: 485-92.
17. Momtazi S, Rawson R. Substance abuse among Iranian high school students. urr Opin Psychiatry 2010; 23: 221-6.
18. Agah S, Fereshtehnejad S, Rahmati NT. Assessment of the prevalence of gallstone in ultrasonography of gallbladder and biliary duct among hospitalized patients in Rasool-Akram hospital during 2000-2004. Razi J Med Sci 2008; 4: 7-13. [in Persian].
19. Druart-Blazy A, Pariente A, Berthelemy P, Arotçarena R. The underestimated role of opiates in patients with suspected sphincter of Oddi dysfunction after cholecystectomy. Gastroenterol Clin Biol 2005; 29: 1220-3.
20. Sherman S, Gottlieb K, Uzer MF, et al. Effects of meperidine on the pancreatic and biliary sphincter. Gastrointest Endosc 1996; 44: 239-42.
21. Zahedi-Nejad N, Narouei S, Fahimy F. Common bile duct (CBD) diameter in opium-addicted men: comparison with non-addict controls. Pol J Radiol 2010; 75: 20-4.
22. Song ST, Shi J, Wang XH, et al. Prevalence and risk factors for gallstone disease: a population-based cross-sectional study. J Dig Dis 2020; 21: 237-45.
23. Wang J, Duan X, Li B, Jiang X. Alcohol consumption and risk of gallstone disease: a meta-analysis. Eur J Gastroenterol Hepatol 2017; 29: e19-28.
24. Méndez-Sánchez N, Chavez-Tapia NC, Motola-Kuba D, et al. Metabolic syndrome as a risk factor for gallstone disease. World J Gastroenterol 2005; 11: 1653-7.
25. Ata N, Kucukazman M, Yavuz B, et al. The metabolic syndrome is associated with complicated gallstone disease. Can J Gastroenterol 2011; 25: 274-6.
26. Sichieri R, Everhart JE, Roth HP. Low incidence of hospitalization with gallbladder disease among blacks in the United States. Am J Epidemiol 1990; 131: 826-35.
27. Jørgensen T. Gall stones in a Danish population. Relation to weight, physical activity, smoking, coffee consumption, and diabetes mellitus. Gut 1989; 30: 528-34.
28. Dhamnetiya D, Goel MK, Dhiman B, Pathania OP. Risk factors associated with gallstone disease. Indian J. Community Health 2018; 30: 133-8.
29. Barbara L, Sama C, Labate AMM, et al. A population study on the prevalence of gallstone disease: the Sirmione Study. Hepatol 1987; 7: 913-7.
30. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002; 288: 1723-7.
31. Park Y-W, Zhu S,Palaniappan L, et al. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2003; 163: 427-36.
32. Heaton K, BRADDON FM, Emmett P, et al. Why do men get gallstones? Roles of abdominal fat and hyperinsulinaemia. Eur J Gastroenterol Hepatol 1991; 3: 745-51.
33. Scragg R, Calvert GD, Oliver JR. Plasma lipids and insulin in gall stone disease: a case-control study. Br Med J (Clin Res Ed) 1984; 289: 521-5.
34. Cortés VA, Barrera F, Nervi F. Pathophysiological connections between gallstone disease, insulin resistance, and obesity. Obes Rev 2020; 21: e12983.
35. Jaruvongvanich V, Sanguankeo A, Upala S. Significant association between gallstone disease and nonalcoholic fatty liver disease: a systematic review and meta-analysis. Dig Dis Sci 2016; 61: 2389-96.
36. Shabanzadeh DM, Skaaby T, Sørensen LT, Eugen-Olsen J, Jørgensen T. Metabolic biomarkers and gallstone disease–a population-based study. Scand J Gastroenterol 2017; 52: 1270-7.
37. Han TS, Lean ME. Metabolic syndrome. Medicine 2015; 43: 80-87.
38. Wang J, Shen S, Wang B, et al. Serum lipid levels are the risk factors of gallbladder stones: a population-based study in China. Lipids Health Dis 2020; 19: 1-6.
39. Vitek L, Carey M. Enterohepatic cycling of bilirubin as a cause of ‘black’pigment gallstones in adult life. Eur J Clin Invest 2003; 33: 799-810.
40. Kitade H, Chen G, Ni Y, Ota T. Nonalcoholic fatty liver disease and insulin resistance: new insights and potential new treatments. Nutrients 2017; 9: 387.
41. Fardi HZ, Mojtahedi K, Maroufizadeh S, Joukar F, Mansour-Ghanaei F. The association between metabolic syndrome and gallstone disease: A cross-sectional study from the PERSIAN Guilan cohort study. Endocr Metab Sci 2025; 17:100221.
42. Wang K, Liu Z, Tang R, et al. Gallstones in the Era of Metabolic Syndrome: Pathophysiology, Risk Prediction, and Management. Cureus 2025; 17: e80541.