WEB OF SCIENTIST: INTERNATIONAL SCIENTIFIC RESEARCH JOURNAL
ISSN: 2776-0979, Volume 4, Issue 7, July, 2023

"RISK FACTORS AFFECTING THE EARLY POSTOPERATIVE PERIOD DEPENDING ON THE BODY WEIGHT OF PATIENTS WITH CALCULOUS CHOLECYSTITIS. LITERATURE REVIEW»

Khudaybergenov S. A.
Abruev B. U.
Urmanova Yu. M.
Tashkent Pediatric Medical Institute, Department of Surgical Diseases,
Department of Endocrinology, Pediatric Endocrinology
Republic of Uzbekistan, 100140, Tashkent, Bogishamol str., house No. 223

Annotation

As you know, acute cholecystitis is a disease that, if left untreated, can develop into systemic inflammation and lead to sepsis, organ failure and even death. In patients with the same acute cholecystitis, the severity of the course varies significantly: from simple inflammation of the gallbladder wall to complications limited to the nearby area, and to concomitant multiple organ failure. In some cases, acute cholecystitis can easily turn into complicated cholecystitis, which in a short time undergoes secondary changes in the form of hemorrhages, gangrenous formations, perforations. However, it is currently difficult to predict whether patients with acute cholecystitis have a complicated or uncomplicated course. Therefore, it is extremely important to develop methods for predicting the progression of acute cholecystitis in patients.

According to various reports, patients who had a longer operation time in laparoscopic cholecystectomy were more prone to biliary tract damage, and obese patients had a higher conversion rate as well as a higher proportion of biliary tract damage. At the same time, there are studies that have not confirmed intra- and postoperative complications associated with obesity.

The above was the reason for this study.

Keywords: obesity, calculous cholecystitis, laparoscopic cholecystectomy

Introduction

Obesity has become a global problem. The increase in the number of obese people has become a national ailment not only in the United States [1] and Europe, but also in Asia and Japan [2]. Moreover, over the past 10 years, the prevalence of obesity in Japan has increased with age [3], and the transition from overweight to obesity has become more pronounced in women than in men [4].

Obesity has been reported to be a positive predictor of surgical morbidity. Some previous reports have shown that obesity is a positive predictor of surgical morbidity or poor prognosis for procedures such as gastrectomy [5], colectomy [6], hepatectomy [7-9], and laparoscopic cholecystectomy (LC) [10, 11]. Meanwhile, others report that obesity does not increase morbidity or mortality after gastrectomy [12] and hepatectomy [13].

HL is a standard surgery for benign gallbladder lesions. As soon as complications arise, the damage to the quality of life of patients becomes very profound. Only a few reports have evaluated the effect of obesity-related comorbidities on operational risk in patients after HL. This study aimed to compare outcomes between obese and non-obese patients after HL.

The first report on the effects of obesity and calorie intake on lipid metabolism in the biliary tract in humans was published in 1975 by Bennion LJ, Grundy SM. [59] . It was concluded that obesity is characterized by excessive hepatic secretion of cholesterol, which leads to a glut of bile. Bile cholesterol saturation did not decrease with weight loss, apparently due to the mobilization of cholesterol from fat depots and the marked reduction in bile acid and phospholipid yield seen in chronic calorie restriction. Acute changes in calorie injection rates did not fully replicate the effects of chronic administration of high- and low-calorie diets. Similarly, chronic consumption of hypercaloric diets by non-obese subjects did not reproduce hypersecretion cholesterol, characteristic of obese people.

The above was the reason for this study.

The aim of the study was to review the literature on the effect of obesity and disorders of carbohydrate and lipid metabolism on the early postoperative period in patients after cholecystectomy.

Prevalence of obesity and calculous cholecystitis. The World Health Organization (WHO) defines overweight and obesity as pathological conditions with abnormal or excessive accumulation of fat. Obesity tends to involve a complex interaction between genetic and environmental factors, such as culture, socioeconomic status, and lifestyle, leading to an alarming health problem in the 21st century. According to the WHO, the overall prevalence of obesity has doubled in the United States and in most Western countries since 1980 and nearly tripled worldwide between 1975 and 2016 [14]. A total of 1.9 billion people were overweight and 650 million adults were obese in 2016, representing 39% and 13% of the world's population, respectively [14].

Obesity rates are expected to continue to rise and are projected to reach 35% by 2025 [15]. Obesity is associated with significant ill health consequences, including cardiovascular disease, hypertension, and diabetes [16]. Consequently, obesity is associated with increased morbidity and mortality compared to the general population [16]. In surgery, obesity is perceived as a risk factor for adverse postoperative outcomes, including a poorer prognosis and increased morbidity [17].
Obesity is a well-known risk factor for gallstones [18,19]. Cholesterol stones are the most common type of gallstones found in obese people. The formation of cholesterol stones in obesity is multifactorial and is primarily associated with metabolic disorders associated with hypersecretion of cholesterol by the liver [20, 21]. This increase in cholesterol secretion is associated with the activation of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which is activated in obesity by hyperinsulinemia [22-24]. The formation of gallstones is also accelerated with rapid weight loss after a very low-calorie diet or after bariatric surgery. Given these associations, obese people are more likely to have symptomatic gallstone disease requiring surgical treatment.
Laparoscopic cholecystectomy (HL) is considered the gold standard for the treatment of acute cholecystitis [25]. Current literature suggests that HL in obese patients is associated with greater technical difficulties, increased conversion to open surgery, and higher rates of infection of the surgical site [26-27]. The technical difficulty during HL in obese patients is related to the problems associated with access to the abdominal cavity due to the larger pannus of the abdominal wall and the large amount of intra-abdominal fat, which makes it difficult to adequately intervene as well as adhesions. which arise as a result of the inflammatory process of cholecystitis with adjacent viscera and fat. These intraoperative findings make it difficult to uncover the anatomy of Kahlo's triangle, and hence conversion to open cholecystectomy may sometimes be necessary. Other causes of conversion during HL in obese patients are severe inflammation and gallbladder necrosis, making laparoscopic dissection risky and unexpected bleeding.

Known risk factors influencing the early postoperative period.

According to the WHO [28], the Asian population has a different relationship between BMI, body fat percentage and health risk than the European population. Thus, it can be assumed that the health risk threshold for Asians is lower than the existing WHO threshold. Some reports used a value of 25 kg/m2 as the BMI threshold for obesity in Japanese [29] and Koreans [30], respectively.
A retrospective study of patients undergoing HL at the North Yokohama Hospital of Showa University from January 2017 to April 2020 (Japan) was conducted. A total of

563 cases were considered. The data were divided into two groups: the obese group (n = 142) (body mass index [BMI] ≥ 25 kg/m2) and the non-obese group (n = 241) (BMI < 25 kg/m2) [31]. The degree of obesity in the patient affected and prolonged the time of surgery, but did not affect the patient's outcome in this study. In conclusion, the authors noted that although surgery time was increased in obese patients, bleeding volume, conversion rate, complications, and length of hospital stay were not increased; therefore, HL can also be safely performed in obese patients with the same efficacy as in non-obese patients.

Other authors have shown that the operation time was significantly longer in obese patients, since the amount of fat in the abdominal cavity was large, which took a long time to remove and remove [32, 33]. In addition, it was difficult to separate the gallbladder from the gallbladder bed.

In 2021, the results of a multi-country study (USA, Taiwan) were published, which showed that morbid (morbid) obesity, but not obesity, is associated with increased mortality in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP). The authors conducted a retrospective cohort study of the U.S. population using nationwide readmission databases (2013–2014). A total of 159,264 eligible patients were identified who had undergone ERCP, of which 137,158 (86.12%) were of normal weight, 12,522 (7.86%) were obese and 9584 (6.02%) were morbidly obese. The primary outcome was in-hospital mortality (greater than 1%). Secondary outcomes were length of stay, total cost, and complications associated with ERCP [34]. This study found that obesity is associated with a higher rate of severe and fatal outcomes.

A systematic study of 16,855 patients undergoing ERCP found that 1.33% of patients developed cardiopulmonary complications after ERCP, which directly led to a mortality rate of 0.07%. [35]. A higher BMI was associated with an increased incidence of sedation-related complications, mainly pulmonary events, including apnea, oxygen desaturation, and airway obstruction with advanced endoscopic procedures.

According to the Indian authors, preoperative and intraoperative factors such as male sex, advanced age, body mass index (BMI), history of abdominal surgery, leukocytosis, and ultrasound findings such as gallbladder distension, thick gallbladder mucosa, injected stone, and accumulation of pericholecystic fluid are risk factors. which makes LH technically complex and time-consuming [60]. At the same time, their The study concluded that gallbladder wall thickness, hammered stone, and previous cholecystitis attacks were significant risk factors in predicting complex laparoscopic cholecystectomy in the setting of acute calculous cholecystitis.

A multicenter study in Sweden in 2022 included 1,634 patients treated for acute cholecystitis at three Swedish centers between 2017 and 2020 [61]. The data was collected from electronic patient records and the Swedish gallbladder surgery registry Gallriks. Logistic regression was used to assess the risk of complications, adjusted for confounding factors: gender, age, BMI, Charlson's comorbidity index, degree of cholecystitis, smoking, and time to surgery. 725 patients were operated on an emergency basis for acute cholecystitis, 195 with SZ-1 (mild systemic disease), 375 with SZ-2 (moderate systemic disease), and 152 with SZ-3 (severe systemic disease). Complications occurred in 9% of patients with SZ-1, 13% with SZ-2, and 24% with SZ-3. Patients with SZ-3 stayed an average of 2 days longer after surgery. After adjusting for other factors, the risk of complications in patients with SZ-3 was 2.5 times higher than in patients with SZ-1. The risk of complications after elective surgery was 5% for patients with SZ-1, 13% for patients with SZ-2 and 14% for patients with SZ-3. Regardless of SZ, 18% of patients receiving conservative treatment had a second complication of cholelithiasis within 3 months.

The effect of obesity on outcomes in patients undergoing emergency cholecystectomy for acute cholecystitis was studied in a multicenter study in Australia (2022). A retrospective review of patients who underwent emergency HL for acute cholecystitis in the period from March 2018 to March 2021 was carried out. A total of 326 patients who were stratified by body mass index (BMI) into two groups: obese (BMI ≥30 kg/m2, n = 156) and non-obese (BMI <30 kg/m2, n = 170). Primary outcomes included length of hospital stay, time to radical surgery, and postoperative complications. Secondary outcomes included total surgery time and intraoperative findings. [62]. This study also found that although obesity was associated with greater difficulty in surgery, emergency HL can be safely performed in the treatment of acute cholecystitis, with similar postoperative outcomes achieved in both obese and non-obese groups. These results are consistent with previous studies that evaluated the safety of elective HL in obese patients, who found that obesity was not associated with higher complications after surgery compared to non-obese patients [63-66]. While most studies did not report significant differences in conversion rates between groups, the Paajanen H. *et al.*found that obesity was associated with a higher conversion rate (11.7% vs. 6.1%, $p = 0.0003$) than in non-obese patients [67].

Features of changes in biomarkers of inflammation in calculous cholecystitis with obesity.

It is now known that white adipose tissue (BLT) is an endocrine organ that plays a key role in regulating metabolism, inflammation, and energy intake in addition to fat

storage [36]. Adipose tissue performs these functions by secreting cytokines, chemokines, and hormones, which are collectively called adipocytokines. Human obesity leads to an increase in leptin and a decrease in the production of adiponectin by adipocytes. These adipokines affect the infiltration of macrophages into fat, which in turn increases the production of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β. [36, 37]. Thus, visceral steatosis causes a local inflammatory process leading to organ dysfunction, with a well-known example of this phenomenon being non-alcoholic steatohepatitis.²In addition, gallbladder inflammation is known to occur in the early stages of gallbladder disease and is partly due to the effects of absorbed lipids from bile.

It is known that hypertrophied adipocytes in obesity produce an increased amount of TNF-α. [38]. Moreover, these adipocytes develop reduced insulin sensitivity, which leads to an increased accumulation of triglycerides and a subsequent increase in adipocytes. [39, 40]. Hirata et al. hypothesized that cytokine secretion increases as the size of fat cells increases [41]. They found that increased triglyceride synthesis in adipocytes was associated with a concomitant increase in TNF-α expression. What's more, inhibition of triglyceride synthesis improved this increased production of TNF-α. We showed a similar phenomenon with triglyceride levels in the gallbladder parallel to the expression of the TNF-α protein. Tumor necrosis factor-α also causes dysfunction of smooth muscle contractility, absorption, insulin resistance, and lipid peroxidation. [42, 43]. In addition, TNF-α increases the secretion of mucin, which is a cholesterol pronucleating agent. Inflammation of the gallbladder wall and hypersecretion of mucin have been shown to occur before gallstones form [44].

Serum FFA levels in obese people have been shown to correlate with serum IL-6 levels [45, 46]. In addition, among FFAs, only saturated palmitic and myristic acids have been shown to correlate with IL-6 levels. [47]. This correlation is confirmed by animal studies showing the induction of IL-6 secretion in adipocytes by palmitates [48]. Authors showed that the total amount of saturated free fatty acids in the gallbladder, palmitic and myristic acids is increased in obese mice on a diet with 45% CHO. In addition, in this group, the level of IL-6 is maximally increased. The consequences of an increase in IL-6 levels are increased insulin resistance, lipid peroxidation, and smooth muscle dysfunction [49]. Xiao et al. have documented that inflammation of the gallbladder leads to increased rates of oxidative stress. [50]. A potential mechanism for this observation may be lipid peroxidation induced by IL-6. In addition, hyperinsulinemia, secondary to increased insulin resistance, has been independently shown to increase oxidative stress in tissues. Oxidative stress, in turn,

causes damage to transmembrane receptors, such as cholecystokinin receptors, resulting in reduced contractility. [51].

-Interleukin-1β, in addition to enhancing the effects of IL-6 on smooth muscle contractility and insulin resistance, also affects gallbladder absorption [51]. Rege et al. have shown that cytokines of the IL-1 family can alter the absorption and secretion of the gallbladder. Normal concentration and acidification of bile protect against the formation of gallstones [52]. Therefore, IL-1β, by altering absorption, can enhance the formation of gallstones. The gallbladders of gallstone patients have been shown to have elevated cholesterol levels and a cholesterol/phospholipid ratio and reduced contractility. [53]. In addition, the elimination of excess cholesterol from the smooth muscles of the gallbladder normalized membrane fluidity and muscle contractility.

These studies document that obesity and dietary carbohydrates increase total fat, triglycerides, and cholesterol in the gallbladder while increasing TNF-α and IL-1β levels in the gallbladder. In addition, obesity increases the amount of free fatty acids and IL-6. These findings suggest that obesity increases gallbladder fat and cytokines, and a high-carbohydrate diet exacerbates this phenomenon. Steatocholecystitis can, in turn, alter the mobility and absorption of the biliary tract, leading to biliary dyskinesia and eventually gallstones.

According to a recent multicenter study in Korea (2020), Serum visfatin levels may reflect the severity of inflammation in patients with acute cholecystitis. Visfatin is a key cytokine released by peripheral blood mononuclear cells (MCCs) as well as adipose tissue, and it is involved in the immune response as well as inflammation. The authors concluded that visfatin is a pro-inflammatory mediator that is activated during acute cholecystitis and is expected to increase for a short time after inflammation. Thus, measuring serum visfatin levels may be useful in predicting the severity of inflammation in patients with acute cholecystitis [54]. When considering the role of visfatin in gallbladder disease, attention should be paid to the fact that obesity is one of the most significant risk factors for gallstones [55 , 56]. It has been reported that in patients with obesity and type 2 diabetes mellitus, the level of circulating visfatin is significantly higher than in the control group [57], suggesting a strong link between visfatin and obesity-related inflammatory diseases, including diabetes, atherosclerosis, dyslipidemia and gallstone disease. Obesity is inevitably accompanied by an inflammatory response, which is characterized by elevated levels of systemic inflammatory cytokines and the accumulation of macrophages in adipose tissue [58] . In conclusion, the authors showed that visfatin may be a valuable early prognostic factor in acute cholecystitis. Patients with acute cholecystitis had higher

levels of visfatin mRNA in the MCPC, higher serum levels of visfatin, and higher levels of visfatin protein in the gallbladder than patients with chronic cholecystitis.

Thus, based on the literature review, we can conclude: there is an increased risk of peri/postoperative complications in patients with SZ-3. Patients with SZ-3, if they are not candidates for emergency care, may be prioritized for elective procedures due to the high risk of second gallstone complications, while patients with SZ-1 and SZ-2 are operated on in acute care settings.

Future studies will aim to identify a subgroup of patients at low risk of complications, even if they are technically SZ-3, for example, morbid obesity-only patients who had myocardial infarction many years ago without functional limitations and transient ischemic attacks but without stroke. In addition, identifying patients who will relapse can further help the decision-making process. There are models for predicting the risk of recurrence of gallstone diseases for targeted surgery in the highest-risk population [68]. However, the risk is mainly determined by the type of complication of cholelithiasis, where pancreatitis poses the highest risk and cholecystitis is the second most dangerous, the authors report [68]

Findings

1. Patients with severe systemic disease have an increased risk of complications, but not death after emergency surgery. 2. The risk is lower with elective procedures, but a significant proportion of patients will have new cholelithiasis complications before elective surgery 3. Further research is needed on the effect of obesity on the outcomes of laparoscopic cholecystectomy due to the inconsistency of the literature to date.

Bibliography

1. Singh GK, Siahpush M, Hiatt RA, Timsina LR. Dramatic increases in obesity and overweight prevalence and body mass index among ethnic-immigrant and social class groups in the United States, 1976–2008. //J. Community Health. 2011;**36**:94–110. doi: 10.1007/s10900-010-9287-9.

2. McCurry J. Japan battles with obesity. //Lancet. 2007;**369**:451–452. doi: 10.1016/S0140-6736(07)60214-1.

3. Kuwahara K, Uehara A, Yamamoto M, Nakagawa T, Honda T, Yamamoto S, Okazaki H, Sasaki N, Ogasawara T, Hori A, Nishiura C, Miyamoto T, Kochi T, Eguchi M, Tomita K, Imai T, Nishihara A, Nagahama S, Murakami T, Shimizu M, Kabe I, Mizoue T, Kunugita N, Sone T, Dohi S. Current status of health among workers in Japan: Results from the Japan Epidemiology Collaboration on Occupational Health Study. //Ind. Health. 2016;**54**:505–514. doi: 10.2486/indhealth.2016-0082.

4. Hasegawa M, Akter S, Hu H, Kashino I, Kuwahara K, Okazaki H, Sasaki N, Ogasawara T, Eguchi M, Kochi T, Miyamoto T, Nakagawa T, Honda T, Yamamoto S, Murakami T, Shimizu M, Uehara A, Yamamoto M, Imai T, Nishihara A, Tomita K, Nagahama S, Hori A, Konishi M, Kabe I, Mizoue T, Kunugita N, Dohi S. Five-year cumulative incidence of overweight and obesity, and longitudinal change in body mass index in Japanese workers: The Japan Epidemiology Collaboration on Occupational Health Study. //J. Occup. Health. 2020;**62**:e12095. doi: 10.1002/1348-9585.12095.
5. Shimada S, Sawada N, Ishiyama Y, Nakahara K, Maeda C, Mukai S, Hidaka E, Ishida F, Kudo S. Impact of obesity on short- and long-term outcomes of laparoscopy assisted distal gastrectomy for gastric cancer. //Surg. Endosc. 2018;**32**:358–366. doi: 10.1007/s00464-017-5684-9
6. Champagne BJ, Nishtala M, Brady JT, Crawshaw BP, Franklin ME, Delaney CP, Steele SR. Laparoscopic colectomy in the obese, morbidly obese, and super morbidly obese: When does weight matter? //Int. J. Colorectal Dis. 2017;**32**:1447–1451. doi: 10.1007/s00384-017-2865-x
7. Yoshida N, Takayama T, Midorikawa Y, Higaki T, Nakayama H, Moriguchi M, Tsuji S. Surgical outcomes in patients with hepatocellular carcinoma associated with metabolic syndrome. //World J. Surg. 2015;**39**:471–477. doi: 10.1007/s00268-014-2828-0.
8. Langella S, Russolillo N, Forchino F, Tesoriere RL, D'Eletto M, Ferrero A. Impact of obesity on postoperative outcome of hepatic resection for colorectal metastases. // Surgery. 2015;**158**:1521–1529. doi: 10.1016/j.surg.2015.07.024.
9. Viganò L, Kluger MD, Laurent A, Tayar C, Merle JC, Lauzet JY, Andreoletti M, Cherqui D. Liver resection in obese patients: Results of a case–control study. //HPB. 2011;**13**:103–111. doi: 10.1111/j.1477-2574.2010.00252.x.
10. Paajanen H, Käkelä P, Suuronen S, Paajanen J, Juvonen P, Pihlajamäki J. Impact of obesity and associated diseases on outcome after laparoscopic cholecystectomy. //Surg. Laparosc. Endosc. Percutan. Tech. 2012;**22**:509–513. doi: 10.1097/SLE.0b013e318270473b.
11. Aziz H, Pandit V, Joseph B, Jie T, Ong E. Age and obesity are independent predictors of bile duct injuries in patients undergoing laparoscopic cholecystectomy. // World J. Surg. 2015;**39**:1804–1808. doi: 10.1007/s00268-015-3010-z.
12. Chen H, Sui W. Influence of obesity on short- and long-term outcomes after laparoscopic distal gastrectomy for gastric cancer. //J. BUON. 2017;**22**:417–423.

13. Guo Z, Zhang J, Jiang JH, Li LQ, Xiang BD. Obesity does not influence outcomes in hepatocellular carcinoma patients following curative hepatectomy. //PLoS ONE. 2015;**10**:e0125649. doi: 10.1371/journal.pone.0125649.
14.Chooi YC, Ding C, Magkos F. The epidemiology of obesity. // Metabolism 92: 6–10, 2019. doi:10.1016/j.metabol.2018.09.005
15.Hayes AJ, Lung TWC, Bauman A, Howard K. Modelling obesity trends in Australia: unravelling the past and predicting the future. Int. //J. Obes. (Lond) 2017; 41: 178–85.
16.Blüher M. Obesity: global epidemiology and pathogenesis. //Nat. Rev. Endocrinol. 2019; 15: 288–98.
17.Simopoulos C, Polychronidis A, Botaitis S, Perente S, Pitiakoudis M. Laparoscopic cholecystectomy in obese patients. Obes. Surg. 2005; 15: 243–6.
18.Cruz-Monserrate Z, Conwell DL, Krishna SG. The impact of obesity on gallstone disease, acute pancreatitis, and pancreatic cancer. Gastroenterol. //Clin. North Am. 2016; 45: 625–37.
19.Lammert F, Gurusamy K, Ko CW et al. Gallstones. //Nat. Rev. Dis. Primers. 2016; 2: 16024.
20.Erlinger S. Gallstones in obesity and weight loss. // Eur. J. Gastroenterol. Hepatol. 2000; 12: 1347–52.
21.Dittrick GW, Thompson JS, Campos D, Bremers D, Sudan D. Gallbladder pathology in morbid obesity. //Obes. Surg. 2005; 15: 238–42
22.Winfield RD, Reese S, Bochicchio K, Mazuski JE, Bochicchio GV. Obesity and the risk for surgical site infection in abdominal surgery. //Am. Surg. 2016; 82: 331–6.
23.Paajanen H, Käkelä P, Suuronen S, Paajanen J, Juvonen P, Pihlajamäki J. Impact of obesity and associated diseases on outcome after laparoscopic cholecystectomy. //Surg. Laparosc. Endosc. Percutan. Tech. 2012; 22: 509–13.
24. Afaneh C, Abelson J, Rich BS et al. Obesity does not increase morbidity of laparoscopic cholecystectomy. //J. Surg. Res. 2014; 190: 491–7.
25.Sugrue M, Sahebally SM, Ansaloni L, Zielinski MD. Grading operative findings at laparoscopic cholecystectomy- a new scoring system. // World J. Emerg. Surg. 2015; 10: 14
26. Farkas DT, Moradi D, Moaddel D, Nagpal K, Cosgrove JM. The impact of body mass index on outcomes after laparoscopic cholecystectomy. //Surg. Endosc. 2012; 26: 964–9.
27. Ammori BJ, Vezakis A, Davides D, Martin IG, Larvin M, McMahon MJ. Laparoscopic cholecystectomy in morbidly obese patients. // Surg. Endosc. 2001; 15: 1336–9.

28. WHO Expert Consultation Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. //Lancet. 2004;**363**:157–163. doi: 10.1016/S0140-6736(03)15268-3
29. Shimada S, Sawada N, Ishiyama Y, Nakahara K, Maeda C, Mukai S, Hidaka E, Ishida F, Kudo S. Impact of obesity on short- and long-term outcomes of laparoscopy assisted distal gastrectomy for gastric cancer. //Surg. Endosc. 2018;**32**:358–366. doi: 10.1007/s00464-017-5684-9.
30. Jang EJ, Roh YH, Choi CJ, Kim MC, Kim KW, Choi HJ. Comparison of outcomes after single-port laparoscopic cholecystectomy in relation to patient Body Mass Index. //JSLS. 2014;**18**(3):e2014.00048. doi: 10.4293/JSLS.2014.00048.
31. Enami Y, Aoki T, Tomioka K, Hakozaki T, Hirai T, Shibata H, Saito K, Takano Y, Seki J, Oae S, Shimada S, Nakahara K, Takehara Y, Mukai S, Sawada N, Ishida F, Murakami M, Kudo SE. Obesity is not a risk factor for either mortality or complications after laparoscopic cholecystectomy for cholecystitis. //Sci Rep. 2021 Jan 27;11(1):2384. doi: 10.1038/s41598-021-81963-5.
32. Sormaz İC, Soytaş Y, Gök AFK, Özgür İ, Avtan L. Fundus-first technique and partial cholecystectomy for difficult laparoscopic cholecystectomies. //Ulus Travma Acil Cerrahi Derg. 2018;**24**:66–70.
33. Tartaglia N, Cianci P, Lascia AD, Fersini A, Ambrosi A, Neri V. Laparoscopic antegrade cholecystectomy: A standard procedure?// Open Med. 2016;**11**:429–432. doi: 10.1515/med-2016-0078.
34. Chen B, Yo CH, Patel R, Liu B, Su KY, Hsu WT, Lee CC. Morbid obesity but not obesity is associated with increased mortality in patients undergoing endoscopic retrograde cholangiopancreatography: A national cohort study. //United European Gastroenterol J. 2021 Jun;9(5):561-570. doi: 10.1002/ueg2.12070. Epub 2021 May 5.
35. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. //Am J Gastroenterology. 2007;102:1781–8
36. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. // Am J Clin Nutr. 2006;83:461S–465S
37. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW., Jr Obesity is associated with macrophage accumulation in adipose tissue. //J Clin Invest. 2003;112:1796–808.
38. Ginanni Corradini S, Ripani C, Della Guardia P, Giovannelli L, Elisei W, Cantafora A, Codacci Pisanelli M, Tebala GD, Nuzzo G, Corsi A, Attili AF, Capocaccia L, Ziparo V. The human gallbladder increases cholesterol solubility in bile by differential lipid

absorption: A study using a new in vitro model of isolated intra-arterially perfused gallbladder. // Hepatology. 1998;28:314–22.
39. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: Direct role in obesity-linked insulin resistance. //Science. 1993;259:87–91.
40. Molina JM, Ciaraldi TP, Brady D, Olefsky JM. Decreased activation rate of insulin-stimulated glucose transport in adipocytes from obese subjects. //Diabetes. 1989;38:991–5.
41. Hirata T, Unoki H, Bujo H, Ueno K, Saito Y. Activation of diacylglycerol O-acyltransferase 1 gene results in increased tumor necrosis factor-alpha gene expression in 3T3-L1 adipocytes. //FEBS Lett. 2006;18;580:5117–21
42. Rege RV. Inflammatory cytokines alter human gallbladder epithelial cell absorption/secretion. J Gastrointest Surg. 2000;4:185–92. circular smooth muscle cell contractility by SP1- and NF-kappaB-mediated induction of ICAM-1. //Gastroenterology. 2004;127:1096–109.
43. Finzi L, Barbu V, Burgel PR, Mergey M, Kirkwood KS, Wick EC, Scoazec JY, Peschaud F, Paye F, Nadel JA, Housset C. MUC5AC, a gel-forming mucin accumulating in gallstone disease, is overproduced via an epidermal growth factor receptor pathway in the human gallbladder. //Am J Pathol. 2006;169:2031–41.
25. Rege RV, Prystowsky JB. Inflammation and a thickened mucus layer in mice with cholesterol gallstones. // J Surg Res. 1998;74:81–5.
44. Fernandez-Real JM, Broch M, Vendrell J, Ricart W. Insulin resistance, inflammation, and serum fatty acid composition. //Diabetes Care. 2003;26:1362–8.
45. Ghanim H, Aljada A, Hofmeyer D, Syed T, Mohanty P, Dandona P. Circulating mononuclear cells in obese are in a proinflammatory state. //Circulation. 2004;110:1564–71.
46. Ajuwon KM, Spurlock ME. Palmitate activates the NF-kappaB transcription factor and induces IL-6 and TNFalpha expression in 3T3-L1 adipocytes. //J Nutr. 2005;135:1841–6.
47. Cao W, Cheng L, Behar J, Fiocchi C, Biancani P, Harnett KM. Proinflammatory cytokines alter/reduce esophageal circular muscle contraction in experimental cat esophagitis. //Am J Physiol Gastrointest Liver Physiol. 2004;287:G1131–9.
48. Xiao ZL, Andrada MJ, Biancani P, Behar J. Reactive oxygen species (H(2)O(2)): effects on the gallbladder muscle of guinea pigs. //Am J Physiol Gastrointest Liver Physiol. 2002;282:G300–6.
49. Juge-Aubry CE, Henrichot E, Meier CA. Adipose tissue: a regulator of inflammation. //Best Pract Res Clin Endocrinol Metab. 2005;19:547–66

50. Jager J, Gremeaux T, Cormont M, Le Marchand-Brustel Y, Tanti JF. Interleukin-1{beta}-induced insulin resistance in adipocytes through down-regulation of insulin receptor substrate-1 expression. //Endocrinology. 2007;148:241–51.
51. Rege RV, Moore EW. Evidence for H+ secretion by the in vivo canine gallbladder. //Gastroenterology. 1987;92:281–9.
52. Gleason MM, Medow MS, Tulenko TN. Excess membrane cholesterol alters calcium movements, cytosolic calcium levels, and membrane fluidity in arterial smooth muscle cells. Circ Res. 1991;69:216–227.
53. Chen Q, Amaral J, Biancani P, Behar J. Excess membrane cholesterol alters human gallbladder muscle contractility and membrane fluidity. //Gastroenterology. 1999;116:678–685.
54. Park JW, Kim OH, Lee SC, Kim KH, Hong HE, Seo H, Choi HJ, Kim SJ. Serum level of visfatin can reflect the severity of inflammation in patients with acute cholecystitis. //Ann Surg Treat Res. 2020 Jul;99(1):26-36. doi: 10.4174/astr.2020.99.1.26.
55. Bonfrate L, Wang DQ, Garruti G, Portincasa P. Obesity and the risk and prognosis of gallstone disease and pancreatitis. //Best Pract Res Clin Gastroenterol. 2014 Aug;28(4):623-35. doi: 10.1016/j.bpg.2014.07.013
56. Shiffman ML, Sugerman HJ, Kellum JH, Brewer WH, Moore EW. Gallstones in patients with morbid obesity. Relationship to body weight, weight loss and gallbladder bile cholesterol solubility. //Int J Obes Relat Metab Disord. 1
57. Chen MP, Chung FM, Chang DM, Tsai JC, Huang HF, Shin SJ, Lee YJ. Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. //J Clin Endocrinol Metab. 2006 Jan;91(1):295-9. doi: 10.1210/jc.2005-1475.
58.Cottam DR, Mattar SG, Barinas-Mitchell E, Eid G, Kuller L, Kelley DE, Schauer PR. The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. //Obes Surg. 2004 May;14(5):589-600. doi: 10.1381/096089204323093345
59. Bennion LJ, Grundy SM. Effects of obesity and caloric intake on biliary lipid metabolism in man. //J Clin Invest. 1975 Oct;56(4):996-1011. doi: 10.1172/JCI108180. PMID: 1159099; PMCID: PMC301956.
60. Paul S, Khataniar H, Ck A, Rao HK. Preoperative scoring system validation and analysis of associated risk factors in predicting difficult laparoscopic cholecystectomy in patients with acute calculous cholecystitis: A prospective observational study. //Turk J Surg. 2022 Dec 20;38(4):375-381. doi: 10.47717/turkjsurg.2022.5816.

61. Osterman E, Helenius L, Larsson C, Jakobsson S, Majumder T, Blomberg A, Wickenberg J, Linder F. Surgery for acute cholecystitis in severely comorbid patients: a population-based study on acute cholecystitis.// BMC Gastroenterol. 2022 Aug 4;22(1):371. doi: 10.1186/s12876-022-02453-0.
62. Wong A, Naidu S, Lancashire RP, Chua TC. The impact of obesity on outcomes in patients undergoing emergency cholecystectomy for acute cholecystitis. //ANZ J Surg. 2022 May;92(5):1091-1096. doi: 10.1111/ans.17513
63. Afaneh C, Abelson J, Rich BS, Dakin G, Zarnegar R, Barie PS, Fahey TJ 3rd, Pomp A. Obesity does not increase morbidity of laparoscopic cholecystectomy. // J Surg Res. 2014 Aug;190(2):491-7. doi: 10.1016/j.jss.2014.02.014.
64. Farkas DT, Moradi D, Moaddel D, Nagpal K, Cosgrove JM. The impact of body mass index on outcomes after laparoscopic cholecystectomy. //Surg Endosc. 2012 Apr;26(4):964-9. doi: 10.1007/s00464-011-1978-5.
65. Ammori BJ, Vezakis A, Davides D, Martin IG, Larvin M, McMahon MJ. Laparoscopic cholecystectomy in morbidly obese patients. //Surg Endosc. 2001 Nov;15(11):1336-9. doi: 10.1007/s004640000019.
66. Bouassida M, Zribi S, Krimi B, Laamiri G, Mroua B, Slama H, Mighri MM, M'saddak Azzouz M, Hamzaoui L, Touinsi H. C-reactive Protein Is the Best Biomarker to Predict Advanced Acute Cholecystitis and Conversion to Open Surgery. A Prospective Cohort Study of 556 Cases. //J Gastrointest Surg. 2020 Dec;24(12):2766-2772. doi: 10.1007/s11605-019-04459-8.
67. Paajanen H, Käkelä P, Suuronen S, Paajanen J, Juvonen P, Pihlajamäki J. Impact of obesity and associated diseases on outcome after laparoscopic cholecystectomy. //Surg Laparosc Endosc Percutan Tech. 2012 Dec;22(6):509-13. doi: 10.1097/SLE.0b013e318270473b.
68. Riall TS, Adhikari D, Parmar AD, Linder SK, Dimou FM, Crowell W, Tamirisa NP, Townsend CM Jr, Goodwin JS. The risk paradox: use of elective cholecystectomy in older patients is independent of their risk of developing complications. //J Am Coll Surg. 2015 Apr;220(4):682-90. doi: 10.1016/j.jamcollsurg.2014.12.012.