



Addiction and the Risk of Common Bile Duct Stones: A 4-Year Retrospective Population-Based Study in Mashhad, Iran

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Abstract

Background: As a common digestive disorder, choledocholithiasis can have serious consequences, including death. Given that opioids have been shown to contribute to the spasm of Oddi's sphincter, which results in biliary stasis in the common bile duct (CBD), it is likely that opioids can also raise the prevalence of choledocholithiasis. In this regard, this study aimed to investigate how common opium addiction was among choledocholithiasis patients in Mashhad, Iran.

Methods: The current retrospective observational study was conducted on 599 patients with choledocholithiasis who underwent endoscopic retrograde cholangiopancreatography (ERCP), utilizing information gathered at the Ghaem hospital in Mashhad, Iran, between 2011 and 2015. Patient data were collected from files and records using certain criteria such as gender, opium addiction, hepatic enzymes (AST, ALT, ALP), plasma levels of total bilirubin, and direct bilirubin. The size of the CBD stones as well as the correlation between the gallbladder and CBD stones were calculated.

Findings: From among 599 patients included, 345 (57.6%) were female and 254 (42.4%) were male. Moreover, 195 patients (32.2%) had opiate addictions. The size of the CBD stone was correlated with the patient's age ($r=0.17$, $P=0.001$). The average stone measured 12.22 ± 3.32 mm. There were notable differences in the mean size of the CBD stone ($P<0.001$) between addicted and non-addicted cases; specifically, the mean CBD stone size in addicted cases was 12.715.13 mm while it was 12.34.33 mm in non-addicted cases.

Conclusion: This study showed patients with CBD stones have a higher rate of opium addiction compared to the general population, indicating a possible link between the two conditions.

Keywords: CBD stone, Choledocholithiasis, Addiction

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Introduction

Choledocholithiasis is the presence of at least one gallstone in the common bile duct (CBD). The prevalence of cholelithiasis among American adults is about 10%, while in Western Europe and Asia, the prevalence rates of 5.9% to 21.9% and 3.2% to 15.6% have been reported.¹ Two serious complications of choledocholithiasis are cholangitis and gallstone pancreatitis.^{2,3} Moreover, in some nationwide cohort studies, gallbladder dysfunction was associated with an increased risk of small bowel cancer.⁴ Unlike cholelithiasis, choledocholithiasis is often symptomatic since it blocks extrahepatic ducts leading to right upper quadrant pain, nausea, and vomiting.³ Other demonstrations of this condition include fever and jaundice. It also causes the elevation of specific serum markers such as amylase and lipase which are also

elevated in patients with pancreatitis.⁵ According to the theories behind choledocholithiasis and CBD stones, bile stasis, bacteria, chemical imbalances, increased bilirubin excretion, pH abnormalities, and the development of sludge are some of the causative factors for the formation of these stones.⁶

Opioid, in general, is a type of chemical compound that has many medical uses. Still, because of its euphoric effects, it is widely a subject of abuse worldwide. Unfortunately, Iran is a major transit route for opiates smuggled from Afghanistan and through Pakistan to the Persian Gulf, Turkey, Russia, and Europe, which causes opiate derivatives to be one of the first substances of abuse among the Iranian population.⁷ The last reports in 2020 indicated that Iran has the highest opium addiction prevalence in the world (~11.9% of the general



population).⁸ Opiate consumption is the most prevalent type of substance abuse among Iranians,⁷ and more than 3.5% of Iranian high schoolers reported a history of opiate derivative consumption in a study.⁹ Opioid addiction is a chronic condition in which a person regularly uses (smokes, inhales, injects, swallows, etc.) opioids without any medical reason, which causes significant health, economic, and social problems.^{9,10} Opioids have many different pharmacological effects on the gastrointestinal tract. Studies have shown that choledocholithiasis is probably more common in opioid addicts; in some studies, 53.6% of patients with gallstones are addicted to opium.¹⁰ One of the impacts of opium on the bile system is manipulating the function of Oddi's sphincter, resulting in delayed emptying of the gallbladder.¹¹⁻¹⁴ This spasm leads to an increase in the intra-CBD pressure and also problems in the discharge of bile into the duodenum.¹⁵ Following this increased intra-CBD pressure, the dilatation of CBD occurs.¹⁶

Despite many studies that investigated the associations between substance addiction and CBD stones in the world, there is a lack of information about the prevalence of substance addiction and its association with CBD stones incidence in the northeast of Iran. Therefore, the present study aimed to investigate the prevalence of opium addiction in patients diagnosed with CBD stones and survey whether it is related to increased age, type of addiction, and duration of addiction. It also intended to find out if opium-induced bile stasis can have a role in facilitating biliary stone formation in patients visiting Ghaem hospital affiliated with Mashhad University of Medical Sciences, Mashhad, Iran, as one of the largest hospitals in the northeast of the country.

Methods

Participants and inclusion/exclusion criteria

This study was conducted on 599 patients (selected using the census method) with gallstones who visited Ghaem hospital affiliated with Mashhad University of Medical Sciences, Mashhad, Iran. Only patients with confirmed choledocholithiasis who underwent endoscopic retrograde cholangiopancreatography (ERCP) were included in the study, and patients with an unregistered, distorted, or unknown history were excluded from the study.

Objectives and data collection

The present retrospective study was conducted by extracting data from the included patients' medical documents in Ghaem hospital affiliated with Mashhad University of Medical Sciences. Demographic characteristics of the patients including age, gender, and kind of substance addiction were collected. Moreover, the simultaneous presence of stones in the gallbladder in ultrasound findings, the size of CBD stones in ultrasound

images, and the plasma serum levels of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and total and direct bilirubin were collected.

Opium addiction was defined as the continued use of opium, whether oral or inhaled, injected, etc., with no medical reason.

Statistical analysis

All data were collected through a checklist and analyzed using SPSS software (version 16). Descriptive statistics including frequency and percentage (for qualitative data), as well as mean and standard deviation (for quantitative data) were reported. The Kruskal-Wallis test was used to analyze quantitative data between groups. A *P* value less than 0.05 was considered significant.

Results

In this study, data were collected from 599 patients, including 254 men (42.4%) and 345 women (57.6%) diagnosed with CBD stones from 2011 to 2015. The patients' age ranged from 15 to 94, with a mean of 63.35 ± 17.06 years. Besides, 195 patients (32.2%) were addicted to opium, 33 patients (5.50%) were cigarette smokers, 21 patients (3.5%) were waterpipe smokers, one patient (0.2%) was a methadone abuser, and one patient (0.2%) was a Naswar abuser (Figure 1). The remaining 348 patients (58.1%) had no history of smoking or addiction. The prevalence of opium addiction in the coexistence of gallbladder stones and concomitant gallbladder is depicted in Table 1.

Investigation of the relationship between the age of the patients and the size of the CBD stone showed a significant positive correlation ($r=0.17$, $P=0.001$) i.e., the higher the age of the patient, the larger the size of the stone. The mean CBD stone size among all patients was 12.22 ± 3.32 mm.

The patients were assigned to three groups to survey the relationship between the type of addiction and the size of the CBD stone as shown in Table 2.

The size of CBD stone was 13.83 ± 50.72 mm in male patients and 11.03 ± 14.86 mm in females indicating no significant relationship ($P=0.73$).

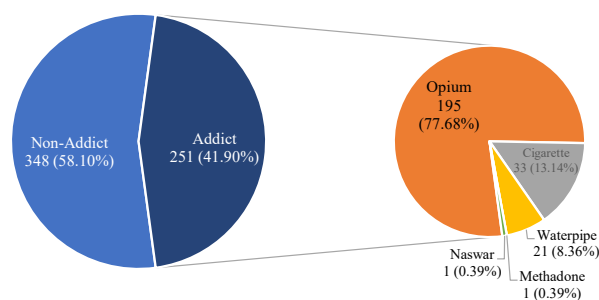


Figure 1. The prevalence of addiction in people with gallstones based on the type of addiction.

Table 1. The coexistence of gallbladder stones in various types of addiction

Opium addiction or not (total count)	Concomitant gallbladder stone	Cholecystectomy	Contracted gallbladder
Addicted (n= 195)	103 (52.8%)	55 (28.2%)	12 (6.1%)
Non-addicted (n= 348)	158 (45.4%)	94 (27%)	20 (5.8%)

Furthermore, there was no significant relationship between CBD stone size and liver function tests ($P > 0.05$) (Table 3).

Discussion

This study reported the increased level of liver function tests in patients with CBD stones which was not correlated with stone size and the age of the patients. Studies show that opium could increase the contraction frequency and pressure of Oddi's sphincter, resulting in increased CBD pressure and dilatation.¹⁵ It is also believed that patients addicted to opioids have asymptomatic dilatation of bile ducts, symptomatic sphincter of Oddi dysfunction, and CBD dilatation.^{14,15,17,18}

Although the present study revealed the prevalence of substance addiction in the studied population was approximately 42%, the prevalence of opiate derivative abuse was between 1.2% to 8.6% among the general population of different locations in Iran,¹⁹ 3.5% among high schoolers,^{9,19} and 14.6% among drivers.²⁰ The current study found that 32% of patients with CBD stones who underwent ERCP were opium-addicted, and the size of CBD stones in addicted patients was about the same as that of non-addicted patients. The prevalence of addiction in the participants of this study was much higher than in the general population. However, certain questions arose to answer which more studies are required in the future: Is there a relationship between opium addiction and CBD stone formation? Does biliary stasis caused by Oddi's sphincter spasticity result in CBD stone in opium addict patients? No similar study was found to investigate the prevalence of opioid addiction in patients with CBD stones.

Other studies have shown a significant relationship between CBD diameter and opium addiction.^{13,16} The present study found a relationship between CBD stone size and addiction where the stones of the addicted patients were significantly bigger. It mainly happens because the opium causes the bile ducts to get dilated, resulting in the stones with a larger diameter blocking the bile flow, thereby leading to the choledocholithiasis signs in the patients. A positive correlation exists between CBD diameter, population age, and the duration of addiction.^{13,17} The present study found a relationship between CBD stone size and the patients' age. On the contrary, Karamanos et al reported that the increase in age was not associated with CBD diameter and the likelihood of choledocholithiasis.²¹ This inconsistency could be due to the differences in imaging methods, patients' ethnicity,

Table 2. The relationship between the type of addiction and size of CBD stone

Type of addiction	CBD stone size (mean \pm SD)	P value
Opium	12.71 \pm 5.13 mm	
Waterpipe and Naswar	9.98 \pm 4.85 mm	<0.001*
None	12.3 \pm 43.39 mm	

*Significant P value <0.05.

Table 3. The relationship between liver function tests and size of CBD stone

	Factor	R	P value
CBD stone size	Total bilirubin (mg/dL)	0.05	0.17
	Direct bilirubin (mg/dL)	0.04	0.28
	AST (U/L)	0.04	0.3
	ALT (U/L)	0.04	0.3
	ALP (U/L)	0.06	0.14

and underlying diseases and conditions between the two studied populations.

The present study demonstrated that there was a significant relationship between the type of addiction and the CBD stone size. Likewise, some previous studies by Sharma et al,¹⁴ Helm et al,¹⁵ Sharma et al,¹⁶ and Farahmand et al¹⁷ confirmed the effect of opium on Oddi's sphincter resulting in bile duct stasis and CBD dilatation. According to a study, addiction to opium and a history of cholecystectomy are associated with CBD dilatation in the absence of an obstructive process.²² Another study reported a minor increase in bilirubin levels in four opium-addicted patients who had Oddi's sphincter dysfunction and CBD dilatation. It was shown that the papillary obstruction is more common than other Oddi's sphincter malfunctions in addicted patients.^{14,16} In some studies, no significant relationship was found between the route of administration of opium and stone size,²³ while some studies suggested that oral opium consumption is significantly associated with the size of bile duct stones.^{24,25} Further studies are highly recommended to investigate this relationship.

It should be noted that this study had some limitations, including diagnostic and measurement errors. Moreover, some patients may have refused to provide information about their addiction. To encourage patients to provide more information, they were reassured that their information would be kept strictly confidential.

Conclusion

The results of this study showed that patients with CBD stones had higher rates of opium addiction than the general population, suggesting that opium addiction may

play a role in the development of CBD stones.

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Authors' Contribution

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Competing Interests

The authors declare no conflict of interest.

Ethical Approval

All ethical principles, including the confidentiality of patients' information and the observance of the rights of the participants, have been taken into consideration. It should also be noted that the data were collected only from the documents that included a written informed consent form. This study was approved by the ethics committee of Mashhad University of Medical Sciences (ID: 941557).

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