

Epidemiology, management, and economic evaluation of screening of gallstone disease among type 2 diabetics: A systematic review

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Abstract

The knowledge of gallstone disease (GSD) is crucial to manage this condition when organizing screening and preventive strategies and identifying the appropriated clinical therapies. Although cholecystectomy still be the gold standard treatment for patients with symptomatic GSD, expectant management could be viewed as a valid therapeutic method for this disorder. If early treatment of GSD decreases the morbidity or avoids further cholecystectomy, it may save clinical care costs in later disease periods sufficiently to offset the screening and early treatment costs. In addition, whether routine screening for GSD is worthwhile depends on whether patients are willing to pay the ultrasonography screening cost that would reduce the risk of cholecystectomy. In this review we discuss the epidemiology, management, and economic evaluation of screening of GSD among type 2 diabetics.

Key words: Gallstone disease; Epidemiology; Management; Economic evaluation; Type 2 diabetes

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Core tip: According to the willingness-to-pay viewpoint, this review indicated that from the societal perspective but not from consumer viewpoint, it is worthwhile to organize a routine ultrasonography screening for gallstone disease in diabetic population for further cholecystectomy prevention.

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INTRODUCTION

Gallstone disease (GSD) is a common gastrointestinal condition with crystalline deposits in the gallbladder and impaired excretion of bile into the intestine throughout the world^[1]. GSD yields a relative lower mortality rate, however, a relative higher risk of mortality in GSD patients is not totally explained by the high mortality rate of related cancer. This high morbidity of GSD substantially affects the economy and public health^[2]. The increasing incidence of GSD over the past several decades is due to parallel modifications in personal dietary habits and physical activity associated with the Western lifestyle^[3]. In the absence of an organized screening program for symptomatic GSD, treating GSD and related complications yields substantial medical burden^[1].

Based on the Wilson criteria, GSD is needed to screen due to it is one of essential health issues; the disease natural course should be known; there should be a recognizable latent or early symptomatic state; a screening process is easy to do and interpret, accurate, acceptable, reliable, and has good sensitivity and specificity; there should be an acceptable treatment recognized for this disorder; treatment is much better if began early; there should be a clinical policy on who should be treated; both diagnosis and treatment have good efficacy; and this condition should be a continuous disease process^[4]. Both obesity and the metabolic syndrome have been viewed as risk factors related to GSD formation^[3,5,6]. Epidemiologic evidence suggested that people with diabetes mellitus were at higher risk of stone formation^[3,7]. Academic studies indicated an increased morbidity of GSD in diabetic patients^[7-9]. In addition, hypertriglyceridemia, hyperinsulinemia, and autonomic neuropathy (leading to gallbladder hypomotility and biliary stasis) were also revealed as associated factors to the incident GSD diabetic population^[7,8]. This implies that GSD formation and diabetes development may share pathophysiologic pathways^[3]. However, how diabetes predisposes to GSD is still not well known^[8].

The choice of ultrasound scanning in GSD evaluation is ideal as it is cheap, non-invasive, safe, and repeatable without known adverse effect on the patients in clinical scenarios^[10]. For symptomatic GSD subjects, expectant management may also indicate a valid clinical therapy although cholecystectomy still represents the gold standard^[11]. From the viewpoint of preventive medicine, early detection of GSD by routine ultrasonography screening followed by appropriate therapy could avoid the further cholecystectomy. This review aims to explore the epidemiology, management, and economic evaluation of screening of GSD among type 2 diabetics.

THE CLINICAL DIAGNOSIS OF GSD

It is often a diagnostic challenge to determine which abdominal symptoms are related to GSD. Typically,

GSD pain occurs in the right upper quadrant of the abdomen, but pain is not specific in this area^[12]. Fewer than 50% of those with GSD actually have clinical symptoms, and fewer than 10% further develop potentially life-threatening complications^[13]. The physicians must depend on the patient's description of the pain and results of laboratory examinations and diagnostic imaging to decide a appropriate diagnosis^[12]. The physical examination also may show mild epigastric or right upper quadrant tenderness, but most patients do not have significant physical characteristics^[13]. The majority of asymptomatic GSD will remain asymptomatic for a long time period.

Mechanisms underlying GSD formation include supersaturation of bile with cholesterol, consequent sedimentation, crystallization, and stone formation and abnormal gallbladder motor function with resultant delayed emptying and stasis of bile^[10]. The availability of ultrasonography as viewed a valid tool for GSD diagnosis has allowed the evaluation of GSD morbidity^[2]. It is safe, fast, and not expensive and involves no radiation exposure^[13]. Positive findings include single or multiple stones, a positive Murphy sign on contact with the ultrasonographic probe, thickening of the gallbladder wall, and pericholecystic fluid^[14]. Patients are usually left feeling unwell for as much as one or two days. If obstruction persists, it worsens movement and palpation, is associated with fever, and is localized to the right upper quadrant part of abdomen, with the pain becoming sharp, which will result in acute cholecystitis^[12,15]. Clinical studies showed higher positive (0.99-1.00) and negative (0.90-0.96) predictive values regarding the diagnostic efficacy, indicating that ultrasonography is a reliable technology for GSD screening^[1,16]. However, a drawback is that its accuracy is dependent on the people who perform and interpret it^[13].

Biliary pain occurs when the neck of the gallbladder is hindered by a gallbladder or stone pressure rises, producing a visceral foregut pain^[15]. Factors that relate to choledocholithiasis include tests of abnormal liver function, common bile duct dilation of eight mm or more, and common bile duct stones identified by ultrasonography^[17]. In addition, the abdominal plain radiography or computer tomography (CT) scan should also exclude the presence of calcified stones^[18-20].

THE MORBIDITY OF GSD

Epidemiological studies in both Eastern and Western countries showed that ultrasonography is an reliable diagnostic tool for GSD morbidity^[2,21-23]. The mechanisms of GSD have been implicated in type 2 diabetes. Some controversy exists regarding the association between diabetes and GSD, although population-based epidemiologic studies have demonstrated a positive relationship between type 2 diabetes and increased morbidity of GSD^[1,24-26]. The possible pathogenic mechanism for this is that type 2 diabetic population

Table 1 Prevalence of gallstone disease in various populations

Ref.	Study year	Screened number	Setting	Prevalence of gallstone disease	Associated factors
Elmehdaw <i>et al</i> ^[8]	2009	327	Benghazi, Libya	DM: 9.75% Non-DM: 17.5%	Age, obesity
Pradhan <i>et al</i> ^[28]	2009	80	Nepal		Non-vegetarian
Acalovschi <i>et al</i> ^[29]	2009	1332	Romania	19% with chronic hepatitis C; 17% controls	Abdominal obesity, steatosis
Khan <i>et al</i> ^[30]	2009	9175 (5050 males, 4125 females)	England	Male fell from 20.2% to 19.1%, females fell from 30.4% to 29.0%	Diabetes, not for CHD, BMI to females, elderly
Friedrich <i>et al</i> ^[31]	2009	9206 (5559 from Danish, 3647 of German)	Denmark, Northeast Germany		Higher BMI, unfavorable lipid levels, higher prevalence of diabetes
Walcher <i>et al</i> ^[32]	2010	2147	Germany	8%	Protective effect: alcohol consumption
Ruhl <i>et al</i> ^[33]	2011	14228	United States	7.10%	Cardiovascular disease, cancer
Al-Bayati <i>et al</i> ^[34]	2012	200	Iraqi	33% of diabetics, 17% of non-diabetics	BMI > 25 kg/m ² , increased duration of DM, increased HbA1C, multiparous females
Jiang <i>et al</i> ^[35]	2013	1270	Shanghai, China	CAD (+): 19.5% CAD (-): 11.3%	CAD
Agunloye <i>et al</i> ^[10]	2013	400	Ibadan, Nigeria	17.5%	Age, BMI, DM, duration of the disease
Yilmaz <i>et al</i> ^[36]	2014	441	Turkey	12.2%	Age, BMI, Gender, metabolic syndrome
Shen <i>et al</i> ^[37]	2014	6511	Taiwan	13.2%	Age, Gender, metabolic syndrome
Ibitoye <i>et al</i> ^[38]	2014	1283	Nigerian	2.9%	

BMI: Body mass index; CHD: Coronary heart disease.

with GSD may cause acute cholecystitis more obvious and make higher likelihood of progression to septicemia compared with non-diabetic subjects, who exhibit functioning gallbladders normally. Type 2 diabetic patients may show a higher lithogenic bile index compared with non-diabetics after adjustment for sex and age^[9]. The association between type 2 diabetes and GSD is stronger among patients who have a history of treated diabetes mellitus than it is among those with a single disease history of diabetes, that is, hyperglycemia may affect gallbladder motility^[21]. The linkage between obesity, diabetes, and GSD most likely originate from metabolic syndrome^[16,27]. In addition, diabetic patients represent cases of hyperglycemia that reflect relevant effects on gallbladder motility^[9].

Tables 1 and 2 indicate that many evidence-based studies of the prevalence, incidence, and risk factors for GSD have been conducted. However, it is difficult to appropriately compare the results of some studies because the heterogeneous nature of these studies (for example, patient selection), which varied significantly. The prevalence of overall GSD was higher than the general Chinese population in Taiwan when using the same methodology of GSD assessment^[8,42]. Previous population based studies had resulted in disparate findings on diabetes mellitus and GSD^[24,25]. In Italy, the estimated prevalence of GSD is significantly higher in diabetic patients than in the general population (24.8% vs 13.8%)^[43]. In New Zealand, the prevalence of GSD in diabetics was estimated to be 32.7% as compared to 20.8% in the control group^[44]. An epidemiological study in Nigeria concluded that 17.5% of the diabetic patients had GSD on ultrasound^[10]. The study about the

prevalence of GSD in Chinese type 2 diabetics is rare or lack of appropriate statistical methods. The overall prevalence of GSD among type 2 diabetics in Kinmen was 14.4%, including single stone 8.0%, multiple stones 3.2%, and cholecystectomy 3.2%^[42]. Further, the overall prevalence among elderly type 2 diabetics was 17.1% (men: 14.5%, women: 19.0%), which included the presence of single stone, 9.1%; multiple stones, 4.4%; and cholecystectomy 3.7%^[45]. Upon international comparison, the prevalence of any type of GSD falls within the range of 10%-32% in type 2 diabetics and is higher than that in non-diabetic patients^[44,46-49].

Cross-sectional study designs only reveal useful information of disease prevalence, but reveal nothing about the incidence or temporality in the study population. To explore the incidence and causal relationships between predictive factors and disease, the population needs to be re-examined regarding follow-up time. The morbidity of GSD increases as age increases, noticeably elevating in people aged 40 years and older and becoming from 4- to 10-fold more likely^[4,16]. The incidence of GSD appears to vary among test diabetic populations and differs among studies conducted in disparate countries^[1]. In the general and elderly Chinese type 2 diabetes population, the incidence of GSD was 3.56% per year (95%CI: 1.78%-6.24% per year) and 4.17% per year (95%CI: 2.22%-7.05% per year), respectively^[9,26]. Previous epidemiologic studies showed that the annual incidence of overall GSD in type 2 diabetics was higher than that in other general population-based studies^[9,22]. In addition, evidence-based studies exploring GSD in the elderly sub-population have focused almost entirely on the consequences of

Table 2 Incidence of gallstone disease in various populations

Ref.	Study year	Screened number	Setting	Incidence of gallstone	Associated factors
Festi <i>et al</i> ^[2]	2008	9611	Italy	0.67% (0.66% in males, 0.81% in females)	Risk factors: In men: increasing age, high BMI, history of diabetes, peptic ulcer and angina, and low cholesterol and high triglyceride levels; In females: increasing age and high BMI Predictors: In men: increasing age and pain in the right hypochondrium In females: increasing age
Halldestam <i>et al</i> ^[39]	2009	621	Sweden	1.39 per 100 person-years	Length of follow-up and LDL-cholesterol levels Inversely: alcohol consumption
Jonas <i>et al</i> ^[40]	2010	8901	Sweden	Surgical group: 122.2/10000 person-years controls: 22.2/10000 person-years	After antiobesity surgery (A fivefold increased risk)
Liu <i>et al</i> ^[25]	2012	108850 (60734 diabetic patients and 48116 control patients)	Taiwan	0.632% per year	Risk factor: increased age Associated: high body mass index, elevated fasting plasma glucose levels, and nonalcoholic fatty liver disease
Chen <i>et al</i> ^[1]	2014	1296	Taiwan	0.632%	High body mass index, elevated fasting plasma glucose levels, nonalcoholic fatty liver disease
Heida <i>et al</i> ^[41]	2014	288	Dutch	5.9%	BMI

BMI: Body mass index; LDL: Low density lipoprotein.

interventions such as percutaneous cholecystostomy and endoscopic retrograde cholangiopancreatography, or on the management of elderly patients with symptomatic biliary disease at hospitals^[50,51]. The annual incidence of GSD in elderly type 2 diabetics was also higher than that in younger diabetic patients or the general population using the same methodology of GSD assessments^[2,26]. To explore the incidence and risk factors for GSD is essential to prevent its development and avoid the further cholecystectomy caused by complications, which is often insidious in nature.

Gallstone formation is multifactorial, and involves constitutional and environmental factors. People with GSD have increased mortality, overall mortality, and mortality from cardiovascular disease and cancer. This relationship exists for ultrasound diagnosed GSD and cholecystectomy^[33]. GSD with complications, especially cholecystitis and cholangitis, in the elderly is related to higher morbidity and mortality rates^[52].

THE NATURAL COURSE OF GSD

The natural course of GSD is usually not malignant, but complications contribute substantially to medical care costs and may even be life threatening^[40]. One of the essential advantages of early detection of GSD is that ultrasonography could diagnose asymptomatic stages, which incurs early treatment and the prevention of major complications such as acute pancreatitis or gallbladder cancer^[53,54]. The increasing magnitude and epidemiologic shifts in the natural history of GSD worldwide qualify for the need of research in different geographical areas, and also to explore the predictive

factors^[55,56]. This is particularly because the majority of risk factors associated with GSD are potentially modifiable^[41]. In addition, cholecystectomy could be used to treat GSD, that is, the estimated utility value in subjects with GSD will be a 0.09 increase from this therapy. Thus, the number of quality-adjusted life years obtained from cholecystectomy would be 1.8 (0.09 × 20) if subjects had a life expectancy of 20 years^[57]. Screening regimes for GSD depend on the incidence and progression rates as well as the risk factors that change these rates. An understanding of the disease progression of GSD would appropriately determine the benefits of prevention strategies.

A chronic disease model according to the epidemiologic information of GSD is necessary to allow the benefits of intervention to be modeled. Since GSD may only persist a short duration before cholecystectomy, a shorter desirable interscreening interval may be warranted. The disease progression of GSD affects the decision of a screening interval for the surveillance of this patient population. In addition, the effectiveness of screening strategy for GSD is determined by the progression of GSD^[58]. Since the natural history of GSD may not be homogeneous across study countries, assumptions of disease progression parameters could not be directly compared from previous results^[11,59]. Several evidence-based studies on the natural history of GSD also have been conducted^[11,58]. A clearer understanding of the risk factors associated with GSD may help us to identify cases and to reduce the risk in some patients^[60].

For the disease natural course of GSD, the four-state Markov chains model following the pathway of

proliferative phase is showed as follows:

λ_{12} λ_{23} λ_{34}
 No GSD → single stone → multiple stones → cholecystectomy
 (State 1) (State 2) (State 3) (State 4)

To estimate the progression rates, let λ_{12} , λ_{23} , and λ_{34} indicate the annual progression rate from state 1 to state 2, from state 2 to state 3, and from state 3 to state 4, respectively. The annual progression rates from single stone to multiple stones and from multiple stones to cholecystectomy are estimated as 0.114 (95%CI: 0.015-0.173) and 0.148 (95%CI: 0.101-0.242), respectively. Corresponding average durations in single stone state and multiple stones stage are 8.77 (95%CI: 5.78-66.67) years and 6.76 (95%CI: 4.13-9.90) years, respectively. The application of parameters to the annual transition probabilities from single stone state to multiple stones state and from multiple stones state to cholecystectomy state are 10.00% and 13.76%, respectively. An annual screening program could reduce cholecystectomy by 82.9% (95%CI: 75.7%-90.4%) compared with the non-screening group. Comparatively, biennial screening, 3-year screening, 4-year screening, and 5-year screening could reduce cholecystectomy by 71.6% (95%CI: 57.0%-88.8%), 64.8% (95%CI: 46.1%-81.5%), 49.6% (95%CI: 23.9%-75.3%), and 32.1% (95%CI: -2.8%-66.7%), respectively^[58]. However, one problem is in four-state Markov chains model, we should be aware that single stone might not always consequentially develop into multiple stone.

Many factors such as obesity and type 2 diabetes have been indicated to be significant risk factors related to GSD^[1,9,11], and the transition state is probably unstable over time. The screening efficacy of preventing cholecystectomy associated with GSD depends on early diagnosis. To choose the frequency of sonographic check-ups as well as sensitivity and specificity, it is helpful to know the disease scenario and progression from the asymptomatic state to the symptomatic state. This characteristic will provide early diagnosis and therapeutic strategies for GSD^[57].

THE MANAGEMENT OF GSD

The treatment options for GSD are according to few crucial steps such as typical symptoms, further complications, and gallbladder function, as well as size and composition of GSD^[18]. Cholecystectomy remains the reliable operation for patients with symptomatic GSD. It is safe because the lowest risk of recurrence and more than 90% of patients with complete biliary pain relief^[12]. Currently, it is also under argumentation if cholecystectomy may be also used for pre-symptomatic GSD. It is generally presumed that surgical procedures are not suggested routinely in symptom-free subjects due to the low rate of complications^[18].

Statins used could relieve hepatic cholesterol biosynthesis and may reduce biliary cholesterol secretion, consequently causing decreased cholesterol concen-

tration in bile^[61]. A larger observational study showed academic evidence that long-term use of statins is related to a decreased rate of diagnosed GSD requiring advanced cholecystectomy^[62]. Another population-based case-control study also indicated that long-term sustained statin use decreases incident GSD in both men and women^[63]. The results may be one of clinical relevancies given that GSD represents a major burden for medical care systems^[62]. In addition, a previous study showed that ezetimibe could not only prevent cholesterol GSD through obstructing intestinal cholesterol absorption so that biliary cholesterol secretion is decreased, and gallbladder motility function is reserved by desaturating bile in gallstone-susceptible C57L mice disputed to the lithogenic diet, but also promote the dissolution of cholesterol GSD through a greater capacity to develop an abundance of unsaturated micelles^[64]. For both prevention and treatment of cholesterol GSD, ezetimibe is viewed as a novel and potential cholelitholytic agent^[65].

Oral bile acids have successfully dissolved GSD in an extremely limited patient population for the nonsurgical treatment of GSD^[12]. The clinical effectiveness of bile acid therapy was determined in symptomatic GSD smaller than 15 mm within a functioning gallbladder^[12]. Oral bile acids could be only selected in symptomatic GSD patients who are unsuitable for cholecystectomy and have small, uncalcified, and cholesterol-enriched stones with a patent cystic duct in a functioning gallbladder^[18,66]. Currently, bile acid therapy is revealed only for patients unsuitable or unwilling to receive cholecystectomy^[12,67].

A previous study showed that acute cholecystitis grows in up to 10% of symptomatic GSD patients and leads to the entire obstruction of the cystic duct^[68]. Once acute cholecystitis is found, patients should be revived with intravenous fluids, accompanying medical conditions should be stabilized, and surgery should be performed at the earliest time^[12]. In addition, GSD could migrate from their primary site in the gallbladder through the cystic duct and into the common bile duct^[12]. An essential treatment for choledocholithiasis includes gallbladder removal and clearance of retained common bile duct stones. The findings of a prospective, multi-center, randomized controlled trial comparing single-stage laparoscopic cholecystectomy (LC) and laparoscopic stone extraction with preoperative endoscopic retrograde cholangiopancreatography followed by LC indicated that the procedures were equally effective in the clearance of common bile duct stones^[69].

THE ECONOMIC EVALUATION OF SCREENING OF GSD

Based on the welfare economic theory, the maximum value of individual's willingness-to-pay (WTP) is defined as the benefit to an individual receiving medical service or intervention^[70]. For the WTP perspective, the payment vehicle not only refers to the means of payment by

a patient, but also is assumed as total cost of both copayment for health insurance scheme and out-of-pocket money which is not covered by health insurance benefit^[71]. An evidenced-based study indicated that 24.4% of subjects would not like to pay a screening cost for GSD detection, implying that they did not think GSD status would influence their daily quality of life. The WTP values were significantly higher in individuals with more advanced GSD than in those with mild GSD. This also suggests that GSD associates with impaired quality of life and thus such patients would pay more to reduce the sequelae of further cholecystectomy^[70].

Economic evaluations are criticized commonly by decision makers for ignoring budget impacts, about which decision makers are desperately concerned. Payers could get into financial difficulty if they adopt too many cost-effectiveness interventions and affordability, which depends on the overall volume of patients, is therefore a prime concern^[11,72]. Few well-organized population-based studies have been conducted to explore the cost and effectiveness of GSD screening regimes. The cost-benefit analysis was used in one study to discuss whether a GSD screening regime compared with non-screening group is worthwhile in Taiwan from different viewpoint. The findings revealed that indirect costs play a main role in the routine GSD screening regime. Annual screening program could save the most discounted indirect costs per case (NTD220345) (US\$6995.1; 31.0NTD = 1USD) compared with non-screening group. Based on the health care payer's viewpoint, annual screening discounted net cost was NTD24893 (US\$790.3) per case. This implied that from health care payer's viewpoint, the clinical efficacy from the routine annual screening regime could not exceed the cost incurred in the GSD screening strategy. To consider the indirect cost, the NTD245238 (US\$7785.3) net saving per case indicates that from the societal perspective, the annual screening program is rather constructive ($P < 0.0001$)^[72]. In Chile, a screening program for GSD in a high risk sub-population reveals significant cost-effectiveness. The incremental cost-effectiveness ratio of universal screening compared with elective intervention, high risk intervention, and selective screening programs were estimated US\$180, US\$147, and US\$481, respectively^[73]. Preventive strategies aimed at GSD screening incur both substantial medical budgetary savings and highly cost-effective clinical care.

METHODOLOGICAL CONSIDERATION

Since GSD has a more complicated clinical aspect, it is not the rule for people with GSD definitely to progress towards more serious complications. In clinic, 60% of the patients with GSD are asymptomatic throughout their life. In these people, early detection may not help them to avoid possible healthy problem. In addition, up to now, there has been no effective early treatment for GSD that could prevent the resulting cholecystectomy. What we could and we should do

now for GSD patients is to find the patients more likely to have a serious outcome in the future and perform an early cholecystectomy to avoid the secondary common bile duct stone, gallstone pancreatitis and possible cancerization. That is why some asymptomatic patients are indicated for cholecystectomy. Also, some asymptomatic patients with diabetes and cardio-cerebrovascular complications should be treated by cholecystectomy in a stable condition to avoid unpredictable attack of GSD. That is currently the aim for GSD screening. Furthermore, since the natural history of GSD may be heterogeneous and more complicated, according to current knowledge, there is no relationship between the number of gallstones and cholecystectomy. We still have no clear idea about how the gallstone produces and what is the progression factors for GSD.

CONCLUSION

In conclusion, GSD is an escalating major health problem and involves constitutional and environmental factors. Considering the fact that oral bile acids could be only selected in an extremely limited patient population (symptomatic gallbladder disease patients who are unsuitable for surgery and have small, uncalcified, and cholesterol-enriched stones), the majority of patients with or without complications will need surgery. Without suitable screening programs for symptomatic GSD, treating GSD and related complications yields substantial medical care costs. Whether routine screening for GSD is worthwhile depends on whether subjects are willing to pay the ultrasonography screening costs that would reduce the risk of further cholecystectomy.

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