Reappraisal of the management of cholelithiasis in diabetics

Salman Y. Guraya, *FRCS.*

ABSTRACT

Recently, dramatic advances in research have elucidated the prognosis of gallstone disease and have permitted a more selective choice of persons for treatment based on symptom status and projected prognosis. Ultrasound-detected-incidental gallstones are infrequently clinically significant, but this finding has prompted the surgeons to have a liberal attitude towards the operative indications for cholelithiasis particularly after the advent of laparoscopy. At the same time, the management of gallstones in the diabetics still remains controversial. Early retrospective studies reported an alarmingly high incidence of gallstones in diabetics as compared with the general population and in view of profound morbidity and mortality rates observed in the diabetics, prophylactic cholecystectomy was generally recommended. However, recent evidence-based studies challenged this approach and concluded that prophylactic cholecystectomy is not justified in diabetic patients with asymptomatic gallstones. It is inferred that, as in the general population, asymptomatic cholelithiasis in diabetics should be managed expectantly and preemptive surgery should not be routinely performed. However, early laparoscopic cholecystectomy is preferred in cases of symptomatic cholelithiasis.

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In the western world, the prevalence of gallstone disease varies from 7-18% in males and 8-23% in females.[1-5] At least two-thirds of the gallstone carriers are asymptomatic, and most of them are unaware of the presence of their gallstones.[2,3,4] There is a general consensus that asymptomatic cholelithiasis should be managed expectantly.[6] This approach is consistent with the results of follow-up studies on the natural history of silent stones showing a benign course of the disease.[7] However, no controlled clinical trials have been carried out as yet in diabetic patients with gallstones.[8] The management of cholelithiasis in patients with diabetes is controversial.[9] Early retrospective and autopsy studies reported a dramatically higher prevalence of gallstones in diabetics as well as a significantly greater morbidity and mortality of cholelithiasis when compared with the general population.[10,11] Recent reports in medical literature have been reflective of improved perioperative care for co-morbid illnesses and have challenged this traditional view.[12] These studies suggest that the prevalence of cholelithiasis and the outcome of cholecystectomy are similar in the diabetics as compared with the well-population.[13,14]

The purpose of this paper is to help formulate a strategy about the management of cholelithiasis in the diabetics. This is a critical review of the risks and benefits of the therapy for gallstone disease in the diabetic patients who are considering treatment to prevent further episodes of biliary pain or its complications.

Incidence and natural history of cholelithiasis in diabetics. Approximately 15-20 million adults in the United States have gallstones, most of which are asymptomatic.[15,16] While symptomatic gallbladder disease is an accepted indication for surgery, more recent research disclosed that only 10-18% of

From the Division of General Surgery, Department of Surgery, King Khalid University Hospital, King Saud University, Riyadh, *Kingdom of Saudi Arabia.*

Address correspondence and reprint request to: Dr. Salman Y. Guraya, Senior Registrar Surgery, PO Box 286896, Riyadh 11323, *Kingdom of Saudi Arabia*. Tel. +966 501665848. Fax. +966 (1) 4679493. E-mail: drsyg7@yahoo.com

asymptomatic patients ever develop symptoms.[17] When symptoms do supervene; they usually begin as non-life threatening biliary colic within 5 years of the original diagnosis.[18] This observation holds true for the diabetics as well as the general population. Diabetes mellitus is often mentioned as an independent risk factor for the development of cholelithiasis.[19] In a prospective study, the prevalence of gallstones by autopsy in diabetics was reported to be as high as 30.2%, compared with 11.6% in non diabetics.[19] Similarly, in a cross-sectional survey performed by the Health Maintenance Organization in the United States, diabetes mellitus was documented in 30% of those with asymptomatic cholelithiasis.[20] However, population-based research in Italy,[21] Denmark,[22] and Japan,[23] as well as a recent case-control study from Sweden,[24] have not corroborated these observations. However, diabetes is associated with both obesity and type IV hyperlipidemia, which are established risk factors for cholelithiasis[23,24] and may confound the effect of diabetes mellitus.

If an increased risk of cholelithiasis in diabetics does exist, the pathogenic mechanism is largely unknown. Biliary stasis may contribute to the risk of gallstones in diabetics. Gallbladder emptying in response to cholecystokinin infusion measured by radionuclide cholescintigraphy was reported to be reduced by 25% in diabetics compared with healthy controls.[25] The reduction was more evident in patients with the stigma of autonomic neuropathy reflecting a neurally mediated mechanism. Once formed, gallstones rarely disappear spontaneously. An exception is the stones formed during the metabolic disturbances that accompany weight reduction[26] or pregnancy, which may spontaneously disappear.[27] Established gallstones may lead to biliary pain or complications like acute cholecystitis, perforation or emphysematous cholecystitis.[28] Gracie and Ransohoff[7] concluded that the rate to develop biliary pain is approximately 2% per year for 5 years and then may decrease over time. Similarly, Friedman et al[29] reported an incidence of 3-4% per year for "any [biliary] event" during the first 10 years of follow-up. These events consist of biliary colic, biliary complications, and "cholecystectomy" for chronic or milder symptoms. The rate decreased to 1-2% per year during the next 10 years. Data from Newman and Detsky[30] can be interpreted to show a 19% cumulative probability to develop over 10 years or approximately 2.2% per year.

Several other studies have convincingly showed that asymptomatic gallstones in the well population rarely lead to life-threatening complications, and therefore the risk and expense of surgery far outweigh the benefit.[31,32] The issue of application of these findings to the patients with diabetes needs to be addressed. Gracie and Ransohoff[33] studied 123 diabetic faculty members with gallstone disease at the University of Michigan (male:female ratio, 1:8.5) and reported no mortality for initially asymptomatic gallstones over 20 years of follow-up. This study revealed that the rate of progression from asymptomatic to symptomatic disease was lower than earlier reported: 10% at 5 years, 15% at 10 years and 18% at 20 years. Because most of the initial presentations of cholelithiasis consisted of uncomplicated biliary pain, only 1.6% of the subjects followed-up required urgent cholecystectomy, a procedure associated with a much higher operative risk than elective cholecystectomy. In the National Cooperative Gallstone Study,[34] 305 patients with gallstones, of whom 16 were diabetic, were followed up prospectively for 2 years. Among 193 asymptomatic patients, 31% developed biliary colic as opposed to 59% cases with no complaints. There was no difference in the incidence of biliary pain among the 16 diabetic patients compared with the non diabetics. This report further substantiates the view that diabetes in not an independent risk factor in the pathogenesis of cholelithiasis.

Complications of cholelithiasis in diabetics. Many health problems have been associated with gallstone disease including old age, alcoholism, smoking, multi-parity, and diabetes mellitus.[35] Cholecystitis in the diabetics is a severe disease as it may present unexpectedly and advance rapidly.[36] This led to a general consensus that prophylactic cholecystectomy should be performed in the diabetic patients with asymptomatic gallstones. More recently, Hickman et al[37] reported that infectious complications occurred in their study group of 109 diabetics at a rate 3 times that of non diabetic case-controls. Moreover, the 4.2% mortality rate in the diabetics in that study was entirely attributed to sepsis. The incidence of advanced concurrent medical conditions including cardiovascular, renal and pulmonary diseases were 35% in the diabetic patients and 15% in non diabetics leading to the conclusion that any single factor can not be held responsible for the increased morbidity. More serious complications of cholecystitis like gangrene, perforation and emphysematous cholecystitis are reported to occur in up to 20-40% of diabetics.[38] These complications necessitate urgent surgical intervention and certainly compound the perioperative risk. Of patients with gallbladder perforations complicating acute cholecystitis, 16-25% cases were found to have diabetes mellitus in a prospective study of 101 patients.[39]

Diabetics are at increased risk of developing emphysematous cholecystitis, a rare condition with a 30-fold increased risk of gangrene and threefold increase of both perforation and death.[40] There seems to be little correlation between the severity of diabetes and the incidence of complications of acute cholecystitis.[3] Walsh et al[41] reviewed 80 diabetics with either acute cholecystitis (29 patients) or who

had elective cholecystectomy (51 patients) and found no difference in the rates of complications between the diabetics, and 95 non diabetic controls. Morbidity was markedly high in the presence of vascular and renal ailments regardless of the diabetic status. Ransohoff et al[42] studied patients with acute cholecystitis over a 20-year-period and observed that death occurred in 3 of 46 patients with diabetes, and in 7 of 263 non diabetic controls: a difference which was not statistically remarkable (p=0.55). In the same study, patients with an elevated blood urea nitrogen level were found to have a significantly higher mortality rate: 27% compared with 2% in patients without renal impairment. This study reaffirmed the finding that renal and vascular complications contribute to the increased risk of biliary tract disease than diabetes alone.

Treatment options for gallstone disease in diabetics. There are 3 basic therapeutic approaches for cholelithiasis in the diabetic and non diabetic subjects: expectant, non surgical and surgical intervention. Expectant management, defined as therapeutic intervention delayed until gallstone symptoms or complications spontaneously develop, involves the tradeoff between the benefit of possibly avoiding an intervention versus the risk of inducing known possible complications of the surgical procedure itself.[43] The non surgical approach involves the removal of gallstones but not the gallbladder. The options include oral dissolution therapy with bile acids, extra corporeal shock wave lithotripsy (ESWL) and contact dissolution with methyl ter butyl ether.[44] Walters et al[45] concluded in their study of cases with asymptomatic gallstones that the awareness of the presence of gallstones leads to prophylactic cholecystectomy in 20-31% of cases, despite the persistence of an asymptomatic state in most of the patients. Oral dissolution therapy can be offered to such patients who want to "get rid of their silent stones" but there is a 5 year recurrence rate of 50% following discontinuation of treatment, which tends to temper enthusiasm for this modality.[45] The ESWL is another non operative method but severe colicky pain secondary to stone fragmentation develops in up to 79% of cases. Therapy with oral bile acids before and after the procedure is required, adding to a cost that is comparable with surgery. After the introduction of laparoscopic cholecystectomy in 1989, there has been lowered threshold and liberal attitude towards the indications of cholecystectomy. Laparoscopic cholecystectomy has numerous advantages over open version including short hospital stay, less post operative pain, faster return to full activity and better cosmesis.[46] However, patients with asymptomatic gallstones are usually not candidates for laparoscopic cholecystectomy according to the "National Institute of Health Consensus Development Conference Statement on Gallstones and Laparoscopic Cholecystectomy".[47] The indications for gallbladder removal should not be expanded even if the procedure is less invasive.[48] Furthermore, it has been shown that prophylactic cholecystectomy for silent stones in the diabetics does not appear to increase either the duration or quality of life, but may in fact reduce it.[49]

In conclusion, the major clinical challenge in the management of gallstone disease in the diabetic patients is to identify those who have the highest risk to develop an acute biliary complication: there are currently no good predictors. There is no convincing evidence that diabetes mellitus is an independent risk factor for cholelithiasis. The increased morbidity and mortality in diabetics with cholecystitis are more often related to the underlying renal and cardiovascular affections, independent of diabetes mellitus. Prophylactic cholecystectomy for asymptomatic gallstones is without benefit, and using the available analysis-based data, routine cholecystectomy for asymptomatic gallstones in the diabetic patients is not recommended. A "watch-and-wait" approach is advised for asymptomatic cholelithiasis in the diabetics when found, and surgical therapy when symptoms specific to cholelithiasis ensue.

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