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EDITORIAL

Management of incidental gallbladder polyps: Do not sacrifice the gallbladder - *try ursodiol first!*

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ABSTRACT

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Introduction:

The management of incidental gallbladder polyps has not received sufficient attention from internists, radiologists, pathologists, and surgeons, although a few consensus statements were published in recent years.[1,2] A scientific study involving these specialties to determine a logical and systematic approach for incidental gallbladder polyp management has yet to be done. *For instance, the failure to try ursodiol treatment as an initial line of treatment for incidental gallbladder polyps is a conspicuous void in existing management protocols.* Current paradigms for treatment of gallbladder polyps mainly rest on radiological surveillance with cholecystectomy if indicated,[1,2] while the threshold for surgical intervention has been lowered in recent years.[3] The purpose of this Editorial is to discuss the potential for an initial nonsurgical management of gallbladder polyps with ursodiol, in parallel with radiological surveillance as indicated, with the intention of reducing the rate of unnecessary cholecystectomies and limiting surveillance periods.

A New Paradigm for Gallbladder Polyp Management:

The incidental detection of gallbladder polyps has accelerated with the advent of ultrasound (US), computerized tomography (CT), and magnetic resonance imaging (MRI) over the past half-century.[1,2] The established management paradigm focuses on cholecystectomy for any gallbladder polyp measuring 10 mm or more on US surveillance, due to the risk of dysplastic or malignant changes.[1-3] More recently, some authors have lowered the bar to include polyps between 6 mm and 9.9 mm for potential consideration for cholecystectomy depending on a variety of risk factors for malignancy.[2,3] Therefore, recent trends lean towards performing many more cholecystectomies for gallbladder polyps than can be justified.[1-3] A major failing of this trend is that we are performing more and more cholecystectomies for incidental gallbladder polyps without taking into consideration whether they are cholesterol or adenomatous polyps. For instance, there is a justification for the use of *ursodiol* as a medical management modality for cholesterol polyps or as an indirect approach to interrogate the histopathology during the period of serial US monitoring of polyps.

The majority of gallbladder polyps are cholesterol polyps with the percentage varying in large studies from 60% to 90%.[4] Therefore, it is not surprising to see that the vast majority of cholecystectomies done for incidental gallbladder polyps are negative for malignant risk and are thus deemed unneeded.[1,2] The justification of current practice is that we cannot easily predict if a gallbladder polyp is a cholesterol polyp or an adenomatous polyp without performing cholecystectomy,[5] and this is important because adenomatous polyps that are large or grow rapidly in size do have a cancer risk.[1,2] The counterargument would be that there is a potential for cholesterol polyps to expose their identity, even without cholecystectomy, if they respond by regressing on ursodiol therapy. Therefore, the existing protocol of radiological surveillance of gallbladder polyps with US but without any medical treatment can potentially be replaced with a more active approach where patients are treated with ursodiol for at least 6-9 months before their next surveillance US. If there is a recognizable reduction in polyp size it is reasonable to infer that the polyps are cholesterol polyps rather than adenomatous polyps and therefore cholecystectomy would not be indicated.

A new paradigm for the management of incidental gallbladder polyps would involve medical therapy with ursodiol supervised by internal medicine specialists (gastroenterologists, internists, or family medicine) in parallel with 6-9 monthly US surveillance by radiologists to evaluate the impact of ursodiol therapy. If the gallbladder polyp size or number are seen to noticeably regress in response to 6-9 months of ursodiol therapy, then the same non-surgical management could continue for a period of time, ranging from 0-24 months, based upon the initial and final size of the polyp. On the other hand, if the polyp size does not reduce even with ursodiol treatment, or if it increases, it could indicate that it is more likely an adenomatous polyp than a cholesterol polyp. A percentage of cholesterol polyps also may not respond to ursodiol. These polyps nonresponsive to ursodiol could be submitted to the radiological surveillance and surgical protocols currently recommended in Europe or the USA based on size, morphology, and rate of growth.[1,2] In effect, ursodiol treatment of at least 6 months duration would have the potential to reduce the number of cholecystectomies done for gallbladder polyps and also reduce US surveillance periods recommended by consensus groups in recent years.

Existing Paradigm for Gallbladder Polyp Management:

For asymptomatic gallbladder polyps found incidentally on imaging, these are the current consensus protocol summaries from Europe[2] and the United States of America[1]:

a) **In Europe**, 4 medical societies published joint guidelines in 2022[2] by updating their 2017 recommendations: European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and other Interventional Techniques (EAES), International Society of Digestive Surgery–European Federation

(EFISDS), & European Society of Gastrointestinal Endoscopy (ESGE). Their main recommendations are summarized below:

i) ***Cholecystectomy*** is considered for a polyp measuring 10 mm, a polyp measuring 6 to 9.9 mm but with risk factors for malignancy (age > 60 years, Asian race, sessile polyp, primary sclerosing cholangitis), or a polyp that grows by ≥ 2 mm in 2 years.

ii) ***Ultrasound surveillance*** at 6, 12, and 24 months for 2 years for polyps 6 to 9.9 mm with no risk factors or polyps ≤ 5 mm with risk factors for malignancy.

iii) ***No follow-up*** is need for any polyp that disappears during surveillance monitoring and for polyps measuring ≤ 5 mm with no risk factors.

b) **In the United States of America,** the Society of Radiologists in Ultrasound met in 2021 and published consensus conference guidelines in 2022[1] after a national collaboration involving radiologists, gastroenterologists, pathologists, and surgeons.[1] They divided gallbladder polyps based on ultrasonic morphological characteristics into three risk groups. Polyp size was then used to determine US surveillance periods or indication for surgical consultation. On follow-up, surgical consultation is recommended for an increase in size of ≥ 4 mm in ≤ 12 months or if it reaches the threshold size for the category. If there is a decrease in size of > 4 mm US surveillance can be terminated.

i) **Extremely low risk polyps (pedunculated):**
Polyp ≤9 mm = No follow up.
Polyp 10-14 mm = Follow up US at 6, 12, 24 months.
Polyp ≥15 mm = Surgical consult.

ii) **Low risk polyps (sessile or pedunculated with thick/wide stalk):**
Polyp ≤6 mm = No follow up.
Polyp 7-9 mm = Follow up US at 12 months.
Polyp 10-14 mm = Follow up US at 6, 12, 24, & 36 months or surgical consult.
Polyp ≥15 mm = Surgical consult.

iii) **Indeterminate risk polyps (focal wall thickening ≥ 4 mm at polyp base):**
Polyp ≤6 mm = Follow up US at 6, 12, 24, 36 months or surgical consult.
Polyp >7 mm = Surgical consult.

Justification for a New Paradigm for Gallbladder Polyp Management:

Of note, neither the European nor the American consensus guidelines include the use of therapeutic or interrogative ursodiol therapy for 6-to-9 months prior to US surveillance. US is preferred to MRI and CT scan for characterizing the morphology of gallbladder polyps and for surveillance.[1,5] Therefore, if ursodiol therapy is begun, surveillance of the polyps should continue with US to maintain consistency of measurement during follow up. Although the other side of the coin is the risk of missed early cancer, recent evidence suggests that such risk is much lower than previously estimated.[6] Additionally, in cases where cholecystectomy is delayed by 6 months for a trial of ursodiol, as in polyps 6-9.9 mm in size with risk factors or polyps ≥10 mm without risk factors, the patient must be made aware of the relative risks although small.

Cholesterolosis is a common finding associated with diseased gallbladders and is often associated with cholelithiasis and also motility disorders of the gallbladder such as symptomatic gallbladder hypokinesia or hyperkinesia.[7-9] Cholesterol deposits in the submucosa and mucosa of the gallbladder start off as cholesterolosis but then grow in size to become large enough to be seen on imaging as "polyps." Adenomatous polyps are true gallbladder polyps while cholesterol polyps are "pseudopolyps" as they are not composed predominantly of cellular tissue but of chemical deposits of cholesterol within macrophages. Multiple gallbladder polyps are more often cholesterol polyps and, therefore, may potentially respond to ursodiol.

Increased cholesterol in bile, as seen in the metabolic syndrome, is a risk factor for gallbladder diseases.[10,11] The precipitation of cholesterol crystals from bile is a shared pathogenic factor in the formation of cholesterolosis, polyps, sludge, and stones in the gallbladder. Ursodiol, a naturally occurring bile acid, has the capacity to keep cholesterol in solution, prevent cholesterol precipitation, and even dissolve precipitated cholesterol over time.[10,11] Ursodiol, also called ursodeoxycholic acid, acts by gradually dissolving the cholesterol-rich solid component of cholesterolosis, cholesterol polyps, or small to medium sized noncalcified cholesterol gallstones.[10,11] After weight reduction surgery, bariatric surgeons have placed their gastric bypass patients on ursodiol during the initial 6-month post-operative period of rapid weight loss to prevent new gallstone formation with good results.[12] Interventional radiologists have removed gallstones from the gallbladder in patients with high medical risk by using US lithotripsy via a cholecystostomy tube, followed by new gallstone prevention with long-term ursodiol treatment, and thus eliminated the

need for cholecystectomy in these cases.[13] Most importantly, ursodiol has been used quite successfully for the dissolution of noncalcified cholesterol gallstones especially when the stones are small in size and few in number.[11] As ursodiol is a naturally occurring component of human bile, the incidence of unwanted side effects is relatively minor.[11]

Although much has been studied about the beneficial effect of ursodiol in the prevention of new gallstone formation in post-gastric bypass surgery and the dissolution of established cholesterol gallstones in high-risk surgical patients,[10] the literature on the effect of ursodiol on cholesterol gallbladder polyps is quite limited. An early article on the impact of ursodiol on gallbladder polyps came from Italy in 1993, where 9-out-of-12 patients (75%) showed polyp regression within 6 months.[14] A 2003 Russian study reported that in 23 patients with gallstones and polyps in the gallbladder, the regression rate was 87% and 56.5%, for stones and polyps respectively, within 7-9 months of ursodiol treatment.[15] In these reports, it is probable that most nonresponsive polyps were adenomas rather than cholesterol polyps. Even though we have started using ursodiol along with US surveillance for patients with gallbladder polyps referred to the *University of Iowa Gallbladder Dysfunction Clinic*, it will be essential to involve multiple medical centers to perform a clinical trial that involves a sufficient number of patients.

The recommended dose of ursodiol varies between 300 mg to 600 mg three-times daily (before breakfast, lunch, and dinner) and can also be calculated based on body weight, 10-15 mg/kg/day, in 3 divided doses before meals. If gallbladder polyp patients show a partial or tepid response to ursodiol treatment during the first six months, the US can be repeated 6 months later after increasing the dose of ursodiol as individual variations shift widely between patients with regard to hepatic cholesterol metabolism and bile cholesterol concentration, especially in relation to the metabolic syndrome.[4] Therefore, active steps can be taken to reduce the size and number of gallbladder cholesterol polyps during the period of US surveillance before arriving at a premature conclusion that cholecystectomy is indicated. *The gallbladder should not be made the proverbial sacrificial lamb slaughtered for the sake of harmless polyps discovered incidentally because the vast majority of cholecystectomies done for these polyps are — in retrospect — pointless.*[1,6]

Conclusion

Multicenter randomized prospective controlled trials are needed to investigate the validity of a new clinical paradigm by testing the *hypothesis that ursodiol therapy in parallel with ultrasound surveillance for the management of incidental gallbladder polyps reduces surveillance periods and cholecystectomy rates.*

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