during laparoscopic cholecystectomy, and more frequent use of cholangiograms may compensate for the loss. In our initial experience with cholangiography, we successfully performed technically satisfactory cystic duct cholangiograms during laparoscopic cholecystectomy in 93% of the patients, disclosing pathological conditions in 8% (12).

Dubois et al. (1) mentioned that cholecystograms could be performed during laparoscopic cholecystectomy, whereas Reddick and Olsen described cystic duct cholangiography and believed it would be possible to perform it in 75% of the patients (2).

The delineation of common duct stones before or during an operation will present a dilemma concerning the patient's management. Should the patient undergo endoscopic stone extraction and laparoscopic cholecystectomy or open cholecystectomy and standard common duct exploration? This question has been difficult to answer in previous studies that discussed the need to eliminate the morbidity of common duct exploration associated with open cholecystectomy. It appears to be the majority opinion that a patient with obstructive jaundice from gallstones, with the gallbladder intact, is appropriately treated by open cholecystectomy and standard common duct exploration (13).

A randomized prospective trial comparing laparoscopic cholecystectomy followed or preceded by endoscopic retrograde cholangiopancreatography and common duct stone extraction compared with standard open cholecystectomy and common duct exploration will determine the success rates and complication rates associated with each approach. However, the latter approach will still have the characteristics of the disability associated with the laparotomy incision.

Lastly, a red flag of caution needs to be raised regarding laparoscopic procedures using $CO_2$ insufflation. In gynecological laparoscopy procedures that are brief and involve healthy, young patients, $CO_2$ absorption is rarely a problem. $CO_2$ is a highly diffusible gas rapidly absorbed by the peritoneum (14). However, very little information is available concerning the effects of intraabdominal $CO_2$ insufflation, under pressure, for the 1 to 2 hr required to perform laparoscopic cholecystectomy. Preliminary information suggests that elderly patients with chronic cardiopulmonary disease develop severe hypercarbia and acidosis during laparoscopic cholecystectomy despite hyperventilation (14). Continued study of the anesthetic problems associated with laparoscopic cholecystectomy is indicated.

The development of this technological advance must assuredly be used only when indicated. Surgeons must restrict the use of laparoscopic cholecystectomy to patients with symptomatic biliary tract disease who otherwise would need open cholecystectomy.

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## BROWN PIGMENT GALLSTONES: THE ROLE OF BACTERIAL HYDROLASES AND ANOTHER MISSED OPPORTUNITY

*Akiyoshi T, Nakayama F.* Bile acid composition in brown pigment stones. Dig Dis Sci 1990;35:27-32.

### ABSTRACT

The bile acids in brown pigment stones and gallbladder bile were fractionated into free acids, glycine and taurine conjugates, and sulfates, using diethylamino-hydroxypropyl-Sephadex LH-20 (DEAP-LH-20) column chromatography, and were quantitated by gas chromatography. Twenty-eight cases of brown pigment stones were studied and divided into two groups: those with and those without bacteria possessing bile acid-deconjugating activity. In the former, free bile acid amounted to 62 ± 34% of the total bile acid, while in the latter, only 0.1% of total bile acid was free bile acid. The fraction of total bile acid made up of free bile acids was found to be consistently higher in brown pigment stones than in the corresponding bile, irrespective of the presence or absence of biliary infection. Free bile acid is present in negligible amounts in normal bile. Total bile acid concentration in the bile of patients with brown pigment stones was significantly less than that of controls (13 vs. 50 mg/ml). Biliary infection is almost always present in cases with brown pigment stones. These findings suggest that

**bacterial infection is present at the initiation of brown pigment stone formation as well as during the period of ensuing stone growth.**

## COMMENTS

Using generally impeccable, state-of-the art methods, the authors have shown that bile acids, like the major calcium bilirubinate and fatty acylate components of brown pigment gallstones, probably appear in these stones as a result of the action of bacterial hydrolases in the infected bile. In each case, the hydrolase cleaves a natural component of bile (conjugated bile salts, bilirubin glucuronides and lecithins, respectively) that is fairly soluble and forms soluble calcium complexes to yield derivatives (unconjugated bile salts, unconjugated bilirubin and fatty acylates, respectively) that are themselves less soluble and also form insoluble calcium salts [1].

All evidence indicates that these anionic components in gallstones are present primarily as their calcium salts [2]. Therefore the important thermodynamic parameters are not the solubility of the anion $(A^-)'$ or its protonated species (HA) but whether the ionic product in bile, $^aCa^{+\times}(^aA^-)^2$, exceeds its apparent solubility product $(K'_{sp})$, the requisite condition for supersaturation and precipitation of the salt [2, 3]. In the ionic product, it is the *activities* of the unbound fractions of the $Ca^+$ and anion that are relevant, not their total concentrations. Strangely, this paper makes no reference to these key concepts or to the elegant work of Jones et al. [3] describing the solubility behavior of calcium salts of glycine-conjugated bile acids. Because the ionized calcium concentrations in the biles were not measured by the authors, the system is incompletely defined. This missed opportunity is a failing of many published papers on the composition of bile and its relationship to gallstone formation.

The study of Jones et al. [3] in Alan Hofmann's laboratory used model systems containing glycine-conjugated bile salts and calcium. The results indicated that the concentrations of both components in normal bile were in excess of the $K'_{sp}$ values, which were $0.2 \times 10^{-8}$ mol/L$^3$ for the glycochenodeoxycholate (GCDC), $1.0 \times 10^{-8}$ mol/L$^3$ for glycodeoxycholate (GDC) and $4 \times 10^{-8}$ mol/L$^3$ for glycoursodeoxycholate (GUDC), but much higher for glycocholate (GC), a trihydroxy bile acid. However, these calcium salts seldom precipitate in gallstones because of (a) decreased monomeric bile salt activity caused by incorporation into micelles, a process facilitated by added lecithin; (b) decreased $Ca^{++}$ activity caused by formation of soluble complexes mainly with bile salt monomers and micelles [2, 3]; and (c) decreased activity of both ions because of the high ionic strength of bile. In addition, the systems showed marked and prolonged metastability, with formation of gels, so that crystalline precipitates developed only very slowly over many months. Unpublished data from the same laboratory has revealed similar phenomena for the unconjugated and taurine-conjugated bile salts, with the same relative solubilities of CDC < DC < UDC < < C. However, the unconjugated bile salts have much lower solubilities, and the taurine-conjugated bile salts much higher solubilities, than their corresponding glycine-conjugates.

These data in model systems seem to explain why, as in this paper, the bacterial hydrolysis of glycine and taurine conjugates would promote precipitation of bile salts and why glycine-conjugated bile salts and CDCA would be preferentially precipitated in the stones and depleted in the bile, as compared with taurine conjugates and CA, respectively. These concepts, however, fail to explain three other observations: (a) Why are there any taurine-conjugated bile salts or cholates in the stones? (b) Why is there a similar percent by weight of bile acids in black pigment gallstones, which are unrelated to infection and contain no unconjugated bile salts? and (c) Why do some brown stones contain unconjugated bile salts, even when the bile supposedly lacks bacteria with deconjugating activity and contains no greater concentrations of unconjugated bile salts than control biles?

Observations (a) and (b) above suggest that mechanisms other than precipitation as insoluble calcium salts may account, at least in part, for the appearance of bile acids in the stones. One possible mechanism is adsorption of bile acid monomers to precipitated calcium carbonate [4, 5], phosphate [6] crystals in the stones or both. This might be especially relevant for black pigment stones, which contain a large proportion of these two inorganic calcium salts. Such adsorption is greater for unconjugated $\geq$ glycine-conjugated > taurine-conjugated bile salts, and with GCDC and GDC > > GC, which is in keeping with the observed relative enrichments of different bile salts in the gallstones. Another possible mechanism is adsorption of bile salts to the nonglycosylated, hydrophobic bonding regions of the peptides in the mucins [7], which are a major component of the structural organic matrix in all gallstones [8].

The presence of unconjugated bile salts in the brown stones and surrounding bile when the bile supposedly lacked bacteria with deconjugating activity may be related to problems with definitions and experimental design. Thus the authors incubated $10^6$ to $10^8$ bacteria with various taurine-conjugated bile salts at a concentration of 0.5 mmol/L, well below that found in bile and defined deconjugating activity as hydrolysis of more than 95% of the conjugates in 24 hr. In fact, therefore, many of the supposedly "inactive" bacteria may actually have exhibited significant, albeit slower, deconjugating activity. It would have been preferable to determine rates of deconjugation by serial assay of unconjugated bile salts formed over a period of 3 to 4 hr. Plots of these rates against the proportion of unconjugated bile salts in the corresponding stones and biles, adjusting for the actual bacterial counts in the bile samples, would likely have demonstrated a relationship between these two variables.

Of interest also is the role of the hydrolysis of lecithins by the bacterial phospholipase $A_1$ [9], which accounts for the high proportion of fatty acylates, especially palmitates, in brown stones. As noted by the authors, this,

combined with the low total bile salt concentration in the biles surrounding brown stones, could decrease cholesterol solubility and account for the high percentage of this sterol in the stones. Second, addition of lecithin enhances interaction of calcium with bile salt micelles (3), so that hydrolysis of lecithin *might* enhance $Ca^{++}$ activity in bile, promoting precipitation of calcium-sensitive anions like bile salts (2). On the other hand, contrary to the discussion in this paper, lecithin decreases solubilization of bilirubin by bile salt micelles (10), so that hydrolysis of lecithin *might* decrease the activity of bilirubinate anions, inhibiting their precipitation. These latter possibilities need to be assessed by studies of the relative effects of (lysolecithin + palmitate) vs. lecithin on the binding of $Ca^{++}$ and bilirubinates by bile salt micelles. It is of interest that the combined hydrolytic products are just as effective as lecithin in enhancing the solubilization of cholesterol by mixed bile salt micelles (11).

Finally, the studies were conducted on brown pigment stones obtained from the gallbladders of 28 Japanese patients, but it was not stated whether ductal stones were present concomitantly. It is thus uncertain whether the results can be applied to the brown stones that are more often found in the bile ducts alone than the gallbladder. Moreover, no information was given regarding the presence of ductal obstruction and/or acute cholangitis/cholecystitis in these patients, factors that might have accounted for some of the observed abnormalities in bile composition.

In summary, more such carefully performed studies are needed, but their value in understanding gallstone formation will be diminished if ionized $Ca^{++}$ activity is not measured also.

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## LICHEN PLANUS AND THE LIVER

*Gruppo Italiano Studi Epidemiologici in Dermatologia* (GISED). Lichen planus and liver diseases: a multicenter case-control study. BMJ 1990;300:227-230.

### ABSTRACT

*Objective* – To assess the association of lichen planus with liver complaints and with known etiological factors of liver diseases.

*Design* – A multicentre case-control study. Interviews were conducted by trained medical investigators on the basis of a structured questionnaire. At the interview patients and controls were asked for consent to blood samples being taken to determine transaminase activities and the presence of hepatitis B virus surface antigen.

*Setting* – Outpatient departments of 27 Italian general and teaching hospitals that were collaborating in the Gruppo Italiano Studi Epidemiologici in Dermatologia (GISED).

*Subjects* – Incident cases and controls were eligible. A total of 577 patients with lichen planus and 1031 controls with dermatological diseases other than lichen planus were interviewed. Less than 1% of the people contacted refused to participate. Patients and controls were matched for sex and age in 5 year intervals.

*Results* – The risk of lichen planus was higher in patients with a history of liver diseases requiring hospital admission or specialist consultation (relative risk = 1.6; 95% confidence interval = 1.2 to 2.2), those who had had liver biopsy (5.5; 1.9 to 15.6) and those with a history of viral hepatitis (1.9; 1.1 to 3.1). High activities of liver enzymes and positive results of tests for hepatitis B virus surface antigen were also associated with lichen planus. The association with alcohol consumption was not clearly confirmed by a dose-risk relationship.

*Conclusion* – This study adds quantitative epidemiological evidence to the clinical observation that liver disease is a risk factor for lichen planus although not a specific marker of it.

### COMMENTS

Lichen planus (LP) is one of the skin conditions that delight dermatologists. Since its classical description by Willan in 1869, the spectrum of this flat-topped, shiny, violaceous eruption of polygonal papules, symmetrically distributed and surmounted by fine white linear striations, has been expanded with a splendid array of elaborately descriptive terminology by many authors. The sun-induced *LP actinicus,* and the blistering from *LP pemphigoides* are aptly named, as are *LP annularis*