Pathogenesis of gallstones in Crohn's disease
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Chapter 2

INTRODUCTION
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Gallstone disease is a very common disorder world-wide.\(^1\) In Europe gallstone prevalence rates of 11-16% in women and 7-9% in men aged 40-49 years are reported.\(^2\) In the United States, approximately 10% of the adult population has gallstone disease and more than 750,000 cholecystectomies are performed each year.\(^3,4\) Most gallstones contain several components, but they are usually subdivided into stones consisting predominantly of cholesterol (cholesterol stones) or bile pigments (black and brown pigment stones). In Western countries, 75-80% of gallstones are cholesterol gallstones, 20% are black pigment stones and less than 5% are brown pigment stones.\(^5\)

Cholesterol gallstones contain per definition at least 70% cholesterol by weight. For cholesterol gallstone formation, supersaturation of bile with cholesterol is required,\(^6\) nucleation has to be accelerated and gallbladder motility must be delayed.\(^7\) The prevalence of cholesterol stones increases with age and female sex, and is positively correlated with obesity, rapid weight loss, family history and parity.\(^7\)

Pigment gallstones consist mainly of bilirubin polymer; in black pigment stones calcium carbonate and calcium phosphate are also found; brown pigment stones contain in addition calcium salts of fatty acids.\(^7\) For pigment gallstone formation the solubility product of calcium (hydrogen) bilirubinate needs to be exceeded.\(^8\) Supersaturation is due to an excess of unbound ionized calcium and/or unbound monoanion bilirubin, a deficiency of bile salts, which bind and solubilize calcium and unconjugated bilirubin in bile, or a combination of both.\(^8\) Black pigment gallstones are associated with alcoholic cirrhosis, malaria and various hemolytic anemias, including prosthetic heart valve-induced hemolysis, but most patients with pigment gallstones have neither hemolysis nor cirrhosis.\(^7\) In general, black pigment stones form in the gallbladder under sterile conditions. Brown pigment gallstones usually form in extrahepatic bile ducts and are associated with biliary stasis and infection.\(^7\) Brown pigment stones have a high contents of free fatty acids and calcium bilirubinates as evidence of bacterial hydrolysis of lecithins and bilirubin conjugates, respectively.\(^8,9\) There is a high prevalence of brown pigment stones in the Orient, but in the West these stones are much less common.\(^7\)

It has been well documented that patients with inflammatory bowel disease (IBD), particularly patients with ileal Crohn's disease and/or ileal resection\(^10-31\) or those treated with
ileal bypass for morbid obesity or hypercholesterolemia, are at increased risk of gallstone disease. Crohn's disease represents a wide and heterogeneous spectrum of clinical symptoms and prevalence rates of gallstones vary. There is controversy about the relative frequency of cholesterol and pigment gallstones and the mechanism by which Crohn's disease enhances the risk of gallstone formation is still unknown. Previously, it was believed that patients with ileal disease, resection or bypass harbor cholesterol gallstones. In patients with ileal resection or disease, fecal bile salt loss in the setting of normal cholesterol secretion into bile was considered the perfect, logical paradigm for the pathophysiology of cholesterol gallstone disease in these patients. Unfortunately this assumption was made on the basis of the radiological characteristics of stones and on chemical analysis of a limited number of stones in the early 1970's. Besides there were no data on biliary lipid secretion in bile salt malabsorptive states. Before the onset of IBD in early middle age or before surgical intervention, prevalence of cholesterol gallstone disease should be the same as in an age-matched population. Therefore, in all epidemiological studies this potentially is a confounding factor. The first dispute on the pathophysiology of gallstone formation in patients with ileal dysfunction emerged from several experimental studies on ileectomized laboratory animals in the 1980's, when essentially all experimental animals acquired black pigment stones when fed a lithogenic diet. Since then, substantial progress has been made in understanding the pathophysiology and physical chemistry of biliary lipid secretion in normal subjects and in patients with ileal dysfunction. Most of the latter patients adequately compensate for gastrointestinal bile salt loss and have normal bile salt secretion rates and gallbladder biles of the majority of patients with Crohn's disease is marginally saturated or unsaturated with cholesterol.

This introduction summarizes epidemiological data on stone prevalence in major ileal disease, bypass and resection. The main alterations of biliary lipid and pigment compositions in animals with ileal resection or bypass as well as in patients with ileal Crohn's disease are discussed. Biles of patients with ileal resection or disease may be enriched in either cholesterol or in bile pigments, possibly placing these patients at risk for cholesterol or black pigment gallstones, respectively.
Prevalence of gallstones in patients with ileal dysfunction

Several studies have reported a strong association between gallstones and Crohn's disease. Table 1 summarizes 20 reports published between 1956 and 1999 with a total of 2,640 adult patients with Crohn's disease with or without prior jejunal, ileal or colonic resection. The reported prevalence rates of gallstone disease in adult Crohn's disease patients vary from 6.6 percent to 43 percent (mean 16 percent). Because Crohn's disease represents a wide and heterogeneous spectrum of clinical symptoms it is not surprising that the prevalence rates of gallstones vary.

The studies listed in Table 1 are also different in terms of size of cohorts, follow-up, methods used for gallstone detection, age, diets and races. The situation is even more complex because treatment schedules and other confounding factors may affect gallstone formation. Indeed, nonsteroidal anti-inflammatory drugs may inhibit the development of gallstones, presumably because of inhibition of prostaglandins that stimulate the synthesis of mucous glycoproteins. The latter act as nucleating or scaffolding agents. Mesalazine (5-aminosalicylic acid), which is used as a therapeutic agent in Crohn's disease, has not been investigated directly but may have a similar effect.

The risk of gallstone disease is increased especially in Crohn's patients with ileal involvement (odds ratio 4.5; 95 percent confidence limits = 1.5-14.1) compared to Crohn's disease patients in whom abnormalities are confined to the colon and to patients with ulcerative colitis (odds ratio 3.3; 95 percent confidence limits = 1.3-8.6). In patients with ileal Crohn's disease, the prevalence rate of gallstones depends on the length of ileum involved or the amount of ileum resected. Patients with Crohn's disease with a history of ileal resection have a gallstone prevalence rate which is 4 to 5 times higher than the prevalence calculated from a large necropsy survey. Among ileectomy patients, those subjects with extensive (>50 cm) ileal resections have a two- to threefold higher frequency of gallstones than patients with less extensive (<50 cm) ileal resections. The gallstone prevalence rate also depends on the duration of ileal disease. The majority of Crohn's disease patients who are subjected to ileal resection develop gallstones within 15 years.
Table 1. Summary of epidemiologic studies on the incidence of gallstone disease in patients with Crohn's disease and/or ileal resection.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Country</th>
<th>No. pts</th>
<th>M/F</th>
<th>Diagnosis (No)</th>
<th>Surgery</th>
<th>Gallstones (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapin (1956)</td>
<td>USA</td>
<td>39</td>
<td>27/12</td>
<td>RE (39)</td>
<td>n.r.</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>Heaton (1969)</td>
<td>UK</td>
<td>72</td>
<td>33/39</td>
<td>RE (67)</td>
<td>IR/IB (62)</td>
<td>23 (31.9)</td>
</tr>
<tr>
<td>Cohen (1971)</td>
<td>USA</td>
<td>50</td>
<td>27/23</td>
<td>RE (50)</td>
<td>IR/IB (9)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Kelly (1972)</td>
<td>USA</td>
<td>52</td>
<td>n.r.</td>
<td>RE (52)</td>
<td>IR (40)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Nelson (1973)</td>
<td>USA</td>
<td>30</td>
<td>n.r.</td>
<td>CC (8), IC (22)</td>
<td>CO (16)</td>
<td>2 (6.6)</td>
</tr>
<tr>
<td>Baker (1974)</td>
<td>USA</td>
<td>189</td>
<td>n.r.</td>
<td>RE (71), IC (32)</td>
<td>ICO (26)</td>
<td>48 (25.5)</td>
</tr>
<tr>
<td>Baker (1974)</td>
<td>USA</td>
<td>30</td>
<td>n.r.</td>
<td>UP (30)</td>
<td>n.r.</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Seiler (1974)</td>
<td>Switzerland</td>
<td>36</td>
<td>19/17</td>
<td>RE (19), CC (4)</td>
<td>IR (17)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Hill (1975)</td>
<td>UK</td>
<td>108</td>
<td>45/60</td>
<td>UC (72), RE (35)</td>
<td>IS, IR</td>
<td>26 (24.5)</td>
</tr>
<tr>
<td>Greenstein (1976)</td>
<td>USA</td>
<td>700</td>
<td>n.r.</td>
<td>RE (213), IC (223)</td>
<td>n.r.</td>
<td>62 (8.9)</td>
</tr>
<tr>
<td>Jones (1976)</td>
<td>UK</td>
<td>55</td>
<td>23/32</td>
<td>UC (55)</td>
<td>IS, IR</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Marks (1977)</td>
<td>USA</td>
<td>24</td>
<td>n.r.</td>
<td>RE (17), UC (7)</td>
<td>IR (9)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Rutgeerts (1981)</td>
<td>Belgium</td>
<td>61</td>
<td>30/31</td>
<td>RE (27), IC (34)</td>
<td>No</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Whorwell (1984)</td>
<td>UK</td>
<td>38</td>
<td>14/24</td>
<td>RE (38)</td>
<td>n.r.</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Kurchin (1984)</td>
<td>USA</td>
<td>152</td>
<td>75/77</td>
<td>UC (81), RE (71)</td>
<td>IS, PC</td>
<td>16 (10.5)</td>
</tr>
<tr>
<td>Bluth (1984)</td>
<td>USA</td>
<td>69</td>
<td>36/33</td>
<td>UC (n.r.), UC (n.r.)</td>
<td>IS</td>
<td>16 (23)</td>
</tr>
<tr>
<td>Scholmerich (1987)</td>
<td>Germany</td>
<td>100</td>
<td>43/57</td>
<td>RE (74), UC (26)</td>
<td>IR (42)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Anderson (1987)</td>
<td>Denmark</td>
<td>107</td>
<td>55/52</td>
<td>RE (107)</td>
<td>IR (107)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Kangas (1990)</td>
<td>Finland</td>
<td>52</td>
<td>30/22</td>
<td>RE (23), IC (17)</td>
<td>IR (33)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Lorusso (1990)</td>
<td>Italy</td>
<td>159</td>
<td>95/64</td>
<td>UC (114), RE (45)</td>
<td>IR (26)</td>
<td>17 (10.7)</td>
</tr>
<tr>
<td>Nightingale (1992)</td>
<td>UK</td>
<td>84</td>
<td>29/57</td>
<td>RE (49), UC (5)</td>
<td>JR (84)</td>
<td>37 (43)</td>
</tr>
<tr>
<td>Hutchinson (1994)</td>
<td>UK</td>
<td>248</td>
<td>95/156</td>
<td>RE (119), CC (75)</td>
<td>IR (81), CO (41), ICO (71)</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Lapidus (1999)</td>
<td>Sweden</td>
<td>185</td>
<td>79/106</td>
<td>RE (59), CC (33)</td>
<td>IR or ICO (75)</td>
<td>55 (30)</td>
</tr>
</tbody>
</table>

**TOTAL** | 2,640 | 431 (16) |

1. M/F: male/female ratio
2. Diagnosis: RE, Regional enteritis; CC, Crohn's colitis; UP, Ulcerative Proctitis; UC, Ulcerative colitis; PC, Proctocolitis; IC, Ileocolitis; ISC, Intestinal ischemia; IRR, Irradiation; OB, Obstruction.
3. Type of Surgery: IR, Ileal resection; IB, Ileal bypass; JR, Jejunal resection; CO, Colectomy; ICO, Ileocolectomy; IS, Ileostomy; PC, Proctocolectomy.
4. n.r.: not reported.

Table 2 summarizes the results of 16 reports published between 1975 and 1990 on the prevalence of gallstone disease in patients with morbid obesity or hypercholesterolemia.
treated with jejunoileal or jejunal bypass or jejunoileostomy. Of 2,316 patients treated surgically, the prevalence of gallstone disease ranged from 5.6% to 58.5%, averaging 16%, which is similar to the mean percentage found in patients with Crohn's disease. Buchwald and colleagues have shown in a large multicenter randomized prospective trial that 17% of patients who underwent a partial ileal bypass surgery (of 200 cm or one third of distal small intestine) for hypercholesterolemia, developed gallstones within ten years. The majority of patients with ileal bypass develop gallstones within the first two years after ileal bypass surgery with an incidence rate of 5.2% per year compared to 2.2% per year before ileal bypass surgery.

Table 2. Summary of epidemiologic studies on the incidence of gallstone disease in patients with ileal bypass for morbid obesity or hypercholesterolemia.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Country</th>
<th>No. pts</th>
<th>M/F</th>
<th>Surgery</th>
<th>Gallstones (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wise (1975)</td>
<td>USA</td>
<td>93</td>
<td>n.r.</td>
<td>Jejunoileal</td>
<td>28 (30.1)</td>
</tr>
<tr>
<td>DeWind (1976)</td>
<td>USA</td>
<td>230</td>
<td>59/171</td>
<td>Jejunoileal</td>
<td>22 (9.6)</td>
</tr>
<tr>
<td>Moss (1976)</td>
<td>USA</td>
<td>89</td>
<td>17/82</td>
<td>Jejunoileal</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Telmos (1977)</td>
<td>USA</td>
<td>82</td>
<td>n.r.</td>
<td>Jejunoileal</td>
<td>48 (58.5)</td>
</tr>
<tr>
<td>Scott (1977)</td>
<td>USA</td>
<td>200</td>
<td>85/115</td>
<td>Jejunoileal</td>
<td>55 (27.5)</td>
</tr>
<tr>
<td>Falloon (1977)</td>
<td>USA</td>
<td>25</td>
<td>n.r.</td>
<td>Jejunoileostomy</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Wise (1978)</td>
<td>USA</td>
<td>70</td>
<td>n.r.</td>
<td>Jejunoileal</td>
<td>9 (12.8)</td>
</tr>
<tr>
<td>Halverson (1978)</td>
<td>USA</td>
<td>101</td>
<td>14/84</td>
<td>Jejunoileal</td>
<td>31 (31)</td>
</tr>
<tr>
<td>Gourlay (1978)</td>
<td>Canada</td>
<td>261</td>
<td>n.r.</td>
<td>Jejunoileal</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Sorensen (1980)</td>
<td>Denmark</td>
<td>265</td>
<td>n.r.</td>
<td>Jejunoileal</td>
<td>26 (9.1)</td>
</tr>
<tr>
<td>Delaney (1980)</td>
<td>USA</td>
<td>156</td>
<td>n.r.</td>
<td>Jejunoileal</td>
<td>16 (10.2)</td>
</tr>
<tr>
<td>Montorsi (1981)</td>
<td>Italy</td>
<td>76</td>
<td>n.r.</td>
<td>Jejunoileal</td>
<td>7 (9.2)</td>
</tr>
<tr>
<td>Hocking (1983)</td>
<td>USA</td>
<td>100</td>
<td>18/82</td>
<td>Jejunoileal</td>
<td>38 (38)</td>
</tr>
<tr>
<td>Dietel (1987)</td>
<td>Germany</td>
<td>63</td>
<td>n.r.</td>
<td>Jejunoileal</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Sorensen (1988)</td>
<td>Denmark</td>
<td>185</td>
<td>45/140</td>
<td>Jejunoileal</td>
<td>26 (14)</td>
</tr>
<tr>
<td>Buchwald (1990)</td>
<td>USA</td>
<td>320</td>
<td>n.r.</td>
<td>Partial ileal</td>
<td>54 (16.9)</td>
</tr>
</tbody>
</table>

**TOTAL** | 2,316 | 378 (16)

*M/F; male/female ratio. n.r.; not reported

Gallstones are rare in childhood, but the gallstone prevalence in children with Crohn's disease is 3%, and almost one quarter of all children suffering from gallstones had been treated with ileal resection in the past.
In conclusion, after three decades both observational and case-control studies have shown an increased risk of gallstone formation in patients with ileal disease, resection or bypass, but the nature of the stones is still elusive.

Animal models of ileal resection or bypass

It was proposed in the 1970's that massive intestinal bile salt loss should alter relative biliary lipid composition, resulting in cholesterol supersaturated bile and placing patients with Crohn's disease at risk for cholesterol gallstones.\(^6\) This assumption was supported by the classical work in the Rhesus monkey,\(^66\) which showed that the bile salt pool size decreased with extensive (i.e. more than one third) ileal resection. Supersaturation occurred when more than 20% of bile flow was diverted and bile salt secretion rate fell below 6 \(\mu\)mols/kg/hr.\(^66\) Although cholesterol saturation of bile increased in the acute phase of interruption, this was not maintained chronically.\(^66\) The unproven tenet that excessive intestinal bile salt loss leads to relative cholesterol supersaturation of bile was widely held. This concept was disputed when studies in laboratory animals clearly showed an increased prevalence of pigment as opposed to cholesterol gallstones after ileal resection or bypass.\(^67-70\) In the early 80s, Coyle et al.\(^70\) showed in gallbladder bile of guinea pigs, animals with only traces of biliary cholesterol and phospholipids, that with 50% distal intestinal bypass the bile salt concentration in gallbladder bile was unaffected, and gallstones were present in 1 of 8 animals. However, with a 90% to 95% distal intestinal bypass, they found a significant decrease in gallbladder bile salt concentration and black pigment (1% cholesterol) gallstone formation in all animals. Bickerstaff and Moossa\(^57\) subjected prairie dogs to resection or bypass of the distal third of the small intestine and noted that the majority of the animals developed calcium bilirubinate stones if those animals were fed trace cholesterol diets. Others\(^68,70\) have confirmed increased pigment gallstone formation in prairie dogs subjected to ileal resection or bypass and showed that gallbladder bile in pigment stone animals contained calcium bilirubinate precipitates and increased biliary calcium and total bilirubin levels. In contrast, cholesterol saturation indexes were normal in ileectomized or ileal bypassed animals.\(^68\) Pitt and colleagues\(^70\) speculated that gallbladder stasis, hormonal changes, gallbladder mucus production, and hemolysis may play a role in pigment precipitation, but insights into possible pathophysiological mechanisms were lacking.
Biliary lipid composition in patients with ileal resection, bypass or disease

The initial pathophysiology in patients with ileal disease is that the hepatic bile salt return decreases and the bile salt pool size shrinks and as a result the liver increases bile salt synthesis. With passage of time, the remaining functional intestine usually shows enhanced bile salt reabsorption. However, in some patients, these adaptive mechanisms remain inadequate to compensate for the increased bile salt loss. The net effect is a reduction in bile salt pool size and the proportions of bile salts in bile and eventually, low bile salt secretion rates. In humans, the bile salt pool size decreases with resections of the small intestine greater than 100 cm. Using isotope dilution techniques, Vantrappen et al. demonstrated that the bile salt pool was 1.48 ± 0.16 g in thirteen patients with Crohn's disease as compared to 3.09 ± 0.27 g in normal subjects.

In humans, cholesterol supersaturation of bile occurs when bile salt secretion rates are lower than 20 μmoles/kg/hr. The earliest research reporting on biliary lipid composition in patients with ileal dysfunction with or without ileal resection showed that such patients developed cholesterol supersaturated bile due to a decreased bile salt pool. However, like the secretory experiments in the Rhesus monkey, these results were not substantiated by later work. Short-term biliary diversion may augment cholesterol saturation of bile, particularly in patients with a preexisting defect in biliary lipid secretion, nonetheless, cholesterol supersaturation of bile is not sustained in the chronic state. It has been well documented that small bile salt pools cycle more frequently. Moreover, because of marked derepression of hepatic cholesterol 7α-hydroxylase activity, the rate limiting enzyme in conversion of cholesterol to bile salts, with the result that more hepatic free cholesterol is channeled into de novo bile salt synthesis. Indeed, gallbladder biles of the majority of patients with Crohn's disease is marginally saturated or unsaturated with cholesterol. Studies in Crohn's disease patients in Finland have shown that biles were supersaturated with cholesterol when fecal bile salt losses were minor, whereas biliary cholesterol secretion and bile lithogenicity decreased with large fecal bile salt losses. More recent studies have shown that gallbladder bile of patients with Crohn's disease is markedly enriched in both conjugated and unconjugated bilirubin, providing sufficient substrate for hydrolysis in the gallbladder to
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eventually supersaturate bile with calcium salts of unconjugated bilirubin and placing these patients at risk for pigment gallstones. However, a small number of patients was studied, fasting duodenal biles were used, and neither hemolysis, ineffective erythropoiesis because of vitamin \( B_{12} \) deficiency, nor elevated bacterial \( \beta \)-glucuronidase activities were excluded as causes of the elevated pigment levels in bile.

Gallstone composition in patients with ileal disease

A systematic analysis of gallstone composition in patients with Crohn's disease is lacking. Most gallstones in ileal Crohn's disease or ileectomy are radiopaque and therefore rich in inorganic calcium salts. Both cholesterol as well as pigment gallstones were reported in patients with Crohn's disease, but stone composition was verified anecdotally only.

Putative mechanisms of cholelithiasis in patients with a compromised ileum

1. Cholesterol supersaturation of bile

As mentioned earlier, a significant number of Crohn's disease patients have cholesterol supersaturated biles, particularly if biliary cholesterol output is high and fecal bile salt losses are minor. It is generally accepted that cholesterol supersaturation of bile is a primary factor in cholesterol gallstone formation.

2. Pro- and antinucleating proteins

In addition to cholesterol saturation, biliary proteins regulate cholesterol crystallization. Both crystallization promoting and inhibiting proteins have been described in bile. Extraction of promoting proteins from bile of cholesterol gallstone patients inhibits crystallization, providing direct evidence for a regulating role by these proteins. Mucin is a pronucleating glycoprotein that is secreted continuously by the gallbladder and is increased during cholesterol lithogenesis. However, the importance of mucin in cholesterol crystallization in vivo is still controversial, since elimination of mucin from native human bile did not result in an increase of cholesterol nucleation time. Mucin forms a viscous gel lining...
the ducts and the gallbladder inner wall and may lead to entrapment of cholesterol crystals functioning as a scaffolding agent. Pro-nucleating proteins in human bile that may be of physiological relevance are immunoglobulin G and M, α-1-acidglycoprotein, haptoglobin, aminopeptidase N, α-1-antichymotrypsin and a low density pronucleator. The only characterized anti-nucleating glycoprotein in human bile that has a crystallization inhibiting effect and that binds to Concanavalin A is Immunoglobulin A (IgA). Whether pro- and antinucleating proteins play a role in cholesterol gallstone formation in patients with Crohn's disease is unknown. Interestingly, many of these proteins are either acute phase proteins or are involved in inflammation and therefore could be expected to be increased in Crohn's disease.

3. Decreased gallbladder motility

Gallbladder emptying is delayed in patients with Crohn's disease. Gallbladder motility is regulated by the interaction of stimulatory hormones such as cholecystokinin and inhibitory agents such as somatostatin, and depends on the integrity of the gallbladder wall. In patients with Crohn's disease especially after ileectomy, the bile salt pool may be depleted diurnally. This would give rise to deficient micellar solubilization of dietary lipid resulting in a weaker fatty acid stimulus to cholecystokinin release from the proximal small intestine. This in turn causes gallbladder hypomotility, which is a known risk factor for gallstone disease.

4. Increased bile pigments

A. Enterohepatic cycling of bilirubin

Increased bilirubin levels in gallbladder bile, as seen in patients with Crohn's disease, might theoretically occur by enhanced return of intestinal bilirubin to the liver via enterohepatic cycling of unconjugated bilirubin. In health, there is virtually no enterohepatic cycling of bilirubin, and bilirubin excretion into bile equals bilirubin production. Because almost all bilirubin is conjugated by the liver before it is secreted into bile, bilirubin molecules are too large and polar to be absorbed from the upper small intestine. In the distal small intestine and colon, bilirubin conjugates are hydrolyzed to unconjugated bilirubin by endogenous or bacterial β-glucuronidase and is potentially absorbed from the intestine. However, unconjugated bilirubin either precipitates as an insoluble calcium salt or is further converted by bacterial catabolism into urobilinogen or
sterocobilinogen. In neonates, enterohepatic cycling of bilirubin is common and together with hemolysis and immaturity of the bilirubin transporting and conjugating system in the liver, this causes physiologic hyperbilirubinemia and overt jaundice. In the neonate, enterohepatic cycling of bilirubin is facilitated for several reasons; bilirubin is conjugated by the liver principally as monoglucuronides rather than diglucuronides and is with only one ester linkage easier hydrolyzed to unconjugated bilirubin. Breastmilk contains β-glucuronidase activity, and unconjugated bilirubin is insufficiently converted into urobilinogen in the developing intestinal flora.

Another common complication in patients with ileal dysfunction is calcium oxalate urolithiasis, which is caused by enteric hyperoxaluria. In health, intestinal absorption of dietary oxalate is prevented because oxalate precipitates with intraluminal calcium. To induce the enteric hyperoxaluric syndrome, bile salts and/or fatty acid spillage as well as an intact colon seem to be necessary. According to Chadwick et al, fat malabsorption due to decreased duodenal bile salt levels might facilitate intestinal absorption of dietary oxalate, because fatty acids may bind intraluminal calcium and precipitate as calcium soaps. Both monocarboxylic or dicarboxylic oxalate and bilirubinate have high affinities for calcium. Therefore an analogous mechanism of increased intestinal bilirubin absorption in patients with Crohn's disease may be expected. As a consequence of bile salt malabsorption, excess colonic bile salts might prevent precipitation of calcium bilirubinate and rapid urobilinogen formation. This in turn might facilitate passive bilirubin absorption from the intestine. After its absorption, unconjugated bilirubin is transported to the liver where it is extracted, reconjugated and resecreted into bile, thus establishing enterohepatic cycling of bilirubin. The latter might be facilitated because bacterial overgrowth in or contamination of the small intestine in Crohn's disease patients due to loss of ileocecal valve barrier might promote deconjugation of bilirubin conjugates, in turn yielding more unconjugated bilirubin available to undergo intestinal absorption. Nevertheless, overgrowth of anaerobic colonic flora in the residual ileum would be expected to enhance urobilinogen formation. A pathophysiological enterohepatic cycling of bilirubin would account for the increased bilirubin levels consistently found in gallbladder bile in Crohn's disease patients.
B. Ineffective erythropoiesis due to vitamin $B_{12}$ malabsorption

Vitamin $B_{12}$ is absorbed predominantly in the ileum and vitamin $B_{12}$ malabsorption in patients with ileal Crohn's disease and following ileectomy may cause megaloblastic anemia, hyperbilirubinemia, increased conjugated bilirubin levels in bile and pigment gallstone formation. Vitamin $B_{12}$ malabsorption is uncommon in Crohn's disease patients with ileal resections of less than 30 cm, but it is a rule in patients with extensive (>200 cm) ileal resections and following ileal bypass surgery. Nowadays, vitamin $B_{12}$ is administered routinely to patients with large ileal resections and vitamin $B_{12}$ deficiency is rare in these patients.

C. Hemolysis

Increased red cell turnover in chronic hemolysis elevates bilirubin conjugates in bile and pigment gallstones are common in patients with chronic hemolysis. There is no a priori reason why increased red cell destruction would occur in patients with Crohn's disease.

D. Increased heme destruction from nonhemoglobin sources

Increased heme catabolism, e.g. by rapid liver regeneration secondary to toxic, infectious, or metabolic injury to the liver may lead to an increase in bile pigment formation. It is not known whether increased tissue heme turnover may occur in patients with Crohn's disease.

5. Increased biliary $\beta$-glucuronidase activity

In gallbladder bile of healthy persons unconjugated bilirubin compromises less than 1% of total bilirubin. Unconjugated bilirubin is presumably not secreted into bile and is thought to be derived from deconjugation, partially nonenzymatically but largely due to the action of nonbacterial $\beta$-glucuronidase in gallbladder bile. The latter enzyme is released by lysosomes of hepatocytes and biliary epithelium. Theoretically, bacterial toxins in patients with Crohn's disease might stimulate the liver or the gallbladder wall to release more $\beta$-glucuronidase. Alternatively, gallbladder bile of patients with Crohn's disease might contain bacterially derived $\beta$-glucuronidase.
**Bile salt malabsorption syndromes**

If increased bile salt concentrations in the colon facilitate bilirubin absorption and if this is the key step in enterohepatic cycling of unconjugated bilirubin, this mechanism should be applicable to all bile salt malabsorption syndromes, leading to either increased biliary bilirubin levels or hyperbilirubinemia, depending on the health and maturity of the liver with respect to bilirubin UCB uptake, conjugation and secretion. Apart from Crohn’s disease, ileal resection or bypass, bile salt malabsorption may occur 1) in ileal disease caused by the acquired immunodeficiency syndrome (AIDS), 2) in newborns due to immaturity of ileal bile salt transporters; 3) in primary bile salt malabsorption syndromes related to a genetic abnormality in the active ileal transport of bile salts, 4) following cholecystectomy or peptic ulcer surgery with vagotomy increasing intestinal transit; 5) in diabetes mellitus, chronic pancreatitis or severe celiac sprue; and 6) with ingested ursodeoxycholic acid, excess dietary cholesterol, high starch (especially crosslinked or resistant starch) diets and bile acid reabsorption inhibitor drugs.

In patients with idiopathic bile acid malabsorption due to a defect in the ileal bile acid transporter, the biliary lipid composition is unaffected and cholesterol saturation of biles in these patients is comparable to controls.

In patients with cystic fibrosis, bile salt malabsorption has been reported as a major problem in about one third. Moreover, cystic fibrosis patients are prone to develop black pigment gallstones. Because most cystic fibrosis patients have ablation in the secretion of pancreatic enzymes and produce little bicarbonate, they often fail to neutralize the acidic gastric contents in the duodenum and jejunum. This results in very low pH levels (pH < 4 to 5) in the proximal small intestine. Under this condition, glycine-conjugated bile salts of both trihydroxy and dihydroxy species precipitate.

Ingestion of large amounts of carbohydrates by man and hamsters, particularly crosslinked and amylase resistant carbohydrates such as starch, may cause bile salt malabsorption. Experimental studies in hamsters have shown that a rice starch diet induces pigment gallstones. Carbohydrate-enriched diets fed to prairie dogs increased concentrations of calcium and total bilirubin in bile inducing calcium bilirubinate sludge and pigment gallstones.
Modalities of gallstone prevention

To prevent gallstone formation in patients with ileal dysfunction, one must be able to non-invasively diagnose and then prevent enterohepatic cycling of unconjugated bilirubin. It has been shown that binding of bilirubin in the gut lumen with agar or activated charcoal can lower serum bilirubin levels in the newborn.\textsuperscript{181} Insoluble calcium phosphate has been proposed as a good chelator of unconjugated bilirubin from bile salts solutions\textsuperscript{182,183} and in fact, oral calcium phosphate/carbonate has been suggested as effective in treating hyperoxaluria in patients with ileal resection.\textsuperscript{184-186} In a recent paper, insoluble calcium salts were shown to suppress serum bilirubin levels in patients with Crigler Najjar Type II syndrome.\textsuperscript{187} Small doses of zinc salts given to hamsters and Gilbert’s patients suppress biliary bilirubin secretion rates \textit{in vivo}, suggesting the inhibition of enterohepatic cycling of unconjugated bilirubin.\textsuperscript{188} New strategies have to be investigated to chelate unconjugated bilirubin selectively in the gastrointestinal tract. This might prevent pigment gallstones in patients at risk from mild degrees of bile salt malabsorption.

References


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