Pathogenesis of gallstones in Crohn's disease
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Chapter 1

OUTLINE OF THE THESIS
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In this thesis in vivo and in vitro studies are presented that may contribute to our understanding of the pathogenesis of gallstones in patients with ileal disease, resection or bypass.

The introduction in chapter 2 gives an overview of prevalence studies on gallstone formation in patients with ileal disease, resection or bypass. The reported incidence of gallstone disease in patients with Crohn's Disease affecting the ileum is higher than that in the general population (30-40% and 10-15%, respectively). There is controversy as to whether patients with ileal disease, resection or bypass are at risk for cholesterol or pigment gallstones. Gallbladder bile of patients with ileal dysfunction may be supersaturated, marginally saturated or unsaturated with cholesterol, but biles of these patients may also be enriched in bile pigments. Hence, Crohn's disease patients may be at risk for either cholesterol or pigment gallstones.

Both animal and human studies are presented testing the hypothesis that bilirubin levels in gallbladder bile are enhanced as a result of increased enterohepatic cycling of bilirubin as a consequence of bile salt malabsorption. Chapter 3 describes experiments in the ileectomized rat. Bilirubin and bile salt secretion into bile were measured via an acute biliary fistula at 3-11 days after surgery and the concentrations of bilirubin and bile salts in the colon were assessed as well as indices of hemolysis in blood. Animals subjected to sham operation, ileal transection, proximal or distal jejunectomy, ileocolonic transposition and ileocecectomy were used as controls.

In chapter 4 it was investigated whether enterohepatic cycling of bilirubin might be induced by oral administration of ursodeoxycholic acid (UDCA) and cholesterol. Both agents cause bile salt malabsorption; the former by competition for and the latter by down-regulation of ileal bile acid transporters. Male inbred C57L/J mice and Sprague-Dawley rats were fed low doses of UDCA, chenodeoxycholic acid (CDCA) or cholesterol added to laboratory chow with simultaneous chow-fed controls. After 1 week (mice) or 2 weeks (rats), bilirubin secretion rates into bile were measured and serum bilirubin and urobilinogen levels were assessed. Bilirubin, urobilinogen and bile salt levels in small and large intestine as well as fecal excretion rates were determined.
In chapter 5 it was examined whether increased enterohepatic cycling of bilirubin might be a pathophysiological mechanism in humans. If increased enterohepatic cycling of bilirubin from the colon occurs, then bilirubin levels in gallbladder bile should correlate with the extent of ileal dysfunction or resection. In a large cohort of Crohn’s patients gallbladder bile was obtained during elective bowel resection. Patients with ulcerative colitis were studied as controls. Bilirubin, total calcium, biliary lipids, β-glucuronidase activities and cholesterol saturation indices in bile were measured. Other causes of increased bilirubin levels in bile such as vitamin B₁₂ deficiency, hemolytic anemia or increased turnover of tissue hemes were excluded.

Chapter 6 addresses the role of cholesterol crystallization in the pathogenesis of gallstones in Crohn disease. The influence of both cholesterol supersaturation and biliary proteins in cholesterol crystallization was studied in gallbladder bile of patients with Crohn’s disease and patients with ulcerative colitis.

Chapter 7 describes some characteristics of in vitro growth of small human cholesterol gallstones incubated in human gallbladder bile from Crohn's disease patients. Biles of patients with ulcerative colitis were used as control. Concentrations of biliary lipids, bile pigments and calcium were determined and accretion of material to the stone was measured. The characteristics of the stone surface was analyzed by scanning electron microscopy.

Finally, the summary (chapter 8) gives an overview of the thesis and places the new insights into perspective of the possible pathogenesis of gallstone disease in Crohn's disease.