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## Intestinal function in cholestasis and essential fatty acid deficiency

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2007

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Los, E. L. (2007). *Intestinal function in cholestasis and essential fatty acid deficiency*. s.n.

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**Summary**

**Nederlandse samenvatting**

**Dankwoord**

**Curriculum Vitae**

**List of publications**

## SUMMARY

Cholestatic liver disease covers a wide range of conditions characterized by defective bile formation associated with reduced bile salt transport from the liver into the intestinal lumen. Physiological consequences include retention of bile salts and other bile constituents in the hepatocytes, limited availability of bile salts in the intestinal lumen and elevated plasma bile salt levels. These consequences eventually lead to liver injury, lipid malabsorption, pruritus, jaundice and potentially peripheral tissue injury. Cholestatic patients, especially children, frequently develop failure to thrive which consists of failure to grow and nutritional deficiencies, including those of fat-soluble vitamins and essential fatty acids (EFA). A malnutritional state strongly affects prognosis of cholestatic patients. Identification of nutritional deficiencies in cholestasis and understanding of the pathophysiology underlying these deficiencies will help to improve the prognosis of cholestatic children by allowing optimization of their nutritional status. We therefore aimed to elucidate the effects of cholestasis and EFA deficiency on intestinal function, with emphasis on digestion and absorption of fats and carbohydrates.

**Chapter 2** relates to the nutritional deficiencies that accompany cholestatic liver disease in children as well as treatment options based on nutrient supplementation. Important factors in the pathophysiology of malnutrition in pediatric cholestasis are poor dietary intake, increased energy expenditure and impaired absorption of fats and fat-soluble nutrients. To counteract malnutrition in cholestasis, dietary energy intake in cholestatic children is usually increased to 120-150% of the recommended daily energy intake. In addition, up to 60% of the fat components, particularly long-chain triglycerides are substituted by medium-chain triglycerides whose absorption occurs relatively independent from the presence of bile components in the intestinal lumen. Pediatric cholestatic patients comprise a heterogeneous group: consequently clinical manifestations of the disease may vary widely. This makes a tailor-made dietary approach for these children crucial.

As stated above, cholestasis is often accompanied by a strongly elevated plasma bile salt level. Many reports have demonstrated that bile salts can induce cellular proliferation or apoptosis, depending on the bile salt species, concentration and cell type involved. We have evaluated whether elevated plasma bile salt concentrations could affect intestinal function, for instance by affecting proliferation, differentiation or apoptosis. In **chapter 3**, we investigated the effect of cholestasis on intestinal function, i.e., on digestion and absorption of sucrose and glucose in rats, with stable isotope methodology. We compared cholestatic rats to control rats and bile-deficient rats, to be able to differentiate between consequences of elevated plasma bile salts and absence of bile from the intestine. Intestinal sucrose digestion and glucose absorption occurred to a similar extent in cholestatic, control and bile-deficient, indicating that this aspect of intestinal function, i.e., carbohydrate digestion and absorption, is preserved in cholestatic conditions.

In **chapter 4**, we studied the effect of conjugated bile salts in cholestatic concentrations on intestinal epithelial cells *in vitro*. The human colon carcinoma cell line Caco-2, which develops small intestinal characteristics upon differentiation, was exposed to cholestatic conditions at different developmental stages. Exposure of proliferating or short-term differentiative cells to conjugated bile salts in cholestatic concentrations did not affect

intestinal cell proliferation, differentiation or apoptosis, indicating that intestinal cells in the respective developmental stages are resistant to cholestatic conditions. Exposure of long-term differentiative cells to cholestatic conditions, however, resulted in decreased sucrase activity, coinciding with increased expression of the bile salt transporter ASBT. Nutrient absorption, including sucrase activity, is most efficient in the jejunum, while active bile salt absorption is restricted to the terminal ileum. We speculated that enterocytes are protected from bile salt-induced effect through absence of the intestinal bile salt transporter ASBT.

Cholestasis-induced fat malabsorption often leads to EFA deficiency. EFA deficiency in itself, however, can also induce fat malabsorption. The pathophysiological basis of EFA deficiency-induced fat malabsorption is incompletely understood, but is probably located at the mucosal level. We have evaluated whether EFA deficiency would also affect carbohydrate digestion or absorption. In **chapter 5**, we tested this theory by subjecting EFA deficient mice to a lactose digestion/glucose absorption test using stable isotope methodology. Lactose digestion, but not glucose absorption, was impaired in EFA deficient mice. Impaired lactose digestion coincided with decreased activity and mRNA levels of lactase in the jejunum. In addition, we found a positive correlation between jejunal lactase activity and membrane phospholipid linoleic acid content, suggesting that altered fatty acid composition of cellular membranes affects lactose digestion during EFA deficiency.

The farnesoid X receptor (FXR) has been implicated in the regulation of bile salt and lipid metabolism. *Fxr*-deficient mice have increased bile flow and bile salt pool size, and a more hydrophobic bile salt composition due to an increased contribution of cholic acid (CA). Interestingly, we previously demonstrated that EFA-deficiency in (wild-type) mice has similar phenotypic characteristics. Based on this similarity, we wondered whether FXR could be involved in EFA deficiency-induced fat malabsorption. In **chapter 6**, we assessed fat absorption and bile salt homeostasis parameters in EFA deficient *Fxr*<sup>-/-</sup> mice compared to EFA deficient control mice. Inactivation of FXR resulted in milder fat malabsorption and increased weight gain, coinciding with increased hydrophobicity of the bile salt pool. Thus, FXR appears to be involved in EFA deficiency-induced fat malabsorption, possibly by modulating the hydrophobicity of the bile salt pool.

According to the work described in this thesis, cholestasis when accompanied by EFA deficiency seems to have a clear negative influence on intestinal function. This information allows us to develop strategies to optimize the nutritional status of cholestatic patients and thereby improve their prognosis.