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Bile acid malabsorption assessed by 7 alpha-hydroxy-4-cholesten-3-one in pediatric inflammatory bowel disease: Correlation to clinical and laboratory findings☆

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Abstract

Background and aims: Measurement of 7 alpha-hydroxy-4-cholesten-3-one (C4) in serum is a semiquantitative test for bile acid malabsorption (BAM). We have previously established pediatric normal values for C4 with an upper limit of normal of 66.5 ng/mL, independent of age and sex. Here we performed the C4 test in 58 pediatric patients with Crohn's disease (CD) and ulcerative colitis (UC).
Methods: C4 was measured using high performance liquid chromatography (HPLC) in fasting serum samples of 44 patients with CD (range 7–19 years) and 14 with UC (4–18 years). Disease activity was assessed by the pediatric CD and UC activity indices (PCDAI and PUCAI, respectively) plus serum (CRP, ESR) and fecal inflammatory markers (calprotectin).
Results: C4 concentrations were increased in 10 CD (23%) (range: 70.8–269.3 ng/mL) but only one UC patient (72.9 ng/mL). CD patients with diarrhea (n = 12) had higher C4-values compared to those without (76.9 vs. 30.4 ng/mL; p = 0.0043). Ileal resection in CD patients (n = 10) was associated with increased C4 concentrations (81.2 vs. 24.3 ng/mL, p = 0.0004). No correlation

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was found between C4 values and inflammatory markers. Six of 7 CD patients with persistent diarrhea but quiescent disease (PCDAI ≤12.5) had C4 values indicating BAM.
Conclusion: Elevated C4 concentrations indicating BAM are common in children with CD. They are associated with ileal resection and non-bloody diarrhea in the absence of active disease or elevated inflammatory markers. The C4-test identifies a subgroup of CD patients with persistent diarrhea in spite of clinical remission which may benefit from bile acid binding therapy.

1. Introduction

Bile acid malabsorption (BAM) has been reported in up to 50% of adult patients[1,2] with Crohn's disease (CD), predisposing to diarrhea, steatorrhea with malabsorption of fat soluble vitamins and formation of gallstones and kidney stones.[3–5]

The gold standard in diagnosing BAM is the TauroH-23-(^{75}Se) selena-25-homocholic acid 23-seleno-25-homo-tauro-cholic-acid-test (SeHCAT).[6] The radio-labeled bile acid ^{75}SeHCAT is administered orally, and after seven days the remaining radioactivity is measured by a gamma camera. A retention of less than 10–15% of the administered tracer indicates BAM.[7]

The measurement of the serum marker 7 alpha-hydroxy-4-cholesten-3-one (C4) to assess bile acid loss was first described by Axelson et al.[8] C4 is an intermediate in the classical pathway of bile acid synthesis reflecting the activity of the rate-limiting step catalyzed by the 7 alpha-hydroxylase (CYP7A1).[9] In patients with BAM, CYP7A1 is upregulated in order to compensate, resulting in an increased synthesis of bile acids and their precursors. C4 is a relatively stable precursor and can be measured by HPLC (high-performance liquid chromatography). Although it is a semi-quantitative test, it has some obvious advantages compared to the SeHCAT method[10]: it is easier to perform, less invasive, less time and cost intensive. The C4 method has been modified by Pettersson[11] and Sauter[12] and showed in several studies a good inverse correlation with remaining tracer in the SeHCAT-test.[12–15] Recently, we have established normal values for the C4 test in a large pediatric population of healthy children (n = 100) of different age groups (0–18 years).[16] C4 concentrations above 66.5 ng/mL were defined pathological indicating BAM. This upper limit of normal was independent of age and gender and corresponds to previous published cut off values in adults.[2,12]

In pediatric IBD (PIBD), only few data are available regarding BAM. Childhood onset IBD occurs in up to 25% of all IBD cases and is characterized by extensive intestinal involvement and rapid early progression.[17,18] While no studies have been performed in PIBD applying the C4-tests, two series including a small number of patients looked at BAM by measuring fecal bile acid excretion. In one study investigating BAM in 31 pediatric IBD patients by measuring the fecal excretion of the intravenous administered radio-labeled bile acid carboxyl-^{14}C-cholic acid, there was no difference between pediatric CD and UC patients (n = 15 and 16, respectively). BAM was detected in patients with radiographically abnormal terminal ileum and a high inflammatory activity in the ascending colon assessed by colonoscopy. No influence of clinical disease activity and stool consistency could be detected.[19] The other study revealed significantly increased total fecal excretion of bile acids in 18 pediatric IBD patients (16 UC, 2 CD, age 10–17 years), all of them were in clinical remission and had normal stools.[20]

In this study, we wanted to clarify the following questions: is bile acid malabsorption a problem in pediatric IBD patients, and if so, is it related to the type of disease? Is it influenced by previous ileocecal-resection, the presence of diarrhea or high disease activity? We speculate that the measurement of C4 concentrations allows identifying children with CD or UC with non-bloody diarrhea that is due to BAM and not a sign of mucosal inflammation. This would have major therapeutic implication.

2. Patients and methods

2.1. Subjects

A total of 58 patients were recruited from the IBD clinic of the Division of Pediatric Gastroenterology and Hepatology at the Dr. von Hauner Children's Hospital, Munich. Forty-four patients with CD (median age 15.5 years, range 7–19 years) and 14 with UC (median 15.8 years, range 4–18 years) were recruited consecutively. There were no special inclusion criteria like suspected BAM. Exclusion criteria were intake of bile acids or bile acid sequestrants, bloody diarrhea and elevated liver enzymes (alanine aminotransferase and aspartate aminotransferase) of more than two times the upper limit of normal. The healthy control group consisted of 100 children (median age 10.0, range 9 months to 18 years, 52% males) recently described in detail.[16]

Disease location was assessed in all patients by upper and lower endoscopy and MRI-enterography. Symptoms and disease activity were assessed at the time of blood sampling by calculation of the pediatric Crohn's disease activity index (PCDAI)[21] in CD patients and the pediatric ulcerative colitis activity index (PUCAI)[22] in UC patients. The PCDAI defines inactive disease by a maximum of 10 out of 100 possible points, *mild activity* between 11 and 30 points and *moderate to severe disease* above 30 points. The PUCAI requires less than 10 points for *inactive*, 10 to 34 points are considered as *mild activity* and *moderate to severe activity* as >35 points. In both indices the presence of non-bloody diarrhea increases the score by 5 to 10 points. For example, the presence of three liquid, non-bloody stools per day causes 5 additional points in PCDAI.

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