



## Original article

## Bile acid malabsorption investigated by selenium-75-homocholeic acid taurine ( $^{75}\text{SeHCAT}$ ) scans: Causes and treatment responses to cholestyramine in 298 patients with chronic watery diarrhoea

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## ABSTRACT

**Background:** The liver produces and secretes bile acids into the small intestine. In the small intestine, most of the bile acids are absorbed in the distal ileum with portal vein transportation back to the liver and resecretion (enterohepatic recycling). Increased spillover of bile acids from the small intestine into the colon (bile acid malabsorption) may affect the secretion of colonic water and electrolytes and result in watery diarrhoea.

The aim of this study was to investigate the frequency of bile acid malabsorption and treatment responses to cholestyramine with  $^{75}\text{SeHCAT}$  scanning among patients suffering from chronic watery diarrhoea.

**Methods:** This was a retrospective study that included all patients who received a  $^{75}\text{SeHCAT}$  scan over a five-year period (2004–2009).

**Results:** In total, 298 patients (198 females, 100 men) with a median age of 42 years (range 16–82 years) were investigated.

Bile acid malabsorption ( $^{75}\text{SeHCAT}$  retention < 15% after seven days) was identified in 201 patients (68%, 95% confidence interval (CI): 62%–73%). Bile acid malabsorption due to ileal dysfunction (Type I) was found in 77 patients, idiopathic bile acid malabsorption (Type II) was found in 68 patients and 56 patients with other conditions had bile acid malabsorption (Type III).

Of the 150 patients who were able to take cholestyramine continuously, 108 patients (71%, CI: 63%–78%) reported a positive effect on their bowel habits.

**Conclusions:** Bile acid malabsorption is a frequent problem in patients with chronic watery diarrhoea. Treatment with bile acid binders was effective regardless of type and severity.

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## 1. Introduction

Bile acid malabsorption is a known cause of chronic watery/semisolid diarrhoea [1–3]. More than 95% of all bile acids are actively reabsorbed in the distal ileum and recycled and reused via the liver. In patients with bile acid malabsorption, an increased amount of bile acids enter the colon and induce increased colonic secretion of water and electrolytes, which thereby causes diarrhoea [4,5].

Different conditions are known to induce bile acid malabsorption and can be divided into three types [6–8]. Bile acid malabsorption Type I is classified as secondary due to ileal dysfunction caused by resection or ileal disease/injury. Bile acid malabsorption Type II is considered idiopathic or primary (with a normal ileum). Finally, bile

acid malabsorption Type III results from miscellaneous disorders (e.g., postcholecystectomy diarrhoea, diabetes mellitus, small intestinal bacterial overgrowth).

Bile acid malabsorption can be diagnosed with the use of  $^{75}\text{Se}$ -labelled homocholeic acid-*taurine* ( $^{75}\text{SeHCAT}$ ), which is a synthetic gamma-emitting bile acid analogue with the ability to recirculate in the enterohepatic circulation after oral administration [9]. In patients with bile acid malabsorption,  $^{75}\text{SeHCAT}$  is lost together with the endogenous bile acids and, as a result, the radiation from  $^{75}\text{SeHCAT}$  decreases. The radiation after 7 days can be compared to the initial radiation (radiation retention) of  $^{75}\text{SeHCAT}$  and used to calculate the retention percentage.

In a review of the prevalence of idiopathic bile acid malabsorption as diagnosed by  $^{75}\text{SeHCAT}$  in diarrhoea-predominant irritable bowel syndrome, the 7-day retention body percentage is defined by bile acid malabsorption severity as follows (10):

<5% 7-day retention radiation of  $^{75}\text{SeHCAT}$ : severe bile acid malabsorption

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5% to <10% 7-day retention radiation of <sup>75</sup>SeHCAT: moderate bile acid malabsorption

10% to <15% 7-day retention radiation of <sup>75</sup>SeHCAT: mild bile acid malabsorption

The bile acid sequestrant cholestyramine can be used in the symptomatic treatment of bile acid malabsorption [2]. It has been shown that lower <sup>75</sup>SeHCAT retention results in a better response to cholestyramine [2,11]. However, the correct dose is very difficult to predict and is therefore based on the individual [1]. It has been reported that up to 26% of the patients who responded well to cholestyramine did not wish to continue the treatment due to adverse effects such as unpalatable taste, obstipation, nausea, bloating and abdominal pain [2,7,8].

The aim of this study was to investigate the prevalence of bile acid malabsorption using <sup>75</sup>SeHCAT scanning in 298 patients with chronic watery diarrhoea and to evaluate the effects of treatment with cholestyramine in patients with bile acid malabsorption.

## 2. Patients and methods

This was a retrospective study that included all patients who received a <sup>75</sup>SeHCAT scan during a five-year period (2004–2009).

Records of the patients' average stool frequency and consistency before the <sup>75</sup>SeHCAT scanning were collected from patients as self-reported diarrhoea frequencies and were noted in the patients' records.

For patients with intestinal resection, information on resection type and length were collected from the surgery record or pathology report.

Cholecystectomized patients were asked in a standardized questionnaire about the time span between surgery and diarrhoea debut, stool frequency, consistency and duration of diarrhoea.

### 2.1. Methods

A synthetic analogue to the naturally occurring bile acid, taurocholic acid (referred to as <sup>75</sup>SeHCAT), was used for bile acid malabsorption diagnoses in this study. It was administered after an overnight fast as an oral capsule (GE Healthcare, Amersham Place, Buckinghamshire, UK) containing 0.37 MBq. Basal activity was measured over the abdomen three hours after swallowing the capsule using a high-resolution collimator. The measurement was repeated after seven days and a fraction was calculated by dividing the seven-day activity by the basal activity. Retention <15% was considered abnormal.

In all of the patients with <sup>75</sup>SeHCAT retention <15%, information on treatment with cholestyramine was gathered along with its effect on stool frequency and consistency.

A normal bowel habit was defined as 1–2 formed stools per day. Response to treatment was defined as a lowered frequency of stools per day and/or a firmer consistency. Side effects of cholestyramine were noted from patients' self-reported complaints.

### 2.2. Statistics

The 95% confidence intervals (CI) were calculated for percentages proportions, and associations between categorical data were evaluated using a chi-square test [12]. A *p*-value <0.05 was considered to be statistically significant.

## 3. Results

In total, 298 patients (198 females, 100 men) were studied, with a median age of 42 years (range 16–82 years).

Of the 298 patients, 201 (68%, 95% confidence interval (CI): 62%–73%) demonstrated abnormal values of the <sup>75</sup>SeHCAT scan, defined as <15% retention of <sup>75</sup>SeHCAT after seven days (Table 1). Out of the

**Table 1**

Bile acid malabsorption recognized by the 7-day retention fraction of <sup>75</sup>Se-labelled homocholic acid-taurine (<sup>75</sup>SeHCAT) in 298 patients with chronic watery diarrhoea.

Type of bile acid malabsorption *	7 day retention of SeHCAT <5%	7 day retention of SeHCAT 5% – <10%	7 day retention of SeHCAT 10%–<15%	7 day retention of SeHCAT >15%	Total N
Type I					
Crohn's disease in terminal ileum	11	4	7	7	29
Crohn's disease with iliac resection	39	1	0	3	43
Small intestine resection	11	1	0	0	12
Radiation injury	1	1	1	0	3
Type II					
Diarrhoea, unknown cause	41	14	13	46	114
Type III					
Cholecystectomy	24	4	3	5	36
Microscopic colitis	1	2	1	8	12
Small intestinal bowel overgrowth	3	2	0	9	14
Diabetes mellitus	6	0	0	1	7
Ulcerative colitis	2	1	0	3	6
Whipple operated	2	0	0	0	2
Rheumatic diseases	1	0	1	2	4
Neuroendocrine tumour (NET)	1	0	0	1	2
Chronic pancreatitis	1	0	0	1	2
Different disorders	0	0	1	11	12
Total	144	30	27	97	298

\* Bile acid malabsorption Type I: secondary bile acid malabsorption due to ileal dysfunction caused by resection or ileal disease/injury.

Bile acid malabsorption Type II: idiopathic or primary (with a normal ileum).

Bile acid malabsorption Type III: miscellaneous disorders (e.g., postcholecystectomy diarrhoea, diabetes, small intestinal bacterial overgrowth).

201 patients with bile acid malabsorption, 174 patients (87%) demonstrated <10% retention of <sup>75</sup>SeHCAT (CI: 81%–91%), and 144 (72%) patients demonstrated severe bile acid malabsorption with a <sup>75</sup>SeHCAT retention <5% (CI: 65%–78%). Ninety-seven patients had a normal uptake of <sup>75</sup>SeHCAT.

Bile acid malabsorption due to ileal dysfunction (Type I) was found in 75 out of 87 patients (86%, CI: 77%–94%) with either Crohn's disease, resection of the distal portion of the ileum or intestinal radiation damage.

Idiopathic bile acid malabsorption (<15%) (Type II) was found in 68 (60%, CI: 52%–67%) of 114 patients without any other cause of chronic diarrhoea. Moderate or severe bile acid malabsorption (<10% 7-day retention radiation of <sup>75</sup>SeHCAT) was found in 55 (48%, CI: 39–57%) of the 114 patients.

Out of 96 patients with other conditions, 56 patients (58%, CI: 50–67%) had bile acid malabsorption (Type III).

### 3.1. Crohn's disease without resection/mucosal disease

Seventy-two patients were known to have Crohn's disease. Twenty-two of the 29 patients (76%, CI: 57%–90%) with known Crohn's disease but without resections had a <sup>75</sup>SeHCAT retention scan consistent with bile acid malabsorption (Table 1). Seven patients had <sup>75</sup>SeHCAT retention above 15%.

### 3.2. Crohn's disease with resection

Out of the 43 Crohn's disease patients with ileal resection, 39 patients had bile acid malabsorption (91%, CI: 78%–87%). The lengths of the resections were available from medical records for 37 of the 43 patients with Crohn's disease and resection of the distal part of the ileum. Thirty-four of the 37 patients (92%, CI: 78%–98%) with ileal resection had severe bile acid malabsorption (Table 1). Resection

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