Lymphatic transport of bile acids in man

Staffan Ewerth, Ingemar Björkhem, Kurt Einarsson, and Lennart Öst

Departments of Surgery, Clinical Chemistry, and Medicine, Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden

Abstract The possibility of a lymphatic transport of bile acids in man was investigated. Four patients were studied 2–4 weeks after renal transplantation. As a part of the postoperative immunosuppressive treatment they all had a thoracic duct fistula for lymphatic drainage. After a standardized meal, lymph and peripheral blood samples were simultaneously collected at 30-minute intervals for 210 minutes. The bile acids, cholic acid, chenodeoxycholic acid, and deoxycholic acid were assayed by a gas–liquid chromatography–mass spectrometry method using deuterium-labeled internal standards. The concentration of cholic acid was about the same in lymph and serum. The concentrations of chenodeoxycholic and deoxycholic acids were 2–3 times higher in lymph than in serum, both in the fasting state and postprandially. These results are explained by a more efficient passive absorption of the less polar dihydroxy bile acids. The transport of bile acids in the lymph was calculated to be only about 0.2% of that in the portal vein.—**Ewerth, S., I. Björkhem, K. Einarsson, and L. Öst.** Lymphatic transport of bile acids in man. *J. Lipid Res.* 1982. **23:** 1183–1186.

Supplementary key words cholic acid • chenodeoxycholic acid • deoxycholic acid • serum bile acids • lymph bile acids

In the enterohepatic circulation (EHC) of bile acids in man, the hepatic uptake of cholic acid (CA) (80–85%) is somewhat more efficient than that of chenodeoxycholic (CDA) and deoxycholic acids (DA) (about 70%). Thus, the ratio between CA and the other bile acids is lower in peripheral venous serum than in portal venous serum (1). As a consequence of the relatively constant hepatic uptake, the peripheral venous concentration of each individual bile acid reflects the portal venous inflow.[1] The principal part of the intestinal absorptive process is located at the distal ileum where an active transport of bile acids takes place (2). In addition, there is a passive absorption in the proximal intestine (jejunum) of the less polar dihydroxy bile acids (CDA and DA) (2, 3). The passive absorption results in an increased rate of EHC of CDA as compared to CA (4). There is also an earlier and more prolonged rise in peripheral serum of CDA and DA compared to CA after a meal (5, 6).[1]

The possibility of a direct uptake of bile acids in intestinal lymph with a transport to systemic blood via ductus thoracicus in man has been suggested by Lindblad, Lundholm, and Scherstén (7). Such a lymphatic transport would offer an additional explanation for the difference in circulation and absorption pattern of the three major bile acids. In an early work, Sjövall and Åkesson (8) found only trace amounts of CA in the lymph of rats. Recently Becket and Percy-Robb (9) reported on a similar low lymphatic bile acid transport of mainly CDA in rats. However, no information is yet available on the lymphatic transport of bile acids in man. The aim of the present study was to *a*) measure the lymphatic transport of bile acids in man and *b*) evaluate its possible physiological relevance.

MATERIALS AND METHODS

Patients

Four patients (one female and three males, aged between 18 and 60 years) were studied 2–4 weeks after renal transplantation. They had no history of gallbladder or intestinal diseases and displayed normal liver function tests. None had steatorrhea. A thoracic duct fistula was performed within 3 days after the transplantation to sustain lymphatic drainage as part of the postoperative immunosuppressive treatment, which also included medical treatment with Imurel^{R} (azathioprin), Prednisolon^{R} (prednisolone), and Mycostatin^{R} (nyastin) in individual dosages. The patients were hospitalized and were given a standardized hospital diet for several days before the study. All patients gave their informed consent and the ethical aspects of the study were approved by the Ethical Committee of Huddinge Hospital.

Sampling procedure

The patients were studied in the morning after a 12-hr fast. They were given a standardized meal containing 30 cal% fat. Before and after this meal, samples were

Abbreviations: CA, cholic acid; CDA, chenodeoxycholic acid; DA, deoxycholic acid; EHC, enterohepatic circulation.

[1] Angelin, B., I. Björkhem, K. Einarsson, and S. Ewerth. 1982. *J. Clin. Invest.* **70.** In press.

TABLE 1. Bile acid concentrations in lymph and serum

Patient	CA		CDA		DA		Total Bile Acids	
	Lymph	Serum	Lymph	Serum	Lymph	Serum	Lymph	Serum
				μmol/l				
A. Fasting state								
AS	1.35	1.17	2.70	1.02	2.18	1.40	6.23	3.59
LD	0.50	0.48	0.70	0.42	<0.10	<0.10	1.20	0.90
ML	1.38	0.70	4.25	0.85	2.50	0.48	8.13	2.03
NT	0.55	0.65	1.55	1.10	1.55	1.55	3.65	3.30
Mean	0.95	0.75	2.30	0.85	1.56	0.85	4.80	2.46
B. Maximal peaking, 120–180 min								
AS	1.32	1.37	8.54	1.57	4.54	1.42	14.4	4.36
LD	1.20	1.42	1.95	0.90	<0.10	<0.10	3.15	2.32
ML	1.38	1.28	3.65	1.00	2.27	0.88	7.77	3.16
NT		1.15		2.90		3.58		7.63
Mean	1.30	1.35	4.71	1.59	2.27	1.47	8.44	4.37
C. At the end of the study, 210 min								
AS	1.22	0.98	4.77	1.22	2.85	1.27	8.84	3.47
LD	1.12	0.92	1.38	0.88	<0.10	<0.10	2.50	1.80
ML	1.05	0.68	2.08	0.68	1.82	0.62	4.95	1.98
NT	0.98	0.92	7.24	2.45	5.60	3.32	13.82	6.69
Mean	1.09	0.87	3.87	1.31	2.56	1.30	7.53	3.49

drawn simultaneously from the lymph catheter and an antecubital vein catheter at 30-min intervals for 210 min. The samples were analyzed for individual bile acids and albumin. The total lymph flow during 24 hr was, on the average, 2.7 liters (range, 1.3–5.2). The triglyceride content in serum and lymph was determined with an enzymatic method.

Analysis of bile acids

The concentration of CA, CDA, and DA were determined with a mass fragmentographic technique described previously (10) which has been modified using more specific ions for each bile acid (11).

RESULTS

Individual data on fasting bile acid concentrations, as well as on the highest bile acid concentrations occurring 120–180 min after the meal, and on the concentrations 210 min postprandially are given in **Table 1.** In one patient (LD), DA could barely be demonstrated with the present technique in serum or lymph. In one patient (NT), lymph for bile acid analysis could, for technical reasons, only be obtained at 0 and 210 min.

The mean fasting concentrations of CA, CDA, and DA were 0.95 μmol/l, 2.30 μmol/l, and 1.56 μmol/l in lymph, and 0.75 μmol/l, 0.85 μmol/l, and 0.85 μmol/l in serum, respectively. Postprandially, the lymph concentrations of CDA and DA increased about 2 times whereas the level of CA did not rise consistently. In serum there was a moderate increase of all three bile acids. **Fig. 1** shows the postprandial response of bile acids in lymph and serum in one of the patients (AS).

The ratios between lymph concentrations and peripheral venous serum concentrations for each individual bile acid (mean values) are given in **Table 2.** There were only minor changes of the ratios postprandially. The ratio CA_{lymph}/CA_{serum} was about 1. The corresponding ratios for CDA and DA were about 2–3.

From the known daily intake of fat and the amount of triglycerides measured in a 24-hr fraction of lymph, the recovery of lymph from the intestine could be calculated to be on the average 52% (range, 36–65%). After correction for recovery, the mean total lymph flow during 24 hr was calculated to be 5.0 liters.

The albumin concentration in lymph was lower than that in serum both in the fasting state (20 ± 2 vs. 31 ± 2 g/l, mean ± SEM) and postprandially (19 ± 2 vs. 32 ± 2 g/l).

DISCUSSION

In the present study the main postprandial peaking of all three bile acids in serum occurred somewhat later, (at 120–180 min), than is generally seen in healthy sub-

jects (5). This may be due to a disturbance of the intestinal motility due to the operation and/or the immunosuppressive treatment.

Our results show that there is a transport of bile acids in human lymph both in the fasting state and postprandially. The lymphatic absorption was found to be most efficient for the lipophilic dihydroxy bile acids, DA and CDA, and the concentration of these bile acids in lymph was two- to threefold higher than in serum, both in the fasting state and postprandially. The lymphatic concentration of CA, on the other hand, was equal to or only slightly higher than that in serum.

Thoracic lymph drains both the intestine and the liver. In the liver the lymphatic drainage takes place in the sinusoidal space, which may be reached by bile acids from the portal venous blood before being taken up by the hepatocytes. Thus, there may be a certain "spill over" of bile acids from the portal blood into the liver lymph and then further to the thoracic lymph. However, this can hardly be the major mechanism for entrance of bile acids into the thoracic lymph. Thus, the lymphatic concentrations of CDA, DA, and CA were different from the corresponding serum concentrations with a more pronounced early rise of CDA and DA in lymph compared to serum. In addition, serum bile acids are mainly transported bound to albumin and a shortcut of importance would result in increased albumin concentrations in lymph postprandially. Such an increase was never observed.

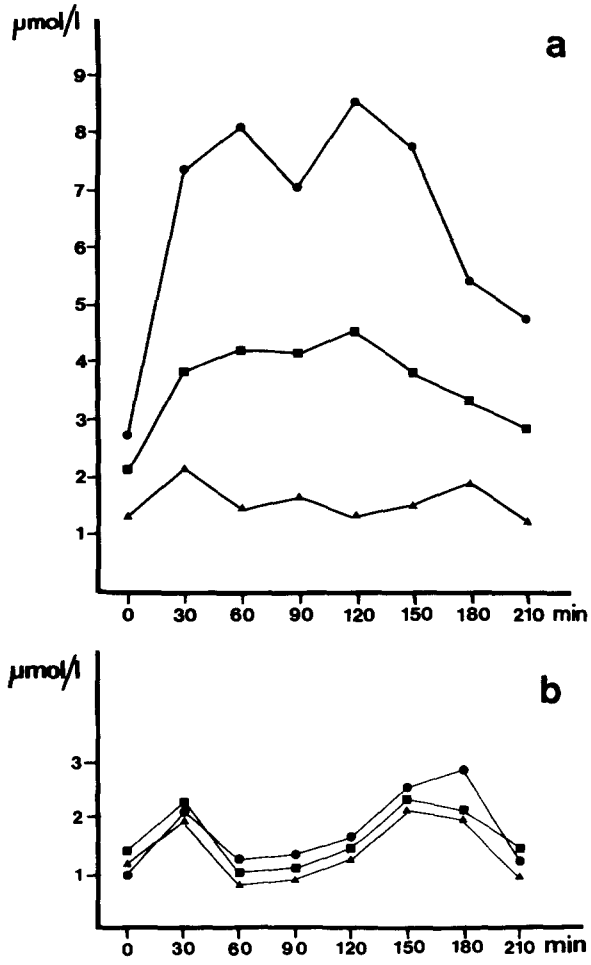

Fig. 1. Postprandial bile acid concentrations of CA (▲), CDA (●), and DA (■) in lymph (a) and in serum (b) of one patient (AS).

TABLE 2. The ratios between lymph concentration and peripheral venous serum concentration for each individual bile acid; mean value and range

Bile Acid Ratio	0 Min	120–180 Min	210 Min
CA_{lymph}/CA_{serum}	1.3 (0.9–2.0)	1.0 (0.9–1.1)	1.3 (1.1–1.5)
CDA_{lymph}/CDA_{serum}	2.7 (1.7–5.0)	3.8 (2.2–5.4)	2.9 (1.6–3.9)
DA_{lymph}/DA_{serum}	2.6 (1.0–5.2)	2.9 (2.6–3.2)	2.3 (1.7–2.9)

Estimating the portal venous circulation to be 0.75 l/min with an average postprandial total bile acid concentration of about 30 μmol/l serum,[1] the average postprandial bile acid circulation in portal venous serum is about 0.8 mmol/hr. The intestinal lymph flow was calculated to be on the average about 0.2 l/hr. With a mean average total bile acid concentration of 7 μmol/l, the lymphatic transport would approximately be of the magnitude 1.4 μmol/hr. This would mean that only about 0.2% of total bile acids is transported in thoracic lymph from the intestine. A lymphatic transport of bile acids of similar small magnitude has recently been reported in the rat by Becket and Percy-Robb (9).

It should once again be pointed out that our patients recently had undergone renal transplantation and were treated with drugs that could influence some of the parameters studied. This can, however, hardly influence the general conclusion that a lymphatic transport of bile acids exists, but is of little physiological importance.

We thank Ms. Gunvor Alvelius for excellent technical assistance. This study was supported by grants from the Swedish Medical Research Council (03X-04793) and Karolinska Institutets Fonder.

Manuscript received 3 December 1981, in revised form 12 March 1982, and in re-revised form 18 May 1982.

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