Changes in cholesterol metabolism during acute upper gastrointestinal bleeding: liver cirrhosis and non cirrhosis compared

Vladimir Hrabovsky[a], Vladimir Blaha[b], Radomir Hyspler[b], Alena Ticha[b], Martina Skrobankova[a], Zdenek Svagera[c]

Background. Cholesterol is derived via de novo synthesis and dietary absorption. Both processes can be monitored by determination of non-cholesterol sterol concentrations (lathosterol for synthesis; sitosterol and campesterol for absorption). The hypocholesterolemia that occurs during acute illness is a result of a multifactorial inability to compensate for the increased needs for this metabolite. The aim of this study was to examine the plasma cholesterol profile and both processes of cholesterol acquisition during acute upper gastrointestinal haemorrhage with emphasis on liver cirrhosis.
Material and Methods. Thirty five patients with acute upper gastrointestinal bleeding (cirrhosis n=14, non-cirrhosis n=21) were evaluated over a 6 day period. The control cohort consisted of 100 blood donors. Serum concentrations of total, LDL (low-density lipoprotein) and HDL (high-density lipoprotein) cholesterol were measured enzymatically. Sterol concentrations were analysed using gas chromatography, data were statistically analysed.
Results. In all patients, we found lower plasma levels of total cholesterol (P<0.001) and decrease of LDL and HDL cholesterol. Patients had also significantly lower plasma levels of sterol concentrations. While the differences in cholesterol profile between cirrhotic and non-cirrhotic bleeding were significant only in HDL cholesterol (P<0.001), comparison of non-cholesterol sterols was statistically significant (P<0.001) in all measured parameters.
Conclusion. Our results showed substantial abnormalities in the cholesterol plasma profile including both the processes of cholesterol acquisition in patients with upper acute gastrointestinal bleeding. The patients with or without liver cirrhosis had similar trends in cholesterol plasma levels. Depression of cholesterol synthesis was, however, prolonged in the cirrhotic group and the data also suggest a different phytosterol metabolism.

Key words: acute gastrointestinal bleeding, lipids, cholesterol, hypocholesterolemia, non-cholesterol sterols, phytosterols, liver cirrhosis

Received: May 9, 2018; Revised: July 31, 2018; Accepted: September 13, 2018; Available online: September 20, 2018
https://doi.org/10.5507/bp.2018.055

[a]Intensive Care Unit, Department of Internal Medicine, University Hospital Ostrava, Czech Republic
[b]Department of Metabolic Care and Gerontology, University Hospital Hradec Kralove, Czech Republic
[c]Department of Clinical Biochemistry, University Hospital Ostrava, Czech Republic
Corresponding author: Vladimir Hrabovsky, e-mail: vladimir.hrabovsky@fno.cz

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) derived from a source proximal to the ligament of Treitz is one of the most life-threatening complications of esophageal, gastric and duodenal diseases. Acute UGIB is divided into variceal and non-variceal and usually manifests as hematemesis and/or melena. Despite early detection and the advantages of endoscopy, both gastrointestinal (GI) emergencies are a frequent cause of hospitalization in internal intensive care units (ICU). The final outcome for bleeding patients is related to the intensity of initial blood loss and especially other comorbidities, currently often potentiated by anticoagulant and antiplatelet therapy[1]. While the variceal bleeding is commonly connected with liver cirrhosis and portal hypertension, non-variceal bleeding is due to other mucosal lesions such as gastroduodenal peptic ulcers, erosions, tumors, Mallory-Weiss syndrome and angiodysplasia. Treatment of UGIB is based on endoscopic hemostasis and the administration of proton pump inhibitors (PPI). When indicated, red blood cell transfusion and correction of coagulopathy should be undertaken. In the case of variceal bleeding, antibiotics and terlipressin are also used. One of the first priorities in UGIB is adequate fluid resuscitation, which is essential to prevent circulatory failure[2]. On the other hand, this may lead to the development of various metabolic abnormalities. Anemia is a typical finding in GI bleeding and decrease in hemoglobin concentration may be accelerated by use of large volumes of crystalloids and colloids. Hemodilution is thus a commonly considered serious potentiating cause of subsequent metabolic imbalance. Reduced cholesterol plasma concentration may be one manifestation.

Hypocholesterolemia has been repeatedly described as a common feature of acute medical conditions. Cholesterol (CH) is known as an acute phase reactant, characterized by decrease of its plasma levels closely connected with increasing of inflammatory markers[3]. The etiology of hypocholesterolemia remains unclear. We know that sepsis, conditions after trauma, surgery and burn injury are regularly connected with hypocholesterolemia[3-6]. This is the result of

inflammatory cytokines, the increased CH needs for tissue repair and the inability to increase cholesterol synthesis as it is an energy-intensive process. Depletion of CH is exacerbated by artificial nutrition that contains no cholesterol[7].

In addition, hypocholesterolemia in critically ill patients is closely connected with poor prognosis and increased mortality[8-10]. For this reason, there is persistent effort to understand lipid profiles in detail. In the field of cholesterol metabolism, the focus of interest is also process of its requirement. CH, as mentioned is derived in two ways: via de novo synthesis and via dietary absorption. Both can be monitored by determination of CH synthesis markers (lathosterol in blood plasma and lathosterol /CH ratio), and CH absorption markers (sitosterol and campesterol in blood plasma) (ref.[11,12]).

The aim of this study was to describe changes in the plasma CH profile and assess the effect of alteration in the synthesis/absorption process in patients with UGIB over a 6-day follow up. We also wanted to investigate potential differences in these metabolic parameters, when the liver cirrhosis was or was not presented.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of the Faculty Hospital in Ostrava. All participants gave their informed consent. A total of 35 adult patients with melena or hematemesis were included. The average age was 60 years (23 male, 12 female). They were divided into two groups: patients with cirrhosis (n=14) and those without (n=21). Participants at high risk of surgical intervention or record of GI haemorrhage during the month before admission were ineligible. None of the patients had any statin medication history. All were admitted to the emergency zone of the Faculty Hospital Ostrava. In all of them gastric aspiration/lavage via nasogastric tube was performed to confirm upper GI haemorrhage and for initial assessment. They then underwent endoscopy and were admitted to the metabolic ICU. Volume resuscitation was started as soon as possible. Saline solutions (no colloids) were used. Those with non-variceal bleeding were treated by bolus followed by continual infusion of PPI in a dose of 8 mg of omeprasole per hour. Variceal bleeding patients received in addition, 1 mg of terlipressin every 4 hour and 1 g of cefotaxime every 8 hour. At the same time, *ad hoc* symptomatic therapy was administered. Patients were not permitted a normal diet for three days following admission until the blood count had stabilized. In this time, parenteral nutrition support was provided by glucose and amino acid solutions. No fat emulsions were administered. In the course of the study, no surgical intervention was performed and no signs of re-bleeding, confirmed by second-look endoscopy on days 2 or 3, occurred. The basic metabolic characteristics of the patients are shown in Table 1.

Routine laboratory tests including blood count, coagulation and other biochemical parameters were carried out immediately on admission and repeated as needed. Serum concentrations of total CH (t-CH), LDL-CH and HDL-CH were determined on days 0, 3, and 6. A venous ethylendiaminetetraacetic (EDTA) blood sample (2 mL) for lathosterol and phytosterols (sitosterol, campesterol) determination was obtained at the same time. The plasma was separated by centrifugation and stored at -80 °C until analysis. Serum concentrations of t-CH, LDL-CH and HDL-CH were measured in an enzymatic colour test with Olympus reagents OSR 6216, 6133, 6287 and 6183, together with an Olympus System Calibrator and chemically analysed in an automated system (Olympus AU 2700, Japan). Non-cholesterol sterols were extracted from the EDTA samples using the Abell-Kendall procedure (alkaline hydrolysis by ethanolic solution of KOH, followed by triple extraction with hexane), derivatized to trimethylsilyl ethers using BSTFA (Supelco, Bellefonte, USA) and analysed using gas chromatography - mass spectrometry (TurboMass, Perkin-Elmer, Wellesley, USA).

Statistical analysis

The data were statistically analysed using the statistical software Sigma Stat 3,1 and the results are expressed as medians (25-75%). We used parametric (t-test) or non-parametric (Mann-Whitney) tests for independent groups (patients and controls). ANOVA was used when the results were compared over days (repeated measures). Spearman's rank correlation coefficient was used to de-

Table 1. Basic metabolic markers in patiens with UGIB (n=35), comparison of both cirhotic (n=14) and non-cirhotic (n=21) subgroups at the start of the study.

Parameter	UGIB	Non-cirrhotics	Cirrhotics	*P*
APACHE score	15 (12-18.75)	16 (12-19)	15.5 (13-17)	n.s.
hemoglobin (g/L)	81 (68.25-101)	83 (76.5-105.7)	71 (55-89)	0.052
hematocrit	0.248 (0.202-0.298)	0.27(0.22-0.31)	0.212 (0.16-0.27)	0.041
RBC-T (mL)	600 (521.25-1107.5)	549 (300-712)	1103 (587-1350)	0.003
IL-6 (ng/L)	11.8 (3.475-17.15)	6.6 (2.9-13.62)	18.85 (10.7-30.9)	0.003
CRP (mg/L)	5.4 (2.825-24.5)	5.1 (5.25-25)	5.4 (2.9-23)	n.s.
albumin (g/L)	29.9 (25.8-35.2)	34.2 (27.15-36.12)	26.3 (24.3-32)	n.s.
prealbumin (g/L)	0.17 (0.075-0.22)	0.2 (0.16-0.24)	0.07 (0.06-0.13)	< 0.001
cholesterol (mmol/L)	2.82 (2.285-3.953)	2.82 (2.48-3.94)	2.71 (2.15-4.45)	n.s.
bilirubin (umol/L)	17.5 (11.12-38.25)	12.2 (8.22-14.42)	60.05 (30.6-97)	< 0.001

RBC-T: red blood cel transfusion during first 48 hours, IL-6: interleukin 6, CRP: C-reactive protein

termine any correlation between CH metabolism markers and red blood cell transfusion (RBC-T) consumption, hematocrit and hemoglobin levels, nutrition (albumin, prealbumin) and inflammatory (CRP, interleukin-6) markers on day 0. The control cohort consisted of 100 blood donors. This group of randomly selected, healthy people aged18 to 65 years old was assumed to reflect the polymorphism of CH metabolism in the population.

RESULTS

The causes of bleeding in this study were peptic ulcer (n=15), erosive gastritis (n=8), erosive esophagitis (n=2) and variceal bleeding (n=10). Liver cirrhosis was found in 14 patients. This corresponds to the above number of variceal bleeding together with the other 4 patients with portal hypertensive gastropathy. Table 1 shows the basic metabolic characteristics of the UGIB patients (n=35) and also cirrhotic (n=14) and non-cirrhotic (n=21) subgroups at the start of the study. Significant differences in bilirubin, interleukin-6, prealbumin, haemoglobin (marginal), hematocrit and also RBC-T were found when these two subgroups were compared.

In all patients with UGIB, serum t-CH, LDL-CH and HDL-CH were decreased (Table 2). The lowest values were found on the day of admission and then they gradually increased. All t-CH levels were significantly lower (P<0.001) during the course of observation than in the controls. Comparison of LDL-CH and HDL-CH concentrations among individual variables within groups showed significant differences in LDL when the results of day 0 were compared with the results of day 6 (P<0.05). Changes in HDL-CH levels were not statistically significant.

Assessment of patients according to liver status showed similar results with a predominant decrease in CH (P<0.001). Comparison of LDL-CH and HDL-CH concentrations showed significant differences only in LDL levels in the non-cirrhotic group if the results of day 0 and 3 were compared with the results of day 6 (P<0.05). The dynamics of the changes are shown in Table 3. The lowest concentrations of monitored parameters were on day 0 in non-cirrhotics and on day 3 in cirrhotics, respectively.

In the whole group of UGIB patients, we found significantly lower plasma levels of CH synthesis and absorption markers: lathosterol (P<0.001), lathosterol-to-cholesterol ratio (P<0.001), campesterol (P<0.001) and sitosterol (P<0.05), compared with the control group. The dynamics of change are shown in Table 2. Non-cirrhotics had similar results but the decrease in the lathosterol-to-cholesterol (LTH/CH) ratio was not significant. In contrast there were no significant decreases in phytosterol plasma levels in cirrhotics (Table 3).

Comparison of the lipid profile and sterols in both subgroups is shown in Table 4. Significant differences were found for HDL-CH and especially sterol plasma concentrations. Lathosterol levels and the LTH/CH ratio in the cirrhotic group were consistently lower and the decrease in phytosterols was not as distinct as in the non cirrhotic group.

The Spearman rank correlation coefficient showed no statistically significant correlation between CH metabolism parameters and changes in blood count (hemoglobin and hematocrit), RBC transfusion consumption or nutrition markers (albumin,prealbumin), investigated on day 0. Data from the other days were not assessed owing to the confounding effect of the transfusions.

DISCUSSION

Upper gastrointestinal bleeding is a serious clinical burden and a major cause of morbidity and mortality. Current data for the incidence of UGIB are roughly 100 cases per 100 000 population per year and mortality due to UGIB is between 6 to 10% overall (ref.[1]). The variables depend on both natural sources of bleeding and age, comorbidities and medication[13,14]. Upper GI tract bleeding

Table 2. Plasma concentration of lipids and sterol in patients with UGIB (n=35). Comparison with control group.

Parameter	Control group	UGIB patients (n=35)		
		Day 0	Day 3	Day 6
t-CH (mmol/L)	4.832 (4.21-5.52)	2.82 (2.285-3.953)**	3.18 (2.275-4.032)**	3.55 (2.952-3.348)**
LDL-CH (mmol/L)		1.62 (1.158-2.51)	1.9 (1.263-2.22)	2.31 (1.753-2.815)
HDL-CH (mmol/L)		0.78 (0.555-0.988)	0.75 (0.555-0.89)	0.82 (0.613-1.01)
LTH (μmol/L)	6.35 (4.85-8.705)	2.468 (1.619-3.959)**	2.677 (1.514-4.441)**	3.44 (1.564-3.59)**
LTH/CH (ratio)	1.325 (1.029-1.866)	0.965 (0.552-1.615)**	0.814 (0.617-1.609)**	0.957 (0.51-1.534)**
CAM (μmol/L)	9.76 (7.46-12.51)	5.99 (4.29-8.742)**	4.695 (3.502-8.486)**	6.207 (4.191-8.423)**
SIT (μmol/L)	4.995 (3.31-6.165)	3.898 (2.651-7.315)	3.458 (2.471-4.547)*	3.803 (2.538-5.534)

Data are expressed as median (25th - 75th percentile)
t-CH: total cholesterol, LDL-CH: low density cholesterol, HDL-CH: high density cholesterol
LTH: lathosterol, LTH/CH: lathosterol to cholesterol ratio, CAM: campesterol, SIT: sitosterol
*: statistical significance P<0.05; **: statistical significance P<0.001

Table 3. Plasma concentration of lipid and sterols with or without cirrhosis. Comparison with control group.

Parameter	Control group	Day 0	Day 3	Day 6
			non-cirhotic patients (n=21)	
t-CH (mmol/L)	4.832 (4.21-5.52)	2.82 (2.48-3.94)**	3.29 (2.8-3.98)**	3.97 (3.37-4.45)**
LDL-CH (mmol/L)		1.5 (1.07-2.46)	1.95 (1.25-2.15)	2.31 (1.78-2.77)
HDL-CH (mmol/L)		0.8 (0.58-0.99)	0.83 (0.73-1.07)	0.93 (0.78-1.17)
LTH (μmol/L)	6.35 (4.85-8.705)	3.272 (2.26-5.09)**	3.57 (2.5-6.56)**	5.25 (3.07-7.71)*
LTH/CH (ratio)	1.325 (1.029-1.866)	1.17 (0.75-1.66)	1.1 (0.8-1.84)	1.33 (0.94-1.58)
CAM (μmol/L)	9.76 (7.46-12.51)	5.89 (4.05-7.65)**	4.04 (2.84-7.09)**	5.86 (3.91-7.71)**
SIT (μmol/L)	4.995 (3.31-6.165)	3.27 (2.27-4.53)*	2.759 (2.3-3.83)**	3.34 (2.43-4.48)*
			cirhotic patients (n=14)	
t-CH (mmol/L)	4.832 (4.21-5.52)	2.71 (2.21-4.45)**	2.39 (2.22-4.28)**	3.3 (2.3-4.02)**
LDL-CH (mmol/L)		1.79 (1.37-2.88)	1.78 (1.3-2.93)	2.31 (1.42-2.88)
HDL-CH (mmol/L)		0.70 (0.54-0.93)	0.56 (0.39-0.75)	0.62 (0.52-0.74)
LTH (μmol/L)	6.35 (4.85-8.705)	1.61 (1.23-2.64)**	1.49 (1.2-1.77)**	1.62 (1.37-1.9)**
LTH/CH (ratio)	1.325 (1.029-1.866)	0.57 (0.42-0.97)**	0.54 (0.37-0.78)**	0.54 (0.36-0.85)**
CAM (μmol/L)	9.76 (7.46-12.51)	6.03 (5.32-10.36)*	5.67 (4.06-9.06)*	8.08 (5.17-10.64)
SIT (μmol/L)	4.995 (3.31-6.165)	5.03 (3.76-9.39)	4.64 (3.46-9.42)	5.42 (3.35-9.19)

Data are expressed as medians (25th - 75th percentile)
t-CH: total cholesterol, LDL-CH: low density cholesterol, HDL-CH: high density cholesterol
LTH: lathosterol, LTH/CH: lathosterol to cholesterol ratio, CAM: campesterol, SIT: sitosterol
*: statistical significance $P<0.05$; **: statistical significance $P<0.001$

Table 4. Comparison of plasma concentration of lipids and sterol in patients with or without cirrhosis.

Parameter	Non-cirrhotics	Cirrhotics	*P*
t-CH day 0 (mmol/L)	2.82 (2.48-3.94)	2.71 (2.15-4.45)	n.s.
t-CH day 3 (mmol/L)	3.29 (2.8-3.98)	2.39 (2.22-4.28)	n.s.
t-CH day 6 (mmol/L)	3.97 (3.37-4.45)	3.3 (2.3-4.02)	n.s.
LDL-CH day 0 (mmol/L)	1.5 (1.07-2.46)	1.79 (1.37-2.88)	n.s.
LDL-CH day 3 (mmol/L)	1.95 (1.25-2.15)	1.78 (1.3-2.93)	n.s.
LDL-CH day 6 (mmol/L)	2.31 (1.78-2.77)	2.31 (1.42-2.88)	n.s.
HDL-CH day 0 (mmol/L)	0.8 (0.58-0.99)	0.70 (0.54-0.93)	n.s.
HDL-CH day 3 (mmol/L)	0.83 (0.73-1.07)	0.56 (0.39-0.75)	< 0.001
HDL-CH day 6 (mmol/L)	0.93 (0.78-1.17)	0.62 (0.52-0.74)	< 0.001
LTH day 0 (μmol/L)	3.272 (2.26-5.09)	1.61 (1.23-2.64)	0.005
LTH day 3 (μmol/L)	3.57 (2.5-6.56)	1.49 (1.2-1.77)	< 0.001
LTH day 6 (μmol/L)	5.25 (3.07-7.71)	1.62 (1.37-1.9)	< 0.001
LTH/CH day 0 (ratio)	1.17 (0.75-1.66)	0.57 (0.42-0.97)	0.015
LTH/CH day 3 (ratio)	1.1 (0.8-1.84)	0.54 (0.37-0.78)	< 0.001
LTH/CH day 6 (ratio)	1.33 (0.94-1.58)	0.54 (0.36-0.85)	< 0.001
CAM day 0 (μmol/L)	5.89 (4.05-7.65)	6.03 (5.32-10.36)	n.s.
CAM day 3 (μmol/L)	4.04 (2.84-7.09)	5.67 (4.06-9.06)	0.057
CAM day 6 (μmol/L)	5.86 (3.91-7.71)	8.08 (5.17-10.64)	0.035
SIT day 0 (μmol/L)	3.27 (2.27-4.53)	5.03 (3.76-9.39)	0.021
SIT day 3 (μmol/L)	2.759 (2.3-3.83)	4.64 (3.46-9.42)	< 0.001
SIT day 6 (μmol/L)	3.34 (2.43-4.48)	5.42 (3.35-9.19)	< 0.008

t-CH: total cholesterol, LDL-CH: low density cholesterol, HDL-CH: high density cholesterol
LTH: lathosterol, LTH/CH: lathosterol to cholesterol ratio, CAM: campesterol, SIT: sitosterol

is about 4 times as common as bleeding from the lower GI tract.

The most common causes of UGIB in our study were peptic ulcers and erosive lesions of stomach or esophagus. Ten patients with liver cirrhosis had variceal and in four cases non-variceal bleeding (portal hypertensive gastropathy). Haemorrhage associated with liver disease is usually characterized by greater blood loss. This accounts for the higher mortality[15]. The results of our observation show significantly lower hemoglobin and hematocrit levels and greater consumption of RBC transfusions during the first 48 hours in these patients (Table 1). Further, the course

of bleeding was probably negatively influenced by poor overall nutrition, blood-clotting disorders and encephalopathy. Unsurprisingly, the nutritional and metabolic markers presented in Table 1 were poorer in the cirrhotic patients.

The metabolic complications of acute diseases are still under discussion, including the development of hypocholesterolemia. Significant changes in the serum profile of lipids and lipoproteins in critically ill patients have been repeatedly described in a number of studies (3-10). In the main, hypocholesterolemia is linked to poor prognosis, increased mortality and the results of long-term observations therefore indicate that CH is an acute phase reactant[9,10]. Although the etiology of hypocholesterolemia remains unclear, a number of factors are involved. The systemic inflammatory response syndrome (SIRS) and the effect of inflammatory cytokines appear to be the most important[4,16]. Hemodilution is also a factor especially in the case of major blood loss. Ambiguous correlation between blood count and CH metabolism abnormalities has been repeatedly described[17,18]. We looked for significant correlations between changes in CH metabolism and decrease in hemoglobin and hematocrit levels together with RBC transfusions but none was found. In accordance with established data, it appears that hypocholesterolemia connected with bleeding cannot be explained by simple hemodilution.

We also found lower serum levels of t-CH, LDL-CH and HDL-CH in our acute UGIB patients. Comparison of the lipid profile in cirrhotic and non-cirhotic groups showed no significant differences with the exception of HDL-CH. We presume this was due to the poor nutrition and metabolic status of patients with liver cirrhosis. The formation of HDL lipoproteins is a complicated process, in which free cholesterol, phospholipids, apoproteins, specific enzymes and transporters are involved[19]. In addition, cholesterol metabolism may be affected by SIRS (ref.[16]) and the patients with liver disease had significantly higher levels of interleukin 6. The evaluation of CH metabolism must take into account cholestasis because of its ability to increase levels of this metabolite. Statistically significant hyperbilirubinemia was found in our patients with cirrhosis (the highest: 151 umol/L) compared with the second group (Table 1).

While a relationship between hypocholesterolemia and acute illness has been established, most studies have not reported changes in lipid metabolism in connection with changes in the CH absorption/synthesis process. Synthesis de novo and absorption from the diet are the two principal modes of cholesterol acquisition in humans and it is possible to assess both, using specific markers[20]. Lathosterol (LTH) is a biochemical precursor of cholesterol synthesis and it is generally used for determination of the CH synthesis process as well as the ratio between lathosterol and cholesterol plasma levels (LTH/CH). Likewise plasma concentrations of phytosterols may reflect the degree of cholesterol absorption. These sterols are plant derived compounds that cannot be synthesized by humans, although they are very similar to cholesterol. From the metabolic viewpoint, they occur naturally in food and are then absorbed from the diet. The best known plant sterols are campesterol (CAM) and sitosterol (SIT).

We found significantly lower plasma levels of LTH as well as decrease in the LTH/CH ratio in both patient groups than in controls. A comparison of these markers in non-cirrhotic and cirrhotic patients showed important differences. Unsurprisingly, patients with cirrhosis had significantly greater decrease in CH synthesis markers. Moreover, LTH concentrations and LTH/CH values were consistently lower in this group, while they increased during the follow up in the second group. In hepatectomised patients, the magnitude of the operation increases the demand for cholesterol in cell and tissue repair. Restitution of the resulting hypocholesterolemia is then limited by the synthetic capability of the residual liver and/or aggravated by cirrhosis[21]. This principle can also be applied to our results. They not only support the presumption of alterations in CH synthesis in acute UGIB patients. They also demonstrate the inability to restore this process in the presence of liver disease.

The plasma concentration of phytosterols was also lower in the present study, as a symptom of altered CH absorption. In all UGIB patients, significantly lower CAM and SIT plasma levels were found than in the control group. The patients were not permitted a normal diet for 3 days after admission. They were fed only parenterally by infusions with carbohydrates, amino acids and always without fat. For this reason it is not surprising that the lower concentrations of phytosterols were caused by lack of dietary intake and they increased by day 6, when normal food intake was restored. Further comparison of CH absorption markers showed significantly lower concentrations in the group of non-cirrhotic haemorrhage patients compared with cirrhotic patients. Dietary plant sterols during digestion are incorporated into mixed micelles and absorbed in the gut. The main regulators of this process appear to be Niemann-Pick C1-Like 1 (NPC1L1) transporter and adenosine triphosphate - binding cassette (ABCG5/ G8) transporters[22,23]. These are able to modify the final level of sterols, which are absorbed and/or secreted back into the intestinal lumen. Although phytosterols are much less absorbed than CH, their excretion via bile is much greater[24]. The formation of bile, of course, depends on liver metabolic activity. Thus, the final blood concentration of phytosterols in cirrhotic patients was fundamentally influenced by inhibited absorption due to interrupted food intake but more importantly the inability of the liver to eliminate these metabolites.

CONCLUSION

This is the first attempt to accurately describe changes in cholesterol metabolism in patients with UGIB based on the presence or absence of liver cirrhosis during haemorrhage. The results show substantial abnormalities in plasma concentrations of cholesterol and non-cholesterol sterols, which are accepted markers of cholesterol acquisition in humans. We conclude that both the synthesis and absorption processes may be altered in patients with acute

UGIB: the hypocholesterolemia cannot be explained solely by hemodilution. Lower markers of cholesterol absorption may also be due to the fact that patients in early phase after bleeding did not receive food naturally. Moreover, patients with cirrhosis have diminished potential for restitution of altered metabolic pathways and their metabolism of naturally absorbed phytosterols is altered. This finding should be considered during the use of long term parenteral nutrition with lipid emulsions, because they contain phytosterols.

Acknowledgement: The authors declare no financial, personal or political support for this work.

Author contributions: VH: study concept and design, manuscript writing, VB: data collection, study design, RH: biochemical analysis, data interpretation, study concept, data analysis, AT: biochemical analysis, figures, manuscript writing, MS: literature search, data collection, manuscript writing ZS: biochemical analysis, study design.

Conflict of interests statement: The authors state that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Valkhoff VE, Sturkenboom MC, Hill C, Veldhuyzen van Zanten S, Kuipers EJ. Low-dose acetylsalicylic acid use and the risk of upper gastrointestinal bleeding: a meta-analysis of randomized clinical trials and observational studies. Can J Gastroenterol 2013; 27:159-67.
2. Khamaysi I, Gralnek IM. Acute upper gastrointestinal bleeding (UGIB) - initial evaluation and management. Best Pract Res Clin Gastroenterol 2013;27:633-8.
3. Chiarla C, Giovannini I, Giuliante F, Zadak Z, Vellone M, Ardito F, Clemente G, Murazio M, Nuzzo G. Severe hypocholesterolemia in surgical patients, sepsis, and critical illness. J Crit Care 2010;25:361.
4. Bonville DA, Parker TS, Levine DM, Gordon BR, Hydo LJ, Eachempati SR, Barie PS. The relationship of hypocholesterolemia to cytokine concentrations and mortality in critically ill patients with systemic inflammatory response syndrome. Surg Infect 2004;5:39-49.
5. Bakalář B, Hyšpler R, Pachl J, Zadák Z. Changes in cholesterol and its precursors during the first days after major trauma. Wien Klin Wochenschr 2003;115:775-9.
6. Giovannini I, Boldrini G, Chiarla C, Guiliante F, Vellone M, Nuzzo G. Pathophysiologic correlates of hypocholesterolemia in critically ill surgical patients. Int Care Med 1999;25:748-51.
7. Giovannini I, Chiarla C, Giuliante F, Vellone M, Zadák Z, Nuzzo G. Hypocholesterolemia in surgical trauma, sepsis, other conditions and critical illness. In: Kramer MA Trends in cholesterol research. Nova Biomedical 2005; 137-161. ISBN 1-59454-378-X.
8. Fraunberger P, Nagel D, Walli AK, Seidel D. Serum cholesterol and mortality in patients with multiple organ failure. Crit Care Med 2000;28:3574-5.
9. Dunham CM, Chirichella TJ. Attenuated hypocholesterolemia following severe trauma signals risk for late ventilator-associated pneumonia, ventilator dependency, and death: a retrospective study of consecutive patients Lipids Health Dis 2011;10:42.
10. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from Honolulu Heart Program: A cohort study. Lancet 2001;358:351-5.
11. Tilvis RS, Miettinen TA. Serum plant sterols and their relation to cholesterol absorption. Am J Clin Nutrition 1986;43:92-7.
12. Pfohl M, Naoumova RP, Kim KD, Thompson GR . Use of cholesterol precursors to assess changes in cholesterol synthesis under non-steady-state conditions. Eur J Clin Ivestig 1998;28:491-6.
13. Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996;38:316-21.
14. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet 2000;356:1318-21.
15. Tiuca N, Sztogrin W. The news of treatment of variceal upper gastrointestinal bleeding. J Med and Life 2011;4:395-9.
16. Hudgins LC, Parker TS, Levine DM, Gordon BR, Saal SD, Jiang XC, Seidman CE, Tremaroli JD, Lai J, Rubin AL. A single intravenous dose of endotoxin rapidly alters serum lipoproteins and lipid transfer proteins in normal volunteers. J Lipid Res 2003;44:1489-98.
17. Bakalar B, Zadak Z, Pachl J, Sidak M, Hyspler R, Crhova D. Hypocholesterolemia after multiple injuries is not caused by simple dilution. Rozhl Chir 2001;80:67-71.
18. Bakalar B, Hyspler R, Pachl J, Zadak Z. Changes in cholesterol and its precursors during the first days after mayor trauma. Wien Klin Wochenschr 2003;115:775-9.
19. Attie AD, Kastelein JP, Hayden MR. Pivotal role of ABCA1 in reverse cholesterol transport influencing HDL levels and susceptibility to atherosclerosis. J Lip Res 2001;42:1717-26.
20. Kuksis A. Plasma non-cholesterol sterols. J Chromatogr 2001;935:203-36.
21. Giovannini I, Chiarla C, Greco F, Boldrini G, Nuzzo G. Characterization of biochemical and clinical correlates of hypocholesterolemia after hepatectomy. Clin Chem 2003;49:317-20.
22. Sudhop T, Lutjohann D, von Bergmann K. Sterol transporters: targets of natural sterols and new lipid lowering drugs. Pharmacol Ther 2005;105:333-41.
23. von Bergmann K, Sudhop T, Lütjohann D. Cholesterol and plant sterol absorption: recent insights. Am J Cardiol 2005;96:10D-14D.
24. Sudhop T, Sahin Y, Lindenthal B, Hahn C, Lüers C, Berthold HK, von Bergmann K. Comparison of the hepatic clearances of campesterol, sitosterol, and cholesterol in healthy subjects suggests that efflux transporters controlling intestinal sterol absorption also regulate biliary secretion. Gut 2002;5:860-3.