

Taurine status and response to intravenous taurine supplementation in adults with short-bowel syndrome undergoing long-term parenteral nutrition: a pilot study

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Taurine deficiency in patients on long-term parenteral nutrition may be involved in cholestasis. We aimed to assess plasma taurine and tauro-conjugated bile acids in adults with short-bowel syndrome and their response to intravenous taurine. Thirty-two adult patients, who had been on taurine-free parenteral nutrition for a mean of 59 (SE 14) months for short-bowel syndrome, were studied retrospectively. In a second study, a subgroup of ten patients with chronic cholestasis received taurine-enriched (6.0 (SE 0.6) mg/kg per d) parenteral nutrition for 55 (SE 13) months. Post-absorptive plasma taurine and bile acid concentrations were measured and liver function tests routinely sampled. At baseline, plasma taurine was lower in patients with a jejunal length of less than 35 cm (group A, *n* 16) than in those with a jejunal length of 35 cm or more (group B, *n* 16): 43 (SE 3) v. 58 (SE 4) $\mu\text{mol/l}$ ($P=0.01$). The groups were no different in terms of chronic cholestasis (12/16 v. 13/16 patients), total bile acids (26 (SE 13) v. 14 (SE 5) $\mu\text{mol/l}$) or the ratio of tauro-conjugated:glyco-conjugated bile acids (5 (SE 2) v. 8 (SE 4) %, usual range 30–60 %). After supplementation, there was an increase in plasma taurine level (63 (SE 8) v. 43 (SE 4), $P=0.007$) but was no change in either total bile acids or the ratio of tauro-conjugated: glyco-conjugated bile acids. There was a significant decrease in aspartate aminotransferase level. Long-term parenteral nutrition for short-bowel syndrome is associated with an impaired tauro-conjugation of bile acids (enterohepatic pool), irrespective of plasma taurine level (systemic pool) and despite long-term taurine intravenous supplementation.

Taurine: Biliary acids: TPN: Short-bowel syndrome

Taurine is the most abundant free intracellular amino acid in the human body. It is involved in numerous functions – brain development, bile acid metabolism, anti-oxidation, retinal and cardiac function, osmoregulation, Ca modulation, and phospholipid–protein and Zn interactions (Huxtable, 1992; Hansen, 2004). After the 4–6-week postnatal period, it is traditionally considered to be a non-essential amino acid in man, but this view has been challenged by studies showing low plasma and blood cell concentrations in children and adults undergoing long-term home parenteral nutrition (HPN; Vinton *et al.* 1986, 1987) as well as by the low concentrations in short-term hypermetabolic or cancer patients on parenteral nutrition (Paauw & Davis, 1990; Gray *et al.* 1994; Chiarla *et al.* 2000). In addition, during HPN in children, abnormalities in visual function have been related to taurine deficiency (Vinton *et al.* 1990).

Chronic intrahepatic cholestasis is a major concern in short-bowel syndrome patients undergoing long-term HPN, and, in a recent study of ninety of these patients, its prevalence was 55 % and 72 % at 2 and 6 years, respectively (Cavicchi *et al.* 2000). Such cholestasis was significantly linked to the occurrence of a complicated HPN-associated liver disease, and, in the subgroup in whom lipid intake was kept lower than 1 g/kg per d, extensive fibrosis or cirrhosis was still documented in 25 % of cases after 3 years of HPN (Cavicchi *et al.* 2000). As taurine is involved in hepatocyte bile acid conjugation, we speculated that a disrupted enterohepatic cycle, owing to a very-short-bowel syndrome leading to chronic intestinal failure and therefore long-term HPN, might be responsible for a deficiency in the biliary taurine pool when taurine was not provided as part of the intravenous amino-acid parenteral nutrition supply. However, because plasma

Abbreviations: HPN, home parenteral nutrition.

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taurine may represent only the systemic taurine pool, access to the biliary taurine pool (through tauro-conjugated biliary acids) seems mandatory to assess the relationship between taurine deficiency and liver dysfunction.

The aims of the present study were therefore to evaluate plasma taurine and plasma biliary salt concentrations in patients with short-bowel syndrome undergoing long-term HPN, and to assess the effects of intravenous taurine supplementation on these parameters and on liver function tests.

Subjects and methods

Subjects

In a first retrospective study, a cohort of thirty-two patients receiving HPN (seventeen men and fifteen women with a mean age of 44 (SE 2) years), who were dependent on parenteral nutrition because of a short-bowel syndrome, were studied. Their post-duodenal jejunal length was measured on a Ba meal follow-through by two independent observers with an opisometer, on the anti-mesenteric edge of the small bowel, starting from the duodeno-jejunal flexure until end-enterostomy, ileo-anastomosis or colonic anastomosis. The length of the colonic remnant, in terms of percentage of normal length, was estimated according to the method of Cummings *et al.* (1974). The aetiology of the short bowel was arterial mesenteric infarction (*n* 9), complication of surgery (*n* 7), venous mesenteric infarction (*n* 5), radiation enteritis (*n* 4), Crohn's disease (*n* 4) and motility disorder (*n* 3). Patients were enrolled in the study if they had a small bowel length of less than 150 cm and no ileal remnant. At the time of the study, all patients were in a stable condition, were not malnourished and had no cardiac, renal, respiratory or hepatic failure; none had evolving cancer. All tested negative for HIV, hepatitis B and hepatitis C viruses. The mean duration of HPN was 59 (SE 14) months. Patients' mean BMI was $19.4 \pm 0.4 \text{ kg/m}^2$.

In a second prospective study, ten consecutive patients aged 41 (SE 4) years (seven men, three women), all part of the cohort from the first study, who had developed chronic intra-hepatic cholestasis during HPN, were supplemented with intravenous taurine and followed up. In these patients, the short-bowel syndrome was due to arterial mesenteric infarction (*n* 3), postoperative short bowel (*n* 2), venous mesenteric infarction (*n* 2), radiation enteritis (*n* 1), Crohn's disease (*n* 1) and motility disorder (*n* 1). Intravenous taurine supplementation was begun 70 (SE 19) months after the onset of HPN, with a 55 (SE 13) month follow-up. Blood samples used to determine pretreatment taurine values were taken 60 (SE 18) months after the onset of HPN. Six of the ten patients were also receiving oral ursodeoxycholic acid (32 (SE 2) mg/kg per d) at the time of the study. The energy and N content of the parenteral nutrition feeds were stable throughout the study. Patients gave their informed consent, and the study was conducted according to the guidelines in the declaration of Helsinki and approved by the local Ethics Committee.

Nutritional intakes

Parenteral nutrition was delivered through a tunnelled silico-catheter (Vygon, Ecouen, France) positioned in the upper vena cava. Frequency, volume and composition of the

infusions were estimated and based upon the patients' needs, which took into account their basal energy expenditure (calculated according to Harris and Benedict's (1919) tables), their activity and their oral intakes.

Patients received all-in-one binary or ternary bags containing macronutrients, vitamins – including pyridoxine – and trace metals. Cyclical (nocturnal) HPN was administered between 2 and 7 d weekly (5.7 (SE 0.2) and provided 19 (SE 1) kcal/kg body weight per d as non-protein energy, and 0.9 (SE 0.1) g protein/kg body weight per d. The average lipid dose was 0.28 (SE 0.07) g/kg per d. No patient received intravenous taurine at baseline. Spontaneous oral intakes were encouraged and were assessed by dietician inquiry. The ten taurine-supplemented patients were administered a mean 6.0 (SE 0.6) mg/kg taurine per d by using the amino-acid solution Vaminolact, which contains taurine at a concentration of 300 mg/l (Fresenius-Kabi, Sèvres, France). Table 1 shows the composition of the amino acid solutions received.

Biological measurements

Blood samples were taken at 08.00 hours, during the post-absorptive period, after a 12–14-h overnight fast without any nutrient infusion (which implied anticipating the infusion in the day for patients fed 7 d a week). Controls were healthy laboratory volunteers (twenty-five men, thirty-two women) without any known metabolic or digestive disease, with a mean age of 29.0 (SE 0.7) years, a mean BMI of 21.8 (SE 0.5) kg/m² and a mean serum albumin level of 42 (SE 1) g/l. No serum specimen was haemolysed.

Plasma concentrations of taurine and its precursors, cysteine and methionine, were determined using ion-exchange chromatography with ninhydrin detection (Neveux *et al.* 2004). The plasma glyco-conjugated and tauro-conjugated primary, secondary and tertiary bile acids were identified and quantified by reverse-phase HPLC (Labbé *et al.* 1989).

Table 1. Composition of the amino-acid solutions infused during the second part of the study

Amount (g/l)	Taurine-free solution (Vamine)*	Taurine-containing solution (Vaminolact)*
L-alanine	3.0	6.3
L-arginine	3.3	4.1
L-aspartate	4.1	4.1
L-cysteine	1.4	1.0
L-glutamate	9.0	7.1
Glycine	2.1	2.1
L-histidine	2.4	2.1
L-isoleucine	3.9	3.1
L-leucine	5.3	7.0
L-lysine	3.9	5.6
L-methionine	1.9	1.3
L-phenylalanine	5.5	2.7
L-proline	8.1	5.6
L-serine	7.5	3.8
L-taurine	0	0.3
L-threonine	3.0	3.6
L-tryptophan	1.0	1.4
L-tyrosine	0.5	0.5
L-valine	4.3	3.6

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For details of subjects and procedures, see this page.

The taurine:glycine ratio (tauro-conjugated:glyco-conjugated bile acids) was calculated. Cholestasis was defined as the presence of elevated serum values on at least two of the three following liver function tests: alkaline phosphatase; γ -glutamyl transpeptidase; total bilirubin. Digestive protein losses were measured on 72 h stools using chemiluminescence, and N absorption (Kjeldahl method) was calculated as the ratio of ingesta minus excreta: ingesta, as previously described (Messing *et al.* 1991).

Statistical analysis

Results are expressed as mean with their standard errors. Linear discriminant analysis, considering differences between plasma taurine concentrations, was used to separate patients into two groups according to their remnant jejunal length. Comparisons between these two groups, and between patients and controls (for plasma amino-acid levels), were performed with Mann-Whitney U tests. Biological values before and after taurine supplementation were compared with Wilcoxon tests. Differences were considered statistically significant for $P < 0.05$.

Results

Baseline study

The mean length of the jejunal remnant was 40 (SE 7) cm (range 0–130 cm), and the mean colonic remnant was 48 (SE 8) % of normal length (twelve of thirty-two patients having no remnant

colon). Linear discriminant analysis, considering differences between plasma taurine concentrations, permitted the separation of patients into two subgroups: patients with a remnant jejunal length of less than 35 cm (group A, n 16); patients with a remnant jejunal length of between 35 and 150 cm (group B, n 16). The characteristics of the two groups are described in Table 2. Patients from the two groups did not differ in terms of the amounts of nutrients infused.

Plasma taurine concentrations were significantly lower ($P < 0.01$) in group A (43 (SE 3) $\mu\text{mol/l}$) than in group B (58 (SE 4) $\mu\text{mol/l}$) patients and than in controls (61 (SE 2) $\mu\text{mol/l}$). Plasma cysteine was lower ($P < 0.01$) in group A than in group B patients, and levels were higher ($P = 0.02$) in the latter than in controls. For plasma methionine levels, there was no difference between these two groups, or between patients and controls. There was no correlation between plasma taurine concentration and remnant jejunal length, protein absorption or duration of HPN.

Cholestasis was present in twenty-five of thirty-two patients (twelve in group A, thirteen in group B). None of the patients had pruritis despite an increased conjugated hyperbilirubinaemia. Liver function tests and bile acid values are presented in Table 2, along with usual laboratory values: there were no statistically significant differences between groups A and B. Total bile acid concentrations were slightly increased, but this increase concerned only glyco-conjugated bile acids, as the total taurine:glycine conjugated bile acid ratio was very low in both groups and lower than usual values. No correlation was observed between plasma taurine concentrations and

Table 2. Characteristics, plasma sulphur amino acids and plasma biliary acids in patients undergoing home parenteral nutrition with short bowel, depending on their post-duodenal jejunal length (Values are means with their standard errors)

	Usual laboratory values		Group A (jejunum < 35 cm)		Group B (35 jejunum < 150 cm)	
	Mean	SE	Mean	SE	Mean	SE
Sex						
Male			7		7	
Female			9		9	
Jejunal length (cm)			13	3	66	9*
Age (years)			39.5	3.2	49.3	3.3
BMI (kg/m^2)			19.4	0.6	19.3	0.5
Remnant colon (%)			56	12	42	10
Duration of parenteral nutrition (months)			55	17	63	24
Plasma taurine ($\mu\text{mol/l}$)	60.6	1.8	48.4†	3.2	58.3*	4.4
Plasma cysteine ($\mu\text{mol/l}$)	52.8	1.1	48.4	4.1	66.2*†	5.6
Plasma methionine ($\mu\text{mol/l}$)	24.3	0.5	27.0	1.7	28.8	1.3
Oral intake/basal energy expenditure (%)			167	22	207	27
Protein absorption (%)			46.5	7.4	52.3	8.5
Alanine aminotransferase (x ULN)			1.9	0.3	2.1	0.3
Aspartate aminotransferase (x ULN)			2.0	0.3	1.6	0.2
Total bilirubin (x ULN)			4.7	2.0	1.9	0.5
Alkaline phosphatase (x ULN)			2.5	0.5	3.1	0.5
γ -Glutamyl transpeptidase (x ULN)			4.2	1.1	5.5	1.0
Total plasma bile acids ($\mu\text{mol/l}$)	< 6		25.6	13.1	13.8	5.2
Cholic and chenodeoxycholic acids (%)	80–85		89.4	3.3	88.9	5.2
Deoxycholic and lithocholic acids (%)	15–20		5.4	2.6	5.7	2.8
Ursodeoxycholic acid (%)	< 3		5.0	3.0	5.4	4.6
Tauro-conjugated:glyco-conjugated bile acids	0.30–0.60		0.05	0.02	0.08	0.04

Mean values were significantly different compared with group A; * $P < 0.05$.

Mean values were significantly different compared with controls; † $P < 0.05$.

ULN, upper limit of normal.

For details of subjects and procedures, see p. 366.

plasma tauro-conjugated bile acid concentrations. The absence of colon did not influence the liver function tests, amino acid profile or plasma biliary acid profile.

Taurine-supplementation study

Ten out of the twelve group A patients with cholestasis from the first study agreed to participate in the second study. Their mean jejunal remnant was 16 (SE 4) cm (range 0–34 cm) long, and the mean colonic remnant was 54 (SE 15) % of normal length.

At the end of a 55 (SE 13) month period of supplementation, there was a significant increase in plasma taurine concentrations (62.5 (SE 7.6) v. 43.2 (SE 4.3) $\mu\text{mol/l}$; $P=0.007$). Normal taurine values were obtained after an 8 (SE 2) month supplementation, and these normal values were maintained for 61 (SE 3) months. Plasma concentrations of taurine precursors remained normal (Fig. 1). However, the taurine:glycine ratio of the plasma bile acids was still lower than normal values and did not change (0.10 (SE 0.07)) in comparison with baseline levels (0.12 (SE 0.05)). Total plasma bile acids were unchanged before and after taurine supplementation (25.7 (SE 11.2) v. 22.0 (SE 9.2) $\mu\text{mol/l}$ respectively). Tauro-conjugated bile acids were also unchanged: taurocholic acid went from 1.1 (SE 1.1) $\mu\text{mol/l}$ to non-detectable levels, taurochenodeoxycholic acid from 1.5 (SE 1.2) to 0.1 (SE 0.1), taurodeoxycholic acid from 0.1 (SE 0.1) to 0.2 (SE 0.10) and tauroolithocholic acid from 0.3 (SE 0.2) $\mu\text{mol/l}$ to non-detectable values. In the six patients receiving both taurine and ursodeoxycholic acid, plasma total ursodeoxycholic acid rose from 0.3 (SE 0.3) to 9.0 (SE 4.5) $\mu\text{mol/l}$ ($P=0.04$), but tauro-ursodeoxycholic acid was detected neither before nor after intravenous taurine supplementation. In the ten patients, there was a statistically significant decrease in aspartate aminotransferase level (2.3 (SE 0.5) v. 1.3 (SE 0.2) times the upper limit of normal; $P=0.02$), even though cholestasis – as previously defined – was not influenced. There were no differences in

plasma biliary acids or amino acids between patients receiving or not receiving ursodeoxycholic acid.

Discussion

The present results indicate that parenteral nutrition-dependent patients with short-bowel syndrome with no remnant ileum have, compared with controls, a significant decrease in plasma taurine level if the post-duodenal remnant jejunal bowel is shorter than 35 cm, and in the plasma ratio of tauro-conjugated:glyco-conjugated bile acids. Notably, the latter finding was independent of the length of the remnant jejunum, all short-bowel syndrome patients having no remnant ileum. Our long-term HPN patients had chronic cholestasis in 78 % of cases, a prevalence close to that recently published in a cohort of ninety long-term HPN patients (Cavicchi *et al.* 2000). In the present study, when taurine-supplemented parenteral nutrition was provided to ten patients for nearly 5 years, there was a trend towards improved liver function tests, contrasting with the natural history, i.e. a worsening of the long-term parenteral nutrition-associated liver disease (Cavicchi *et al.* 2000). Indeed, during the 5-year follow-up, no clinical symptom indicating a complicated liver course was observed in these ten patients. This occurred, along with a normalisation of plasma taurine levels, despite the fact that patients failed to normalise the very low (<10 %) ratio of tauro-conjugated:glyco-conjugated plasma bile acids.

Our long-term HPN patients received amino-acid solutions providing cysteine and methionine, which are both taurine precursors, as well as pyridoxine, the limiting co-factor for cysteine sulfinic acid dehydrogenase, which is the key enzyme in the conversion of cysteine to taurine. Interestingly, cysteine and methionine plasma levels were normal in our patients, and methionine levels were even slightly higher than in controls; therefore, these data do not seem to indicate an increased need of taurine precursors via the intravenous route. Low plasma and blood cell taurine values have previously been reported in children receiving HPN in whom intestinal absorption is the most impaired (Helms *et al.* 1999), and these results are consistent with the low plasma taurine levels measured in our shortest-gut adult patients. An impaired absorption of proteins including taurine, which is found in meat at a level ranging from 11 to 827 mg/100 g (Laidlaw *et al.* 1990), is consequently one explanation for the depleted systemic taurine pool in the very-short-gut adult patients who do not receive taurine-enriched amino-acid solutions.

The biliary taurine pool is usually considered to be only a tiny part of the whole-body taurine pool, but turnover of the biliary pool is far more rapid than that of the whole-body pool (Férézou *et al.* 1993). In the present study, the biliary pool, indirectly assessed by the plasma ratio of tauro-conjugated:glycol-conjugated bile acids, was depleted in all our short-bowel patients. This happened irrespective of long-term supplementation with intravenous taurine, which was similar (i.e. 6–10 mg/kg per d) and resulted in a comparable increase in plasma taurine levels than in previous studies (Cooke *et al.* 1984; Kopple *et al.* 1990; Gray *et al.* 1994; Paauw & Davis, 1994). Although we did not measure urinary taurine excretion, it is likely that excess taurine has been lost in the urine (Vinton *et al.* 1987).

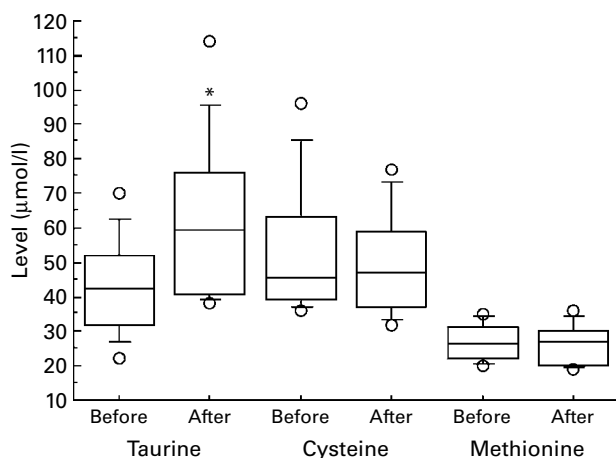


Fig. 1. Evolution of plasma sulphur amino acids in parenteral nutrition-dependent patients with short-bowel syndrome and cholestasis receiving intravenous taurine. Boxes represent medians and quartiles; low and high horizontal bars represent the extreme values (falling within 1.5 times the interquartile range). \circ , outliers (i.e. outside 1.5 times the interquartile range). * $P<0.01$.

For details of subjects and procedures, see p. 366.

In rabbits, the jejunal intestinal taurine transporter has only 10% of the capacity of the ileal transporter (O'Flaherty *et al.* 1997). As none of our HPN patients had a remnant ileum, they presumably had a highly compromised enterohepatic cycle of biliary acids owing to huge faecal losses of bile acids, with increased hepatic bile acid synthesis (Férézou *et al.* 1993). Indeed, the increase in level of total plasma biliary acids was moderate even though there was a significant intrahepatic liver cholestasis and, interesting to note, none of our hyperbilirubinaemic patients complained of pruritis. Taurine malabsorption combined with large faecal losses of biliary salts (O'Flaherty *et al.* 1997) therefore appears to be responsible for the constant decrease in plasma ratio of tauro-conjugated:glyco-conjugated bile acids. Because the ratio of tauro-conjugated:glyco-conjugated plasma bile acids remained far below usual values in every short-bowel patient, despite normalisation of the plasma taurine level with taurine-enriched amino-acid solutions, it can be postulated that huge faecal losses of biliary acids are, owing to their disrupted enterohepatic cycle, along with a limited liver taurine compared with glycine bile acid synthesis, the main consequence of this deficit. Unfortunately, faecal bile acids were not measured in the present study, and this is certainly a limitation. The six patients who were receiving oral ursodeoxycholic acid along with a supplemented taurine-enriched amino-acid solution were unable to tauroconjugate it.

Other data support the concept of a partition between the systemic and enterohepatic taurine pools: there is no correlation between liver and muscle taurine concentrations (Hardison, 1978); there is a significant correlation between the tauroconjugation of bile acids and liver taurine concentrations (Hardison & Proffitt, 1977); only intraduodenal taurine administration in patients with surgically interrupted enterohepatic circulation was able to induce a 5–10% increase in hepatic tauroconjugation within 2 h (Hardison, 1978). Liver taurine concentration might therefore be mainly dependent on intestinal absorption. Such data, along with the duration of the depletion (the duration of short-bowel syndrome before treatment was started), could explain the ineffectiveness of parenteral taurine-enriched amino-acid solutions to induce a significant increase in plasma tauro-conjugated bile acids.

In addition, the daily dose provided in the parenteral nutrition solution may be too low, and a dose-ranging study should be performed to clarify this point. The failure of taurine supplementation to improve cholestasis may also be the consequence of aetiologies of parenteral nutrition-associated cholestasis other than taurine deficiency, which it does not address. Finally, whether other tissues (e.g. heart, muscle, brain) are taurine depleted and whether parenteral taurine can restore stores at the tissue level is unknown.

In multivariate analysis of factors contributing to HPN-associated liver disease, we previously demonstrated that a very short bowel, i.e. less than 50 cm, was a significant risk factor for chronic cholestasis with a relative risk of 2.1 (range 1.2–3.7; Cavicchi *et al.* 2000). We may hypothesise that the conjunction of systemic taurine depletion and disturbed enterohepatic bile acid synthesis might therefore be the link between HPN-associated liver cholestasis and very-short-gut syndrome associated with permanent intestinal failure (Messing *et al.* 1999). Several lines of evidence favour a protective role of taurine in liver injuries in parenteral

nutrition patients: taurine increases bile flow and reportedly reduces parenteral nutrition-associated cholestasis in the guinea-pig (Guertin *et al.* 1991); taurocholate protects the liver against amino-acid-induced cholestasis in the isolated perfused rat liver (De Bandt *et al.* 1999); taurine has been reported to correct parenteral nutrition-induced liver membrane modifications (an increase in the lipid:protein ratio, and a fall in PUFA) in guinea-pigs (Guertin *et al.* 1993). Until now, however, long-term parenteral taurine-enriched amino-acid solutions have failed to show any significant improvement in liver function tests (Cooke *et al.* 1984; Kopple *et al.* 1990). In the present study, there was a trend towards a normalisation of liver function tests in taurine-supplemented patients with a significant decrease in aspartate aminotransferase levels. However, the small number of patients and the fact that six of ten taurine-supplemented patients also received oral ursodeoxycholic acid prevent us from drawing any definite conclusions on the influence of taurine on HPN-induced liver disease.

In conclusion, in very-short-bowel syndrome adult patients undergoing long-term parenteral nutrition, there is a systemic taurine deficiency that can be corrected by long-term intravenous taurine supplementation; such supplementation in children reportedly normalises the whole-blood taurine pool, as well as electroretinograms (Geggel *et al.* 1985). However, in adult short-bowel HPN patients, this study raises arguments that intravenous taurine supplementation seems unable to normalise the biliary taurine pool. In very-short-bowel syndrome patients undergoing long-term parenteral nutrition, both routes of supplementation – oral and intravenous – may be necessary to normalise biliary and systemic taurine pools. The efficacy of oral supplementation remains, however, to be tested and is speculative at the moment. Therefore, this pilot study calls for a large randomised trial of the effects of taurine supplementation on taurine pools and cholestasis in short-bowel HPN patients.

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