Continuous terlipressin infusion is associated with improved diet intake and muscle strength in patients awaiting liver transplant
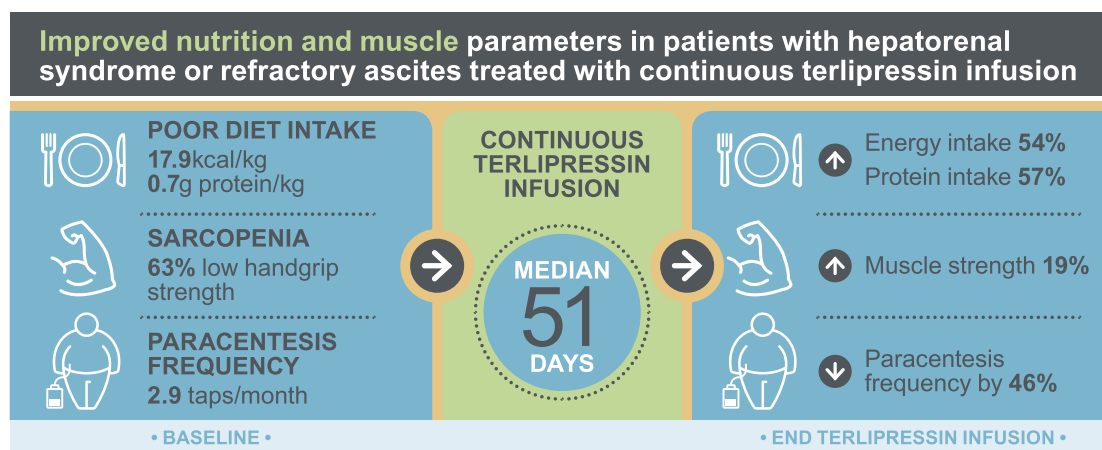
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Graphical abstract

Highlights

- Malnutrition and poor muscle strength are highly prevalent in cirrhotics with hepatorenal syndrome.

- Terlipressin infusion increased energy and protein intake in patients with hepatorenal syndrome.

- Handgrip strength continued to increase with every day of terlipressin therapy

- Medium to long-term terlipressin infusion was safe and efficacious as a bridge to liver transplant.

Lay summary

Malnutrition and poor muscle strength are common in liver disease and often get worse while patients await liver transplant. Terlipressin is a medication used to treat portal hypertension in patients with hepatorenal syndrome. It is usually given for a few days or weeks in patients confined to hospital. Our centre provides outpatient terlipressin for weeks to months as a bridge to liver transplant. In patients treated with terlipressin at our hospital, we observed a substantial increase in their dietary intake and muscle strength, which may improve their quality of life and outcomes after liver transplant.

Continuous terlipressin infusion is associated with improved diet intake and muscle strength in patients awaiting liver transplant

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Background & Aims: Portal hypertension contributes to the pathogenesis of malnutrition and sarcopenia in cirrhosis via multiple mechanisms. Terlipressin is a vasopressin analogue that we administer via continuous outpatient infusion, as a bridge to transplantation in patients with hepatorenal syndrome or refractory ascites. We describe, for the first time, the impact of outpatient terlipressin on nutritional and muscle parameters.
Methods: Nutrition (subjective global assessment), handgrip strength, dietary intake (energy, protein), frequency of paracentesis and severity of liver disease (model for end-stage liver disease score) were prospectively recorded at terlipressin commencement and follow-up (transplantation, cessation or census date).
Results: Nineteen patients were included (89% male, median age 59.6 years, median model for end-stage liver disease score 24), of whom 12 had hepatorenal syndrome and 7 had refractory ascites. All patients were malnourished at baseline, 63% (n = 12) had sarcopenic-range grip strength, and mean paracentesis frequency was 2.86 ± 1.62/month. Median duration of terlipressin was 51 days (interquartile range 29–222). Fourteen patients (74%) were transplanted, 2 delisted (10%) and 3 (16%) continued terlipressin. Energy and protein intake improved significantly following terlipressin, from 17.94 ± 5.43 kcal/kg to 27.70 ± 7.48 kcal/kg, and 0.74 ± 0.28 g/kg to 1.16 ± 0.31 g/kg, respectively (both $p < 0.001$). Handgrip strength increased from 25.36 ± 8.13 kg to 28.49 ± 7.63 kg ($p = 0.001$). Linear regression analysis demonstrated hand grip strength increased 0.075% for every 1-day of terlipressin ($p = 0.005$). The frequency of large-volume paracentesis reduced by 46%, to 1.57 ± 1.51/month ($p = 0.001$).
Conclusion: Continuous terlipressin infusion reduces the complications of portal hypertension and is associated with an improvement in nutritional and muscle parameters in patients on the liver transplant waiting list, in whom such characteristics usually demonstrate progressive decline. This validates both the aetiological role of portal hypertension in malnutrition and represents a promising new anabolic therapy.

Introduction

Malnutrition is ubiquitous in end-stage liver disease and is increasingly recognised as a key prognostic factor in cirrhotic patients. Malnutrition increases the frequency and severity of decompensation, is a major contributor to sarcopenia, and is associated with increased infection rates and reduced survival both before and after liver transplantation (LT).[1–4] Although the importance of malnutrition in cirrhosis is well recognised, effective interventions are lacking, therefore nutrition and physical status continue to decline as liver disease progresses.[5]

The cause of nutritional and functional deterioration in liver disease is multifactorial, with the adverse effects of portal hypertension on gastrointestinal function playing a significant role. Reduced gastric reserve from tense ascites, protein losses from

paracentesis, slowed intestinal transit and malabsorption are all major contributors to malnutrition and sarcopenia.[1,6,7] Enteropathy also increases bacterial translocation, with associated systemic inflammation that contributes to the hypercatabolic state.[8,9]

Effective treatments to reverse malnutrition and sarcopenia in the face of deteriorating liver function have mostly remained elusive. In a limited number of studies where advancements in muscle mass or strength have been realised, significant improvements in mortality and clinical complications (hepatic encephalopathy, sepsis) have been described.[5,10,11] LT offers an obvious theoretical 'cure', by arresting portal hypertension and other factors that negatively impact nutrition, yet malnutrition and sarcopenia often do not reverse after LT.[12] Pre-transplant deconditioning has been identified as a powerful negative predictor of achieving physical recovery post-transplant.[12] When skeletal muscle quality and quantity is considered in addition to the model for end-stage liver disease (MELD) score, it has shown to more accurately predict post-transplant mortality than MELD alone.[13] Malnutrition and sarcopenia should therefore be targeted prior to LT to provide the greatest chance of optimising patients' physical function and clinical outcomes after transplantation.

The most damaging manifestation of portal hypertension in advanced cirrhosis is hepatorenal syndrome-acute kidney injury

(HRS-AKI), which occurs in 26% of hospitalised patients with cirrhosis[14] and carries an extremely poor prognosis. HRS-AKI treatment guidelines recommend terlipressin therapy in conjunction with albumin for volume expansion.[15] Terlipressin acts as a potent vasoconstrictor to reverse the effects of severe splanchnic vasodilation and improve renal perfusion, though little is known about the effects of terlipressin administered for extended periods or outside of the acute care setting. Our centre provides continuous outpatient terlipressin infusion to patients with HRS who have relapsed or who have refractory ascites as a bridge to LT. Here we describe effects of continuous terlipressin infusion (CTI) on nutritional and functional muscle characteristics in this novel patient cohort.

Materials and methods

Study design and patients

This is a single-centre prospective observational study of adult patients awaiting LT who were commenced on CTI from May 2013 to March 2018. Patients in this study received CTI for 1 of 2 reasons; diagnosis of HRS as per nomenclature provided by the International Club of Ascites (ICA, including HRS-AKI, non-AKI-HRS [HRS-NAKI], and HRS-AKI on HRS-chronic kidney disease [HRS-CKD])[15,16] who had relapsed following their initial successful treatment with terlipressin, or those with refractory ascites awaiting LT. Data were prospectively recorded at baseline and again at follow-up (LT, cessation of terlipressin, or census date 31st March 2018). Those without full nutritional data or with an infusion duration of less than 2 weeks were excluded from the analysis.

The study was approved by the Austin Health Human Research Ethics Committee.

Terlipressin infusion

All patients prescribed terlipressin for indication of HRS-AKI, HRS-NAKI, HRS-AKI on HRS-CKD and refractory ascites initially received inpatient bolus terlipressin at a dose of 0.85 mg every 6 h to assess efficacy and tolerance with concurrent albumin therapy (40 g/day) for the first 3 days. After 24-72 h, patients were then switched to CTI. Those deemed suitable for home therapy were educated and provided informed consent, whilst those considered too unstable for home CTI remained inpatients until LT. CTI was administered via a SureFuser pump (Nipro, Australia) through a peripherally inserted central catheter (PICC). The terlipressin (3.4 mg) was prepared in 80 ml of 0.9% sodium chloride to give a final infusion volume of 100 ml, delivered at a rate of 4.2 ml/h. In order to maintain the infusion at or below 25°C, the SureFuser pump was carried in a 3-compartment waist bag containing an icepack, worn by the patient. Under our centre's hospital-in-the-home (HITH) program, nursing staff attended the patient's home once daily to administer the terlipressin infusion. Clinical assessment including measurement of haemodynamics and PICC site evaluation was conducted at each visit. PICC dressing changes were performed once weekly by trained nursing staff. Any clinical concern was reported immediately to the treating physician. After the initial hospitalisation, patients did not receive daily albumin infusion in the home setting. Biochemistry was measured at a minimum frequency of weekly. Individual response to terlipressin therapy was classified as per ICA-AKI definition;[16] no response (no regression of AKI), partial response (regression of AKI stage with a reduction of serum creatinine [sCr] to ≤0.3 mg/dl [≤26.5 umol/L] above baseline value) or full response (return of sCr to within 0.3 mg/dl [26.5 umol/L] of

baseline value). Medical and dietary review were performed at the outpatient clinics on a 1 to 4 weekly basis.

Nutritional status

Nutritional status was determined by subjective global assessment (SGA), a non-invasive validated bedside tool that comprises 6-month history of (dry) weight, dietary intake (assessment and impact factors), physical examination (fat loss, muscle wasting, oedema and ascites) and functional impairment.[17] On the basis of this assessment, patients were classified as well nourished (SGA A), moderately malnourished (SGA B) or severely malnourished (SGA C).

Dietary intake

All patients received dietary counselling according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines[18], which suggest aiming for a high-energy high-protein salt-restricted diet during the initial transplant assessment, outpatient clinic attendance and follow-up hospitalisation for terlipressin treatment. Dietary intake was determined by 24-h diet recall and food frequency questionnaire, with energy (kJ/kcal) and protein (g) intake calculated and compared to individual requirements as estimated by ESPEN prediction equations for decompensated cirrhosis (147–168 kJ/kg/d (35–40 kcal/kg), 1.2–1.5 g/kg).[18]

Muscle strength

Hand grip strength (HGS) was measured by digital hand dynamometer (TTM®, Japan) as a measure of functional muscle strength. Participants were asked to perform a maximal contraction with the non-dominant hand on 3 occasions while seated, with 20–30 seconds rest between contractions. The maximal contraction was recorded (kg), and the result noted as being above or below the established gender-specific cut-off for sarcopenia (30 kg for men, 20 kg for women).[19]

All nutritional data and muscle strength assessments were carried out by experienced liver transplant dietitians.

Biochemistry

Serum sodium, creatinine, bilirubin, albumin and international normalized ratio (INR) were recorded at baseline and then daily during the acute hospital admission, and weekly until cessation of terlipressin, LT or census date.

The severity of liver disease was measured by Child-Pugh, MELD and Na-MELD scores.

Paracentesis frequency

Frequency of paracentesis and thoracentesis were obtained retrospectively from hospital records in all patients for the 90-day period prior to commencing terlipressin therapy. Mean paracentesis frequency per 30 days over this period was then determined. Paracentesis frequency for the duration of terlipressin therapy was prospectively recorded and also expressed as a 30-day average to allow comparison with pre-terlipressin data. Volume of paracentesis was not universally recorded and hence was not included in the analysis. All patients who underwent paracentesis and thoracentesis were treated with concurrent plasma volume expansion as per the European Association for the Study of the Liver guidelines (albumin infusion 8 g/L of ascites removed).[15] To ensure reduction in paracentesis frequency was not confounding analysis, we compared those who had greater than 50% reduction in paracentesis over the course of their CTI, with those that did not.

Complications and patient outcomes

Complications of terlipressin therapy, the number of days of terlipressin treatment and patient outcome (cessation of terlipressin prior to LT, LT, or continuation of terlipressin at census date) were recorded for all patients. Survival data and renal function post-transplant were also recorded for those who underwent LT during the study period.

Subgroup analysis

Eleven of 19 patients were active on the transplant waiting list for several months prior to development of HRS-AKI and commencement of terlipressin. These patients had all been assessed and counselled by the liver transplant dietitian from the time of transplant listing, so they had available nutrition and muscle strength data from this time and could serve as an historical control group. Changes in nutritional status, dietary intake and HGS for this patient subgroup were compared before and after initiation of CTI. The remaining 8 patients not included in this subgroup analysis were started on terlipressin within days of their initial nutritional assessment and thus lacked historical data.

Statistical analysis

Univariate analysis was utilised to determine data distribution and central tendency. Continuous variables with a normal distribution (by Shapiro-Wilk analysis) are reported using mean ± SD whilst those with non-normal distribution are reported as median and interquartile range. Paired sample t tests were performed to compare variables pre- and post-treatment with terlipressin, whilst unpaired t tests compared the difference between those with and without improvement in paracentesis frequency. Linear regression analysis allowed exploration of biochemical and clinical factors predictive of nutritional and functional status, and to determine if reduced paracentesis frequency predicted nutritional parameters.

Using ANOVA where pre-CTI data were available, HGS and caloric intake at first measure, commencement of CTI, and immediately prior to transplantation were compared. Data homogeneity was tested using Levene's test for homogeneity of variances and where data were not homogenous, *post hoc* analysis was completed using Games-Howell method. Data are reported as percent change ± SEM. A p value in all analysis <0.05 was considered significant. All statistical analysis was performed using SPSS (Version 20.0; IBM, Armonk, NY).

Results

Nineteen patients awaiting LT treated with CTI were eligible for inclusion in the analysis. Indication for CTI was HRS-AKI on HRS-CKD for the majority of patients (n = 11, 57.9%), whilst 1 patient (5.3%) had HRS-AKI and 7 (36.8%) received CTI for refractory ascites. Sixteen patients were discharged from the acute setting and received CTI at home via the HITH program, whilst 3 patients remained inpatients on CTI until LT. Patient demographics are presented in Table 1.

Terlipressin therapy was associated with significant improvements in multiple nutritional, functional and biochemical parameters (Table 2). At baseline, energy and protein intake were inadequate in all patients, with mean energy (17.94 ± 5.43 kcal/kg) and protein (0.74 ± 0.28 g/kg) intake only 51% and 62% of the lower end of estimated requirements, respectively. Dietary energy and protein consumption increased following terlipressin therapy, approaching recommended requirements in the majority of patients. Dietary intake was 80% of predicted energy (27.70 ± 7.48 kcal/kg) (Fig. 1) and 97% of protein (1.16 ±

0.31 g/kg) (Fig. 2) requirements after terlipressin treatment (both p <0.001).

Improved muscle strength, as measured by HGS was observed in 16 of 19 patients, increasing from a mean of 25.36 ± 8.13 to 28.49 ± 7.63 kg after terlipressin treatment (p = 0.001) (Fig. 3). The degree of severe malnutrition (SGA C) reduced from 37% to 26%, though malnutrition persisted (SGA B or C) in almost all patients (18/19). There was a significant reduction in MELD that was primarily driven by improved renal function, whilst serum bilirubin, albumin and INR were not significantly affected by terlipressin treatment.

Linear regression analysis identified that in this cohort, for every 1-day of terlipressin there was a 0.075% increase in HGS (p = 0.005), 0.078% increase in energy intake (p = 0.015), and a 0.065% increase in protein intake (p = 0.040). Changes in renal function or MELD score were not predictive of changes in functional or nutritional status.

Paracentesis frequency reduced by 46%, from 2.86 ± 1.62 drains per 30 days in the 3 months prior to terlipressin therapy, to 1.57 ± 1.51 per 30 days whilst on terlipressin treatment (p = 0.001). There was no significant difference in energy intake (p = 0.338), protein intake (p = 0.470) or functional muscle strength (p = 0.372) in those with greater than 50% reduction in paracentesis frequency compared to those with less than 50% reduction. Furthermore, by linear regression analysis, the variability in

Table 1. Baseline patient demographics, nutritional status and functional muscle assessment.

Baseline Parameter	Result
Sex (M/F), n (%)	17(89.5)/2(10.5)
Age (years), median (IQR)	59.64 (55.70–64.80)
Liver aetiology, n (%)	
Alcohol	7 (36.8)
Hepatitis C virus	5 (26.3)
Cryptogenic cirrhosis	3 (15.8)
Non-alcoholic steatohepatitis	2 (10.5)
Primary sclerosing cholangitis	1 (5.3)
Autoimmune hepatitis	1 (5.3)
Severity of liver disease, median (IQR)	
Child Pugh score	10 (9–12)
MELD	24 (19–31)
Na-MELD	27 (23–32)
Indication for commencing terlipression, n (%)	
HRS-AKI	1 (5.3)
HRS-AKI on HRS-CKD	11 (57.9)
Refractory ascites	7 (36.8)
Functional muscle strength	
Mean ± SD, kg	25.36 ± 8.13
Below sarcopenia cut-off, n (%)	12 (63.2)
Nutritional status, n (%)	
Well nourished (SGA A)	0 (0)
Moderately malnourished (SGA B)	12 (63.2)
Severely malnourished (SGA C)	7 (36.8)
Duration of terlipressin (days), median (IQR)	51 (29–222)

AKI, acute kidney injury; CKD, chronic kidney disease; HRS, hepatorenal syndrome; IQR, interquartile range; MELD, model for end-stage liver disease; SGA, subjective global assessment.

Table 2. Change in outcome measures following terlipressin treatment.

Parameter	Pre-terlipressin, mean ± SD	Post-terlipressin, mean ± SD	Change, mean ± SD	*p* value
Handgrip strength, kg	25.36 ± 8.13	28.49 ± 7.63	3.13 ± 3.55	0.001
Energy intake, kcal/kg	17.94 ± 5.43	27.70 ± 7.48	9.76 ± 7.30	<0.001
Protein intake, g/kg	0.74 ± 0.28	1.16 ± 0.31	0.41 ± 0.29	<0.001
% energy requirements met	53.26 ± 16.66	80.68 ± 17.1	27.42 ± 18.28	<0.001
% protein requirements met	56.53 ± 19.13	86.05 ±15.62	29.53 ± 17.90	<0.001
MELD	24.42 ± 6.28	19.32 ± 6.46	-5.11 ± 5.27	<0.001
Na MELD	27.11 ± 5.88	21.05 ± 6.43	-6.05 ± 5.80	<0.001
Creatinine, μmol/L	185.42 ± 66.05	108.95 ± 24.25	-76.47 ± 64.97	<0.001
Sodium, μmol/L	131.16 ± 6.24	135.63 ± 4.96	4.47 ± 6.53	0.008
INR	1.78 ± 0.48	2.02 ± 0.89	0.24 ± 0.80	0.206
Bilirubin, μmol/L	78.05 ± 88.05	69.32 ± 69.99	-8.74 ± 72.54	0.606
Albumin, g/L	35.16 ± 5.36	34.84 ± 6.03	-0.32 ± 8.45	0.872
Paracentesis frequency per 30 days	2.86 ± 1.62	1.57 ± 1.51	-1.29 ± 1.42	0.001

INR, international normalized ratio; MELD, model for end-stage liver disease.

HGS (R^2 0.070; $F_{(1,17)}$ = 1.284, p = 0.273), energy intake (R^2 = 0.001; $F_{(1,17)}$ = 0.009, p = 0.925) or protein intake (R^2 <0.001; $F_{(1,17)}$ = 0.001, p = 0.982) could not be accounted for by the reduction in paracentesis frequency.

Whilst the primary objective was not to assess renal outcomes, for the purpose of ongoing provision of terlipressin, patient response to treatment was monitored as per the ICA-AKI definition.[16] One patient (5.3%) demonstrated partial response to therapy, whilst 18 patients (94.7%) demonstrated full response, which was durable for the duration of terlipressin therapy. There were no complications directly attributable to terlipressin. Complications relating to the PICC line were encountered in 5 patients, and included migration, blockage and infection requiring PICC line replacement in each instance.

Fourteen of 19 patients were transplanted with median time to transplant of 46 days following commencement of CTI (range 24–291 days). All patients received liver-only grafts. Two patients ceased terlipressin therapy prior to LT (n = 1 recovery following successful direct acting antiviral therapy for HCV whilst on CTI, n = 1 alcohol recidivism and delist), and 3 patients remain on CTI awaiting LT (median 222 days on terlipressin at census date).

Survival post-LT is 93% (n = 13), with mean post-transplant follow-up of 490.5 days (range 1–1,759 days). Median creatinine post-LT was 118 μmol/L (range 81-186 μmol/L) at census date.

Eleven of 19 (58%) patients had nutrition and muscle strength data collected prior to commencement of CTI. Amongst these patients, there was a median duration of 180 days from first assessment to starting CTI. Thereafter, patients were on CTI a median of 42 days until transplantation. As determined by ANOVA, there was a statistically significant difference between HGS percent change ($F_{[2, 30]}$ = 8.101, p = 0.002) and caloric intake percent change ($F_{[2, 30]}$ = 5.841, p = 0.007) at measured
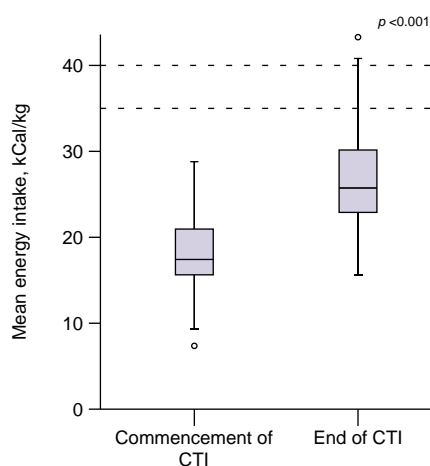

Fig. 1. Change in energy intake following terlipressin therapy. Box and whisker plot of mean energy intake (kcal/kg) at start and end of terlipressin treatment. Levels of significance: *p <0.001 determined by 2-sided *t* test. Dashed lines represent recommended energy intake (35–40 kcal/kg) for decompensated cirrhosis as per ESPEN guidelines.[17] CTI, continuous terlipressin infusion; ESPEN, European Society for Parenteral and Enteral Nutrition
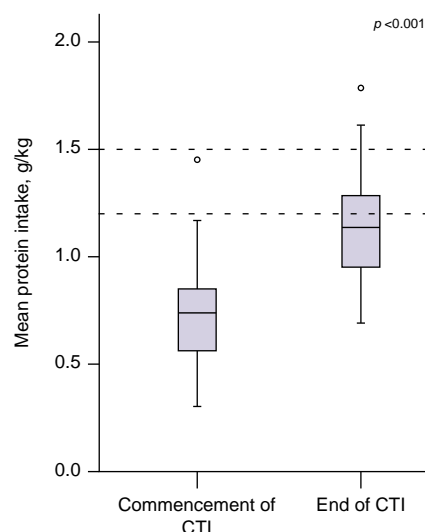

Fig. 2. Change in protein intake following terlipressin therapy. Box and whisker plot of mean protein intake (g/kg) at start and end of terlipressin treatment. Levels of significance: *p <0.001 determined by 2-sided *t* test. Dashed lines represent recommended protein intake (1.2–1.5 g/kg) for decompensated cirrhosis as per ESPEN guidelines.[17] CTI, continuous terlipressin infusion; ESPEN, European Society for Clinical Nutrition and Metabolism.
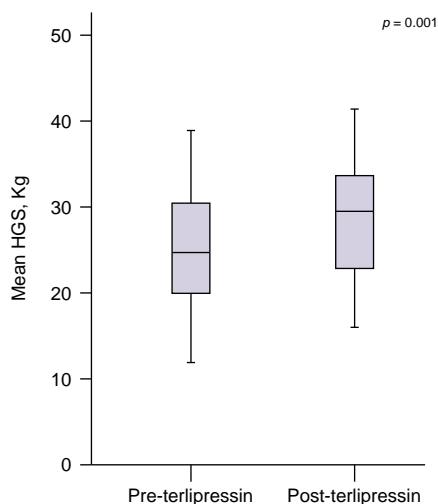
Fig. 3. Change in HGS following terlipressin therapy. Box and whisker plot of mean HGS (kg) at start and end of terlipressin treatment. Level of significance: *p = 0.001 determined by 2-sided *t* test. HGS, hand grip strength.

time points (Fig. 4A and 4B, respectively). Games-Howell *post hoc* analysis noted a significant decline in mean HGS percent (-12.53 ± 2.88%, *p* = 0.004) and a non-significant decline in mean caloric intake percent (-12.24 ± 9.01%, *p* = 0.397) between first assessment and commencement of CTI. There were significant increases in both mean HGS percent change (15.49 ± 5.00%, *p* = 0.016) and mean caloric intake percent change (58.90 ± 22.27%, *p* = 0.048) after the initiation of CTI (Fig. 4).

Discussion

CTI was associated with significant improvements in both nutrition and functional muscle measures in cirrhotic patients on the LT waiting list, in whom such parameters typically demonstrate a progressive deterioration. Dietary intake increased substantially such that energy and protein consumption approached adequacy, muscle strength was enhanced and a reduction in the severity of

malnutrition was observed. The magnitude of shift from nutritional decline and muscle catabolism to anabolism in this patient group was significant with median HGS increasing by 19%, and energy and protein consumption increasing by 54% and 57%, respectively.

This study is the first to measure nutritional status, dietary intake and muscle strength in LT candidates with hepatorenal syndrome and evaluate the potential impact of longitudinal terlipressin therapy on these parameters. Malnutrition is common in cirrhotic patients and is known to increase in prevalence as severity of liver disease progresses.[1,2] Indeed, malnutrition was universal in our patients commencing CTI, with severe malnutrition (SGA C) evident in more than one-third (37%) of patients. We have previously shown that nutritional status progressively declines whilst patients await LT, with malnutrition increasing from 67% at waitlisting to 77% at the time of LT.[20] Subgroup analysis of our patients with pre-terlipressin information confirm this data. These historical controls demonstrated slow deterioration in not only nutritional status but also energy intake and muscle strength whilst awaiting LT, despite expert nutritional advice and regular dietetic follow-up which was consistent with the nutritional interventions they received after starting on terlipressin. The initiation of CTI coincided with reversal of the observed nutritional decline, and the subsequent improvement in calorie intake (58.9%) and HGS (15.5%) in this subgroup was comparable to that experienced by those who did not have dietetic intervention before starting terlipressin (43% and 15.7%, respectively).

The landmark FrAILT study by Lai and colleagues also describes the physical regression commonly observed in patients awaiting LT.[5] In their study detailing the functional characteristics of 309 LT candidates, all physical measures (HGS, short physical performance battery, gait speed, chair stands) deteriorated in the pre-transplant period, and all were significantly associated with waitlist mortality. Specifically, grip strength reduced by -0.38 kg for every 3 months awaiting LT. Reduction in HGS was even more rapid in our historical controls, worsening by -1.36 kg per 3 months, but this may be explained by the higher severity of liver disease in our HRS cohort. Importantly, the FrAILT study was able to demonstrate that patients who improved their physical function also had improved survival, such that for every 1 kg increase in grip strength, the risk of waitlist mortality decreased by 11% (*p* <0.01). Thus, it is possible that the observed increase
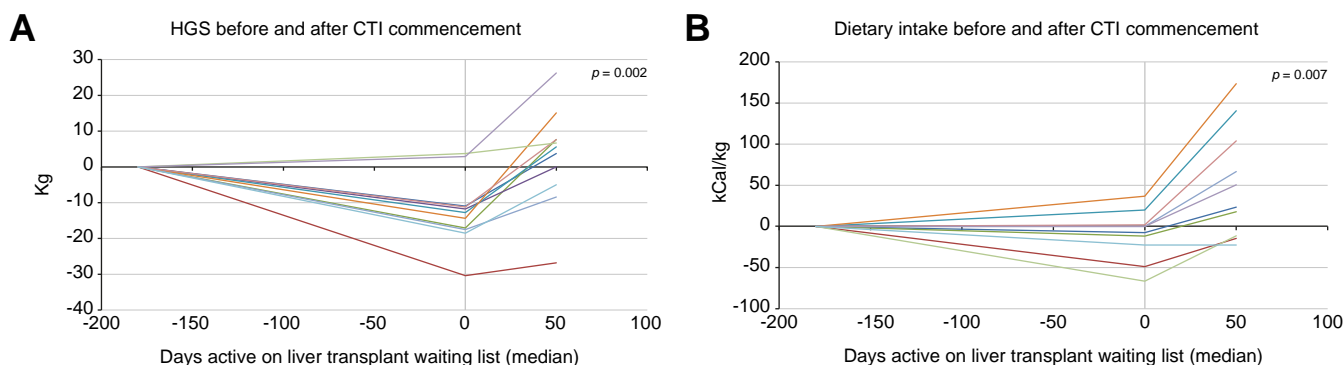

Fig. 4. Change in HGS and energy intake before and after initiation of terlipressin therapy. Line graph of individual percentage change in (a) HGS (kg) and (b) energy intake (kcal/kg) before and after terlipressin treatment in a subset of 11 patients with available HGS and dietary intake data whilst awaiting liver transplant for at least 6 months prior to commencing CTI. Vertical solid line at 0 days indicates commencement of CTI. Level of significance: *p = 0.002 and **p = 0.007 determined by ANOVA. HGS, hand grip strength; CTI, continuous terlipressin infusion.

in HGS in response to terlipressin therapy may translate to improved survival in our patients.

Potential mechanisms responsible for the observed effect of CTI on nutritional and muscle parameters are numerous. Sustained reduction in portal hypertension decreased ascites, which culminated in a reduction in paracentesis frequency and associated protein losses. In 16 patients with refractory ascites who reduced large-volume paracentesis frequency following Alfapump® implantation, Bureau *et al.* reported significant improvements in HGS (4.03 kg, *p* = 0.044), mid arm muscle circumference (1.8 cm, *p* = 0.008) and triceps skinfold thickness (1.898 mm, *p* = 0.003) after 90 days follow-up.[21] Increased gastric reserve is an obvious explanation for the subsequent increased dietary intake and net gain of muscle strength, however we observed objective improvement in nutritional parameters even in the absence of reduced paracentesis rates, whilst change in nutritional variables could not be accounted for by paracentesis frequency using regression analysis. Ultimately, these findings suggest alternative mechanisms other than a simple increase in gastric capacity in our cohort. Enteral absorption may have improved from a combination of reduced gut oedema and bacterial translocation, which has the net effect of reducing adverse gastrointestinal symptoms, and decreasing the pro-inflammatory state of cirrhosis and associated excessive protein catabolism; thus, allowing the patient to 'feel better' and experience improved appetite.

Previous studies in which portal hypertension has been successfully treated have also demonstrated improvement in nutritional status and sarcopenia. Allard *et al.* reported improvement in dry weight and total body nitrogen after transjugular intrahepatic portosystemic shunt (TIPS), though, unlike in our cohort, dietary intake and muscle force remained unchanged.[22] Plauth *et al.* demonstrated increased energy and protein intake (by 26% and 33%, respectively) as well as significant gains in muscle size (18%, *p* = 0.001), body cell mass (15%, *p* <0.025) and total body potassium (15%, *p* <0.01) in 21 patients over 12 months following TIPS insertion.[23] A recent study reported CT-measured muscle area significantly increased in 41 out of 57 patients after TIPS (*p* <0.0001).[10] Failure to reverse sarcopenia in this group was associated with higher mortality (43.5% *vs.* 9.8%, *p* = 0.007). Praktiknjo *et al.* similarly demonstrated reduced survival in patients who failed to show an improvement in sarcopenia after TIPS (*p* <0.05).[11] These data demonstrate that not only does treating portal hypertension improve sarcopenia, but this improvement in muscle mass is likely to correlate with better survival.

The pathogenesis of malnutrition is complex in end-stage liver disease and this patient group present a unique challenge in achieving nutritional targets. Not only are the adverse effects of decompensation on dietary intake compounded by impaired digestion and absorption, but elevated nutritional requirements arising from multi-organ failure often result in unattainable energy and protein requirements.[24,25] Assessment of energy balance in 73 patients awaiting liver transplant found 100% of patients failed to consume adequate calories, although the energy deficit became significantly worse as severity of liver disease progressed (-749 kcal, -612 kcal and -1,210 kcal in patients with Child-Pugh Class A, B and C, respectively) (*p* <0.001).[26] Energy intake was inadequate in all of our patients at baseline, with energy consumption only half of predicted requirements (17.94 kcal/kg *vs.* 35 kcal/kg). This occurred despite intensive nutritional counselling regarding high-energy/protein diet and commencement of oral supplements, suggesting an inability of patients with HRS to meet their nutritional target via the oral route. In this study, patients demonstrating a partial or full response to terlipressin delivered via continuous infusion increased their energy intake by an additional 10 kcal/kg (equivalent to an extra 800 kcal per day for the average 80 kg patient) to 80% of energy needs. To our knowledge, no other medical therapy has been shown to exert such a powerful impact on volitional dietary intake in patients with advanced liver disease.

Results of this study are dramatic and represent the potential to change future clinical management of patients with portal hypertension waitlisted for transplantation, however further research is clearly required to confirm these promising findings. This study was limited by its small sample size conducted in a single centre, and lack of a formal control group. To our knowledge, our centre is the first to institute longitudinal outpatient terlipressin for treatment of portal hypertension, hence patient numbers are small as this therapy remains in its infancy. A randomised placebo-controlled study design was not feasible as it was deemed unethical to withhold terlipressin (standard of care) from those with HRS, and a matched control group of patients without HRS was unable to be included as they did not demonstrate a comparable degree of liver failure in terms of MELD score and symptoms of decompensation. For this reason, patients were utilised as their own controls pre- and post-terlipressin, wherever possible (11 of 19 patients), in order to demonstrate that the influence of terlipressin was independent of nutritional advice.

Conclusion

Patients treated with CTI demonstrated a reduction in portal hypertensive complications which we propose mediated a significant increase in both dietary intake and handgrip strength in waitlisted cirrhotics for whom such parameters usually exhibit progressive decline. Longitudinal CTI appears to be an effective treatment for patients with HRS and refractory ascites as a bridge to LT, and potentially provides benefit above that of survival alone. The current findings suggest it is one of very few therapies that has the ability to improve nutritional measures and functional strength, which is likely facilitated by both a demonstrated reduction in ascites and other unknown mechanisms associated with reduction in portal hypertension. Whether this nutritional repletion and physical improvement translates into enhanced patient or graft outcomes following LT is unknown. Confirming the initial results described in this study with larger numbers in a prospective, randomised trial is warranted.

Please refer to the accompanying ICMJE disclosure forms for further details.

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