5

# LUMINARY LEARNINGS

## GASTROINTESTINAL DISORDERS

**Continuing Education**
Complications of biliopancreatic diversion and duodenal switch

**Beyond Medicine**
Succession planning and leadership development

Access the contents and videos on the online portal:
http://collections.medengine.com/gastrointestinal/luminary-learning-gastrointestinal-disorder/

Springer Healthcare Education

# IN PANCREATIC AND HEPATOBILIARY DISORDERS, COMPLEMENT YOUR TREATMENT WITH

*Introducing*

## Viadek™

Multivitamin with Zinc and Curcuma longa Extract Tablets

FIRST TIME IN INDIA

As per RDA ICMR Recommendation





INDVDK191338 22 MAR 2019

Disclaimer: Images shown are for representational purpose only TM- Trademark of Abbott India Ltd.

**ABBOTT INDIA LIMITED**
16th Floor, Godrej BKC, Plot-C, "G" Block, Bandra-Kurla Complex, Bandra (East), Mumbai–400 051, India.


Abbott

# Luminary Learnings

## Gastrointestinal Disorders

Springer Healthcare Education

September 2019

Springer Healthcare

This edition is published by Springer Nature India Private Limited.
Registered Office: 7th Floor, Vijaya Building, 17, Barakhamba Road, New Delhi 110 001, India.
T: +91 11 4575 5888
www.springerhealthcare.com

Part of the Springer Nature group

# Contents

## Continuing Education



## Beyond Medicine



**Step by step procedure for online viewing:**

1. Go to http://collections.medengine.com/gastrointestinal/luminary-learning-gastrointestinal-disorder/ or scan QR code.


2. Web page of the issue will open on the screen.
3. View and read the PDF version online.
4. The PDF file can be downloaded too for offline reading.

# Complications of biliopancreatic diversion and duodenal switch

**Nabil Tariq, Jihad Kudsi**

## Introduction

Though the duodenal switch without any gastric resection has been described before for the treatment of bile gastritis and biliopancreatic diversion was described in 1979 by Scopinaro, this chapter will mostly talk about biliopancreatic diversion with duodenal switch [1, 2]. This version involves the preservation of the pylorus, a sleeve gastrectomy, a 250 cm alimentary limb, and a 100 cm common channel. We will also briefly refer to a newer version of this, the SADI (single-anastomosis duodeno-ileal bypass), where relevant.

Though the total number of BPD-DS surgeries being performed around the world has not decreased, the proportion it forms of total surgeries certainly has decreased. According to one survey of bariatric surgery national societies, the proportion of BPD-DS has decreased from 4.9% in 2008 to 1.5% in 2013 [3]. This is partly due to the sleeve gastrectomy becoming the dominant procedure, especially in the U.S.A. However, increasingly the BPD-DS or its younger sibling—the SADI—is being touted as an option for weight regain after sleeve gastrectomy. This means that the total number of cases of BPD-DS/SADI will likely increase. It is very important and relevant to be aware of the potential short-term and long-term complications associated with these operations.

## Early Complications

### Mortality

Though the BPD-DS may be the most effective in weight loss and resolution of comorbidities among the current bariatric procedures, it does come at a cost: mortality rates are higher than for other bariatric operations. Morality from BPD-DS varies significantly between published series, perhaps because of small numbers of patients. Kim and colleagues reported a rate of 5.6% in their

**N. Tariq (✉), J. Kudsi**
Assistant Professor of Surgery, Houston Methodist Hospital, Department of Surgery, Weill Cornell College of Medicine, Houston, TX, USA
e-mail: ntariq@houstonmethodist.org; j.kudsi@gmail.com

series of 54 patients, with around half the patients having an open procedure. The mortality was 7.6% (2 of 26 patients) for the laparoscopic group [4]. In a systematic review and meta-analysis, Buchwald and colleagues found that the 30-day mortality was around 1.11% for laparoscopic DS and 0.7% for open DS [5]. Comparatively, the overall mortality for all bariatric procedures was only 0.28% [5].

Results such as these have caused widespread concern, resulting in decreased performance of these procedures. There are, however, several series now that have demonstrated lower mortality rates. Weiner and colleagues published a series with 63 patients without mortality [6]. Parikh and colleagues reported on no mortality in 43 patients, and Rabkin and coworkers also reported no deaths in 345 patients with a mean BMI of 50 kg/m$^2$ [7, 8]. Prachand and coworkers published their large series of 198 super obese patients, and only had one mortality, for a rate of 0.51% [9].

In one of the largest series published to date, Biertho and coinvestigators described perioperative complications in 1000 consecutive duodenal switch patients. There were 228 patients that were done laparoscopically and 772 that were done in an open fashion. They had one perioperative mortality, with the patient expiring from a pulmonary embolism, for a mortality rate of 0.1% [10]. In another series of 121 laparoscopic duodenal switch patients from the UK, Magee and coworkers reported a 0% 90-day mortality [11].

Whether these improved mortality rates are indicative of refinement of technique or more experience, especially with the laparoscopic approach, is unclear, but both likely play a role, as well as improved perioperative and multidisciplinary care over the years.

As BPD-DS is frequently performed in those with a BMI > 50 kg/m$^2$ or super obese, it has been suggested that the morbidity and mortality may be reduced by staging the operations and performing the sleeve gastrectomy portion first and then adding the malabsorption part of the procedure later [12].

## Infectious Complications

### Wound Infections

Superficial wound complications are reported but are relatively uncommon, especially in the laparoscopic DS procedures. In a series of 1000 patients by Biertho and coworkers, the wound infections occurred in 1.3% in the laparoscopic group and 3.5% in the open group [10]. Magee and coinvestigators reported a wound infection rate of 2.5% in their 121 patients [11]. In another more recent report from 2016 by Biertho and coworkers, their wound infection rate was only 0.4%, an impressively low rate in this series of 566 patients undergoing laparoscopic DS [13]. Overall the rates are similar to other bariatric procedures.

### Anastomotic/Staple Line Leaks

Anastomotic leak rates are generally considered to be higher than for other procedures, such as the gastric bypass. The signs and symptoms are similar to other leaks as described elsewhere.

These include tachycardia, tachypnea, hypoxia, and/or hypotension. Like in other obese patients, abdominal pain and tenderness may not be dominant symptoms. Delayed diagnosis can be associated with increased risk of mortality, and the clinician must always have a high index of suspicion.

In a systematic review and meta-analysis of a single institution, Hedberg and coworkers compared 599 patients who underwent DS to 929 patients who underwent gastric bypass. The leak rates reported were 5% for DS and 2.2% for gastric bypass [14]. In a series of 345 laparoscopic or hand-assisted DS, the total leak rate was 3.2%, with 2% at the gastric staple line and 1.2% at the duodenal anastomosis [8]. Biertho and collaborators reported a total rate of 3% in their 1000 patient series, with 1.5% each of gastric leak and duodenal leak. They also had one small bowel anastomosis leak [10]. In the recent series of 566 laparoscopic DS patients published from the same group, these rates were significantly reduced to 0.7% for duodenal leak and 0.2% for gastric leak. However, there was a 0.5% intra-abdominal abscess rate reported [13]. In the series by Magee and coinvestigators, they reported a 3.3% leak rate, with half the leaks occurring at the gastric staple line and the other half at the duodenal anastomosis or stump [11].

Though the rates of major leaks have improved overall, they are still higher than other bariatric procedures. This may be because of the number of areas in which the gastrointestinal tract is divided. This reason—and the fact that the DS is frequently done in the super obese (BMI≥ 50 kg/m$^2$)—results in general acceptance of these increased risks.

As there are multiple potential points of leakage, the diagnosis is best achieved through a CT scan of the abdomen and pelvis with water-soluble oral contrast, though upper GI contrast studies are often useful and complementary. Intravenous contrast can be helpful but not always needed, especially if renal function is worsening. Duodenal stump leaks may need a nuclear biliary scan to diagnose them definitively.

The treatment of these leaks can be complex and may require multimodal staged therapy. The gastric staple line leaks are treated similar to sleeve gastrectomy leaks, which involves drainage, possible stent placement, distal feeding, and antibiotics. If the leak is small, and especially if presenting in a delayed fashion with an abscess, it can be treated with radiological drainage, antibiotics, and distal feeding or parenteral nutrition. Most of the duodenal area leaks reported in various series did require surgical intervention with drainage and distal feeding access, such as a jejunostomy tube in the biliopancreatic limb. Gastric decompression with a nasogastric (NG) tube is useful if the leak is from the duodenoileostomy, but an NG tube is not needed if the leak is from the duodenal stump. With these measures, most leaks will resolve with time.

### Venous Thromboembolism

Venous thromboembolism remains one of the main causes of mortality in the bariatric surgery patient. Deep vein thrombosis (DVT) has been reported in 0.3–3.5% of patients, and pulmonary embolism (PE) in up to 1.5% of patients [15–20]. These rates are predicted to be higher in patients undergoing the DS, as they tend to have higher BMI and more comorbidities.

In a series of 362 patients that underwent laparoscopic DS procedures, the DVT rate was 2.2% and PE rate was 1.1% [21]. In their protocol, patients received perioperative subcutaneous

heparin, including a dose preoperatively. Those with a BMI> 50 got extended prophylaxis for 2 weeks. Prophylactic inferior vena cava (IVC) filters were also placed in 28.2% of patients. This did not increase DVT rates, but it did result in increased operative time and length of stay [21]. Rabkin and collaborators published a combined DVT and PE rate of 1.5% in 345 patients [8]. In the two large series by Biertho and collaborators, the PE rates were 0.2–0.8% [10, 13]. These rates are either similar to or slightly higher than those reported for other bariatric procedures like the gastric bypass [22]. Given their higher BMI and more frequent comorbidities, patients undergoing DS are at higher risk for thromboembolism, and aggressive perioperative chemical prophylaxis is likely warranted.

## Bleeding

Given the more extensive nature of the DS procedure, bleeding rates were traditionally thought to be higher. In early series, especially the early laparoscopic experience, postoperative bleeding rates were as high as 6–10% [23–26]. The rates were reported to be lower in the open series, as shown in Table 1.

However, more recent series note a lower postoperative bleeding rate. In a series of 1000 DS procedures by Biertho and collaborators, the rates of bleeding were similar in the open and laparoscopic groups at around 0.5% [10]. Buchwald and collaborators reported a 1.6% rate of postoperative bleeding that required re-exploration in the operating room (3/190 patients) [32]. Biertho and coinvestigators reported a reoperation rate of 0.4% for bleeding (2/566 patients) [13]. Some of the variation in reported rates also may be related to whether they are reporting any bleeding, bleeding enough to require a transfusion or bleeding enough to require a procedure or an operation.

Bleeding can be intraluminal or intraperitoneal. As in other bariatric procedures, hematemesis and melena indicate a luminal bleed. These can be managed expectantly with fluid resuscitation and transfusion as needed but may require upper endoscopy for evaluation and management if bleeding persists. In a DS, only the gastric staple line and the duodenoileostomy will be reachable with a regular endoscope in the early postoperative period. Appropriate therapy with clipping or injection may be used if a bleeding area is identified. Cautery is generally avoided early postoperatively.

For hemodynamic instability or persistent bleeding, laparoscopic or open exploration may be needed for diagnosing and treating an intraperitoneal bleed.

## Early Bowel Obstruction

Early small bowel obstructions are more common after BPD-DS than other procedures. Hedberg and coinvestigators found early small bowel obstructions (SBO) in 2.9% (7/245) of BPD-DS patients and in 1.1% (3/271) of Roux-en-Y gastric bypass patients [14]. Rabkin and coinvestigators reported on rate of early SBO of 1.5% (5/345 patients), with 3 of the 5 requiring an operation. Biertho and coinvestigators reported a 0.5% rate of early SBO requiring surgery [8, 13]. Treatment depends on intraoperative findings and may involve revision of an anastomosis.

**Table 1: Complications of open and laparoscopic biliopancreatic diversion and duodenal switch procedures.**

| First author, year | PE % | Leak % | Bleeding % | Pancreatitis % | Delayed gastric emptying % | Wound infection/ dehiscence % | Marginal ulcer % | Stomal stenosis % | Incisional hernia % | Revisions for protein malnutrition % |
|---|---|---|---|---|---|---|---|---|---|---|
| *Open BPD-DS* | | | | | | | | | | |
| Marceau, 1998 [27] | 0.7 | 4.9 | – | 1.7 | 6.2 | 1 | 0 | – | – | 0.1% per year |
| Hess, 1998 [28] | 0.5 | 4 | 1.4 | – | – | – | 0 | – | – | 2.3 |
| Rabkin, 1998 [24] | 5.4 | 54. | – | 2.7 | – | 5.4 | – | – | 24 | 12.2 |
| Baltasar, 2001 [25] | 0.8 | 4 | 1.6 | 0 | – | 0.8 | – | – | 5.8 | 2.4 |
| Anthone, 2003 [29] | 0.6 | 0.7 | 0.7[a] | – | – | 0.7 | – | – | – | 5.7 |
| Dolan, 2003 [26] | 0 | 6.5 | 0 | 0 | 0 | –8 | – | – | 0 | – |
| *Laparoscopic BPD-DS* | | | | | | | | | | |
| Ren, 2000 [30] | 0 | 2.5 | 10 | 0 | 0 | 0 | – | – | – | – |
| Baltasar, 2002 [31] | 0 | 0 | 6.3 | – | 6.3 | 18.8 | – | – | – | – |
| Rabkin, 2003[a] [8] | 0.9 | 4.3 | – | – | – | – | – | 1.7 | – | – |
| Dolan, 2004 [26] | 0 | 6.6 | 6.6 | 3.3 | 0 | – | – | 0 | – | – |

Used with permission of Springer Science from Ren [23]
[a]Includes three splenectomies

### Miscellaneous Complications

There are several other rare complications that have been reported. These include myocardial infarction, pneumonia, pancreatitis or pancreatic leak, biliary leak, and acute renal failure. There are almost no reports of marginal ulcers after BPD-DS.

Gastric outlet obstruction from duodenoileostomy stenosis is possible but fortunately rare. In the early postoperative period, this can occur from technical error, as the duodenal diameter is small when making the anastomosis. Delayed stenosis can occur from ischemia, suture material, or a subclinical leak causing prolonged inflammation. Stricture may respond temporarily to dilation, but these stenoses frequently require surgical revision.

## Long-term Complications

### Internal Hernias

The internal hernias that can follow DS are similar to those seen after gastric bypass. Hernias can occur at the mesenteric defect of the ileoileostomy or under the free, cut edge of the mesentery of the Roux limb (Petersen defect). If the reconstruction is done retrocolic, a herniation between the Roux limb and the mesocolon is another potential site (Fig. 1a, b). While most surgeons close the ileoileostomy mesenteric defect, closing the Petersen defect is more controversial. Even when those potential hernia sites are closed, the defects can open again in a few months, as the mesentery becomes thinner with weight loss. There are minimal data regarding internal hernia after DS, but extrapolation can be made from large numbers of gastric bypass patients. The few studies that do report these findings don't always differentiate between internal hernias and postoperative

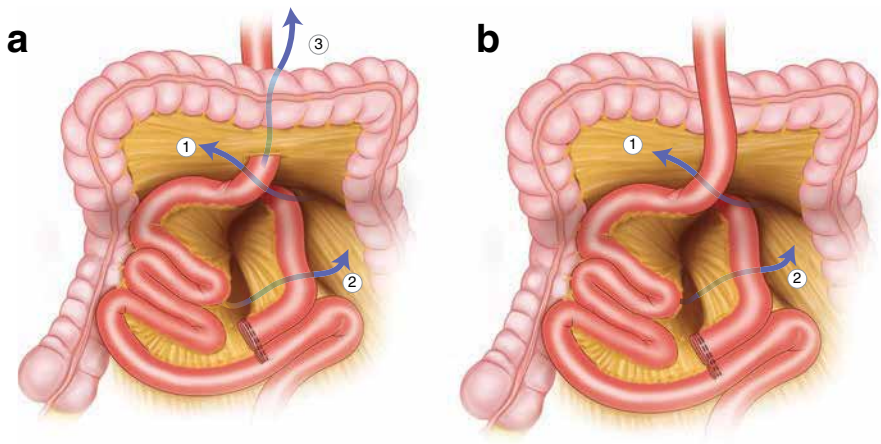



**Fig. 1:** (**a**, **b**) Sites of internal hernias: *1*. Petersen's defect. *2*. Ileoileostomy defect. *3*. Retrocolic mesenteric defect.

small bowel obstructions, but the rates seem similar to or slightly higher than gastric bypass patients [13, 14, 23, 33, 34].

Internal hernias commonly present with abdominal pain without nausea or vomiting. An increase in liver enzymes or bilirubin might indicate an obstruction of the biliopancreatic limb, in which case the patient might still be passing gas and having bowel movements. Biliopancreatic limb obstruction can progress rapidly to small bowel ischemia as the limb cannot be decompressed with a nasogastric tube. Duodenojejunal dilation can be detected on CT, and urgent surgical intervention is warranted. A delay in diagnosis can result in catastrophic complications, such as ischemia of a majority of small bowel. The surgeon must have a low threshold for returning to the operating room for exploration. In addition to the classic findings of small bowel obstruction on CT, mesenteric swirl is considered one of the best predictors of an internal hernia [35].

Usually surgical repair of an internal hernia can be achieved laparoscopically by evaluating the small bowel starting at the ileocecal valve and running it proximally toward the ileoileostomy, where the surgeon should assess for any bowel loops herniating through a mesenteric defect. If this is normal, the remainder of the small bowel should be inspected proximally up to the duodenoileostomy as well as the biliopancreatic limb. The surgeon should inspect for any small bowel herniating through the Petersen defect. Any identified mesenteric defects should be closed with a permanent suture. The authors use a 2–0 ethibond suture on an SH needle to repair mesenteric defects.

### Gastrointestinal Symptoms: Diarrhea, Bloating, and Steatorrhea

Duodenal switch is associated with substantial malabsorption of protein, fat, calcium, iron, and vitamins B12, A, D, E, and K, which can lead to foul-smelling stools and diarrhea. Intestinal bacterial overgrowth can occur despite the lack of a blind limb. Having malabsorption and undigested food can create an environment of bacterial overgrowth that can lead to symptoms such as abdominal bloating, diarrhea, and proctitis. A diet lower in protein and higher in carbohydrates can exacerbate this. Treatment with diet modification and antibiotics to treat bacterial overgrowth can be successful [23]. Persistent and refractory cases may have to be treated with a procedure to lengthen the common channel, which is described in the next section. Dumping syndrome is not common after duodenal switch, as the pylorus remains intact.

### Nutritional Deficiencies

Duodenal switch is associated with substantial malabsorption of macronutrients, which results in significant weight loss. Twenty-five percent of protein and 72% of fat are not absorbed, which can lead to diarrhea, protein-calorie malnutrition, and micronutrient malabsorption, including fat-soluble vitamins [36]. Secondary malabsorption can occur as a consequence of the decrease in gastrointestinal transit time and limited contact of food with the brush border in the shortened common channel [36].

## Protein Deficiencies

Giving the significant malabsorption that follows DS operations, protein-calorie malnutrition is possible. There are three components that can affect protein metabolism. These are the size of remaining stomach after gastrectomy, the length of the alimentary limb, and the length of the common channel [37]. Additional protein losses may occur from intestinal exposure to acid without buffering by bile and/or changes in intestinal and colonic flora, but these mechanisms are not well understood.

In the classic BPD, protein needs are thought to double over baseline. With the DS modification, including preservation of the pylorus and a larger residual stomach, protein requirements are less than for the traditional BPD. With preservation of pylorus, antropyloric titration of food passage, and lack of dumping syndrome, ingested protein is better prepared for absorption in the small bowel [37]. A slightly longer common channel, from 50 cm to 75–100 cm, also helps this.

The incidence of severe protein malnutrition following DS operations is reported to be around 3–4% [3, 5]. However, temporary hypoproteinemia can be detected in 10–20% of patients in the first year and improves later on as protein intake improves [38]. Symptoms of hypoproteinemia include edema, weight loss, fatigue, and skin, nail, and hair problems. Low albumin and serum total protein levels can be detected on laboratory testing.

Increased oral protein intake might be enough to reverse a mild protein deficiency. The recommended amount is at least 90 grams per day [37, 39]. Parenteral nutrition is needed in an estimated 3% of this patient population [40, 41].

If parenteral nutrition is consistently required, a revisional surgery to lengthen the common channel may be indicated. Revisional surgery for excessive malabsorption has been reported in 0.5–4.9% of patients after BPD-DS, which is lower than what is reported for BPD alone (3–18.5%) [42]. Revisional surgery has been reported more commonly when the common channel length is 50 cm, compared to 100 cm. Half of revisional surgery performed after DS is attributed to protein malnutrition. The most common revisional option involves lengthening of the common channel by at least 100 cm for BPD-DS and 150 cm for BPD [42]. This is shown in Fig. 2A, B.

Reversal can also be done as shown in Fig. 3A–D. Creating a side-to-side jejunoileostomy can be a simple way to reduce malabsorption as shown in option B in Fig. 3A–D.

## Micronutrient Deficiencies

Obese patients suffer from deficiencies in micronutrients even before any weight loss surgery. Special attention should be paid to detecting any deficiencies and correcting them preoperatively [43]. Significant numbers of vitamin and mineral deficiencies are found in DS patients, despite vitamin supplementation [26, 39].

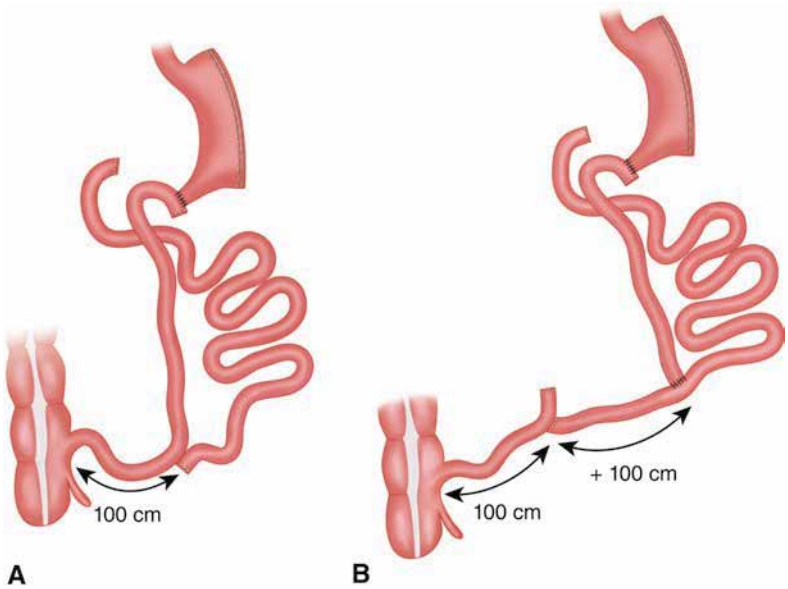



**Fig. 2:** (**A**, **B**) Common channel elongation after biliopancreatic diversion with duodenal switch. (**A**) Initial procedure. (**B**) Revisional procedure.

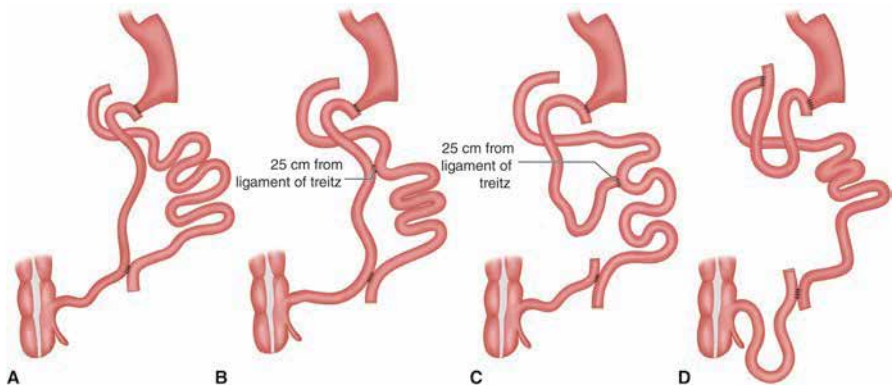



**Fig. 3:** (**A**–**D**) Restoration options after biliopancreatic diversion with duodenal switch. (**A**) Initial procedure. (**B**–**D**) Reversal options.

### *Fat-soluble Vitamins/Zinc*

Normal absorption of fat-soluble vitamins occurs passively in the upper small intestine. Given that fat malabsorption is associated with the DS, vitamins and minerals relying on fat metabolism, including vitamins D, A, E, K, and zinc, are affected [24].

*Vitamin A* deficiency is common after DS, present in an estimated 30–69% of patients [39, 44]. Despite this, clinical consequences such as night blindness are very rare. Recommended Vitamin A supplementation for DS patients is 10,000 IU/d [45].

*Vitamin D* deficiency is common. Studies have shown that up to 60% of patients have low Vitamin D levels at 4 years postoperatively [39, 44]. Osteoporosis may result from chronic Vitamin D deficiency, which is also exacerbated by poor calcium absorption. Recommended Vitamin D supplementation for DS patients is at least 3000 IU/d to maintain D,25 (OH) levels 4–30 ng/mL [45].

*Vitamin K* deficiency can occur in approximately 60% of patients [39, 44]. While low levels are commonly detected, it is not usually associated with clinically significant decreases in coagulation factor activity or bleeding [46]. Recommended Vitamin K supplementation for DS patients is 300 μg/d [45].

*Vitamin E* deficiency occurs in an estimated 5% or fewer patients [39]. Recommended Vitamin E supplementation for DS patients is 15 mg/d [45].

Since *zinc* is a nutrient that depends on fat absorption, it is common to have zinc deficiency after DS, with deficiencies noted in as many as 90% of patients. Zinc has a major role in cell growth and differentiation, and its deficiency can have significant effects on tissues with a rapid cell turnover, such as cells of the skin, gastrointestinal tract mucosa, and immune system [47]. Recommended zinc supplementation for DS patients is 16–22 mg/d [45].

Repletion recommendations for micronutrient deficiency can be found in Table 2.

### *Calcium*

Hypocalcemia is reported in up to 50% of patients following DS and is associated with increased serum parathyroid hormone values in almost 70% of patients. Hypocalcemia, in conjunction with Vitamin D deficiency, can be severe enough to cause osteoporosis. Evidence of increased bone resorption is noted in 3% of patients [39]. Recommended calcium supplementation for DS patients is 1800–2400 mg/d [45].

### *Iron/Copper/Selenium/Magnesium/Potassium*

Absorption of iron is most efficient in the duodenum and proximal jejunum. While iron deficiency after DS is multifactorial, bypassing the duodenum is a major contributing factor. Iron deficiency is present in 40% of DS patients [44]. Iron deficiency is usually asymptomatic unless it is significant enough to cause anemia, which would present with fatigue and a diminished capacity to exercise. Recommended iron supplementation for DS patients is 45–60 mg of elemental iron daily [45]. Taking Vitamin C with iron increases absorption.

### *Copper, Selenium, and Magnesium*

Copper is absorbed by the stomach and proximal small bowel. Copper deficiency is present in an estimated 90% of DS patients. Deficiencies in copper can cause anemia and myelopathy, with

**Table 2: Repletion recommendations for post-WLS micronutrient deficiency.**

| |
|---|
| *Thiamine* |
| Practitioners should treat post-WLS patients with suspected thiamine deficiency before or in the absence of laboratory confirmation of deficiency and monitor and evaluate resolution of signs and symptoms (Grade C, BEL 3) √ |
| Repletion dose for TD varies based on route of administration and severity of symptoms: |
| Oral therapy: 100 mg two to three times daily until symptoms resolve (Grade D, BEL 4) √ |
| IV therapy: 200 mg three times daily to 500 mg once or twice daily for 3–5 d, followed by 250 mg/d for 3–5 d or until symptoms resolve, then consider treatment with 100 mg/d orally, usually indefinitely or until risk factors have been resolved (Grade D, BEL, 4) √ |
| IM therapy: 250 mg once daily for 3–5 d or 100–250 mg monthly (Grade C, BEL 3) √ |
| Simultaneous administration of magnesium, potassium, and phosphorus should be given to patients at risk for refeeding syndrome (Grade C, BEL 3) √ |
| *Vitamin B12 (cobalamin)* |
| Post-WLS patients with B12 deficiency should take 1000 µg/d to achieve normal levels and then resume dosages recommended to maintain normal levels (Grade B, BEL 2) √ |
| *Folate (folic acid)* |
| All post-WLS patients with folate deficiency should take an oral dose of 1000 µg of folate daily to achieve normal levels and then resume recommended dosage to maintain normal levels (Grade B, BEL 2)√ |
| Folate supplementation above 1 mg/d is not recommended in post-WLS patients because of the potential masking of vitamin B12 deficiency (Grade B, BEL 2) |
| *Iron* |
| In post-WLS patients with post-WLS iron deficiency, oral supplementation should be increased to provide 150–200 mg of elemental iron daily to amounts as high as 300 mg two to three times daily (Grade C, BEL 3) |
| Oral supplementation should be taken in divided doses separately from calcium supplements, acid-reducing medications, and foods high in phytates or polyphenols (Grade D, BEL 3). Recommendation is downgraded to D, since majority of evidence is from non-WLS patients |
| If iron deficiency does not respond to oral therapy, intravenous iron infusion should be administered (Grade C, BEL 3) |
| *Vitamin D and calcium* |
| Vitamin D levels must be repleted if deficient or insufficient to normalize calcium (grade C, BEL 3) √ |
| All post-WLS patients with Vitamin D deficiency or insufficiency should be repleted with the following doses: |
| Vitamin D3 at least 3000 IU/d and as high as 6000 IU/d, or 50,000 IU, Vitamin D2 one to three times weekly (Grade A, bel 1)√ |
| Vitamin D3 is recommended as a more potent treatment than Vitamin D2 when comparing frequency and amount needed for repletion. However, both forms can be efficacious, depending on the dosing regimen (Grade A, BEL 1) √ |
| The recommendations for repletion of calcium deficiency varies by surgical procedure (Grade C, BEL 3): |
| BPD/DS: 1800–2400 mg/d calcium |
| LAGB, SG, RYGB: 1200–1500 mg/d calcium √ |

(Cont'd...)

(...Cont'd.)

| |
|---|
| *Vitamin A* |
| In post-WLS patients with Vitamin A deficiency without corneal changes, a dose of Vitamin A 10,000–25,000 IU/d should be administered orally until clinical improvement is evident (1–2 wk) (Grade D, BEL 4) |
| In post-WLS patients with Vitamin A deficiency with corneal changes, a dose of Vitamin A 50,000–100,000 IU should be administered IM for 3 d, followed by 50,000 IU/d IM for 2 wk. (Grade D, BEL 4) |
| Post-WLS patients with Vitamin A deficiency should also be evaluated for concurrent iron and/or copper deficiencies because these can impair resolution of Vitamin A deficiency (Grade D, BEL 4) |
| *Vitamin E* |
| The optimal therapeutic dose of Vitamin E in post-WLS patients has not been clearly defined. There is potential for antioxidant benefits of Vitamin E to be achieved with supplements of 100–400 IU/d. This is higher than the amount typically found in a multivitamin; thus, additional Vitamin E supplementation may be required for repletion (Grade D, BEL 4) |
| *Vitamin K* |
| For post-WLS patients with acute malabsorption, a parenteral dose of 10 mg Vitamin K is recommended (Grade D, BEL 4) |
| For post-WLS patients with chronic malabsorption, the recommended dosage of Vitamin K is either 1–2 mg/d orally or 1–2 mg/wk. parenterally (Grade D, BEL 4) |
| *Zinc* |
| There is insufficient evidence to make a dose-related recommendation for repletion. The previous recommendation of 60 mg elemental zinc orally twice a day needs to be reevaluated in light of emerging research that this dose may be inappropriate |
| Repletion doses of zinc in post-WLS patients should be chosen carefully to avoid inducing a copper deficiency (Grade D, BEL 3)√ |
| Zinc status should be routinely monitored using consistent parameters throughout the course of treatment (Grade C, BEL 3)√ |
| *Copper* |
| In post-WLS patients with copper deficiency, the recommended regimen for repletion of copper will vary with the severity of the deficiency (Grade C, BEL 3) √: |
| Mild to moderate deficiency (including low hematologic indices): Treat with 3–8 mg/d oral copper gluconate or sulfate until indices return to normal |
| Severe deficiency: 2–4 mg/d intravenous copper can be initiated for 6 d or until serum levels return to normal and neurologic symptoms resolve |
| Once copper levels are normal, monitor copper levels every 3 mo (Grade C, BEL 3) √ |

Used with permission from Buchwald *et al*. [5] and Parrott *et al*. [45]
*WLS* weight loss surgery, *BEL* best evidence level, *TD* thiamine deficiency, *IV* intravenous, *IM* intramuscular, *BPD/DS* biliopancreatic diversion/duodenal switch, *LAGB* laparoscopic adjustable gastric band, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass
√: New recommendation since Aills *et al*. [36] is noted by √; otherwise, there is no change in the current recommendation

symptoms similar to those of Vitamin B12 deficiency. Copper deficiency should be considered in any DS patient who presents with signs and symptoms of neuropathy but who has normal B12 levels [36]. Recommended copper supplementation for DS patients is 4 mg/d [45].

Multiple studies have found decreased selenium, magnesium, and potassium levels following bariatric surgery. All these studies highlight the importance of multivitamin supplements that are complete in minerals [26, 48, 49].

### *Water-soluble Vitamins : Vitamins B1, B6, and B12 and Folate*

*Thiamine* (Vitamin B1) is absorbed primarily in the duodenum and proximal jejunum [50], which puts DS patients at a particularly high risk, as their alimentary path bypasses these absorptive territories. The body's store of thiamine may be depleted in 18–20 days. Deficiency can be exacerbated by postoperative vomiting.

Thiamine deficiency often presents with symptoms of peripheral neuropathy or Wernicke's encephalopathy and Korsakoff's psychosis [51]. The incidence of this rare complication is largely unknown, but more than 30 cases of Wernicke's encephalopathy have been reported following different bariatric procedures [52]. Intravenous solutions containing glucose without thiamine or other vitamins might deplete the remaining available thiamine and precipitate Korsakoff's syndrome. Recommended thiamine supplementation for DS patients is at least 12 mg thiamine daily [45].

*Vitamin B12* deficiency can lead to macrocytic anemia or may present with polyneuropathy, paresthesia, or permanent neural impairment. With a significant decrease in hydrochloric acid, pepsinogen is not converted into pepsin, which is necessary for the release of Vitamin B12. While B12 stores are known to exist for long periods (3–5 years), some studies have predicted that B12 deficiency might occur 8 months after DS [53]. Recommended B12 supplementation for DS patients is 350–500 micrograms daily orally by disintegrating tablet, sublingual, or liquid [45].

*Folate* absorption occurs preferentially in the proximal portion of the small intestine. Malabsorption and low oral intake caused by DS operations can result in folate deficiency. Folic acid stores can be depleted within a few months after surgery. Most patients who are folate deficient are asymptomatic, but chronic deficiency can lead to macrocytic anemia. Recommended folate supplementation for DS patients is 400–800 micrograms oral folate daily. A multivitamin is enough to correct this deficiency in most bariatric patients [45].

*Vitamin B6* is not routinely measured so little information is available about its changes following DS operations. Vitamin B6 deficiency is rare but can be caused by malabsorption and low oral intake associated with DS operations. Symptoms of B6 deficiency include anemia, weakness, insomnia, cheilosis, and stomatitis. Normal range is 5–24 ng/mL. Treatment dose is 50 mg/d [36]

Repletion recommendations for post weight loss surgery micronutrient deficiency can be found in Table 2.

## Single-anastomosis Duodeno-ileal Bypass with Sleeve Gastrectomy (SADI-S)

The single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) includes the creation of a sleeve gastrectomy but replaces the Roux-en-Y reconstruction of the DS with a single

anastomosis consisting of a duodenoileostomy. Common channel length is usually 200 cm in SADI, though the operation originally was described with a 250 cm common channel [54]. New modifications have been described that include creating a smaller sleeve gastrectomy and a longer 300 cm common channel to maximize gastric restriction and minimize malabsorption [55]. This has been called stomach intestinal pylorus sparing surgery (SIPS) [56]. There are limited data regarding long-term nutritional effects of SADI, but the combination of a tighter sleeve combined with malabsorption might put SADI patients at higher risk for the aforementioned nutritional complications. Special attention should be made to assure appropriate supplementation as previously described. See Fig. 4.

Short-term results are encouraging. Surve and coinvestigators compared their experience of 62 BPD-DS patients vs 120 SIPS patients. In the BPD-DS group, they reported rates of 3.2% for anastomotic leak, 3.2% for postoperative bleeding, 1.6% for duodenal stump leak, and 1.6% for

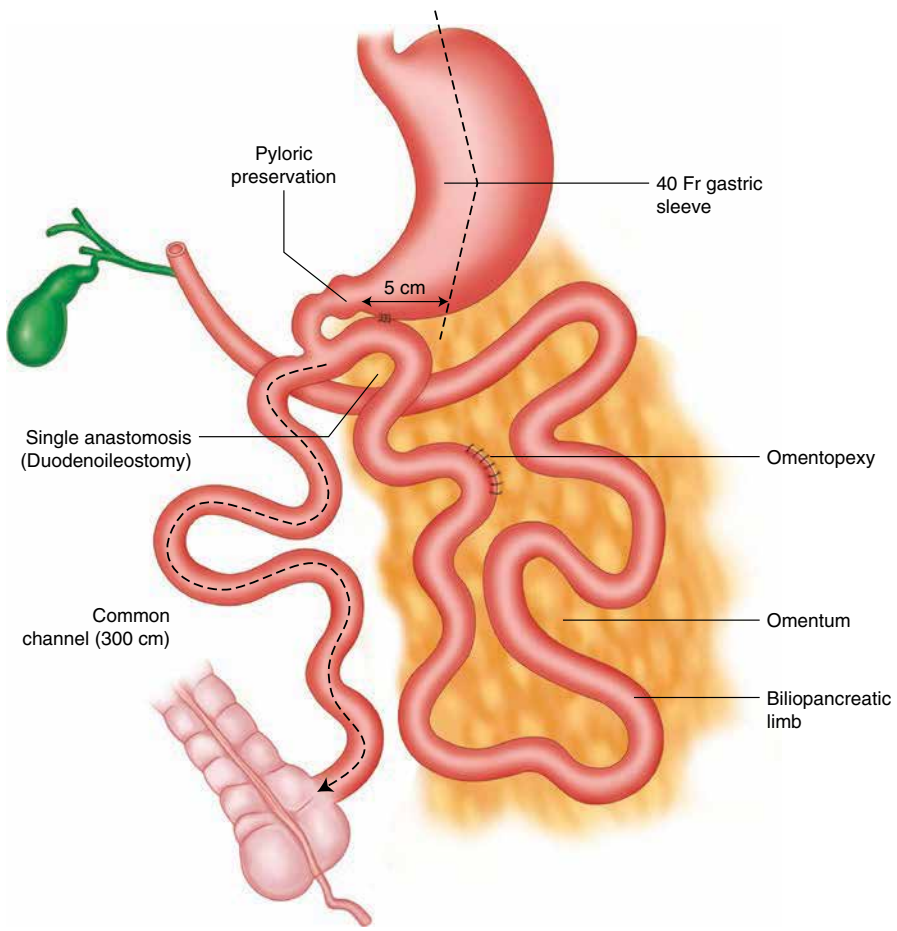



**Fig. 4:** Stomach intestinal pylorus sparing surgery (SIPS).

postoperative SBO rate, while the SIPS group had a 0% rate for all these complications. They do admit, however, that the BPD-DS procedures were associated with a learning curve, and the SIPS procedures were performed following their experience with the BPD-DS [56]. With respect to long-term complications (up to 24 months), diarrhea was reported in 11.2% and malnutrition in 8% of BPD-DS patients. In SIPS patients, both were reported as only 0.8% each. There were no significant differences in vitamin and mineral levels checked at 2 years [56].

Topart and coinvestigators recently published a review of the current literature on SADI or SIPS patients and found a total of 1041 patients from 9 institutions. Early data on excess weight loss appear similar to or slightly less than the BPD-DS, with the mean EWL (excess weight loss) of 78% at 1 year with SADI [57]. There were no deaths reported and a very low overall reoperation rate in most of the series [57]. There is a pending randomized trial comparing SADI and BPD-DS.

## References


1. DeMeester TR, Fuchs K, Ball C, *et al*. Experimental and clinical results with proximal end-to-end duodenojejunostomy for pathologic duodenogastric reflux. Ann Surg. 1987;206(4):414–26.
2. Scopinaro N, Gianetta E, Civalleri D, *et al*. Bilio-pancreatic bypass for obesity: II.Initial experience in man. Br J Surg. 1979;66(9):618–20.
3. Angrisani L, Santonicola A, Iovino P, *et al*. Bariatric surgery worldwide 2013. Obes Surg. 2015;25(10):1822–32.
4. Kim WW, Gagner M, Kini S, *et al*. Laparoscopic vs. open biliopancreatic diversion with duodenal switch: a comparative study. J Gastrointest Surg. 2003;7:552–7.
5. Buchwald H, Estok R, Fahrbach K, *et al*. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. Surgery. 2007;142:621–35.
6. Weiner RA, Blanco-Engert R, Weiner S, *et al*. Laparoscopic biliopancreatic diversion with duodenal switch: three different duodeno-ileal anastomotic techniques and initial experience. Obes Surg. 2004;14:334–40.
7. Parikh MS, Shen R, Weiner M, *et al*. Laparoscopic bariatric surgery in super-obese patients (BMI _50) is safe and effective: a review of 332 patients. Obes Surg. 2005;15:858–63.
8. Rabkin RA, Rabkin JM, Metcalf B, *et al*. Laparoscopic technique for performing duodenal switch with gastric reduction. Obes Surg. 2003;13:263–8.
9. Prachand VN, DaVee RT, Alverdy JC. Duodenal switch provides superior weight loss in the super-obese (BMI _50 kg/m$^2$) compared with gastric bypass. Ann Surg. 2006;244:611–9.
10. Biertho L, Lebel S, Marceau S, *et al*. Perioperative complications in a consecutive series of 1000 duodenal switches. Surg Obes Relat Dis. 2013;9:63–8.
11. Magee CJ, Barry J, Brocklejurst J, *et al*. Outcome of laparoscopic duodenal switch for morbid obesity. Br J Surg. 2011;98:79–84.
12. Baltasar A, Serra C, Perez N, *et al*. Laparoscopic sleeve gastrectomy: a multi-purpose bariatric operation. Obes Surg. 2005;15:1124–8.
13. Biertho L, Simon-Hould F, Marceau S, *et al*. Current outcomes of laparoscopic duodenal switch. Ann Surg Innov Res. 2016;10:1.
14. Hedberg J, Sundstrom J, Sundbom M. Duodenal switch versus roux-en-Y gastric bypass for morbid obesity: systematic review and meta-analysis of weight results, diabetes resolution and early complications in single-centre comparisons. Obes Rev. 2014;15:555–63.
15. Abou-Nukta F, Alkhoury F, Arroyo K, *et al*. Clinical pulmonary embolus after gastric bypass surgery. Surg Obes Relat Dis. 2006;2:24–8.
16. Carmody BJ, Sugerman HJ, Kellum JM, *et al*. Pulmonary embolism complicating bariatric surgery: detailed analysis of a single institution's 24-year experience. J Am Coll Surg. 2006;203:831–7.
17. Gonzalez QH, Tishler DS, Plata-Munoz JJ, *et al*. Incidence of clinically evident deep venous thrombosis after laparoscopic roux-en-Y gastric bypass. Surg Endosc. 2004;18:1082–4.
18. Gonzalez R, Haines K, Nelson LG, Gallagher SF, Murr MM. Predictive factors of thromboembolic events in patients undergoing roux-en-Y gastric bypass. Surg Obes Relat Dis. 2006;2:30–5.

19. Prystowsky JB, Morasch MD, Eskandari MK, Hungness ES, Nagle AP. Prospective analysis of the incidence of deep venous thrombosis in bariatric surgery patients. Surgery. 2005;138:759–63.
20. Sapala JA, Wood MH, Schuhknecht MP, Sapala MA. Fatal pulmonary embolism after bariatric operations for morbid obesity: a 24-year retrospective analysis. Obes Surg. 2003;13:819–25.
21. Rezvani M, Sucandy I, Das R, *et al*. Venous thromboembolism after laparoscopic biliopancreatic diversion with duodenal switch: analysis of 362 patients. Surg Obes Relat Dis. 2014;10:469–73.
22. Chan MM, Hamza N, Ammori BJ. Duration of surgery independently influences risk of venous thromboembolism after laparoscopic bariatric surgery. Surg Obes Relat Dis. 2013;9:88–93.
23. Ren CJ. Laparoscopic malabsorption procedures: complications. In: Schauer PR, Schirmer BD, Brethauer SA, editors. Minimally invasive bariatric surgery. New York: Springer Science; 2007.
24. Rabkin RA. Distal gastric bypass/duodenal switch procedure, Roux en Y gastric bypass and biliopancreatic diversion in a community practice. Obes Surg. 1998;8:53–9.
25. Balatasar A, Bou R, Bengochea M, *et al*. Duodenal switch: an eggective therapy for morbid obesity-intermediate results. Obes Surg. 2001;11:54–8.
26. Dolan K, Hazifotis M, Newbury L, *et al*. A clinical and nutritional comparison of biliopancreatic diversion with and without duodenal switch. Ann Surg. 2004;240(1):51–6.
27. Marceau P, Hould FS, Simard S, *et al*. Biliopancreatic diversion with duodenal switch. World J Surg. 1998;22:947–54.
28. Hess DS, Hess DW. Biliopancreatic diversion with duodenal switch. Obes Surg. 1998;8:267–82.
29. Chapter 22.5 - laparoscopic malabsorption procedures: complications. In: Schauer PR, Shirmer BD, Brethauer SA, editors. Minimally invasive bariatric surgery. New York: Springer Science; (2007). (9, 23, 25–32).
30. Ren CJ, Patterson E, Gagner M. Early results of laparoscopic biliopancreatic diversion with duodenal switch for morbid obesity: a case series of 40 consecutive patients. Obes Surg. 2000;10:514–23.
31. Baltasar A, Bou R, Miro J, *et al*. Laparoscopic biliopancreatic diversion with duodenal switch: technique and initial experience. Obes Surg. 2002;12:245–8.
32. Buchwald H, Kellogg TA, Leslie DB, *et al*. Duodenal switch operative mortality and morbidity are not impacted by body mass index. Ann Surg. 2008;248(4):541–8.
33. Rissstad H, Sovik TT, Engstrom M, *et al*. Five-year outcomes after laparoscopic gastric bypass and laparoscopic duodenal switch in patients with body mass index of 50 to 60: a randomized clinical trial. JAMA Surg. 2015;150(4):352–61.
34. Kim Y, Crookes PF. Complications of bariatric surgery. In: Huang C-K, editor. Essentials and controversies in bariatric surgery: InTech; 2014.
35. Lockhart ME, Tessler FN, Canon CL, Smith JK, Larrison MC, Fineberg NS, Roy BP, Clements RH. Internal hernia after gastric bypass: sensitivity and specificity of seven CT signs with surgical correlation and controls. Am J Roentgenol. 2007;188:745–50.
36. Allied Health Sciences Section Ad Hoc Nutrition Committee, Aills L, Blankenship J, *et al*. ASMBS allied health nutritional guidelines for the surgical weight loss patient. Surg Obes Relat Dis. 2008;4:S73.
37. Picard M, Frédéric Simon H, Stefane L, *et al*. Complications of combined gastric restrictive and malabsorptive procedures: Part 2. Curr Surg 2003;60(3):274–279; discussion 279–8.
38. Strain GW, Torghabeh MH, Gangner M, *et al*. The impact of biliopancreatic diversion with duodenal switch (BPD/DS) over 9 years. Obes Surg. 2017;27:787–94.
39. Slater GH, Ren CJ, Seigel N, *et al*. Serum fat-soluble vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery. J Gastrointest Surg. 2004;8:48–55.
40. Gracia JA, Martínez M, Elia M, Aguilella V, Royo P, Jiménez A, Bielsa MA, Arribas D. Obesity surgery results depending on technique performed: long-term outcome. Obes Surg. 2009;19(4):432–8.
41. Ballesteros-Pomar MD, González de Francisco T, Urioste-Fondo A, González-Herraez L, Calleja-Fernández A, Vidal-Casariego A, Simó-Fernández V, Cano-Rodríguez I. Biliopancreatic diversion for severe obesity: long-term effectiveness and nutritional complications. Obes Surg. 2016;26(1):38–44.
42. Topart T, Becouarn G. Revision and reversal after biliopancreatic diversion for excessive side effects or ineffective weight loss: a review of the current literature on indications and procedures. Surg Obes Relat Dis. 2015;11(4):965–72.
43. Tucker ON, Szomstein S, Rosenthal RJ. Nutritional consequences of weight-loss surgery. Med Clin N Am. 2007;91:499–514.
44. Homan J, Betzel B, Aarts EO, *et al*. Vitamin and mineral deficiencies after biliopancreatic diversion and biliopancreatic diversion with duodenal switch-the rule rather than the exception. Obes Surg. 2015;25(9):1626–32.
45. Parrott J, *et al*. American society for metabolic and bariatric surgery integrated health nutritional guidelines for the surgical weight loss patient 2016 update: micronutrients. Surg Obes Relat Dis. 2017;13(5):727–41.

46. Homan J, Ruinemans-Koerts J, Aarts EO, Janssen IM, Berends FJ, de Boer H. Management of vitamin K deficiency after biliopancreatic diversion with or without duodenal switch. Surg obes Relat Dis: official journal of the American Society for Bariatric Surgery. 2016;12(2):338–44.
47. Sallé A, Demarsy D, Poirier AL, *et al*. Zinc deficiency: a frequent and underestimated complication after bariatric surgery. Obes Surg. 2010;20:1660.
48. Schauer PR, Ikramuddin S, Gourash W, Ramanthan R, Luketich J. Outcomes after laparoscopic roux-en-Y gastric bypass for morbid obesity. Ann Surg. 2000;232:515–29.
49. Crowley LV, Seay J, Mullin G. Late effects of gastric bypass for obesity. Am J Gastroenterol. 1984;79:850–60.
50. Iannelli A, Addeo P, Novellas S, Gugenheim J. Wernicke's encephalopathy after laparoscopic Roux-en-Y gastric bypass: a misdiagnosed complication. Obes Surg. 2010;20(11):1594.
51. Gollobin C, Marcus WY. Bariatric beriberi. Obes Surg. 2002;12:309–11.
52. Singh S, Kumar A. Wernicke encephalopathy after obesity surgery: a systematic review. Neurology. 2007;68: 807–11.
53. Skroubis G, Sakellarapoulos G, Pouggouras K. Comparison of nutritional deficiencies after Roux-en-Y gastric bypass and biliopancreatic diversion with Roux-en-Y gastric bypass. Obes Surg. 2002;12:551–8.
54. Sánchez-Pernaute A, Rubio MA, Pérez-Aguirre E, *et al*. Single-anastomosis duodenoileal bypass with sleeve gastrectomy: metabolic improvement and weight loss in first 100 patients. Surg Obes Relat Dis. 2013;9(5):731–5.
55. Cottam A, Cottam D, Medlin W, *et al*. A matched cohort analysis of single anastomosis loop duodenal switch versus Roux-en-Y gastric bypass with 18-month follow-up. Surg Endosc. 2016;30(9):3958–64.
56. Surve A, Zaveri H, Cottam D, *et al*. A retrospective comparison of biliopancreatic diversion with duodenal switch with single anastomosis duodenal switch (SIPS-stomach intestinal pylorus sparing surgery) at a single institution with two year follow-up. Surg Obes Relat Dis. 2017;13:415–22.
57. Topart P, Becouarn G. The single anastomosis duodenal switch modifications: a review of the current literature on outcomes. Surgery for Obesity and Related. 2017;13(8):1306–12.

---

Source: Tariq N., Kudsi J. (2018) Complications of Biliopancreatic Diversion and Duodenal Switch. In: Reavis K., Barrett A., Kroh M. (eds) The SAGES Manual of Bariatric Surgery. Springer, Cham. https://doi.org/10.1007/978-3-319-71282-6_34. 

2

# Supplementation with branched-chain amino acids ameliorates hypoalbuminemia, prevents sarcopenia, and reduces fat accumulation in the skeletal muscles of patients with liver cirrhosis

**Yoichiro Kitajima[1,3], Hirokazu Takahashi[1], Takumi Akiyama[1], Kenichiro Murayama[1], Shinji Iwane[1], Takuya Kuwashiro[1], Kenichi Tanaka[1], Seiji Kawazoe[4], Naofumi Ono[3], Takahisa Eguchi[3], Keizo Anzai[1], Yuichiro Eguchi[2]**

## Abstract

*Background* Liver cirrhosis induces marked metabolic disorders, protein-energy malnutrition, and sarcopenia. The objective of the study reported here was to investigate the effects of dietary branched-chain amino acids (BCAAs) on systemic glucose metabolism, skeletal muscle, and prognosis of patients with liver cirrhosis.

*Methods* Japanese patients with liver cirrhosis ($n = 21$) were enrolled into a longitudinal study in which their diets were supplemented with BCAAs. We evaluated glucose metabolism and analyzed the skeletal muscle area index (SAI) and intramuscular adipose tissue content (IMAC) using computed tomography.

*Results* After 48 weeks of supplementation with BCAAs, there were no changes in glucose metabolism and skeletal muscle findings. In patients with ameliorated hypoalbuminemia, IMAC was significantly decreased and SAI was preserved concomitant with decreasing 90- and 120-min post-challenge plasma glucose levels ($P < 0.01$ each). In patients without increased albumin levels, IMAC was significantly increased and the SAI was significantly decreased ($P < 0.01$ each). Liver-related event-free survival rates for 72 months were 63.6% in patients with decreased IMAC and 20.0% in patients with increased IMAC.

**Yuichiro Eguchi (✉)**
eguchiyu@cc.saga-u.ac.jp
[1]Division of Metabolism and Endocrinology, Faculty of Medicine, Saga University, Saga, Japan
[2]Liver Center, Saga Medical School, Saga, Japan
[3]Department of Clinical Gastroenterology, Eguchi Hospital, Ogi, Japan
[4]Hepatobiliary and Pancreatology Division, Department of Internal Medicine, Saga Prefectural Hospital Kosei-kan, Saga, Japan

*Conclusions* Amelioration of hypoalbuminemia associated with BCAA supplementation correlated with decreased fat accumulation in skeletal muscle, maintenance of skeletal muscle mass, and improved glucose sensitivity, all factors which may contribute to improving the survival of patients with liver cirrhosis.

**Keywords:** Branched-chain amino acids, Skeletal muscle steatosis, Sarcopenia, Liver cirrhosis

## Introduction

Hypoalbuminemia is an important factor that affects the quality of life (QOL) and vital prognosis of patients with decompensated liver cirrhosis [1–3]. Protein and energy malnutrition (PEM) frequently occurs in patients with liver cirrhosis and causes hypoalbuminemia associated with decreased levels of branched-chain amino acids (BCAAs) [4–7]. Dietary supplementation with BCAAs ameliorates hypoalbuminemia and contributes to improved event-free survival rates of patients with liver cirrhosis [8–10].

Glucose sensitivity is improved by administering a BCAA granule preparation to patients with liver cirrhosis [11–13]. A large-scale clinical study on the efficacy of using BCAA granule supplementation for decompensated liver cirrhosis (LOTUS study) showed that the BCAA preparation reduced the risk of liver cancer for patients with liver cirrhosis accompanied by obesity and insulin resistance, which are potential risk factors for liver cancer [3]. There is evidence indicating that the effect of BCAAs on glucose metabolism can be attributed to the induction of glucose transporter translocation to the cell membrane, which occurs mainly in skeletal muscle, and to increased glucose uptake through increased glycogen synthesis [14]. Inhibition of the postprandial blood glucose level increase may prevent excess release of insulin from pancreatic islets.

Skeletal muscle likely plays an important role in glucose metabolism in patients with liver cirrhosis as well as in healthy individuals [14]. The loss of skeletal muscle (sarcopenia) is known to be a common comorbidity that is associated with liver cirrhosis [15, 16]. Therefore, we hypothesized that dietary supplementation with BCAAs would mediate glucose metabolism to improve the condition of skeletal muscle and improve the prognosis of patients with liver cirrhosis. To obtain evidence supporting hypothesis, we used noninvasive computed tomography (CT) to quantify fat accumulation in skeletal muscle and skeletal muscle mass with the aim to evaluate the associations among fat accumulation in skeletal muscle and skeletal muscle mass, and sarcopenic obesity in patients with chronic liver diseases [17–19]. The aim of our study was to assess the effects of BCAAs on skeletal muscle findings, glucose metabolism, and the prognosis of patients with liver cirrhosis.

## Methods

### Study Design

Saga Medical School, Saga Prefectural Hospital Kosei-kan, and Eguchi Hospital participated in this study, which was named the "BCAA effect on Insulin resistance of liver cirrhosis in Saga

medical school, Kosei-kan hospital, and Eguchi hospital Trial" (BISKET). Patients who had liver cirrhosis with serum albumin levels of ≤3.5 g/dL were eligible for enrolment in this study. Exclusion criteria were: (1) administration of BCAA supplementation within 6 months before enrollment; (2) congenital abnormality of branched-chain amino acid metabolism; (3) abnormality of amino acid metabolism other than hepatopathy; (4) severe diabetes or suspected abnormality of glucose metabolism in patients treated with high-dose steroids; (5) history of liver cancer and current liver cancer.

### Intervention Protocol

Patients first underwent physical examinations, serum biochemistry analyses, and CT screening to obtain and evaluate their baseline characteristics. Patients orally ingested one packet of BCAA granules three times daily after meals. Each packet of BCAA (Livact Granules; Ajinomoto Co., Inc., Tokyo, Japan) contained 952 mg L-isoleucine, 1904 mg L-leucine, and 1144 mg L-valine. A dietician instructed the patients to adjust their total energy intake to 25–35 kcal/kg/day and their protein intake to 1.0–1.4 kg/day, according to the guidelines established by the European Society for Parenteral and Enteral Nutrition [19]. Adherence to BCAA supplementation was evaluated monthly for 48 weeks using interviews and a set of questionnaire. Patient prognosis was retrospectively observed after the 48-week intervention with BCAA.

### Patients

Each patient provided written informed consent to participate in the clinical study. The Ethics Committee of each participating institution approved this study, which was performed in accordance with the principles of the 1975 Declaration of Helsinki. The study was performed between January 2009 and January 2013. A total of 23 patients were ultimately enrolled in the study, of whom two were excluded from statistical analysis (one due to the development of hepatocellular carcinoma and the other due to termination of participation in the study) [Electronic Supplementary Material (ESM) Fig. S1].

### Physical Examinations and Serum Biochemistry

Body weight and height were measured, and body mass index (BMI) was calculated as the body weight in kilograms divided by the square of height in meters. Venous blood samples were taken at approximately 0900 hours after a 12-h overnight fast. Blood samples for the 75-g oral glucose tolerance test (OGTT) were taken at 0, 30, 60, 90, and 120 min to measure plasma glucose concentrations. Aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, total cholesterol, triglycerides, albumin, total bilirubin, platelet count, blood urea nitrogen (BUN), creatinine, ammonia, branched-chain amino acid-to-tyrosine ratio (BTR), fasting plasma glucose, and fasting plasma insulin (FPI) were determined using enzyme immunoassays. Insulin resistance was calculated using the homeostasis model of assessment–insulin resistance (HOMA-IR),

which primarily reflects hepatic insulin resistance (HOMA-IR = fasting plasma insulin × fasting plasma glucose/405) [20]. The quantitative insulin sensitivity check index (QUICKI) was determined as a marker of skeletal muscle insulin resistance using the formula QUICKI = 1/(log fasting plasma insulin + log fasting plasma glucose) [21].

### Abdominal CT Protocol and Data Assessment

Unenhanced spiral images of the liver were acquired during a breath-hold, using the following settings: 20.0-mm collimation, 27.5-mm/rotation table speed (helical pitch 1.375:1), 120 kV (p), and auto mA (Bright Speed ELITE SD; GE Healthcare, WI, U.S.A.). Images were reconstructed at 10-mm intervals. All patients underwent abdominal CT in the morning after a 12-h overnight fast. CT regions of interest (ROIs; 40 $mm^2$) were placed along the peripheries of the liver and spleen, away from major vessels, at five points in each organ. The mean values of five ROIs (Hounsfield units) were used to determine the liver–spleen attenuation ratio as an index of hepatic fat accumulation [22, 23]. The subcutaneous fat area (SFA; $cm^2$) and visceral fat area (VFA; $cm^2$) were calculated using Fat Scan software according to measurements taken at the umbilical level (N2 System Co., Osaka, Japan) [24].

### Computed Tomography Analysis of the Lumbar Muscle

The lumbar muscle of a 45-year-old man is shown in Fig. 1. Subfascial muscular tissue in the lumbar muscle was traced on umbilical-level cross-sectional CT images. CT values (Hounsfield units) and the area ($cm^2$) were measured using Advantage Workstation 4.3 software (GE Healthcare, Chicago, IL) in five 60-$mm^2$ ROIs of subcutaneous fat that were located at a distance from major vessels. The mean values were used to determine the lumbar muscle-to-fat attenuation ratio, which was designated the intramuscular adipose tissue content (IMAC) [17, 18]. The skeletal muscle area index (SAI) was calculated as the abdominal lumbar muscle area ($cm^2$) divided by the square of the height in meters to adjust for differences in physique. This normalization procedure, i.e., dividing by the square of the height, was performed in previous studies to obtain the skeletal muscle index [SMI; skeletal muscle weight (kg)/square of the height in meters], which was measured using bioelectrical impedance analysis [25, 26]. It has also been reported that SMI correlates with dual-energy X-ray absorptiometry and imaging procedures [27, 28]. We confirmed the significant positive correlation among SAI, SMI, and CT-measured skeletal muscle volume in the 26 patients who underwent bioelectrical impedance analysis in this study (ESM Fig. S2). Blood sampling and CT scans were performed at baseline and at 24 and 48 weeks after BCAA supplementation.

### Statistical analysis

Descriptive statistics (mean and standard deviations) were calculated for all continuous variables. Differences between the two groups were compared using the Mann–Whitney test. The

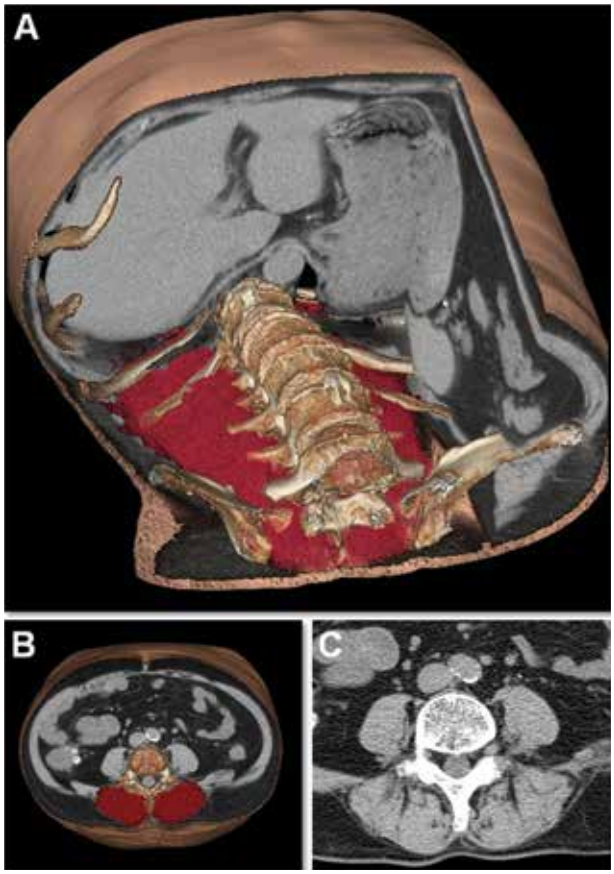



**Fig. 1:** Image of the lumbar muscle and surrounding tissues (*red*). **A** Computed tomography (CT) images of the muscles behind the vertebral bodies that are covered with the same fascia, **B**, **C** intramuscular adipose tissue content (IMAC) values of muscle according to the CT findings at the umbilical level that were used to quantify visceral fat accumulation [17, 18].

Wilcoxon signed-rank test was used to compare data acquired before and after the administration of BCAAs. The effects of increased IMAC were evaluated according to the changes (Δ) in a variable, where Δ = variable after intervention − variable before intervention. Spearman's rank correlation coefficient ($\rho$) was used to compare ΔIMAC with each change in parameter (Δ parameter). Survival rates were calculated using the Kaplan–Meier method and compared using the log-rank (Mantel–Cox) test, and the Cox proportional hazards regression model was used to identify the factors that contributed to the each patient's prognosis. Significance was set at $P < 0.05$. All analyses were performed using SPSS (version 19.0; IBM Corp., Armonk, NY).

## Results

### Patients' characteristics

The baseline characteristics of the patients ($n = 21$; 9 men, 12 women) are summarized in Table 1. Serum albumin, platelet count, and the branched-chain amino acid-to-tyrosine ratio were below

the lower limit of normal ranges. Ten patients were classified as Child–Pugh grade A. Hepatitis C virus infection was the most common etiology for liver cirrhosis. The SFA and IMAC were significantly higher in the female patients than in the male patients, whereas total bilirubin, creatinine, and the SAI were significantly higher in the men than the women. There were no significant differences between the sexes for the other parameters (Table 1).

**Table 1: Baseline characteristics of patients with liver cirrhosis.**

| Variables | All patients (*n* = 21) | Male patients (*n* = 9) | Female patients (*n* = 12) | *P* value |
|---|---|---|---|---|
| Age (years) | 71.3 ± 7.9 | 70.6 ± 9.7 | 71.8 ± 6.7 | 0.9431 |
| Weight (kg) | 56.6 ± 9.6 | 58.9 ± 6.4 | 54.9 ± 11.5 | 0.1551 |
| BMI (kg/m$^2$) | 23.9 ± 4.0 | 22.4 ± 2.6 | 24.9 ± 4.6 | 0.1021 |
| SFA (cm$^2$) | 164.4 ± 92.8 | 99.2 ± 53.9 | 213.3 ± 86.3 | <0.01 |
| VFA (cm$^2$) | 90.9 ± 43.3 | 100.9 ± 48.6 | 83.4 ± 39.4 | 0.3938 |
| ALT (IU/L) | 49.1 ± 28.9 | 47.2 ± 17.0 | 50.6 ± 36.1 | 0.5689 |
| γ-GTP (IU/L) | 77.0 ± 127.0 | 130.6 ± 184.6 | 36.8 ± 21.1 | 0.4548 |
| TC (mg/dL) | 140.4 ± 30.8 | 144.0 ± 32.6 | 138.1 ± 30.7 | 0.6159 |
| TG (mg/dL) | 76.3 ± 23.6 | 86.7 ± 30.4 | 70.3 ± 17.2 | 0.1896 |
| FPG (mg/dL) | 113.6 ± 31.7 | 127.3 ± 40.0 | 103.3 ± 19.8 | 0.0880 |
| FPI (μU/mL) | 14.2 ± 11.8 | 9.9 ± 6.9 | 16.7 ± 13.6 | 0.2367 |
| HOMA-IR | 3.9 ± 3.0 | 3.1 ± 1.9 | 4.4 ± 3.5 | 0.7998 |
| QUICKI | 0.33 ± 0.05 | 0.34 ± 0.05 | 0.33 ± 0.05 | 0.7998 |
| Serum albumin (g/dL) | 3.2 ± 0.4 | 3.1 ± 0.3 | 3.3 ± 0.4 | 0.2533 |
| Total bilirubin (mg/dL) | 1.2 ± 0.5 | 1.4 ± 0.7 | 1.0 ± 0.3 | <0.05 |
| Platelet count (×10$^4$/μL) | 10.2 ± 6.3 | 8.8 ± 3.2 | 11.2 ± 7.8 | 0.4770 |
| BUN (mg/dL) | 13.4 ± 3.8 | 13.2 ± 5.0 | 13.5 ± 2.7 | 0.4136 |
| Creatinine (mg/dL) | 0.7 ± 0.2 | 0.8 ± 0.2 | 0.6 ± 0.1 | <0.05 |
| Ammonia (μg/dL) | 57.7 ± 30.1 | 70.8 ± 35.6 | 47.9 ± 21.9 | 0.1450 |
| BTR | 3.7 ± 1.0 | 3.5 ± 0.8 | 3.8 ± 1.2 | 0.6698 |
| L/S ratio | 1.17 ± 0.15 | 1.14 ± 0.19 | 1.20 ± 0.13 | 0.6756 |
| IMAC | −0.11 ± 0.16 | −0.22 ± 0.12 | −0.03 ± 0.14 | <0.01 |
| SAI (cm$^2$/m$^2$) | 12.4 ± 2.7 | 13.8 ± 2.6 | 11.3 ± 2.2 | <0.05 |
| Child–Pugh grade (A/B/C) | (10/11/0) | (3/6/0) | (7/5/0) | 0.2218 |
| Etiology (HCV/HBV/alcoholic/others) | (18/2/1) | (7/1/1) | (11/1/0) | |

Values in table are presented as the mean ± standard deviation (SD), with the exception of those for Child–Pugh grade and Etiology which are presented as the number of patients

*BMI* body mass index, *SFA* subcutaneous fat area, *VFA* visceral fat area, *ALT* alanine aminotransferase, *γ-GTP* γ-guanosine triphosphate, *TC* total cholesterol, *TG* triglycerides, *FPG* fasting plasma glucose, *FPI* fasting plasma insulin, *HOMA-IR* homeostasis model assessment, *QUICKI* quantitative insulin sensitivity check index, *BUN* blood urea nitrogen, *BTR* branched chain amino acid and tyrosine ratio, *L/S ratio* liver-spleen ratio, *IMAC* intramuscular adipose tissue content, *SAI* skeletal muscle area index, *HCV*/*HBV* hepatitis C/B virus

## Effects of BCAA Therapy on Clinical Characteristics

The effects of BCAA therapy on the clinical characteristics of the patients are shown in Table 2. BCAA therapy was associated with a significant increase in BUN, creatinine, BTR, and BCAAs, but not with any significant differences in IMAC, SAI, and glucose metabolism. All patients

**Table 2: Changes in variables before and after therapy with branched-chain amino acid supplementation.**

| Variables | Before BCAA supplementation therapy (*n* = 21 patients) | After BCAA supplementation therapy (*n* = 21 patients) | *P* value |
|---|---|---|---|
| Age (years) | 71.2 ± 7.9 | 72.1 ± 7.9 | <0.001 |
| Weight (kg) | 56.6 ± 9.6 | 55.7 ± 9.9 | 0.2045 |
| BMI (kg/m$^2$) | 23.9 ± 4.0 | 23.5 ± 3.8 | 0.1698 |
| SFA (cm$^2$) | 164.4 ± 92.8 | 159.3 ± 97.6 | 0.5202 |
| VFA (cm$^2$) | 90.9 ± 43.3 | 85.9 ± 37.1 | 0.0680 |
| ALT (IU/L) | 49.1 ± 28.9 | 51.7 ± 28.9 | 0.6264 |
| γ-GTP (IU/L) | 77.0 ± 127.0 | 64.5 ± 80.4 | 0.5014 |
| TC (mg/dL) | 140.4 ± 30.8 | 148.7 ± 42.4 | 0.3270 |
| TG (mg/dL) | 76.3 ± 23.6 | 83.4 ± 46.2 | 0.2428 |
| FPG (mg/dL) | 113.6 ± 31.7 | 108.5 ± 27.7 | 0.5661 |
| FPI (μU/mL) | 14.2 ± 11.8 | 15.7 ± 16.5 | 0.3088 |
| HOMA-IR | 3.9 ± 3.0 | 4.5 ± 5.4 | 0.4925 |
| QUICKI | 0.33 ± 0.05 | 0.33 ± 0.04 | 0.2659 |
| Serum albumin (g/dL) | 3.2 ± 0.4 | 3.3 ± 0.5 | 0.3311 |
| Total bilirubin (mg/dL) | 1.2 ± 0.5 | 1.4 ± 0.9 | 0.1659 |
| Platelet count (×10$^4$/μL) | 10.2 ± 6.3 | 8.4 ± 3.3 | 0.5593 |
| BUN (mg/dL) | 13.4 ± 3.8 | 15.1 ± 4.5 | <0.01 |
| Creatinine (mg/dL) | 0.71 ± 0.17 | 0.75 ± 0.18 | <0.05 |
| Ammonia (μg/dL) | 57.7 ± 30.1 | 51.1 ± 24.2 | 0.2371 |
| BTR | 3.7 ± 1.0 | 4.7 ± 2.8 | <0.05 |
| BCAA (μmol/L) | 394.6 ± 95.6 | 511.1 ± 232.0 | <0.0001 |
| Tyrosine (μmol/L) | 111.5 ± 24.7 | 118.4 ± 35.0 | 0.1023 |
| L/S ratio | 1.17 ± 0.15 | 1.14 ± 0.20 | 0.3132 |
| IMAC | −0.11 ± 0.16 | −0.12 ± 0.17 | 0.7504 |
| SAI (cm$^2$/m$^2$) | 12.4 ± 2.7 | 12.0 ± 2.8 | 0.0735 |
| Child–Pugh grade (A/B/C) | 10/11/0 | 15/5/1 | |
| Child–Pugh score | 6.5 ± 0.8 | 6.4 ± 1.4 | 0.5699 |

Values in table are presented as the mean ± SD, with the exception of Child–Pugh grade which is presented as the number of patients
*BCAA* branched-chain amino acid, *BTR* branched chain amino acid and tyrosine ratio

included in this study maintained 100% adherence to BCAA supplementation according to the questionnaire (data not shown).

### Changes in Clinical Parameters after BCAA Supplementation According to the Effect on Serum Albumin Levels

After BCAA therapy, 11 patients (52.4%, 6 men, 5 women) experienced ameliorated hypoalbuminemia (3.1 ± 0.3–3.4 ± 0.3 g albumin/dL; $P < 0.01$), significant decreases in VFA, 90-min post-challenger plasma glucose, 120-min post-challenger plasma glucose, ammonia, IMAC, and Child–Pugh score, and significant increases in BUN, BTR, and BCAAs (Table 3; Fig. 2). Ten patients (47.6%, 3 men and 7 women) experienced decreased serum albumin levels (3.4 ± 0.3–3.1 ± 0.6 g albumin/dL; $P < 0.05$), significant decreases in QUICKI and SAI, and significant increases in FPI, BCAAs, and tyrosine. There were no significant differences changes in post-challenge plasma glucose levels in the patients pre- and post-therapy (Table 3; Fig. 2). Eleven patients with increasing serum albumin levels also showed an improvement in IMAC (ESM Fig. S3). Subanalyses were performed to test whether sex and basal IMAC level influenced the effect of BCAA supplementation on the improvement of IMAC (ESM Fig. S4). Similar to the analysis involving all patients, the basal IMAC of the female patients tended to be higher than that of the male patients (−0.198 vs. 0.000; $P = 0.0996$) [17, 18]; however, delta-IMAC was not different between the male and female patients (−0.053 vs. 0.046; $P = 0.7112$). In both male and female patients, decreasing IMAC seemed to be similar in those patients with relatively higher basal IMAC and those patients with relatively lower basal IMAC. Among these 11 patients, there were six patients with significant increasing SAI (ESM Fig. S5). To analyze the characteristics of the patients who achieved increasing SAI with BCAA supplementation, we compared the clinical backgrounds between the six patients with increasing SAI and the ten patients without improvement of IMAC or SAI (non-responders) (ESM Table S1). Patients with increasing SAI had lower BMI, SFA, and VFA than non-responders, but this difference was not statistically significant. Platelet count was significantly higher in non-responders than in patients with increasing SAI.

### Correlation Between the Changes in Serum Albumin Level and Other Parameters

There were significant correlations between serum albumin and total cholesterol ($\rho = 0.544$, $P < 0.05$), triglycerides ($\rho = 0.472$, $P < 0.05$), 90-min post-challenge plasma glucose ($\rho = -0.685$, $P < 0.05$), 120-min post-challenge plasma glucose ($\rho = -0.808$, $P < 0.01$), ammonia ($\rho = -0.447$, $P < 0.05$), IMAC ($\rho = -0.710$, $P < 0.01$), SAI ($\rho = 0.608$, $P < 0.01$), and the Child–Pugh score ($\rho = 0.839$, $P < 0.001$) (Table 4).

### Effect of Improvement of IMAC by BCAA Supplementation on the Prognosis of Liver Cirrhosis

The 72-month probability of liver-related events occurring (refractory pleural effusion, ascites, or both, varices rupture or treatment, and hepatocarcinogenesis) was 63.6% in patients with IMAC

**Table 3: Characteristics of patients with liver cirrhosis and those with/without improvements in albumin before and after therapy with branched-chain amino acid supplementation.**

| Variables | Patients with improvements in serum albumin (*n* = 11) | | | Patients with no improvement in serum albumin (*n* = 10) | | |
|---|---|---|---|---|---|---|
| | Before BCAA supplementation therapy | After BCAA supplementation therapy | *P* value | Before BCAA supplementation therapy | After BCAA supplementation therapy | *P* value |
| Sex (male/female) | 6/5 | 6/5 | | 3/7 | 3/7 | |
| BMI (kg/m$^2$) | 23.4 ± 3.5 | 22.7 ± 3.3 | 0.0754 | 24.4 ± 4.6 | 24.3 ± 4.4 | 0.7989 |
| SFA (cm$^2$) | 138.9 ± 79.5 | 128.8 ± 68.5 | 0.1549 | 192.5 ± 102.1 | 193.9 ± 111.7 | 0.7213 |
| VFA (cm$^2$) | 85.3 ± 44.5 | 76.3 ± 36.3 | <0.05 | 97.0 ± 43.6 | 96.5 ± 36.9 | 0.6465 |
| ALT (IU/L) | 48.7 ± 36.2 | 49.2 ± 32.6 | 0.7220 | 49.6 ± 20.1 | 54.5 ± 25.8 | 0.3323 |
| γ-GTP (IU/L) | 59.4 ± 60.9 | 44.5 ± 34.4 | 0.2858 | 96.4 ± 175.9 | 86.6 ± 109.6 | 0.9527 |
| TC (mg/dL) | 147.9 ± 33.2 | 161.7 ± 47.9 | 0.1386 | 131.2 ± 26.5 | 132.9 ± 29.6 | 0.7671 |
| TG (mg/dL) | 73.3 ± 19.9 | 79.4 ± 27.8 | 0.1250 | 79.7 ± 28.0 | 88.2 ± 63.7 | 0.8588 |
| FPG (mg/dL) | 118.8 ± 38.2 | 104.3 ± 24.8 | 0.1823 | 107.9 ± 23.3 | 113.1 ± 31.3 | 0.4133 |
| 60-PG (mg/dL) (*n* = 17) | 199.4 ± 39.8 | 191.8 ± 42.8 | 0.5002 | 220.4 ± 63.9 | 230.0 ± 78.7 | 0.4618 |
| 90-PG (mg/dL) (*n* = 17) | 208.3 ± 38.2 | 180.0 ± 47.8 | <0.05 | 212.0 ± 81.6 | 216.5 ± 87.4 | 0.2367 |
| 120-PG (mg/dL) (*n* = 17) | 196.0 ± 57.6 | 150.9 ± 52.4 | <0.01 | 191.6 ± 89.2 | 210.8 ± 110.2 | 0.0684 |
| FPI (μU/mL) | 16.6 ± 15.3 | 9.3 ± 5.3 | 0.3980 | 12.0 ± 7.7 | 20.2 ± 20.3 | <0.05 |
| HOMA-IR | 4.6 ± 3.5 | 2.3 ± 1.1 | 0.3980 | 3.3 ± 2.4 | 6.1 ± 6.7 | 0.1688 |
| QUICKI | 0.32 ± 0.05 | 0.34 ± 0.02 | 0.4990 | 0.34 ± 0.05 | 0.32 ± 0.04 | <0.05 |
| Serum albumin (g/dL) | 3.1 ± 0.3 | 3.4 ± 0.3 | <0.01 | 3.4 ± 0.3 | 3.1 ± 0.6 | <0.05 |

cont'd...

...cont'd.

| | | | | | | |
|---|---|---|---|---|---|---|
| Total bilirubin (mg/dL) | 1.2 ± 0.5 | 1.3 ± 0.5 | 0.6445 | 1.2 ± 0.6 | 1.5 ± 1.2 | 0.1392 |
| Platelet count ($\times 10^4/\mu L$) | 11.7 ± 7.4 | 8.9 ± 3.9 | 0.3981 | 8.5 ± 4.5 | 7.8 ± 2.6 | 0.9998 |
| BUN (mg/dL) | 14.1 ± 4.0 | 16.8 ± 5.2 | <0.01 | 12.6 ± 3.5 | 13.3 ± 2.9 | 0.4142 |
| Creatinine (mg/dL) | 0.78 ± 0.18 | 0.83 ± 0.20 | 0.0825 | 0.63 ± 0.14 | 0.66 ± 0.10 | 0.2119 |
| Ammonia (μg/dL) | 57.5 ± 29.3 | 39.8 ± 16.8 | <0.01 | 57.9 ± 32.6 | 63.4 ± 25.8 | 0.3574 |
| BTR | 3.4 ± 0.8 | 5.3 ± 3.7 | <0.05 | 4.0 ± 1.2 | 4.1 ± 1.2 | 0.6465 |
| BCAA (μmol/L) | 377.4 ± 102.2 | 541.9 ± 292.8 | <0.01 | 413.4 ± 89.2 | 477.2 ± 147.9 | <0.01 |
| Tyrosine (μmol/L) | 114.0 ± 27.0 | 117.0 ± 43.5 | 0.7221 | 109.7 ± 22.9 | 119.9 ± 24.8 | <0.05 |
| L/S ratio | 1.21 ± 0.13 | 1.20 ± 0.17 | 0.4401 | 1.13 ± 0.17 | 1.08 ± 0.22 | 0.2829 |
| IMAC | −0.11 ± 0.18 | −0.16 ± 0.18 | <0.01 | −0.12 ± 0.15 | −0.07 ± 0.16 | <0.01 |
| SAI ($cm^2/m^2$) | 12.4 ± 3.0 | 12.5 ± 3.2 | 0.4236 | 12.3 ± 2.3 | 11.5 ± 2.4 | <0.01 |
| Child–Pugh score | 6.8 ± 0.6 | 5.9 ± 0.7 | <0.01 | 6.2 ± 0.9 | 7.0 ± 1.8 | 0.0633 |

Values in table are presented as the mean ± SD, with the exception of those for Sex which are presented as a number
*60-PG* 60-min post-challenge plasma glucose, *90-PG* 90-min post-challenge plasma glucose, *180-PG* 180-min post-challenge plasma glucose

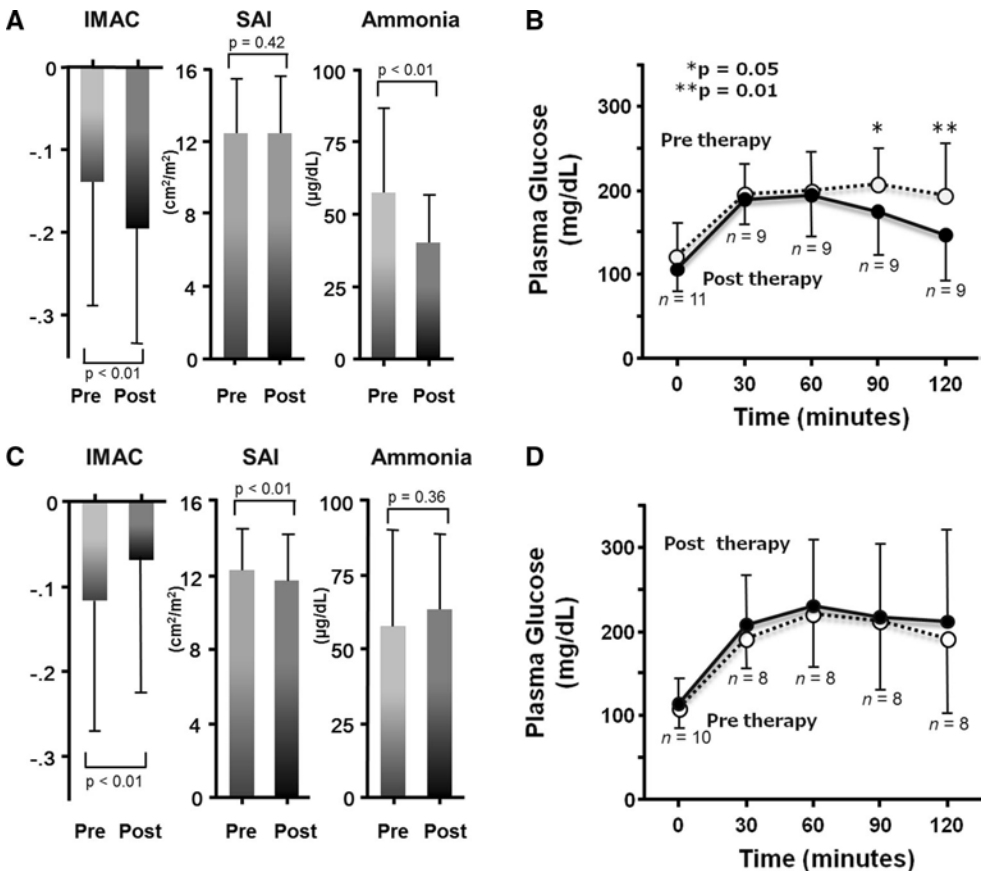



**Fig. 2:** Analyses of patients with increased albumin levels. **A** IMAC and ammonia level improved significantly (**$P$ < 0.01 each). **B** Glucose metabolism decreased significantly at 90 and 120 min post-challenge with plasma glucose (*$P$ < 0.05 and **$P$ < 0.01, respectively). *Open circle* pre therapy, *filled circle* post therapy. **C** In patients without increased albumin levels, IMAC increased significantly (**$P$ < 0.01). **D** There were no significant differences in ammonia and glucose metabolism. *SAI* Skeletal muscle area index

improvement and 100.0% in patients without IMAC improvement ($P$ = 0.0591; Fig. 3a). There was a tendency for lower cumulative occurrence rates in patients with improved IMAC compared with those without improved IMAC. The 72-month probability of liver-related mortality and survival (liver failure, varicose vein rupture, or hepatocellular carcinoma mortality) was 63.6 and 20.0%, respectively ($P$ = 0.1161; Fig. 3b). The multivariate analysis showed that improvement of IMAC and Δalbumin tended to be an independent factor that negatively related to the occurrence of liver-related events [IMAC improvement: odds ratio (OR) 0.06, $P$ = 0.052; Δalbumin: OR 0.2, $P$ = 0.087). Sex (female) and SAI improvement were significant independent factors for event occurrence rates (ESM Table S2). IMAC improvement, SAI improvement, and sex (female) were independent factors that negatively contributed to liver-related mortality and survival (IMAC improvement: OR 0.03, $P$ = 0.027; improvement of SAI: OR 0.06, $P$ = 0.038; female sex: OR 0.03, $P$ = 0.003; ESM Table S3).

**Table 4: Relationships between changes in serum albumin and changes in other parameters in liver cirrhosis patients with branched-chain amino acid supplementation.**

| Variables | All patients ($n$ = 21) | |
|---|---|---|
| | $\rho$ | $P$ |
| Δ BMI (kg/m$^2$) | −0.051 | 0.8198 |
| Δ SFA (cm$^2$) | −0.106 | 0.6341 |
| Δ VFA (cm$^2$) | 0.015 | 0.9465 |
| Δ ALT (IU/L) | −0.027 | 0.9045 |
| Δ γ-GTP (IU/L) | −0.043 | 0.8458 |
| Δ TC (mg/dL) | 0.544 | <0.05 |
| Δ TG (mg/dL) | 0.472 | <0.05 |
| Δ FPG (mg/dL) | −0.269 | 0.2298 |
| Δ 60-PG (mg/dL) ($n$ = 17) | −0.185 | 0.5581 |
| Δ 90-PG (mg/dL) ($n$ = 17) | −0.685 | <0.05 |
| Δ 120-PG (mg/dL) ($n$ = 17) | −0.808 | <0.01 |
| Δ FPI (μU/mL) | −0.390 | 0.1191 |
| Δ HOMA-IR | −0.212 | 0.3962 |
| Δ QUICKI | 0.231 | 0.3564 |
| Δ Total bilirubin (mg/dL) | −0.200 | 0.3701 |
| Δ Platelet count (×10$^4$/μL) | 0.015 | 0.9452 |
| Δ BUN (mg/dL) | 0.409 | 0.0672 |
| Δ Creatinine (mg/dL) | 0.252 | 0.2604 |
| Δ Ammonia (μg/dL) | −0.447 | <0.05 |
| Δ BTR | 0.279 | 0.2114 |
| Δ BCAA (μmol/L) | 0.176 | 0.4316 |
| Δ Tyrosine (μmol/L) | −0.179 | 0.4236 |
| Δ IMAC | −0.710 | <0.01 |
| Δ L/S ratio | 0.147 | 0.5222 |
| Δ SAI (cm$^2$/m$^2$) | 0.608 | <0.01 |
| Δ Child–Pugh score | −0.839 | <0.001 |

$\rho$ Spearman's rank correlation coefficient or Spearman's rho, Δ change in the variable: the value of the variable after BCAA supplementation–the value of the variable before BCAA supplementation

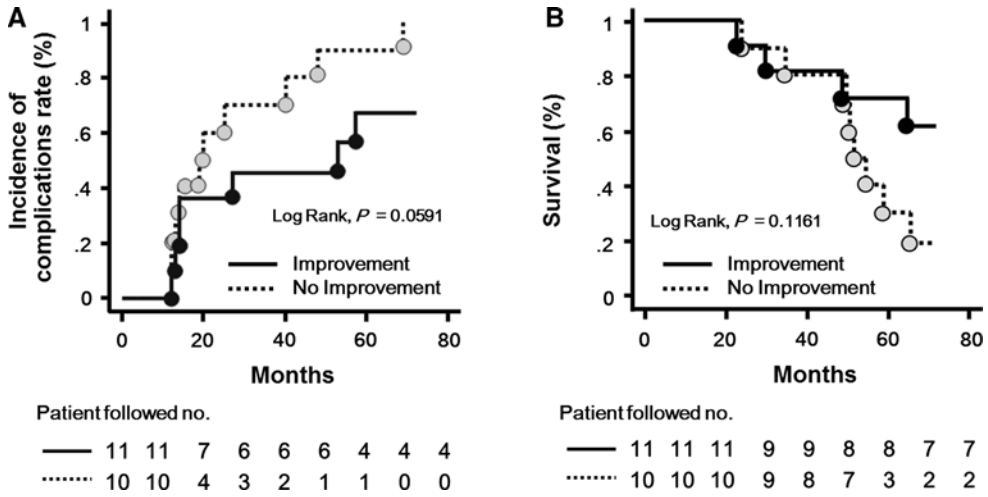



**Fig. 3:** Kaplan–Meier curves comparing patients with and without increased IMAC. **A** Cumulative occurrence rates of liver-related events (refractory pleural effusion, ascites, or both, varices rupture or treatment, and hepatocarcinogenesis). The 72-month probabilities were 63.6% in patients with an improvement in IMAC and 100.0% in the patients without an improvement of IMAC ($P = 0.0591$). **B** Liver-related event-free survival rates. The 72-month probabilities of survival were 63.6% in patients with an improvement in IMAC and 20.0% in patients without an improvement in IMAC ($P = 0.1161$). The data were compared using the log-rank test. *Dotted line* Increased IMAC, *continuous line* unchanged IMAC

## Discussion

In the study reported here, we analyzed the long-term effects of dietary supplementation with BCAA on the skeletal muscle characteristics and glucose metabolism of patients with liver cirrhosis. In patients with ameliorated hypoalbuminemia, the glucose level, particularly during the later phase of OGTT significantly decreased, suggesting that glucose uptake in skeletal muscle was improved. Insulin resistance in skeletal muscle was evaluated using QUICKI, and it was ameliorated after BCAA supplementation; ΔQUICKI was significantly correlated with the decrease in fat accumulation in skeletal muscle. Therefore, fat accumulation in skeletal muscle may reflect hypoalbuminemia and abnormal glucose metabolism in the pathogenesis of liver cirrhosis.

Overall, the patients showed a tendency for skeletal muscle mass to decrease during the 48-week observation period (Table 2). In patients whose hypoalbuminemia did not improve, skeletal muscle mass significantly decreased, whereas patients with ameliorated hypoalbuminemia maintained skeletal muscle mass (Table 3). All patients with improved hypoalbuminemia demonstrated an improvement in fat accumulation in skeletal muscle, including the six patients who experienced increasing SAI (ESM Table S1; ESM Figs. S3 and S5). In addition, ΔIMAC and ΔSAI significantly correlated with the Δserum albumin level (Table 4). These data suggest that BCAA supplementation prevented the progression of sarcopenia associated with liver cirrhosis, which needs to be accompanied by an increased level of serum albumin.

We investigated the clinical features of the six patients who experienced increased skeletal muscle mass, decreased fat accumulation in skeletal muscle, and an improvement in hypoalbuminemia (ESM Table S1). The platelet count of these patients was significantly higher than that of the non-responders, whereas there was no significant difference in the other parameters. To confirm that platelet count is an indicator of patient responsiveness to BCAA supplementation, further studies, including a larger cohort with detailed evaluation of portal hypertension, are required.

Results from numerous basic studies and clinical trials show that BCAAs are pharmacologically active and induce, for example, increased albumin levels, improved ammonia metabolism, and increased insulin sensitivity [8, 10, 14, 29]. There is evidence indicating that the mechanism of the BCAA-induced elevation in the albumin level in hepatocytes involves the induction of mRNA and protein synthesis by L-leucine, which in turn activates mammalian target of rapamycin signaling [30–32]. Moreover, glutamic acid is produced in skeletal muscle through a reaction with α-ketoglutaric acid, which promotes ammonia metabolism [33]. It has been shown that insulin resistance improves through increased glucose transport in response to enhanced GLUT4 expression in skeletal muscle [14], as well as by increased glycolysis and glycogen synthesis by GLUT2 and glucokinase in the liver [29, 34]. Further, a study using an animal model found that BCAAs decrease lipid accumulation [35, 36].

It remains to be determined whether BCAAs act directly on skeletal muscle to mitigate fat accumulation in skeletal muscle tissue and to mediate improved physical activity and QOL concomitant with an increased albumin level [2, 3, 37, 38]. Numerous potential direct effects of BCAAs on skeletal muscle have been reported. For example, BCAAs induce the translocation of GLUT4 to the skeletal muscle cell membrane through an insulin receptor-independent signaling pathway [14, 39]. Further, BCAAs increase free fatty acid (FFA) oxidation and improve insulin sensitivity, which are associated with increased FFA oxidation through activation of peroxisome proliferator-activated receptor-α and increased uncoupling of protein 2 in the liver and of ponerotein 3 in skeletal muscle [29, 35, 36]. Further study is required to identify direct and indirect mechanisms of BCAA activities that affect skeletal muscle.

The albumin level significantly improved in 52.4% of the BCAA-treated patients, and this was accompanied by a significant increase in BTR levels in our study, suggesting that the patients had good adherence to the protocol. However, albumin levels did not improve in 47.6% of patients. Tyrosine levels significantly increased only in the patients who did not experience an increase of albumin levels. These data suggest that there are variations in the changes of amino acid in response to BCAA supplementation.

Hypoalbuminemia is an independent prognosticator of liver cirrhosis, and BCAA supplementation is used as a therapeutic strategy that increases albumin levels in patients with hypoalbuminemia and improves the prognosis of patients with liver cirrhosis [3]. Abnormal glucose metabolism correlates with PEM, sarcopenia, the prognosis of liver cirrhosis [40–43], and hepatocellular carcinoma recurrence rates after curative therapy [44]. Our results show that dietary supplementation with BCAAs mitigated hypoalbuminemia, improved glucose metabolism, decreased the accumulation of fat in skeletal muscle, and contributed to an improved prognosis

of patients with liver cirrhosis. However, some patients were refractory to BCAA supplementation and showed no increase in albumin levels, no improvement in glucose metabolism, and no improvement in skeletal muscle features. Further study is required to characterize BCAA supplementation in "nonresponders", who we consider to be at risk for poor prognosis.

In our previous study of patients with nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, skeletal muscle steatosis improved only in patients who engaged in sufficient exercise therapy [17, 18]. Therefore, BCAA supplementation may "mimic" exercise training to ameliorate skeletal muscle steatosis and glucose tolerance. However, the effects and safety of exercise training on the glucose metabolism of patients with liver cirrhosis is unknown [45–47]. BCAA supplementation may therefore represent both a less invasive and a more consistent therapy to prevent or inhibit the pathogenesis of liver cirrhosis and may contribute to a more favorable prognosis.

A limitation of our study is that dietary changes, the amount of physical activity, and adherence to BCAA after 48 weeks were not investigated, and these factors may affect skeletal muscle findings and the patient's prognosis. In addition, although the serum albumin level is a common and established indicator of the prognosis of liver cirrhosis [3], multivariate analysis in our study did not show any contribution of Δalbumin to the prognosis. The small number of patients included in this study is also a potential limitation that could affect confounding factors in the multivariate analysis between changes in serum albumin and other parameters, including IMAC and SAI.

In conclusion, increased albumin levels in patients with hypoalbuminemia were associated with dietary supplementation with BCAAs and were related to decreased fat accumulation in skeletal muscle, which maintained skeletal muscle mass and ameliorated glucose tolerance. These positive responses to BCAAs likely contributed to the more favorable prognoses of patients with liver cirrhosis.

**Acknowledgements** We thank the medical staff at Eguchi Hospital and Professor Kyuichi Tanikawa (International Institute for Liver Research) for excellent advice. This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (2010) (#22590741 to Y.E.).

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Gross CR, Malinchoc M, Kim WR, *et al*. Quality of life before and after liver transplantation for cholestatic liver disease. Hepatology. 1999;29:356–64.
2. Marchesini G, Bianchi G, Merli M, *et al*. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology. 2003;124:1792–801.
3. Muto Y, Sato S, Watanabe A, *et al*. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2005;3:705–13.
4. Plauth M, Merli M, Kondrup J, *et al*. ESPEN guidelines for nutrition in liver disease and transplantation. Clin Nutr. 1997;16:43–55.
5. Greco AV, Mingrone G, Benedetti G, *et al*. Daily energy and substrate metabolism in patients with cirrhosis. Hepatology. 1998;27:346–50.
6. Tajika M, Kato M, Mohri H, *et al*. Prognostic value of energy metabolism in patients with viral liver cirrhosis. Nutrition. 2002;18:229–34.

7. Moriwaki H, Miwa Y, Tajika M, *et al*. Branched-chain amino acids as a protein- and energy-source in liver cirrhosis. Biochem Biophys Res Commun. 2004;313:405–9.
8. Hidaka H, Nakazawa T, Kutsukake S, *et al*. The efficacy of nocturnal administration of branched-chain amino acid granules to improve quality of life in patients with cirrhosis. J Gastroenterol. 2013;48:269–70.
9. Muto Y, Sato S, Watanabe A, *et al*. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2005;3:705–13.
10. Marchesini G, Bianchi G, Merli M, *et al*. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology. 2003;124:1792–801.
11. Urata Y, Okita K, Korenaga K, *et al*. The effect of supplementation with branched-chain amino acids in patients with liver cirrhosis. Hepatol Res. 2007;37:510–6.
12. Tabaru A, Shirohara H, Moriyama A, *et al*. Effects of branched-chain-enriched amino acid solution on insulin and glucagon secretion and blood glucose level in liver cirrhosis. Scand J Gastroenterol. 1998;33:853–9.
13. Kawaguchi T, Taniguchi E, Itou M, *et al*. Branched-chain amino acids improve insulin resistance in patients with hepatitis C virus-related liver disease: report of two cases. Liver Int. 2007;27:1287–92.
14. Nishitani S, Takehana K, Fujitani S, *et al*. Branched-chain amino acids improve glucose metabolism in rats with liver cirrhosis. Am J Physiol Gastrointest Liver Physiol. 2005;288:G1292–300.
15. Lautz HU, Selberg O, Körber J, *et al*. Protein-calorie malnutrition in liver cirrhosis. Clin Investig. 1992;70(6):478–86.
16. Kachaamy T, Bajaj JS, Heuman DM. Muscle and mortality in cirrhosis. Clin Gastroenterol Hepatol. 2012;10(2): 100–2.
17. Kitajima Y, Eguchi Y, Ishibashi E, *et al*. Age-related fat deposition in multifidus muscle could be a marker for nonalcoholic fatty liver disease. J Gastroenterol. 2010;45:218–24.
18. Kitajima Y, Hyogo H, Sumida Y, *et al*. The severity of nonalcoholic steatohepatitis is associated with substitution of adipose tissue in skeletal muscle. J Gastroenterol Hepatol. 2013;28(9):1507–14.
19. Plauth M, Cabré E, Campillo B, *et al*. ESPEN guidelines on parenteral nutrition: hepatology. Clin Nutr. 2009;28: 436–44.
20. Haffner SM, Kennedy E, Gonzalez C, *et al*. A prospective analysis of the HOMA model. The Mexico City Diabetes Study. Diabetes Care. 1996;19:1138–41.
21. Katz A, Nambi SS, Mather K, *et al*. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab. 2000;85:2402–10.
22. Saadeh S, Younossi ZM, Remer EM, *et al*. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology. 2002;123:745–50.
23. Piekarski J, Goldberg HI, Royal SA, *et al*. Difference between liver and spleen CT number in the normal adult: its usefulness in predicting the presence of diffuse liver disease. Radiology. 1980;137:727–9.
24. Yoshizumi T, Nakamura T, Yamane M, *et al*. Abdominal fat: standardized technique for measurement at CT. Radiology. 1999;211:283–6.
25. Janssen I, Baumgartner RN, Ross R, *et al*. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. Am J Epidemiol. 2004;159(4):413–21.
26. Mourtzakis M, Prado CM, Lieffers JR, *et al*. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997–1006.
27. Ling CH, de Craen AJ, Slagboom PE, *et al*. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. Clin Nutr. 2011;30(5):610–5.
28. Janssen I, Heymsfield SB, Baumgartner RN, *et al*. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol. 2000;89(2):465–71.
29. Kawaguchi T, Izumi N, Charlton MR, *et al*. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. Hepatology. 2011;54:1063–70.
30. Ijichi C, Matsumura T, Tsuji T, *et al*. Branched-chain amino acids promote albumin synthesis in rat primary hepatocytes through the mTOR signal transduction system. Biochem Biophys Res Commun. 2003;303:59–64.
31. Nishitani S, Ijichi C, Takehana K, *et al*. Pharmacological activities of branched-chain amino acids: specificity of tissue and signal transduction. Biochem Biophys Res Commun. 2004;313:387–9.
32. Matsumura T, Morinaga Y, Fujitani S, *et al*. Oral administration of branched-chain amino acids activates the mTOR signal in cirrhotic rat liver. Hepatol Res. 2005;33:27–32.
33. Hayashi M, Ohnishi H, Kawade Y, *et al*. Augmented utilization of branched-chain amino acids by skeletal muscle in decompensated liver cirrhosis in special relation to ammonia detoxication. Gastroenterol Jpn. 1981;16:64–70.

34. Higuchi N, Kato M, Miyazaki M, *et al*. Potential role of branched-chain amino acids in glucose metabolism through the accelerated induction of the glucose-sensing apparatus in the liver. J Cell Biochem. 2011;112:30–8.
35. Nishimura J, Masaki T, Arakawa M, *et al*. Isoleucine prevents the accumulation of tissue triglycerides and upregulates the expression of PPARalpha and uncoupling protein in diet-induced obese mice. J Nutr. 2010;140:496–500.
36. Arakawa M, Masaki T, Nishimura J, *et al*. The effects of branched-chain amino acid granules on the accumulation of tissue triglycerides and uncoupling proteins in diet-induced obese mice. Endocr J. 2011;58:161–70.
37. Nakaya Y, Okita K, Suzuki K, *et al*. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition. 2007;23:113–20.
38. Ichikawa T, Naota T, Miyaaki H, *et al*. Effect of an oral branched chain amino acid-enriched snack in cirrhotic patients with sleep disturbance. Hepatol Res. 2010;40:971–8.
39. Nishitani S, Matsumura T, Fujitani S, *et al*. Leucine promotes glucose uptake in skeletal muscles of rats. Biochem Biophys Res Commun. 2002;299:693–6.
40. Müller MJ, Böker KH, Selberg O. Metabolism of energy-yielding substrates in patients with liver cirrhosis. Metabolism of energy-yielding substrates in patients with liver cirrhosis. Clin Investig. 1994;72(8):568–79.
41. Campillo B, Bories PN, Pornin B, *et al*. Influence of liver failure, ascites, and energy expenditure on the response to oral nutrition in alcoholic liver cirrhosis. Nutrition. 1997;13(7–8):613–21.
42. Selberg O, Böttcher J, Tusch G, *et al*. Identification of high- and low-risk patients before liver transplantation: a prospective cohort study of nutritional and metabolic parameters in 150 patients. Hepatology. 1997;25(3):652–7.
43. Englesbe MJ, Patel SP, He K, *et al*. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010;211: 271–8.
44. Kamachi S, Mizuta T, Otsuka T, *et al*. Sarcopenia is a risk factor for the recurrence of hepatocellular carcinoma after curative treatment. Hepatol Res. 2016;46(2):201–8.
45. Campillo B, Fouet P, Bonnet JC, *et al*. Submaximal oxygen consumption in liver cirrhosis. Evidence of severe functional aerobic impairment. J Hepatol. 1990;10(2):163–7.
46. Román E, Torrades MT, Nadal MJ, *et al*. Randomized pilot study: effects of an exercise programme and leucine supplementation in patients with cirrhosis. Dig Dis Sci. 2014;59(8):1966–75.
47. Nishida Y, Ide Y, Okada M, *et al*. Effects of home-based exercise and branched-chain amino acid supplementation on aerobic capacity and glycemic control in patients with cirrhosis. Hepatol Res. 2017;47(3):E193–200.

---

Source: Kitajima, Y., Takahashi, H., Akiyama, T. *et al. J Gastroenterol* (2018) 53: 427. https://doi.org/10.1007/s00535-017-1370-x.

3

# Nutritional assessment and management for hospitalized patients with cirrhosis

**Barbara Lattanzi[1], Daria D'Ambrosio[1], Veronica Fedele[1], Manuela Merli[1]**

## Abstract

*Purpose of Review* The purpose of this review is to summarize recent knowledge on malnutrition and sarcopenia in liver cirrhosis with special focus on hospitalized cirrhotic patients. Assessment tools and treatment options are briefly discussed.
*Recent Findings* During hospitalization, cirrhotic patients frequently deteriorate their nutritional status due to multiple factors. Evaluation of nutritional risk followed by nutritional assessment has been suggested in cirrhotic patients and may alert the need of special nutritional care in those hospitalized. Few recent studies, although in small series, proposed to ameliorate sarcopenia in cirrhotic patients by protein/calorie supplementation and also encouraging physical activity.
*Summary* Malnutrition and sarcopenia are negative predictors of morbidity and mortality in hospitalized cirrhotic patients. When malnutrition is diagnosed, care should be taken to provide adequate nutritional support. Physical movement, whenever possible, has been suggested for prevention of muscle loss.

**Keywords:** Malnutrition, Sarcopenia, Cirrhosis, BCAA, Nutrition, Physical activity

## Introduction

Malnutrition is a common finding associated with liver cirrhosis with an incidence ranging from 20 to 90%, depending on the population studied and the diagnostic tools used for the diagnosis

This article is part of the Topical Collection on *Management of Cirrhotic Patient*

**Manuela Merli (✉)**
Manuela.merli@uniroma1.it
[1]Gastroenterology, Department of Clinical Medicine, 'Sapienza' University of Rome, Viale dell'Universita' 37, 00185 Rome, Italy

[1–3]. Malnutrition is associated with an increased risk of mortality, higher prevalence of portal hypertension-related complications and infections, and longer hospital stay [2–5]. The main component of malnutrition in liver cirrhosis is represented by sarcopenia, a condition of progressive and generalized loss of muscle mass and strength [6]. Recently, many studies have reported that sarcopenia is an independent predictor for morbidity and mortality in cirrhotic patients [2, 7, 8]. On the other hand, obesity may also be associated with cirrhosis, and cirrhotic patients may develop simultaneous loss of skeletal muscle and gain of adipose tissue, culminating in a condition of "sarcopenic obesity" [9•]. This observation is relevant because the number of obese patients, with end-stage liver disease due to non-alcoholic steatohepatitis, is increasing, and obese patients with cirrhosis are increasing among those who wait for liver transplantation [10].

Patients with advanced liver disease are frequently hospitalized due to acute events inducing decompensation. In some circumstances, surgical treatment may also be needed. During hospitalization, cirrhotic patients frequently experience a further reduction in caloric intake in comparison with their general lifestyles, being not accustomed to hospital food and time at which meals are served and due to the need of fasting for hospital procedures and invasive exams. Moreover, hospitalized patients use to spend all the day sitting or lying down avoiding any physical activity. All these factors contribute to further worsen the patients' nutritional status already compromised due to the chronic liver disease. Nutritional status should therefore be always assessed in hospitalized cirrhotic patients in order to adopt specific measures and possible corrections for this potentially modifiable condition [11].

Ideally, at the time of hospitalization, all cirrhotic patients should be screened to know if they are at "risk of malnutrition" and, in this case, a more accurate nutritional assessment to confirm the presence and quantifying malnutrition should be performed [12••]. Unfortunately, nutritional assessment and screening are performed infrequently, due to the absence of a validated "easy-to-perform" bedside tool and due to multiple confounders (water retention, decreased hepatic protein synthesis, etc.), which make more difficult the interpretation of nutritional parameters in patients with liver cirrhosis.

The term malnutrition covers two main groups of conditions: under-nutrition and over-nutrition.

In this chapter, we will refer "malnutrition" to under-nutrition and more specifically, we will deal to protein depletion and sarcopenia.

## Nutritional Screening

As mentioned above, to prevent or adopt measures to treat malnutrition, all hospitalized cirrhotic patients (either for an acute event or a planned admission) should undergo a rapid screening to evaluate if they are at risk of having or of developing malnutrition during the hospital stay.

To be practical, a screening test needs to be not time consuming and able to easily identify the population at risk. Since the prevalence of malnutrition and sarcopenia is higher in patients with advanced liver disease, as already suggested [12••], all Child-Pugh C patients should be considered at risk to be sarcopenic. Similarly, Child-Pugh B patients admitted for an acute decompensation

should be considered at risk. Finally, even though body mass index (BMI) in patients with liver cirrhosis is not too useful because of water retention, while a high BMI does not rule out the presence of sarcopenia, a BMI < 18.5 kg/m$^2$ has been proposed to identify a population at risk for muscle wasting [13].

Therefore, all patients hospitalized with a diagnosis of liver cirrhosis Child-Pugh C, Child-Pugh B with an acute decompensation or with a BMI < 18.5 kg/m$^2$, should undergo a more accurate nutritional assessment and nutritional monitoring and support during the period of hospitalization. A possible score for nutritional screening in cirrhotic patients that can also be applied is a 3-min score that includes the presence of fluid overload and impact on dietary intake, knowledge of unplanned weight loss, and awareness of having a reduced dietary intake in the last months. This score classifies the nutritional risk as low (0 points), moderate (1 point), or high (2–7 points) [14]. An additional short six questions score has been proposed for nutritional screening. This includes questions regarding modification of nutrient intake, weight loss, subcutaneous fat loss, muscle mass loss, water retention, and decline in muscle performance [15]. These screening can be reiterated during follow-up.

## Nutritional Assessment

The assessment of sarcopenia ideally requires both the evaluation of muscle mass and muscle function [16]. The diagnosis of skeletal muscle loss requires an accurate technique exploring muscle mass, as well as the availability of normal values, for gender and age, to define the appropriate cutoff [17••, 18,–20]. Unfortunately, there is heterogeneity in the literature about the definition of sarcopenia in liver cirrhosis, and different surrogate tools have been proposed for the diagnosis. Moreover, the diagnostic techniques proposed are not all available as bedside tools, which might be an important factor for an early and repeatable diagnosis in hospitalized cirrhotic patients (Table 1). A proposed algorithm for nutritional screening and assessment in hospitalized cirrhotic patients is shown in Fig. 1.

## Tools for the Assessment of Muscle Mass

### Computed Tomography and Magnetic Resonance Imaging

The European Consensus Statement has identified computed tomography (CT) and magnetic resonance imaging (MRI) as the gold standard for the detection of muscle wasting in clinical trials nevertheless in clinical practice; the execution of CT and MRI is difficult to be justified only for quantifying muscle mass [16]. Furthermore, even if most cirrhotic patients undergo imaging techniques for surveillance of focal liver lesions, hepatocellular carcinoma, vascular disease, and pre-transplant evaluation, not all the centers have the availability of a software through which the muscle area can be calculated. For these reasons, the evaluation of the presence of sarcopenia by CT or MRI can be challenging, not immediately available, and difficult to repeat to monitor changes during time.

**Table 1: Tools to assess malnutrition/sarcopenia in cirrhotic patients.**

| Tool | What is measured | Advantages | Disadvantages |
|---|---|---|---|
| Computed tomography and magnetic resonance images | • Abdominal muscle area at L3-L4 as skeletal muscle index (SMI) | High sensitivity and specificity for the assessment of central sarcopenia | Difficult to repeat in short time<br>Specific software not always available<br>High costs |
| Dual-energy X-ray absorptiometry | • Fat-free mass index (FFMI)<br>• Fat mass index (FMI)<br>• Appendicular skeletal muscle index (ASMI) | Easy to perform<br>Repeatable<br>Regional body composition analysis<br>Lower radiation exposure than CT | FFMI influenced by water retention<br>Often unsuitable for bedside utilization |
| Ultrasonography | • Thigh muscle thickness | Easy to perform<br>Repeatable<br>Non-invasive<br>Bedside suitable | Not yet validated in a large population of cirrhotic patients<br>Normal values not available |
| Functional tests | • Handgrip (HG)<br>• 6-minutes-walking-test (6MWT) | Easy to perform<br>Repeatable<br>Self-pace<br>Good correlation with CT | Unsuitable for bed-utilization |
| Anthropometric measures | • Mid arm muscle circumference (MAMC)<br>• Triceps skin fold (TSF) | Easy to perform<br>Non-invasive<br>Rapid<br>Repeatable<br>Cost-effective<br>Good correlation with CT | Operator-dependent |
| Bioelectrical impedance | • Fat-free mass index (FFMI)<br>• Fat mass index (FMI) | Easy to perform<br>Non operator-dependent | Confounded by fluid retention, diuretic use, and high intensity exercise<br>Not always available |

Although heterogeneity exists about which abdominal muscles should be measured (psoas or total abdominal wall) and the site (third or fourth lumbar vertebra) [21••], the measurement of the abdominal muscle area at L3-L4 is considered the gold standard due to the relative independence from the activity level and water retention [7]. However, until now, validated reference values in healthy subjects based on ethnicity, age, sex, and location, which will help to specify more accurately the diagnosis of sarcopenia, are still lacking [22]. Multiple studies used different cutoff values for the definition of sarcopenia in cirrhotic patients utilizing threshold values from patients with cachexia due to malignancy or pulmonary disease, or proposing new cutoffs based on the mortality risk in patients with advanced liver disease [21••, 23]. Some studies suggested to utilize the psoas area for the diagnosis of sarcopenia in cirrhotic patients because of its depth and difficulty to be affected by abdominal distension in patients with ascites. Additionally, the psoas muscle can be easily identified on a CT scan [24–29]. However, this proposal has not been yet validated in large populations of cirrhotic patients.

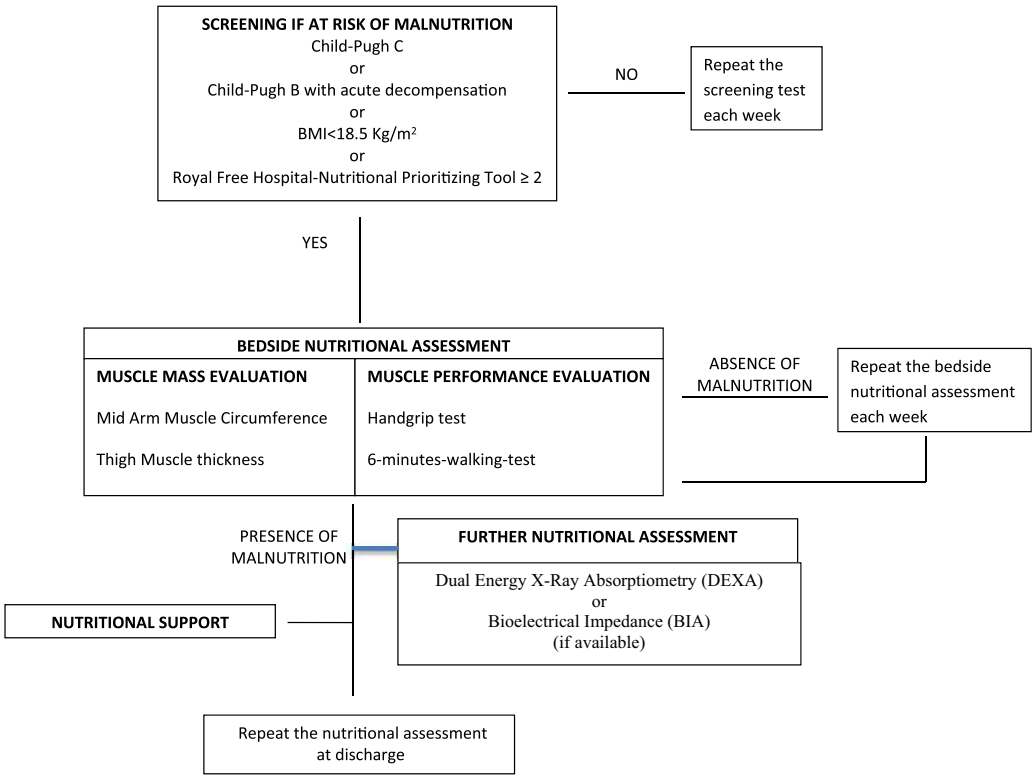



**Fig. 1:** Proposed algorithm for nutritional screening and assessment in hospitalized patients with cirrhosis.

Due to the above-mentioned limitations, other techniques have also been proposed as surrogate tools for malnutrition and sarcopenia assessment in liver cirrhosis.

## Anthropometric Measures

Anthropometric measures have been utilized to evaluate the nutritional status being objective, non-invasive, rapid, easy to perform, and cost-effective. Although anthropometric measures are defined inaccurate by some studies, they have been recommended in the European Guidelines of the Society of Parenteral and Enteral Nutrition [30]. At variance with BMI, the use of the mid arm muscle circumference (MAMC) is accepted because it explores the upper limb muscle where water retention is generally less relevant. Thus, anthropometry still represents the most repeatable and easy to use tool for the diagnosis of muscle wasting in hospitalized cirrhotic patients [31, 32]. The efficiency of anthropometry in assessing muscle depletion in cirrhosis was recently shown by the correlation of muscle mass area assessed by CT scan at the lumbar level and MAMC [33].

### Bioelectrical Impedance

Bioelectrical impedance analysis (BIA) remains a relatively controversial tool in assessing nutritional status because of its possible confounders, as fluid retention, diuretic use, liquid and food intake before the test, physical activity, and BMI value. All these issues make uncertain the measurements obtained through this method. Recently, the role of phase angle BIA has been emphasized because this technique is less influenced by overhydration [34]. However, the unavailability of the MFBIA in all centers and the impracticality to perform the test at bedside make this technique unsuitable for the nutritional assessment of hospitalized cirrhotic patients.

### Dual-energy X-ray Absorptiometry

Dual energy X-ray absorptiometry is an easy, reproducible, and accurate method to analyze body composition, which also allows a regional body composition analysis to study changes in fat mass and fat-free mass of selected body sites, which may be affected by muscle depletion at different rates. The main limit of this technique is that its validity is dependent on the assumptions relating the density and hydration fraction of the fat-free mass, which can be disturbed in patients with advanced liver disease due to water retention. Moreover, there are also discrepancies between men and women in DEXA, resulting from different characters of tissue loss. In cirrhotic women, more reduction in fat stores is observed with the maintenance of lean tissue, as in early starvation. In men, the loss of lean tissue is the most featured phenomenon that is also present in other chronic diseases. DEXA appendicular lean mass seems to slightly underestimate sarcopenia compared to muscle mass CT assessment [33]. Radiation exposure with DEXA is low but this technique is not always available and bedside utilization is not possible, making this technique unsuitable for the nutritional assessment of hospitalized cirrhotic patients.

### Thigh Muscle Thickness by Ultrasonography

Muscle mass and nutritional status are dynamic measures that can change very quickly. For this reason, repeatable and reproducible assessments are required to track changes over time. In a recent prospective study, the evaluation of thigh muscle thickness by ultrasonography identified sarcopenia almost as well as cross-sectional imaging [35]. This is an interesting result because thigh ultrasound is a low-cost, reliable, reproducible, and accurate measure of muscle mass that can be completed at the bedside or in a clinic setting and can be repeated without concern of radiation exposure. This technique, although promising, has not been yet validated in different cirrhotic populations and still lacks cutoffs or normal values.

## Tools for the Assessment of Muscle Performance

As already mentioned, the definition of sarcopenia should also include an assessment of muscle function. There are few well-validated techniques to measure muscle strength, among them the

hand grip (HG) test and the six-minute walk test (6MWT). Studies have shown that both these measures have prognostic importance.

### Handgrip Test

Handgrip strength of the non-dominant arm is a surrogate measure for muscle strength and is predictive of clinical outcomes [11, 16]. Some studies have reported that handgrip strength assessment is a good indicator of skeletal muscle function in cirrhosis as well as a predictor of decompensation of liver disease [36, 37]. The diagnosis of decreased muscle strength was based on HGS < 5th percentile according to standard values for the general population matched for age and sex [2]. Furthermore, in one study, an increase in hand grip strength of 1 kg led to a decrease in waitlist mortality of 11% [38].

### Six-minute Walk Test

A 6MWT lower than 250 m was found to be able to identify patients at increased risk for mortality before liver transplantation (sensitivity 90%); every 100-m improvement in the 6MWT was associated with a 52% reduction in mortality [39]. Although these results need to be further confirmed, it appears that 6MWT allows for objective measurement of sarcopenia and is a useful tool to monitor responses to interventions [11].

## Treatment

In mixed populations of malnourished patients, the benefits of nutrition therapy are evidenced by reductions in mortality, infections, systemic inflammatory responses, and hospital length of stay [40]. For cirrhotic patient, specific studies are limited by cohort size and trial design and there is no evidence-based effective nutritional interventions. The end points of these studies are frequently heterogeneous (regain in muscle strength, disappearance of sarcopenia, mortality, complications of portal hypertension, etc.) which make the results more difficult to analyze even through meta-analysis. One further explanation is that the mechanisms of muscle loss in liver disease are still not well understood which makes nutritional interventions not specifically targeted. Treatment approaches to date have focused on different strategies: calories or protein supplementation, stimulation of protein synthesis, encouragement to increase exercise and physical activity, use of anabolic hormones, and ammonia-lowering strategies. Some of these studies are summarized in Table 2. A proposed algorithm for nutritional support in hospitalized cirrhotic patients is shown in Fig. 2.

A crucial aspect of malnourishment management is to ensure that the patient's rehabilitative diet has the correct amount of each essential nutrient or macromolecule according to the current guidelines [3]. It is also recommended to shorten the duration of fasting periods during the day as there is evidence that a late evening and an early morning snack containing proteins are likely to have the greatest benefit on preventing continued muscle loss in cirrhosis [25].

**Table 2: Recent studies on nutritional intervention and/or exercise in cirrhotic patients.**

| | Protocol | Treatment | Patients | Aims | Results |
|---|---|---|---|---|---|
| Hiraoka *et al.* [41] | Interventional study | BCAA supplement (protein 13.5 g, 210 kcal/day) as a late evening snack + walking exercise (additional 2000 steps/day prescribed)<br>Time 12 weeks | 33 cirrhotic patients | Evaluate the improvement of muscle volume (using BIA) and function (leg and handgrip test). | Muscle volume, leg strength, and handgrip strength increased at 12 weeks ($p < 0.01$) |
| Koya *et al.* [42] | Interventional study | In-hospital exercise: a combination of stretching, strength training, balance practice, and endurance training (20 min/day)<br>Time: median length of therapeutic exercise was 7.5 days | 54 hospitalized cirrhotic patients with hepatocellular carcinoma | Investigate the effects of therapeutic exercise on liver function, 6-minute walk test, and skeletal muscle mass (using BIA). | Physical ability improved without worsening of liver function. No changes in 6MWT. Skeletal muscle mass significantly reduced (20.6 vs. 20.0 kg, $p = 0.03$). |
| Plank *et al.* [43] | Randomized clinical trial double blind | Perioperative immunonutrition (7.5 g arginine+3 g omega-3 fatty acid + 0.8 ribonucleic acid + water yields 600 ml er 1 kcal/mL) vs. isocaloric but not isonitrogenous product.<br>Time: until transplantation (2–3 months) | 101 patients undergoing liver transplantation (52 immunonutrition vs. 49 controls) | Evaluate the effect of immunonutrition on nutritional status, postoperative recovery, and postoperative infectious complications. | Loss of total body protein was seen in both groups at 30 days after liver transplantation ($P < 0.0001$). No difference in rate of infections and days for recovery |
| Roman *et al.* [44] | Randomized clinical trial | Exercise program vs relaxation program<br>Time: 1-h sessions, 3 days a week for 12 weeks | 25 cirrhotic patients (15 exercise program vs. 10 relaxation program) | Investigate the effects of moderate exercise on functional capacity (by cardiopulmonary exercise test), body composition (by DEXA), and risk of falls (by TUG). | Increase in functional capacity and muscle mass ($p = 0.01$) and decreased fat mass ($p = 0.003$) in patients following the exercise program. TUG decreased at the end of the study with respect to baseline ($p = 0.02$) only in the exercise group. |

cont'd...

...cont'd.

| | | | | | |
|---|---|---|---|---|---|
| Roman *et al*. [45] | Randomized pilot study | Exercise program + leucine supplementation (10 g/day) vs leucine 10 g/day<br>Time: 12 weeks | 17 cirrhotic patients (8 exercise + leucine vs 9 leucine) | To evaluate the efficacy and safety of an exercise program and leucine supplementation to increase exercise capacity and muscle mass. | In the exercise group, exercise capacity improved: an increase in the 6-min walk test from 365 m (160–420) to 445 m (250–500) ($p = 0.01$) and in the 2-min step test ($p = 0.02$). |
| Zenith *et al*. [46] | Randomized clinical trial | Exercise training vs no exercise training<br>Time: 8 weeks | 20 cirrhotic patients (10 exercise program vs. 10 controls) | To evaluate the safety and efficacy of 8 weeks of supervised exercise on peak exercise oxygen uptake, quadriceps muscle thickness, and quality of life. | Peak exercise oxygen uptake ($P = 0.001$); thigh circumference ($P = 0.01$) and thigh muscle thickness ($P = 0.01$) were higher in the exercise group compared to those with controls. |

*BCAA* branched-chain amino acids, *BIA* bioelectrical impedance analysis, *DEXA* dual-energy X-ray absorptiometry, *LEU* leucine, *TUG* time up & go

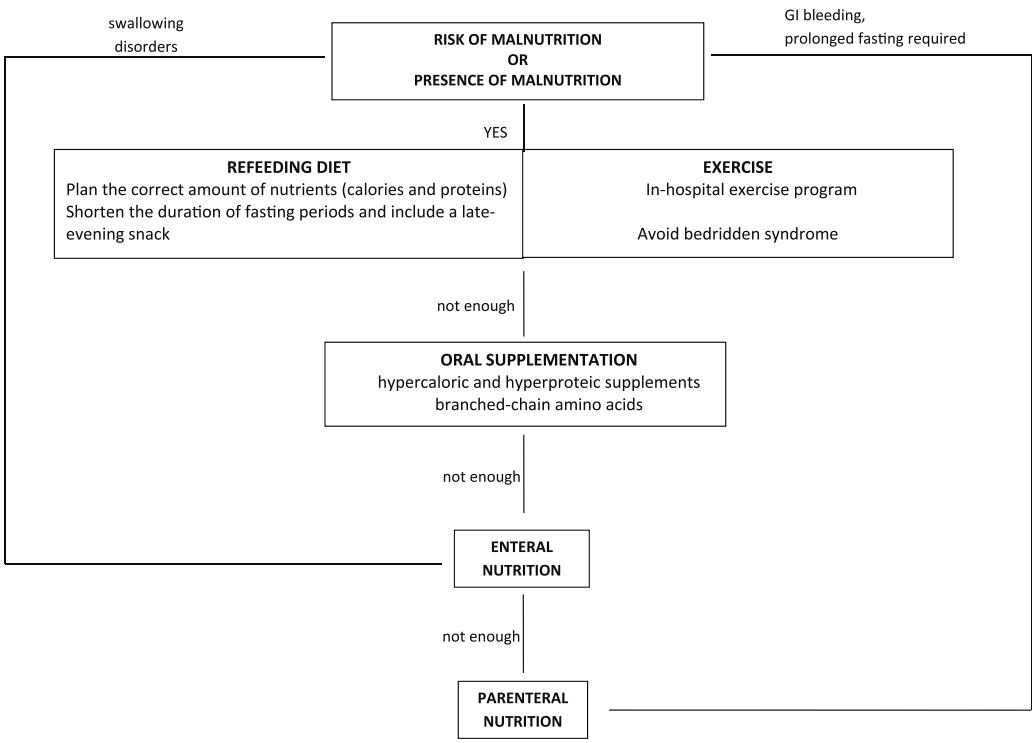



**Fig. 2:** Proposed algorithm for nutritional support in hospitalized cirrhotic patients.

Since caloric and protein intake is frequently decreased in patients with liver cirrhosis, and even more during hospitalization, regimens providing extra calories via high caloric feeding and/or enteral feeding have been proposed but results have been controversial. Long-term nutritional supplementation before liver transplantation, and immunonutrition supplement given before and perioperatively to liver transplant patients or a short-term nutritional support following gastrointestinal bleeding [43, 47, 48] have not been found to be beneficial vs control groups in randomized controlled trials. On the other hand, nutritional support with enteral nutrition in hospitalized malnourished cirrhotic patients and perioperative nutrition in cirrhotic patients undergoing surgery for hepatocellular carcinoma were found to improve patient's outcome and/or survival [49, 50].

Another important strategy in the treatment of malnutrition in cirrhotic patients is protein supplementation. Adequate protein intake to meet the increased protein requirements in patients with a diagnosis of liver cirrhosis with malnutrition has been defined as 1.2–1.5 g/kg body weight daily by the ESPEN guidelines [3]. A hyper-caloric and hyper-proteic oral diet in cirrhotic patients hospitalized for hepatic encephalopathy has been found to be beneficial and protein re-feeding is a possible target for malnourished cirrhotic patients [51, 52]. Few patients are really intolerant to a progressive increase in their diet protein content; however, in these cases, further strategies have been proposed such as the use of vegetable diets or the introduction of branched-chain amino

acids (BCAA) supplements [53]. Hepatic insufficiency causes an increase in aromatic amino acids and a decrease in plasma BCAA (leucine, isoleucine, and valine), and following this observation, BCAA supplementation was initially proposed mainly for the treatment of hepatic encephalopathy [54]. However, previous data on the use of iv BCAA in patients with overt hepatic encephalopathy have been controversial [55]. More recently, BCAA supplementation has been utilized mainly in long-term studies considering the opportunity to increase patients' protein intake and taking advantage from their possible anti-catabolic effect [56]. Some of these studies showed amelioration in muscle mass and function and the ability of BCAA supplementation and exercise to prevent a decrease in muscle volume in hospitalized HCC patients [41, 42, 57].

Furthermore, leucine directly activates mTORC1 that stimulates protein synthesis and decreases autophagy and in a recent small study in six alcoholic cirrhotic patients and eight healthy controls, a single oral BCAA mixture enriched with leucine was able to reverse the mechanism of muscle wasting in muscle biopsies [58, 59•]. Clinical studies evaluating the effect of BCAA supplementation during a hospitalization in cirrhotic patients are not yet available.

As shown by previous studies in sarcopenic cirrhotic patients, a concomitant intervention introducing a moderate daily exercise in association with BCAA supplementation may act synergistically to improve muscle function [44–46].

## Conclusions

In conclusion, cirrhotic patients are at high risk of deterioration of their nutritional status during hospitalization. For this reason, a nutritional screening for early identification of those at risk of malnutrition and a subsequent nutritional assessment is of great importance to take care of the nutritional needs of these patients. The assessment of sarcopenia is helpful to identify patients with higher probability to develop complications and expected to have a longer hospital stay. There are a number of tools to assess sarcopenia in hospitalized patients with cirrhosis. While the muscle area assessed by CT is considered at present the gold standard, other methods can be utilized based on availability and considering their limits. Nutritional support to reverse or prevent deterioration of malnutrition in hospitalized cirrhotic patients should be always considered although clinical trials have produced not univocal results. BCAA supplementation and exercise are promising measures that could be adopted but how to optimize these interventions is still to be defined. Moreover, taking into account the improving knowledge about the molecular mechanism of sarcopenia in liver cirrhosis, target therapies, through myostatin antagonists, direct mTORC1 activators, antioxidants, and mitochondrial protective agents, might have the potential to benefit skeletal muscle [58, 59•, 60].

Careful mechanistic studies are necessary with preclinical testing before these interventions can be translated to clinical practice [17••].

**Compliance with Ethical Standards**

**Conflict of Interest** Barbara Lattanzi, Daria D'Ambrosio, and Veronica Fedele declare no conflicts of interest. Manuela Merli reports personal fees from Kedrion and grants from Griffols, outside the submitted work.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance


1. Amodio P, Bemeur C, Butterworth R, Cordoba J, Kato A, Montagnese S, *et al*. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. Hepatology. 2013;58(1):325–36. https://doi.org/10.1002/hep.26370
2. Merli M, Giusto M, Lucidi C, Giannelli V, Pentassuglio I, Di Gregorio V, *et al*. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. Metab Brain Dis. 2013;28:281–4. https://doi.org/10.1007/s11011-012-9365-z
3. Plauth M, Merli M, Kondrup J, Weimann A, Ferenci P, Müller MJ. ESPEN guidelines for nutrition in liver disease and transplantation. Clin Nutr. 1997;16:43–55.
4. Merli M, Giusto M, Gentili F, Novelli G, Ferretti G, Riggio O, *et al*. Nutritional status: its influence on the outcome of patients undergoing liver transplantation. Liver Int. 2010;30:208–14. https://doi.org/10.1111/j.1478-3231.2009.02135.x
5. Merli M, Riggio O, Dally L. Does malnutrition affect survival in cirrhosis? PINC (Policentrica Italiana Nutrizione Cirrosi). Hepatology. 1996;23:1041–6. https://doi.org/10.1002/hep.510230516
6. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, *et al*. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) 'cachexia-anorexia in chronic wasting diseases' and 'nutrition in geriatrics'. Clin Nutr. 2010;29:154–9. https://doi.org/10.1016/j.clnu.2009.12.004
7. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, *et al*. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol. 2012;10:166–173 e161. https://doi.org/10.1016/j.cgh.2011.08.028
8. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, *et al*. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. Liver Transpl. 2012;18(10):1209–16. https://doi.org/10.1002/lt.23495
9.• Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CM, Sawyer MB, Beaumont C, *et al*. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle. 2016;7(2):126–35. https://doi.org/10.1002/jcsm.12039. **A study that clarifies that sarcopenic obesity is very common in cirrhotic patients and is associated with higher mortality in cirrhosis**.
10. Charlton M. Evolving aspects of liver transplantation for nonalcoholic steatohepatitis. Curr Opin Organ Transplant. 2013;18:251–8. https://doi.org/10.1097/MOT.0b013e3283615d30
11. Bhanji RA, Narayanan P, Allen AM, Malhi H, Watt KD. Sarcopenia in hiding: The risk and consequence of underestimating muscle dysfunction in nonalcoholic steatohepatitis. Hepatology. 2017;66(6):2055–65. https://doi.org/10.1002/hep.29420
12.•• Tandon R, Mourtzakis M, Merli M. A Practical Approach to Nutritional Screening and Assessment in Cirrhosis. Hepatology. 2017;65(3):1044–57. https://doi.org/10.1002/hep.29003. **A study that identifies the relevance of malnutrition in patients with liver cirrhosis, and suggests methods of screening and assessment**.
13. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, *et al*. Diagnostic criteria for malnutrition—an ESPEN consensus statement. Clin Nutr. 2015;34:335–40. https://doi.org/10.1016/j.clnu.2015.03.001
14. Borhofen SM, Gerner C, Lehmann J, Fimmers R, Görtzen J, Hey B, *et al*. The Royal Free Hospital-Nutritional Prioritizing Tool Is an Independent Predictor of Deterioration of Liver Function and Survival in Cirrhosis. Dig Dis Sci. 2016;61(6):1735–43. https://doi.org/10.1007/s10620-015-4015-z
15. White JV, Guenter P, Jensen G, Malone A, Schofield M, Acad-emy Malnutrition Work Group, *et al*. Consensus statement: Acade-my of Nutrition and Dietetics and American Society for Paren-teral and Enteral Nutrition: characteristics recommended for thei dentification and documentation of adult malnutrition (undernutrition). JPEN J Parenter Enteral Nutr. 2012;36:275–83. https://doi.org/10.1177/0148607112440285
16. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, *et al*. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412–23. https://doi.org/10.1093/ageing/afq034
17.•• Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol. 2016;65:1232–44. https://doi.org/10.1016/j.jhep.2016.07.040. **An extensive review that clarifies the main pathogenic mechanisms of sarcopenia and explains how to diagnose it and possible treatment approaches**.
18. Kallwitz ER. Sarcopenia and liver transplant: The relevance of too little muscle mass. World J Gastroenterol. 2015;21:10982–93. https://doi.org/10.3748/wjg.v21.i39.10982

19. Dasarathy J, Alkhouri N, Dasarathy S. Changes in body composition after transjugular intrahepatic portosystemic stent in cirrhosis: a critical review of literature. Liver Int. 2011;31:1250–8. https://doi.org/10.1111/j.1478-3231.2011.02498.x
20. Merli M, Romiti A, Riggio O, Capocaccia L. A multicenter study to define sarcopenia in patients with end-stage liver disease. Optimal nutritional indexes in chronic liver disease. JPEN J Parenter Enteral Nutr. 1987;11:130S–4S.
21.•• Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, *et al*. Fitness, Life Enhancement, and Exercise in Liver Transplantation Consortium. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transpl. 2017;23(5):625–33. https://doi.org/10.1002/lt.24750. **A multicenter study that identifies the cutoff for the diagnosis of CT assessed sarcopenia in cirrhotic patients predicting mortality at 6 months**.
22. Holt EW, Frederick RT, Verhille MS. Prognostic value of muscle wasting in cirrhotic patients. Clin Gastroenterol Hepatol. 2012;10(9):1056; author reply 1056-7. https://doi.org/10.1016/j.cgh.2012.03.019
23. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, *et al*. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010;211:271–8. https://doi.org/10.1016/j.jamcollsurg.2010.03.039
24. Durand F, Buyse S, Francoz C, Laouenan C, Bruno O, Belghiti J, *et al*. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. J Hepatol. 2014;60:1151–7. https://doi.org/10.1016/j.jhep.2014.02.026
25. Tsien C, Garber A, Narayanan A, Shah SN, Barnes D, Eghtesad B, *et al*. Postliver transplantation sarcopenia in cirrhosis: a prospective evaluation. J Gastroenterol Hepatol. 2014;29:1250–7. https://doi.org/10.1111/jgh.12524
26. Kim TY, Kim MY, Sohn JH, Kim SM, Ryu JA, Lim S, *et al*. Sarcopenia as a useful predictor for long-term mortality in cirrhotic patients with ascites. J Korean Med Sci. 2014;29:1253–9. https://doi.org/10.3346/jkms.2014.29.9.1253
27. Krell RW, Kaul DR, Martin AR, Englesbe MJ, Sonnenday CJ, Cai S, *et al*. Association between sarcopenia and the risk of serious infection among adults undergoing liver transplantation. Liver Transpl. 2013;19:1396–402. https://doi.org/10.1002/lt.23752
28. Cruz RJ Jr, Dew MA, Myaskovsky L, Goodpaster B, Fox K, Fontes P, *et al*. Objective radiologic assessment of body composition in patients with endstage liver disease: going beyond the BMI. Transplantation. 2013;95:617–22. https://doi.org/10.1097/TP.0b013e31827a0f27
29. DiMartini A, Cruz RJ Jr, Dew MA, Myaskovsky L, Goodpaster B, Fox K, *et al*. Muscle mass predicts outcomes following liver transplantation. Liver Transpl. 2013;19:1172–80. https://doi.org/10.1002/lt.23724
30. Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, *et al*. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr. 2006;25(2):285–94. https://doi.org/10.1016/j.clnu.2006.01.018
31. Kalafateli M, Mantzoukis K, Choi Yau Y, Mohammad AO, Arora S, Rodrigues S, *et al*. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. J Cachexia Sarcopenia Muscle. 2017;8(1):113–21. https://doi.org/10.1002/jcsm.12095
32. Figueiredo FA, Dickson ER, Pasha TM, Porayko MK, Therneau TM, Malinchoc M, *et al*. Utility of standard nutritional parameters in detecting body cell mass depletion in patients with end-stage liver dis-ease. Liver Transpl. 2000;6:575–81. https://doi.org/10.1053/jlts.2000.9736
33. Giusto M, Lattanzi B, Albanese C, Galtieri A, Farcomeni A, Giannelli V, *et al*. Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry. Eur J Gastroenterol Hepatol. 2015;27(3):328–34. https://doi.org/10.1097/MEG.0000000000000274
34. Belarmino G, Gonzalez MC, Torrinhas RS, Sala P, Andraus W, D'Albuquerque LA, *et al*. Phase angle obtained by bioelectrical impedance analysis independently predicts mortality in patients with cirrhosis. World J Hepatol. 2017;9(7):401–8. https://doi.org/10.4254/wjh.v9.i7.401
35. Tandon P, Low G, Mourtzakis M, Zenith L, Myers RP, Abraldes JG, *et al*. A Model to Identify Sarcopenia in Patients With Cirrhosis. Clin Gastroenterol Hepatol. 2016;14(10):1473–1480.e3. https://doi.org/10.1016/j.cgh.2016.04.040
36. Hirsch S, Bunout D, de la Maza P, Iturriaga H, Petermann M, Icazar G, *et al*. Controlled trial on nutrition supplementation in outpatients with symptomatic alcoholic cirrhosis. JPEN J Parenter Enteral Nutr. 1993;17:119–24. https://doi.org/10.1177/0148607193017002119
37. Alvares-da-Silva MR. Reverbel da Silveira T. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. Nutrition. 2005;21:113–7. https://doi.org/10.1016/j.nut.2004.02.002
38. Lai JC, Dodge JL, Sen S, *et al*. Functional decline in patients with cirrhosis awaiting liver transplantation: Results from the functional assessment in liver transplantation (FrAILT) study. Hepatology (Baltimore, Md). 2016;63(2):574–80. https://doi.org/10.1002/hep.28316
39. Carey EJ, Steidley DE, Aqel BA, *et al*. Six-minute walk distance predicts mortality in liver transplant candidates. Liver Transpl. 2010;16(12):1373–8. https://doi.org/10.1002/lt.22167
40. McClave SA, DiBaise JK, Mullin GE, Martindale RG. ACG Clinical Guideline: Nutrition therapy in the adult hospitalized patient. Am J Gastroenterol. 2016; https://doi.org/10.1038/ajg.2016.28

41. Hiraoka A, Michitaka K, Kiguchi D, Izumoto H, Ueki H, Kaneto M, *et al*. Efficacy of branched-chain amino acid supplementation and walking exercise for preventing sarcopenia in patients with liver cirrhosis. Eur J Gastroenterol Hepatol. 2017;29(12):1416–23. https://doi.org/10.1097/MEG.0000000000000986
42. Koya S, Kawaguchi T, Hashida R, Goto E, Matsuse H, Saito H, *et al*. Effects of in-hospital exercise on liver function, physical ability and muscle mass during treatment of hepatoma in patients with chronic liver disease. Hepatol Res. 2016;47:E22–34. https://doi.org/10.1111/hepr.12718
43. Plank LD, Mathur S, Gane EJ, Peng SL, Gillanders LK, McIlroy K, *et al*. Perioperative immunonutrition in patients undergoing liver transplantation: a randomized double-blind trial. Hepatology. 2015;61(2):639–47. https://doi.org/10.1002/hep.27433
44. Román E, García-Galcerán C, Torrades T, Herrera S, Marín A, Donate M, *et al*. Effects of an exercise programme on functional capacity. Body composition and risk of falls in patients with cirrhosis: a randomized clinicaltrial. PLoS One. 2016;11:e0151652. https://doi.org/10.1371/journal.pone.0151652
45. Román E, Torrades MT, Nadal MJ, Cárdenas G, Nieto JC, Vidal S, *et al*. Randomized pilot study: effects of an exercise programme and leucine supplementation in patients with cirrhosis. Dig Dis Sci. 2014;59(8):1966–75. https://doi.org/10.1007/s10620-014-3086-6
46. Zenith L, Meena N, Ramadi A, Yavari M, Harvey A, Carbonneau M, *et al*. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. Clin Gastroenterol Hepatol. 2014;12:1920–6. https://doi.org/10.1016/j.cgh.2014.04.016
47. Le Cornu KA, McKiernan FJ, Kapadia SA, Neuberger JM. A prospective randomized study of preoperative nutritional supplementation in patients awaiting elective orthotopic liver transplantation. Transplantation. 2000;69:1364–9.
48. de Lédinghen V, Beau P, Mannant PR, Borderie C, Ripault MP, Silvain C, *et al*. Early feeding or enteral nutrition in patients with cirrhosis after bleeding from esophageal varices? A randomized controlled study. Dig Dis Sci. 1997;42(3):536–41.
49. Cabre E, Gonzalez-Huix F, Abad-Lacruz A, Esteve M, Acero D, Fernandez-Bañares F, *et al*. Effect of total enteral nutrition on the short-term outcome of severely malnourished cirrhotics. A randomized controlled trial. Gastroenterology. 1990;98(3):715–20.
50. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med. 1994;331(23):1547–52. https://doi.org/10.1056/NEJM199412083312303
51. Gheorghe L, Iacob R, Vădan R, Iacob S, Gheorghe C. Improvement of hepatic encephalopathy using a modified high-calorie high-protein diet. Rom J Gastroenterol. 2005;14(3):231–8.
52. Kondrup J, Müller MJ. Energy and protein requirements of patients with chronic liver disease. J Hepatol. 1997;27(1):239–47. Review
53. Amodio P, Caregaro L, Pattenò E, Marcon M, Del Piccolo F, Gatta A. Vegetarian diets in hepatic encephalopathy: facts or fantasies? Dig Liver Dis. 2001;33(6):492–500. Review
54. Vergara M, Castro-Gutiérrez V, Rada G. Do branched chain amino acids improve hepatic encephalopathy in cirrhosis? Medwave. 2016;16(Suppl5):e6795.
55. Gluud LL, Dam G, Les I, Marchesini G, Borre M, Aagaard NK, *et al*. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2017;5:CD001939. https://doi.org/10.1002/14651858.CD001939.pub4
56. Dasarathy S. Consilience in sarcopenia of cirrhosis. J Cachexia Sarcopenia Muscle. 2012;3:225–37. https://doi.org/10.1007/s13539-012-0069-3
57. Les I, Doval E, García-Martínez R, Planas M, Cárdenas G, Gómez P, *et al*. Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy: a randomized study. Am J Gastroenterol. 2011;106(6):1081–8. https://doi.org/10.1038/ajg.2011.9
58. Carroll B, Korolchuk VI, Sarkar S. Amino acids and autophagy: cross-talk and co-operation to control cellular homeostasis. Amino Acids. 2015;47:2065–88. https://doi.org/10.1007/s00726-014-1775-2
59.• Tsien C, Davuluri G, Singh D, Allawy A, Ten Have GA, Thapaliya S, *et al*. Metabolic and molecular responses to leucine-enriched branched chain amino acid supplementation in the skeletal muscle of alcoholic cirrhosis. Hepatology. 2015;61(6):2018–29. https://doi.org/10.1002/hep.27717. **A study showing that leucine-enriched branched chain amino acid supplementation improves sarcopenia and the mechanisms by which it exerts this action in patients with alcoholic cirrhosis**.
60. Han HQ, Zhou X, Mitch WE, Goldberg AL. Myostatin/activin pathway antagonism: molecular basis and therapeutic potential. Int J Biochem Cell Biol. 2013;45(10):2333–47. https://doi.org/10.1016/j.biocel.2013.05.019

Source: Lattanzi, B., D'Ambrosio, D., Fedele, V. *et al*. *Curr Hepatology Rep* (2018) 17: 88. https://doi.org/10.1007/s11901-018-0398-6.

4

# Succession planning and leadership development

**Paul Turner**

## The Importance of Leadership and Management

Leadership is an essential health sector practice which has a direct impact on clinical and organisational outcomes and an indirect effect on all other elements of the operational environment (Longenecker and Longenecker 2014; Redknap *et al.* 2015: 266; Sarto and Veronesi 2016), and leaders are critical to the success of healthcare systems in implementing and sustaining strategic change (Block and Manning 2007). Hence, developing high-performing leaders at multiple levels in the sector is important if the vision for transforming healthcare is to be realised (Mazzoccoli and Wolf 2016). It follows that understanding the characteristics inherent in such leaders is a priority for any leadership development activity. Amongst the identified leadership styles in this context are to be values-driven (Dye 2017) and to adopt authentic leadership which can foster relational social capital and positive health outcomes (Read and Laschinger 2015). However, these are just two of a 'vast number of frameworks and theories' (Edger 2012: 115) that have fed into the leadership debate.

Leaders have been defined as those who could 'mobilise others to want to get extraordinary things done in organisations … transform values into actions, visions into realities, obstacles into innovations, separateness into solidarity, risks into rewards … create a climate in which people turn challenging opportunities into remarkable successes' (Kouzes and Posner 2007: 8), or they were those who could influence a group of people to commit willingly to a common goal (Edger 2012), or they fit the profile of Collins's *Good to Great* 'Level 5' (2001), balancing personal humility and professional will to make the right decisions happen. A significant study synthesised the traits of effective leaders as charisma, clarity of vision and strategic objectives, decisiveness, inspirational communication, integrity, trust and delegation, honesty and consistency with a genuine interest in staff (Alimo-Metcalfe and Alban-Metcalfe 2003). Other analyses of the attributes of leaders included those associated with behavioural and style theories, contingency and situational leadership, whether leaders were transformational or transactional in their approach,

**Paul Turner**
Leeds Business School, Leeds Beckett University, Leeds, UK

and the importance of emotional leadership. In most of these analyses, leaders are those people at the apex of the organisation who are responsible for setting strategy and policy. These definitions often focused on the inherent competences or characteristics of individuals and had a focus on individual traits. Unsurprisingly, given their importance, creating a sufficient number of leaders to operate at the highest level, leaders who could either provide continuity in the organisation's strategy or transform it to a new ideal, leaders who could make the right decisions and who were able to persuade others to deliver the operational outcomes of the decisions has been the focus of talent management to date.

But traditional approaches to leadership have come under some scrutiny with the conclusion that 'although it is one of the most-observed concepts, no universally accepted definition or theory of leadership actually exists' (Scully 2015: 439). Subsequent analyses identified the need to extend the definition of leadership beyond the 'role of charismatic individuals … in setting compelling visions to which all organizational actors are expected to subscribe' (Collinson and Tourish 2015). It was noted that the traditional definition paid little attention to power dynamics, the importance of organisational and environmental context, and the significance of follower engagement. Nor did it take sufficient account of the fact that leadership took place at levels other than at the most senior. Goffee and Jones's (2006) point of view that leadership was situational and non-hierarchical has significance and is one which resonates most in a world no longer characterised by bureaucratic lines of demarcation with complex and fluid organisational networks and matrices supplementing classic hierarchies. Furthermore, there is recognition of the difference between the concept of *leader*, a person who has appropriate individual traits and emotional intelligence, and *leadership*, which concerns the social exchanges that take place in organisations at multiple levels.

This dynamic picture of leaders and leadership has implications when considering talent management and, in particular, leadership development. It also has an impact on which people and roles should be considered in the succession planning process. In both instances, a contemporary view is that leaders exist at and leadership takes place at multiple levels. Understanding the implications of this for both succession planning and leadership development is critical to the success of talent management.

## Leadership at the Highest Levels of Healthcare Organisations

The constant and rapid change that is a feature of healthcare highlights the need for strong leaders and leadership at the highest levels of health sector organisations (McAlearney 2010). The abilities of health leaders have been identified as being critical to the achievement of the organisation's objectives, whether these relate to clinical outcomes (Ang *et al.* 2016) or business and operational performance. Effective leadership is essential to an effective healthcare strategy (Wells and Hejna 2009).

In this context, leaders in health have been defined as 'people who can guide others to achieve a desired goal and demonstrate the ability to augment productivity, create sustainable change, and inspire others to engage in professional development' (Chan *et al.* 2015: 342). It was noted

that to be successful 'a leader must have a clear understanding of where the organization is today, the current health care climate, and the mission and vision of the organization. Understanding the gaps that exist in care and developing creative ways to fill those gaps with the team is imperative to empower staff and engage them in solutions' (Elwell 2015: 313). Health sector leaders are those who 'establish direction, align people, motivate and inspire colleagues towards a common goal' (Scully 2015: 439), often in an environment of unprecedented complexity (Daly *et al*. 2015). It has been argued that, amongst these multiple definitions, 'servant leadership aligns well with the needs for leadership in health care because health care providers' work, and their life calling, is to serve their patients. The ethical and moral aspects of servant leadership require a healthcare provider to put the physical, emotional, and financial needs of the patient first. The skill set of listening, empathy, awareness, healing, and persuasion all contribute to a healthy healthcare provider-patient relationship' (Trastek *et al*. 2014: 380).

It is important to have clarity because leaders are critical in achieving the care, compassion, courage, commitment, communication and competency enshrined in healthcare organisations (Leigh *et al*. 2015) in three ways. Firstly, they articulate the vision of the future to which the organisation aspires and which enables business decisions, plans and activities to be directed accordingly (Gulati *et al*. 2016). Secondly, they create a culture in which talented individuals can deliver these objectives and at the same time achieve their full potential. Thirdly, leadership at multiple levels is an important factor in delivering high-impact healthcare programmes. It is out of the recognition of these points that strenuous efforts are being made to spread leadership training and development on a global basis to ensure that health sector organisations will be best equipped wherever they are based.

For many, leaders exist at and leadership takes place at the highest levels of the organisation and this has produced a positive impact on motivation during times of transformation and change (Deschamps *et al*. 2016). The implication is that the presence of skilled and knowledgeable leaders will facilitate the organisation's ability to deal with such change. To do so, health leaders manage 'the gap between the former traditional model of healthcare and a future emerging model that remains shrouded in the mist' by examining 'the scope and nature of the change we are facing during this period of turmoil and ambiguity, in order to develop effective strategies for leading organizations and the profession into the future' (Fitzsimmons and Rose 2015: 34); and on the other hand, leaders can facilitate shared governance and a united voice as means to successful transformation of healthcare organisations (Nelson and Pilon 2015).

The complexity of leadership in health with demands for public advocacy, networking and negotiation (Kumar *et al*. 2015) as well as those skills 'normally' associated with the role places a particular emphasis on the type of leader and leadership required. A European study demonstrated the scale of the challenge by identifying fifty-two competences in eight domains for health leaders, including the ability to understand health issues and synthesise divergent viewpoints and an understanding of reflective leadership, servant leadership, adaptive leadership and the application of emotional leadership (Czabanowska *et al*. 2014). Furthermore, in India, leaders in healthcare were expected to have competence in multiple domains, including technical, cognitive, and emotional competences, because 'to be a successful leader one needs to regularly review

one's emotional competences and improve these by learning from interactions one could have done better' (Kumar *et al*. 2015: 161). In the complex and changing landscape of the U.S. health, 'effective leaders at the frontline' (Kim *et al*. 2014: 545) needed the ability to negotiate through the complexity and provide strategic direction. A growing number of clinical specialists moving to senior healthcare leadership positions adds a further dimension (Henson 2016).


**Fig. 1:** The competences associated with leaders and leadership in the health sector. Sources: Czabanowska *et al*. (2014), Day *et al*. (2014), de Jong *et al*. (2014), Goleman (1996, 1998), Kim *et al*. (2014), Scully (2015), Kumar *et al*. (2015), Love and Ayadi (2015), Shariff (2015), Hamlin *et al*. (2002, 2010).

In the UK public health sector, 'five talents for public health leadership' were identified—mentoring-nurturing, shaping-organising, networking-connecting, knowing-interpreting and advocating-impacting (Day *et al.* 2014)—whilst in Africa the ability to influence, communicate effectively and build relationships (Shariff 2015) was important because influencing health policy was a prime objective of health leaders.

A synthesis of the analysis that has taken place for leadership in the health sector highlights three critical areas of competence. The first is the personal insight that should be demonstrated by leaders at whichever level they operate. This will include popular concepts such as emotional intelligence. The second is that of professional credibility which will need to be demonstrated in whichever leadership role is undertaken (clinical, technical or managerial) if followership is to be secured. The third is that of an understanding of the organisation's dynamics if the leader is to negotiate his or her way through systems and processes in order to secure resources to deliver unit or departmental objectives. Figure 1 shows some of the characteristics within these three areas.

These studies reflect the fact that at the highest level of the organisation leadership in health is a complex process. Having the right leaders in place, backed up by effective leadership development to support individuals through this complexity, is critical. Successfully doing so can have a positive impact on the achievement of the organisation's mission, goals, strategy, stewardship and policy. This is why leadership has been the main focus for talent management in many health organisations.

## Devolved Leadership in the Health Sector

The performance of leaders and their influence on health strategy were instrumental in increasing the number of active health professionals and the opening of new institutions for higher education in healthcare and training schools for paramedical staff and midwives (Kingue *et al.* 2013). Furthermore, investing in transformational leadership development reduced turnover among public sector mental health providers (Green *et al.* 2013). Where organisations in the South African healthcare sector (Stander *et al.* 2015) encouraged authentic leadership, it led to higher levels of optimism, trust in the organisation and eventually work engagement. It can also moderate follower intentions (Green *et al.* 2013). These examples show the power and importance of high-level leadership. But there is also evidence for a broader scope in the definition of leadership in health which is important to deal with organisational complexity.

The situational and non-hierarchical nature of the contemporary leadership view implies that the concept is extended beyond a few at the very top of the organisation and their successors. In such cases, the question of overlaps with what has traditionally been considered management is raised, for example, by describing nurse leaders as leaders and at the same time 'the most senior people in the hospital—the executive and board—are regularly described as the leadership team … consequently, there seems to be little in the way of an easy explanation as to what leadership and management are' (Ellis and Abbott 2015).

There have been attempts to differentiate between the two over time. Bennis (2001), for example, tried to distinguish the leader role from that of the manager, believing that managers

administered whilst leaders innovated, that managers maintained the running of the organisation whilst leaders developed new ideas, strategies and concepts, and that managers were concerned mainly with systems and processes whilst leaders with people. This had credibility where roles were clearly delineated and the boundaries between what was leadership and what was management could be identified. But more recent analyses concluded that leaders could not simply delegate management; and Mintzberg (2011) argued that instead of being distinguished from leaders as performing separate roles, managers should be seen as leaders and that leadership should be seen as management practiced well; 'the operation of leadership forms one of the elements of management practice. Different situations require the application of different skill sets, but those skill sets can reside in the same person' (Ellis and Abbott 2015: 97).

The enhanced view of leaders and leadership has been caused, in part, because health sector organisations are inundated with change caused by 'multifaceted developments in the technological, political, financial, professional, scientific, and social realms are rapidly redefining the nature of healthcare and healthcare delivery' (Fitzsimmons and Rose 2015: 33). In this context, leadership will be essential at multiple levels if organisations are to perform effectively.

In the British NHS, for example, the emphasis has moved over time from a main focus on a cadre of senior leaders who could manage large-scale transformation (still a critical area), to leaders and managers at multiple levels embracing smaller clinical units and multi-disciplinary teams, to those leaders who are skilled at working across systems and boundaries (Department of Health 2009). This is leadership along a spectrum. It is distributed leadership as noted by the UK National Leadership Council, which proposed that 'world-class leadership talent and leadership development will exist at every level in the health system to ensure high quality care for all' ('*The changing role of managers in the NHS*' 2011). The need for this was reinforced by the multiple recommendations highlighted in the NHS by the 2013 'Francis Report', which advocated the creation of a culture which integrated essential shared values into all processes, the accountability of leaders and senior managers, and the enhancement of leadership recruitment, education, training and support.

## Leadership from Board to Ward

The emphasis on leaders and leadership in the health sector is based on the necessity to deal with complex challenges and at the same time satisfy the aspirations of a wide range of stakeholders in meeting these challenges (including patients, consumers of health services, the health workforce, regulators and financial stakeholders) such that 'effective clinical leadership at board level is essential and has never been more necessary' (King's Fund 2009: iv). But these aren't the only forces that have an impact on the quantity and quality of leaders. Additional factors are complex business models, such as multi-hospital healthcare systems, which have unique leadership challenges due to the scale of operations (McAlearney 2010), local or regional health leadership needs (Mansour *et al*. 2010), and the global nature of talent challenges. To deal with these forces will require clarity about what leadership in health is and how far into the organisation the concept extends.

There is some progress towards resolving this dilemma and particularly between the roles of leaders and managers. Given that the concept of leadership is complex and multi-dimensional and that no universally accepted definition or theory of leadership exists, there is increasing clarity about the overlaps and differences between leadership and management (Scully 2015). Lawrence and Richardson's UK study (2014) of the leadership experiences in an acute unit within the NHS found that local leaders did not follow a single leadership approach but in fact adapted the approach to their environment. Here, leadership was contextual and non-hierarchical, contained elements of what might be traditionally referred to as management and combined both into an effective single modus operandi.

Increasingly, leaders will be, for example, 'staff nurses who exert significant influence over other individuals in the healthcare team, and although no formal authority has been vested in them facilitates individual and collective efforts to accomplish shared clinical objectives' (Chavez and Yoder 2015: 90) or those at the point of care from where effective leadership has been shown to improve patient safety and satisfaction and decrease mortality (Wong and Cummings 2007) and those in devolved positions of leadership (with different types of leadership strengths) in all parts of the health organisation with evidence of multiple positive outcomes (Titzer *et al*. 2013: 972; Chan *et al*. 2015). Extending the concept of leadership in this way will require crafting if it is to be delivered effectively.

Health sector leadership will drive transformation and change, it will create a unifying vision around which the workforce can mobilise and it will inculcate a culture of fairness and transparency, opportunity and engagement. But this is only one part of the leadership paradigm for health, and recognition that leadership takes place at all levels will allow a more holistic scope to both succession management and leadership development in a way that balances the needs of multiple types and levels of leadership practice. This will be necessary to satisfy the dual objectives of leaders to deal with leadership at the point of care as well as organisation-wide change and transformation.

These points of view highlight the fact that different health contexts, organisation structures and cultures demand different types of leadership moving towards the devolved and non-hierarchical. Indeed, the complexity of the health sector environment would favour leaders of different styles and temperament. These would include those with strategic vision and the ability to steer the organisation along a particular path on the one hand; and on the other with the ability to craft a strategy within complex environmental boundaries and subject to unpredictable forces of. In all cases, leadership in health will require personal insight, professional credibility and an understanding of organisational dynamics.

To date, much of the activity in talent management in health has been focused on those in the highest level of leadership, based on the view of the necessity of the right level of competent leaders as the organisation goes through periods of change. It is unlikely that a small group of high-level leaders would be able to deal with such a wide and diverse range of forces without leadership interventions at multiple levels. How this plays out in reality will determine how talent management can contribute to their recruitment, development, management and retention of leaders in the healthcare sector.

## Defining Succession Planning in the Health Sector

In support of the identification and development of leaders, succession planning contributes to ensuring a sufficient quantity, with the right outlook and skill set and continuity in leadership for the organisation over time (Carriere *et al*. 2009; Baron *et al*. 2010; Griffith 2012: 901; Titzer *et al*. 2013). This is a planned and systematic approach which frames succession planning in a range of leadership competences, traits or attributes and relates these to both organisational objectives and talent strategy.

In this context, succession planning in the health sector has been defined as 'a strategic process involving identification, development and evaluation of intellectual capital, ensuring leadership continuity within an organisation' (Titzer *et al*. 2013: 972) or as 'a deliberate and proactive process of identifying key, generally senior-level positions' which if became vacant would be detrimental to the organisation's performance (Kurec 2012: 23). For the most senior positions, identifying desired leadership competences was considered to be the foundation of succession from which to inform subsequent elements of talent management such as leadership development (Titzer *et al*. 2013); in other contexts, the ability to function as a leader and to influence and direct is important through to the point of care. Effective succession planning 'incorporates those actions, activities and interventions intended to ensure that capable, motivated and talented individuals are ready to assume the leadership roles for which they have been selected' (Griffith 2012: 901–902). Research has shown the positive effects of succession planning in health (Patidar *et al*. 2016). Organisations in the sector can use these results to make informed decisions about investing in leadership development programmes.

Distinct elements have been identified in the succession process (Carriere *et al*. 2009) which include strategic planning, its translation into skills and competences to achieve strategic goals, key positions and the selection of suitable candidates to fill them. Once this has taken place, talent management tools such as mentoring and coaching or other developmental activities are introduced and the final element of evaluation is put in place. Succession planning and its association with talent apply to a broad range of scenarios. In the first instance, there is a need to ensure that high-level leadership and managerial roles are fulfilled as well as key technical and clinical roles. The objective is to both develop and retain 'knowledgeable personnel to meet organisational needs' (Carriere *et al*. 2009). Succession planning provides the basis for determining the optimum mix of internal and external recruitment and the consequent level of leadership or management development. Interpretations of the nature of succession vary among health organisations around the world from the process of identifying 'superheroes' (Day *et al*. 2014) to integrated succession planning for nurse practitioners (Rafferty 2013; Kim *et al*. 2014).

Succession planning is a process by which the organisation 'can manage the current workforce changes effectively as well as forecast and plan according to future human capital needs, such as when the organization grows, and build a talent agile culture to lead the way' (Martin 2015). It consists of a combination of development plans and talent reviews (Lamoreux *et al*. 2009) targeted towards a health sector unit or combination of units and is usually led by HR, OD or talent practitioners.

## Case Study: A Comparative Study of the Development of Managerial Talent in the Health Sectors of Egypt, Mexico, Romania and the United Kingdom

**Professor Robert Hamlin, University of Wolverhampton**

**Dr Taran Patel, Grenoble Ecole de Management, Grenoble, France**

**Dr Carlos Ruiz, Associate Professor of Management, School of Business, Georgia Gwinnett College, Lawrenceville, GA, U.S.A.**

Good management and leadership produce good healthcare, whereas poor management and leadership generate poor healthcare (Borrill *et al*. 2004; Flowers *et al*. 2004; Michie and West 2002). But relatively little is known from contemporary empirical research about what differentiates effective healthcare managers from ineffective ones. The lack of consensus on definitions and theorisation of leadership behaviour and effectiveness has compounded this problem. A contribution to knowledge in the area of healthcare-related managerial effectiveness research has been made by a series of cross-geography studies based on the use of critical incident and factor analytic techniques on middle and frontline levels of management which have since been replicated within a 'specialist' NHS Trust hospital (Hamlin and Cooper 2007) and public hospitals in Egypt (Hamlin *et al*. 2010), Mexico (Hamlin *et al*. 2011) and Romania (Hamlin and Patel 2012). A recent cross-case comparative analysis of findings obtained from these inquiries lends strong empirical support for a healthcare-specific behavioural taxonomy of managerial and leadership effectiveness composed of a set of generic positive and negative behavioural criteria.

The emergent positive behavioural criteria include the following:

- Organisation and planning (e.g., good planning, organisation, directing, execution and control and effective problem prevention and resolution)
- Active supportive leadership (e.g., backs staff ideas, gives practical support when they are under exceptional pressure, and gives thanks and praise)
- Giving support to individual staff (e.g., listens to staff concerns/worries and handles personal issues sensitively)
- Open and personal management approach and style (e.g., gets to know staff as individuals, develops a sense of trust, and is readily available to them)
- Inclusive decision making (e.g., involves staff in discussions/decisions, consults with them, and seeks staff ideas)
- Looking after the interests/needs of staff (e.g., promotes the importance/needs of the department and its staff and actively addresses the learning and personal development needs of staff)
- Empowerment and delegation (e.g., delegates roles and responsibilities, gives staff freedom to make decisions, and encourages them to reconcile differences/work through problems with each other)
- Informing people (e.g., communicates regularly with staff and keeps staff informed on matters affecting them)

And negative behavioural criteria:

- Dictatorial/autocratic management (e.g., imposes decisions/change with no prior discussion/consultation, refuses to admit to own mistakes, and adopts an authoritarian style)
- Intimidating behaviour (e.g., exhibits threatening/bullying behaviour)
- Negative approach (e.g., emphasises negative views and is closed-minded)
- Undermining behaviour (e.g., is dismissive in dealing with staff, makes cutting/off-hand remarks, chastises staff in public, overrides colleague managers, fails to follow hospital polices/rules or by-passes systems, and exhibits manipulative/politicking behaviour)
- Avoidance and ignoring behaviour (e.g., refuses to recognise problems/deadlines, avoids making decisions, and procrastinates in taking action)
- Failing to inform other people (e.g., neglects to share with staff information or give advance notice on matters that will affect them and fails to impart accurate, reliable or up-to-date information)
- Not receiving or using information (e.g., omits to seek, use, or take into account the views/needs of staff)
- Exhibiting poor planning and organisation (e.g., acts before obtaining/checking the facts or thinking through the implications, gives insufficient to time to organising and administration, adopts short-term view and exhibits poor forward planning, and fails to prioritise)
- Self-serving and uncaring management (e.g., is inconsistent; fails to be open, honest, forthright or up-front when communicating; and is unfair/shows favouritism in dealings with staff)
- Lack of concern for staff (e.g., places unrealistic workloads or expectations on staff, is unwilling to address staff concerns, gives little instruction/support in change situations, and denies staff opportunities for self-development)
- Abdicating roles and responsibilities (e.g., passes the buck, fails to monitor/take control of performance problems, and omits to provide adequate cover for foreseen staff absence)

Potentially, this universalistic taxonomy, once fully developed, would be useful in crafting an evidence-based approach to the development of managerial talent within the health sector.

## The Links Between Succession Planning, Leadership Development and Talent Management

Talent management, succession planning and leadership development can exist in a series of bilateral relationships. That between talent management and leadership development, for example, is a process of challenge and response. A shortage of the skills necessary to deal with the organisation's current or forward leadership needs will prompt those responsible for talent management to design appropriate interventions (leadership programmes, secondments or executive coaching). When there is an abundance of skills, talent management will provide new ideas based on prevailing wisdom for how leaders should be developed and initiate programmes, will be the source of tools to assess potential leaders, and from these results will provide nominations to

talent pools. Succession planning will have a similar bilateral interface with leadership development. Individuals will be nominated for key posts and their development set in train.

But there are limitations to this binary approach. For example, succession planning can be little more than replacement planning, matching names of candidates to high-level roles and responding to development needs of individual leaders in an ad hoc way. Or succession planning becomes an annual event from which the next year's leadership development needs are identified. Similarly, talent management may be viewed as a necessary process but without any sense of alignment to the organisation's purpose. The way to address these issues is through a more holistic approach in which there would be greater integration between the three areas of talent management, leadership development and succession planning. Thus, talent management would be part of an organisationally aligned talent strategy; leader development would become leadership development and include more people at more levels within its sphere and would include organisational skills in addition to traditional leader competences. In this context, succession planning would become succession management.

The key elements of such an approach are included in Fig. 2.

There is evidence of this fresh perspective. In the U.S. health sector, for example, there was integration between the institution's strategic plan, key positions associated with this, and career ladders designed to support people development into these positions. Employee profiles and talent inventory were all undertaken to 'identify education, talent, and experience, as well as areas

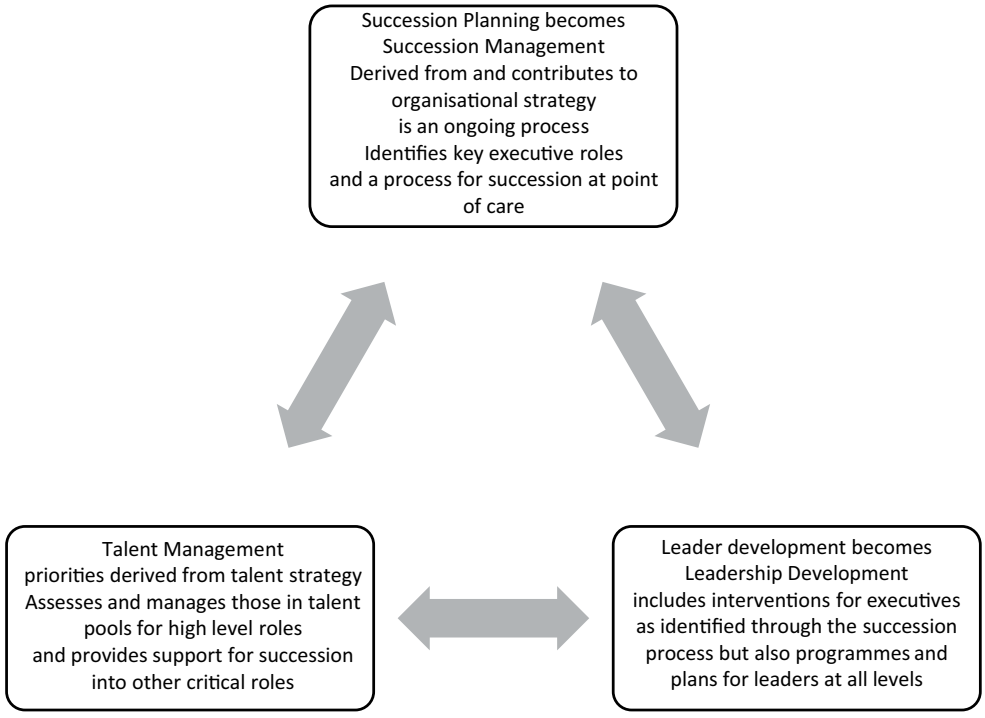



**Fig. 2:** An integrated approach to talent management, leadership development and succession management in healthcare.

that need improvement' (Ellinger *et al*. 2014: 369). Furthermore, research has shown that 90% of the U.S. executive leadership programmes surveyed were able to link such programmes with strategic goals (McAlearney 2010). The potential value is clear for greater coordination between talent management, leadership development and succession management. There will be benefits for both the individual (better understanding and alignment to the organisation's direction) and the organisation (better returns on its investment in people development). To bring clarity to such an approach, it is worth investigating how leadership in the health sector interfaces with talent management and how the two can be brought into succession management to form an integrated whole.

Amongst the elements of succession planning in health identified by Carriere *et al*. (2009) and Trepanier and Crenshaw (2013) were desired skills identification and the identification of key positions and candidates. These formed the framework for succession, whilst leadership development programmes, including coaching and mentoring, were the tools of implementation. Talent management played a critical part in defining the competences for succession (aligned to the organisation's objectives), the assessment processes in identifying which people would have the potential for succession roles, and developmental actions or programmes to address individual needs.

It is essential to reflect on the duality of leadership perspectives in succession management processes to ensure a supply of health sector leaders at all levels. This will require a transition from what we might call replacement planning to a more inclusive approach to succession. Indeed, it is increasingly recognised that talent management and leadership development are part of a wider system whilst both are critical to healthcare organisations. Programmes for succession planning are equally important (Satiani *et al*. 2014).

## Succession Management in Place of Succession Planning

In spite of the considerable benefits, there are also some limitations to this approach. The most notable are that the process is normally targeted towards the most senior leaders in the organisation and that it is often a stand-alone process. Integration with other operational, talent management or human resource practices can be piecemeal. To overcome these shortfalls, *succession management* has emerged. This targets all critical positions in the organisation, at all levels and in a way that is cross-organisation (as opposed to a single unit or department), aligned to overall strategy and utilising the full range of people management and development tools.

In the health sector, this has grown in prominence. In nursing, for example, global nursing shortages that have had a significant impact on healthcare make the adoption of succession management for roles at all levels a priority for nursing leaders (Griffith 2012). The challenge for health sector organisations is to ensure that they have succession management as part of their overall strategy-setting process and a well-thought-through set of leader and leadership propositions to provide candidates for succession posts. This is true on many levels. For example, the need for 'a deliberate strategy to ensure an adequate leadership pipeline among nurse managers has never been more apparent' in the U.S.A. (Titzer *et al*. 2013).

Succession management is becoming important to both strategic organisational governance and operational continuity in the health sector. It is argued that a formal succession management process is critical not only for financial and operational performance but also to sustainability (in, for example, acute care hospitals; Trepanier and Crenshaw 2013). Succession management is an integrated part of business strategy and planning 'that promotes effective leadership transition and continuity while maintaining productivity'.

## Assessing People for Succession and Leadership Development in Healthcare Organisations

An important facet of talent and succession management is to identify those characteristics that would single out a particular individual for a leadership role and match a percentage of individuals in the organisation against these competences, often in the form of a talent pool of people who have been chosen to fast-track into senior leadership positions. In this respect, traditional leadership selection and assessment have been based on the selection of leaders against competency frameworks.

The critique of this is that such a process assumes that organisations are driven by 'a single form of leader dominated rationality rather than social or emotional processes' (Grint 2007: 232). Too often the criteria for the selection of leaders are based on leadership theory rather than leadership practice. In fact, leadership is a complex, multi-faceted process and the translation of theory to practice is 'never simply a unilinear act of transmission' (Grint 2007: 233). Furthermore, Hlupic (2014) has argued that leadership is in transition from a traditional to an emergent style characterised by the distribution of formal power and decision making, the creation of interactive informal networks, and a learning mindset. As organisations become more complex, the greater the need for leaders who eschew a top-down ethos and move towards a direction that is derived from network activity, who use inspiration and intuition instead of toughness and control, and who are comfortable with adaptation through decentralised systems. Hence, the most effective leadership development is a mixture of theoretical input, tools and techniques and a reflective process of application.

Organisations in the health sector have adopted a variety of practices to assess and identify leaders though the competency-based approach to leadership assessment. This will assess leaders on the basis of their match to the competences (knowledge, skills, attitudes and behaviours) that will lead to superior performance.

A study of leadership performance against such competences was carried out in Asia by using an instrument known as AHEAD (Aspiring leaders in Healthcare—Empowering individuals, Achieving excellence, Developing talents). The study covered those from a broad range of professions, including dietetics and podiatry, and found a strong relationship between this approach and Kouzes and Posner's Leadership Practices Inventory (Ang *et al*. 2016). Furthermore, a competency model was used in the British health sector spearheaded by the National Association for Healthcare Quality, which undertook the development and validation of a competency-based model in support of healthcare leaders' assessment of strengths which provided the basis for

developmental interventions (Garman and Scribner 2011). In North America, the Healthcare Leadership Alliance proposed five competency domains for healthcare: communication and relationship management, professionalism, leadership, knowledge of the healthcare system, and business skills and knowledge to be applied to practitioner communities (Stefl 2008). In Finland, the Nurse Managers Leadership and Management competences scale (Kantanen *et al*. 2015) provided a self-assessment test against 194 items and divided competence into general competence and special competence. The instrument was used to evaluate nurse managers' leadership and management competences which would lead to developmental actions.

There is evidence of the use of a range of sophisticated assessment tools for leaders and managers in the healthcare sector around the world. The basis for most is a competency analysis creating domains of varying levels of depth and applicability. In some, as in nursing, there is commonality in these approaches. But this is not universal across the professions.

## Leadership Development Practices

The importance attached to leader and leadership development is consistent throughout the healthcare sector on the basis of evidence that effective frontline clinical leadership can improve both clinical outcomes and patient satisfaction for patients and providers (Blumenthal *et al*. 2012). Leader development can be viewed as an intervention to improve the abilities of people to lead. It will consist of programmes to hone classic leader skills often based on well-structured competency frameworks. Three-hundred-and-sixty-degree feedback processes and executive or performance coaching may also feature (McAlearney 2010). But leadership development extends the process and includes more people for more roles (over and above the board or executive team) whilst having specific tailoring to suit the mission and objectives unique to an organisation or group of organisations (for example in a multi cultural context El Amouri and O'Neill 2014).

As well as including the skills required to run an organisation in an operational sense such as general management and finance, leadership development might include developing an understanding in organisational dynamics (politics) and the process of guiding the organisation as a whole to its strategic targets through inclusion and engagement.

The importance of the strategic alignment of the leadership development processes of organisations in the health sector has also been emphasised. In their evidence-based analysis, Anderson and Garman (2014) concluded that this was essential for the success of any subsequent leadership development activities. This would be characterised by senior leadership involvement in the process and the leaders would act as mentors and learning facilitators. Clarification of the objectives of leadership development is an important criterion and where research has taken place on this subject in the health sector these criteria include the achievement of organisational goals but also developing the employees, improving the workforce, contributing to being the employer of choice, and showing a commitment to education, learning, training and development (McAlearney 2010).

There are richness and diversity in leadership development practices in the healthcare sector worldwide (Table 1).

**Table 1: Examples of leadership development practices in the health sector.**

| Succession planning and management | Leadership and management development programmes | Executive coaching, performance coaching and mentoring | Professional networking, projects and secondments |
|---|---|---|---|
| • Linking leadership development to health unit succession plans<br>• Succession planning to ensure continuity of hospital business or operational leadership<br>• Succession planning for nurse executives<br>• Succession management directly linking development plans to overall talent management | • Strategic alignment of leadership development to organisational goals<br>• Development of executives in multi-unit hospital systems<br>• Development of frontline clinical leaders<br>• Physician leadership development<br>• Formal leadership training for specialist groups (e.g., radiologists)<br>• Formal leadership training for health administrators<br>• Leadership development integrated with high-performance teamwork<br>• High-potential programmes for high-performing managers<br>• Leadership development for point-of-care roles<br>• Competency models to assess leadership candidates | • Executive coaching as part of leadership development programme<br>• Career planning advice for healthcare executives<br>• Mentoring for nurse leaders<br>• Coaching and mentoring for high-potential employees<br>• Understanding and developing emotional intelligence<br>• 360° assessment processes for clinical leaders<br>• Mentoring for a wide range of employees in a hospital environment<br>• Development or assessment centres | • Sponsoring membership of professional organisations<br>• Networking outside of the health sector to broaden perspectives<br>• Job rotation<br>• Cross-departmental projects<br>• Organisation-wide projects (information technology systems and so on)<br>• Stretch assignments |

- Executive leadership development programmes grew in North America from 2003 onwards (McAlearney 2010). They have become particularly popular in smaller health systems or groups of organisations. Research has shown that they have been successful in delivering programme objectives and sustained budgetary commitment.
- The creation of high-potential leadership programmes was prominent and these were found to be run through a centralised system of management (Anderson and Garman 2014), whilst nursing leadership development programmes and performance coaching were the least centralised.
- Leadership development has been focused on the growing number of physicians who are moving into leadership positions. Whilst they will have shown excellent technical skills, these may not be sufficient for the complexities of healthcare administration. Leadership development programmes involve training in 'interacting with unfamiliar constituencies, such as senior administrative leaders in nursing or finance, in the complex and continually evolving healthcare landscape' (Henson 2016). An additional element of understanding emotional intelligence, learning agility and 'learning about self' were also recommended for inclusion on the development agenda (Larkin 2015; Moodie 2016).

- Leadership development, where it is integrated with teams, can show significant results where it is applied to leadership at all levels and where it involves working with other teams in the health system (by providing a pathway to lead and manage to improve performance) (Morsi 2010).
- Leadership training for professional healthcare administrators in North America (Jackowski and Burroughs 2015) showed benefits in terms of focus, job satisfaction and the ability to inspire a shared vision.
- Increasing diversity can be enhanced by leadership development through effective talent management. In the U.S. healthcare organisations, for example, the 'lack of depth of women leaders' was identified as being both perplexing and challenging given the transformation that was taking place in the sector. The opportunity was presented because 'women, who make up the majority of the workforce in healthcare organizations are largely an untapped resource for many of the leadership gaps that will result from this trend'. The recommendation from the research was 'to provide the support and sponsorship necessary to develop women in leadership roles', creating a leadership pipeline with significant organisational benefits (Hauser 2014).
- Coaching and mentoring were common features of leadership programmes. In a study of North American leadership development, 86% of programmes involved the use of executive coaches (McAlearney 2010). Other examples included a one-year formal mentoring programme supported by physicians and management to develop those with potential to be future leaders in a rehabilitation unit in North America (Stuart and Wilson 2014). This included diversity in the choice of mentors backed up by a well-defined process for matching mentors and mentees and a formal programme to embed the process.
- Sponsoring membership of professional organisations to increase networking and the transfer of knowledge with networking opportunities that would expose physician leaders to new perspectives (Henson 2016). Networking is a common feature of leadership development in healthcare and was identified as a characteristic of successful healthcare executives with the advice to have an extensive network that goes beyond the immediate clinical or professional expertise but is extended to people outside of the sector (Schlosser 2014).
- Support in career planning for healthcare executives (a survey showed that 12% of early careerists, 22% of mid-careerists and 49% of senior careerists had a career plan), emphasising that the traditional career ladder has been replaced by a career lattice, involving lateral as well as vertical career moves (Broscio 2014). To navigate such a career plan would require regular reviews and a career consultation process. The relevance of this is that 'an increasing number of physicians are embarking on a pathway from clinical practice to senior healthcare leadership positions that historically have been held by seasoned nonmedical or allied health professionals' (Henson 2016).
- There were examples of developmental experiences such as 'cross-departmental or system-wide performance improvement initiatives, participation in special projects such as building projects, enterprise-wide IT implementation, or fundraising campaigns, or even full-time rotation into other positions to provide exposure to different parts of the organization and/or system' (Anderson and Garman 2014).

In the future, if the above assumptions about the devolved nature of leadership in the health sector are accepted, leadership development will be not only about high-level programmes for those at the top of the organisation (though these are still critical to success) but also about a broad range of developmental activities for those in leadership positions at the point of care and elsewhere in health sector organisations. Where such an approach has taken place (as in the case of nurse leaders in North America), the results of development activity showed increased self-confidence, positive changes in leadership styles, and a broader appreciation of environmental issues within the practices within which they worked (MacPhee *et al.* 2011).

## Conclusions and Implications for Practice

The above analysis shows the importance of talent management in the processes of leadership development and succession management. The move from a series of bilateral relationships between the three areas into an integrated holistic model was identified to ensure integration from point of strategy to point of care—from board to ward—in a way that is sustainable (through leadership development) whilst providing continuity (through succession management). To achieve this goal has implications:

- It is important for the healthcare organisation to have a clear definition of what is covered by the term leadership. If this is something that applies to the leaders who are at the apex of the organisation structure, then this has implications for the priorities and processes of both talent management and leadership development. If, on the other hand, a non-hierarchical view of leadership has been adopted, then the greater number of people will be included within the boundary and a range of leadership development solutions will be required.
- Subsequently, the opportunity to ensure an integrated approach to talent management, leadership development and succession management will be possible. Developing clear linkages between the three areas is an important activity. This involves ensuring that succession management is aligned with the organisation's goals and that leadership development is focused on the needs identified in this process and having the talent management tools and techniques that are relevant, fit for purpose and provide measures of the outcomes of developmental interventions.
- There is the possibility to move from replacement or succession planning to one of succession management. This will regard succession as less of a phenomenon and more of an ongoing activity. It also implies that succession 'planning' starts at an earlier stage than the traditional process of one-off ad hoc responses. Succession management can be a process that covers the whole of the leadership life cycle and can apply to greater numbers than those who are being developed for the most senior positions (although activity in the latter area remains mission-critical for most organisations).
- There is evidence that combinations of leadership activity will be effective. Thus, organisations in the healthcare sector match leadership programmes with coaching, combine leadership development with secondment or project opportunities and are creative in the use of mentoring as a tool for both leadership and management programmes.

Talent management has a key role to play in the integration process between succession management and leadership development. It acts as a recipient of intelligence from the organisation's strategy, its people strategy and its strategic workforce plan and is a provider of solutions (leadership programmes and interventions).

## References


Alimo-Metcalfe, B., & Alban-Metcalfe, J. (2003). Under the influence. *People Management*, 16 March, 32–35.

Anderson, M. M., & Garman, A. N. (2014). *Leadership development in healthcare systems: Toward an evidence-based approach*. Chicago: National Center for Healthcare Leadership.

Ang, H.-G., Koh, J. M., Lee, J., & Pua, Y.-H. (2016). Development and preliminary validation of a leadership competency instrument for existing and emerging allied health professional leaders. *BMC Health Services Research,* 16, 64.

Baron, A., Clake, R., Pass, S., & Turner, P. (2010). *Workforce planning*. London: CIPD Publications.

Bennis, W. (2001). The new leadership. In S. Crainer & D. Dearlove (Eds.), *Financial times handbook of management* (2nd ed.). London: Prentice Hall.

Block, L., & Manning, L. J. (2007). A systemic approach to developing frontline leaders in healthcare. *Leadership in Health Services,* 20(2), 85–96.

Blumenthal, D. M., Bernard, K., Bohnen, J., & Bohmer, R. (2012). Addressing the leadership gap in medicine: Residents' need for systematic leadership development training. *Academic Medicine,* 87(4), 513–522. doi: 10.1097/ACM.0b013e31824a0c47.

Borrill, C. S., West, M. A., & Dawson, J. F. (2004). *The relationship between leadership and trust performance*. Department of Health Report. Birmingham: Aston University.

Broscio, M. A. (2014). Career management in today's healthcare environment. *Journal of Healthcare Management,* 59(6), 395–398.

Carriere, B. K., Muise, M., Cummings, G., & Newburn Cook, C. (2009). Healthcare succession planning; an integrative review. *Journal of Nursing Administration*. Retrieved from www.ncbi.nlm.nih.gov/pubmed/19955970

Chan, Z., Bruxer, A., Lee, J., Sims, K., Wainwright, M., Brooks, D., & Desveaux, L. (2015). What makes a leader: Identifying the strengths of Canadian physical therapists. *Physiotherapy Canada,* 67(4), 341–348.

Chavez, E. C., & Yoder, L. H. (2015). Staff nurse clinical leadership: A concept analysis. *Nursing Forum,* 50(2), 90–100.

Collins, J. (2001). *Good to great*. New York: Harper Business.

Collinson, D., & Tournish, D. (2015). Teaching leadership critically: New directions for leadership pedagogy. *Academy of Management Learning and Education,* 14(4), 576–594.

Czabanowska, K., Smith, T., Könings, K. D., Sumskas, L., Otok, R., Bjegovic-Mikanovic, V., & Brand, H. (2014). In search for a public health leadership competency framework to support leadership curriculum-a consensus study. *European Journal of Public Health,* 24(5), 850–856.

Daly, J., Jackson, D., Rumsey, M., Patterson, K., & Davidson, P. M. (2015). Building nursing leadership capacity: An australian snapshot. *Nurse Leader,* 13(5), 36–39.

Day, M., Shickle, D., Smith, K., Zakariasen, K., Moskol, J., & Oliver, T. (2014). Training public health superheroes: Five talents for public health leadership. *Journal of Public Health,* 36(4), 552–561.

de Jong, N., Könings, K. D., & Czabanowska, K. (2014). The development of innovative online problem-based learning: A leadership course for leaders in European public health. *Journal of University Teaching and Learning Practice,* 11(3).

Department of Health. (2009). *Inspiring leaders: Leadership for quality; Guidance for NHS talent and leadership plans*, Department of Health Workforce Directorate, Publication date 22 January.

Deschamps, C., Rinfret, N., Lagacé, M. C., & Privé, C. (2016). Transformational leadership and change: How leaders influence their followers' motivation through organizational justice. *Journal of Healthcare Management,* 61(3), 194–213.

Dye, C. F. (2017). *Leadership in healthcare; essential values and skills*. Chicago: ACHE Management Series.

Edger, C. (2012). *Effective multi-unit leadership: Local leadership in multi-site situations*. Farnham: Gower Applied Research Press.

El Amouri, S., & O'Neill, S. (2014). Leadership style and culturally competent care: Nurse leaders' views of their practice in the multicultural care settings of the United Arab Emirates. *Contemporary Nurse: A Journal for the Australian Nursing Profession,* 48(2), 3552–3573.

Ellinger, L. K., Trapskin, P. J., Black, R., Kotis, D., & Alexander, E. (2014). Leadership and effective succession planning in health-system pharmacy departments. *Hospital Pharmacy,* 49(4), 369–375.

Ellis, P., & Abbott, J. (2015). Exploring the differences between leaders and managers. *Journal of Renal Nursing*, 7(2). ISSN: 2041-1448.

Elwell, S. M. (2015). Defining leadership in a changing time. *Journal of Trauma Nursing,* 22(6), 312–314.

Fitzsimmons, M. J., & Rose, R. (2015). Designing structure to meet demands, and recruiting talent to achieve results. *Nurse Leader,* 13(1), 1–84.

Flowers, C., Sweeney, D., & Whitefield, S. (2004). Leadership effectiveness: Using partnership to develop targeted leadership training. *Nursing Management-UK,* 11(6), 23–27.

Garman, A., & Scribner, L. (2011). Leading for quality in healthcare: Development and validation of a competency model. *Journal of Healthcare Management,* 56(6), 373–382.

Goffee, R., & Jones, G. (2006). *Why should anyone be led by you*. Boston: Harvard Business School Press.

Goleman, D. (1996). *Emotional intelligence*. New York: Bloomsbury.

Goleman, D. (1998). *Working with emotional intelligence*. New York: Bantam Books.

Green, A., Miller, E., & Aarons, G. (2013). Transformational leadership moderates the relationship between emotional exhaustion and turnover intention among community mental health providers. *Community Mental Health Journal,* 49(4), 373–379.

Griffith, M. B. (2012). Effective succession planning in nursing: A review of the literature. *Journal of Nursing Management,* 20(7), 900–911.

Grint, K. (2007). Learning to lead: Can Aristotle help us to find the road to wisdom. Retrieved from lea.sagepub.com/content/3/2/231

Gulati, R., Mikhail, O., Morgan, R. O., & Sittig, D. F. (2016). Vision statement quality and organizational performance in U.S. Hospitals. *Journal of Healthcare Management,* 61(5), 335–350.

Hamlin, R. G. (2002). A study and comparative analysis of managerial and leadership effectiveness in the National Health Service: An empirical factor analytic study within an NHS Trust Hospital. *Health Services Management Research,* 15, 1–20.

Hamlin, R. G., & Cooper, D. J. (2007). Developing effective managers and leaders within healthcare and social care contexts: An evidence-based approach. In S. Sambrook & J. Stewart (Eds.), *HRD in the public sector: The case of health and social care* (pp. 187–212). London: Routledge.

Hamlin, R. G., Nassar, M., & Wahba, K. (2010). Behavioural criteria of managerial and leadership effectiveness within Egyptian and British public sector hospitals: An empirical study and multiple-case/cross-nation comparative analysis. *Human Resource Development International,* 13(1), 43–64.

Hamlin, R. G., & Patel, T. (2012). Behavioural indicators of perceived managerial and leadership effectiveness in Romanian and British public sector hospitals. *European Journal of Training and Development,* 36(2–3), 234–261.

Hamlin, R. G., Ruiz, R., & Wang, J. (2011). Perceived managerial and leadership effectiveness within Mexican and British public sector hospitals: An empirical study and cross-nation comparative analysis. *Human Resource Development Quarterly,* 22(4), 491–517.

Hauser, M. C. (2014). Leveraging women's leadership talent in healthcare. *Journal of Healthcare Management,* 59(5), 318–322.

Henson, J. W. (2016). Five ideas for the development of successful physician leaders. *Journal of Healthcare Management,* 61(3), 171–175.

Hlupic, V. (2014). *The management shift*. London: Palgrave Macmillan.

Jackowski, M. B., & Burroughs, B. (2015). The relationships between self-reported leadership practices, job satisfaction, and demographics of radiology administrators. *Radiologic Technology,* 87(1), 10–20.

Kantanen, K., Kaunonen, M., Helminen, M., & Suominen, T. (2015). The development and pilot of an instrument for measuring nurse managers' leadership and management competencies. *Journal of Research in Nursing,* 20(8), 667–677.

Kim, C. S., King, E., Stein, J., Robinson, E., Salameh, M., & O'Leary, K. J. (2014). Unit-based inter-professional leadership models in six US hospitals. *Journal of Hospital Medicine,* 9(8), 545–550.

King's Fund. (2009). *The nurse executive's handbook*. Published on behalf of Burdett Trust for Nursing by The King's Fund, London. ISBN 978-1-85717-582-0

Kingue, S., Rosskam, E., Bela, A. C., Adjidja, A., & Codjia, L. (2013). Strengthening human resources for health through multisectoral approaches and leadership: The case of Cameroon. *Bulletin of the World Health Organization,* 91(11), 864–867.

Kouzes, J. M., & Posner, B. Z. (2007). *The leadership challenge*. San Francisco: Jossey Bass.

Kumar, S., Kumar, N., Adhish, V. S., & Reddy, R. S. (2015). Strategic management and leadership for health professionals – Skills to leverage resources to achieve health goals. *Indian Journal of Community Medicine,* 40(3), 158–162.

Kurec, A. S. (2012). Succession planning: A forgotten strategy. *Clinical Leadership and Management Review,* 26(4), 22.

Lamoreux, K., Campbell, M., & Smith, R. (2009). *High-impact succession management.*Center for Creative Leadership (NJ1). Retrieved from www.ccl.org/leadership/pdf/…/HighImpactSuccessionManagement

Larkin, H. (2015). The new health care CEO. *Hospitals and Health Networks,* 89(6). ISSN: 1068-8838.

Lawrence, N., & Richardson, J. (2014). To explore and understand the leadership experiences of modern matrons, within an acute NHS trust. *Journal of Nursing Management,* 22, 70–79.

Leigh, J. A., Wild, J., Hynes, C., Wells, S., Kurien, A., Rutherford, J., Rosen, L., Ashcroft, T., & Hartley, V. (2015). Transforming community services through the use of a multidimensional model of clinical leadership. *Journal of Clinical Nursing,* 24(5–6), 749–760.

Longenecker, C. O., & Longenecker, P. D. (2014). Why hospital improvement efforts fail: A view from the front line. *Journal of Healthcare Management,* 59(2), 147–157.

Love, D. B., & Ayadi, M. F. (2015). Redefining the core competencies of future healthcare executives under healthcare reform. *Administrative Issues Journal: Education, Practice & Research,* 5(2), 3–16.

MacPhee, M., Skelton-Green, J., Bouthillette, F., & Suryaprakash, N. (2011). An empowerment framework for nursing leadership development: Supporting evidence. *Journal of Advanced Nursing,* 68(1), 159–169. Blackwell Publishing.

Mansour, M., Mansour, J. B., & El Swesy, A. H. (2010). Scaling up proven public health interventions through a locally owned and sustained leadership development programme in rural Upper Egypt. *Human Resources for Health,* 8(1), 18. doi: 10.1186/1478-4491-8-1.

Martin, A. (2015). Leadership: Talent management: Preparing a "ready" agile workforce. *International Journal of Pediatrics and Adolescent Medicine,* 2(3–4), 112–116.

Mazzoccoli, A., & Wolf, G. (2016). Mentoring through the leadership journey: From novice to expert. *Nurse Leader,* 14(4), 253–256.

McAlearney, A. S. (2010). Executive leadership development in U.S. health systems. *Journal of Healthcare Management,* 55(3), 206–222. American College of Healthcare ISSN: 1096-9012.

Michie, S., & West, M. A. (2002). *Measuring staff management and human resource performance in the NHS.* London: Commission for Health Improvement.

Mintzberg, H. (2011). *Managing*. London: FT Prentiss Hall.

Moodie, R. (2016). Learning about self: Leadership skills for public health. *Journal of Public Health Research,* 5(1), 679.

Nelson, K. E., III, & Pilon, B. (2015). Managing organizational transitions: The chief nurse perspective. *Nurse Leader,* 13(3), 71–76.

Patidar, N., Gupta, S., Azbik, G., & Weech-Maldonado, R. (2016). Succession planning and financial performance: Does competition matter? *Journal of Healthcare Management,* 61(3), 215–227.

Rafferty, C. (2013). Nurse practitioner succession planning: Forward thinking or just an after-thought? *Australian Health Review*. Retrieved from www.ncbi.nlm.nih.gov/pubmed/23838033

Read, E. A., & Laschinger, H. K. S. (2015). The influence of authentic leadership and empowerment on nurses' relational social capital, mental health and job satisfaction over the first year of practice. *Journal of Advanced Nursing,* 71(7), 1611–1623.

Redknap, R., Twigg, D., Rock, D., & Towell, A. (2015). Nursing practice environment: A strategy for mental health nurse retention? *International Journal of Mental Health Nursing,* 24(3), 262–271.

Sarto, F., & Veronesi, G. (2016). Clinical leadership and hospital performance: Assessing the evidence base. *BMC Health Services Research,* 16, 169.

Satiani, B., Sena, J., Ruberg, R., & Ellison, E. C. (2014). Practice management: Talent management and physician leadership training is essential for preparing tomorrow's physician leaders. *Journal of Vascular Surgery,* 59(2), 542–546.

Schlosser, J. (2014). The management springboard: Eight ways to launch your career as a healthcare leader. *Journal of Healthcare Management,* 59(1), 14–16.

Scully, N. J. (2015). Leadership in nursing: The importance of recognising inherent values and attributes to secure a positive future for the profession. *Collegian,* 22(4), 439–444.

Shariff, N. J. (2015). A Delphi survey of leadership attributes necessary for national nurse leaders' participation in health policy development: An East African perspective. *BMC Nursing,* 14(1), 13.

Stander, F. W., de Beer, L. T., & Stander, M. W. (2015). Authentic leadership as a source of optimism, trust in the organisation and work engagement in the public health care sector, *South African*. *Journal of Human Resource Management,* 13(1), 12.

Stefl, M. E. (2008). Common competencies for all healthcare managers: The healthcare leadership alliance model. *Journal of Healthcare Management,* 53(6), 360–373.

Titzer, J., Phillips, T., Tooley, S., Hall, N., & Shirey, M. (2013). Nurse manager succession planning: Synthesis of the evidence. *Journal of Nursing Management,* 21(7), 971–979.

Trastek, V. F., Hamilton, N. W., & Niles, E. E. (2014). Leadership models in health care – A case for servant leadership. *Mayo Clinic Proceedings*, 89(3), 374–381. doi: 10.1016/j.mayocp.2013.10.012.

Trepanier, S., & Crenshaw, J. T. (2013). Succession planning: A call to action for nurse executives. *Journal of Nursing Management,* 21(7), 980–985.

Wells, W., & Hejna, W. (2009). Developing leadership talent in healthcare organizations: There are five key areas in which healthcare organizations can better foster the development of strong leaders among their employees. *Healthcare Financial Management,* 63(1), 66–69.

Wong, C., & Cummings, G. (2007). The relationship between nursing leadership and patient outcomes: A systematic review. *Journal of Nurse Management,* 15, 508–521.

---

Source: Turner P. (2018) Succession Planning and Leadership Development. In: Talent Management in Healthcare. Palgrave Macmillan, Cham. https://doi.org/10.1007/978-3-319-57888-0_7. 

*Notes:*

*Notes:*

*Notes:*

Abbott

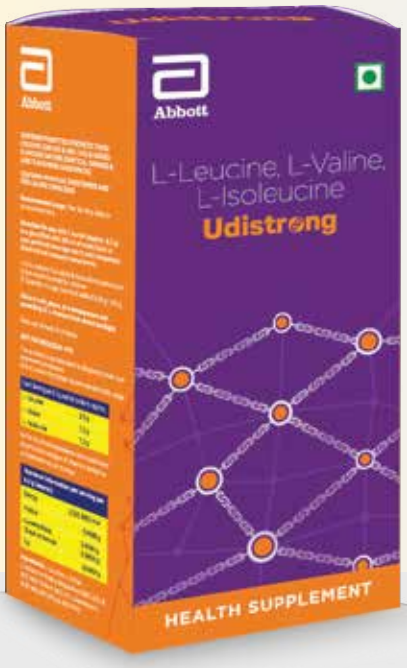
For registered use of medical practitioner, hospital or laboratory only

# Support the treatment in your HE patients.

## Udistrong

L-Leucine, L-Valine, L-Isoleucine

Recharge Life




BCAA support recommended by

**AASLD[1] EASL[2] ESPEN[3] ISHEN[4]**

- Helps restore BCAA:AAA ratio[5,6]
- Helps improve Hepatic Encephalopathy[6,7]
- Helps prevent progression of hepatic failure[6]
- Helps improve muscle mass[6]


**References:**

1. Vilstrup H, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715-35.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on Nutrition in Chronic Liver Disease. J Hepatol. 2019;70(1):172-93.
3. Plauth M, et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr. 2006;25(2):285-94. Epub 2006 May 16.
4. Bémeur C, Butterworth RF. Nutrition in the management of cirrhosis and its neurological complications. J Clin Exp Hepatol. 2013;4(2):141-50.
5. Tajiri K, Shimizu Y. Branched-chain amino acids in liver diseases. World J Gastroenterol 2013; 19(43): 7620-7629.
6. P.H. Ooi, et. al. Effects of branched amino acid supplementation on patient care outcomes in adults and children with liver cirrhosis: A systematic review. Clinical Nutrition ESPEN 28 (2018); 41-51.
7. Aftab Ahmed Soomro et. al. Role of Branched Chain Amino Acids in the Management of Hepatic Encephalopathy. World Journal of Medical Sciences 2008, 3(2): 60-64.


**AASLD:** American Association for the Study of Liver Diseases, **EASL:** The European Association for the Study of the Liver, **ESPEN:** European Society for Clinical Nutrition and Metabolism, **ISHEN:** International Society for HE and Nitrogen Metabolism.


Address: Medical Sciences Division, Abbott India Ltd, Floor 16, Godrej BKC, Plot No. C – 68, BKC, Near MCA Club, Bandra (E), Mumbai – 400 051.



INDUSG191545 09 APR 2019

INDVDK193958 29 Aug 2019