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# Lung transplantation in cystic fibrosis, a South African case study

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#### Introduction

Cystic fibrosis (CF), an autosomal recessive genetic disorder, is characterized by mutations in the genetic material encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein.<sup>[1](#page-6-0)</sup> More than 2 000 CFTR mutations and defects have been described that may result in defects or deficiencies of this channel protein, but not all of these are diseasecausing. The role of the CFTR protein is to transport sodium and chloride ions across cell membranes throughout the body. Defective or insufficient transportation of these ions results in poor hydration of the cell membrane, thus resulting in thick, sticky mucus formation, which affects the functioning of organs and creates a breeding ground for pathogens. The result is organ dysfunction and, in some cases, eventual organ failure. Organs most commonly affected are the lungs, pancreas, liver, kidneys, intestines, and reproductive organs.

The latest South African Cystic Fibrosis Association Consensus Guidelines from 2017 estimate that 1 in 2 000 Caucasian babies, 1 in 12 000 babies of mixed ancestry, and up to 1 in 32 000 African babies are born with CF in South Africa.<sup>2</sup> Based on the most recent South African Cystic Fibrosis Registry Report (2021), there are 523 people living with CF in South Africa.<sup>[3](#page-6-2)</sup>

# Lung disease and eventual lung transplantation in cystic fibrosis

Lungs are the primary cause of morbidity and mortality in patients with CF, as they are particularly vulnerable to the thickened mucus associated with the disease. The thickened mucus obstructs the airway and creates poor mucociliary clearance, resulting in respiratory failure and increased infection risk. Recurrent infections and inflammation further damage the lungs. Eventually lung function deteriorates beyond the point of repair, and patients become oxygen dependent, thus requiring lung transplantation. CF is the most common indication for lung transplantation in patients younger than 50 years old, accounting for 16.8% of all lung transplants. Lung transplantation in CF offers a superior life-extending effect when compared with lung transplantation for other conditions. The 10 year survival rate post-transplantation is 45% in CF, compared with only 34% for all other conditions.<sup>[2](#page-6-1)</sup>

# <span id="page-0-1"></span>Bi-directional relationship between lung function and malnutrition

A bi-directional relationship exists between nutritional status and lung function, which is indicated in [Figure 1](#page-1-0).

Poor nutritional status is associated with poorer pulmonary functions. Research shows that when compared with patients who have a normal body mass index (BMI), patients with a lower BMI were six times more likely to have severe respiratory disease characterised by a forced expiratory volume (FEV1) of <span id="page-0-2"></span>less than [4](#page-6-3)0% of predicated.<sup>4</sup> Poor nutritional status may lead to poor pulmonary function by weakening respiratory musculature and development, with interventions that improve nutrition in early life leading to improvements in lung function later. Malnutrition also increases infection risk, and the inflammation associated with infection worsens pulmonary health.

On the other hand, poor pulmonary function is shown to be metabolically expensive due to the work of breathing and increase in energy expenditure related to infections, leading to an increase in metabolic rate, and thus exacerbating malnutrition. There is also an increased difficulty in meeting energy requirements due to decreased intake-related shortness of breath, coughing, loss of appetite, and increased work of breathing.

#### Pancreatic insufficiency in cystic fibrosis

Another organ greatly affected by CF is the pancreas. Pancreatic insufficiency is very common, occurring in more than 81% of the South African cystic fibrosis population. $3$  Exocrine pancreatic insufficiency (EPI) begins in utero. The thick, sticky mucus associated with CF obstructs the flow of pancreatic enzymes into the duodenum, creating a pancreatic enzyme deficiency with maldigestion and subsequent poor absorption of food. Pancreatic enzyme replacement therapy (PERT), including lipase, protease, and amylase, is a required therapy to correct this maldigestion and absorption. The European Society for Clinical Nutrition and Metabolism (ESPEN), the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), and the European Cystic Fibrosis Society (ECFS) support this as a Grade A recommendation with strong consensus agreement.<sup>[1](#page-6-0)</sup> EPI is diagnosed by a faecal elastase of  $<$  100 ug/g (normal:  $>$  200 ug/g). Of note, PERT should be initiated in patients without delay where EPI is suspected, as faecal elastase tests can be conducted concurrently with PERT. Waiting for these tests, which often take a long time to process, can delay essential treatment. The suggested doses of PERT in CF are summarized in [Table 1.](#page-1-1)<sup>[1](#page-6-0)</sup>

## <span id="page-0-0"></span>Patient presentation

A 16-year-old male presented with W1282X/ R7758X mutations and sweat test chloride of 110 mmol/l (with values of > 60 mmol/l being diagnostic of CF). He was diagnosed early in life with failure to thrive and intestinal failure, which prompted further investigation and a confirmed diagnosis of CF.

Forced expiratory volume (FEV1) measures the amount of air a person can force out of their lungs in 1 second. The patient concerned presented with an FEV1 at 30% of the predicted value, indicating severe respiratory failure and a dependence on supplemental oxygen. He was therefore referred to a tertiary care facility for lung transplantation workup. His condition was complicated by frequent acute respiratory exacerbations and multiple colonizing pathogens, including Aspergillus, Pseudomonas,

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Figure 1: Bidirectional relationship between malnutrition and poor pulmonary function (adapted from Thoracic Key<sup>[5](#page-6-4)</sup>).

methicillin-resistant Staphylococcus aureus, Stenotrophomonas, Klebsiella, and Escherichia coli. Additionally, he had EPI and was on PERT.

## Presenting anthropometry

His weight on presentation was 38.5 kg, with a height of 1.55 m, and a BMI of 16 kg/m<sup>2</sup>. He plotted below the 3rd percentile for all growth parameters based on the Centers for Disease Control and Prevention (CDC) growth charts. Based on the CDC growth charts, the normal BMI range for his age is from 19–22.8 kg/m<sup>2</sup>, which correlates to a normal weight of 45–55 kg. His ideal bodyweight (IBW) was calculated as 44 kg (at a BMI of 18.5 kg/m<sup>2</sup>), which was used for nutritional calculations.

#### Nutritional requirements

ESPEN/ESPHAGAN/ECFS suggests that energy requirements can be estimated as 120–150% of normal requirements for age, and protein should make up at least 20% of total energy.<sup>[1](#page-6-0)</sup> Calculated requirements were estimated at 2 099–2 623 kcal total energy (TE) by using the Schofield equation and multiplying by 120– 150%, and protein requirements were estimated at 20% of total energy at 104–131 g of protein per day. This is equivalent to 47–60 kcal/kg TE and 2.3–2.9 g/kg protein based on IBW.

## Feeding strategy: lung transplantation workup and nutritional prehabilitation

Early placement of a percutaneous endoscopically placed gastrostomy (PEG) tube is the cornerstone of nutritional prehabilitation

<span id="page-1-1"></span>Table 1: Dosage recommendations for pancreatic enzyme replacement therapy (PERT) in cystic fibrosis. (Table adapted from Wilschanski et al.  $2024^{\frac{1}{}})$  $2024^{\frac{1}{}})$  $2024^{\frac{1}{}})$ 



 $U =$  units, ml = millilitre, kg = kilograms bodyweight.

prior to lung transplantation in patients with a low BMI and/or experiencing weight loss despite efforts to improve oral intake and nutritional status. His PEG was placed in 2017 due to poor nutritional status. PEG feeds were utilised to provide full nutrition support, with less focus placed on oral intake.

Initially, a polymeric formula was provided in line with ESPEN/ ESPHAGAN/ECFS guidelines, which indicate that most individuals tolerate high-calorie (1.5–2 kcal/ml) polymeric formulas well. $<sup>1</sup>$  $<sup>1</sup>$  $<sup>1</sup>$  However, if this regimen is not well tolerated, an elemen-</sup> tal or semi-elemental feed may be beneficial, especially in cases of pancreatic insufficiency. Semi-elemental or elemental formulae have predominantly hydrolysed forms of macronutrients, and are therefore not dependent on pancreatic enzymes for digestion and absorption. The difficulty of using a polymeric enteral formula as a continuous or cyclic feed in patients with CF and EPI is related to the difficulties of timing in administering PERT, and thus decreased digestion and absorption of the polymeric formula. Although there is no strong evidence, some guidelines suggest that PERT can be administered orally at the start of the polymeric continuous feed, and again during the feed where possible.<sup>[1](#page-6-0)</sup> This guideline is vague and is likely to lead to maldigestion and malabsorption of the formula. Bolus feeds of polymeric formulae may require more frequent and higher doses of PERT, and the same concerns regarding maldigestion and malabsorption may remain. Thus a semielemental formula is preferred in these patients as they do not require PERT administration during PEG feeds and absorption is ensured. A decision was made to change his PEG feeds from polymeric to semi-elemental feeds. Initially semi-elemental feeds were prescribed, providing the same energy and protein amounts as the polymeric formula. Despite the

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Figure 2: Weight change over 13 days following the change from polymeric to semi-elemental gastrostomy feeds.



<span id="page-2-0"></span>Table 2: Biochemical values over the period of nutritional management

mmol = millimole, l = litre, g = grams, dl = decilitres, fl = femtolitres, µmol = micromoles, U = units, MCV = mean cell volume, WCC = white cell count, HbA1C = glycated haemoglobin, ALT = alanine aminotransferase, AST = a GGT <sup>=</sup> gamma-glutamyl transpeptidase, ALP <sup>=</sup> alkaline phosphatase.

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Figure 3: Indirect calorimetry readings from 10 and 52 days post-transplantation with an energy expenditure of 1 739kcal (RQ 0.84) and 1 260kcal (RQ 0.83) respectively. RQ = respiratory quotient.

similarities in nutritional delivery, the semi-elemental formula resulted in improved weight gain as indicated in [Figure 2](#page-1-2).

The initial semi-elemental prescription included 1500 ml of formula providing 1 995 kcal TE and 99 g protein (45 kcal/kg TE and 2.25 g/kg protein on IBW). The prescription was adjusted to meet the upper end of this patient's calculated requirements. The revised prescription included 2 000 ml of a semi-elemental formula providing 2 660 kcal and 132 g protein (59 kcal/kg TE and 3 g/kg protein on IBW). He was encouraged to eat as tolerated and continued to use PERT with oral intake.

Monitoring of biochemistry is essential when providing patients with increased amounts of protein and energy. Biochemistry was measured at six and eight weeks post-initiation of this higher energy and protein load, which is indicated in [Table 2](#page-2-0) (Nutritional Prehabilitation). Based on the normal biochemical results, he was maintained on this nutritional prescription until an organ became available for transplantation.

# Nutritional support immediately post lung transplantation

After two months of nutritional prehabilitation, a set of lungs became available and the transplantation was performed successfully.

He was successfully extubated on day 1 post transplantation and remained clinically stable. Nutrition support was initiated

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Figure 4: Changes in anthropometry post-transplantation. Point 'a' marks the start of a decline in bodyweight and muscle mass, accompanied by an increase in body fat percentage. This period preceded the diagnosis of new-onset diabetes after transplantation (NODAT), which contributed to the deterioration of the patient's nutritional status. Point 'b' indicates the start of appropriate glycaemic control and monitoring, which relates to an improvement in bodyweight and muscle mass, with a normalization of body fat percentage. Point 'c' indicates the period when the PEG was no longer used for feeding.

<span id="page-4-1"></span><span id="page-4-0"></span>



PERT = pancreatic enzyme replacement therapy, ng = nanograms, mg = milligrams, l = litre, ml = millilitre, mmol = millimole, IU = international units, HDL = high-density lipoprotein.

from day 1 post-transplantation at 25% of pre-transplant requirements, and increased in a stepwise manner to 50% and 75% of pre-transplant requirements by day 2 and 3 posttransplantation respectively. This nutritional regimen providing 75% of his pre-transplantation requirements was maintained consistently for the duration of his intensive care unit (ICU) and ward stay, and on discharge home. The regimen included 1 500 ml of semi-elemental feeds provided through his PEG, providing 2 010 kcal TE and 100 g protein (45 kcal/kg TE and 2.2 g/kg protein on IBW). He was also encouraged to eat meals orally, including the use of PERT.

There is a paucity of evidence regarding the appropriate nutritional requirements during this early post-transplantation phase due to heterogeneity within the lung transplant recipient population. Indirect calorimetry (IC) is recommended as the gold standard for measuring energy requirements, but in the absence of this predictive equations are used. While ESPEN intensive care guidelines are often followed in this postoperative period (25–30 kcal/kg TE), Jomphe et al. highlight that it would be important to consider the pre-transplant nutritional status and diagnosis of the patient, and to use this when estimating post-transplantation nutritional quidelines.<sup>6</sup> It has therefore been suggested that a malnourished CF patient with EPI and sepsis may require up to  $40-50$  kcal/kg TE.<sup>[6](#page-6-5)</sup>

## Estimating nutritional requirements long term posttransplantation

There is limited guidance on energy requirements long term post-transplantation. Post-transplantation, energy requirements are expected to decrease due to the reduced work of breathing and fewer respiratory infections. On the contrary, energy requirements may be increased due to heightened mobility and the body's demand for wound healing and recovery after surgery. Given these conflicting factors affecting energy expenditure, IC is strongly suggested as the gold standard for determining resting energy expenditure and respiratory quotient (RQ). Using this method, Hollander-Kraaijeveld et al. indicate that there is a significant reduction in resting energy expenditure post-transplantation.<sup>[7](#page-6-7)</sup> Kalnins et al. also showed this reduction in energy expenditure, with a mean decline in resting energy expenditure of  $20 \pm 10\%$  from the pre-transplant period to one year post-transplantation.<sup>[8](#page-6-8)</sup>

<span id="page-5-1"></span><span id="page-5-0"></span>IC was performed at 10 and 52 days post-transplantation, indicating resting energy expenditures of 1 739 kcal (RQ of 0.84) and 1 260 kcal (RQ of 0.83) respectively (see [Figure 3\)](#page-3-0). This represents a 27% decrease in resting energy expenditure over the seven-week post-transplantation period. It is important to note that these readings reflect resting energy expenditure. To estimate total energy expenditure, an activity factor must be added. Considering an activity factor of 25% is added for the reading at day 10, and an activity factor of 50% is added at day 52 due to increasing activity, his total energy expenditure was estimated at 2 173 kcal/day (49 kcal/kg TE) at day 10, and 1 890kcal/day (43 g/kg TE) at day 52 post-transplantation.

Improving the sufficiency of oral intake and removal of the PEG tube became the top priority in the post-transplant period. To achieve this, the amount of semi-elemental feeds provided through the PEG was decreased over time, while oral intake and polymeric oral nutritional supplementation intake was encouraged, including the use of PERT. Over the subsequent two months his weight continued to increase slowly, with a steady increase in muscle mass, despite less nutrition support provided through the PEG. [Figure 4](#page-3-1) outlines the anthropometric changes over this period. Point 'a' marks the start of a decline in bodyweight and muscle mass, accompanied by an increase in body fat percentage. This period preceded the diagnosis of new-onset diabetes after transplantation (NODAT), which contributed to the deterioration of his nutritional status.

## New onset diabetes after transplantation (NODAT)

NODAT is characterised by the onset of diabetes mellitus posttransplantation in the absence of the condition prior to transplantation. This common condition affects 40% of patients by two years post-transplantation, with cystic fibrosis patients being at increased risk. $6$  The primary cause of NODAT is the impact of calcineurin inhibitors and corticosteroids on blood glucose regulation. These medications are an essential component of the immunosuppression regime required post-transplantation. [Table 3](#page-4-0) provides a summary of common posttransplantation medications and their nutritional implications. The diagnosis of NODAT was confirmed 131 days post-transplantation by a glycated haemoglobin (HbA1c) reading of 7.7% (see [Table 2](#page-2-0)). In response, a continuous glucose monitor was implemented, along with insulin therapy, glycaemic control education, and dietary counselling. Management of NODAT requires close collaboration between the transplant team, including dietitians, and the diabetes team, including diabetic educators and endocrinologists. Effective nutritional management involves ensuring nutritional requirements are met without compromising glycaemic control. As PEG feeds are decreased with an increase in oral intake, insulin requirements need to be tapered accordingly through strict monitoring and analysis. This coordinated approach is essential for improving nutritional status and achieving glycaemic targets.

Once glycaemic targets were reached and NODAT management was under control, the patient's nutritional status began to improve. This is shown in [Figure 4,](#page-3-1) point 'b', which indicates an improvement in anthropometry with an increase in bodyweight and muscle mass, with a normalisation of body fat percentage.

#### Feeding progression post-transplantation

Once glycaemia management was achieved, the next objective was to improve oral intake to facilitate the removal of the PEG tube. To ensure he could maintain adequate oral intake, a decision was made to keep the PEG tube in place for an additional month without using it, in order to prevent premature removal. Oral intake was encouraged and monitored, consisting of home food intake and polymeric oral nutritional supplement drinks providing an additional 750 kcal of energy and 40 g of protein, taken with PERT. Following this, there was a slight decrease in weight, but this stabilised, with a steady increase in muscle mass and a decline in body fat percentage (as shown in [Figure 4](#page-3-1), point 'c'). Following a trial period, his PEG tube was successfully removed, and he is maintaining his nutritional status well with oral intake alone.

## Conclusion

The nutritional management of cystic fibrosis is complex, and necessitates multidisciplinary collaboration due to the complex nature of the disease and its implications for health. Dietitians play a critical role in the transplant team and nutritional input is required at every stage of managing a cystic fibrosis patient, from ensuring optimal preoperative nutritional status to improve outcomes post-surgery, to managing posttransplantation side effects.

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