Chapter 1.5

Consequences of undernutrition

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1.5.1 Introduction and background

Undernutrition is complex, with interacting factors that both precipitate or exacerbate each other, leading to a vicious cycle in which the patient’s condition spirals downwards. This chapter aims to discuss the broad range of complications that can arise from undernutrition with or without disease.

Some of the common clinical consequences of undernutrition are shown in Box 1.5.1. However, many of these are also implicated in the causes of undernutrition. This means it is difficult to find clear evidence of causal relationships between undernutrition and these listed consequences. Most evidence is observational or epidemiological, so although associations may be established, it can be difficult to untangle which event came first. In addition, it is difficult to ascertain the effect of different nutrients from one another; vitamins and minerals play a role alongside macronutrients. To prove cause and effect, intervention trials are required, of which there are few. However, a range of studies have provided evidence of a link between poor outcomes and undernutrition.

There are several recent systematic reviews of disease-related undernutrition and nutrition support, and although nutrition interventions improve energy and protein intake, and body weight, the data remain equivocal on clinical and functional outcomes such as physical function, gastrointestinal function, wound healing, complications, length of stay and mortality [1,2]. Observational data suggest associations between undernutrition and these outcomes but the evidence is insufficient to demonstrate causality [3]. Undernutrition may simply be a marker of the severity of disease. There is a consensus that large-scale, well-designed randomised intervention studies able to clarify these issues need to be carried out. Other systematic reviews in specific patient groups (such as hip fracture and liver transplant patients) have found low-quality evidence for the use of nutrition support in reducing unfavourable outcomes such as complications and mortality [4,5].

Evidence from starvation studies quantifies the effects of undernutrition on the human body. Periods of famine and acts of hunger strike have provided further insight into the mechanisms associated with prolonged fasting. Keys’ Minnesota experiments created a model of semi-starvation, allowing researchers to study the processes and consequences of weight loss in a controlled environment [6]. In Keys’ study, 32 lean male participants lost an average of 25% body weight over 24 weeks, following a diet designed to produce a deficit of approximately 1 kg per week. Total abstinence from food has generated more acute weight losses, with 18% body weight loss seen over a 43-day period in eight Brazilian prisoners on hunger strike [7] and at 60 days the average weight loss was 38% in 30 Irish hunger strikers [8]. Keys proposed
that weight loss over 18% would cause significant disruption to homeostasis, with death highly likely at weight loss of 50%.

### 1.5.2 Physical consequences of undernutrition

**Undernutrition and mortality**

A body mass index (BMI) of 13 kg/m² in men and 11 kg/m² in women is considered the lowest sustainable, after which death is highly probable [9]. Keys [6] put forward the hypothesis that a greater fat mass is advantageous in fasting conditions, with higher body fat mass providing protection in the metabolic response to starvation. In starvation, fat is the primary energy source, contributing 78% and 94% of the energy expended in lean and obese subjects respectively. Obese individuals have both a higher fat mass and fat-free mass (FFM) but despite the higher protein stores, protein oxidation provides a smaller amount of energy. This suggests a protein-sparing effect in individuals with a larger proportion of body fat, resulting in smaller protein losses and a reduced rate of protein loss over the starvation period [10].

Without food, it is estimated that a healthy adult will survive for approximately 70 days having lost approximately 40% of their body weight [8]. This is supported by data from the 30 men participating in the Irish hunger strike in 1981; after about 70 days, the group had lost a mean of 38% of their body weight and 10 had died [8]. The nature of the weight loss appears to
be important to survival, with 40% body weight loss being fatal in situations of complete starvation, compared to 50% in semi-starvation.

Populations at highest risk of mortality from undernutrition include older adults, those who have been recently hospitalised or had a stroke, those with a lower grip strength and/or gait speed, and those who are unable to perform activities of daily living. Current smoking, black race, higher weight and lower waist circumference also increased mortality risk [11]. Using weight loss as an indicator of undernutrition, the large, prospective Cardiovascular Health Study \( (n=4714) \) compared older participants with weight losses of over 5% to those who gained weight over a 4-year period. They demonstrated that individuals with weight loss had a greater risk of death (hazard ratio = 1.67, 95% confidence interval (CI) 1.29–2.15) [11], confirming that even a modest reduction in body weight can be an important and independent marker mortality risk in older adults. A systematic review of observational studies explored mortality in older adults following a period of rehabilitation [12]. The included studies were heterogeneous and sample size relatively small, but the authors concluded that undernutrition during rehabilitation was negatively associated with physical function and quality of life, and positively associated with risk of institutionalisation, hospitalisation and mortality [12].

Whilst death as a consequence of undernutrition is rare in children and younger adults in the developed world, data from 2011 showed that 45% of child deaths in developing countries were attributable to undernutrition [13]. A review discussed mortality in pregnant women and children, reporting a link between low mid-upper arm circumference and all-cause mortality in pregnant women [14].

### Undernutrition and muscle mass and function

In the presence of undernutrition, muscle mass is depleted relative to the type and duration of the exposure. Much of the available evidence comes from the Minnesota semi-starvation experiments [6], where individuals were losing an average 1 kg total body weight per week and consuming a protein-poor diet. Results demonstrated a mean muscle loss of 18% over 168 days. In complete starvation, muscle breakdown is more rapid, with initial losses of approximately 75 g/day of protein [15]. For a 70 kg person with 10 kg of muscle, this would equate to a 15% loss in 10 days, reducing total protein stores to nothing in under 70 days. This rate of muscle utilisation is not sustained; instead, the body adapts, sparing protein in favour of mobilising fat stores for energy.

Studies in obese subjects undergoing weight loss regimens provide information about the composition of the tissues lost with weight loss. One systematic review combined 16 studies (low calorie diet (LCD); very-low calorie diet (VLCD) and pharmacological intervention) with a pre/post design, demonstrating that the level of energy restriction was positively associated with the degree of FFM loss \( (r^2=0.31, \ P=0.006) \). Median FFM losses were 14%, 23% and 38% for LCD, VLCD and pharmacological intervention respectively, with several studies exceeding the safe value of 22% weight loss from FFM [16].

Muscle tissue is essential due to the relationship between muscle mass, muscle strength and function. Whilst the pathogenesis is unclear, both undernutrition and loss of muscle have been associated with reduced muscle function, suboptimal activities of daily living scores and handgrip strength [3,6,17]. However, nutrition interventions have not shown consistent improvements to muscle mass or function in recent systematic reviews [1,2]. Due to the range of outcome measures used, heterogeneous study designs and quality of studies, further large-scale intervention studies are needed before conclusions can be drawn.

In older adults, muscle loss can be masked by a concurrent increase in fat mass. As metabolically active lean tissue is lost, energy requirements can reduce by a third (where dietary intake and exercise levels remain stable), leading to weight gains [18]. Studies have shown correlation between muscle mass and metabolic disorders such as glucose metabolism, with decreases in the ratio of skeletal muscle...
mass to total body weight associated an increased risk of insulin resistance and diabetes.

In addition to its roles in skeletal muscle, muscle protein is integral to the function of major organs such as the heart, liver and kidneys, and these protein stores are not immune to the effects of undernutrition. Atrophy of internal organs is a critical feature of undernutrition, affecting the cardiovascular and respiratory systems by reducing muscle size and function. Congestive heart failure is aggravated by undernutrition, with heightened risk of tricuspid regurgitation and right atrial pressure [19]. Loss of diaphragm mass has been shown to decrease respiration rate and consequentially oxygen consumption, impacting on recovery following chest infection and weaning from ventilation [20]. Individuals with chronic obstructive pulmonary disease (COPD) and poor nutritional status experience worse clinical outcomes including suboptimal respiratory function, reduced ability to expectorate and heightened fatigability. Pneumonia is a common cause of death once muscle mass is reduced to 60% of normal [20].

**Undernutrition and immunity**

There is a strong relationship between infection, nutritional status and mortality, with elements of non-specific and specific immunity affected by a state of suboptimal nutrition. Host defence mechanisms include physical barriers, such as skin and mucous membranes, acting as the first line of defence to protect the body from infection. Inadequate nutrient availability compromises the barrier function of the skin and tract linings so that in a state of undernutrition, the GI tract becomes more permeable and more susceptible to bacteria, increasing infection risk [21]. Immunoglobulin secretion is limited, reducing the level of protection provided to epithelial cells of the respiratory tract, small intestine and urinary tract. Ordinarily, lysozymes and complement cells work together to digest invading bacteria, and T- and B-lymphocytes form part of the adaptive immune response, produced following exposure to infection. However, in a state of undernutrition, complement activity is limited and the number of available lysozymes and T-cells is reduced [22].

In a retrospective cohort study, patients were screened with Subjective Global Assessment on admission to one of 25 Brazilian hospitals. Multiple logistic regression was used to isolate nutritional status, concluding that undernourished participants experienced more infectious complications than well-nourished subjects, irrespective of diagnosis (27% and 17% respectively) [21]. The rate of sepsis and abdominal abscess post surgery was also increased, with 3.7% versus 1.1% and 2.1% versus 0.4% for undernourished and nourished participants respectively.

**Undernutrition and non-infectious complications**

The incidence of non-infectious complications, such as respiratory and cardiac failure, cardiac arrest and wound dehiscence, has also been shown to differ significantly between undernourished and well-nourished individuals. A significantly higher incidence of non-infectious complications was demonstrated in undernourished patients (undernourished 20.5% versus well nourished 8.4%), with ‘severe’ undernutrition increasing the risk of an infectious or non-infectious complication [21].

Skin is weakened by undernutrition; with poor nutrient supply and minimal fat stores, the skin loses its integrity, becoming thin and delicate with a reduced capacity to repair. By lengthening the inflammatory phase, reducing fibroblast proliferation and collagen synthesis, undernutrition reduces wound strength and may result in chronic, non-healing wounds [23]. The loss of fat and muscle as protective cushioning leads to increased pressure from bones, causing damage to both the surface and underlying layers of the skin and allowing sores to develop spontaneously. Prevalence ranges from 3% to 66% in the hospital setting, with immobile older patients most at risk [24].

There is convincing epidemiological evidence for a relationship between undernutrition and the increased incidence and severity of pressure ulcers, but evidence from trials is limited.
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Multivariate analyses show that poor nutritional status, described by low body weight, BMI and suboptimal food intake, is independently associated with pressure ulcers. In a meta-analysis that included four randomised controlled trials comparing the development of pressure ulcers in at-risk populations, there was a significantly lower incidence of pressure ulcers in participants receiving nutrition support compared to those receiving usual care (n=1224; odds ratio (OR) 0.75, 95% CI 0.62–0.89) [24]. However, these studies were generally short term and in older adults with underlying illness, which complicates interpretation. Studies exploring the effect of nutrition support on subjects with existing pressure ulcers are limited and with a lack of randomised controlled trials, so firm conclusions on the effect of nutrition support on pressure sore healing are not possible.

Micronutrient deficiencies can also have negative effects on wound healing. The wound healing process involves clotting, blood vessels and tissue repair and specific micronutrients may affect different stages in this pathway. Amino acids (glutamine, methionine, cysteine, lysine and proline) have been implicated in fibroblast proliferation and collagen synthesis but there is little evidence to support the use of these amino acids in healing wounds. Vitamins A and C are also important and supplements may be recommended in specific situations. Trace elements magnesium, copper and zinc are crucial to cellular metabolism and a lack may influence healing. Zinc, in particular, may be supplemented to enhance wound healing but evidence is limited [23].

1.5.3 Psychological consequences of undernutrition

Undernutrition and quality of life

The effects of undernutrition on health-related quality of life are thought to be indirect, resulting from a combination of the physical, functional and cognitive changes discussed above, raising infection risk, delaying discharge from hospital and increasing dependence [25]. Apathy and lethargy as symptoms of undernutrition have been described by Keys [6]. Keys observed depression and reduced motivation in his cohort, exemplified by participants’ withdrawal from university classes as their body weight and macronutrient intakes reduced.

A systematic review exploring the relationship between nutritional status and quality of life in older adults found that quality of life was better in well-nourished individuals compared to undernourished (OR 2.85; 95% CI 2.20–3.70, P<0.001, from 15 studies) [25]. It also showed that nutrition interventions to treat undernutrition improved both physical and mental quality of life domains (physical domain: standard mean difference 0.23, CI 0.08–0.38, P=0.002; mental domain: standard mean difference 0.24, CI 0.11–0.36, P<0.001). The authors included both interventional and observational data, and only used studies which employed validated techniques to measure quality of life, but found evidence of publication bias and limitations in the design of studies [25], so some caution is required when interpreting these data. However, more recent studies continue to suggest that there is a link between nutritional status and quality of life, in specific patient groups and in children as well as adults [26].

Undernutrition and depression and anxiety

The relationship between mood and nutritional status is complicated and may be reciprocal. For example, undernutrition seems to play a causal role in depression but the symptoms of depression include reduced appetite, which may lead to undernutrition. This makes studying these symptoms more difficult as it is necessary to establish that the state of undernutrition came first and that treating the undernutrition will result in improvements in mood. Two aspects of mood that are commonly studied are depression and anxiety.

A systematic review of the factors related to undernutrition in nursing home residents consistently found an association with depression [27] and suggested that since this factor was modifiable, targeting depression may help
reduce weight loss and undernutrition in the population, making the assumption that depression resulted in weight loss. Yet, the data were unable to demonstrate a causal link between depression and undernutrition, only establishing an association, and it may be that undernutrition caused the depression. Similarly, a review explored the relationship between undernutrition, depression and anxiety in patients with anorexia nervosa, and concluded that evidence of undernutrition resulting in depressive symptoms or anxiety was very limited [28]. The quality of the studies available was poor, the variability in the tools to assess all three outcomes was great, and the findings were contradictory. This indicates that further work to establish the causal link between undernutrition and mood is required.

There are acknowledged mechanisms by which a lack of certain micronutrients may influence mood, including minerals and trace elements (zinc, magnesium, lithium, iron, calcium, chromium, copper, selenium, iodine and vanadium) and vitamins (B complex, C, D and E); these are comprehensively reviewed elsewhere [29–31]. They offer an explanation as to why undernutrition may result in detrimental mood changes. However, unless micronutrient deficiency is examined in populations studied for undernutrition and the treatment focus is moved from energy and protein repletion to specific nutrients, the evidence for these micronutrients is likely to remain weak.

Undernutrition and cognitive function

It has long been thought that food restriction will have some effect on cognitive function, which includes domains such as psychomotor ability, memory, processing speed, visual attention and executive function. The evidence to support a detrimental effect of semi-starvation and undernutrition is inconsistent or absent. Some studies show no effect of prolonged fasting whilst others suggest deficits in short-term memory, encoding, attention, reaction time and/or vigilance [32].

Understanding the acute effects of fasting on cognition in healthy adults may help to elucidate the unfavourable consequences of undernutrition; this has been explored in a recent systematic review [32]. The findings show no consistency in the effect on any of the cognitive functions studied. This presents an incomplete picture of what is and what is not affected by acute fasting and hunger and so consequently offers limited evidence as to how the brain may be influenced by undernutrition. The lack of consistency, however, was mainly due to the variation in study design (inconsistent fasting conditions, procedures used, test settings and populations used) and confounding variables (unreported gender, age, culture, circadian rhythm, etc.). Despite the problems with the existing literature, some important findings were that reaction time and processing speed did appear to be slower in relation to fasting, but interpretation was complicated because motivation and fatigue were not always controlled for. Memory was highly studied and data seemed to suggest that although short-term memory was not impacted by fasting, time to retrieval was. Attention capacity did appear to be affected by low blood glucose concentrations and further study of this aspect of cognition was recommended [32].

1.5.4 Economic consequences of undernutrition

Health economics is the study of how scarce resources are allocated among alternative uses for the care of sickness and the promotion, maintenance and improvement of health, including the study of how healthcare and health-related services, their costs and benefits, and health itself are distributed among individuals and groups in society [33]. This field of study has gained increasing prominence as healthcare resources become more limited and recently a subspecialism of nutrition economics has been established [34].

The economic costs arising from undernutrition are attributable to increased length of hospital stay and the treatments associated with higher complication rates and prolonged recovery. The overall costs of disease-related undernutrition (as opposed to poverty and food scarcity) are
estimated to be €31 billion in Europe [35], $157 billion in the USA [36] and $66 billion in China [37]. These figures are comparable and modelled using similar assumptions with data from published studies on prevalence, morbidity and mortality, agreed healthcare costs and assessments of quality of life. There are other published figures, for example £19.6 billion in England [38] and €1.9 billion in the Netherlands [39], but these authors have used different methodologies.

Nevertheless, given that much undernutrition is preventable, there is a high cost associated with failure to prevent and treat it. These costs also place a substantial burden on health and social care systems, with the majority spent on more frequent, lengthier hospital admissions and the greater demand for social care. The healthcare cost of managing an undernourished person is estimated to be more than twice that of an adequately nourished person [40]. Nevertheless, the heterogeneity of research and varying definitions of undernutrition make cost estimate comparison difficult and precise estimates should be treated with some caution [41].

The most recent systematic review on how treatments may reduce hospital-related costs of undernutrition found surprisingly few studies (n=3), although these were moderate or high quality. The authors concluded that this lack of evidence limits the ability of clinicians or managers to make informed decisions about what is cost-effective. The three included studies all showed cost savings ranging from €76 to €252 per patient in the treatment group. However, the methods and assumptions made were highly variable, making comparisons difficult [41]. Another systematic review with broader inclusion criteria (included eight studies) also showed consistent cost savings for the use of enteral medical nutrition [42]. Studies on specific patient groups have also demonstrated cost savings; for example, undernourished colorectal cancer patients undergoing surgery were found to have longer length of stay compared to well-nourished patients (3.4 days longer, P=0.017) and correspondingly higher costs (€3360 higher) [43]. Similar data exist for community-dwelling populations showing higher costs, greater use of healthcare resources (such as general practitioner consultations, nurse and dietitian visits, hospital outpatient appointments, etc.) [40,44].

1.5.5 Summary

The consequences of undernutrition are detrimental, both physical and psychological, and far-reaching, with associated costs (financial and quality of life) affecting both individuals and society. The relationship with disease is complicated since undernutrition may precipitate disease and be precipitated by disease, which makes studying the outcomes of undernutrition challenging. Other chapters in the book discuss in more detail the assessment and treatment of undernutrition, as well as particular issues relating to specific conditions or settings.

References

SECTION 1: Background to undernutrition

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