Ethem Murat Arsava
Editor

Nutrition in Neurologic Disorders

A Practical Guide

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Preface

There is a very close and multidimensional interplay between nutritional status and neurologic diseases. On one hand, nutritional problems can predispose to certain neurologic disorders. On the other hand, both acute and chronic neurological disorders have a significant impact on body metabolism. In addition, these patients comprise a high-risk group who can rapidly develop malnutrition secondary to their disabilities related to manifestations of the underlying disease, like swallowing problems or mobility issues. Malnutrition, unless prevented or efficiently treated, is a well-known factor that contributes to increased morbidity and mortality in patients with neurologic diseases. Despite its importance and high prevalence, neurologists are generally not motivated in implementing nutritional plans to their patients. One contributing factor in this regard is the scarcity of publications that primarily focus on the issue of nutritional management of neurological patients.

In this publication, we aim to cover practical aspects of nutrition from a neurology perspective. The book starts with a concise review of macronutrient metabolism in the human body and familiarizes the reader on how this highly critical body function is disturbed in disease settings. The section is followed by a detailed summary of commonly used screening and assessment tools in identifying patients with malnutrition, where the normal physiology has been exhausted by impaired food and calorie supply. Epidemiologic facts on nutritional issues in neurological disorders and their impact on the disease course, discussed in the ensuing chapter, highlight the importance why nutritional evaluation and planning should be inherent tasks of neurologists. The part on methods of clinical nutrition presents basic knowledge on the principles of how these plans should be implemented. Specific chapters dedicated to nutritional support in neuro-intensive care unit patients and patients with amyotrophic lateral sclerosis and chronic neurodegenerative diseases provide a handy guide for nutritional management of neurologic patients encountered in various clinical settings. The concept of dysphagia, a critical and highly prevalent contributor of disease-related malnutrition among neurology patients, is discussed extensively from a multitude of aspects including its pathophysiology, diagnosis, treatment, and rehabilitation. Our work is finalized by a chapter on the newly developing and provoking concept of neuro-nutrition—the use of certain nutrients for the treatment of neurologic disorders—an area where the scientific community has kept its distance for a long time but could not avoid anymore due to the immense pressure from the lay media and general public.

We believe that this work would be an important resource for filling the gap in the field and would prove to be useful not only for practicing neurologists but also for medical personnel from other fields like clinical nutrition, critical care, or geriatric medicine. We hope that the book will meet the expectations of our valuable readers.

Ankara, Turkey Ethem Murat Arsava

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1.1 Introduction

Almost all energy, which circulates within life cycles, originates from the Sun. The green plants accumulate energy of the Sun into substrates which are composed of carbon, hydrogen, oxygen, and nitrogen supplemented with relatively small amounts of other atoms (electrolytes and trace elements). The animals ingest, metabolize, and oxidize such plant substrates, which are called macronutrients; some animals (including humans) eat macronutrients that originate from both plants and animals.

Appropriate and adequate nutrition is absolutely essential for animal life. If the intake of nutrition is interrupted, the energy necessary for survival is obtained from body reserves; such a situation is called negative energy balance. A long-term negative energy balance leads to body depletion, the loss of 30–40% of body proteins is life-threatening. Such a fatal loss of body mass occurs after 50–70 days of uncomplicated fasting; however, during periods of critical illness, this interval is considerably shorter due to reduced adaptation to negative energy balance and increased protein catabolism.

There are three main components of nutrition:

- Macronutrients—carbohydrates, lipids, and proteins
- Water and electrolytes (Na, K, Ca, Mg, Cl, P)
- Micronutrients—vitamins and trace elements

Quantitatively, macronutrients constitute the largest part of nutrition; however, they are not solely sources of energy, as usually declared. Macronutrients are also the source of substrates necessary for body development, growth, protection against

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injury or microbial invasion (inflammation and immune reaction), wound healing, recovery after disease, rehabilitation, and adaptation.

1.2 Carbohydrates

Carbohydrates (CHOs) are quantitatively the biggest part of energy in a normal diet; they meet 40–55% of the daily energy intake. Subjects with moderate activity (2500 kcal/day) should consume 300–400 g of CHOs per day, while very active individuals may need up to 60% more than these amounts. It is generally suggested that CHOs are the basic source of energy for organism; however, they do not only serve as energy substrates. Especially glucose possesses several metabolic functions in various cells, tissues, and organs, and its metabolism is much more complex than just provision of energy. This is apparent from the several possibilities present in glucose metabolism.

Key pathways of glucose metabolism are:

- Krebs cycle—full and effective oxidation of glucose to CO_2 and H_2O with subsequent production of energy in the form of ATP.
- Cori cycle—glycolysis and subsequent gluconeogenesis—glycolysis is the source of energy in ischemic tissues or tissues without oxidative metabolism (e.g., absence of mitochondria).
- Anaplerotic reactions—reloading metabolites for Krebs cycle.
- Cataplerotic reactions—removal of metabolites from Krebs cycle for biosynthesis of many other molecules (mostly amino acids).
- Pentose cycle—production of:
  - Reducing equivalents (NADPH) for synthetic reactions
  - Reducing equivalents for free radical scavenging
  - Ribose for nucleic acid synthesis
- Synthesis of extracellular matrix and glycocalyx.
- Glycation of physiologically active proteins (e.g., membrane receptors and transporters).

All these roles are important for life, defense reactions—inflammation, recovery from disease and rehabilitation, and growth or repletion of body compartments in severely depleted patients. CHOs are also important for preservation of tissue proteins by reducing the need for gluconeogenesis from amino acids. Moreover, glucose is an important regulatory factor in lipid metabolism; it reduces lipid oxidation and ketogenesis and also stimulates storage of triglycerides in adipose tissue.

1.2.1 Carbohydrates as Energy Substrate

Most cells of the body, including the central and peripheral nervous systems, as well as blood cells and ground substance of healing tissues, may use glucose as energy substrate. The complete oxidation of one mole of glucose to water and CO_2 yields 36 moles of ATP and two moles of guanosine triphosphate (GTP). On the other side,

glycolysis generates only two moles of ATP and two moles of lactate, which is further metabolized in the reverse pathway of glycolysis (gluconeogenesis) to glucose—this cycle is called Cori cycle. Gluconeogenesis from lactate requires six moles of ATP; it means that energy balance of Cori cycle is minus 4 ATP, derived from fatty acid oxidation in the liver.

Glucose is a substrate, which can be fully oxidized in most tissues; however, it is not fully oxidized during hypoxia when glycolysis with subsequent lactate production is the leading pathway of energy production. Red cells and tubular cells in the kidney fully rely on glycolysis for ATP generation.

Dependence on glycolysis as basic energy-producing reaction is usually due to:

- Absence of mitochondria—red blood cells
- Hypoxic conditions in some organs—renal medulla, all tissues during hypoxia

Glycolysis is also present in rapidly proliferating cells even if oxygen provision is normal (see below).

Glucose is preferably oxidized in the central nervous system, probably due to poor permeability of the blood–brain barrier for fatty acids bound to albumin. However, during prolonged fasting, more than 60% of brain energy is obtained from oxidation of ketone bodies [1]. Moreover, glucose is not fully oxidized during shortage of CHOs in the diet, although glucose cycling is still present in this situation [2].

1.2.2 Nonenergy Roles of Carbohydrates

Glucose is not only an energy substrate but also is an important substrate for body growth, tissue regeneration, immune cell proliferation, and other synthetic processes, as well as antioxidative reactions.

Rapidly proliferating cells exhibit a low activity of oxidative metabolism of glucose; this phenomenon was first described for cancer cells as the Warburg effect [3]. The presence of this effect (non-oxidative glucose metabolism in the presence of oxygen) was later demonstrated in other rapidly proliferating cells. The metabolism of these cells is changing from full glucose oxidation in the quiescent state to glycolysis and enhancement of non-oxidative glucose metabolism in the proliferating state. Insulin resistance and glucose cycling are also present in other situations when rapid cell proliferation is necessary (immune cells during inflammation, regenerating organs, growth, anabolic processes) [4]. Proliferating enterocytes are good examples; they utilize glucose, however this substrate is not consumed only as a source of energy production, but glucose is also substrate for anaplerotic and then cataplerotic reactions. Proliferating cells can use fatty acids as sources of energy and partially metabolize glutamine (producing aspartate, glutamic acid, pyruvate, and NH_3).

Glucose is the principal substrate for the pentose phosphate pathway (PPP or pentose cycle). This cycle provides crucial reducing equivalents (NADPH) for maintenance of the redox state and also for synthetic processes. The PPP is also indispensable for synthesis of pentoses, which are important for production of nucleic acids and cell division [5].

1.2.3 Regulation of Glucose Metabolism

Glucose metabolism is regulated by:

- Hormones—insulin, glucagon, cortisol, and growth hormone
- Neural factors—sympathetic and parasympathetic nervous system
- Local factors—cytokines and prostaglandins

Insulin is the central anabolic hormone, which plays an important role in glucose metabolism. The secretion of this hormone is directly dependent on blood glucose levels. Insulin stimulates transport of glucose into the cells within insulin-sensitive tissues (skeletal muscle and adipose tissue). Insulin also inhibits hepatic glucose production and stimulates storage of glucose as glycogen in the liver and muscles. Moreover, it also stimulates glucose utilization and oxidation and also influences lipid and protein metabolism. In this way, insulin is an important stimulator of many anabolic processes.

On the other site, catabolic hormones (glucagon, adrenaline, cortisol) exhibit an opposite effect. They inhibit glucose uptake in insulin-sensitive tissues (skeletal muscle and adipose tissue) and stimulate hepatic glucose production. These hormones are increasingly produced during fasting, stress, or inflammation. The role of hormones in glucose metabolism is presented in Table 1.1.

Insulin secretion rises and the secretion of catabolic hormones falls, after ingestion of CHO-containing meal. On the other side, catabolic hormones stimulate hepatic glucose production during fasting. Moreover, energy deficiency inside the cell leads to stimulation of glucose uptake and its utilization.

1.2.4 Effects of Stress on Glucose Metabolism

Stress response (during trauma, disease, and inflammation) leads to stimulation of the sympathetic nervous system and increased secretion of catabolic hormones together with decrease in insulin secretion. Stress also decreases sensitivity of several tissues to insulin (so-called insulin resistance). This response leads to stimulation of gluconeogenesis in the liver and lipolysis in adipose tissue.

The inflammation is always connected with increased production of TNFα and interleukins (IL_1, IL_2, and IL_6). These cytokines (together with catabolic hormones) increase hepatic glucose production and turnover, which cannot be fully suppressed

Table 1.1 Effects of hormones on whole-body glucose metabolism [7]

	Insulin	Glucagon	Cortisol	Adrenaline	Growth hormone
Glycogenolysis	↓↓	↑↑		↑↑	
Gluconeogenesis	↓	↑	↑↑	↑	↑
Muscle/adipose glucose uptake	↑↑		↓	↓	↓
Glycogen storage	↑	↓	↑	↓	↓
Glucose oxidation	↑		↓	↓	↓

after CHO administration. This condition is associated with an increased breakdown of body proteins [6]. The glucose production increases from 2–5 g/kg/day after overnight fast to 5–10 g/kg/day during critical illness [7]. An increased lipid mobilization and oxidation are therefore necessary to generate energy, which is essential for such a high rate of gluconeogenesis in the liver.

Long-term inflammation leads to metabolic responses characterized by high and prolonged hyperglycemia and loss of muscle mass, a situation that is associated with poor clinical outcome. However, it is not fully known if hyperglycemia is dangerous per se [8] or if it is only an epiphenomenon of critical illness, which is regularly connected with enhanced proteolysis and loss of body cell mass. Glucose turnover is markedly elevated (1.5–2 times), and a large part of glucose is recycled after aerobic glycolysis into lactate in the presence of oxygen (also known as Warburg effect), which is again substrate for hepatic gluconeogenesis [9]. It is obvious that oxidative metabolism of glucose is not increased in the same proportion as turnover. Rather, there is a substantial rise in glucose recycling via different pathways.

1.2.5 Glucose Metabolism During Fasting or Low Carbohydrate Intake

There are limited stores of glucose in the human body. It can be stored as glycogen in the liver and in the skeletal muscle; however, only liver glycogen can serve as a direct source of plasma glucose. When the hepatic reserves of glycogen are exhausted, glucose must be produced via gluconeogenesis. During fasting hepatic glucose production amounts to 2.5–3 mg/kg/min, which is equivalent to 3.6–4.3 g/kg/day. This amount equals approximately 250–300 g of glucose in a person weighing 70 kg [10]. This production increases during acute diseases and is fueled by ATP derived from the oxidation of fat or fat-derived ketone bodies. Glucose is produced from lactate, amino acids (mainly alanine), and glycerol (from triglycerides) in the liver and partially (from glutamine) in the kidney. However, only glycerol and carbons from some glucogenic amino acids are precursors for truly new formation of glucose; Cori cycling (gluconeogenesis from lactate and alanine) in fact does not provide new glucose. The reason for such cycling is not fully understood; however, the nonenergetic role of glucose should be taken into account [5].

1.2.6 Carbohydrates in Nutrition

CHOs given in enteral nutrition can be divided into:

- Monosaccharides—glucose and fructose
- Disaccharides—sucrose (sugar) and lactose
- Oligosaccharides—maltodextrins
- Polysaccharides—starch and fiber

1.2.6.1 Monosaccharides

Monosaccharides (e.g., glucose) constitute only a small proportion of the CHOs in enteral feeds, since they considerably increase the osmolality of the feed. On the other site, glucose is the only CHO source in parenteral nutrition admixtures. Fructose or polyols (sorbitol and xylitol), which were used as alternatives of glucose in diabetic patients, are no longer used because of the risk of fructose-induced liver failure in subjects with aldolase B deficiency [11].

1.2.6.2 Disaccharides

Saccharose (sugar) is the disaccharide that is used in enteral nutrition mainly as a sweetener. High intake of sugar is connected to development of obesity and metabolic syndrome, as well as with occurrence of dental caries. Lactose is present in milk and dairy products; the deficiency of lactase (enzyme which cleaves lactose) in intestinal cells leads to severe diarrhea. As lactase deficiency is frequent (more than two thirds of the world population have lactase deficiency), lactose is absent in enteral nutrition formulas.

1.2.6.3 Oligosaccharides

Oligosaccharides (maltodextrins) are polymers of 15–30 glucose units connected with 1–4α bonds. These oligosaccharides are industrially produced form starch. They are frankly soluble, minimize the osmolality of the feed, and are also easily hydrolyzed. Maltodextrins in nutrition are very well tolerated and therefore are used as important CHO components in many enteral nutrition products.

1.2.6.4 Polysaccharides

Polysaccharides are the most abundant CHOs in a normal diet. However, only starch is easily hydrolyzed to glucose that is subsequently absorbed in the small bowel. Other CHOs (e.g., cellulose, hemicellulose, pectin, and inulin) are not hydrolyzed and absorbed in the small intestine, but are fermented by bacteria in the large bowel, and the products of fermentation (short-chain fatty acids—acetate, propionate, and butyrate) are absorbed. Short-chain fatty acids are also important substrates for large bowel epithelial cells. After ingestion, starch is split by the sequential actions of amylases, isoamylases, and brush border enzymes to glucose, which is then absorbed into the portal circulation.

Optimally, the maximum of CHOs should be ingested in complex forms, as polysaccharides or starch. Then glucose is the major monosaccharide that is absorbed into the portal blood (90% of monosaccharides). The content of fructose in portal venous blood can be higher during high intake of saccharose (sugar) or fructose. Such higher intake of saccharose is suggested to be responsible for increased incidence of dental caries and also for obesity, atherosclerosis, and dyslipidemia.

1.2.7 Dosages of Carbohydrates in Nutrition

Glucose can be metabolized by all cells of our body. Its maximal oxidation is dependent on intake and energy expenditure. In sedentary subjects or in adult patients restricted to bed rest, the oxidation rate is dependent on energy expenditure, and its

maximal rate amounts to approximately 4–5 mg/kg/min. Therefore, in resting conditions or in hospitalized adult patients, the daily CHO intake should not exceed 7 g/kg. However, during anabolic situations like growth, healing, or muscle gain (convalescence phase after acute disease or during rehabilitation therapy), the dosage of glucose could be higher. This is because glucose is not a source of energy but also substrate for other important metabolic pathways (anaplerosis and cataplerosis).

1.3 Lipids

Lipids are important macronutrients, and due to their high-energy content (1 g of triglyceride involves 9 kcal) and low hydration, lipids are an ideal form of energy stored in the body. The standard quantity of energy stored in adipose tissue in a healthy adult is 150,000 kcal; this amount can be much higher in obese subjects.

Besides being a source of energy, lipids are important constituents of all cells and tissues. The phospholipid bilayer is the basic component of all cellular membrane structures. In addition, membrane phospholipids are metabolically important molecules, which are split by various enzymes connected with cell receptors to yield bioactive molecules such as prostaglandins, leukotrienes, inositol phosphate, etc. By means of such mechanisms, lipids and their metabolites serve as local hormones and second messengers of hormones and other bioactive molecules.

1.3.1 Lipid Metabolism

1.3.1.1 Digestion and Absorption

After oral intake fat is mechanically emulsified by chewing and by gastric and intestinal contractions. An enzymatic hydrolysis is initiated in the stomach by means of lingual lipase. In the duodenum and jejunum, hydrolysis continues due to the combined actions of pancreatic lipase, trypsin-activated colipase, phospholipase, cholesterolase, and other esterases. After this initial hydrolysis, smaller particles (micelles) are formed via the detergent properties of bile (biliary acids). The triglycerides in these micelles are finally hydrolyzed to fatty acids and β-monoacylglycerol, which together with cholesterol, lysophospholipids, and fat-soluble vitamins form another type of particle—mixed micelles. They represent an aqueous suspension within the intestinal lumen [12]. Mixed micelles release lipid molecules (fatty acids, monoacylglycerol), fat-soluble vitamins, and cholesterol, which are then transported to mucosal cells; the residual bile acids are again reabsorbed in the terminal ileum.

Inside the enterocyte, glycerol and mono-acyl-glycerides are again re-esterified with free fatty acids (FFAs) to triglycerides. These triglycerides form particles together with absorbed cholesterol, cholesterol esters, phospholipids, and fat-soluble vitamins and acquire apoproteins (apo-B-48 and apo-A-1). Final particles, so-called chylomicrons, are released into lymphatic vessels and reach the systemic venous circulation via the thoracic duct. On the other hand, medium-chain fatty acids (six to ten carbons) are water soluble and are therefore not esterified in intestinal epithelial cells, but transported directly to the liver via the portal blood.

1.3.1.2 Metabolism of Plasma Lipoproteins

In circulation chylomicrons acquire further apoproteins (C-I, C-II, C-III, E, A-IV); then about 80% of core triglycerides are hydrolyzed by endothelial lipoprotein lipase, and fatty acids are stored in peripheral organs—mainly in adipose tissue. The reduced particles (remnants) transport residual triglycerides, cholesterol, and fat-soluble vitamins to the liver.

Endothelial lipoprotein lipase in adipose tissue is activated by insulin. That is why after consumption of a mixed meal, CHOs (which stimulate insulin secretion) are preferably utilized and lipase releases fatty acids from chylomicrons; the released fatty acids are again re-esterified and stored in adipose cells as triglycerides [13].

In the liver the remnant particles are either metabolized (mainly oxidized and metabolized to ketone bodies) or repackaged into very low-density lipoproteins (VLDLs) and low-density lipoproteins (LDLs). VLDLs transport triglycerides and lipid-soluble vitamins, while LDL particles transport mainly cholesterol, phospholipids, and lipid-soluble vitamins to peripheral tissues. In peripheral tissues VLDL is hydrolyzed by lipoprotein lipase, and the resulting LDL particles are bound to specific LDL receptors and subjected to endocytosis. High-density lipoproteins (HDLs), which are also formed in the liver, are important for the reverse transport of cholesterol from the periphery back to the liver.

1.3.2 Lipid Metabolism in Fasting Conditions

In the fasting period, triglycerides in adipose tissue are hydrolyzed into glycerol and FFAs, which are then released into the circulation. Circulating FFAs bind to albumin and can serve as energy substrates for many tissues including skeletal and cardiac muscles.

FFAs are also metabolized in the liver in different ways. They can be oxidized as a source of energy, re-esterified to triglycerides and phospholipids, or used for cholesterol synthesis; the resulting metabolites are then secreted to the bloodstream in VLDL or LDL particles. During prolonged fasting, FFAs are metabolized to ketone bodies in the liver. Ketone bodies are good energy substrates for many tissues, including the brain.

The lipolysis in adipose tissue that is responsible for FFA release is regulated by the balance between hormones that stimulate (adrenalin, noradrenalin, and corticoids) and inhibit (insulin) hormone-sensitive lipase—HSL. The turnover of FFA in blood is rapid; the half-life is only a few minutes. The rate of fatty acid turnover exceeds that of fat oxidation; non-oxidized FFAs are re-esterified back into triglycerides in the liver and then secreted in the form of VLDL into the bloodstream [14]. This turnover of FFA and lipoprotein is called fatty acid cycle. During stress or physical activity, lipid mobilization may increase several times, but only part of them is oxidized [15]. Food intake or nutritional support partially reduces this cycle, but does not completely suppress it. Therefore, even after a mixed meal, a substantial proportion of VLDL triglycerides are derived from recycling fatty acids from adipose tissue in the fatty acid cycle [16].

1.3.3 Influence of Trauma, Sepsis, and Organ Failure

During stress or in critical illness, HSL is activated by catecholamines, corticoids, and pro-inflammatory cytokines (e.g., TNFα and interleukin-1). This increases the rate of FFA mobilization from adipose tissues; nonetheless the resulting release of FFA into the plasma is consistently higher than that of fat oxidation. The released fatty acids are cleared by peripheral tissues, where they are utilized as sources of energy. Substantial part of FFA is cleared by the liver and other tissues and re-esterified again into triglycerides; often the subsequent rise in triglyceride production is not matched by an equivalent escalation of VLDL secretion, which in turn results in steatosis of the liver, muscle, and some other tissues [17].

There is a significant difference in lipid metabolism during uncomplicated surgery and severe sepsis [18]. Triglyceride clearance is usually increased and plasma triglyceride levels are usually normal after uncomplicated surgery. In contrast, triglyceride clearance and fat oxidation may be decreased during severe sepsis and critical illness; this results in higher plasma triglyceride levels and accumulation of triglyceride in the liver and peripheral tissues including the heart, pancreas, and muscle. In contrast to triglycerides, cholesterol concentration is low both in trauma and sepsis, with a strong inverse connection to the extent of tissue damage and inflammatory response.

1.3.4 Lipids in Nutrition

Lipids in the diet include a combination of triglycerides, phospholipids, or sterols. The main component (90%) is triglycerides, while the remaining 10% is made up of phospholipids and sterols (mainly cholesterol). Dietary lipids are important sources of essential fatty acids (linoleic and α-linolenic acids), which cannot be synthesized by the human body. Moreover, fat in diet is also an important transporter for fat-soluble vitamins (vitamins A, D, E, and K) [19].

It is supposed that the minimal amount of fat that is necessary for adequate absorption of fat-soluble vitamins (especially vitamins A and E) and contains adequate amount of essential fatty acids should constitute 10–15% of basic energy intake (approximately 20–30 g). However, fat consumption higher than 35–40% of total energy intake is associated with an increased risk of obesity and related diseases like type 2 diabetes, atherosclerosis, and coronary heart disease or cancer (breast, ovary, prostate gland, and colon) [20].

Triglycerides are composed of glycerol and fatty acids. Dietary fatty acids can be subdivided into saturated, monounsaturated, and polyunsaturated, as listed below:

– *Saturated fatty acids* are mainly found in animal mammalian products. The chronic and high intake of saturated fatty acids can increase plasma levels of LDL cholesterol and has been associated with an increased risk of type 2 diabetes and atherosclerosis. Current recommendations suggest keeping the intake of saturated fats <10% of total energy intake.

– *Monounsaturated fatty acids* such as oleic acid have beneficial health effects. They are the main component of the "Mediterranean diet," which appears to decrease the level of LDL cholesterol and incidence of cardiovascular disease. They also prevent several digestive diseases by stimulating hepatic bile secretion and gallbladder contraction and improve glycemic control in patients with diabetes mellitus.
– *Polyunsaturated fatty acids* (*PUFAs*), found particularly in safflower, sunflower, soybean, and corn oil, are subdivided into ω-3 (n-3) and ω-6 (n-6) fatty acids. They include linoleic (ω-6) acid and linolenic (ω-3) acid. PUFAs are also termed "essential fatty acids" because they cannot be synthesized in the human body and therefore must be obtained from the diet. It is recommended to supplement 2% of the total daily energy intake as ω-6 PUFA and 0.5% as ω-3 PUFA. Attention has also been focused on oil of fatty fishes, which is rich in ω-3 fatty acids and has been shown to decrease plasma triglyceride levels, blood pressure, clotting time, as well as the overall risk of heart disease. Interestingly, if the intake of PUFAs falls below a threshold of ~5% of the total energy intake, cholesterol-raising properties of certain saturated fatty acids are greatly increased.

The intake of lipids during enteral or parenteral nutrition may account for 20–40% of nonprotein calories, depending on the individual patient's tolerance to both CHO and lipids. Lipids are not only very important energy substrates, but some fatty acids and lipid-soluble vitamins also act as metabolic regulators [21].

After ingestion of a mixed meal, fat is preferentially stored in adipose tissue, whereas CHOs are oxidized. During fasting, fatty acids are released from adipose tissue and utilized as energy substrates in the liver and extrahepatic tissue. This process is effectively controlled by hormones, which regulate hormone-sensitive lipase and lipoprotein lipase.

1.3.4.1 Parenteral Nutrition

Intravenous lipid emulsions are analogous to chylomicrons; their core is made of triglycerides and some lipid-soluble vitamins, and the surface is made of phospholipids, free cholesterol, and remaining lipid-soluble vitamins. However, lipid emulsions do contain neither apoproteins nor esterified cholesterol. These particles rapidly acquire exchangeable apoproteins (C-I, C-II, C-III) upon their delivery to the bloodstream, and their metabolism is similar to those of chylomicrons.

It is not recommended to provide intravenous lipid infusions to patients with marked hypertriglyceridemia (more than 4–5 mmol/L or 350–450 mg/dL) or to provide only small amounts (using a low infusion rate) to patients with moderately elevated (2.0–3.5 mmol/L or 190–260 mg/dL) plasma triglycerides.

1.4 Proteins

Proteins or peptides are the essential components of body cell mass. They have also many functions for the organism because they are:

– Principal structural components of all cells and tissues (e.g., collagen, actin, myosin)
– Enzymes in almost all biochemical reactions
– Components important for transport functions (e.g., hemoglobin, transferrin, albumin)
– Essential for immune responses (immunoglobulins, C-reactive protein, opsonins)
– Gene transcription and translation regulators (e.g., histones)
– Membrane transporters (transport proteins)

The basic structure of protein is a chain composed of amino acids, which are mutually connected by peptide bonds. This chain is not linear, but is folded into a three-dimensional structure; this structure is usually maintained by disulfide bridges and is crucial for protein function. Usually these three-dimensional proteins are combined into larger complexes composed of several protein units. The proteins are constantly synthesized and broken down, at specific rates which are dependent on conditions such as starvation, stress, and undernutrition.

The amino acids are not only building blocks of proteins, but have other important functions in the organism. They are precursors of neurotransmitters (e.g., catecholamines) and hormones (e.g., serotonin) or themselves metabolic regulators (e.g., arginine, glutamine, etc.). Amino acids can be divided into essential (cannot be synthesized in the body), conditionally essential (are essential under specific conditions), and nonessential (can always be synthesized in the human body irrespective of specific conditions) (Tables 1.2 and 1.3).

Table 1.2 Essential and conditionally essential and nonessential amino acids

Essential	Conditionally essential	Nonessential
Histidine Isoleucine Leucine Lysine Methionine Phenylalanine Threonine Tryptophan Valine	Tyrosine Cystine Glutamine Arginine	Alanine Asparagine Aspartic acid Glutamic acid Serine

Table 1.3 Effect of some conditionally essential amino acids

Cysteine	Premature infants and term infants, subjects with liver disease (diminished capacity for trans-sulfuration)
Tyrosine	Premature infants and term infants, chronic renal failure (partial inhibition of phenylalanine hydroxylation in the kidney)
Glutamine	Episodes of infection, inflammation, other types of catabolic stress, and malnutrition (glutamine-supplemented nutrition is associated with reduced morbidity and mortality)
Arginine	Synthesis of mediators (NO, agmatine, polyamines), important for wound healing

It should be stressed that all proteins in the body have specific functions; therefore, the loss of body protein is always connected with loss of function. A good example is the skeletal muscle, which is the biggest "store of protein"; the loss of muscle protein always leads to muscle weakness. On the other hand, excessive intake of protein without any need for protein synthesis (e.g., muscle gain during rehabilitation) is connected with increased protein oxidation and subsequent production of urea and other compounds of protein catabolism. In a similar fashion, excessive intake of protein without exercise will not increase muscle mass, but, contrarily, may result in exceeding the metabolic capacity of the liver and kidney with subsequent rise in plasma urea level. However, if higher protein intake is required (exercise and planned muscle gain), it is not advised to diminish protein intake even in patients with renal insufficiency or hepatic insufficiency. The minimum daily intake of protein is 0.8 g/kg body weight for healthy adults, irrespective of sex or body mass index [22].

1.4.1 Synthesis of Proteins

After unraveling a section of DNA, a complementary messenger RNA (mRNA) is synthesized by a process called transcription. The sequence of the nucleotides in mRNA is translated into a sequence of amino acids (translation) using transfer RNA (tRNA). After synthesis, proteins are modified (posttranslational modification—PTM), which induces, modifies, or inhibits their function [23].

Examples of PTM:

- *Cleavage of proteins* to produce an active protein (e.g., cleaving C peptide from proinsulin molecule to produce insulin)
- *Modifications of amino acids* in the protein (e.g., proline to hydroxyproline, histidine to 3-methylhistidine, arginine to citrulline or asymmetric dimethylarginine)
- *Glycosylation* (CHOs are attached to amino acids), phosphorylation (e.g., serine), or acetylation of newly synthesized proteins

Moreover, final proteins are modified in different way, and this modification influences their function. The most frequent modifications are:

- *Oxidation of the protein*: for example, formation of disulfide bridges between free cysteine molecules in the protein chain and free cysteine, glutathione, or peroxided fatty acids.
- *Non-covalent binding*: binding of glucose (glycation), tyrosine, and other substances to the protein.
- *Oxidative stress*: may also lead to the formation of tyrosyl radicals and other radicals inside the protein; two tyrosyl radicals in proteins may induce cross-links between protein chains and subsequent aging of different proteins [24].

1.4.2 Breakdown of Proteins

The breakdown of proteins in the cell is also tightly controlled. The most important pathways of protein breakdown are:

- *Lysosomal degradation*: Extracellular proteins undergo endocytosis and are completely degraded within lysosomes by specific enzymes called cathepsins.
- *Ubiquitin–proteasome pathway*: In this pathway, proteins are first marked for degradation by linkage to a small protein cofactor: ubiquitin [25]. Subsequently, through a series of reactions, the protein is cleaved into small peptides in the proteolytic complex: the proteasome. Enhanced breakdown of muscle protein through the ubiquitin–proteasome pathway has been observed during fasting, renal failure, septic state, and diabetes.
- *The calpain-dependent pathway*: This involves enzymes within the cytosol that are activated according to the intracellular concentration of calcium [26]. These are dedicated to cytoskeleton remodeling.

1.4.3 Protein Turnover

All proteins are continuously and simultaneously broken down and synthesized. The balance between the two determines if there is net production, *protein gain*, or net protein degradation, *protein loss*. Continuous protein turnover allows:

- Repair of the damage that is caused by several noxious factors such as oxidative stress, which leads to cross-linking and thereby negatively influences functions of structural proteins such as myosin and actin.
- Rapid adaptation to changing situations such as starvation and stress. By slightly modifying synthesis and degradation in opposite directions, the net effect may be gain or loss of protein as required by the specific metabolic situation.

The whole-body synthesis and breakdown rate of proteins in an adult and stable subject is 300 g/day. Protein turnover differs between different types of proteins (e.g., albumin, collagen, structural muscle proteins, sarcoplasmic proteins, immunoglobulins, acute-phase proteins). The protein turnover is also dependent on the clinical state of the subject. In stress situations (especially during inflammation), the newly synthesized proteins are in great part associated with inflammatory response [27]. These proteins have much higher turnover rates than proteins localized in the muscle, skin, or bone.

The extent of net protein gain is dependent on requirement. Net protein gain is important especially:

- In growing children, who need more proteins as they are building new tissues.
- During the process of rehabilitation, when new muscle mass is synthesized. Muscle protein synthesis must be always connected with an equivalent level of physical activity.

– During wound healing, where new tissue is generated.
– For synthesis of missing plasma proteins (including immunoglobulins).

The complex metabolism of amino acids and proteins explains why during the quiescent healthy state, a normal adult consuming well-balanced meals requires 0.8–1.0 g of high-quality protein/kg of body weight per day. If protein intake exceeds requirements, protein may be directly degraded to yield urea and to furnish carbon skeletons for oxidation or incorporation into fat or glycogen depending on the nature of their carbon skeleton (keto- or glucogenic amino acids).

1.4.4 Changes in Protein Turnover

Protein turnover is influenced by physiological and pathological situations, including starvation and food intake:

Feeding
Protein degradation is decreased, while protein synthesis is moderately increased after food intake. This leads to temporal net protein gain; however, during a postabsorptive phase (during the night), protein degradation prevails. Therefore, in a stable subject, the net protein balance is zero.

Starvation
The body mobilizes and utilizes its own energy substrates (CHOs, fat, proteins) during starvation. Glucose necessary for metabolic pathways is exhausted after the first 24 h and then needs to be produced from glycerol and glucogenic amino acids. This leads to increased protein degradation and to negative protein balance. During long-term starvation, fatty acids and ketone bodies are the major energy substrates, and glucose production from amino acids is reduced. Therefore, the daily loss of proteins decreases, and the rate of protein catabolism is 10–40% lower than the rate of protein degradation during the postabsorptive phase.

Stress Situations
During disease, infection, trauma, burns, and other stress situations, protein turnover is increased by 20–40% in comparison to previously healthy subjects. The protein is mobilized predominantly from the muscle and in a lesser extent from the skin and bone. The released amino acids are reutilized in organs, which operate in the defense against the stress imposed. The immune system (including immune cells, liver, and spleen) accumulates protein in the form of cells, but wound proteins and acute-phase proteins (fibrinogen, albumin, immunoglobulin, collagen) are also produced at increased rates. In severely malnourished individuals subjected to stress, protein turnover cannot be upregulated in this manner. This explains a deficient response to stress, flawed inflammatory reaction, and failure to heal.

Growth and Recovery from Disease and Rehabilitation
During growth, almost all proteins accumulate due to higher rates of synthesis than rates of degradation. The same situation is apparent when the convalescence and recovery phase after disease begins. Acute disease is usually accompanied by (semi) starvation and inflammation with consequent protein catabolism. During recovery period the body can gradually switch to net protein anabolism and, in particular, to start rebuilding peripheral protein mass—especially in muscles. Therefore, in this stage sufficient protein and energy intake and ongoing exercise are essential.

Chronic Diseases
Both whole-body synthesis and breakdown of proteins are elevated in chronic diseases (chronic obstructive pulmonary disease, HIV infection, or rheumatoid disease). This increased turnover is due to chronic inflammation and increased production of acute-phase proteins. However, loss of appetite and decreased synthesis of muscle proteins lead to muscle wasting and development of cachexia.

1.4.5 Nonprotein Functions of Amino Acids

The existence of a complex series of pathways clearly demonstrates that amino acids are not only used as the building bricks of protein but also serve as precursors for the biosynthesis of numerous important biological and physiological compounds. An outline of the metabolic products and specific functions of amino acids is given in Table 1.4.

1.4.6 Recommended Protein Intake

- Recommended daily intake of protein for a healthy adult subject should be 0.9–1.0 g/kg of body weight.
- Daily requirements of protein for infants are 2.4 g/kg during the first month of life, declining to 1.85 g/kg within the next 6 months.
- Pregnant women should receive additional 6 g of protein every day.
- Lactating women should receive 17.5 g of protein in addition to daily amount recommended for nonpregnant women.

During illness and convalescence, an intake of 1.5 g/kg is desirable. However, a general recommendation for protein requirements in disease is difficult, because particular diseases affect protein needs differently and each disease process varies in intensity. Body protein is usually lost during states like fever, fracture, burns, and surgical trauma. Therefore, the intake of protein must be increased during convalescence phase.

Table 1.4 Metabolic products and specific functions of amino acids

Amino acid	Product	Physiological function
Glutamic acid	Glutamine	Nitrogen shuttle
		Glutathione precursor
		Metabolic fuel
	γ-Aminobutyric acid (GABA)	Cell constituent (especially in the brain)
		Neurotransmitter
Aspartic acid	Pyrimidine bases	Constituents of nucleic acids and nucleotides
Glycine	Purine bases	Constituents of nucleic acids and nucleotides
	Porphyrin	Constituent of hemoglobin and cytochrome
	Creatine	Creatine phosphate precursor
	Hippuric acid	Detoxification
	Conjugated bile acids	Necessary for fat digestion
Serine	Ethanolamine	Phospholipid constituent
	Choline, acetylcholine	Transmitter
Histidine	Histamine	Hormone, transmitter
Lysine	OH-lysine	Collagen constituent
	Carnitine	Transporter of fatty acids
Cysteine	Taurine	Glutathione precursor
		Constituent of bile acids
		Antioxidant
Tyrosine	Adrenaline	Hormone
	Noradrenaline	Hormone, transmitter
	Thyroid hormone	Hormone
	Melanin	Pigments in the hair and skin
Tryptophan	Serotonin	Transmitter
	Nicotinic acid	Constituent of pyridine nucleotide
Arginine		NO precursor
	Creatine	Creatine phosphate precursor
	Polyamines	Gene expression

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Screening and Assessment of Malnutrition

2

Miguel León-Sanz and Maria Angeles Valero

2.1 Introduction

Forty years ago, there were preliminary reports pointing out that malnutrition is not only seen in persons living in poor socioeconomic conditions, but it can also be observed in patients admitted to hospitals or living in the community associated to an underlying disease [1]. Many disorders can cause a deterioration of nutritional status. Neurological diseases can be associated with malnutrition due to decreased appetite and intake, frequent occurrence of dysphagia, and varying degree of hypermetabolism [2].

Although common sense would predict that it is not difficult to characterize malnutrition, it is well known that it is not easy to define it [3]. There is a need of a gold standard that allows clinicians and scientists to achieve a consensus definition of malnutrition. A few years ago, a group of experts in clinical nutrition were invited to answer a questionnaire aimed at identifying the main features of malnutrition. The deficiencies of energy or protein and the decrease in fat-free mass were most often cited to be particularly important in defining malnutrition. From the perspective of elements important in delineating malnutrition, involuntary weight loss, body mass index (BMI), and no nutritional intake were also mentioned. However, opinions on cutoff points regarding these elements differed strongly among experts [4].

A few years later, an international consensus committee established a classification of malnutrition syndromes [5]:

– Chronic starvation without inflammation (e.g., anorexia nervosa or major depression with lack of interest in eating)

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– Chronic disease-associated malnutrition, when inflammation is chronic and of mild to moderate degree (e.g., organ failure, pancreatic cancer, rheumatoid arthritis, or sarcopenic obesity)
– Acute disease or injury-associated malnutrition, when inflammation is acute and of severe degree (e.g., major infection, burns, trauma, or closed head injury)

These syndromes are dynamic, in the sense that a patient may change among them and starvation may overlap with acute to chronic inflammatory conditions. Acute conditions may also develop in patients with starvation or chronic disease-related malnutrition. These patients with mixed syndromes have even more reason to need close nutritional attention.

Clinical outcomes such as infectious complications, survival, and rate of recovery from illness are influenced by nutritional status. They can be used as hard measures of nutritional interventions. However, they depend on many physiologic mechanisms and treatments of the underlying disease. Despite its importance from different perspectives, in many diseases, it is difficult to show an improvement in these clinical outcomes with nutritional therapy because its effect is diluted by many other factors. On the other hand, an optimal nutritional status has been related to the ability of maintaining or attaining a body composition and physiologic function that are optimal for the health and long-term survival of the individual. Nutritional intake is one of the factors necessary to accomplish these goals, and, therefore, nutritional assessment will evaluate if any given nutritional intake will fulfill these objectives in a particular individual. However, nutritional status and nutrient intake also depend on other factors such as the presence or absence of disease, physical activity, environment, drug therapy, hormone regulation, central and peripheral nervous system influence, and, especially in disease-related malnutrition, the degree of inflammation [6].

The changes and influences of these factors on nutritional status may be difficult to measure in an objective way. To facilitate the assessment of nutrition, surrogate markers are used. However, it is not possible to establish a perfect direct relationship between a determined marker and nutritional status. The sensitivity, specificity, and validity of each surrogate marker are quite variable per se and in each individual. The underlying disease can influence many surrogate markers. Weight is a useful marker of nutritional status, but edema secondary to heart or renal failure can modify it. In consequence, we cannot be naive and identify an alteration, high or low, of a proposed marker with malnutrition of different degree. In general, the validity of a particular variable as a nutritional marker may vary intensely depending on the clinical situation. The lack of specificity forces the clinician to consider this alteration in the context of the clinical status of the patient [7]. For example, a low albumin concentration does not automatically mean malnutrition or insufficient nutrition intake. It may be due to decrease in hepatic synthesis or catabolism, body losses through diarrhea or urine, and, very significantly, extracellular volume expansion secondary to systemic inflammatory response.

After stressing the difficulties and limitations of nutritional evaluation, we will move forward to analyze the process by which we can estimate the nutritional status of patients. This process has different steps: screening, assessment, nutritional planning, monitoring, registration along with diagnostic coding, and, finally, audit of the whole process [8].

2.2 Nutritional Screening

Nutritional screening identifies patients who are at nutritional risk and will benefit from further nutritional assessment and intervention. Severe malnutrition is clinically obvious, but there is more uncertainty about recognizing lesser degrees of malnutrition. Therefore, in the absence of universally accepted criteria for identifying malnutrition with high sensitivity and specificity, the concept of risk was introduced. Risk is a measure of likelihood that malnutrition is present or likely to develop. In many texts and in usual clinical practice, the terms malnutrition and nutritional risk are often used interchangeably. This may add some confusion in the field of nutritional evaluation.

Numerous screening tools have been developed to identify patients at risk of malnutrition [9]. Any particular tool has to be simple to administer, asking easily answered questions, useful in a particular clinical setting or appropriate across a broad range of conditions and with an acceptable validity. Experts of the European Society for Clinical Nutrition and Metabolism (ESPEN) stated that any nutritional screening tool has to be evidence based and validated. It should include at least three elements:

- Current BMI
- Involuntary recent weight loss
- Information of recent food intake

Figure 2.1 shows the historical development of the most important screening tools that we now will briefly describe.

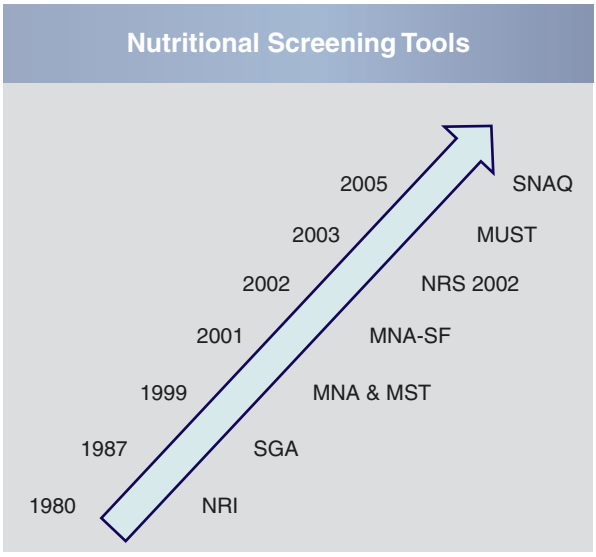

Fig. 2.1 Historical development of nutritional screening tools. Acronyms are described within the text

1. *Nutritional risk index* (*NRI*) is a combination of weight loss percentage and serum albumin concentration [10]. It was used as an inclusion criterion in the Veteran Administration Total Parenteral Nutrition clinical trial to identify patients who were malnourished.

   NRI is calculated according to the formula:

$$\left[1.519 \times \text{serum albumin}\left(\text{g} / \text{L}\right)\right] + \left[0.417 \times \left(\text{present weight} / \text{usual weight} \times 100\right)\right].$$

   NRI > 100 indicates no., 97.5–100 indicates mild, 83.5 ≤ 97.5 indicates moderate, and <83.5 indicates severe malnourishment.

2. *Subjective global assessment* (*SGA*) (Table 2.1) [11], described in 1982, aimed particularly for patients with medical or surgical gastrointestinal diseases. There are five questions focusing on history of unintentional weight loss over the past 6 months (pattern and amount of it), dietary intake change (relative to normal), gastrointestinal symptoms >2 weeks (nausea, vomiting, diarrhea, anorexia, etc.), functional capacity (energy level: daily activities, bedridden), and metabolic demands of underlying condition. Physical examination explores muscle, fat mass, and the existence of edema. Each feature is noted as normal, mild, moderate, or severe according to clinician's subjective impression. Finally, the clinician awards a subjective grade: A, well nourished; B, moderately malnourished; and C, severely malnourished. Scoring may predict development of infection and post operatory complications. It has been validated in different conditions and it does not require laboratory testing. It has been considered a gold standard to which new screening tools have been compared. However, health-care providers need a short training to use it so that the results coincide among different observers. Its administration takes some time, and it is not sensitive enough to use in following nutritional status changes.
3. *Mini nutritional assessment* (*MNA*), described in 1987, aimed for individuals over 65 to assess nutritional status as a part of the standard geriatric evaluation in outpatient settings, nursing homes, and hospitals [12]. It contains six initial questions that work as a screening tool [13]. If the individual is at risk of malnutrition, 12 further questions actually perform a nutritional assessment, divided into anthropometrics, general, dietary, and subjective assessment (Fig. 2.2). Therefore, this tool carries out both a screening and an assessment of the individual. The price to pay is that it takes longer to administer than many other screening tools. This tool has been used in many papers dealing with geriatric patients in multiple care settings. It is difficult to administer in patients on enteral or parenteral nutrition and in those unable of communicating a subjective assessment. On the other hand, it could be used for following up nutritional interventions in the elderly.
4. *Malnutrition screening tool* (*MST*) is a simple tool with three questions related to unintentional weight loss and reduced appetite [14]. It was developed and validated in medical/surgical adult hospital patients in Australia (Table 2.2). The authors started to work with 21 nutritional screening questions and chose SGA as the reference method for defining malnutrition. In this way, they selected three questions that had the best sensitivity and specificity at predicting nutritional

Table 2.1 Subjective global assessment (Adapted from Detsky et al. [11], Reprinted with permission from J Parenter Enter Nutr, 11, AS Detsky et al., What is subjective global assessment of nutritional status? 8–13, 1987. SAGE Publications)

A. History
1. Weight change
Overall loss in past 6 months: amount: …… kg; % loss: ……
Change in past 2 weeks: ☐ Increase
☐ No change
☐ Decrease
2. Dietary intake change (relative to normal)
☐ No change
☐ Change
duration: …… weeks
type:
☐ Suboptimal solid diet
☐ Full liquid diet
☐ Hypocaloric liquids
☐ Starvation
3. Gastrointestinal symptoms (that persisted for >2 weeks)
☐ None
☐ Nausea
☐ Vomiting
☐ Diarrhea
☐ Anorexia
4. Functional capacity
☐ No dysfunction (e.g., full capacity)
☐ Dysfunction
duration: …… weeks
type:
☐ Working suboptimally
☐ Ambulatory
☐ Bedridden
5. Disease and its relation to nutritional requirements
Primary diagnosis (specify): ……
Metabolic demand (stress): ☐ No stress
☐ Low stress
☐ Moderate stress
☐ High stress
B. Physical (for each trait specify: 0 = normal, 1+ = mild, 2+ = moderate, 3+ = severe)
…… Loss of subcutaneous fat (triceps, chest)
…… Muscle wasting (quadriceps, deltoids)
…… Ankle edema
…… Sacral edema
…… Ascites
SGA rating (select one)
☐ A. Well nourished
☐ B. Moderately (or suspected of being) malnourished
☐ C. Severely malnourished

status according to the SGA. A cutoff score of 2 was established to indicate malnutrition out of a possible higher score of 7. A weekly reassessment was recommended for patients not at risk of malnutrition, and those identified as "at risk"

Mini Nutritional Assessment MNA®

Nestlé Nutrition Institute

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers.
Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake ☐

B Weight loss during the last 3 months
0 = weight loss greater than 3kg (6.6lbs)
1 = does not know
2 = weight loss between 1 and 3kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F Body Mass Index (BMI) = weight in kg / (height in m)^2
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

Screening score (subtotal max. 14 points) ☐☐
12-14 points: Normal nutritional status
8-11 points: At risk of malnutrition
0-7 points: Malnourished
For a more in-depth assessment, continue with questions G-R

Assessment

G Lives independently (not in nursing home or hospital)
1 = yes 0 = no ☐

H Takes more than 3 prescription drugs per day
0 = yes 1 = no ☐

I Pressure sores or skin ulcers
0 = yes 1 = no ☐

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals ☐

K Selected consumption markers for protein intake
- At least one serving of dairy products (milk, cheese, yoghurt) per day yes ☐ no ☐
- Two or more servings of legumes or eggs per week yes ☐ no ☐
- Meat, fish or poultry every day yes ☐ no ☐

0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes ☐.☐

L Consumes two or more servings of fruit or vegetables per day?
0 = no 1 = yes ☐

M How much fluid (water, juice, coffee, tea, milk...) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups ☐.☐

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem ☐

O Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem ☐

P In comparison with other people of the same age, how does the patient consider his / her health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better ☐.☐

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC greater than 22 ☐.☐

R Calf circumference (CC) in cm
0 = CC less than 31
1 = CC 31 or greater ☐

Assessment (max. 16 points) ☐☐.☐
Screening score ☐☐.☐
Total Assessment (max. 30 points) ☐☐.☐

Malnutrition Indicator Score
24 to 30 points ☐ Normal nutritional status
17 to 23.5 points ☐ At risk of malnutrition
Less than 17 points ☐ Malnourished

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For more information: www.mna-elderly.com

Fig. 2.2 Mini nutritional assessment (MNA) (Reprinted with permission from Nestlé. Further information for MNA can be obtained from www.mna-elderly.com)

Table 2.2 Malnutrition screening tool (MST); a total score of ≥2 signifies patient at risk of malnutrition (Adapted from Ferguson et al. [14], Reprinted with permission from Nutrition 15, Ferguson M et al. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients, 458–64, 1999. Elsevier)

Question	Score
1: Have you lost weight recently without trying?	
No	0
Unsure	2
If yes, how much weight (kg) have you lost?	
1–5	1
6–10	2
11–15	3
>15	4
Unsure	2
2. Have you been eating poorly because of a decreased appetite?	
No	0
Yes	1

of malnutrition should receive a more detailed nutritional assessment, to decide the most appropriate nutritional intervention.

5. *Nutritional risk screening* (*NRS 2002*) uses unintentional weight loss, low BMI, disease severity, age >70 years, and impaired condition [15]. As seen in Table 2.3, two scores are calculated: one for impaired nutritional status and one for severity of disease. These scores are then added up and a final score is obtained. If the patient is over 70 years of age, 1 point is added to the final score. A score of ≥3 indicates the need to start nutritional support. This tool anticipates several scenarios, patients who are either severely malnourished (score of 3 for impaired nutritional status) and/or severely ill (score of 3 for severity of disease) or moderately undernourished and mildly ill (2 + 1, total score of 3) or mildly undernourished and moderately ill (1 + 2, total score of 3). In any case, the tool makes recommendations about a nutritional care plan for those patients with a score ≥3, from administration of extra food, oral supplements, tube feeding, to parenteral nutrition. One weakness of this tool is the subjective assessment of severity of illness, which can cause some confusion among clinicians. The tool was validated retrospectively, showing that it was capable of distinguishing those patients with a positive clinical outcome due to nutritional intervention from those that showed no benefit of nutritional support. Prospectively, patients with complications who received intervention according to NRS 2002 results had significant shorter length of stay, compared to those who received no nutritional intervention [16]. It is interesting to point out that the main goal of the developers of this screening tool was to identify those patients who will benefit from nutritional intervention rather than classifying them according to the risk of malnutrition.
6. *Malnutrition universal screening tool* (*MUST*) was developed in 2003 by the Malnutrition Advisory Group of the British Association for Parenteral and Enteral Nutrition (BAPEN) [17]. According to the intention of its developers, it eases the communication of nutritional status across different care settings, since it has been validated in primary care, home care, acute care, and long-term care, which has the benefit of allowing comparable nutritional screening data across care settings. In hospitals, MUST predicts length of hospital stay, type of

Table 2.3 Nutritional risk screening (NRS 2002) (Adapted from Kondrup et al. [15], Reprinted with permission from Clinical Nutrition, 22, Kondrup J, et al., ESPEN Working Group, Nutritional Risk screening (NRS 2002): a new method based on analysis of controlled clinical trials, 321–36, 2003. Elsevier)

Initial screening			
Is BMI <20.5?		Yes	No
Has the patient lost weight within the last 3 months?		Yes	No
Has the patient had a reduced dietary intake in the last week?		Yes	No
Is the patient severely ill? (e.g. in intensive therapy)		Yes	No
If the answer is Yes to any question, proceed to Formal Screening section below *If the answer is No to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status*			
Formal screening			
Impaired nutritional status		*Severity of disease* (*~ stress metabolism*)	
Absent Score 0	Normal nutritional status	*Absent* Score 0	Normal nutritional requirements
Mild Score 1	Weight loss >5% in 3 months *or* Food intake below 50–75% of normal requirement in preceding week	*Mild* Score 1	Hip fracture, patients admitted to hospital due to complications associated with a chronic disease such as cirrhosis, COPD, chronic hemodialysis, diabetes, oncology
Moderate Score 2	Weight loss >5% in 2 months *or* BMI 18.5-20.5 with impaired general condition *or* Food intake 25-50% of normal requirement in preceding week	*Moderate* Score 2	Patient confined to bed due to illness, such as major abdominal surgery, stroke, severe pneumonia, hematologic malignancy
Severe Score 3	Weight loss >5% in 1 month (~>15% in 3 months) *or* BMI <18.5 with impaired general condition *or* Food intake 0–25% of normal requirement in preceding week	*Severe* Score 3	Head injury, bone marrow transplantation, intensive care patients (APACHE >10)
An additional score of 1 is added to patients ≥70 years of age; a composite score of ≥3 is suggestive of a patient nutritionally at risk and necessitating nutritional support			

discharge destination, and mortality. In community care, malnutrition scores predict rate of hospital admissions and general practitioner visits. It also shows that appropriate nutritional intervention improves outcome. MUST uses unintentional weight loss, BMI, disease severity, and problems with food intake to classify malnutrition risk (Fig. 2.3). A score ≥2 indicates malnutrition risk. This tool recommends an action plan for the treatment of patients at risk of malnutrition, either with local management protocols or with some general pieces of advice.

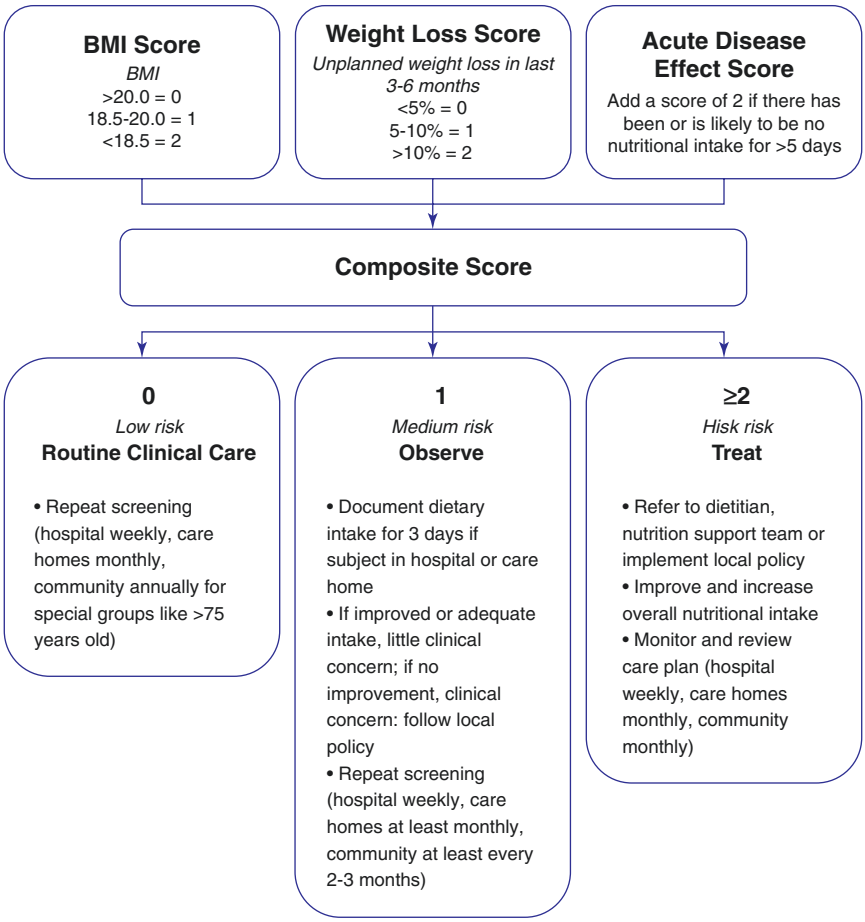

Fig. 2.3 Malnutrition universal screening tool (MUST) algorithm for adults (Adapted from Stratton et al. [17], Reprinted with permission from Br J Nutr, 92, RJ Stratton et al., Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the "malnutrition universal screening tool" ('MUST') for adults. 799–808, 2004. Cambridge University Press). Further information can be obtained from www.bapen.org.uk

7. *Short nutritional assessment questionnaire* (*SNAQ*) consists of three questions, unintentional weight loss, appetite loss, and use of nutritional supplements or tube feeding [18] (Fig. 2.4). It was developed in the Netherlands and published in 2005. In this country universal nutritional screening is now mandatory in hospitals. The SNAQ is administered by nurses after patient admission to the hospital. Patients are classified as well nourished, moderately malnourished, and severely malnourished. For those with malnutrition, there is a treatment plan ranging from enrichment of meals to parenteral nutrition, guided by the evaluation of a dietitian. With the SNAQ, patients identified as malnourished had a significantly higher care complexity and reduced quality of life, physical

Fig. 2.4 Short nutritional assessment questionnaire (SNAQ) (Reprinted with permission from Dutch Malnutrition Steering Group. Further information can be obtained from http://www.fightmalnutrition.eu)

functioning, and fat-free mass index [19]. In a further expansion of their initiative, the Dutch authors have developed specific nutritional screening tools for people over 65 years old and for people living in residential care (Figs. 2.5 and 2.6) [20].

The description and explanation of these tools have had an academic purpose. There is not a perfect nutritional screening tool. It is conceivable that the different tools may detect different rates of malnutrition, since their basic assumptions, target population, and normal range values were different.

A systematic review of screening tools for the hospital setting concluded that currently we do not have one single screening or assessment tool that is capable of adequate nutritional screening as well as predicting poor nutrition-related outcome. Further studies comparing different tools within one patient population were recommended, and development of new tools was discouraged [21].

However, readers are encouraged to choose the tool that best adapts to their clinical practice. It is worth remembering that ESPEN proposes screening methods NRS 2002, MUST, and MNA, while the American Society for Parenteral and Enteral Nutrition (ASPEN) adds to these methods MST and SNAQ6 [22]. Some methods are preferred in the countries where they have been developed, like MUST in United Kingdom, MST in Australia, or SNAQ in the Netherlands. Important criteria to be taken into consideration in this election are what population will be evaluated by a particular tool and the relation with prognosis or with therapeutic response to

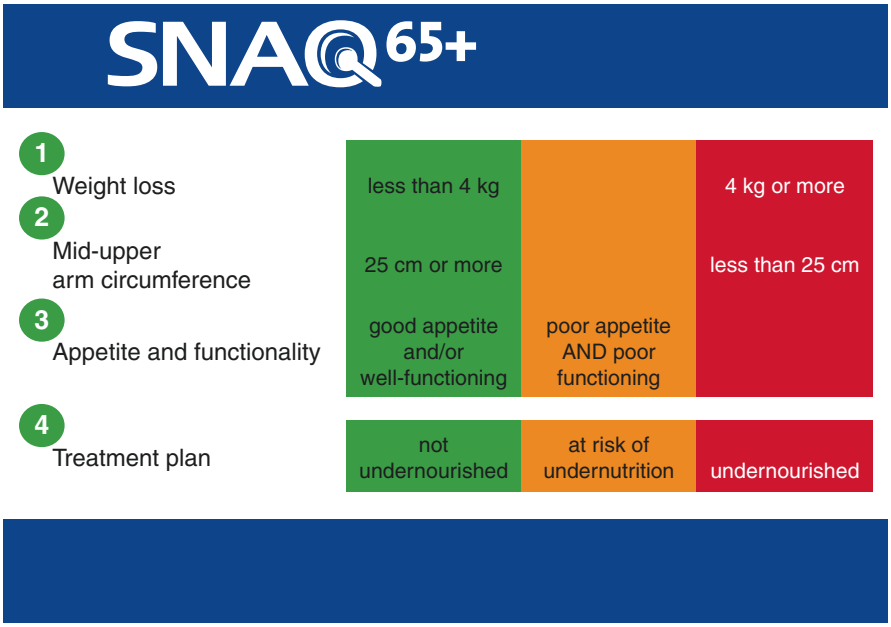

Fig. 2.5 Short nutritional assessment questionnaire for people over 65 years old (SNAQ 65+) (Reprinted with permission from Dutch Malnutrition Steering Group. Further information can be obtained from http://www.fightmalnutrition.eu)

nutritional intervention. These tools have been divided into comprehensive or quick and easy tools. Comprehensive screening tools, like MUST and NRS 2002, are more time demanding and need a better training of nurses. With the incorporation of electronic medical records to clinical practice, it is easier to calculate BMI and percentage of unintentional weight loss. On the other hand, quick and easy screening tools, like MST and SNAQ, were not developed for diagnostic purposes and do not allow following patients in time. However, for the objective of identifying patients at risk of malnutrition, they could be as useful as the comprehensive tools [23].

It is essential that the screening tool chosen in a particular clinical setting be linked to an algorithm that indicates what will be the next steps and the protocol of periodic reassessment of patients. The result of the screening and assessment has to be incorporated to the medical record, making it easier that the diagnosis of malnutrition, if exists, appears in the discharge report and in the diagnostic codes. The reimbursement obtained by the health-care organization, either hospital or outpatient clinic, will be increased if the nutritional component of the clinical care is registered.

Nutritional screening should be universal and mandatory for patients admitted to the hospital, but it should also be performed in the ambulatory setting and repeated according to the nature of the underlying process. Some authors have stated that it should be part of routine care, in the same way as assessing physiologic measures,

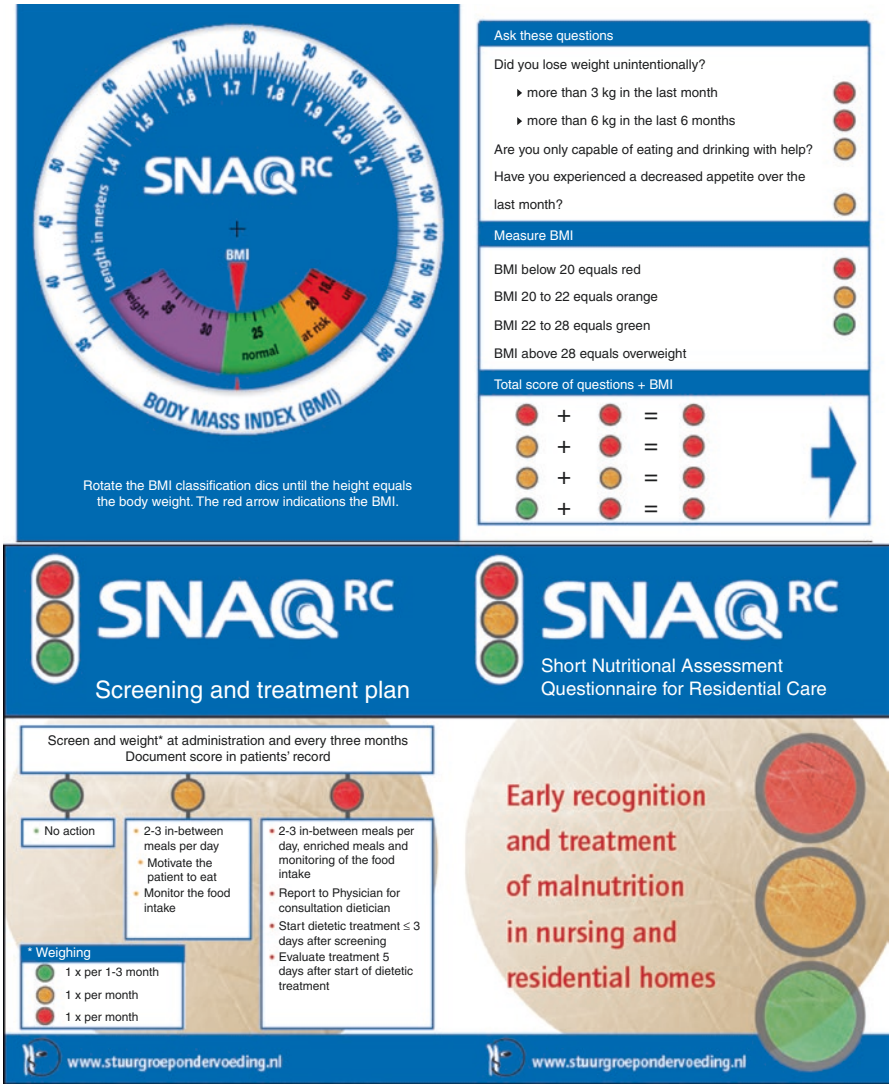

Fig. 2.6 Short nutritional assessment questionnaire for residential care (SNAQ^{RC}) (Reprinted with permission from Dutch Malnutrition Steering Group. Further information can be obtained from http://www.fightmalnutrition.eu)

such as body temperature or blood pressure, starting from the time of patient's admission to the hospital or when the patient is seen in the outpatient clinic [23]. A good initiative is to include nutritional screening among the quality indicators of the medical center. Its different health-care providers will be trained in the correct administration of the screening tool approved for use in the center, although the professionals in charge of carrying out the nutritional screening have to be clearly identified.

Neurological disorders may have specific elements that have an influence on nutritional screening and assessment. They will be extensively discussed in the next chapters. Here we can just mention some factors. Malnutrition per se may cause muscular atrophy, especially of muscular fiber type II. It may cause dysfunction of muscles participating in swallowing, breathing, or standing and walking. These alterations are added to those developed in the course of the underlying neurological disease.

Patients with neurological diseases may have difficulties for standing, making it difficult in obtaining a reliable height and weight measurement. Equations used to estimate energy expenditure include height and weight as variables. If the validity of these equations in neurological diseases may be problematic [24], the inability of getting correct data of height and weight augments the difficulty of the task of estimating energy and protein requirements in these patients. The height may be estimated based on arm span, knee height, or length of the forearm (ulna). Several knee height equations have been developed with data coming from different communities, with different race mixtures [25]. Clinicians should determine if it is acceptable to use them in their clinical setting. Similarly, the tables that allow estimating the height based on the length between the point of the elbow (olecranon process) and the midpoint of the prominent bone of the wrist (styloid process) (left side if possible) have to be valid in the community from where the patients come. One example of these tables comes in the MUST booklet, freely available on BAPEN website.

When it is not possible to determine BMI by lack of data of height or weight, it can be estimated from mid-upper arm circumference (MUAC), which is quite easy to measure. The subject's left arm should be bent at the elbow at a 90° angle, with the upper arm held parallel to the side of the body. In practical terms, the explorer should measure the distance between the bony protrusion on the shoulder (acromion) and the point of the elbow (olecranon process). The midpoint should then be marked, and the measurement be performed around the upper arm at this point. There are different equivalents in MUST and in SNAQ 65:

In MUST:

- If MUAC is <23.5 cm, BMI is likely to be <20 kg/m^2.
- If MUAC is >32.0 cm, BMI is likely to be >30 kg/m^2.

In SNAQ 65:

- If MUAC is <23.5 cm, BMI is likely to be <18.5 kg/m^2.
- If MUAC is 23.5–25.0 cm, BMI is likely to be 18.5–20 kg/m^2.
- If MUAC is >25.0 cm, BMI is likely to be >20 kg/m^2.

Again, it is necessary to be certain that these cutoff limits are valid in the population we work with. As we will discuss below, muscular measurements may be altered not only by malnutrition but also by the underlying neurological disorder.

Even when height and weight can be measured, the desirable range of BMI in a particular neurological disease may be different from healthy individuals. As an example, in amyotrophic lateral sclerosis, the ideal BMI range is 30–35 kg/m^2,

because it is associated with a better overall survival [26]. This casts some doubt on the validity of the ranges of BMI used in the above-described screening tools in patients with this disease. There are no similar data in other neurological disorders, but we may assume a similar scenario.

2.3 Nutritional Assessment

After nutritional screening, following the identification of individuals at risk, the next step is nutritional assessment that will direct to choosing the best intervention to correct the malnutrition status. It is a detailed evaluation of nutritional status and nutritional needs, ideally performed by a dietitian/nutritionist or other trained health-care provider. It estimates functional status, diet intake, and body composition compared to normal populations. In the specific case of patients with neurological disorders, it is well known that they are at risk of both undernutrition and obesity.

There is no universally accepted method of nutritional assessment. Many factors need to be taken into consideration. It has to be based on a comprehensive approach. Symptoms, signs, and biochemical, anatomical or functional measures may be ambiguous with insufficient specificity and sensibility. Therefore, clinicians have to interpret findings obtained in each individual according to the patient's overall situation. As an example, it is not adequate to say that a patient has to receive artificial nutrition because he/she has a low serum albumin concentration. A broader assessment and evaluation of the perspectives for a sufficient or insufficient intake plus a consideration of the gastrointestinal tract function would be key elements to establish the indication of that nutritional intervention.

Items frequently covered in nutritional assessment are:

- Medical history, with emphasis on details regarding weight change, diseases with an impact on nutritional status, hospitalizations, surgery, changes in appetite, smell and taste alterations, dysphagia, intestinal dysmotility, alcohol or other addictions, medications, food-drug interactions, level of physical activity, daily living activities, etc.
- Dietary history, with evaluation of what and how much the person is eating, as well as habits, beliefs, and social conditions, availability and preparation of food; eating independence; cultural, religious, and ethnic food preferences; age-related nutritional issues, etc. Usual tools for dietary assessment are:
  - 24-h recall.
  - Food frequency questionnaire.
  - Food diary.
  - In patients with neuromuscular disorders, it is important to analyze the ability of feeding themselves, how much time it takes to eat each meal, early fatigue, safety of swallowing, etc.
- Social history, economic status, occupation, education level, living and cooking arrangements, and mental status.

- Physical examination, looking for findings of soft-tissue wasting, hydration status, and evidence of vitamin and mineral deficiencies, knowing that most signs indicate more than one nutrient deficiency and that signs are generally not observed unless severe deficiencies exist.
- Anthropometry:
  - Weight: usual, current, adjusted, ideal, and weight variation history
  - Height: actual or estimated by different methods, as described above
  - BMI
  - Skinfold thickness: triceps, biceps, subscapular, suprailiac. It estimates subcutaneous fat stores to assess total body fat.
  - Circumferences: arm, calf, and waist. It estimates skeletal muscle mass (somatic protein stores) and body fat distribution, respectively. It is important to remember that the underlying neurological disease or immobilization may alter muscular mass per se and cause muscular atrophy. Therefore, body composition techniques may better reflect the nutritional status than BMI or muscular circumferences in the arm or in the calf.
- Body composition: bioimpedance analysis, computed tomography, magnetic resonance, dual-energy X-ray absorptiometry, and air displacement plethysmography.
- Functional measures: handgrip dynamometry and gait speed. Neurological muscular atrophy may alter the results, and they can be of little use in these disorders.
- Laboratory parameters:
  - Serum proteins, such as albumin, prealbumin, retinol-binding protein. They are synthesized in the liver and behave like negative acute-phase reactants with reduced levels during systemic inflammation. Other reasons for abnormal results are renal and hepatic disease, wounds and burns, cancer, and hydration status. However, in the absence of inflammation or these disorders, a low concentration of these proteins may correlate with malnutrition
  - C-reactive protein.
  - Cholesterol.
  - Electrolytes.
  - Hemogram.
  - Vitamin and minerals.
- Evaluation of nutritional requirements to check if current food intake meets the estimated requirements of the patient.

In the nutritional assessment of any patient with a neuromuscular disease, it is essential to check his/her *hydration status*. Many factors may explain why these patients are at risk of dehydration. Some of them are not able to have access to liquids. Others present difficulties in swallowing liquids and are afraid of penetration of liquids into the respiratory airway during swallowing. Comorbidities, such as diabetes mellitus, diabetes insipidus, Addison's disease, chronic heart failure or renal failure, and some drug therapies, may lead to abnormal water losses, or water restriction, adding further troubles for maintaining a stable hydration status.

A negative hydric balance has clinical consequences in a short term. Many usual symptoms presented by patients with neuromuscular disorders get worse. Dehydration causes asthenia, dizziness, constipation, hypotension, renal failure, somnolence, lower consciousness, and even coma. Dryness of the oral mucosa may worsen dysphagia, with lower production of saliva, changes in the formation of the bolus, and development of oral infectious complications.

Hydration status has to be evaluated periodically after the diagnosis of the neurological disease, especially when symptoms and signs of dysphagia appear. Healthcare providers have to estimate hydric needs of patients and take the measures to warrant that they receive them in an effective and safe way.

2.4 Diagnostic Criteria of Malnutrition

The result of nutritional assessment will be a diagnosis of malnutrition that should be added in the medical record and in the discharge report, along with the nutritional intervention that has been recommended and implemented. Despite the existence of an international consensus to describe the three main malnutrition syndromes, there are different sets of diagnostic criteria established by ASPEN and ESPEN.

The Academy of Nutrition and Dietetics and ASPEN have extended this diagnostic construct with a recent consensus document highlighting characteristics recommended for the identification and documentation of malnutrition in adults [27].

The proposed criteria are:

- *Insufficient energy intake*: % nutrients consumed/administered vs. requirement
- *Unintended weight loss*: can occur at any BMI
- Physical examination:
  - Loss of *muscle mass*
  - Loss of *subcutaneous fat*
  - Evidence of *fluid accumulation* (localized or generalized)
- Diminished physical function:
  - *Handgrip strength*
  - SPPB (short physical performance battery) for elderly patients
  - Other

In bold the six characteristics that are used to diagnose malnutrition are indicated. A positive finding in any two characteristics indicates malnutrition. For each characteristic, there are different thresholds for both severe and no severe (moderate) malnutrition, in the three syndromes of malnutrition, acute illness or injury-related malnutrition, chronic disease-related malnutrition, and social- or environmental-related malnutrition (Tables 2.4 and 2.5). Specific thresholds for each situation can be found in the tutorial prepared by Malone and Hamilton, which provides very useful recommendations for the assessment of edema and of body fat and muscle mass in specific anatomic areas to help for an objective evaluation of subcutaneous fat and muscle mass loss, respectively [28].

Table 2.4 Severe malnutrition in adults (Adapted from Academy of Nutrition and Dietetics and ASPEN clinical characteristics criteria [27]. Reprinted with permission from J Acad Nutr Diet, 112, White JV et al., Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition), 730–8, 2012. Elsevier)

ICD-9 code 262	Acute illness/injury setting	Chronic illness setting	Social/environmental circumstances setting
Energy intake	≤50% of estimated requirement for ≥5 days	<75% of estimated requirement for ≥1 month	≤50% of estimated requirement for ≥1 month
Weight loss	>2%/1 week >5%/1 month >7.5%/3 months	>5%/1 month >7.5%/3 months >10%/6 months >20%/1 year	>5%/1 month >7.5%/3 months >10%/6 months >20%/1 year
Body fat	Moderate loss	Severe loss	Severe loss
Muscle mass	Moderate loss	Severe loss	Severe loss
Fluid accumulation	Moderate to severe	Severe	Severe
Grip strength	Measurably reduced (not recommended in intensive care units)	Measurably reduced	Measurably reduced

Table 2.5 Non-severe (moderate) malnutrition in adults (Adapted from Academy of Nutrition and Dietetics and ASPEN clinical characteristics criteria [27]. Reprinted with permission from J Acad Nutr Diet, 112, White JV et al., Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition), 730–8, 2012. Elsevier)

ICD-9 code 263.0	Acute illness/injury setting	Chronic illness setting	Social/environmental circumstances setting
Energy intake	<75% of estimated requirement for >7 days	<75% of estimated requirement for ≥1 month	<75% of estimated requirement for ≥3 months
Weight loss	1–2%/1 week 5%/1 month 7.5%/3 months	5%/1 month 7.5%/3 months 10%/6 months 20%/1 year	5%/1 month 7.5%/3 months 10%/6 months 20%/1 year
Body fat	Mild loss	Mild loss	Mild loss
Muscle mass	Mild loss	Mild loss	Mild loss
Fluid accumulation	Mild	Mild	Mild
Grip strength	Not applicable	Not applicable	Not applicable

The Academy of Nutrition and Dietetics and ASPEN recommend ICD-9 code 262 for the diagnosis of severe protein-calorie malnutrition and ICD-9 code 263.0 for moderate (no severe) malnutrition. These ICD-9 codes have definitions that best match the malnutrition criteria for severe and moderate (no severe) malnutrition according to the consensus document. Nevertheless, the criteria developed in support of the diagnosis of severe and no severe malnutrition may be adapted in the

future according to further development and testing. The equivalent ICD-10 codes would be E43 and E44, respectively.

ESPEN has lately proposed some criteria for the diagnosis of disease-related malnutrition [29]. The objective of ESPEN statement was to provide malnutrition diagnostic criteria that are independent of etiology, in contrast with ASPEN, as we have just seen. A consensus group was in charge of achieving objective, simple, clear, and generally diagnostic criteria of malnutrition. Several agreements were made by this group. Food intake and appetite were contemplated as important items for screening, but they were not considered as required diagnostic criteria, because any reduction would be reflected by weight loss. Visceral proteins, like serum albumin or prealbumin, were thought of as markers of inflammation, disease severity, and outcome with little specificity as nutritional markers. In relation to inflammation, it is seen more as an etiologic factor than a defining criterion of malnutrition, and inflammation markers were not included in the criteria.

As ASPEN, ESPEN recommends universal screening, without advising any particular tool. Those patients at risk of malnutrition will be diagnosed with malnutrition if they satisfy the following criteria:

I. Patient fulfills criteria for being "at risk" of malnutrition by any validated risk screening tool.

II. Patient meets the criteria of alternative 1 or 2:

Alternative 1:

- BMI <18.5 kg/m^2

Alternative 2:

- Weight loss (unintentional) >10% indefinite of time or >5% over the last 3 months combined with either
  - BMI <20 kg/m^2 if <70 years of age or <22 kg/m^2 if ≥70 years of age or
  - Fat-free mass index (FFMI) <15 and 17 kg/m^2 in women and men, respectively.

Therefore, according to ESPEN, the three variables that most accurately reflect malnutrition are weight loss (generally self-reported and at risk of recall bias), reduced BMI, and reduced FFMI. Nevertheless, their criteria have been criticized because they are very strict, leaving out patients with lower weight loss or with higher BMI, if they were previously obese. Furthermore, in some European countries, reimbursement of oral nutritional supplements is linked to a diagnosis of malnutrition, which is generally less stringent. The ESPEN consensus group repeatedly insisted on the need of considering risk of malnutrition as a disease category with its own code in the ICD and in the DRG system. That would solve the problem of indication for reimbursement. A different option is to apply to malnutrition a similar approach as in chronic renal failure, where five different stages have been established. With this concept in mind, the ESPEN criteria would be like restricting the concept of chronic renal failure only to those patients on dialysis. On the other hand,

if the concept of malnutrition stages were accepted, it would be easier that earlier stages or the risk category of malnutrition could be diagnosed and reimbursed.

Recently, a study has described for the first time the prevalence of malnutrition according to the ESPEN definition in four diverse populations, acutely ill middle-aged patients, geriatric outpatients, healthy old individuals, and healthy young individuals [30]. Subjects were screened for risk of malnutrition using the SNAQ. Screening identified 30, 10, 0.5, and 0% as being at risk of malnutrition, respectively. The prevalence of malnutrition was 0% in healthy young, 0.5% in healthy old individuals, 6% in geriatric outpatients, and 14% in the acutely ill middle-aged patients. Prevalence of low FFMI was observed in all four populations (14–33%), but was not always associated with weight loss (0–13%). Interestingly, participants classified as malnourished based only on low BMI <18.5 kg/m^2 were mainly acutely ill middle-aged patients. It can be assumed that the underlying disease was responsible for the weight loss. Conversely, that low BMI was observed very infrequently in geriatric outpatients and healthy old individuals. This may be due to the increase of BMI with age noticed in many epidemiological studies. In the first three groups, low FFMI was better associated to unintentional weight loss. In consequence, measuring FFMI in addition could detect malnutrition better than only BMI. The problem is to find reliable methods of body composition analysis available in routine clinical practice.

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Malnutrition in Neurological Diseases

3

Levent Gungor

3.1 Introduction

Most of the diseases encountered in daily neurology practice lead to severe functional disabilities at a certain stage of the disease. In the course of these diseases, either during the acute or chronic phases, nutritional status and the ability to provide nutritional needs may be disturbed (Tables 3.1 and 3.2). Among these, cerebrovascular diseases, neuromuscular diseases, and neurodegenerative diseases are the main three groups, which may lead to nutritional deficiencies. Malnutrition, if encountered during the course of a neurological disease, increases the morbidity and mortality associated with that disease.

Despite its importance the clinician can ignore the evaluation of nutritional status, the risk of dysphagia, and measures that need to be taken to prevent malnutrition, while trying to treat specifically the neurological situation and its life-threatening complications. If malnutrition risk and neurogenic oropharyngeal dysphagia are identified at a timely manner, appropriate nutritional support and dysphagia treatment will successfully decrease the related morbidity and mortality.

3.2 Metabolic Consequences of Insufficient Food Intake in Neurological Disorders

Patients suffering from acute stroke or acute neuromuscular disorders like Guillain–Barre syndrome or myasthenia gravis, where dysphagia is a common companion of the clinical picture, might not fulfill the criteria for malnutrition according to the generally used screening tools as subjective global assessment. Some of these

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Table 3.1 Neurological disorders which carry risk of dysphagia in the acute phase

Central nervous system diseases	Neuropathies involving lower cranial nerves	Neuromuscular disorders	Myopathies	Others
1. Cerebrovascular disease Ischemic stroke Intracranial hemorrhage 2. Central nervous system infections Meningitis Encephalitis Brain abscess Poliomyelitis Rabies Progressive multifocal leukoencephalopathy 4. Demyelinating disorders Osmotic demyelination syndrome ADEM 5. Hypoxic ischemic encephalopathy	1. Guillain–Barre syndrome and variants 2. Neoplastic cranial nerve involvement (leukemia, lymphoma, nasopharyngeal carcinoma) 3. Diphtheria	1. Myasthenia gravis 2. Botulism	1. Inflammatory myositis Dermatomyositis Polymyositis Inclusion body myositis 2. Necrotizing myopathy	1. Craniocervical trauma 2. Tardive dyskinesia

Table 3.2 Neurological diseases which may lead to malnutrition in the chronic phase and need nutritional assessment and support during follow-up

Central nervous system diseases	Neurodegenerative diseases	Myopathies	Others
1. Cerebrovascular disease Ischemic stroke Intracranial hemorrhage 2. Central nervous system infections Listeria Neurobrucellosis Tuberculosis Neurosyphilis Lyme disease HIV 3. Creutzfeldt–Jakob disease 4. Demyelinating disorders Multiple sclerosis 5. Hypoxic ischemic encephalopathy 6. Cerebral palsy	1. Motor neuron disease Amyotrophic lateral sclerosis 2. Dementia Alzheimer's disease Vascular dementia Lewy body dementia Frontotemporal dementia 3. Parkinsonian syndromes Parkinson's disease Multiple system atrophy Corticobasal ganglionic degeneration Huntington's disease Neuroacanthocytosis Wilson's disease 4. Spinocerebellar ataxias	1. Inflammatory myositis Dermatomyositis Polymyositis Inclusion body myositis 2. Hereditary myopathies Muscular dystrophies (Duchenne, Becker, facioscapulohumeral, oculopharyngeal, myotonic dystrophy) 3. Mitochondrial myopathies MNGIE Kearns–Sayre syndrome	1. Myasthenia gravis 2. Chronic polyneuropathies involving lower cranial nerves 3. Arnold–Chiari syndrome 4. Syringobulbia

patients can even be overweight. Nonetheless, the presence of even large amounts of lipid in their bodies does not mean that these patients do not need nutritional support and they can burn their fat stores as an efficient calorie source.

In the case of starvation, blood glucose levels decrease rapidly, and within a few hours, hepatic glycogen reserves start to be used to replace glucose deficiency. The depot of glycogen in the liver suffices at most for 24 h. Approximately 4 h after starvation, together with glycogen catabolism, hepatic gluconeogenesis is activated. Hepatic gluconeogenesis makes its peak at the first 24–48 h, later decreases to a steady level and continues for days. The energy coming from glycogenolysis and gluconeogenesis, however, are not sufficient for the whole of the organism, especially in catastrophic conditions like large strokes or myasthenic crisis. The adipose tissue takes a crucial role as a salvage ATP supplier in the case of starvation. Glucagon and epinephrine act directly on the adipose tissue, and fat stores are broken down to release glycerol and fatty acids [1]. Fatty acids are reverted to acetyl coenzyme A in the mitochondria, which is then introduced into the citric acid cycle to produce ATP. Despite the fact that fatty acids are high-energy sources, cells without mitochondria—like red blood cells—cannot use them as a source of energy. The brain has a highly active metabolism, so it needs a continuous supply of energy. The brain comprises about 1/40–50 of the body weight but receives one fifth of the total blood volume and glucose. Neurons indeed have mitochondria to burn fatty acids, but fatty acids cannot pass the blood–brain barrier because of their high molecular weight and high water solubility. Therefore, fatty acids are not good candidates of energy supply for the brain, and especially in the acute stages of starvation, human brain is still primarily dependent on glucose [2, 3].

In the case of starvation, another source of ATP is ketone bodies. They are produced from fatty acids in the liver. The three main ketone bodies are acetone, acetoacetate, and beta-hydroxybutyrate. They are oxidized to acetyl-CoA in the mitochondria and used for energy production through the tricarboxylic acid cycle. Ketone bodies are highly water soluble and can pass through the blood–brain barrier. These properties make ketone bodies a source for supplemental energy for the brain during prolonged starvation. The main cells in the central nervous system, which use ketone bodies, are the astrocytes, not the neurons themselves [4, 5].

Astrocytes may synthesize a small amount of glycogen, and this can meet the energy need of neurons in minuscule amounts. Also, there is proof for the presence of gluconeogenesis in the brain, restricted to astrocytes only. Considering that no major source of energy supply for the brain comes from lipids or hepatic glycogen stores, amino acid stores in the organism are depleted to supply ATP (via gluconeogenesis) to neurons in a patient who is unable to eat related to the acute neurological condition. This protein catabolism starts rapidly within a few days. A healthy adult has approximately 7 kg of protein in the body, which corresponds to 30,000 kcal. In case of starvation, every day 300 g of muscle tissue is lost. This is equivalent to 75 g of protein. It is important to note that the loss of 40% or more of whole body protein culminates with death of the patient [5].

3.3 Muscular Consequences of Insufficient Food Intake

The lack of food taken orally and depletion of energy sources, if not handled appropriately, rapidly lead to degradation of muscle proteins. Together with this muscle catabolism, restriction of movement due to the primary neurological disease and paralysis contributes to the risk for sarcopenia. Sarcopenia, in fact, seems to be a clinical entity, which is probably underdiagnosed in neurology clinics and neurointensive care units [6]. As of today, sarcopenia is a well-described disease. According to the consensus criteria developed in Rome in 2009 and Albuquerque in 2010, sarcopenia is defined as the decrease in muscle mass together with functional loss [7, 8]. Although the condition can be observed even in the healthy elderly, it is generally a major consequence of neurological conditions in the acute phase. It is important to note that sarcopenia may develop rapidly. An individual in the geriatric age group loses approximately 1 kilogram of lean body mass if he/she is placed into bed rest for 1 week. The prevalence of sarcopenia is reported to be between 56 and 71% in intensive care units [9, 10]. Extremity volume of the hemiparetic side is 25% less than the healthy side after 6–12 months in stroke survivors [8].

Four main mechanisms are considered to be responsible for the development of sarcopenia:

1. *Immobilization* is the major preceding factor for sarcopenia. Mammalian target of rapamycin (mTOR) is a cellular protein, which is activated by various hormones and factors, and regulates muscle protein synthesis by directly affecting DNA. mTOR facilitates translation of proteins, which are essential for muscle cell growth and proliferation, especially in the setting of stress, inflammation, and hypoxia. mTOR has two types of cellular receptors in muscle cells. mTORC1 induces translation of many cellular proteins in the nucleus, while mTORC2, when activated, induces synthesis of some cytoskeletal proteins, cell surface receptors, and molecules, which play a role in intracellular signal transduction. A dysregulation or reduced activity of this molecule seems to be crucial in the development of sarcopenia. Inversely, mTOR and muscle protein synthesis is induced by exercise and high-protein nutrition. During long-lasting rest, amino acid transmitter systems within the muscle cells are inhibited, and muscle protein synthesis induced by amino acids is reduced [11].
2. *Dysphagia and decrease in nutritional intake* directly lead to calorie and protein deficiency, which in result contribute to muscle wasting.
3. *Inflammation* has an important role in sarcopenia pathophysiology. IL6, IL10, IL15, T lymphocyte receptor 4 (TCL4), CD68, and nuclear factor kB1 levels increase in the wasting muscle. Blood levels of C-reactive protein, IL6, macrophage inflammatory protein-1β, tumor necrosis factor-α (TNFα), and interferon-ɣ are all elevated in sarcopenic animals. The exact cellular and biochemical

mechanisms of how these inflammatory proteins induce muscle degradation still remain unclear. However, TNFα is shown to inhibit mTOR pathway of actin and activate muscle catabolism.

4. *Decrease in anabolic vitamin levels* facilitates sarcopenia. Especially, the levels of vitamin D, androgen, and estrogens are reduced in the elderly, both due to decreased oral intake and reduced synthesis. These three molecules have crucial roles in muscle protein synthesis. Muscle cell nuclei include specific receptors for vitamin D [6].

Several other factors may play a role in the development of sarcopenia. Muscle catabolism is increased in rats and mice fed with high-fat diet. High-fat diet seems to cause overexcretion of adiponectin and activation of E3 ubiquitin ligase together with activation of insulin receptor 1, all of which is called as *lipotoxicity*. Aging muscle has low blood supply, and this *microvascular insufficiency* of muscle tissue is supposed to facilitate the development of sarcopenia. Finally, motor unit number decreases with aging, and type II muscle fiber atrophy becomes evident. TrkB activity, which supplies neuromuscular transmission, is reduced by aging. This overall *decreased neural stimulation* may also have an impact on muscle tissue loss [12].

Myostatin is a molecule, which has a clear effect on muscle turnover. When it binds to its sarcolemmal receptor, mTOR is inactivated. The myostatin receptor works with intracellular signal transmitting molecules, MAP kinase and SMAD. Activation of these two molecules with myostatin binding to its receptor inhibits the synthesis of three important proteins in muscle cell nucleus, myogenin, myf5, and MyoD. MyoD exists in satellite cells, which are progenitors of myoblasts, and is responsible for differentiation of myoblast as a muscle cell. Myogenin provides muscle cell proliferation and repair of myofibrils. Myf5 is responsible for muscle cell differentiation. Rather than being a step in the pathogenesis of sarcopenia, myostatin is a candidate target for the treatment of sarcopenia with myostatin inhibitors. In 1997, myostatin knockout animals were found to have excess muscle mass. For today, research is ongoing with myostatin inhibitors like GASP-1, FLRG, and follistatin. Preliminary results are promising with increased gain of muscle strength in forearms of rats [13, 14].

The pathologic findings of sarcopenia differ from muscle atrophy. The most prominent histopathologic findings of sarcopenia include atrophy of type II fibers; necrosis and loss of intercellular elements, which bind muscle fibers to each other; and reduction of size and number of muscle cell mitochondria. Collagen fibers are degraded and form irregular deposits. The muscle tissue is replaced with lipid-rich fibrocollagenous material. The main difference of sarcopenia from muscle atrophy is the loss of muscle fibers with a significant decrease in their number [15, 16]. In other words, new muscle cell synthesis is needed for recovery from sarcopenia, which indeed is difficult and long lasting, especially in an elderly neurological disease survivor. On the other hand, muscle atrophy is easier to reverse, by increasing the muscle fiber size with exercise after successful reinnervation.

3.4 Intestinal Consequences of Insufficient Food Intake

Intestinal wall integrity is maintained not only by its excellent blood supply from mesenteric arteries but also from the nutritional products in the lumen. Dietary nutrients are mandatory for gastrointestinal function. Mammalian guts have nutrient-stimulated local growth factors such as gastrin, peptide YY, cholecystokinin, glucagon-like peptide 2, and neurotensin. The lack of nutrients in the lumen leads to the loss of these local factors. Intestinal epithelial cell integrity is very important for neurointensive care patients. The single layer of epithelium is responsible not only for absorption of nutrients, water, and electrolytes, but is also critical for providing a selective barrier against the complex and potentially noxious environment of the gut lumen. In addition, the intestinal wall acts as a complex and active immune organ. If there is cessation of oral or enteral feeding, villus length and crypt depth in intestinal mucosa are reduced rapidly. The mucosal atrophy results in increased intestinal permeability. Bacteria comprising the intestinal flora easily turn into pathologic species and pass through the intestinal wall. Bacterial translocation and sepsis may be the result of empty gut in neurointensive care patients [17, 18].

3.5 The Incidence of Dysphagia and Malnutrition in Neurology Practice

3.5.1 Stroke

Dysphagia is a common problem in the onset of acute stroke; swallowing problems occur in 24–53% of strokes in the acute phase [19, 20]. The prevalence changes according to the method used for evaluation. The frequency of dysphagia after stroke increases with the severity of the stroke. Large hemispheric strokes and brain stem strokes have the highest risks of dysphagia. Patients with loss of consciousness should not be fed orally. Aphasic or noncooperative patients should be evaluated closely for dysphagia risk and enteral feeding. Periventricular white matter lesions and cortical left hemispheric lesions are the most common lesions for lingual discoordination and swallowing apraxia. Dysphagia in the acute phase of stroke generally resolves within weeks. The rate of dysphagia decreases to 8% 6 months following stroke. Overall 2% of all survivors end up with permanent dysphagia and the need for enteral feeding via gastrostomy [21].

The patient with an inability to swallow has an increased risk of dehydration, malnutrition, and aspiration. Dysphagic stroke patients have elevated rates of mortality and morbidity and longer durations of hospitalization [22]. About 6% of stroke patients are lost due to the complications associated with aspiration within 1 year [23].

Malnutrition rate during admittance ranges between 3.8 and 36% in stroke patients according to several studies using different methods for assessment of malnutrition [20, 24–29]. The rate is higher in older patients admitted to intensive care

units, with a prevalence of 28% for moderate malnourishment and 6% for severe malnourishment [30]. Malnutrition on admission is more frequent in females, diabetics, older patients, patients coming from institutions or poor social circumstances, patients with previous gastrointestinal diseases like peptic ulcer, and patients with cognitive impairment and physical disability [22]. On the other hand, overnutrition may be higher especially in Western countries [31]. Malnutrition is correlated with poorer functional recovery and higher mortality among stroke survivors [29, 32]. Nutritional support, energy intake, and improvement of nutritional parameters lead to better functional scores [33, 34, 35].

It is more probable that malnutrition may develop during the hospital or neurointensive care unit stay. Stroke itself, especially large infarcts or hemorrhages, causes higher amounts of cortisol release and a greater stress response. Together with accompanying infections, energy demand in admitted stroke patients is elevated. The amount of patients with protein energy malnutrition increases by 125% in the first week [22] and by 200% after 2 weeks [24]. Five percent of cerebrovascular patients without malnutrition at admission become malnourished after 2 weeks [24]. Serum protein levels decrease by 1.5 g/dL, and serum albumin concentrations decrease by 1.2 g/dL by day four if only low-calorie peripheral venous solutions are infused after an acute cerebrovascular insult. Enteral and parenteral feeding can successfully reverse this protein loss within 2 weeks [36]. The estimated cost of stroke-associated malnutrition reaches $1,165 billion annually in the USA, taking the fourth place among diseases leading to malnutrition [37].

Nutritional care during rehabilitation is more important, as patients with cerebrovascular diseases in rehabilitation centers are more likely to have poor nutritional status than patients in acute care hospitals [38]. Stroke, in the long term, may lead to eating difficulties and nutritional impairment not only by causing dysphagia but also by visuospatial perceptual deficits, upper extremity paralysis or apraxia, attention–concentration deficits, forgetting to eat, combativeness or rejecting food, eating too fast or too slowly, chewing constantly or overchewing food, right and left disorientation, visual neglect, disturbance of sensory function, agnosia, and depression [39]. Nutritional support must therefore be a potential therapeutic strategy for patients with cerebrovascular disease in both acute and rehabilitation phases.

3.5.2 Neuromuscular Disorders

The most common neuromuscular disorders leading to dysphagia are myasthenia gravis, amyotrophic lateral sclerosis, Guillain–Barre syndrome, and their variants. All these diseases may easily affect swallowing muscles. The incidence of dysphagia ranges between 15 and 40% among generalized myasthenia patients, and dysphagia is the admittance symptom in 6%. Dysphagia is generally accompanied by other bulbar symptoms. Dysphagia and aspiration have in fact a complex mechanism even including a dysfunction of esophageal smooth muscles in some [40, 41]. However, swallowing and eating difficulties resolve rapidly with the appropriate immune therapies and cholinesterase inhibtion. Malnutrition rate in myasthenia

gravis is very low and occurs rarely in chronic and old myasthenic patients with prominent muscle atrophy. Long-term nutritional support through a nasogastric or PEG tube is rarely needed [42].

Acute polyneuropathies may sometimes affect lower cranial nerves. Guillain–Barre syndrome and its variants, especially Miller Fisher syndrome and pharyngeal–cervical–brachial variant, might lead to severe dysphagia. Twenty-eight percent of patients with Guillain–Barre syndrome need tube feeding in the acute stage. The duration of need for enteral feeding is generally short but may last for up to 6 months. Thirty-six percent of patients have dysfunction during the oral phase of swallowing and 71% have dysfunction during the pharyngeal phase. Immunotherapies with intravenous immunoglobulin and plasmapheresis and neurointensive care support generally result with good surveillance and recovery. Persistent dysphagia needing placement of gastrostomy is very rare, with a maximum rate of 4% in these diseases [43, 44].

Motor neuron disease, principally amyotrophic lateral sclerosis, starts with swallowing dysfunction in 10–30% of cases. Irreversible dysphagia and permanent enteral feeding tube placement is the natural consequence of the disease. The principles and timing for nutrition in amyotrophic lateral sclerosis will be discussed in detail in Chap. 6.

3.5.3 Neurodegenerative Diseases

Two major prototypes of neurodegenerative diseases in which eating and swallowing are disturbed are Parkinson's disease and Alzheimer's disease. These patients should be evaluated and followed closely for a nutritional plan at each stage of their disease.

The rate of malnutrition among patients with dementia is 7%. Considering that the prevalence of dementia is also high (as high as 7%), dementia is by far the greatest contributor of disease-associated malnutrition in the USA. The cost of dementia-associated malnutrition is estimated to be $8.7 billion annually. Although the prevalence of dementia in those aged 65 and over is higher than the young population (12.5 vs. 6%), the rate of malnourished cases in older dementia patients is not higher than the young cases (6 vs. 7.8%) [37].

Alzheimer's disease gives its initial symptoms as memory impairment and difficulty in conducting daily activities. Swallowing function is generally the last higher cortical function to be destroyed in Alzheimer's disease. These patients fail in various aspects of nutrition generally because of their inability to reach food, loss of appetite, and forgetting how to eat at earlier stages of dementia. They are thereby at high risk of malnutrition. The best way for nutritional support for dementia patients seems to be frequent time spending oral feeding sessions known as careful hand feeding. Permanent gastrostomy is not advised in most patients, especially in their terminal stages [45, 46].

Prevelanece of malnutrition is reported to be 0–24% and risk of malnutrition to be 3–60% in Parkinson's disease. Symptoms of constipation, reduced gastric emptying and loss of weight can be seen, even in the pre symptomatic phase of

Parkinson's disease. Advanced disease and older age, higher UPDRS scores, prolonged disease duration, higher L-dopa need, living alone, accompanying dementia, depression and hypothyroidism increase the rate of malnutrition. The resting energy expenditure is increased in Parkinson's disease because of altered hypothalamic metabolism and higher effort for motion, dyskinesias and tremor. Besides, food intake is diminished in Parkinson patients. Delay in gastric emptying, constipation, sometimes malabsorption, usage of low protein diet, reduced hand coordination, inability to reach and prepare food, gastrointestinal side effects of dopaminergic drugs and dysphagia are the reasons of decreased food intake [47, 48].

Parkinson's disease may cause dysphagia by disturbing the oral and pharyngeal phases of swallowing. It is mainly due to bradykinesia and rigidity of swallowing muscles. Tongue movements and tongue pumping of the food bolus is reduced in parkinsonism. Oral transit time and swallowing is delayed. Laryngeal elevation and closing may be disturbed leading to penetration and aspiration. Cough is ineffective and several clearing swallows are needed in Parkinson's disease patients. Esophageal dysmotility may also accompany the clinical picture [49]. Dysphagia is a common symptom of Parkinson's disease and may be present in about 40–80% of cases. Swallowing disturbance may be overcome by diet modification, drugs, and swallowing rehabilitation. Temporary nasogastric tube feeding may be essential during worsening episodes [50]. Dysphagia is more common in other parkinsonian degenerative disorders such as progressive supranuclear palsy and multiple system atrophy, and continuous tube feeding may be essential in some cases [51, 52, 53].

Clinicians should check the nutritional status of patients with dementia and parkinsonism at each visit. The assessment methods for malnutrition screening will be described elsewhere in this book. However, sometimes, these assessment methods may overlook sarcopenia. The functional loss related to sarcopenia is generally assessed by the walking capacity in routine geriatrics practice. However, gait performance is disturbed in neurodegenerative diseases as well, and it is challenging to distinguish if the impairment of skeletal muscle function is due to parkinsonism or sarcopenia. In this instance, diagnosis of sarcopenia depends on the evidence of decrease in muscle mass. DEXA, computed tomography, magnetic resonance imaging, and bioelectrical impedance analyses may be helpful to diagnose sarcopenia in these cases [54].

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Methods of Clinical Nutrition

4

R. Haldun Gundogdu

4.1 Introduction

After making the decision to administer nutritional support (NS) to a patient either with malnutrition or at nutritional risk, the first thing to do is to define the method. There are many options for the administration of NS on a large scale (Fig. 4.1). On one end of these methods, there is oral supplementation, and on the other, there is total parenteral nutrition (TPN). It is proper to classify the techniques of delivering NS as oral-enteral methods and parenteral methods. However, it is frequently necessary to use these methods together in clinical practice.

4.2 Enteral Nutrition

4.2.1 Indications for Enteral Nutrition

Varying forms of enteral nutrition (EN) may be used in patients with a functioning gastrointestinal (GI) system who are unwilling to eat enough to fulfill their requirements or whose oral intake is insufficient. EN causes fewer complications than parenteral nutrition (PN) [1], it is safer, and its cost is seven times less when compared to PN [2].

In patients who are identified to have malnutrition or be at nutritional risk, the first method to consider for delivering NS is EN.

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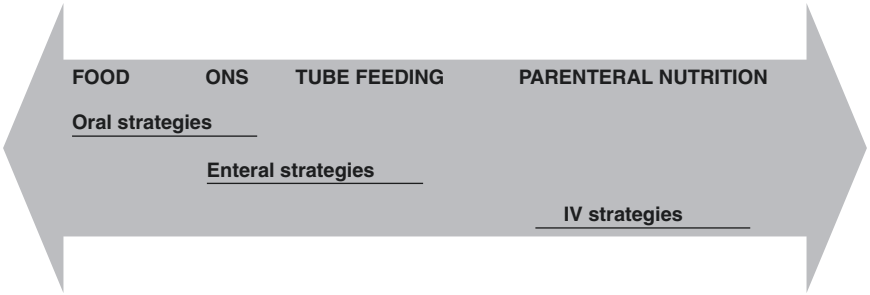

Fig. 4.1 The methods of nutritional support

4.2.2 Contraindications for Enteral Nutrition

Although EN is the first option, there may be occasions that it may be contraindicated [3]. These are:

- Intestinal insufficiency, the loss of intestinal function due to situations such as severe inflammation or postoperative ileus
- Complete intestinal obstruction
- Impossibility to access the enteral route
- High-flowing enterocutaneous fistula
- Situations that may cause ethical problems such as patients in the terminal stage

4.2.3 Access for Enteral Nutrition

The selection of the route of administration may vary depending on the underlying disease, expected time for enteral feeding, and the patient's preference (Fig. 4.2) [4].

4.2.3.1 Oral Nutritional Support

The oral intake of nutrients is the physiological form of feeding and has a strong influence on salivary secretion, which has substantial antibacterial properties. Therefore, the use of the oral route must be preferred in every possible occasion. Oral nutritional support (ONS) is the most appropriate choice if the patient cannot or is unwilling to eat sufficient amount of food. ONS is also used in the elderly and in patients with various health and eating problems (neurological disorders, etc.) to facilitate oral food intake.

There is enough evidence regarding the benefits of ONS in the literature. In a systematic review of patients living in the community setting, ONS was demonstrated to improve total food intake, body weight, and function across various patient groups (chronic obstructive pulmonary disease, cystic fibrosis, Crohn's disease, HIV patients, liver disease, and cancer) [5]. A recent meta-analysis displays many favorable results, particularly regarding the increase in body weight and also the decrease in mortality and complication rates [6].

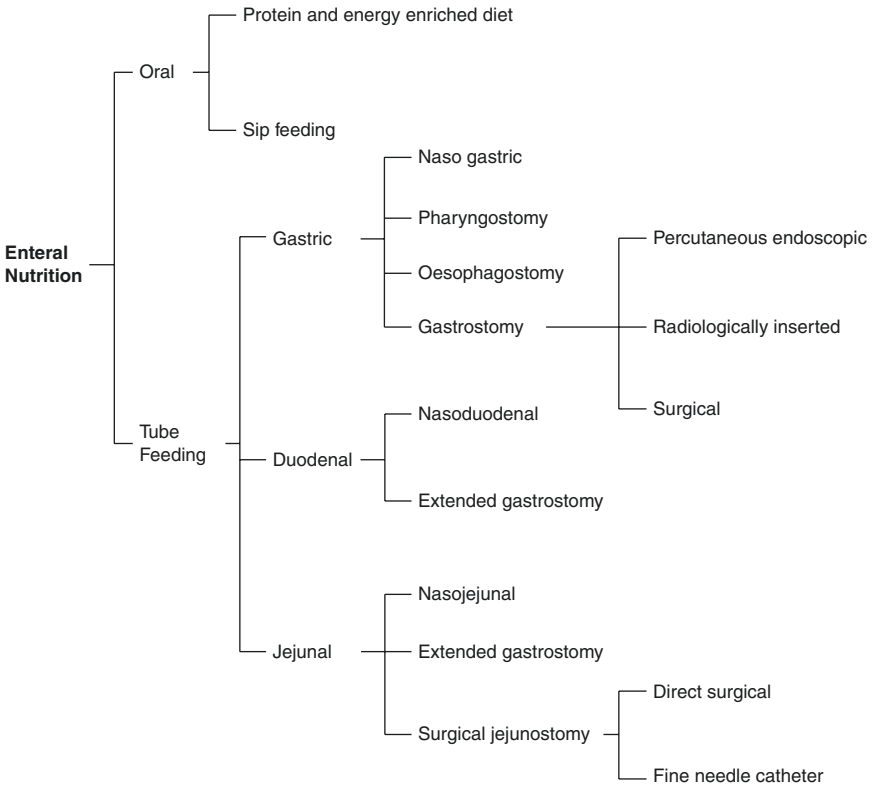

Fig. 4.2 Routes for enteral nutritional support

There are many ONS products on the market, and the selection of the appropriate product must be made according to the specific requirements of the patient. The ideal ONS product must be concentrated (small in volume) and must cause a rather short period of satiety. Thus, it will not cause insufficient food intake during the meals or throughout the day.

It is essential to consider patient's preference of flavor, style, and presentation to maximize compliance to ONS. This compliance may be difficult; however, it is possible to overcome this difficulty by a controlled management. It must also be emphasized that ONS should not decrease or replace the intake of normal or enriched food intake.

4.2.3.2 Transnasal Route

Nasoenteral nutrition is generally used in short term (less than 4 weeks).

The cases in which nasogastric or nasoenteral route is used are the patients with neurologic or psychiatric problems who do not have enough oral intake or the ones who cannot eat due to oropharyngeal or esophageal disorders. Other conditions that may benefit from this sort of feeding include burns, varying GI diseases or patients receiving chemotherapy or radiotherapy [7]. Nutrition via nasoenteral tubes can

also be used in the period of transition from TPN to the combination of parenteral and EN or normal oral intake.

Nutrition via nasoenteral tubes is contraindicated in patients with severe GI dysfunction. In patients with postoperative gastric emptying problems, the risks of nausea, vomiting, and acute gastric dilatation can be decreased by feeding via the direct enteral route. For this purpose, the feeding tube must be placed into the small bowel radiologically or endoscopically (nasoduodenal or nasojejunal feeding).

There are similar techniques for the placement of nasogastric, nasoduodenal, and nasojejunal tubes at the bedside. The lubricated tip of the tube is inserted through the more patent nostril and passed into the nasopharynx. Then the patient is told to swallow (if he/she is able), and the tube is placed into the stomach. The patient lies on his right side, and thus, the peristaltic movements of the stomach facilitate the passage of the tip of the tube through the pylorus into the duodenum. Lately, endoscopic and radiologic placements techniques are used more frequently [8].

Postpyloric nutrition may prevent the problems that result from the reflux and aspiration of enteral contents. However, findings of the studies regarding this issue are conflicting.

In lethargic patients or patients with an impaired coughing reflex, it is important to detect the final location of the tip of the nasoenteric tube. Auscultation of the air insufflated through the tube may be misleading since the insufflated air from a tube that is placed into the main bronchus may sound as if it is coming from the stomach. The simplest way to confirm that the tube is properly placed into the GI tract is the aspiration of the gastric or enteric content. If this is not possible, radiologic confirmation of the location of the tube is the most reliable method. A direct radiogram will be adequate for this purpose since the feeding tubes are radiopaque. If there is still uncertainty about the location of the tube, injection of a small volume of contrast material will help confirmation.

An important problem is the care of the nasoenteric tubes. Skin irritation is common due to adhesive tapes. What is more critical is the dislocation of the tube resulting from a loose tape, which is quite commonly seen in patients with impaired consciousness. When used properly, hypoallergenic adhesive tapes or specifically designed clips can secure the tube effectively.

The complication rate regarding the bedside placement of nasoenteric tubes is reported to be 0.5–15%. Bleeding, bronchial placement, and GI perforation are the most common complications. The leading risk factors are advanced age, neurologic disorders, and anatomic abnormalities [9].

4.2.3.3 Percutaneous Endoscopic Gastrostomy

The percutaneous endoscopic technique must be considered if EN will be needed for more than one month. Percutaneous endoscopic gastrostomy (PEG) was first applied in 1980 and has since become the first choice to administer enteral NS in the long term [10].

Patient selection for PEG must be done very carefully. Diagnosis, prognosis, predicted duration for NS, the will of the patient, and the predicted impact on the quality of life need to be considered before PEG placement. Ethical issues should

also be debated before the intervention. It was demonstrated that for long-term NS, PEG was preferred by the patients over nasogastric tubes. It is less disturbing for the patient, has a higher nutritional efficacy, and has a lower prevalence of complications [11, 12].

PEG indications include swallowing disorders due to neurologic reasons (i.e., stroke, brain tumors, Parkinson's disease, etc.), upper GI tract cancers, polytrauma, patients needing long-term mechanical ventilation, and perioperative period in oropharyngeal surgery [13]. PEG is more cost-effective compared to surgical gastrostomy [13, 14].

Invasive and costly interventions should be avoided in patients with an unfavorable prognosis (patients who have a life expectancy of less than 30 days after PEG placement) and in individuals with advanced dementia, where an alternative feeding plan must be offered. Trying feeding with nasogastric tubes or oral supplements for experimental periods may be more favorable for many of these patients. Feeding with PEG may be reconsidered in these patients if the general condition of the patient gets better or remains stable [15].

PEG must be avoided in every condition which constitutes a contraindication for EN, like pharyngeal or esophageal obstructions which hinder endoscopic interventions, in situations of complete obstruction of the GI tract and in severe coagulopathy [13]. Massive ascites, peritoneal dialysis, severe portal hypertension, and anatomic alterations due to previous surgery or inflammation constitute relative contraindications for PEG.

Techniques for PEG Placement

There are a number of PEG placement techniques, but the most frequently used is the pull method developed by Gauderer and Ponsky [10].

Pull method: Endoscopy is performed under sedation. The intervention should be performed under sterile conditions and using standard surgical techniques. The entry point on the skin must be infiltrated with a local anesthetic. After performing diaphanoscopy with the help of the endoscope to show the point where the stomach is closest to the abdominal wall, a Seldinger needle is used for puncturing the front wall of the stomach. A string guide is passed through the needle and caught using a biopsy forceps. The string is then pulled out of the mouth together with the endoscope. The feeding tube is attached to the string and pulled into the stomach and out through the abdominal wall. The tube is secured by a fixing plate in the stomach and a disk on the skin (Fig. 4.3).

Push method: In this method, the PEG tube is placed over a Seldinger wire [16]. The successful puncture of the stomach using the Seldinger technique enables the placement of the PEG tube in patients with esophageal obstruction (i.e., due to esophageal tumors). This method may also be performed using sonography or radiology.

The development of the new "introducer" method, which uses the combination of double gastropexy and an introducer with a peel-away sheath, has enabled the safer placement of the intragastric balloon. This method may be suitable for patients in which the standard pull method is avoided because of an increased risk of esophageal cancer dissemination during the passage of the endoscope.

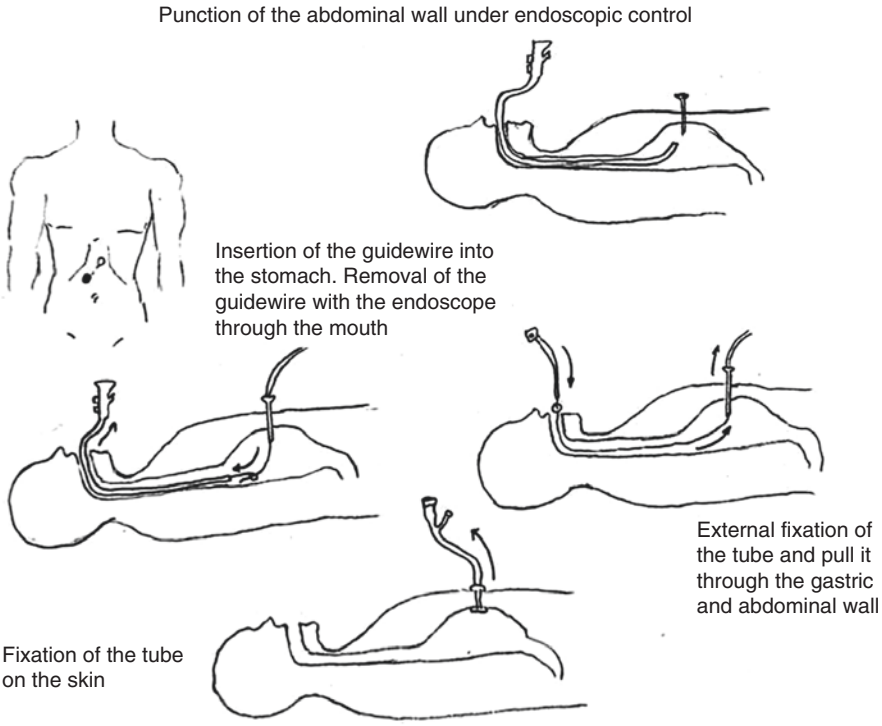

Fig. 4.3 The pull method for percutaneous endoscopic gastrostomy

Guidelines recommend initiation of feeding 12–24 h after PEG placement. Wound dressing should be changed the day after PEG placement, and this should be repeated every day for the first week. There is no need to change the tube unless it is worn off or obstructed. The PEG tube should not be removed for at least six weeks once it is placed. This period is necessary for the maturation of the tract and to prevent the gastric content to contaminate the peritoneal cavity [13].

Endoscopists with enough experience in PEG placement have achieved a 99% (76–100%) success rate with a low mortality and a low prevalence of complications. The mortality rate related to the intervention is less than 1%. Complications related to PEG tube placement can be classified into short- and long-term complications. One to four percent of patients undergoing this intervention develop major complications, and 13–40% develop minor complications (Table 4.1) [17, 18].

Peristomal infections are seen in 5–25% of the patients [17]. Draining local infections at the PEG site are generally secondary to the foreign body reaction and are the most frequently seen complications. These can be treated with local wound care and antibiotics.

The benefit of using antibiotic prophylaxis before the procedure is debatable. Some studies, however, have demonstrated a decrease in wound infections and systemic infection rate after antibiotic use [19]. The single-dose administration of a wide spectrum antibiotic 30–45 min before tube placement has decreased

Table 4.1 PEG complications

Minor complications	Major complications
Tube obstruction	Pulmonary aspiration
Damaging of the tube	Bleeding
Peristomal infection	Peritonitis
Buried bumper	Perforation
	Severe peristomal infection or necrotizing fasciitis
	Gastro-colo-cutaneous fistula

peristomal wound infection rate from 29 to 7%. There is strong evidence showing that antibiotic prophylaxis in high-risk patients (i.e., impaired immune function, patients receiving chemotherapy, patients with leucopenia, severe malnutrition, or diabetes) decreases the risk of wound infections.

Buried bumper syndrome can occur in tubes with an internal bumper as early as 3 weeks after PEG tube insertion. Excessive traction to the tube should be avoided since it may result in buried bumper syndrome [20].

If the tube is unintentionally pulled out during the first week, there must not be an attempt to place it back blindly. In this case, the treatment of choice should be nasogastric decompression, treatment with antibiotics and follow-up. A new PEG tube can be placed 6–10 days later if there is no sign of peritonitis [17].

Experts have suggested using a "cut and push" technique for removal of PEGs in adults. The patient can eat normally only a few hours after the removal [21].

Button gastrostomy: Button gastrostomy is a skin-level device, which was developed to reduce the psychological discomfort caused by the PEG tube and improve the quality of life [22]. This tube, which leaves only a button head at the skin level, enabled a high level of patient compliance, especially in children and the elderly.

To place the button, first, the stoma tract must be established. Therefore, a PEG tube must be introduced initially and then replaced with the button system after 4 weeks.

4.2.3.4 Jejunostomy

PEG Jejunostomy (PEG-J)

In the presence of gastric outlet stenosis, pulmonary aspiration risk, or critical illness, PEG may be extended into a PEG-J system. The easiest technique for performing this procedure is to introduce a postpyloric tube over a guidewire or by an endoscope. The tip of the tube should be placed distally to the Treitz ligament [18].

PEG-J enables gastric decompression and transpyloric feeding at the same time. Because of the smaller diameter of the jejunal feeding tubes, they have a higher prevalence of occlusion and fracture.

Direct Percutaneous Endoscopic Jejunostomy (D-PEJ)

D-PEJ can be performed after gastrectomy and Billroth II reconstruction or in patients with recurrent dislocation of the PEG-J tube [23].

An endoscope or a colonoscope is placed into the small bowel after the pull technique. When diaphanoscopy is seen, the abdominal wall and the jejunal wall are

punctured using a 21-gauge needle into the jejunal lumen. The grasping of the needle tip using a biopsy forceps helps the stabilization of this segment of the jejunum. Using this needle as a guide, a larger trocar is introduced to enable the placement of the thread, and a feeding tube can be placed using the pull technique.

4.2.3.5 Surgical Gastrostomy-Jejunostomy

If percutaneous endoscopic placement is impossible, surgical techniques can be used for EN [24]. This method is most frequently needed in cases, which a tumor obstruction makes it impossible to perform an endoscopy. However, most of the surgical gastrostomies and jejunostomies are performed during major surgical operations for trauma or cancers of the upper GI tract.

Stamm and Witzel techniques are the most frequently performed methods. When compared with PEG, surgical gastrostomy has a higher rate of morbidity and mortality and, however, also a higher rate of successful placement [14]. Aspiration and wound infections are the main complications. What is more, the time for recovery in surgical patients is longer and more expensive.

Advantages of surgical gastrostomy over endoscopic techniques include the possibility of placing larger diameter tubes, easier prevention of perforation and laceration of other intraabdominal organs, and safe fixation of the stomach to the abdominal wall, which reduces the risk of intraabdominal leakage.

Needle catheter jejunostomy: During major operations of the upper GI tract (i.e., esophagectomy, gastrectomy, Whipple procedure), the preferred route of EN is needle catheter jejunostomy (NCJ) [24, 25].

The placement of NCJ must be done right before the closure of the abdominal wall. Initially, a polyurethane catheter is inserted into the abdominal cavity through the abdominal wall using a needle to puncture the wall of the abdomen. The preferred location of entry is the middle one-third of the line bridging the umbilicus to the left costal arch. Then, a 4–6 cm long submucosal tunnel is formed on the antimesenteric side of the jejunal segment using a guide catheter. After that, the catheter is inserted through the needle and secured to the intestine using a purse string suture. The small intestine is then sutured to the inner abdominal wall.

4.2.4 Feeding by the Enteral Tube

After choosing the route of nutrition and the nutrition product, the method of delivering this to the patient should be decided. A multidisciplinary approach considering every problem, like concomitant treatments and nursing schedules, should be undertaken. The patient and caregivers should be involved in these decisions, especially in the case of a long-term nutrition plan [4, 26].

The principles of enteral tube feeding are:

- All the nutritional requirements of the patient should be given.
- Periodic flushing of the tube both avoids tube obstruction and helps the patient to fulfill his/her need for water.

- If the tube has been placed in the small bowel, the delivery of the nutrients must be slow and controlled.
- The risk of infection should be reduced to the minimum by careful handling of the tube and minimum possible number of connections.
- The delivery of medications should only be done according to pharmaceutical recommendations.

Applications:

- *Continuous*: The feeding solution is delivered by an infusion pump in a continuous manner.
- *Bolus*: Bolus feeding closely resembles normal eating and drinking. The planned amount is slowly given by an injector through a decided interval of time (generally as boluses of 200–250 mL, 6–8 times a day). This method is applied when the patient is mobile or prefers not to be connected to the infusion pump. Bolus feeding can be used when the tip of the tube is located in the stomach. It may not be tolerated by diabetic patients, by patients who have impaired gastric emptying due to neurologic problems or in the postoperative period.
- *Intermittent*: The feeding is applied intermittently throughout the day. This method facilitates the mobility of the patient.
- *Overnight*: To allow the patient more freedom during the day, the feeding is administered through the night. This is a useful technique in patients whose oral feeding needs to be supported; however, the possible consequences of high volume fluid delivery must be kept in mind.

4.2.5 Enteral Nutrition Products

The ready to use nutrition products specifically produced by the nutrition industry are called "dietary foods for special medical purposes." They are always marketed in sterile packages as either liquids with varying osmolarities or powders. These products are usually categorized into one of the following:

- Polymeric formulas
- Oligomeric and monomeric diets
- Disease-specific formulas
- Modular diets

Polymeric formulas: These formulas, which are the "standard" approach in EN, are nutritionally complete and are generally composed of intact nutrition elements. Therefore, their use requires a functional GI system. They are suitable to be used both by hospitalized patients and in an outpatient setting. Standard polymeric formulas involve both macro- and micronutrients in daily reference values. They are also suitable mostly for use in cases of specific organ dysfunction and severe illness [7]. In their composition, they involve whole proteins as a source of

nitrogen; carbohydrates in the form of oligosaccharides, maltodextrin, or starch; vegetable oils; minerals; vitamins; and trace elements. Polymeric formulas do not contain lactose and are mostly lactose-free. Since the nutrients are not hydrolyzed, the osmolarity is close to physiologic values (300 mOsm/l). Caloric density varies in a range from 0.5 to 2 kcal/mL allowing adjustment to individual requirements.

Oligomeric and monomeric diets: Oligomeric and monomeric enteral formulas, which are frequently misnamed as "elemental diets," involve macronutrients enzymatically hydrolyzed in varying degrees. Thus, they need minimal digestion, and they are almost totally absorbed. In addition to being lactose and gluten-free, both types of formulas have low residues. Their osmolarities are high and they therefore may cause diarrhea.

Disease-specific formulas: There are specifically designed nutritional products to meet some disease-specific and organ-specific nutritional needs. These include specific formulas for hepatic diseases, renal diseases, diabetes, pulmonary insufficiency, heart failure, GI dysfunction, and conditions of metabolic stress such as trauma or sepsis. These formulas are more costly compared with standard EN, and their inappropriate use may lead to complications. There is still not enough evidence regarding the benefit of these products.

Modular diets: A modular formula is an incomplete supplement that contains specific nutrients, usually a single macronutrient (carbohydrate, protein, or fat). Different modules can be combined to result in a nutritionally complete diet. Modular diets can be tailored to an individual's needs but are generally complex to design and may fail to meet all of the patient's nutritional needs.

4.2.6 Complications of Enteral Nutrition

EN is safe, effective, and generally well tolerated in patients with normal GI functions. The complications of EN can generally be classified as gastrointestinal, mechanic, and metabolic. Most of these complications may be avoided, and it is important to know that many result from wrong applications.

4.2.6.1 Gastrointestinal Complications

Nausea and vomiting: 10–20% of the patients receiving EN experience nausea and vomiting [18]. In most of these patients, the primary disease is the primary cause of these symptoms. Although there may be many etiological reasons, nausea and vomiting are most commonly associated with delayed gastric emptying. Also, these symptoms are strongly provoked by antineoplastic agents.

In the presence of nausea and vomiting in a patient who receives EN, the following should be addressed:

- The ruling out of intestinal obstruction
- The assessment of the patient's medications regarding the presence of drugs that trigger nausea and vomiting

- Decreasing the infusion rate or adding prokinetic agents when delayed gastric emptying is suspected
- Initiating a relevant dose of antiemetics/analgesics in patients receiving chemotherapy

Diarrhea: Diarrhea is probably the most frequent complication of EN; its incidence ranges from 5 to 65% depending on the definition. The accepted definitions for diarrhea are liquid or soft stool >200–250 g/day and defecation frequency ≥3 to >5 times/day [18, 27].

The rate of this complication can be reduced by paying attention to the infusion rate adjusted for each patient and anatomic location of administration. EN is mostly not the reason of diarrhea. It was demonstrated that the cause was generally antibiotics or pathogens in the microflora such as *Clostridium difficile.* If the diarrhea is clinically serious, the following should be reviewed [28]:

- The EN prescription of the patient should be reviewed.
- Stool microscopy and culture, as well as *Clostridium difficile* toxin analysis, should be performed to rule out infectious diarrhea.
- The patient's medications should be reviewed for drugs that have the potential to cause diarrhea such as long-term antibiotics, antacids, and prokinetics.

For stubborn diarrhea, consider the following:

- If the administration is intermittent, it may be shifted into continuous infusion.
- Infusion rate can be decreased.
- The product can be switched to a formula that contains soluble fiber.
- The product can be changed with an oligomeric or monomeric diet if malabsorption is suspected.

If diarrhea still persists in spite of these mentioned measures, the dose of EN may be decreased, and EN may be combined with PN. Very few patients require TPN due to diarrhea [29].

Constipation: The causes of constipation are the lack of activity, decreased intestinal motility, decreased intake of water (hypercaloric products), impaction, or inadequate intake of fiber. Decreased intestinal motility and dehydration may result in impaction or abdominal distention. In the presence of constipation, intestinal obstruction must be clearly ruled out. Enough hydration and use of products containing insoluble fibers can overcome constipation [30]. If constipation persists, stool softeners or intestinal stimulants may be required.

4.2.6.2 Mechanic Complications

Aspiration: Pulmonary aspiration is seen in 1–4% of patients, and this may be a serious and life-threatening complication of EN [31]. In patients on mechanical ventilation, silent microaspirations have a higher incidence than apparent aspirations of larger volumes. Most of these patients aspirate in the early period after the

initiation of EN and have a high incidence of developing nosocomial pneumonia [32]. Dyspnea, tachypnea, wheezing, tachycardia, agitation, and cyanosis are the most apparent symptoms. However, in patients receiving EN, fever may be the only symptom of aspiration pneumonia resulting from the aspiration of small amounts of the product.

The risk factors for aspiration are:

- Impaired consciousness
- Impairment of gag reflex
- Neurologic impairment
- Failure of the lower esophageal sphincter
- Supine position
- Utilization of large diameter tubes
- Large amount of gastric residue

Although there are varying opinions regarding the amount of gastric residual volume that poses aspiration risk, its periodic measurements are essential in high-risk patients. The infusion should be decreased or ceased if in consecutive measurements the residual volume is more than 250 mL [4, 32]. Some authors suggest routine use of prokinetics. This issue is contentious, however, and must be weighed against potential adverse effects. The following precautions must be undertaken in order to prevent aspirations:

- The measurement of the gastric residue and adjustment of the infusion rate
- Giving the patient a semi-recumbent (30–45°) position
- Preference of a nasojejunal instead of a nasogastric tube

Tube-related complications: The most common complication (25–35%) during EN is the obstruction of the tube [18]. Most of the tube obstructions are generally associated with coagulation or inefficient flushing of the tube. Kinking of the tube and administration of some drugs that have a potential to precipitate are other causes of tube obstruction. The chances of tube obstruction are closely related to the width of the tube, quality of nursing, and the duration since the tube has been placed. Restoring the patency of the obstructed tube is generally preferred to the replacement of the device. Methods that can be used to dislodge the obstruction may vary from applying gentle pressure using hot water and aspirating to use of pancreatic enzymes and sodium bicarbonate dissolved in water [33]. The use of acidic solutions is usually less effective.

The incorrect positioning of the tube may result in bleeding or tracheal, parenchymal, or GI tract perforations [18]. The malposition of the tube can be diagnosed by proper examination and must be corrected immediately. Attempting to verify the location of the tube by auscultation of the insufflated air is not sufficient. This method may mislead even an experienced member of the staff. If the

pH value of the aspirated content is lower than 5, it may be concluded that the tube is inside the stomach. In the case of persisting uncertainty, radiologic evaluation is recommended.

The feeding tube may cause necrosis, ulcerations, and abscesses on the nasopharyngeal, esophageal, gastric, and duodenal spots of pressure [18]. It may also induce pulmonary complications, necrotizing fasciitis, fistula, and wound infections. Using modern, small-diameter tubes, which are made of polyurethane or silicone, can decrease the incidence of these complications. These fine-bore tubes (7–8 Fr/Ch) are soft, flexible, and suitable for long-term use.

4.2.6.3 Metabolic Complications

In spite of having a lower incidence and being less severe, metabolic complications of EN are very similar to PN. These problems, details of which are mentioned in Table 4.2, can be reduced or averted by careful monitoring [18].

Refeeding syndrome: Refeeding of patients with severe malnutrition or after a long duration of starvation may result in "refeeding syndrome" [34]. Potentially life threatening, this metabolic complication may be induced both by EN and PN. It develops as a result of sudden and rapid feeding after long-term fasting. It is associated with water and salt retention and potassium, magnesium, and phosphate deficiency. Neurologic and cardiac symptoms are the leading symptoms. Therefore, it is crucial to have a high level of anticipation to diagnose the syndrome. Some recommendations for prevention of the refeeding syndrome are:

- Be aware of patients at risk.
- Provide adequate assessment, care plans, and follow-up.
- Monitor cardiovascular functions and fluid balance in patients at risk.
- NS should be instituted carefully and gradually increased within 1–2 weeks.

Table 4.2 Metabolic complications of enteral nutrition

Complication	Reason	Intervention
Hyperglycemia	High caloric intake Insufficient insulin	Reassess caloric intake Adjust the dose of insulin
Dehydration	Diarrhea Inadequate fluid intake	Assess the reason of diarrhea Increase total amount of water
Hyponatremia	Overhydration	Consider altering the formula Restrict administration of fluids
Hypernatremia	Inadequate fluid intake	Increase total amount of water
Hypokalemia	Diarrhea Refeeding syndrome	Assess the reason of diarrhea Replace potassium deficit
Hyperkalemia	Renal insufficiency	Consider altering the formula
Hypophosphatemia	Refeeding syndrome	Increase the intake of phosphate Decrease the energy load
Hyperphosphatemia	Renal insufficiency	Consider altering the formula

4.3 Parenteral Nutrition

PN is the administration of all or some of the nutrients by the intravenous route when EN is insufficient or impossible due to the anatomic or functional impairment of the GI tract in long-lasting diseases with a severe catabolic phase [35]. PN might either be introduced via catheters placed into peripheral veins as an adjunct to EN or via catheters inserted into central veins to deliver all of the essential nutrients parenterally (i.e., TPN). In the short-term peripheral parenteral nutrition (PPN), which is used for supporting EN, it is possible to administer low-calorie and low-protein formulas via the peripheral veins. However, the infusion of TPN solutions with osmolarities higher than 800–1000 mOsm/L requires a central venous route.

4.3.1 Routes of Parenteral Nutrition

4.3.1.1 Peripheral Parenteral Nutrition

Since hyperosmolarity may cause thrombophlebitis, PN lasting for more than seven days is usually administered via a central vein. However, on some special occasions and in cases that require a short-term PN, nutritional solutions may be provided via the peripheral route.

PPN was first described by Brunschwig et al. in 1945 when they first fed a patient with multiple fistulas using protein hydrolysate and 10% glucose solution for several weeks. PPN was acknowledged as hypocaloric nutrition when hyperalimentation was introduced by Dudrick in 1968 [36].

The term "peripheral vein" defines superficial veins, especially of the upper extremities. Lower extremity vessels should not be used for PN, especially in adult patients, since this increases the risk of thrombophlebitis and causes the immobilization of the patient [37].

The decision to administer PN via a peripheral vein depends on the osmolarity and pH of the solution, the rate of infusion, the material of the catheter (polyurethane and silicone are preferred to teflon), and the diameter of the catheter (lower diameters are preferable) [37, 38].

Hypertonic solutions may irritate the veins, their infusions resulting in pain, phlebitis, and thrombosis. Adding lipid emulsions and increasing the volume decreases osmolarity. What is more, lipid emulsions possess a protective effect for the vascular endothelium. Therefore, meeting a substantial proportion of the energy requirement is necessary for appropriate peripheral feeding of the patient.

Indications for PPN

- Short-term PN (less than 7 days)
- Cases in which central venous catheterization is contraindicated or impossible
- Catheter sepsis or bacteremia

The advantages of PPN are easy venous access that does not necessitate the presence of experienced medical staff, the avoiding of short- and long-term morbidities

such as technical complications associated with central venous catheterization and septic complications related to long-term catheterization, and early recognition of phlebitis at the insertion site.

Catheter Placement

The intervention ideally begins with the choosing of a suitable peripheral vein on the forearm. Either a tourniquet or a sphygmomanometer cuff is applied, the selected site is shaved, and the skin is sterilized. The catheter is inserted, the return of blood is observed, and the tourniquet is removed. After flushing with 0.9% saline, the catheter is connected to the intravenous tubing. The insertion site of the catheter is then covered by sterile gauze or dressing.

Peripheral catheters are advised to be kept in place as long as possible until the early signs of phlebitis are recognized. Thus, the catheter can be used for four days without extra measures. The cannula should be treated like a central catheter, and always aseptic techniques should be applied. Training of the personnel and strict protocols for the care of the catheter are crucial for avoiding high rates of morbidity and infection and the loss of peripheric veins [38].

Peripheral Parenteral Nutrition Solutions

In the beginning, PPN was delivered as amino acids, 10–20% glucose, and 10–20% lipid emulsions in separate bottles and with the addition of necessary additives. These solutions were administered by separate infusion sets connected by Y connectors or three-way stopcocks. The development of All in One (AIO) bags enabled PPN administration to become much easier and to be commonly practiced in most of the hospitals. In hospitals that do not possess compounding machines, ready to use three-chamber bags specifically designed for PPN can be easily used for short-term PN.

Complications

Phlebitis is the most common complication (3–30%) of PPN. On some occasions, phlebitis may result in serious consequences such as local infections, tissue necrosis, bacteremia, and even sepsis [39]. The addition of heparin (1000 IU/L) and/or cortisone (5–10 mg/L) may reduce the venous endothelial reaction.

4.3.1.2 Central Parenteral Nutrition

The infusion of solutions with a high concentration and low volume necessitates the administration of PN via a central vein. The cannula is usually placed into the superior vena cava, which has a large diameter and a high flow rate. Inferior vena cava may be used when this is not possible.

Central Venous Catheters

Modern central venous catheters (CVC) are made of polyurethane or silicone. Some catheters are coated with antibiotics to prevent colonization and reduce the risk of catheter-related blood stream infections (CRBSI) that result from bacterial migration along the outer surface of the catheter. The use of these catheters is encouraged in the case of increased risk of CRBSI [40].

CVCs can be classified into subgroups according to [37, 41]:

- Number of lumens in the catheter: single, double, or triple
- Method of insertion: percutaneous or cut down
- Duration of PN: short term or long term
- Tunneled or non-tunneled
- The location of the end of the catheter outside the venous lumen: subcutaneously implanted or catheter with an external hub

The ideal access to superior vena cava for PN is via a catheter inserted into the subclavian or internal jugular vein. The subclavian vein should be the route of choice whenever possible, since the management of subclavian catheters is much easier and the infection rates are lower. The catheterization of the internal jugular vein causes an increased risk of infection because of the difficulty of securing the device and applying a sterile dressing to the entry site of the catheter on the neck. Therefore, when the internal jugular vein is going to be used for PN for a long term, it is appropriate to place the exit site of the catheter to the chest wall by tunneling. Catheter insertion may also be done via the external jugular vein. However, this is often a difficult way to advance the catheter into the subclavian vein or superior vena cava.

Recently, newly developed small-diameter, peripherally inserted CVCs have been in use as low-risk, cost-effective devices. These are inserted antecubitally, and the tip is advanced into the superior vena cava. The greatest advantage of central vein catheterization via the peripheral route is the prevention of complications associated with the direct catheterization of subclavian or internal jugular vein and the simplicity of insertion [37].

The method of central vein catheterization by subcutaneous tunneling was first developed for preventing septic complications by reducing bacterial advancement on the catheter between the insertion site on the skin and the site of entry into the venous lumen. Such an effect, however, has not been verified in prospective studies. This is due to the fact that mostly the bacterial entry site is not the point of exit on the skin, but the outer tip of the catheter. The most important advantages of the tunneled catheters are fixation for long-term use and easier care of the exit site.

Catheter Placement

Sometimes, previously placed catheters, such as the ones that have been placed during surgery, may be used for PN in short term. However, it must be kept in mind that these catheters may not always be placed under ideal conditions, which may result in a higher risk of contamination and sepsis.

It must be remembered that the insertion of a CVC for PN is an elective intervention and must be done under ideal conditions. There are some general principles for central venous catheterization [37, 42, 43].

- Insertion of the CVC is a surgical procedure and must be done with an aseptic technique.
- The intervention should be explained to the patient and a good level of cooperation should be achieved.

- A subclavicular approach should be preferred.
- The point of insertion should be marked after infiltration with a local anesthetic.
- Aspiration of the venous blood helps ensuring that the punctured vessel is the vein.
- The needle should not be dislocated during the placement of the catheter.
- Locked infusion sets should be used for minimizing the risk of infection.
- The catheter should be fixed to the skin by suturing after placement to prevent breaking and kinking.
- The site of intervention should be cleaned, disinfected with povidone-iodine (or chlorhexidine), and dressed with a sterile drape.
- A chest X-ray should be performed immediately.
- A guidewire should not be used when changing the catheter since this can increase the risk of infection.

Since more than half of the cases of major venous thrombosis are asymptomatic, Doppler ultrasound evaluation is advisable, particularly in patients with a history of intervention or thrombophlebitis [44].

Always tunneled catheters should be selected for long-term use. It is important to examine the patient before the intervention both at standing and sitting positions and to select the catheter insertion site so that it can be easily seen and reached by the patient, by both hands, especially in individuals who will receive PN at home.

Regarding the placement of totally implanted catheters, the only difference is the necessity to create a pouch for the port. Generally, the port is placed 3–4 cm lateral to the sternal edge on the chest wall, and it is fixed.

Catheter Care

The quality of catheter care is the defining factor in its serving duration. The maintenance of external CVCs and totally implanted catheters must be undertaken very carefully to avoid infections and obstructions. This must preferably be done according to written protocols and type of the catheter being used [37, 45, 46].

Selection of the optimal insertion point, hand hygiene, skin antisepsis, daily examination of the insertion site, and assessment of the ongoing necessity of the catheter are the most important components of catheter care. The exit site of the catheter should be dressed with air permeable, waterproof, self-adhesive materials. If gauze pads are used, the dressing should be changed once in every two days or when soiled. Self-adhesive dressings should be changed twice a week or when moistened. Sterile techniques must be used during all the manipulations [47, 48].

Following each use, the cannula must be flushed with 0.9% saline. If the period between the infusions is less than six hours or the CVC has a pressure-sensitive valve, the use of heparin is unnecessary. For longer intervals between infusions, the catheter should be flushed using 0.9% saline, filled with 100–500 IU/mL heparin, and closed. No excessive force should ever be used for flushing the catheter [37, 48, 49].

The CVC should be click-clamped whenever infusion sets are connected and disconnected and whenever the lumen has contact with the air, to prevent air embolism or thrombosis that may form during the blood reflow into the catheter [37, 48].

The duration that the infusion sets, extension tubing, and caps can be used differs between 1 to 7 days according to the CVC or the equipment type or local protocols. The safest approach is carrying out the producer's instructions [37, 48].

Although in-line filters may be used in order to prevent microbial or particular contamination, there are no strong data confirming the benefit of these filters in long-term PN.

Critical components of CVC aftercare are avoiding the unnecessary utilization of extension sets and stopcocks. Also the catheter should only be used for PN, rules should strictly be followed when connecting and disconnecting infusion sets, and the catheter should be closed when it is not in use.

4.3.2 Systems for the Administration of Parenteral Nutrition

4.3.2.1 Multiple Bottle Systems

In the beginning, multiple bottle system was used for the administration of PN [50]. In this system, amino acids, glucose, and fat emulsions were delivered from separate bottles. The minerals and vitamins were added to these bottles separately. The staff had to change six to eight bottles every day, adjust separate flow rates, and add many supplements. The only advantage of this practice was the ease in administering specific PN treatment for each patient. It is argued that compatibility problems may be overcome by using this system. However, the synchronous infusion of different nutrients without testing may cause an increased risk of physicochemical incompatibilities. What is more, mistakes in preparation and infusion of the solutions increase the risk of hyperglycemia and electrolyte disorders.

4.3.2.2 All in One Systems

In AIO system, every component of PN is contained in a single bag. Cost-effectiveness, better nutritional balance, ease of administration, lower risk of contamination, and reduced rate of metabolic complications are the advantages of the AIO system. What is more, the addition of lipid emulsions decreases osmolarity and reduces venous irritation, enabling these formulations to be infused via peripheral veins [50, 51]. Thanks to the more simple nature of the AIO system, the administration of home PN has become easier, more effective, and safer.

One disadvantage of the AIO system is the impossibility of removing any of the components of PN that is already present in the container. Also, AIO necessitates the presence of trained staff, special equipment, and clean room, which require extra expenses to ensure quality control and safety standards.

Today, these systems are preferred extensively in many countries.

Preparing the AIO Mixture ("Compounding")

PN is usually administered from a single personalized admixture that is prepared using sterile components in a special unit or from a single, ready to use, commercially available bag.

Mixtures, specifically prepared for individuals, are transferred into disposable plastic bags under aseptic conditions and presented as ready to infuse solutions in single containers as large volume, pharmaceutical formulations. It is possible to meet personal nutritional needs of individual patients using customized PN. This becomes critical in patients on long-term PN and cases with rapidly changing nutritional needs.

The preparation of AIO bags is usually performed in central intravenous admixture services present in hospital pharmacies. In these units, there are trained and experienced staff members working in clean rooms with laminar airflow benches. These staff members strictly follow regulations regarding the preparation of PN admixtures under aseptic conditions. The produced AIO admixtures need to be consumed immediately. They have a low stability and therefore produced either daily or weekly. However, they can be stored for a short time (7–10 days) at 2–8 °C [52, 53].

Manufactured Mixtures

The evolution of PN compounding technologies and especially advances in the manufacturing of plastic bags has led to the mass production of standard PN bags with each PN component contained in separate chambers.

In these multiple chamber containers, the components can simply be mixed by squeezing or shaking immediately before utilization. These systems enable standard formulations to be easily stored at room temperature before mixing. Still, they require the addition of trace elements, vitamins, and occasionally extra electrolytes. Industrially manufactured bags present a solution for the problems regarding the high risk of contamination in hospitals without aseptic production facilities and in emergency situations. However, still, the addition of all of the supplements must be done by experienced staff according to written protocols, which include the properties of every product and the sequence of addition.

It should also not be forgotten that these ready to use bags do not meet the specific requirements of patients with rapidly changing metabolic needs.

4.3.3 The Issue of Stability and Compatibility in Parenteral Nutrition

The meaning of stability is that the components do not degrade in the PN admixture, whereas compatibility means that the ingredients do not interact with each other in a given time. In some occasions, the addition of some nutrition components such as specific amino acids, polyunsaturated fatty acids, and micronutrients to the admixture may be necessary. All of these components, addition sequence of the additives, and the means of delivery impact the stability of the admixture. Therefore, simply mixing all of these ingredients may not be safe. These ingredients must be added in line with the instructions of the producers, results of specific analyses, and the data in the literature. AIO admixture must be prepared according to the guidelines regarding the macro- and micronutrients and their quantities, under strictly

controlled conditions and pharmaceutical supervision. The direct inspection and controlling of the precipitation, changes in color, gas formation, aggregation, creaming, and coalescence of the ingredients before or during the infusion are very important for maintaining a safe, effective, and high-quality PN therapy [53–55].

4.3.4 Drugs and Parenteral Nutrition

In patients on TPN, it is a necessity to deliver also other medications via the parenteral route. Adding these medications to the PN admixture to avoid additional intravenous interventions may simplify complicated drug therapies. It may decrease the volume overload in a patient with fluid restriction. However, there is a wide variety of PN regimens and drug doses, and there is limited data regarding the potential interactions. Also, the variety of PN ingredients and differences in drug formulations such as pH make it difficult to set up general rules on interactions between one drug and manufacturer and another. Although there are some commonly added medications like ranitidine and insulin, PN admixtures are not suitable for adding medications due to multiple and complex potential interactions. If a drug has to be added to the admixture, then the effectiveness and stability must be documented [55, 56].

The most common method is infusing the drugs using a Y-connector or a three-way stopcock into the same catheter. Medications without certain information of compatibility must not be administered using the same line. Even in the case of proven compatibility, certain rules must be followed when adding the dissolved medication to the PN admixture to prevent contamination and disastrous errors related to medications.

It must be remembered that adding drugs into PN admixtures results in the formation of a new formulation with altered characteristics, which may change the bioavailability of both the drug and PN.

Suggestions for drug treatment in patients receiving PN [55, 56]:

- Multiple lumen catheters must be used for separate drug treatments in patients receiving short-term PN.
- Intermittent infusions after sufficient flushing of the line must be preferred instead of addition of drugs to PN.
- When the addition of a drug is necessary, the pharmacist member of the nutrition team should be consulted.
- It is imperative to know the physicochemical properties of the active component of the drug to predict compatibility.
- The admixing must be done just before to infusion, with maximum dilution and inspecting the formulation for changes.
- Admixing should never be considered under the following conditions:
  - In the presence of solubilizers that dissolve lipophilic drugs
  - In the presence of drugs that have chemical instability
  - In the presence of drugs that possess narrow therapeutic indices or ranges
  - In the presence of drugs that have short elimination half-lives

4.3.5 Planning Parenteral Nutrition

The PN composition and administration of the specific nutrients should be planned meticulously according to the requirements and metabolic condition of the patient.

Nutrients delivered by the intravenous route rapidly become an important component of the internal setting of the patient and are metabolized, assimilated, or excreted. Patients fed by the intravenous route cannot control their internal setting by intestinal absorption.

Patients on PN may have previously existing micronutrient deficiencies. Restoring the patient into the anabolic state by PN may make apparent or aggravate these deficiencies, which may result in "refeeding syndrome."

Some patients who require PN may have various organ dysfunctions, sepsis, cancer, or trauma. The metabolism of the nutrients in such patients may be much different from that of healthy individuals. Also, patients may need widely varying amounts of PN and varying ratios of PN ingredients and tolerate varying amounts depending on the activity of the patient, the phase of the disease, accompanying organ dysfunctions, and metabolic impairments.

TPN should include all the essential nutrients in sufficient amounts and ratios. Under some circumstances (metabolic disorders due to diseases or organ dysfunctions, previously existing or accompanying deficiencies, conditions that require pharmaconutrition or adjustment of the amount or composition of the nutrients), preparation of patient-specific nutritional formulations may be required.

There is no exact solution to avoid metabolic disorders or the development of refeeding syndrome, and no precise method to measure the needs and the metabolic capacity of the patient. Therefore, the appropriate approach is to start PN with a dose less than the calculated or predicted energy need of the patient and to increase the delivered amount of nutrients gradually according to the metabolic response of the patient. By this cautious approach, it is possible to avoid refeeding syndrome in most of the patients.

In patients with apparent starvation accompanying critical disease or other severe disorders, one must avoid rapidly correcting malnutrition or feeding disorders. Although intense NS via the parenteral route seems attractive in these patients, it may result in unwanted consequences. Even delivering the half or two-thirds of the calculated needs will be much over the amount of daily food intake the patient is accustomed to. The patient with a reduced metabolic capacity secondary to starvation requires time to adapt to the increased amount of delivered nutrients. A full dose of calculated nutrient needs may be safely administered only after this duration of time.

When starting the administration of PN, a careful approach and close monitoring of the patient are the safest way to achieve nutritional rehabilitation and to support the normal metabolism with minimum complications and unwanted consequences.

4.3.6 Complications of Parenteral Nutrition

Current developments in administration methods and better comprehension of the etiology of complications due to practices in implementation led to a decrease in the risks of TPN administration. However, in spite of the presence of experienced

staff and well-developed treatment protocols, complications may still be seen. Complications of TPN may be categorized in three groups: technical, septic, and metabolic.

4.3.6.1 Technical Complications

These can be divided into two groups: early complications related to the placement of the CVC and late complications related to the placement of inappropriate catheters, the exit site, and catheter care.

Early complications are:

- Complications related to failure of proper insertion or positioning
- Bleeding
- Arterial puncture or laceration
- Air embolism
- Airway injury
- Arrhythmias
- Hemothorax
- Pneumothorax
- Cardiac tamponade
- Injury of the thoracic duct and chylothorax

The insertion and care of the CVCs by experienced staff and following protocols for catheter care will reduce the risk of complications. Also, proper hydration, correction of coagulopathy, inspection of the venous anatomy using Doppler ultrasound, correct positioning of the patient, decreasing PEEP, using small-gauge needles to define the location of the vein, and using the Seldinger technique are helpful in decreasing the complication rate [37].

Urokinase, sodium hydroxide, hydrochloric acid, or 70% ethanol may be used for reopening obstructed catheters. Rarely, catheters may be broken in their intravascular portion and be embolized. In such a case, the embolized catheter fragment may have to be removed surgically or radiologically [57].

Central vein thrombosis is a frequent complication if evaluated using ultrasound. However, its clinical symptoms are unusual. It is a hazardous complication that may cause a high morbidity and a mortality rate of roughly 25% in serious cases. Thrombosis formation can be avoided by careful selection of the site of insertion and the location of the tip of the catheter, careful placement, the use of infusion and flushing techniques, and subcutaneous injection of heparin immediately after the placement. Antithrombotic medication should regularly be administered to patients with a high thrombosis risk. In cases of thrombosis, removing of the catheter may not always be necessary if treatment with the plasminogen activator, urokinase, or streptokinase is successful [44, 49, 58].

4.3.6.2 Septic Complications

CRBSI continues to be the most dangerous complication of central venous catheterization [47, 59]. Practically, these infections can be defined as:

- Colonization: The growth of pathogen microorganisms in samples taken from the hub, blood drawn from the catheter, the removed catheter, or by intraluminal brushing without findings of local or general infection.
- Presence of infection on the catheter exit site**,** in the tunnel, or the pouch of the totally implanted catheter. The catheter or the port should be removed and suitable local and systemic therapy administered.
- Presence of catheter-related bacteremia and sepsis. This is the most serious complication of CVC's and may happen anytime (2–15%).

Catheter-related infections are most commonly related to Gram-positive microorganisms such as *Staphylococcus epidermidis* and *Staphylococcus aureus* [60, 61].

To avoid catheter-related infections, every precaution should be taken, every connection should be made under aseptic conditions, and dressings should be changed according to the protocols prepared and supervised by the nutrition committee [37, 61, 62]. It is usually not recommended to use prophylactic antibiotics and intraluminal filters. In patients with short-term catheterization having a high risk of CVC-related infections in spite of other precautions, utilization of antimicrobial coated-catheters should be kept in mind.

4.3.6.3 Metabolic Complications

Metabolic complications may arise from inadequate or excess administration or inappropriate composition of PN. These complications may be classified into states of deficiency, acute, and chronic complications [63].

When administration of macro- and micronutrients is insufficient or unbalanced, deficiencies may occur in the short term or the long term. It is usually difficult to define the precise nutritional needs of the patient. During long-term PN, the deficiency of one of the essential nutrients may result in serious consequences. Although rare, the insufficiency of essential fatty acids, zinc, copper, chromium and water-soluble vitamins are the most common deficiencies.

The acute metabolic complications may result in life-threatening functional disorders (Table 4.3). Among acute deficiencies, hypoglycemia, hypophosphatemia, hypokalemia, and thiamin deficiency deserve extra attention since they are the basic components of the refeeding syndrome.

Table 4.3 Acute metabolic complications of parenteral nutrition

Complication	Prevention and treatment
Water and electrolyte disorders	Daily weight and biochemical monitoring
Hyper or hypoglycemia	Blood glucose monitoring and, if necessary, insulin infusion
Hypercalciuria	Avoid vitamin D toxicity
Hypertriglyceridemia	Monitoring of serum lipid level and lower lipid emulsion dosage, alter lipid formulation
Liver steatosis	Decrease fat and carbohydrate intake, use cyclical PN

Excessive feeding causes a metabolic burden, which may result in organ dysfunction. The only way of avoiding this complication is the careful evaluation of the patient and to gradually increase the NS treatment under close monitoring.

Acute complications may be prevented by blood and urinary evaluations. The frequency of biochemical monitoring should be decided according to the phase of the PN and the clinical and nutritional condition of the patient. Before the initiation of PN, detailed blood and urinary evaluation of the patient must be performed, the electrolyte disorders must be corrected, basic data should be collected for later comparisons, and hepatic or renal disorders must be determined. In the early stage (3–5 days) of PN in which the administration of macronutrients is gradually increased, blood glucose, urea, sodium, potassium, magnesium, phosphate, and calcium levels should be checked daily. In patients with severe disease, arterial blood gasses should be added to the daily measurements. When the targeted values that may be tolerated are reached, the entire laboratory measurements should be repeated every two to three days.

Long-term complications of PN are cholestatic liver disease, hepatosteatosis, and bone demineralization.

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Nutritional Support in the Neurointensive Care Unit

5

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5.1 Introduction

The significance of nutrition in the critical care setting cannot be underestimated. Critical illness is known to be associated with a catabolic state which can be associated with complications such as secondary neurologic injury, increased rates of infections, multiple organ dysfunction, prolonged intubation, further morbidity, and worsened mortality. Additionally, in critical neurologic diseases, there is often associated dysphagia, prolonged partial or complete immobilization, and other metabolic pathways that need to be considered. Therefore, nutrition is not only for support of metabolic processes but also for therapy to attenuate catabolic state, oxidative cellular injury, and immune responses.

Nutritional requirements are dependent on many factors, including a patient's baseline metabolic status, severity and temporal progression of illness, use of mechanical ventilation, and use of sedatives. Various approaches have been established to estimate nutritional requirements. The appropriate doses of nutrition should be administered early in course, once the patient is hemodynamically stable. Improper administration leads to overfeeding, underfeeding, or poor glycemic control leading to worse outcomes.

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5.2 Metabolic Pathophysiology in Acute Neurologic Injury

There is growing evidence to suggest that neurologic injury induces disruptions in homeostatic mechanisms by activating inflammatory responses, sympathetic nervous system, and endocrine pathways. It has been described that during brain ischemia and after traumatic brain injury (TBI), intrinsic inflammatory mechanisms mediated by leukocytes release cytokines and chemokines and are collectively considered as the neuroinflammatory cascade. Genetic studies have shown that inflammatory genes are upregulated in the acute phase after stroke and TBI. Tumor necrosis factor-α (TNF-α); interleukins 1, 5, 6, and 8; and other cytokines are responsible for alterations in endothelial cells, vessels, and neurons and modulation of systemic inflammation. TNF-α has an important role in stroke-related neuronal damage, suggesting that it serves in the activation of microglia and astrocytes, glutamatergic transmission, synaptic plasticity, and blood-brain barrier permeability. Its actions are mediated by increasing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor density on cell surfaces and decreasing the expression of γ-aminobutyric acid (GABA) receptors which are related to direct neurotoxic effects. Damage in TBI is initially due to mechanical factors causing injury to neurons, axons, glia, and blood vessels. Secondary injury occurs by increased glutamate-linked excitotoxic mechanisms, neuronal apoptosis, lipid degradation, oxidative damage, and inflammatory activation. These mechanisms ultimately lead to blood-brain barrier disruption and cerebral edema [1–3].

Additionally, a hormonal response is seen in these injuries via the hypothalamus-pituitary-adrenal axis. Afferent stimuli from an injured site are integrated in the hypothalamus, thereby releasing corticotropin-releasing hormone, which stimulates the anterior pituitary gland and activates sympathetic nerve endings throughout the body. This leads to the secretion of adrenocorticotropic hormone, which activates the adrenal medulla to secrete catecholamines. These sympathetic and adrenocortical responses to injury are correlated with the severity of injury and magnitude of hypermetabolic and stress responses [4]. These processes have specific effects on glucose, protein, lipid, and micronutrient metabolism.

A net negative energy balance has been shown to result in protein catabolism and depletion of amino acids required for cell repair and host defenses. This primarily occurs by the glucose-alanine cycle as a part of gluconeogenesis. In critical illness, vital organs are preferentially maintained during the catabolic state. It has been shown that clinically this manifests as low levels of amino acids such as glutamine [5]. Glutamine is released from muscle and other tissues serving as a stress signal [6]. Mechanistically, it has been shown to regulate the expression of many genes involving metabolism, signal transduction, cell defense, and repair [7].

Altered glucose metabolism is a common abnormality in critically ill patients. Patients often have hyperglycemia primarily as a result of increased sympathetic drive. With increased cortisol, glucagon, and catecholamines, the liver using lactic acid, pyruvic acid, and amino acid substrates produces glucose [4]. Data indicate that blood glucose should be carefully monitored in these patients; however, optimal management practices remain to be clarified [8]. As indicated in a recent

meta-analysis, there is a significant risk of hypoglycemia without a mortality benefit with tight glycemic control [9].

Lipid peroxidation along with free radical formation causes irreversible oxidative damage to enzymes, receptors, and membrane transport systems. The omega-3 fatty acids may mitigate lipid peroxidation by competing with lipoxygenase and cyclooxygenase and reducing the effect of metabolic products of arachidonic acid, which serve as metabolic modulators. This has been shown to improve physiologic profiles in acute respiratory distress syndrome (ARDS) and septic patients [10, 11].

5.3 General Nutrition Considerations in the Neurocritically Ill Patient

5.3.1 Quantifying Nutritional Need

The nutritional assessment of a critically ill patient begins with an evaluation of their nutritional risk and resting energy expenditure (REE). The REE represents the amount of energy in kilocalories spent by the body in resting conditions over 24 h and can be directly measured by indirect calorimetry. The total energy expended in 24 h by a normal, healthy, active adult includes the REE, the amount of physical activity, and the thermal effect of food itself. However, since physical activity and the thermal effect of food are highly variable and difficult to quantify, REE is often the overall predictor of 24-hour energy expenditure [12]. The Harris-Benedict equations, first published in 1918, were the first calculations found to predict REE [13]. Since then, over 200 subsequent equations predicting REE have been developed, all of which have accuracies ranging from 40 to 75% when compared to indirect calorimetry [14].

In intensive care unit (ICU) patients, the prediction of energy expenditure is complicated by body temperature, sepsis, level of sedation and sedatives used, physical therapy, and even the visitation of relatives [15]. While indirect calorimetry remains the gold-standard method of measuring REE, it is cumbersome and rarely found in the clinical setting. Indirect calorimeters can be limited by many factors at the bedside of the ICU patient, such as chest tubes, air leaks, supplemental oxygen sources, positive end-expiratory pressure, anesthesia, and continuous renal replacement therapy [16]. Nonetheless, the case for using indirect calorimetry to measure REE at the bedside has been demonstrated in two randomized, prospective trials that used it to target energy administration and showed improvement in both morbidity and mortality [17, 18]. Three other prospective studies comparing various feeding strategies showed that administering excessive energy correlated with an increase in infection rates and longer ICU stays [19], but targeting lower caloric administration showed no differences in outcome [20, 21]. Thus, targeting the precise nutritional prescription for a patient may have important benefits.

Many neurocritically ill patients have poor volitional intake of nutrition because of their various brain and spinal injuries. The use of a nutritional risk indicator can be used to identify those patients who are most likely to benefit from early enteral

nutrition (EN) therapy. The Nutritional Risk Screening 2002 (NRS-2002) and the Nutritional Risk in the Critically Ill (NUTRIC) scores determine nutritional status while taking disease severity into account and have become widely used to define nutritional risk in randomized controlled trials in the critically ill populations [22, 23]. The NRS-2002 features nutritional status and disease severity subscores, both of which are added to produce a total (please see Chap. 2 for details). Notably, head injury imparts the highest disease severity score, which automatically necessitates nutritional support. The newer NUTRIC score incorporates patient's age, APACHE-II score, SOFA score, comorbidities, days between hospital admission to ICU admission, and the serum biomarker interleukin-6. Speaking to their robustness, these two scores are recommended in the Society for Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) 2016 guidelines [24].

Measuring adequacy of protein provision is important in the critically ill patient and can be quantified by the nitrogen balance. Critical illness is a catabolic process that involves breakdown of proteins into amino acids, increasing overall nitrogen expenditure. If no nutrition were provided in this state, a loss of body mass and circulating proteins would occur. The majority of nitrogen excreted by a patient can be measured via the amount of urea nitrogen excreted in urine in 24 h. An estimate of protein requirements of a critically ill adult can be given at a rate of 1.2–2 g/kg/day (using actual body weight in kg), a figure that may be higher in burn or multitrauma patients. A negative nitrogen balance is influenced by increased inflammatory markers such as C-reactive protein (CRP) and transthyretin and has been associated with a poor outcome at three months after subarachnoid hemorrhage (SAH) and increased risk of hospital acquired infections [25]. In TBI, the rate of excretion of urea nitrogen has been shown to increase four- or fivefold [26], and in the overall critically ill population has been associated with impaired immunity and worse survival [27].

Bedside ultrasonography of muscle mass has been shown to provide an expedient indicator of proper nutritional support [28, 29]. In the two studies that support this claim, lower extremity muscles including the medial gastrocnemius, rectus femoris, and quadriceps have been regularly measured for atrophy. Previous studies have shown that the greatest muscle loss in the critically ill occurs in the first ten days of ICU admission and is accelerated in patients with multi-organ failure, associated with increased inflammatory markers [30]. Thus, ultrasound can be used as a surrogate marker of nutritional adequacy.

5.3.2 Enteral Nutrition

Initiating EN early in the course of the neurocritically ill patient is important in mitigating the catabolic state. The 2016 ASPEN guidelines recommend initiating EN within 24–48 h in patients who cannot maintain volitional intake because it maintains gut structural integrity, which is lost in a time-sensitive manner [24]. The

guideline's authors performed a meta-analysis of 21 randomized control trials comparing early to delayed EN and found that early EN was associated with a significant reduction of mortality and infectious morbidity. These findings echo previous meta-analyses that have shown early EN to associate with reduced mortality, infectious morbidity, length of stay, and pneumonia [31–33].

Though the benefits of early EN continue to be evident in patients receiving stable doses of one or more vasopressors, initiating EN in patients who are hypotensive (mean arterial pressure <50 mm Hg) and in whom vasopressor doses are increasing is not recommended [24]. Catecholaminergic vasopressors, including high-dose dopamine (>5 μg/kg/min), phenylephrine, epinephrine, and norepinephrine, can have varying degrees of splanchnic vasoconstriction and decreased gastric motility [34]. For patients receiving EN while on vasopressors, vigilance must be maintained for abdominal distention, nausea, vomiting, or rising gastric residual volumes as signs of intolerance.

5.3.3 Parenteral Nutrition

EN should be used over parenteral nutrition (PN) whenever possible as it promotes the normalization of gut flora growth, motility, and normal balance of nutrient uptake. However, in certain situations, such as bowel discontinuity after surgical procedures, PN should be used. PN should also be used for patients in whom EN is unable to supply at least 60% of energy and protein requirements [24]. The timing of when to start PN differs depending on baseline nutrition status. In patients who are at low nutritional risk (NRS-2002 ≤3 or NUTRIC ≤5), PN should be withheld seven days after ICU admission and started only if EN remains unfeasible. A subset of patients in the EPaNiC study (Early versus late Parenteral Nutrition in Critically Ill adults) in whom PN was started on day three had worse infectious morbidity and survival to discharge than those who started PN on day 8 [19]. However, in patients who are at high nutritional risk (NRS-2002 ≥5 or NUTRIC ≥6), PN should be initiated as early as possible as it has been shown to reduce overall mortality and infection rates [35].

5.3.4 Dosing Enteral/Parenteral Nutrition

For patients with high nutritional risk, EN or PN should be started as soon as possible and advanced as quickly as tolerated in 24–48 h. This should be done with a goal to achieve >80% of calculated goal energy and protein within 48–72 h, which has been shown to lower mortality [22]. Because initiating nutrition this rapidly can cause hyperventilation as part of the refeeding syndrome (see below), patients with acute lung injury and ARDS on ventilators can be given lower rates of feeding (10–20 kcal/h up to 500 kcal/day) [21].

5.3.5 Adverse Effects of EN and PN

The major risk to monitor while initiating nutrition is occurrence of refeeding syndrome, which consists of decreased serum levels of phosphate, potassium, and magnesium, and fluid shifts and can include Wernicke's syndrome [36]. Refeeding syndrome is more likely to affect patients with chronic malnutrition or electrolyte losses. In these patients, electrolytes and fluid balance should be carefully monitored, and feeding should be initiated at half the patient's energy requirements on the first day and slowly increased. Additionally, patients at risk should receive intravenous thiamine 200–300 mg daily for the first three days of starting feeding [36]. In patients who receive PN, hypertriglyceridemia, hyperglycemia, cholestasis, hepatic steatosis, and central line-related infections are common complications that can occur [37].

Diarrhea is also commonly encountered with EN and can be attributed to lack of fiber, increased feed osmolality, prokinetic medication use, *Clostridium difficile* infection, and sorbitol-containing products. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPS) are poorly absorbed short-chain carbohydrates that exert an osmotic effect and can also be attributed to diarrhea [38]. According to ASPEN guidelines, EN should not be paused for diarrhea but should continue while the etiology of diarrhea is investigated [24].

5.3.6 Effects of Medications on Feeding

The effects of intravenous infusions of sedatives have various effects on the nutritional support of neurologically ill patients. In general, most anesthetic agents cause decreased gut motility and absorption and thus feeding intolerance. Pentobarbital, used for refractory status epilepticus or elevated intracranial pressure, both decreases gut motility and systemic and cerebral metabolism [39]. Reintroducing feeding on patients with pentobarbital infusion may result in refeeding syndrome. Propofol also decreases cerebral metabolism, but because it is a lipid emulsion, simultaneously provides 1.1 kcal/mL, and must be factored into equations determining total caloric intake goals. Narcotics such as fentanyl and morphine can cause constipation and ileus, also leading to refeeding syndrome. Thus, with the use of any anesthetic drug, a robust bowel regimen including cathartics and promotility agents such as metoclopramide or erythromycin should be initiated.

Other medications commonly used in the neurocritically ill population can have adverse interactions with EN and PN as well. Phenytoin is notable for a decrease in absorption up to 70% when administered orally with gastric feeding [40]. This has led to the commonplace practice of holding tube feeding for 2 h before and after administration of oral phenytoin. Corticosteroids can cause hyperglycemia, hyperlipidemia, and muscle atrophy when used for extended periods of time. Demeclocycline, used for syndrome of inappropriate antidiuretic hormone secretion (SIADH), can cause decreased serum calcium, iron, and magnesium levels by binding to these cations in the blood.

5.3.7 Percutaneous Endoscopic Gastrostomy Placement and End-of-life Care

Generally, a swallow assessment should be performed daily on patients receiving EN or PN. However, in the neurocritically ill population, brain injury prevents patients from regaining the alertness and muscle function to be able to swallow, and thus evaluation should be repeated daily until the patient passes. The optimal time to wait before placement of a percutaneous endoscopic gastrostomy (PEG) tube is unknown. For example, PEG placement is usually performed 2–3 weeks after an ischemic stroke, and early placement in this group has shown worse outcomes compared to nasogastric feeding [41]. However, due to adverse effects of chronic nasogastric tube placement (discomfort, nasal skin breakdown), PEG placement is preferred, but outcome data is generally lacking.

Artificial nutrition and hydration do not improve the outcome of terminally ill patients, and thus are not recommended to continue in end-of-life care. In many terminally ill patients, poor oral intake and dehydration are well tolerated, and one pilot study has shown no signs of discomfort and suffering due to this [42]. However, cultural, ethnic, religious, or personal beliefs may supersede these facts and force the continuation of nutrition. Clear communication with patients' surrogates and families, respect for dignity and autonomy, setting realistic goals of therapy, and involving an interdisciplinary ethics committee when issues cannot be resolved can help to support ethical care of these patients.

5.4 Specific Patient Populations

5.4.1 Traumatic Brain Injury

TBI induces a hypermetabolic response. Injury has been shown to be correlated with increased catecholamine release, cardiac index, and oxygen consumption [4]. The metabolic response has been correlated with a resting metabolic expenditure similar to that of a burn patient affecting 20–40% of body surface area [43]. A meta-analysis of 24 randomized controlled trials found that REE is variable between 75 to 200% of predicted values during the first 30 days following injury and is dependent on the degree of injury [44]. Protein catabolism is greatly increased, and positive nitrogen balance is difficult to maintain [45].

Patients who have sustained TBI have feeding intolerance due to damage to neurologic circuits responsible for swallowing, occurring in a majority of patients [46]. Many moderate to severe TBI patients require mechanical ventilation, which necessitates enteral feeding. Early nutrition once a patient is hemodynamically stable is an important goal in the care of these patients. An analysis of a large database of trauma centers in New York State found that initiation of early nutrition within the first 5 days was independently associated with a lower rate of mortality [47].

5.4.2 Stroke

Literature on nutritional considerations in this group of patients is found primarily for ischemic stroke. There is limited research in SAH, intracerebral hemorrhage (ICH), hypoxic injury, vasculitis, vascular malformations, or posterior reversible encephalopathy syndrome.

In ischemic stroke, malnourishment occurs within the first 24 h [48]. As catabolic processes are activated, there becomes a necessity to optimize interventions, specifically of EN, hyperglycemic management, and formulation of provided nutrition to minimize further consequences from a hypermetabolic state.

A recognized phenomenon in these patients is post-stroke hyperglycemia (PSH). Nearly two in every three acute stroke patients have an elevated blood glucose at presentation [49]. It is unclear if this is representative of uncontrolled diabetes, newly diagnosed diabetes, or because of the physiological stress response. PSH is an independent prognosticator of morbidity and mortality in this patient population [49, 50]. The effect of hyperglycemia to the brain differs from peripheral tissues as metabolism is more complex and energy consumption is higher [51]. Insulin is the preferred glucose-lowering therapy in an inpatient setting to minimize risk of hypoglycemia, as seen with oral agents, and ease of administration in the setting of dysphagia and poor cognitive status. Furthermore, insulin has been shown to promote the activity of endothelial nitric oxide and has immune modulating effects that may control infarction size, thereby affecting prognosis [52–54]. The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial is currently underway aimed at determining functional outcome differences between sliding scale insulin and continuous insulin infusion, during the acute period, which may provide further clinical guidance [55].

Current basic approaches in nutrition in stroke patients come from the Feed or Ordinary Diet (FOOD) trial, which is a multicenter study consisting of three linked trials [56]. The first trial compared a normal hospital diet versus a normal hospital diet with the addition of oral supplements, concluding that there was no significant difference on length of hospital stay, poor outcome, or death. The early versus delayed feeding trial found that there was a minimal, nonsignificant reduction in risk of death with early tube feeding and nonsignificant reduction in poor outcome or death. The nasogastric versus PEG trial was found to have an increased risk of death or poor outcome to suggest avoidance of early PEG placement in stroke patients with dysphagia [56].

In SAH, there is a hypermetabolic response similar to that of severe TBI [57, 58]. The degree of hypermetabolism is dependent on clinical severity. Patients with a Hunt-Hess grade of 4–5 have a REE of nearly 200% of predicted energy expenditure on post-bleed day 10 [58]. The pathophysiology is likely similar to stroke and TBI and is supported by a study involving SAH with cerebral microdialysis sampling demonstrating that there is an increase in TNF-α. Additionally, there is an association with intraventricular blood, aneurysm size, and elevated brain interstitial glucose [59].

One study performed on ICH patients evaluated the effects of therapeutic hypothermia on basal metabolic rates (BMR) [60]. Thirteen patients with ICH were randomized to either moderate hypothermia to 33–34 °C or normothermia, and indirect

calorimetry showed a greater decrease in BMR compared to the Harris-Benedict or Penn State equations in the hypothermia group.

Despite early nutritional support in SAH and ICH, patients are often at a negative energy balance which is associated with secondary complications such as infections [25, 61]. A negative nitrogen balance is associated with poor outcome at 3 months. Tight glucose control and increased glucose variability have been shown to induce cerebral metabolic distress by measure of lactate to pyruvate ration using cerebral microdialysis, which has been shown to be associated with worse hospital mortality rates. During metabolic distress, insulin administration is associated with reduction in brain glucose that is independent of serum glucose [62]. There is evidence that lipid peroxidation may mediate the relationship between hypermetabolism and delayed cerebral ischemia in SAH patients. Elevated *n*-6 and *n*-3 free fatty acid levels are associated with a higher O_2 consumption and severity of initial hemorrhage [63]. Furthermore, an *n*-6:*n*-3 free fatty acid ratio $\geq$8.8 was found to have a sensitivity of 93% and specificity of 80% for predicting delayed cerebral ischemia, which is associated with poor 3-month outcome [63]. In a prospective pilot study, eicosapentaenoic acid (EPA), an *n*-3 fatty acid, administration was associated with a decreased frequency of symptomatic vasospasm and cerebral infarction [64].

5.4.3 Spine Injuries

In this patient population, evidence currently suggests an obligate increase in nitrogen excretion, and a negative nitrogen balance exists despite adequate nutrition. The degree of these metabolic effects appears to be associated with the level of injury, with larger changes seen in upper spinal injuries. Failure to account for REE can lead to overfeeding and impaired ventilator weaning [65, 66]. Furthermore, this significant catabolic state leads to muscle breakdown, spasms, and inflammation. For cervical spine-injured patients, oral intake becomes a significant problem due to swallowing problems, necessitating percutaneous gastric feeding and thus introducing infection risk.

5.4.4 Neuromuscular Disorders

These patients have numerous risk factors for poor nutritional status including profound neuromuscular weakness, bulbar weakness leading to dysphagia, ventilator dependency, prolonged steroid use, and prehospital weight loss. Patients with Guillain-Barré syndrome (GBS) have significant hypermetabolism and hypercatabolism similar to TBI patients [67]. Little evidence is available for these patients; therefore nutritional therapy is best guided by principles outlined for the general critical care population.

Critical illness myopathy is a recognized phenomenon that occurs in primarily elderly patients in the ICU and is characterized by diffuse weakness and difficulty with ventilatory weaning due to decreased muscle mass resulting from the effects of

inflammation, hypercatabolism, and malnutrition. Amino acid-dependent gluconeogenesis occurs within 24–48 h in the setting of inadequate nutrition. Upregulation of muscle autophagy provides the needed glutamine and alanine to support gluconeogenesis. During this process, type II muscle fibers are preferentially subject to proteolysis [68]. A retrospective study of 149 severely injured elderly patients at a level I trauma center found an association between sarcopenia, as estimated by muscle cross-sectional area at the level of third lumbar vertebrae by computed tomography, and mortality. Efforts should be taken for early nutritional therapy and aggressive early mobility.

5.5 Future Considerations

5.5.1 Immunonutrition

As the practice of critical care progresses toward understanding the immunological and genetic basis of the body's response to inflammation, knowledge of the immunological reaction to nutrition is currently an emerging field of study. Immune-modulating enteral formulations supplemented with arginine, EPA, docosahexaenoic acid (DHA), glutamine, and nucleic acids have been shown to be associated with reduction of hospital length of stay in the medical ICU (MICU) population [69]. This has not been replicated in further studies and currently is not recommended for the septic MICU population. Similar heterogeneity in results has been found in literature studying these additives in patients with ARDS. However, in TBI, immunomodulating supplements have been shown to decrease infection rates [70] and accelerate recovery [71] and are recommended in the 2016 ASPEN guidelines. Further studies will be needed to validate these findings and should be undertaken to evaluate these additives individually.

5.5.2 Exercise and Nutrition

Neuromuscular weakness after prolonged ICU admission is a common occurrence in patients who require prolonged mechanical ventilation and immobility and is frequent among the neurocritically ill population. Studies in non-critically ill populations have found that combining protein supplementation and resistance-type exercise interventions have greater effects on good outcome than nutrition or exercise alone. This combined approach can translate to decreased sarcopenia and improved vasoreactivity in the critically ill population. Indeed, systematic reviews and meta-analyses in stroke patients have shown that the earlier exercise is started, the better their outcomes [72, 73]. However, the correct time to mobilize patients, and exactly what regimen of exercise and activity should be used, is yet to be determined. In a multicenter single-blinded study from Asia, the United Kingdom, and Australia, a decreased likelihood of 3-month favorable outcome (modified Rankin score 0–2) was noted with vigorous mobilization in stroke patients within 24 h [74].

Conclusion

The nutritional considerations of the neurocritically ill patient are intricate and evolving. Evaluating the need for nutrition and monitoring its adequacy is a challenge for all critically ill patients, and research continues to be performed validating scores such as the NRS-2002 and NUTRIC. Active research is being done on the effects of immunomodulation for this population. Overall, acute neurological injury creates a unique challenge for nutritional therapy, necessitating a careful evaluation of the underlying mechanism, comorbidity, and course of illness.

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Nutritional Support in Amyotrophic Lateral Sclerosis

6

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6.1 Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disorder of the upper and lower motor neurons, causing weakness and wasting of muscles controlling limb movement, speech, swallowing, and breathing, leading to eventual death, usually from respiratory complications [1]. Clinically, approximately 30% of patients present bulbar, 65% limb, and 5% respiratory symptom-onset ALS, and with disease progression, all regions are eventually being involved [2]. Although ALS affects primarily the motor neurons, it is also linked to cognitive impairment, behavioral deficits, as well as psychological and anxiety disorders. A subgroup of approximately 14% patients can develop frontotemporal dementia, while up to 40% present subtle behavioral changes, predominantly of their executive functions, when cognitive testing is undertaken [3].

ALS is the third most common adult-onset neurodegenerative disorder, following Alzheimer's and Parkinson's disease [4], with an incidence of 1.5–2.4 per 100,000 person-years and annual prevalence of 4.1–7.9 per 100,000 population in Europe [5]. ALS affects slightly more men than women by a ratio of approximately 1.4:1. Men also present a higher incidence of limb-onset ALS compared to women by a ratio of approximately 1.8:1 [2]. Disease onset is uncommon in younger people (i.e., those aged <40 years), peaks between the ages of 50–80 years, and swiftly decreases with advanced aging [2]. ALS is a devastating illness with a profound personal, societal, and financial cost. Life expectancy for most patients is usually 2–3 years from symptom onset, although there are those who have worse prognosis, as well as a 5% who survive more than 10 years [6]. Poor prognostic factors include bulbar onset, older age at onset, higher rate of decline in the revised amyotrophic

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lateral sclerosis functional rating scale (ALSFRS-R), short diagnostic delay, malnutrition, cognitive impairment, and weight loss [7–11].

Several key pathways have been implicated in the pathogenesis of ALS including glutamate excitotoxicity, oxidative stress, mitochondrial dysfunction, RNA dysregulation, and disruption in axonal transport [12]. It is likely that it is a complex interaction between these that results in motor neuron death; however, the exact etiology remains elusive. Most cases of ALS are sporadic with an estimated 5–10% being genetically inherited with a Mendelian pattern (familial ALS or FALS) [12]. Several genetic studies over the past two decades have uncovered the role of a number of genes in the pathogenesis of the disease, accounting for approximately 65% of all familial and 11% of all sporadic cases [13]. Despite the advances in the understanding of the genetic underlying mechanisms leading to motor degeneration, the role of environmental factors remains unknown, as so far no study has provided robust, replicable, and definitive evidence of a causal relationship between a single or a combination of environmental factors and ALS [14]. The most frequently studied environmental factors include exercise, football, smoking, heavy metals, pesticides, chemicals, occupation, armed service, electric shock, geographical clustering, and cyanotoxins [14].

There is no cure for ALS. Riluzole, a glutamate modulator, has been shown to have a modest beneficial effect on survival, slowing disease progression by approximately 3 months [15]. In the absence of more effective pharmacological treatments, disease management relies heavily on clinical interventions for symptom palliation with the intention to maintain patient function, autonomy, quality of life, and dignity for as much, and as long, as possible. These interventions focus on aspects of ALS such as respiratory function, nutrition, secretions, pain, mobility, speech function, palliative care, end-of-life decisions, cognitive changes, emotional lability, depression, sleep disturbance, quality of life, and support for informal carers [1, 6, 16]. The greatest effect on the disease course results from the use of noninvasive ventilation (NIV), which can prolong survival by at least 7 months [17]. Care for ALS patients is often managed by a multidisciplinary team, and there is evidence that survival is improved if care is delivered in this way, as opposed to being delivered in an uncoordinated way by nonspecialists [9].

6.2 Malnutrition in ALS

Malnutrition poses a serious challenge in the management of patients with ALS. Its exact prevalence in the general ALS population is difficult to estimate; nevertheless, it is a frequent symptom affecting an estimated 16–53% of patients, depending on the adopted malnutrition assessment measure, disease stage, and variance in the clinical characteristics of the cohorts under investigation [18, 19]. There are many methods of assessing nutritional status in patients with ALS. These include dietary recall; anthropometric measurements, such as variation in weight, body mass index (BMI), triceps skinfold (TSF) thickness, and mid-arm muscle circumference (MAMC); bioelectrical impedance analysis (BIA); dual-energy X-ray absorptiometry (DEXA);

indirect calorimetry; and biochemical indices, such as serum albumin or creatinine levels [20]. Of these, weight and BMI variance are the most commonly used in clinical practice. Although no general consensus among clinicians exists, patients are usually considered to be malnourished when weight loss is greater than 5–10% from premorbid, BMI <18.5 kg/m^2 for patients aged 18–65 years, and BMI <20 kg/m^2 for patients aged over 65 years [20].

The causes of malnutrition and weight loss are complex and driven by a combination of ALS consequences, including suboptimal oral dietary intake, muscle atrophy secondary to continued denervation, hypermetabolism, physical exertion, and the potential presence of other comorbidities affecting metabolism [21–24]. Calorie intake in patients with ALS has been observed to be lower than their requirements as indicated by recommended daily allowance (RDA), doubly-labeled water technique, and 25–30 kcal/kg body weight formula or the Benedict-Harris equation [25]. In two separate cohorts, calorie ingestion of less than the RDA was seen in 70 and 94% of ALS patients [26, 27]. A plethora of reasons, both physiological and psychological, can lead to a reduced nutritional intake in ALS, although they may vary from patient to patient depending on individual personal circumstances and clinical characteristics. Dysphagia, i.e., difficulty in swallowing, is the single most important reason and can present relatively early on in the disease course in patients with bulbar-onset ALS. With disease progression, it eventually also affects patients with limb-onset ALS. It is estimated that dysphagia can potentially affect at least 75% of all patients over the course of their illness [28]. Advanced dysphagia is associated with nutritional decline, dehydration, weight loss, choking and coughing on attempting to swallow, frequent aspiration, and prolonged and effortful mealtimes affecting patients and their family members who often act as carers [28–30]. Anorexia affects many patients with ALS and can also contribute to a reduced dietary intake and subsequent weight loss. Although its exact effect on clinical outcomes, such as survival and quality of life, is yet to be fully understood, a prospective study over a 6-month period demonstrated that patients with severe loss of appetite experienced an average of 5% weight loss, compared to a 2% weight loss in those with unaffected appetite [31]. Other factors contributing to a suboptimal nutritional intake include limb weakness and subsequent diminishing patient mobility and dexterity; cognitive, behavioral, and psychological impairment; loss of independence; and absence of informal carers. As a result, patients face difficulties in preparing and consuming food, their eating habits change, and they become reliant on others to feed [30, 32, 33].

Compounding the reduced calorie intake is the frequent observation of hypermetabolism (i.e., an abnormal increase in the body's rate of basal metabolic activity) in up to 67% patients with ALS; however, its exact cause remains elusive [22, 25, 34–37]. Early studies linked hypermetabolism to a greater effort of breathing but this has subsequently been shown not to be the case [36]; indeed, it is now hypothesized that hypermetabolism may be a result of mitochondrial dysfunction [38].

Malnutrition has been linked to a series of detrimental consequences, which especially for patients with ALS may aggravate the underlying condition by setting off a vicious circle of further clinical deterioration. These consequences include

weight loss, which in most cases may be rapid and excessive; shortened survival; increased muscle weakness; fatigue; compromised respiratory and cardiovascular function; exposure to, and increased recovery time from, infections; increased risk of pressure ulcers; and poor wound healing [32, 39].

Indeed, it has been well established that indicators of malnutrition such as weight loss and reduction in BMI are independent risk factors for survival in ALS and, in particular, associated with a poor prognosis [8, 18, 40–43] (Fig. 6.1). Just over 50% of patients with ALS experience weight loss of more than 5% of their premorbid weight at the time of diagnosis (of which, 36% patients experience a weight loss of more than 10%) [45]. Patients in the >10% weight loss subgroup at the time of diagnosis exhibit an increased risk of death by 45%, compared to those who have not lost weight or have lost up to 5% of premorbid weight at the time of diagnosis [45]. Similarly, it has been demonstrated that a subgroup of malnourished patients with ALS, i.e., those with BMI <18.5 kg/m^2, exhibited a 7.7-fold decreased survival, compared to patients with BMI higher than this threshold [18]. On the other hand,

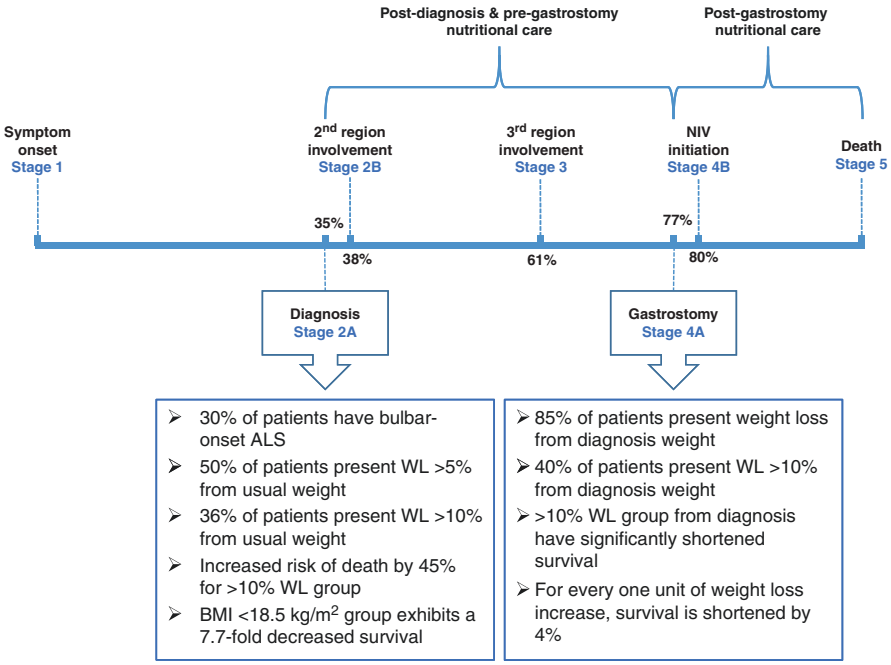

Fig. 6.1 Diagram depicting the key stages of ALS [44]. Evidence suggests that, at diagnosis, weight loss from premorbid weight and low BMI are poor prognostic factors [18, 45]. Following the diagnosis, and during the early stages of ALS, pre-gastrostomy care for patients who can safely swallow involves regular monitoring of nutritional status and swallow deterioration, dietary advice, food fortification, and provision of ONS [23, 28, 46]. Patients tend to undergo gastrostomy at a relatively late stage over the course of ALS, when they are more likely to feel the burden of other consequences of the disease, such as respiratory problems and the loss of mobility and speech [44]. Evidence suggests that excessive weight loss from diagnosis is associated with shorter post-gastrostomy survival [40]

mild obesity (BMI of 30–<35 kg/m^2) in patients with ALS appears to have a mild beneficial effect in terms of survival, compared to other BMI subgroups [43].

BMI may also influence the risk of developing ALS. Individuals who are overweight (BMI 25–<30 kg/m^2) and obese (BMI ≥30 kg/m^2) have significantly lower chances of developing ALS, compared to those with a healthy BMI (<18.5–<25 kg/m^2), and that for each five-unit rise in BMI, ALS incidence is reduced by 21%, which further consolidates the protective role of high BMI [47].

6.3 Nutritional Care in ALS

Given the adverse outcomes of malnutrition, and its links to increased morbidity, disability, and mortality, the nutritional care of patients with ALS is undoubtedly an important element of disease management. The aim is to maintain an optimal nutritional intake and minimize the effects of weight loss either by preventing its occurrence or by compensating for any loss that has already taken place.

Several strategies, following the diagnosis and during the early stages of the disease, exist to achieve this for patients who can safely swallow. These involve frequent monitoring of nutritional status, regular assessment of swallowing function, dietary advice, food fortification, support with safe swallowing techniques and adaptive eating utensils, modification of diet texture, and provision of oral nutritional support (ONS) [23, 28, 33, 46]. The use of ONS, in particular, has been proven to be beneficial in minimizing weight loss in other patient groups [46, 48]. Evidence from a retrospective questionnaire study in a small group of patients with ALS who had suffered weight loss suggests that high calorie supplement consumption may avert further weight loss and even lead to weight gain; however, this evidence is currently limited [49]. The exact effect of ONS on patients with ALS has yet to be determined. Two randomized controlled trials (RCTs) with patients with ALS, one in France (NCT02152449) and one in Germany (NCT02306590), are currently underway investigating the potential of high calorie nutritional supplementation as a disease modifier by looking into its impact on disease outcomes such as patient survival, nutritional state, respiratory function, quality of life, and other functional characteristics. Current guidelines set out by the European Federation of Neurological Societies (EFNS) and the American Academy of Neurology (AAN) contain recommendations for the nutritional care of patients with ALS [50, 51]; however, these are based more on consensus among panels of healthcare professionals rather than on robust evidence from appropriately designed trials, which is lacking.

6.3.1 Enteral Feeding

Enteral feeding is a well-established practice in ALS [52], recommended both by AAN and EFNS [50, 51], and commonly used for the nutritional support of patients who have lost the ability to maintain an adequate nutritional intake by mouth or for

whom oral intake is unsafe or contraindicated. The delivery of liquid feeds to the stomach can be achieved either via nasogastric tube (NGT) or gastrostomy insertion [53]. Enteral access beyond the stomach to the duodenum or jejunum is not common in this patient group and is usually reserved for those in whom gastric feeding is contraindicated [54]. Gastrostomy is favored over NGT feeding in patients with ALS due to the unsuitability of the latter for long-term (i.e., beyond 4–6 weeks) nutritional support [55]. Nasogastric tubes may provide a quick and easy access to the stomach; nonetheless, they are prone to blockages, due to their relatively small-bore size (5–8 French gauge) as well as accidental dislodgement, increasing the chances of aspiration [56] (although this may be avoided by bridling) [57]. NGT use is unpopular with patients, as it is associated with nasal discomfort and poor aesthetics, but remains a reliable short-term option of enteral feeding and is usually reserved for emergencies [56].

6.3.1.1 Gastrostomy Methods

There are three main methods of gastrostomy insertion in patients with ALS, namely, the percutaneous endoscopic gastrostomy (PEG), radiologically inserted gastrostomy (RIG), and peroral image-guided gastrostomy (PIG). Surgical gastrostomy is very rarely operated in patients with ALS and is typically reserved for those in whom all other insertion methods have been ruled out as unsuitable or have been attempted but failed [52].

PEG is performed under endoscopic guidance with the patient in the supine position and requires conscious sedation. During PEG, a large-bore (15–28 French gauge) gastrostomy tube is passed over a guide wire through the mouth and esophagus into the stomach and pulled through an abdominal wall incision in situ [52, 58]. PEG tubes are typically fixed securely with a bumper-retention system, hence reducing the chances of tube displacement [59]. However, during PEG, patients with severe bulbar symptoms and/or moderate to severe respiratory dysfunction (i.e., forced vital capacity 30–50% of predicted) are at increased risk of aspiration and/or significant respiratory compromise, because of the need for patients to lie flat, receive pharyngeal anesthesia, and have their throat intubated with an endoscope [52]. The use of NIV during PEG for patients requiring respiratory support is possible [60] but impractical in many cases and thus less common, as it is technically challenging requiring the presence of more skills.

RIG, also known as percutaneous radiological gastrostomy (PRG), is an alternative method of gastrostomy insertion in patients with ALS. It presents many advantages over PEG, especially for patients with compromised respiratory function, as it does not require conscious sedation or the use of an endoscope (it is performed under X-ray fluoroscopy instead and requires only local anesthesia), and patients can assume a semi-reclining position during the procedure. During RIG, the stomach is stitched to the abdominal wall; a guide wire is pushed into the stomach from the outside through an abdominal wall incision, followed by track enlargement with a series of dilators [58]. A relatively small-bore (10–14 French gauge) gastrostomy tube is then pushed over the guide wire from the outside through the enlarged track and fixed in position typically with a balloon-retention system [52]. The

disadvantage of RIG is the need for stitches, which increases post-procedural pain and the nature of the tubes used which are prone to blockages and dislodgement.

PIG is a fairly new method of gastrostomy insertion in patients with ALS [52, 61], combining the advantages and minimizing the disadvantages of both PEG and RIG. This "hybrid" procedure is performed under X-ray fluoroscopy, with the use of minimal conscious sedation or local anesthesia, and the patient can assume a semi-reclining position as in the RIG procedure. However, the insertion technique, type of tube, and tube fixation are exactly the same as in the PEG procedure, described above [52, 61]. Thus, PIG allows the placement of robust, securely fixed gastrostomy tubes even in patients with compromised respiratory function. It is though, a more complex procedure, requiring more skills.

6.3.1.2 Optimal Gastrostomy Method

A survey of the practice of gastrostomy in the UK, including all major ALS care centers and clinics across the country, revealed that the clinical decision-making in relation to gastrostomy method was based on a range of factors including access to a specific gastrostomy service, patient respiratory function, contraindications for the use of a specific method, overall patient clinical condition, previously failed gastrostomy with a specific method, and clinician preference as to which method offers a most favorable post-insertion tube management [52]. There is a clear clinician inclination to refer for PEG, patients with good respiratory function (forced vital capacity-FVC >50% of predicted) and overall clinical condition, i.e., those who are more likely to tolerate endoscopy and receive sedation. On the other hand, more frail patients who cannot lie flat nor tolerate endoscopy as well as those with compromised respiratory function (FVC <50% of predicted) are more likely to be referred for either RIG or PIG [40, 52].

Several retrospective and prospective studies have looked into the issue of gastrostomy procedure safety, represented by 30-day mortality post-procedure, to determine the superiority of a specific method over another [62]. A meta-analysis of studies reporting mortality data following PEG and RIG/PIG in patients with ALS demonstrated that the weighted estimate of the expected 30-day mortality rate was 10% (95% CI: 5–15%) and 6% (95% CI: 3–9%), respectively. The estimate of the absolute difference in 30-day mortality rate in studies, which reported within-study comparisons of PEG vs. RIG/PIG, was 2.1% higher for PEG (95% CI: −6.3 to +11.2%); however, this estimate was imprecise and together with other limitations of the meta-analysis did not provide robust evidence on the issue at hand [52]. Nevertheless, a large prospective cohort study in the UK, called ProGas, which was designed with the purpose of comparing PEG vs. RIG vs. PIG in patients with ALS, concluded that the three methods were as safe as each other in relation to procedure risk and that survival in general was independent of gastrostomy method (after adjusting for variables such as age at onset of ALS, weight loss, functional decline rate, FVC, site of ALS onset, and treatment center) [40]. ProGas suggested though that the optimal method should perhaps be decided upon which method offers the easiest post-insertion tube management. In ProGas, complications following RIG (with the use of narrower and less secure balloon-retention tubes), such as tube

leakage (21%), displacement (31%), replacement (30%), and repeated gastrostomy (15%), were significantly higher compared, respectively, with 10, 1, 3, and 1% for PEG or PIG (with the use of broader and more secure bumper-retention tubes). Ease of post-insertion management is of main importance, especially for frail and severely disabled patients who undergo gastrostomy at a late stage of the disease, when they are more likely to be burdened by respiratory problems, immobility, and speech impairment [40]. An alternative type of an RIG-inserted tube with an improved mushroom-cage retention system is now available which may have an improved complication rate [63]. Hence, ProGas favored PEG as the optimum method of gastrostomy in patients with generally unimpaired respiratory function and PIG when respiratory function is significantly compromised [40].

6.3.1.3 Gastrostomy Timing

The optimal timing for gastrostomy feeding initiation is highly contested and subjective. It has been described that, generally, patients with ALS tend to undergo gastrostomy relatively late, i.e., after the disease has run its course by approximately 80% [44] (Fig. 6.1). Clinicians act on what they think would be in the patients' best interest, considering own wishes of patients, their clinical experience, individual personal circumstances, as well as existing evidence and guidelines [21]. Patient decision-making over the timing of gastrostomy insertion is complex and, understandably, very difficult. Some of the factors which may delay patients to accept gastrostomy, even in the presence of increasing swallowing and eating difficulties, include patient reluctance to give up oral feeding, negative opinions about gastrostomy, uncertainty over the disease trajectory, not realizing potential benefits of gastrostomy [30], and the ability to derive pleasure from feeding by mouth [64].

The EFNS guidelines advise that gastrostomy should be introduced when weight loss is >10% from premorbid weight [50], and AAN recommends PEG when there is significant dysphagia or weight loss and when FVC is still >50% of predicted [51]. The findings of recent large prospective studies suggested that patients with rapid weight loss before gastrostomy are more likely to experience shortened survival and no meaningful weight gain, if any at all, following the procedure, compared to those with no excessive weight loss [40, 65]. For instance, one study demonstrated that patients who had lost less than 5 kg of their usual weight at the time of PEG had an increased survival by 3 months following the procedure, compared to those who had lost equal or greater than 5 kg of their usual weight [65]. ProGas demonstrated that the odds for 30-day mortality were 10.7 times higher for patients who had lost more than 10% of their weight from diagnosis, compared to those who had lost 10% or less of weight. Furthermore, the percentage of weight difference at gastrostomy compared with weight at diagnosis was an independent risk factor for survival following gastrostomy (for every one unit of weight loss increase, survival was shortened by 4%) [40] (Fig. 6.1). ProGas further revealed that the subgroup of patients who at the time of gastrostomy had lost more than 10% of their weight from diagnosis were significantly less likely to recover this loss, in the first 3 post-procedural months, and had a significantly shorter survival compared to those who had lost less than 10% of their weight at diagnosis. From a clinical point

of view, these findings cast doubt on the purpose and usefulness of gastrostomy in improving patient outcome (especially for those with excessive weight loss). Based on this evidence, it is recommended that gastrostomy is performed before substantial weight loss and a new recommended threshold is that of 5% weight loss, compared to weight at diagnosis [40]. However, it is still unclear what the outcomes would be if patients did not undergo gastrostomy.

6.3.1.4 Efficacy of Gastrostomy Feeding

There is a dearth of evidence on the effectiveness of gastrostomy feeding in patients with ALS. No RCTs have been performed to suggest whether gastrostomy feeding is superior to continued oral feeding in terms of survival and other disease-related outcomes [62]. Existing evidence from observational studies implies a potential benefit of gastrostomy feeding; nevertheless, this evidence is limited [19, 66–68]. Likewise, despite the belief that this nutritional intervention will improve patient quality of life, the evidence base is poor and contradictory [62]. In fact, although a handful of observational studies suggested that gastrostomy feeding led to improved quality of life for patients with ALS [19, 69], ProGas suggested that the effect of gastrostomy on patient quality of life was neutral [40].

Equally, the effect of gastrostomy feeding on the nutritional outcome for patients with ALS has not been thoroughly investigated [62]. Neurologists are more likely to recommend gastrostomy in the hope that it will stabilize nutrition and hydration of patients with ALS [52], and some evidence from small prospective studies seemingly supports this belief [19, 20]. Nevertheless, emerging evidence from a recent large prospective study has raised a question mark over the use of gastrostomy feeding and its ability to adequately support the nutritional needs of patients with ALS. ProGas demonstrated that gastrostomy feeding had a weak effect on stabilizing the nutrition of the patients in its cohort. Surprisingly, at 3 months following gastrostomy, approximately 50% of patients lost more than 1 kg, 25% of patients had experienced a loss or gain of 1 kg or less, and only 25% of patients made significant gains of 1 kg or more compared with weight at gastrostomy [40]. The underlying reasons for this fairly poor nutritional outcome are unclear and, nevertheless, might be related to the natural disease progression with continued denervation-induced muscle atrophy causing largely loss of fat free mass; patient factors, such as feed tolerance; feeding logistics (e.g., personnel to assist with feed and lack of time to give feed); lack of knowledge regarding feeding in patients, carers, or healthcare professionals; or incorrect calculation of calorie requirements in the presence of hypermetabolism. On the other hand, interestingly, there is a growing evidence from a fairly new area in the post-gastrostomy nutritional care of patients with ALS suggesting that high calorie enteral feeding is well tolerated and may convey a survival benefit in patients with advanced disease, despite the presence of hypermetabolism [65, 70].

6.3.1.5 Enteral Feed Administration

There is currently no disease-specific formula feed for patients with ALS [22]. A typical feed provides 1 kcal of energy and 0.04 g of protein per mL (with or without fiber); however, different formulas exist to meet individual patient, nutritional needs

[55, 71]. Given the challenging metabolic state of patients with ALS and the effects of muscle loss, it is still unclear what the optimal nutritional protocol for artificial nutrition might be. It has been proposed though that feeds should be of a high caloric density and contain increased lipids, antioxidants, and fibers and reduced carbohydrates [22]. Feed administration varies and depends on personal circumstances, preferences, and choices. Bolus feeding permits delivery of 100–400 mL of feed formula (through a syringe and, usually, by gravity) over a relatively short period of time (10–30 min) at frequent (3–6 h) intervals. Other techniques include continuous (24 h), cycled continuous (e.g., for 16–18 h with 2–4 h breaks), and intermittent (e.g., for 4–6 h with 2–4 h breaks) feeding with the use of an infusion pump or, alternatively, a gravity drip set [55, 71, 72]. Although bolus feeding is relatively simple, quick, and cheap, it has also been linked to increased bloating, diarrhea, aspiration [55, 72], and additional feeding time burden, which may have a detrimental effect on patient quality of life [73]. Overnight pump feeding permits the delivery of 1.5–2 L of feed formula over 8–12 h, at a controlled rate [72], with less side effects and reduced strain of having to feed multiple times during the day. It is, however, more complicated and requires expensive equipment; it is not practical nor suitable for all [73] and is clinically contraindicated for patients at high risk of aspiration because of the required reclining position for feeding during sleep [55].

6.3.2 Parenteral Feeding

Total parenteral nutrition (TPN) is an alternative long-term option for the nutritional support of patients in whom enteral feeding is contraindicated or impossible, i.e., for patients with chronic gastrointestinal tract dysfunction or in whom the gastrointestinal tract is not accessible as well as when gastrostomy has been deemed unsafe [74, 75]. Home parenteral nutrition (HPN) can be achieved through a tunneled venous catheter or, alternatively, an implantable port [76]. There is currently insufficient evidence to determine the efficacy of HPN in patients who are either severely malnourished or have highly catabolic disease processes [77]. However, a small study in patients suffering from ALS compared a group of patients that received gastrostomy vs. a group that received HPN. All patients at the time of the intervention had experienced significant weight loss and severe respiratory insufficiency. Post-interventional survival was similar for the two groups and independent of the type of the intervention. These results suggested that HPN is tolerable and may be an option for patients with ALS [78]. HPN is a complicated treatment, requires continuous support from highly trained healthcare professionals, and costs an estimated six times more than enteral feeding [78]. Furthermore, HPN can cause serious complications like catheter-related sepsis and venous thrombosis and metabolic and vascular disorders and is also unsuitable for moderately to severely disabled patients who are not able to maintain their lines and infusions [56, 76]. Hence, parenteral feeding remains unpopular among clinicians and patients and is infrequently practiced in patients with ALS.

6.4 Summary

Patients with ALS are at an increased risk of nutritional deterioration and subsequent increased morbidity, disability, and mortality. Artificial nutritional interventions such as the use of ONS and enteral feeding are frequently used as a means to stabilize nutrition of patients with ALS. However, the effectiveness of these interventions on nutrition, quality of life, survival, and other disease-related outcomes is largely unproven. Emerging evidence that gastrostomy insertion may not prevent further weight loss in a large segment of patients is unexpected from a clinical point of view. The reasons behind this are not well understood and require further investigation. In terms of timing of enteral feeding, existing evidence suggests that delay of gastrostomy may yield diminishing benefits in terms of survival and nutritional outcomes. In terms of the optimal method of enteral feeding, NGT feeding is not suitable for prolonged use; hence, gastrostomy feeding is the method of choice. For those having a gastrostomy tube, large-bore bumper-retention tubes are optimal, in terms of post-insertion complications, compared to balloon-retention gastrostomy tubes, and consequently, the methods allowing placement of the former (i.e., via either PEG or PIG) should be favored. Current clinical guidelines are based more on consensus among panels of healthcare professionals, rather than the results of appropriately designed trials. There is therefore now a need to understand the effect of artificial nutrition on key outcomes such as nutritional status, quality of life, disease course, and carer burden.

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Nutritional Support in Chronic Neurodegenerative Diseases

7

Rainer Wirth

7.1 Introduction

Dementia and Parkinson's disease are the two most prevalent chronic neurodegenerative diseases in developed countries. The World Alzheimer Report estimated that 46.8 million people are living with dementia worldwide in 2015. These figures are expected to almost double every 20 years. The prevalence of dementia in the age group above 80 is about 25%. The prevalence of Parkinson's disease (PD) in this age group is only about 3% but is likewise rising [1]. Both conditions are strongly associated with feeding difficulties, weight loss, and dysphagia. Therefore, in both conditions nutritional management has the potential to support medical treatment and decrease complications during the course of the disease. The same is true for other more rare neurodegenerative diseases, but less evidence is available in this field. However, the principles of nutritional support in dementia and PD may be translated into this area.

7.2 Nutritional Problems in Dementia

Dementia syndromes become a common picture in our aging societies, but dementia is not normal healthy aging. It is a malignant and devastating disease leading to a loss of autonomy, numerous potential complications, and finally death. Dementia is characterized by a global cognitive impairment with a decline in memory function and other cognitive domains, mostly involving also executive function. It leads to behavioral and psychiatric disturbances and is associated with a general impairment of the patients' functional abilities [2]. Many cardiovascular risk factors

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contribute to dementia, and many diseases may lead to a dementia syndrome. Alzheimer's disease (AD) is by far the most frequent cause. Even in most patients with vascular dementia, the Alzheimer's pathology is a main contributing factor. The pathogenesis of PD with dementia and dementia with Lewy bodies is distinct from that of AD but may also be mixed with it. Advanced age, the apolipoprotein ε4 genotype and cardiovascular risk factors are the most important risk factors for AD. Typically, dementia leads to anxiety, depression, and behavioral disturbances, which lead to a high burden for patients and their families [3]. The first changes of the brain due to AD occur many years before dementia becomes evident. The transition from an asymptomatic state over mild cognitive impairment to early, mild, moderate, and severe dementia can be classified by the use of rating scales such as the Clinical Dementia Rating scale and the Global Deterioration scale [4, 5]. This may be important, especially for nutritional support, as these scales do not rate the function of memory but the patient's ability to perform the activities of daily living, which are closely related to the ability to perform food supply, to cook, and to eat and, respectively, to nutritional problems.

Weight loss is a frequent finding in dementia patients [6, 7]. Remarkably, it is often present even years before the start of the disease [8]. The mechanisms of weight loss in dementia are multifactorial, variable, partly stage dependent, and not completely understood [6]. As studies about the type of weight loss are inconsistent, it is still under debate whether the weight loss of demented patients is predominantly a loss of fat mass or whether there is an above average loss of fat-free mass.

Genetic factors, inflammatory processes, metabolic and structural changes in specific brain regions, as well as behavioral disturbances have been addressed in several studies and seem to be associated with weight loss in AD. In one study the presence of apolipoprotein E-e4 allele was strongly associated with weight loss in women with AD [9]. High levels of inflammatory cytokines are found in patients even with incident or early AD and are linked to the pathophysiology of the disease. It is well known that elevated inflammatory cytokines are associated with weight loss and frailty in AD [10, 11]. Pathological changes in the olfactory system that regularly occur years before the onset of the dementia syndrome are suggested to contribute to anorexia and weight loss in AD [12]. Furthermore, dementia-related brain atrophy may affect brain areas involved in appetite regulation and eating behavior. Especially the atrophy of the mesial temporal cortex seems to be associated with a low body mass index (BMI) in AD [13]. In addition, even in the early stages of the disease, changes of food preferences and food intake can be observed and are generally associated with reduced energy intake [14] (Fig. 7.1).

All these factors play a potential role in the pathogenesis of weight loss in AD, which may have varying importance, dependent of the stage of the disease. In the early stages of AD, demented patients may have problems with adequate shopping and preparation of food and may forget the sensation of appetite and whether they have already eaten. Dietary habits of patients with dementia change and typically result in a reduced variety of diet and an unbalanced nutrient intake. In the advanced stages of the disease, patients may no longer know what to do with the food, behavioral problems emerge, and eating skills are lost. Behavioral problems such as

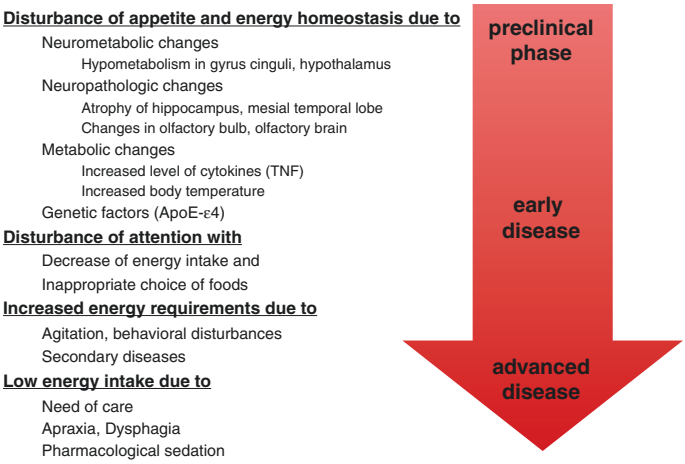

Fig. 7.1 Potential causes of weight loss in dementia

hyperactivity may make mealtimes difficult and increase energy requirements [15, 16]. On the other hand, pharmacological therapy of agitation and hyperactivity may reduce eating drive and dietary intake. Mostly during the advanced stages of the disease, patients develop oropharyngeal dysphagia, which is often aggravated by side effects of neuroleptics [17]. Dysphagia leads to impaired food and fluid intake, stress during meals, and aspiration [18]. Thus, pneumonia, not always recognized as aspiration pneumonia, is a very common cause of death in patients with dementia [19]. In addition to these dementia-specific problems, multiple comorbidities of older patients may as well lead to reduced food intake and malnutrition. As a typical example of clinical experience, it may be described that dementia patients often do not explicitly report pain, which may lead to agitation and malnutrition instead.

The majority of persons with dementia live in the community where care is provided by family caregivers [20]. Especially eating difficulties substantially contribute to caregiver burden. Family caregivers as well as professionals feel responsible for an adequate food intake of patients with dementia [21]. Male spousal caregivers seem to be more concerned about nutritional care than females, as they mostly are not familiar with household activities and cooking [22]. Therefore, female dementia patients are at higher risk of malnutrition than men [23]. Supervising shopping, cooking, and meals and assisting a demented person in daily routine are an everyday challenge, which is demanding and emotionally stressful. In particular dealing with the refusal of meals, the real causes of which is often difficult to find, is an extremely stressful situation for family caregivers.

Weight loss and malnutrition have adverse effects on general outcome, especially in older persons [24]. Loss of body weight results in loss of muscle mass, which leads to functional decline and frailty, and is associated with an increased risk of morbidity and mortality [25]. Regarding general nutritional status, a close relation between malnutrition in the form of weight loss [26, 27] and low BMI [23, 28] with disease

severity is documented in older patients with dementia. In addition, several prospective observational studies have demonstrated that weight loss and malnutrition are associated with accelerated disease progression and cognitive decline [26, 29–31]. Even in patients with very mild AD, a poorer nutritional status assessed by the Mini Nutritional Assessment was found to be a predictor of disease progression [32].

Energy in general and numerous specific nutrients play an important role for brain metabolism, brain integrity, and health. Energy is permanently required in large amounts, nutrition provides precursors of neurotransmitters, and brain tissue mainly consists of nutrients. It is well known that deficiencies of several micronutrients, e.g., thiamine, folate, and vitamin B12, are accompanied by cognitive disorders, and it is assumed that other nutrient deficiencies may also contribute to impaired cognition and dementia [33]. Epidemiological evidence suggests that specific dietary patterns such as Mediterranean diet may decrease the risk of dementia and cognitive decline and that vice versa unfavorable dietary patterns are associated with increased risk of dementia [34]. Low plasma levels of several nutrients are found in patients with cognitive impairment and dementia [35], which however may be caused by previous unfavorable dietary habits as well as being a metabolic or nutritional consequences of the disease.

7.3 Nutritional Support in Dementia

There is no evidence that the supplementation of any micronutrients is beneficial for patients without a deficiency of specific micronutrients [36]. Supplementation is therefore not recommended without verification of deficiency [36]. Considering the fact that folate and cobalamin deficiency are frequent findings in older persons, every person with the diagnosis of dementia should be screened for these deficiencies at time of first diagnosis [37]. If there is evidence for deficiency, the deficient micronutrients should be adequately supplemented [36], although there is no evidence for its beneficial effects from prospective randomized controlled trials. Some supplementation studies have been performed in patients with high homocysteine but normal serum levels of B-vitamins, which showed no beneficial results on cognition [36]. Such studies have not been performed in subjects with any deficiency, because it would be unethical to not supplement an overt deficiency. However, some uncontrolled studies demonstrated beneficial effects on cognition if a cobalamin deficiency is reversed [38, 39]. Therefore, patients with dementia should be screened for frequent deficiencies such as cobalamin deficiency and the deficiency should be reversed.

Because many patients with dementia demonstrate weight loss even in the initial phase of the disease, every dementia patient should be screened for weight loss and other signs of malnutrition [36]. The body weight history should be documented and patients should be rescreened on a regular basis. If weight loss or other signs of malnutrition occur, nutritional support should be performed immediately. Besides the general principles of nutritional support such as elimination of potential causes of malnutrition, enrichment of food, and offering oral nutritional supplements (see Chap. 4), there are some dementia-specific approaches that will be summarized at

this point, based on the recommendations of a recently published evidence based guideline [36]. During all stages of the disease, it is important to offer regular meals in a homelike atmosphere without any distraction from eating. For patients living in a nursing home, it was demonstrated that meals offered in a family-style manner are supporting nutritional intake and weight gain of residents with dementia. For dementia patients living in the community, it has been shown that caregiver education concerning nutritional problems in dementia results in a significantly better weight course. If nutritional intake is insufficient despite these interventions, then enrichment of meals and if necessary oral nutritional supplements are indicated to cover the nutritional needs of dementia patients. Although there is no consistent evidence that the use of oral nutritional supplements has any beneficial effects on cognition, there is plenty of evidence for a reduction of complications and mortality in older persons. The systematic use of disease-specific medical foods for persons with dementia is not recommended, because the scientific evidence for any cognitive improvement is scarce.

If the nutritional intake is very low and tube feeding or parenteral nutrition is considered, the indication for artificial nutrition should be drawn with respect to the stage of the disease. If patients with mild or moderate dementia are in a crisis situation such as delirium, artificial nutrition should be performed like in any other patient without dementia to overcome the crisis situation, i.e., for a limited period of time. If the patient suffers from severe dementia, tube feeding is not recommended. Despite the fact that there are no randomized controlled trials about tube feeding due to methodological reasons, a large prospective observational study has not demonstrated any benefit on survival [40] and a benefit for the quality of life of such patients cannot be expected. However, each decision has to be made on an individual basis, and it is advisable to utilize formal ethical counseling or discuss the positive and negative aspects of the individual indication within the treatment team. Sometimes it may be advisable to recommend a treatment trial over a predefined period with predefined and documented treatment aims. During the decision-making process, one should be aware of the fact that artificial nutrition, especially the insertion of a percutaneous endoscopic gastrostomy, is a medical procedure that may induce considerable complications and mortality [41]. These risks have to be taken into account while weighing the advantages and disadvantages of artificial nutrition.

7.4 Nutritional Problems and Nutritional Support in Parkinson's Disease

Patients with PD often experience changes in body weight during the course of the disease. Both, weight loss and weight gain may occur, but weight loss is more frequent and is associated with increased dyskinesia, higher mortality, accelerated disease progression, and poor quality of life [42]. The causes of weight loss in PD are not yet clear. Particularly changes in energy expenditure and eating behavior seem to be associated with weight loss [43]. Weight loss may be already present at first diagnosis, and a meta-analysis has demonstrated that PD patients have significantly

lower BMI than healthy controls [44]. The worsening of dyskinesia and rigidity plays an important role in increasing energy expenditure, which is not sufficiently compensated by an adequate increase of energy intake [45].

Although weight loss is most prevalent in PD, weight gain is sometimes observed in the initial stages of the disease and is likely dependent on dopaminergic treatment, which improves motor symptoms and may modulate eating behavior [43]. Weight gain in the advanced stages of the disease is only seen in deep brain stimulation, due to a reduction of energy expenditure, reduced motor symptoms, and changes in eating behavior [46]. Although weight loss in PD mainly involves fat mass, with maintenance of skeletal muscle mass and comparatively low risk of sarcopenia [47], malnutrition has been associated with disease severity [42, 43]. Therefore, any weight loss in PD should be avoided and counteracted. If nutritional counseling was not effective, caloric enrichment of meals and oral nutritional supplements would be the next step. Depending on the duration and severity of the disease, nearly every PD patient develops oropharyngeal dysphagia which puts the patient at risk of aspiration pneumonia [48] but which also severely hampers nutritional intake. In this condition, sometimes tube feeding is necessary in addition to swallowing training, to provide adequate nutrition and medication for patients with advanced disease. The regular provision of medication via the tube will be an important argument for the advantages of tube feeding in this situation. However, the first treatment approach in PD with severe dysphagia should be the insertion of a nasogastric tube, which is mostly well tolerated and is sometimes only necessary for a limited period of time. Likewise in dementia the decision for or against tube feeding has to be made on an individual basis.

Patients with PD show also some changes of micronutrient status. Low levels of vitamin D have been associated with the risk of developing PD, and serum levels are lower in PD patients than in healthy controls [49, 50]. Supplementation of vitamin D should be considered as it may slow disease progression in patients with a high-risk genotype of the vitamin D receptor [51]. PD patients also present a lower bone-mineral density with increased risk for falls, which may increase the risk of fractures [52] that can be reduced by supplementation [53].

Interestingly, studies have shown that levodopa-treated PD patients have also lower circulating levels of folate and vitamin B12 [54, 55]. In addition, PD patients treated with levodopa show an elevation of homocysteine [56]. Administration of folate and vitamin B12 is effective in reducing homocysteine levels [57–59] and should be considered if serum levels of such vitamins are low.

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Pathophysiology, Diagnosis, and Medical Management of Dysphagia

8

Francesco Mozzanica, Nicole Pizzorni,
and Antonio Schindler

8.1 Introduction

Swallowing is a series of sequential coordinated events that ensures passage of any substance (food, liquid, saliva, mucus, drugs) from the mouth to the stomach via the pharynx and esophagus, avoiding the passage of the swallowed substance into the airway. Dysphagia is the term used to describe any difficulty in swallowing; therefore, the term dysphagia does not represent a medical diagnosis, but a symptom a patient reports to the physician; in common language and clinical practice, the term dysphagia also refers to any swallowing disorder, reported by the patient or recognized by a clinician through a clinical assessment or an instrumental examination [1]. Different diseases of different origins, neurological and non-neurological, may lead to dysphagia (Table 8.1). The importance in recognizing and managing dysphagia lies in the fact that, irrespective of the original disease, dysphagia can lead to severe complications such as aspiration pneumonia, malnutrition, and dehydration that severely impact patient's survival, clinical management, and health costs [2]. Adequate management of dysphagia is of pivotal importance for the neurologists as dysphagia complications are often the leading cause of mortality in several neurological diseases such as stroke, Parkinson's disease, motor neuron disease, and muscular diseases.

In this chapter basic information on swallowing physiology will be reported, so that pathophysiology of dysphagia can be better understood, together with dysphagia complications. Strategies commonly adopted to recognize and assess dysphagia are then analyzed and possible medical treatments outlined.

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Table 8.1 Major diseases causing dysphagia

Etiological category	Disease
Iatrogenic origin	Pharmacological treatment (chemotherapy, neuroleptic, etc.) Surgery (head and neck, brain, cervical spine) Radiotherapy (head and neck, brain)
Infectious origin	Tonsillitis Botulism Lyme disease Syphilis Mucositis (herpes, *Cytomegalovirus*, *Candida*, etc.)
Neurogenic origin (peripheral nervous system)	Connective tissue diseases (overlap syndrome) Dermatomyositis Myasthenia gravis Myotonic dystrophy Oculopharyngeal dystrophy Polymyositis Guillain-Barrè syndrome Sarcoidosis Paraneoplastic syndromes
Neurogenic origin (central nervous system)	Brainstem tumors Traumatic brain injury Stroke Cerebral palsy Huntington disease Multiple sclerosis Post-polio syndrome Tardive dyskinesia Metabolic encephalopathies Motor neuron diseases Parkinson's disease Dementia
Psychogenic origin	Phobic disorders Somatoform disorders
Structural origin	Upper esophageal achalasia Zenker's diverticulum Cervical scars Oropharyngeal, laryngeal, and esophageal tumors Cervical osteophytes

8.2 Swallowing Physiology

Swallowing physiology is a complex process; for teaching purposes seven stages can be identified in adults' swallowing (Table 8.2, Fig. 8.1) [3–5]. In the oral preparatory stage, the food is taken into the mouth, chewed and insalivated, while the largest concentration and variety of receptors of the whole body analyze taste, odor, texture, and temperature. For mastication chewing muscles elevate the mandible, the anterior neck muscles actively open the mouth, while the tongue moves the food in the molar region and the buccinators push it from the vestibulum oris. This phase is fully voluntary and conscious in normal adults. When the bolus is

Table 8.2 Function and localization of swallowing stages

Stage	Function	Localization
Anticipatory	Preparing the anatomical structures involved in swallowing and digestion through the vision and smell of food, which excite salivation and gastric secretion and activate cranial nerves	Extraoral
Extraoral preparatory	Modifying the consistency, viscosity, temperature, and volume of food before it enters the oral cavity, also involving the use of dishes, cutlery, chopsticks etc.	Extraoral
Oral preparatory	Converting food particles into a bolus through mastication, tongue manipulation, and salivation	Oral cavity
Oral Transport	Propelling the bolus posteriorly in order to trigger the swallowing response	From tongue surface to the faucial pillars
Pharyngeal	Propelling the bolus through the pharynx and upper esophageal sphincter to the esophagus and switching the oropharynx from respiratory to swallowing configuration	From the faucial pillars to the upper esophageal sphincter
Esophageal	Transporting the bolus to the stomach through the esophagus	From the upper esophageal sphincter to the lower esophageal sphincter
Gastric	Digesting the bolus and absorbing the digested nutrients	From the lower esophageal sphincter to the duodenum

considered ready to be swallowed by the sensory oral systems, it is placed in the middle of the tongue and pressed against the palate by sequential contraction (oral transport stage). As the bolus reaches the faucial pillars, the so-called swallowing reflex starts, and the pharyngeal phase takes place; its complexity emerges as a consequence of the common shared pathway between the respiratory and gastrointestinal pathways [6]. In order to prevent passage of food into the airway, the pharynx configuration should change from respiratory to digestive, and apnea should be inserted in normal breathing; velopharyngeal closure, laryngeal elevation and anteriorization, laryngeal closure including tilting of the epiglottis, and relaxation of upper esophageal sphincter (UES) are the key points of pharyngeal reconfiguration, while tongue base retraction and pharyngeal peristalsis are the driving force for moving the bolus from the oral cavity into the upper esophagus. Laryngeal elevation is obtained by the contraction of suprahyoid muscles and laryngeal closure relies on intrinsic laryngeal muscles, while epiglottic tilting results as a combination of tongue base retraction, bolus pressure, and laryngeal elevation/anteriorization. UES opening is due to laryngeal anteriorization, cricopharyngeal muscle (CM) relaxation, and bolus pressure [7]. The most common pattern of swallowing/breathing coordination is expiration-swallowing-expiration; only in rare cases, swallowing is followed by inspiration [8]. The pharyngeal phase is automatic and not conscious. Once in the esophagus, the bolus proceeds to the stomach thanks to esophageal peristalsis, a mechanism mainly related to intrinsic

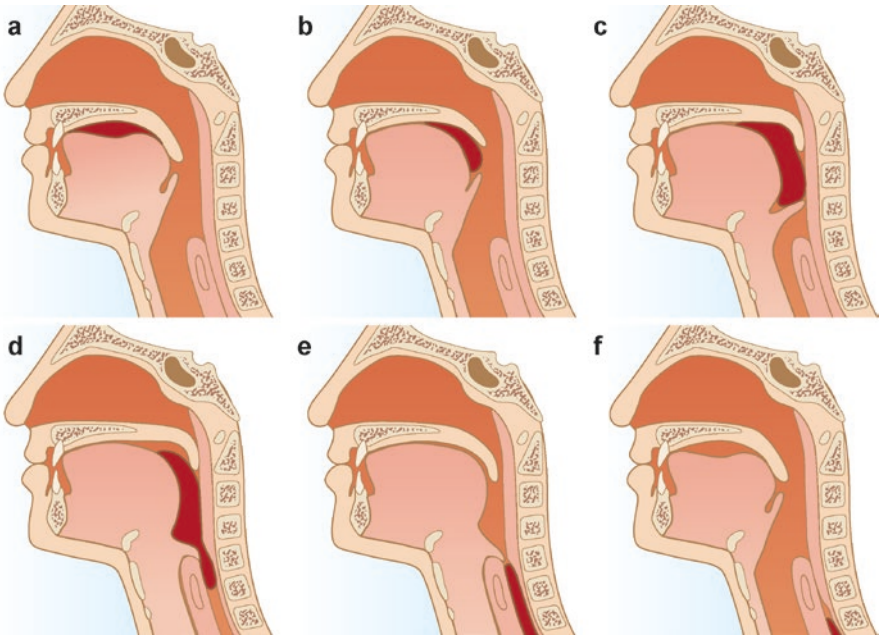

Fig. 8.1 Schematic representation of the different phases of swallowing. (**a**) oral phase: the bolus (represented in *red*) lies in on the midportion of the tongue; (**b**) end of the oral phase: the bolus has reached the faucial pillar and lies on the tongue base; (**c**) pharyngeal phase: the bolus is in the valleculae, and the soft palate is elevated; (**d**) pharyngeal phase: the bolus is in the pharynx, and the epiglottis is inverted; (**e**) esophageal phase: the bolus is passing through the upper esophageal sphincter; (**f**) esophageal phase: the bolus is passing in the cervical esophagus

nerve plexuses in the esophagus and characterized by the relaxation of the downstream smooth muscles and contraction of the upstream smooth muscles. The passage of the bolus into the stomach is possible thanks to the relaxation of the lower esophageal sphincter (LES); during the gastric phase, the bolus lies in the stomach, and the LES prevents reflux into the esophagus, while the pylorus avoids premature passage into the duodenum.

8.2.1 Neurophysiology of Swallowing

Cerebral neuronal activation influences the mechanical behavior of the pharynx and esophagus. Two regions of the central nervous system (CNS) have a role in the control of swallowing: the brain stem and the supramedullary areas. The brain stem is responsible for the reflex part of the swallowing mechanism: both the sensory and motor nuclei of the cranial nerves involved in swallowing as well as the interneurons connecting them lie in this part of the CNS; moreover the sequential and rhythmic patterns of motor neurons controlling the swallowing muscles are generated by a group of neurons of the medulla oblongata, called as the central pattern generator.

Afferent inputs from cranial nerves V, IX, and X, of which the superior laryngeal branch, the superior laryngeal nerve, is the most important, represent one possible way to trigger pharyngeal swallowing. The brain stem sequential activity may be triggered or modulated also by the supramedullary regions including the supplementary motor area, the pre- and postcentral gyri, the insula, the anterior cingulate gyrus, the basal ganglia, and the cerebellum [9].

A large number of oral and pharyngeal reflexes are controlled by the neuronal connections of the brain stem and play a vital role in the complex behavior of swallowing (Table 8.3); these reflexes modify motor neurons' activity, which receive synaptic input from supramedullary regions, and function as supporting networks of neurons assisting in the control of complex motor responses, such as speech,

Table 8.3 Oral and pharyngeal reflexes: sensory input, motor output, and effect of each reflex are shown

Type of reflex	Sensory input	Motor output	Effect
Tongue-tongue reflex	Touching tongue	Hypoglossal motor neurons	Tongue tip orients toward stimulus
Lip-lip reflex	Tap upper lip	Facial motor neurons	Lip muscles contract
Oral-lip reflex	Intraoral pressures	Facial motor neurons	Excite lip muscles
Tongue-facial reflex	Hypoglossal nerve	Facial motor neurons	Excite facial muscles
Lingual-hypoglossal reflex	Lingual nerve or mechanical stimulation of tongue	Hypoglossal motor neurons	Excite or inhibit different tongue muscles
Masseter-hypoglossal reflex	Masseteric nerve	Hypoglossal motor neurons	Inhibit tongue muscles and excite tongue-protruding muscles
Inferior alveolar-hypoglossal reflex	Inferior alveolar nerve	Hypoglossal motor neurons	Inhibit both tongue-protruding and retrusive muscles
Glossopharyngeal-hypoglossal reflex	Glossopharyngeal nerve	Hypoglossal motor neurons	Excite protrusive muscle/ some intrinsic muscles and inhibit retrusive muscles
Jaw-hypoglossal reflex	Rotating and opening jaw	Hypoglossal motor neurons	Opening jaw increases tongue protruding
Temporalis-hypoglossal reflex	Temporalis muscle	Hypoglossal motor neurons	Stretching temporalis increases styloglossus activity
Taste-hypoglossal reflex	Glucose to tongue	Hypoglossal motor neurons	Lateral tongue movement to side of stimulus
Oral/jaw-closing muscles reflex	Oral region	Trigeminal motor neurons	Primarily inhibiting jaw-closing muscles
Jaw-opening reflex	Oral region	Trigeminal motor neurons	Jaw lowers

(continued)

Table 8.3 (continued)

Type of reflex	Sensory input	Motor output	Effect
Periodontal-masseteric reflex	Periodontal region	Trigeminal motor neurons	Jaw lowers
Lateral mandibular reflex	Rapid pressure on incisor	Trigeminal motor neurons	Jaw moves to contralateral side
Gag reflex	Oropharyngeal region	Nucleus ambiguus, trigeminal and hypoglossal motor neurons	Expulsion movements
Apneic reflex	Lingual nerve, water on laryngeal surface of epiglottis	Phrenic and nucleus ambiguous motor neurons	Cessation of breathing
Aspiration reflex	Trigeminal nerve branches, glossopharyngeal branches	Phrenic motor neurons	Brief inspiratory burst
Respiration reflexes	Pharyngeal region	Intercostal motor neurons, autonomic ganglionic neurons	Forced expiration, bronchi secretions and constriction
Cardiovascular reflexes	Pharyngeal region	Autonomic ganglionic neurons	Bradycardia

Adapted from Miller [10]. Reprinted from Crit Rev Oral Biol Med, 13, Miller AJ, Oral and pharyngeal reflexes in the mammalian nervous system: their diverse range in complexity and their pivotal role of the tongue, 409–425, 2002, with permission from SAGE Publications

intraoral transport of food, chewing, and swallowing [10]. Supramedullary control of swallowing is an area of active research through animal models as well as different kinds of brain imaging techniques; although definitive understanding is not reached, five functional modules have been suggested: (1) sensorimotor areas and the cingulate cortex, establishing a sensorimotor output for which other areas converge; (2) the inferior frontal gyrus, corpus callosum, basal ganglia, and thalamus, involved in movement planning and implementation of other voluntary motor behaviors; (3) the premotor cortex and posterior parietal cortex, serving to integrate sensory information about the bolus with the internal representation of swallowing movements; (4) the cerebellum, whose role is to facilitate the modulation of the internal representation for swallowing and coordination among the multiple effectors and effector states during swallowing; (5) the insula, recruited for synchronizing the kinematics of the movements [11].

8.3 Pathophysiology of Dysphagia

Different diseases of neurologic and non-neurologic origin may cause dysphagia. For appropriate dysphagia management, disease diagnosis and treatment are often not sufficient, and the mechanism underlying swallowing impairment should be found. The major signs of dysphagia are penetration (Fig. 8.2) and aspiration (Fig. 8.3), residue

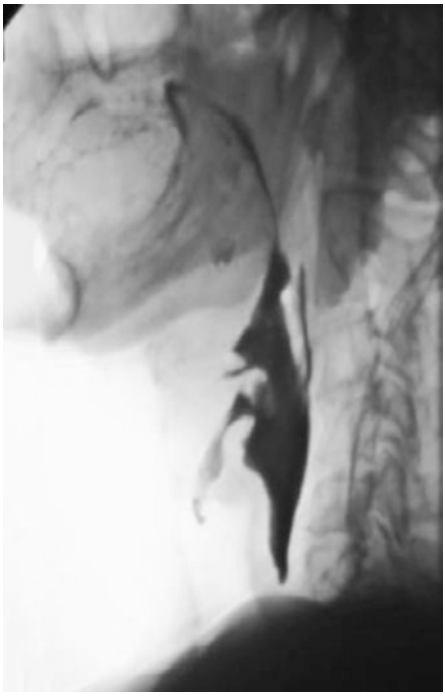

Fig. 8.2 Videofluoroscopic image of a penetration

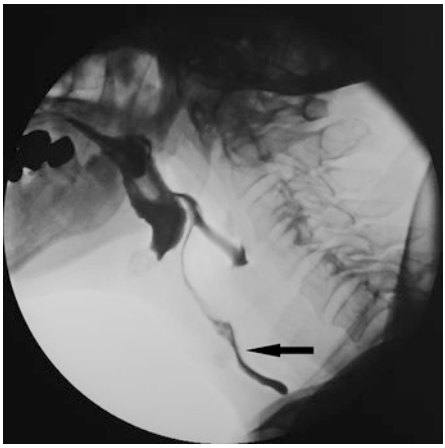

Fig. 8.3 Videofluoroscopic image of an aspiration: the *arrow* shows the portion of the bolus that is going down the trachea

along the oropharyngoesophageal tract (Fig. 8.4) and regurgitation either from the oropharynx into the rhinopharynx or from the esophagus into the hypopharynx. The term penetration means that part of the bolus enters the laryngeal vestibule, while aspiration means that the bolus passes the vocal folds and reaches the tracheobronchial tree. Penetration and aspiration usually cause reflexive cough, but in cases of laryngeal and/or tracheobronchial sensitivity reduction, cough may be absent (silent penetration/aspiration). Penetration/aspiration may be divided in pre-deglutitive, intra-deglutitive, and post-deglutitive depending whether it occurs respectively before, during, or after the swallowing reflex has started [12]. While dysphagia signs confirm the presence of a swallowing impairment, the underlying mechanism should be identified for appropriate treatment (Table 8.4) [13].

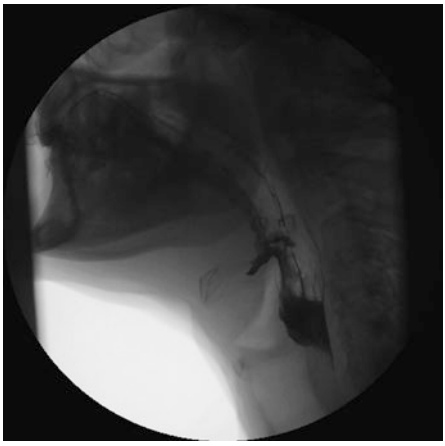

Fig. 8.4 Videofluoroscopic image of residue in the pyriform sinuses

Table 8.4 Mechanisms underlying the signs of dysphagia

Dysphagia signs	Underlying mechanism	Description
Pre-deglutitive penetration/aspiration	Spillage	During oral bolus preparation or bolus transport, the bolus prematurely passes into the pharynx, while the larynx and the pharynx are in respiratory configuration
	Delayed swallowing reflex	The triggering of pharyngeal reconfiguration is delayed
Intra-deglutitive penetration/aspiration	Functional laryngeal closure defect	Vocal fold paralysis
	Structural laryngeal closure defect	Defect due to surgery (cordectomy, partial laryngectomy)
Post-deglutitive penetration/aspiration	Residue	The residue in the valleculae or in the pyriform sinus is aspirated during post swallow inspiration
	Esophago-pharyngeal regurgitation	The bolus regurgitate into the pharynx and is aspirated during post swallow inspiration

Table 8.4 (continued)

Dysphagia signs	Underlying mechanism	Description
Oral residue	Tongue weakness	Due to structural of muscular impairment, the tongue does not move the whole bolus into the pharynx
	Uncoordinated tongue movements	Due to poor coordination, the tongue does not move the whole bolus into the pharynx
Valleculae residue	Tongue base propulsion deficit	Due to structural of muscular impairment, the tongue base does not move the whole bolus into the hypopharynx and esophagus
	Pharyngeal obstruction	Due to intrinsic or extrinsic pharyngeal obstruction, part of the bolus cannot reach the hypopharynx and esophagus
Pyriform sinus residue	Reduced laryngeal elevation	Due to poor laryngeal elevation, the UES is not adequately opened
	Reduced pharyngeal propulsion	Due pharyngeal weakness/paralysis, the pharyngeal stripping wave is reduced
	Defective UES relaxation	Due to neurogenic mechanisms, the UES does not relax during swallowing
	Obstruction of the cervical esophagus	Due to intrinsic or extrinsic cervical esophageal obstruction, part of the bolus cannot reach the esophagus
Nasal regurgitation	Structural deficit of the velopharyngeal sphincter	Due to malformation or previous surgery, the velopharyngeal sphincter does not separate the rhinopharynx from the oropharynx
	Functional deficit of the velopharyngeal sphincter	Due to pharyngeal paralysis, the velopharyngeal sphincter does not separate the rhinopharynx from oropharynx
	Pharyngeal phase incoordination	Due to incoordination the bolus passes into the pharynx, while the velopharyngeal sphincter is open
	Residue in the pharynx	Sever residue in the pharynx may move into the rhinopharynx after the swallow
Esophago-pharyngeal regurgitation	Esophageal obstruction	Due to intrinsic or extrinsic esophageal obstruction, part of the bolus cannot reach the stomach and regurgitate into the pharynx
	Esophageal motility impairment	Due to esophageal motility impairment, part of the bolus cannot reach the stomach and regurgitate into the pharynx
	Zenker's diverticulum	The bolus accumulates into the diverticulum and regurgitate into the pharynx
	Defective UES relaxation	Due to neurogenic mechanisms, the UES does not relax during swallowing, and part of the bolus regurgitates into the pharynx

8.4 Complications of Dysphagia

Dysphagia complications include but are not limited to aspiration pneumonia, malnutrition, dehydration, and chronic aspiration; while pulmonary complications are the result of impaired safety of swallowing leading to tracheobronchial aspiration, malnutrition and dehydration are due to impaired efficacy of swallowing with reduced oral intake of nutrients.

8.4.1 Aspiration Pneumonia

Pulmonary complications are probably the most common and severe complications of dysphagia. They are the results of an impaired balance between defense mechanisms of the lower respiratory tract, oropharyngeal bacterial colonization, and impaired efficacy of swallowing with aspiration of the bacteria [14] (Fig. 8.5). The lower respiratory tract is protected by several defense mechanisms: airway clearance, including both cough and mucociliary action, lymphatic clearance, and cellular immune defense by macrophages, lymphocytes, and neutrophils. Several clinical conditions can reduce these defense mechanisms, increasing the risk of pulmonary complications whether food or liquid aspiration occurs. Among pulmonary complications, aspiration pneumonia is defined as the development of an infiltrate in the dependent portions of the lung in people who are at increased risk for aspiration of oropharyngeal contents (microaspiration) containing bacteria with associated symptoms and signs of lung infection [15]. Different papers showed an increased relative risk of developing pneumonia in patients with aspiration; however, the role played by the various risk factors was not equal in the different populations [16–21]. Other factors, such as advanced age, medical conditions, mental status, poor nutritional status, and oropharyngeal colonization of pathogenic bacteria appeared as risk factors for developing aspiration pneumonia [22]. The role of oral care has been investigated in a series of studies [23–25]; it has been demonstrated that oral care reduces pneumonia and death from pneumonia in both dentate and edentate patients [25].

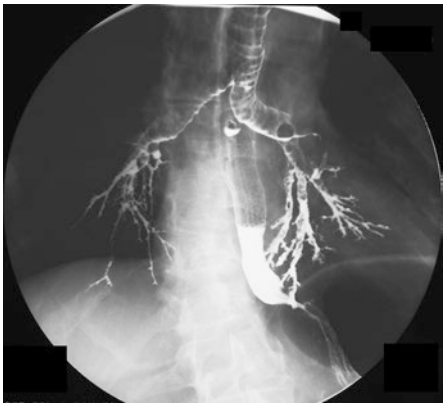

Fig. 8.5 Videofluoroscopic image of an aspiration: the contrast material in the tracheobronchial tree is clearly visible

8.4.2 Dehydration

Dehydration is frequently reported in hospitalized or institutionalized patients**.** Clinical factors, as undiagnosed dysphagia or cognitive impairment, sociocultural factors, as inability to speak, and institutional factor, as inadequate number of knowledgeable staff, contributed to inadequate fluid intake [26]. When the presence of dysphagia is recognized and aspiration of thin liquids is reported through an instrumental assessment of swallowing, thickened liquids are often recommended [27], in particular when a coexisting language and/or cognitive impairment reduce the possibility to effectively use compensatory strategies (e.g., postures) that may reduce aspiration of thin liquids. Despite the reduction of liquids' aspiration, different studies report an inadequate liquid intake (<1500 ml/day) in poststroke patients requiring thickened liquids [28–31], while the positioning of enteral nutrition has a significant and positive impact on dehydration in patients with severe dysphagia [29]. Factors associated with poor fluid intake in poststroke patients with thickened liquids are the presence of functional deficits in cognition reducing the compliance with clinicians' recommendation, the frequency of beverage offerings and the availability of thickened liquids to patients, and the inaccurate preparation of thickened beverages, often too thick [30]. Therefore, fluid intake in poststroke dysphagic patients could be increased with protocols for the provision and monitoring of thickened liquids' consumption, through adequate education of nursing staff and caregivers, and by integrating hydration using non-oral supplementary routes.

8.4.3 Malnutrition

Malnourishment is common in hospitalized patients with a prevalence of up to 50% in surgical, medical, geriatric, and stroke patients [32]. This reported high prevalence is related to a number of factors, including sensory losses, chewing or swallowing problems, and anorexia, together with acute or chronic diseases that may compromise dietary intake and lead to nutritional deficiencies and malnutrition [32].

As far as the swallowing problems are concerned, the relationship between dysphagia and malnutrition is debated. A recent systematic review concluded that the odds of malnutrition were increased in elderly, frail and institutionalized persons, in patients with excessive polypharmacy, general health decline, cognitive decline, eating dependencies, and dysphagia [33]. However, only five of the eight studies included in the review reported significant associations between dysphagia and malnutrition, and the pooled analysis revealed a significant effect only for trials conducted several weeks following stroke.

It is possible that malnutrition may develop as a consequence of dysphagia if nutritional intake is substantially reduced in relation to requirements over the course of days or weeks. For those who are able to eat orally, fear of eating and/or choking, unwillingness to eat, and the decreased palatability of texture-modified diets may lead directly to inadequate intake. However, other factors that often accompany dysphagia may also have an impact indirectly on an individual's desire or ability to eat. This is

particularly true in neurologic patients where fatigue, motor impairment, visuospatial perceptual problems, depression, and cognitive deficits may be contributory.

8.4.4 Chronic Aspiration

Chronic aspiration may not cause acute infections within the lungs (aspiration pneumonia) but can lead to diseases such as chronic lipoid pneumonia, obliterative bronchiolitis, and diffuse aspiration bronchiolitis. Typically, the aspiration is silent, and the patient often presents with slowly progressive symptoms of cough, shortness of breath, recurring fevers, and lung opacities on chest radiograph. On CT scan the disease usually presents as diffuse basilar centrilobular nodules and/or tree-in-bud pattern with airway and interstitial thickening. Often the diagnosis is not elucidated until biopsy reveals granulomatous inflammation associated with particulate matter consistent with oral or gastric origin, such as vegetable, lipid, or talc particles. Chronic occult aspiration has been associated with refractory asthma and idiopathic pulmonary fibrosis [34].

8.5 Dysphagia Assessment

Dysphagia assessment is of pivotal importance not for the search of the etiology but also to identify patients with dysphagia, recognize its severity, estimate risk of complications, and provide the most appropriate management.

8.5.1 Screening

The prevalence of dysphagia exceeds 50% in stroke patients, accounts for 10–30% of individuals older than 65 years, and may be as high as 84% in patients with Parkinson's disease [35]; in many of them, dysphagia is not recognized. Early identification of dysphagia is mandatory since it can reduce the incidence of clinical complications and may improve the outcome in these patients; for these reasons several dysphagia screening tools have been proposed [36]. The large part of them have been developed for stroke population, and only a few screening tools are available for patients with different diagnoses. One of the most promising of them is the Royal Brisbane and Women Hospital (RBWH) dysphagia screening tool [37]. This is a nurse-administered, evidence-based swallow screening tool, based on the triaging concept that can be applied in everyday clinical practice in the management of dysphagia in heterogeneous populations. The RBWH dysphagia screening tool consists of three steps: (1) a two-phase question screen; (2) a water swallow test, as appropriate; and (3) a swallowing management plan. The two-phase question screen reflects the perception that identification of "at-risk" patients should come from a combination of (1) previous medical history/records and (2) specific clinical indicators. The second phase consists of a water swallow test with 90 ml of water. The nurse is prompted to observe for (1) coughing during or between swallows or up to 1 min after swallowing, (2) wet or "gurgly" voice quality post swallow, and

(3) increased respiratory rate post swallow [37]. Depending on the results of the screening evaluation, patients with a positive result in the dysphagia screening examination are referred to a swallowing specialist.

8.5.2 Bedside Evaluation (BSE)

The bedside examination (BSE) is the clinical assessment performed by a swallowing expert, usually a speech and language pathologist, without the support of any instrument; the aims are to detect the presence of an alteration of the swallowing process, to decide how to provide nourishment to the patient, to set the rehabilitation goals and program, and to underline the need of an instrumental assessment. The BSE also includes the assessment of aspects different from swallowing, guiding the clinician in the identification of possible barriers, facilitators, and patient's resources.

The BSE should include:

- Collection of anamnestic data, i.e., diagnosis, medical history, previous clinical and instrumental assessments of dysphagia, rheological modifications of liquids and foods, and recent modification of nutritional status, respiratory status, alcohol abuse
- Observation of vigilance, communication efficacy, presence and characteristics of tracheal cannula, sialorrhea, oral hygiene, presence of neglect, auditory and visual defects, and independence
- Morphodynamic assessment of swallowing structures (the lips, tongue, hard and soft palate, jaw, larynx, and head and trunk control)
- Oral praxis assessment
- Sensitivity assessment
- Normal reflexes assessment (cough, gag, and swallowing reflex)
- Pathological reflexes assessment
- Swallowing trials with different consistencies and volumes

Several studies have demonstrated that as nowadays there still exists an inconsistency in the clinical assessment of dysphagia [38, 39]. However, different protocols including all the aspects that should be investigated during the BSE are available in literature. In particular, one of the most widespread protocols is the Mann Assessment of Swallowing Ability (MASA) [40]. After BSE the main pathophysiologic signs of impaired swallowing can be detected; however, pathophysiologic interpretation of signs may be difficult. Moreover, silent aspiration cannot be detected.

8.5.3 Instrumental Assessment of Swallowing

The aim of instrumental assessment of swallowing is to perform a thorough assessment of swallowing in order to understand whether a disorder is present, oral feeding is safe, or rehabilitation is necessary. In order to perform instrumental assessment, specific knowledge and skills are necessary; if the examiner holds only part of the

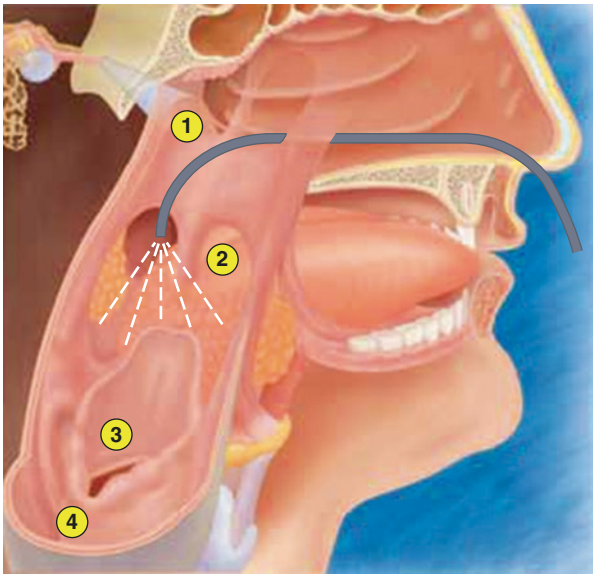

Fig. 8.6 Schematic representation of a fiber-optic endoscopic examination: the endoscope is passed through the nose and lies just below the soft palate. The numbers show the position; the tip of the endoscope should have to study the soft palate and the velopharyngeal movements (number 1), the oropharynx and the larynx (number 2), the vocal folds and the upper trachea (number 3), and the cricopharyngeal region (number 4)

requested knowledge and skills, an incomplete examination will be performed, the information obtained will be misleading, the prescription inadequate, and the clinical decision potentially wrong.

The acronym FEES (fiber-optic endoscopic evaluation of swallowing) is usually applied to mean the assessment of swallowing thanks to a flexible endoscope (Fig. 8.6). FEES may be performed in different settings: at the bedside, in the office, and at home; depending on the circumstances, instrumentation may vary, but a fiberscope and a light source are always needed. The procedure to perform FEES may be divided into five major steps: swallowing structures anatomic assessment; swallowing structures' sensorimotor assessment, secretion management, bolus transit assessment with foods of different volumes (5 cc, 10 cc, 20 cc), and consistency (thin liquid, nectar, honey, puree, soft solid, solid); response to therapeutic maneuvers; and interventions to improve swallowing. All the swallowing structures should be fully observed including the rhinopharynx, the velum, the oro- and hypopharynx, the larynx, the upper part of the trachea, the pyriform sinuses, and the retro-cricoid region, the tongue base, and the valleculae. The assessment of swallowing structures' motion is of key importance as it gives information on the neuromotor functionality of the system; it includes specific maneuvers to examine individual movements such as blowing to assess velopharyngeal movements, squeezing maneuver (high-pitch strained voice) to assess pharyngeal wall motion, breathing, voicing to assess laryngeal movement, and Valsalva maneuver to assess laryngeal

vestibule closure. In order to assess laryngeal sensibility, the tip of the scope could gently touch the epiglottis, the arytenoids, the laryngeal vestibule, and the vocal folds. In the presence of secretions, its characteristics (serous, mucus), site (oro-/hypopharynx, larynx), and spontaneous or induced management are also of key importance to understand the physiology of swallowing structures. The most important part of the FEES is the assessment of bolus transit: the scope could be positioned just below the velum (high position) or close to the laryngeal vestibule (low position), according to whether the examiner is more interested in a general view of the pharynx and larynx or is more focused on the larynx. At least three food consistencies should be used (liquids, puree, solid), with increasing volumes for each consistency. One of the major advantages of FEES is its versatility as any kind of food could be tested. Finally, the main postures and maneuvers according to their specific rationale (see following chapter) should be tested in case a swallowing impairment is found. In selected cases FEES can also be used for rehabilitation as a biofeedback system.

During bolus transit, FEES does not allow to see the bolus itself. In fact as the bolus enters the oropharynx, the pharyngeal phase of swallowing is triggered, and the pharynx changes its configuration from respiratory to swallowing: the tongue base retracts, the pharyngeal wall is squeezed, and the vision is lost (so-called whiteout phase). As the respiratory configuration of the pharynx is restored, the whiteout phase ends, and the bolus is already in the esophagus. The main abnormal findings include (1) anticipated passage of the bolus from the oral cavity to the oro- and hypopharynx; (2) pooling of the part of the bolus in the oral cavity, in the valleculae (Fig. 8.7) or in the pyriform sinuses (Fig. 8.8); (3) penetration and aspiration (Fig. 8.9); (4) regurgitation from the oropharynx in the rhinopharynx; and (5) regurgitation from the esophagus into the pharynx. The understanding of the underlying mechanism is of key importance for the interpretation of FEES [41].

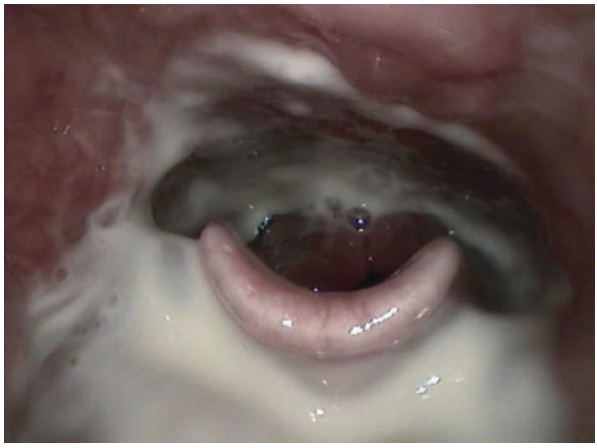

Fig. 8.7 Video-endoscopic image of a fiber-optic endoscopic examination of swallowing: residue of pudding in the valleculae and coating of the pharyngeal wall are clearly visible

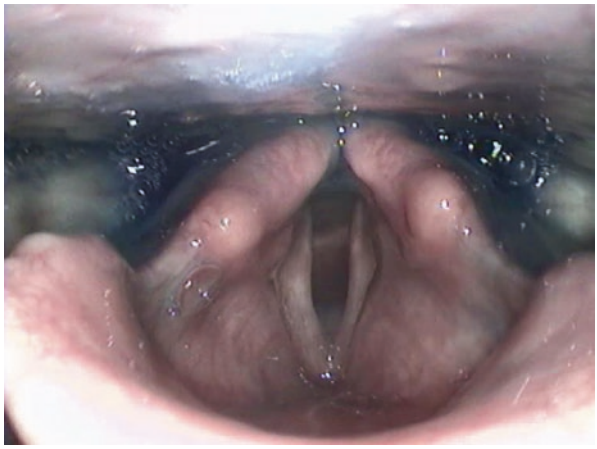

Fig. 8.8 Video-endoscopic image of a fiber-optic endoscopic examination of swallowing: residue of blue dyed water in both pyriform sinuses are clearly visible

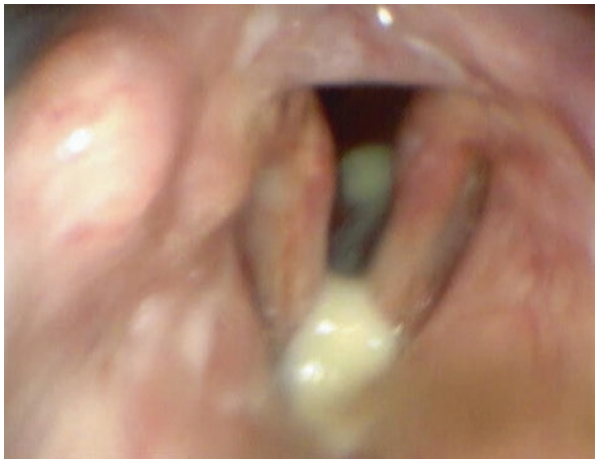

Fig. 8.9 Video-endoscopic image of a fiber-optic endoscopic examination of swallowing: part of the semisolid bolus lies in the anterior commissure and part is clearly visible below the vocal folds

The videofluoroscopic swallow study (VFSS) is a radiologic technique providing a comprehensive evaluation of the oral, palatal, pharyngeal, pharyngoesophageal, and esophageal segments of swallowing. The patient is positioned upright in an examination chair within the fluoroscopy unit in the lateral position and then in anterior-posterior view. The protocol proceeds in a stepwise fashion. Patients are administered liquid, nectar, honey, and puree barium of precise aliquot of increasing volumes; barium-coated solids are also administered. For each bolus the patient is asked to hold the bolus in the oral cavity and swallow when asked to; the whole process is video-recorded with a frame rate of 25–30 frames per second, in order to interpret the examination after the examination and not while performing it. Frame-by-frame analysis is often necessary for precise interpretation of the VFSS. During VFSS not only the contrast bolus is clearly visible but also the following structures and their movements: the lips, mandible, maxilla, tongue, velum, hyoid bone,

vallecula, epiglottis, arytenoid cartilage, false vocal folds, true vocal folds, laryngeal vestibule, pyriform sinuses, pharyngeal muscles, CM, trachea, and cervical spine.

Abnormal findings assessed through VFSS include prolonged oral preparation time, tongue pumping due to difficulty in triggering the pharyngeal phase, and serial swallows also known as piecemeal deglutition due to weakness of the oral and pharyngeal musculature, poor bolus formation, oral stasis, poor mastication, nasal regurgitation, delayed swallowing reflex, penetration/aspiration, reduced hyoid elevation, reduced laryngeal elevation, vallecular or pyriform residue, deviant epiglottic function, reduced laryngeal elevation, cricopharyngeal bar due to a defect in cricopharyngeal opening or closing, pharyngeal diverticula, esophageal diverticula, strictures and rings, and esophageal motor impairment.

FEES and VFSS can be considered the two frontline instrumental examinations to assess a person with a potential or known swallowing impairment; both FEES and VFSS can be used to test treatment strategies (see Chap. 9). These two examinations should not be considered overlapping but rather complementary, as the information they provide are not the same. VFSS allows better assessment of oral phase, allows assessment of esophageal phase, and should be considered the optimal examination, especially for cricopharyngeal dysfunction evaluation; on the other side, FEES allows better definition of residue, penetration, and secretion management; besides, FEES can be prolonged and is a better examination for assessment of fatigue. Finally, FEES can be performed consecutively as needed and in almost any setting, regardless of patient positioning and general conditions [42].

8.5.4 High-Resolution Manometry

High-resolution manometry (HRM) is a diagnostic system that measures intraluminal pressure activity in the gastrointestinal tract from the pharynx to the stomach using a series of closely spaced pressure sensors during 5 ml of liquid swallow. HRM provides a topographic mapping of the space-time patterns of hypopharyngeal pressures by means of colored contour plots emerging from 36 sensors spaced at 1 cm interval. Three-dimensional data are displayed on a two-dimensional planar surface: the pressure levels as color bars (mmHg), the sensor position (cm) on the y-axis, and the time (s) on the x-axis. Mainly developed for esophageal diagnostics, its application in the pharynx is getting an increasing importance. For this purpose the oropharyngeal swallowing process can be viewed as a pressure generation mechanism powered by a two-pump system, the oropharyngeal propulsion pump and the hypopharyngeal suction pump. The oropharyngeal pump reflects the combined activity of the tongue base muscles and the upper pharyngeal constrictor muscles, while the hypopharyngeal suction pump reflects the suction forces in the pharyngeal chamber which are the result of the antero-cephalad movement of the hyoid-laryngeal complex. At that same instant, the CM relaxes, enabling traction forces to open it, while the lower pharyngeal constrictor muscles push the bolus

into the esophagus. Various features can be defined, such as the UES resting pressure, duration of UES relaxation, nadir pressure during relaxation, duration and pressure of UES post relaxation contraction, peak pharyngeal pressure, intrabolus pressure, and the coordination of the pharyngeal peak within the UES relaxation period [43].

8.5.5 Other Assessment Tools

While FEES and VFSS represent the two gold standard techniques, other instrumental tools have been developed. Each of them can have a diagnostic role for specific clinical conditions but may be misleading if not applied after clinical examination and either FEES or VFSS. The two most important instrumental assessment tools besides those previously described are the oropharyngoesophageal scintigraphy (OPES) and the electromyography of swallowing (EMGS). During OPES the patient is given liquid or semisolid with radionuclide technetium-99 and is asked to swallow while placed under a gamma camera. Thanks to the gamma camera, a quantitative picture of radionuclide transit and metabolism can be shown as a plot of radioactivity versus time; while OPES has suboptimal temporal and anatomical resolution, it represents the ideal tool for quantification of residue and aspiration [44]. EMGS allows optimal analysis of muscle contraction duration. Usually EMGS includes surface EMG of submental muscles, needle EMG of the CM, and application of a mechanical transducer on the larynx; simultaneous recording from these three lines allows optimal temporal analysis of submental muscle contractions, laryngeal elevation, and cricopharyngeal relaxation. EMGS is the optimal technique for the identification of CM relaxation impairment that may be treated through botulinum toxin injections [45].

8.6 Medical Management of Dysphagia

8.6.1 Treatment of the Original Disease

As stated in the introduction of this chapter, dysphagia is not a disease, but it is a symptom or a sign of a given disease. Management of dysphagia starts with adequate diagnosis and provision of the best treatment available of the underlying disease. Although dysphagia is often caused by neurological diseases for which no significant treatment is available, as in the case of motor neuron disease, in some other cases, a pharmacological treatment can dramatically improve the clinical condition, as, e.g., in myasthenia gravis. It is therefore imperative to properly treat all neurological diseases, keeping in mind that improvement in neuromuscular function might impact swallowing also; for example, L-DOPA can improve movements in patients with Parkinson's disease and, if given before mealtime, can improve swallowing too.

8.6.2 Pharmacological Treatment

Swallowing physiology relies on a complex neuromuscular chain of events, regulated by a network of neurons throughout the brain; it is therefore theoretically possible to improve swallowing function by pharmacologic agents that act on the regulation of neurotransmitters involved in these systems. While research is trying to move forward in this direction, especially stimulating the availability of substance P for glossopharyngeal and superior laryngeal nerve, eventually using irritants to the pharynx as capsaicin, there is no evidence in the application of a pharmacological treatment in clinical practice [46].

While no pharmacological treatment to improve swallowing is available, a large number of medications, spanning several classes of pharmacological agents, have undesirable effects on swallowing and should be avoided if possible. One of the most common causes of medication-induced dysphagia is xerostomia; dryness of the mouth impairs bolus transport, increasing the residue in both the oral cavity and the oropharynx. Medicines that depress CNS activity are another large class of medications that interfere with swallowing; decreased arousal and coordination induced by anxiolytics, antihistamines, antipsychotics, and opiates may contribute to dysphagia development. Medications such as theophylline, nitrates, calcium channel blockers, and benzodiazepines reduce LES tone, resulting in gastroesophageal reflux, which injure the mucosa of the upper aerodigestive tract and contribute to dysphagia [47].

8.6.3 Botulinum Toxin

Botulinum toxin is a protease exotoxin produced from *Clostridium botulinum*. It works by blocking the release of acetylcholine from cholinergic nerve endings causing inactivity of muscles or glands. Its effects are transient and may be graded by varying the dose and frequency of administration [48]. Botulinum toxin has been also used in the treatment of drooling (excessive pooling and poor control of saliva due to dysphagia). Drooling may occur in many patients with neurogenic dysphagia including those with cerebral palsy, neuromuscular diseases such as myasthenia gravis, amyotrophic lateral sclerosis, and neurodegenerative diseases such as Parkinson's disease. Local injection of botulinum toxin into the salivary glands under ultrasound guidance results in inhibition of cholinergic parasympathetic and postganglionic sympathetic activity causing a reduction of salivary secretion. The effect starts at 1 week and lasts for approximately 3–5 months after injection [49]. The botulinum toxin has been proposed for the treatment of CM incoordination causing dysphagia. The CM is the major component of the UES between the hypopharynx and the esophagus. It is a ring-shaped muscle with horizontal and oblique fibers. The structure and biochemical properties of the CM maintain constant basal tone and luminal occlusion at rest but allow rapid relaxation and contraction during swallowing. The muscle contraction closes the pharyngoesophageal segment, preventing the

esophageal reflux and air from entering the esophagus during inspiration. CM dysfunction may result from a delay or failure of relaxation of the fibers during deglutition. Often the underlying cause is not treatable, or it remains unknown. In these cases, EMG-guided botulinum toxin injections to the muscle can be performed either percutaneously [50] or endoscopically [51] and have been found to be effective in the treatment of this selective kind of dysphagia [52].

8.6.4 Surgical Treatment

Severe dysphagic patients with chronic aspiration and/or recurrent aspiration pneumonia, who failed an extensive nonsurgical swallowing rehabilitation, require a strict tube feeding regimen, either by means of a nasogastric tube or a percutaneous gastrostomy tube. However, this will not always result in a complete abolishment of chronic aspiration, as the production and swallowing of saliva will still continue; in addition, lifetime tube feeding is often considered unacceptable for many patients. For this reason, several surgical procedures aimed to the restoration of oral intake have been proposed [53].

UES myotomy can be useful in patients affected by UES dysfunction, while partial pharyngectomy was found to be effective in patients affected by pharyngeal hemiparesis [54]. However, in patients with severe aspiration, inadequate deglutition coordination and diminished laryngeal sensation, more drastic procedures, such as total laryngectomy or other procedures of tracheoesophageal separations, are required. The result is a permanent anatomic separation of the airway and digestive tract with the invariable loss of normal voice and respiration [55]. A valuable alternative to tracheoesophageal separation procedures is the laryngeal elevation in which the larynx is permanently fixed in the position that would normally be obtained during the pharyngeal phase of swallowing. The suspension of the larynx protects the airways from aspiration since the epiglottis is lowered over the laryngeal vestibule, and the larynx is pulled out of the way of the food bolus' path. In addition, because the UES is attached to the larynx, anterior and cranial displacement of the larynx results in the opening of the esophageal inlet, thus facilitating the passage of the food bolus. Laryngeal elevation was found to be effective in dysphagic patients with severe aspiration caused by deficient laryngeal elevation, insufficient opening of the UES, and lack of pharyngeal constrictor activity. In these patients laryngeal elevation could be considered a valuable alternative to more drastic procedures [55].

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Dysphagia Rehabilitation

9

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9.1 Introduction

Normal swallowing is transporting food from the mouth to the stomach. It depends on the anatomical and functional integrity of neural structures including both the central and peripheral nervous system. Several neurological diseases cause dysphagia due to the lesions in the cerebral cortex, basal ganglia, brainstem, cerebellum, and lower cranial nerves. Serious complications including pulmonary aspiration, dehydration, and malnutrition are seen in neurogenic dysphagia. These complications are usually preventable if the dysphagia is diagnosed early and managed appropriately [1].

The clinical management of dysphagia should be planned according to the understanding of the physiological and biomechanical properties of normal swallowing and the deviations from these normal patterns. The analysis of the oral, pharyngeal, and esophageal swallowing dynamics is completed through clinical and instrumental evaluation of swallowing function. This analysis provides descriptive information to the clinician, but it should not be forgotten that swallowing phases do also overlap. Besides the swallowing dynamics, whole body functions of the individual suffering from dysphagia including posture, cognition, respiration, etc. are also important during treatment planning, as swallowing involves multisystem responses. Thus, treatment techniques should be applied to the impaired mechanisms in a systematic and holistic manner [2].

The primary goal of the management of swallowing disorders is to ensure safe swallowing. The management of swallowing disorders can be divided as medical

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treatment, surgical approaches, and rehabilitative approaches [1]. This chapter will review the rehabilitative approaches used in dysphagia management.

9.2 Rehabilitative Approaches

Rehabilitative approaches require a problem solving process, which includes administration of appropriate diagnostic techniques to patients with dysphagia, interpretation of the diagnostic results, determination of the swallowing problem in a correct fashion, and planning of dysphagia treatment for each patient individually. This process takes part in a clinical decision-making model.

There are two options, including direct and indirect rehabilitative treatments, for dysphagia clinicians to use during rehabilitation process. Direct rehabilitative treatment uses food and/or liquids as part of treatment protocol to facilitate physiologic deglutitive change. During direct therapy, food is introduced into the mouth and supports the appropriate behaviors and motor control during swallowing function. Indirect rehabilitative treatment uses specific exercise principles and techniques without food or liquid as part of treatment regimen. If the patient aspirates on all food consistencies and volumes, and consequently is unsafe for oral intake, indirect therapy is used [3]. The results of the clinical and instrumental swallowing studies are utilized to make a decision. If the presence or absence of aspiration cannot be clearly determined during clinical swallowing examinations, instrumental swallowing studies, especially videofluoroscopy, and/or fiber-optic endoscopic swallowing studies should be performed. Clinicians should also consider the etiology of dysphagia, medical and cognitive status, and performance level of the patients during selection of one of the treatment techniques [1].

The rehabilitative approaches include sensory stimulation techniques (e.g., thermal stimulation, electrical stimulation), exercises (e.g., lingual strengthening, Shaker exercise, expiratory muscle strength training), and compensatory strategies. Any of the therapy modalities can be done indirectly or directly. The rehabilitation program should be planned with combination of each method and designed to improve impaired swallowing function, create differences in swallowing physiology, correct the swallowing pattern, and prepare the patient to a new and safe swallowing pattern.

9.2.1 Sensory Stimulation Techniques

Sensorimotor control of swallowing is crucial for normal swallowing function. The cortical center of swallowing receives peripheral sensory feedback during swallowing, and these sensory inputs are necessary for the initiation and modulation of the swallowing response. Sensory deficits of the oropharyngeal region are very common in many neurological diseases and are associated with the swallowing dysfunction, especially with aspiration [4, 5]. Thus, increasing sensorial input in a variety of ways such as chemically, physically, or electrically is used in oropharyngeal dysphagia rehabilitation.

9.2.1.1 Thermal Stimulation

Thermal tactile stimulation (TTS) is a sensory technique where stimulation is applied to the anterior faucial arches to trigger the pharyngeal swallow. The anterior faucial arches are located bilaterally on the oral side of the velum and form from the soft palate. They are innervated by the maxillary branch of the trigeminal and glossopharyngeal nerve. This area is one of the richest regions in terms of touch and thermal receptors. The TTS is based on the idea that mechanical and thermal sensory receptors in the anterior faucial arches are the most reflexive area to trigger swallowing reflex, and when it is stimulated via a cold object by applying a light pressure, the pharyngeal swallow is initiated [6]. Thus, TTS is appropriate for patients with reduced oral awareness, prolonged oral transit time, and delay in triggering pharyngeal swallow. The therapy involves tapping or stroking with a cold stimulus vertically along the anterior faucial arches to facilitate the pharyngeal swallow. Five strokes are completed along each arch and followed by asking the patient to swallow. If the patient tolerates small amounts of liquids, a small amount of liquid is given after stimulation and the patient is asked to swallow. If non-oral feeding is recommended to the patient, saliva swallowing can be used. Five to ten minutes' sessions, 3–4 times a day, are recommended [1]. There are several studies in the literature about the effect of TTS on neurogenic dysphagia. Lazzara L. et al. showed that swallowing reflex was improved in 23 out of 25 neurologically impaired patients after one session of TTS [6]. In a study of patients with Parkinson's disease, TTS reduced pharyngeal transit time, total transit time, and pharyngeal delay time compared with no stimulation [7]. Another study, which investigated the cortical representation of swallowing during TTS, showed that there was an increase in cortical activation after TTS [8].

9.2.1.2 Electrical Stimulation

Surface neuromuscular electrical stimulation (sNMES) is a treatment option for pharyngeal dysphagia. The aim of the sNMES is to restore or improve the muscles that participate in swallowing function with surface electrodes [9]. The electrical current is used to create a contraction by depolarizing nerves that are responsible for motor innervation to a particular muscle or muscle fibers. sNMES is applied with two bipolar electrodes that are adhered to the skin surface overlying the target muscle(s) or the motor point of the target muscle(s). There are two types of stimulation modes including sensory stimulation and sensory-motor stimulation. Stimulation at the sensory level occurs when the current intensity stimulates only cutaneous afferents. Sensory-motor stimulation occurs when the current intensity stimulates both cutaneous afferents and motor nerves for muscle contraction [10]. Namely, if the stimulation intensity is increased, deeper structures in the body are stimulated. The tissues in the electrical field will be stimulated to various degrees depending on the stimulation intensity; thus, sNMES does not offer specificity for stimulating muscles. This is a limitation for swallowing rehabilitation with sNMES because the neck and face muscles are small, short, too close, and superimposed to each other and may have different functions.

Neurological patients are one of the most studied patient populations regarding the immediate and long-term effects of sNMES [11–15]. The sNMES protocol was reported to reduce penetration and aspiration scores and improve swallowing function in patients with neurogenic dysphagia.

9.2.2 Exercises

There are a variety of exercises that have been recommended to improve swallowing ability by targeting range of motion, by increasing swallowing effort volitionally, or through resistive exercises [1, 16–21]. The goal of the swallowing exercises is to improve range, speed, strength, endurance, and coordination of movement.

9.2.2.1 Range of Motion (ROM) Exercises

Range of motion (ROM) exercises are done to maintain flexibility and mobility of the joints on which they are performed. Patients with neurological problems may present with limitations in the range of oral, facial, pharyngeal, and laryngeal movements. To facilitate increased range of movement can be effective in the recovery of the swallowing function. While performing ROM exercises for swallowing function, patients are asked to imitate the targeted movements. Lip movements, tongue movements (protrusion, retraction, lateral movements), exercises to increase the mobility and flexibility of the temporomandibular joint, gesture exercises, etc. are the most commonly used exercises in clinical practices.

9.2.2.2 Strength Training

Strength training is used to increase muscle strength and coordination by promoting an increase in the number of muscle fibers and neural activity of muscles [21]. Resistive exercises may be applied to the muscles of the neck, lips, and tongue. Lingual strengthening exercises, Shaker exercise, chin tuck against resistance (CTAR), vocal cord adduction exercises, and expiratory muscle strength training are included in strength training.

Lingual Strengthening Lingual strengthening exercises result in increased tongue strength, thus providing decreased oral transit time, improved strength/pressure during swallowing, and increased squeezing during swallowing. Bolus clearance is also improved with lingual strengthening [19, 22].

A tongue depressor and the Iowa Oral Performance Instrument (IOPI®) can be used to improve lingual strength. The KayPentax Swallow Workstation® is also a part to be used in lingual exercises. These instruments are used for isometric lingual exercises. The patient is asked to compress the sensor between the tongue and hard palate. The baseline maximum pressure is initially determined, and the patient is trained with the 60% of the baseline maximum level during the first week. Then, the patient is trained with the 80% of the maximum level for 7 weeks. This protocol is completed 3 times a day, 3 days a week for 8 weeks [20, 23]. When this protocol was applied to stroke patients with dysphagia by using IOPI® for 8 weeks, increased

isometric and swallowing pressures, tongue hypertrophy, decreased oral transit time, airway invasion, and pharyngeal wall residue were reported [23]. In another study of stroke patients who performed 8 weeks of lingual isometric exercise program, maximum isometric pressure generation, swallow pressure, and pharyngeal response duration were increased, and oral transit time and pharyngeal residue were decreased [20].

Gargling, yawning, and tongue retraction exercises are also used to improve lingual function, particularly for the retraction of tongue base [24].

Shaker Exercise The Shaker exercise consists of 30 consecutive repetitions of head raising from the bed (isotonic part) and 1-min head lift for 3 times (isometric part) in the supine position. The patient is asked to raise his/her head from the bed to look at his/her feet during isotonic part of the exercise. For the isometric part, the patient is asked to raise his/her head from the bed high enough to be able to observe his/her toes for 1 min and relax for 1 min. The therapist should consider preventing shoulder compensation during Shaker exercises. It is also mentioned to breathe while performing this exercise. The protocol is completed 3 times a day for 6 weeks [25]. The aim is to improve hyolaryngeal elevation and anteroposterior upper esophageal sphincter opening during swallowing by strengthening suprahyoid muscles. The contractions of the thyrohyoid, mylohyoid, geniohyoid, and anterior belly of digastric muscles provide the upward and forward movement of the hyolaryngeal structures during Shaker exercise. Thus, this exercise protocol strengthens these suprahyoid muscles and increases the upper esophageal sphincter opening. It was shown that the Shaker exercise could be used in patients with aspiration due to residue and abnormal upper esophageal sphincter opening [26].

Chin Tuck Against Resistance (CTAR) The CTAR is a similar exercise model to Shaker exercise, which is aimed to increase upper esophageal sphincter opening by strengthening suprahyoid muscles. It also has both isometric and isotonic components as Shaker exercise. The patient is asked to compress a ball between the chin and sternum for 10 times and also asked to compress for 10 s long [27].

Vocal Cord Adduction Exercises The larynx includes the true and false vocal cords, which are localized just below where the pharynx splits into the trachea and esophagus. Airway protection is one of the crucial biological features of the pharyngeal swallow. There are several airway protective mechanisms preventing aspiration before or during swallowing including vocal cord closure. Vocal cord adduction exercises are used to improve sufficient vocal cord closure [28]. Vocal cord adduction exercises can be performed in different ways. The combination of lifting, pushing, and vocalization is appropriate to improve vocal cord adduction because these activities increase laryngeal muscle activity and improve laryngeal closure during swallowing. For example, the patient is asked to push down with his/her arms on the seat and bear his/her weight on his/her arms as he/she pushes while saying “ah” or the patient is asked to sit and pull up on the seat with both hands while prolonging “ah”. It was reported that these exercises provide

improvement within 2–3 weeks; however, a patient may also require 6–8 months to achieve adequate airway protection [28].

Expiratory Muscle Strength Training Expiratory muscle strength training (EMST) is another treatment option for swallowing disorders. The mechanism of EMST in improving swallowing function can be explained by different ways. One of the mechanisms is by increasing maximal expiratory pressure and improving cough. Cough is a mechanism of airway clearance, which is composed of an inspiratory effort that is followed by rapid vocal cord adduction and contraction of the expiratory muscles, including all abdominal muscles, with the majority of force produced from the internal and external oblique muscles. EMST initially provides dynamic narrowing of the airways and vocal cord adduction and then vocal cord opening to increase maximal expiratory pressure by producing high expiratory airflow velocity [29]. Another mechanism is that the pressure load creates a condition that results in peripheral adaptations to the respiratory and swallowing muscles. Namely, the EMST may improve swallowing ability through afferent stimulation to brainstem swallowing centers through peripheral sensory receptors in the tongue and oropharynx and by strengthening oropharyngeal, laryngeal, and supralaryngeal muscles involved in swallowing. EMST is trained by a device with a calibrated, one-way, spring-loaded valve to overload the expiratory muscles mechanically. The valve blocks the airflow until a sufficient expiratory pressure is produced. Once the targeted pressure is produced, the valve opens and air begins to flow through the device. The physiologic load on the targeted muscles can be increased or decreased depending on the device settings. There are some studies conducted in patients with neurogenic dysphagia. There is an improvement in cough and swallow following EMST training in patients with Parkinson's disease who are at risk for aspiration [29]. EMST is found as an effective treatment for the development of suprahyoid muscle activity in stroke patients with dysphagia. Decreased penetration and aspiration scores were also observed [30]. Thus, the EMST is an important treatment option for neurogenic dysphagia.

9.2.3 Hyolaryngeal Mobilization

Hyolaryngeal mobilization is designed by Hacettepe University, Faculty of Health Sciences, Department of Physical Therapy and Rehabilitation, Swallowing Disorders Unit. There is no published data about its effects on swallowing function yet.

Elevation of the hyolaryngeal complex is critical and central for the complicated set of movements required to transfer a bolus from the oral cavity through the pharynx and into the esophagus. The hyolaryngeal complex consists of the hyoid bone, laryngeal cartilages, and muscles intrinsic to the hyoid and larynx, including the thyrohyoid. Proper hyolaryngeal elevation pulls the airway anteriorly, stretches the upper esophageal sphincter, and opens the esophagus effectively. Inadequate hyolaryngeal elevation can result in aspiration or bolus retention, putting the patient

at risk for inadequate oral intake, the need for an altered diet, and pneumonia [31]. Thus, adequate hyolaryngeal elevation is essential for safe swallowing. The mobility of hyolaryngeal complex is crucial to provide adequate hyolaryngeal elevation. Based on this opinion, the hyolaryngeal mobilization was developed to provide adequate hyolaryngeal elevation.

In physical therapy, mobilization is generally considered to be a safer technique and improves mobility and function [32]. Hyolaryngeal mobilization includes passive movements of hyolaryngeal complex, e.g., passive laryngeal movement in right, left, up, and down directions and passive hyolaryngeal movement in up and down directions by a physical therapist manually. It is performed to support hyolaryngeal elevation for 15 min. Research to prove its effects on swallowing function should be done.

9.2.4 Compensatory Strategies

Compensatory strategies for swallowing disorders include postural techniques, swallowing maneuvers, bolus volume, viscosity, taste, and temperature adjustments. These techniques are used for patients with dysphagia who are able to continue safe oral intake with these compensatory techniques. The modifications related to swallowing function may help to prevent problems like penetration and aspiration and facilitate the task-specific activity of swallowing.

These techniques provide immediate effects; their long-term effects have not been identified yet. The patient's underlying swallowing impairment and also cognitive capacities should be considered while determining the optimal compensation [33].

9.2.4.1 Postural Techniques

Compensatory postural techniques are used to facilitate the efficiency and safety of bolus passage from the oral cavity to pharyngeal and esophageal area by altering oropharyngeal anatomy. The most common techniques are chin down (chin tuck), chin up, and head rotation. The nature of the swallowing difficulty, integrity of swallowing structures, and effectiveness of the technique during instrumental swallowing examination should be considered during selection of the appropriate technique for a patient.

Chin Down (Chin Tuck) The chin down posture (Fig. 9.1) is tucking the chin into the neck. The use of chin down posture has been indicated to reduce the aspiration that occurs before and during swallowing [34]. It is the most frequently used postural maneuver in the treatment of neurogenic oropharyngeal dysphagia. The effect of the posture occurs by widening the vallecular space to provide greater space for preventing preswallow spillage and prevent preswallow aspiration, narrowing of the hypopharynx, which compensates for delay in glottic closure during swallowing, and also narrowing the distance between the tongue base and the posterior pharyngeal wall to reduce aspiration during swallowing [34, 35]. It was reported that the

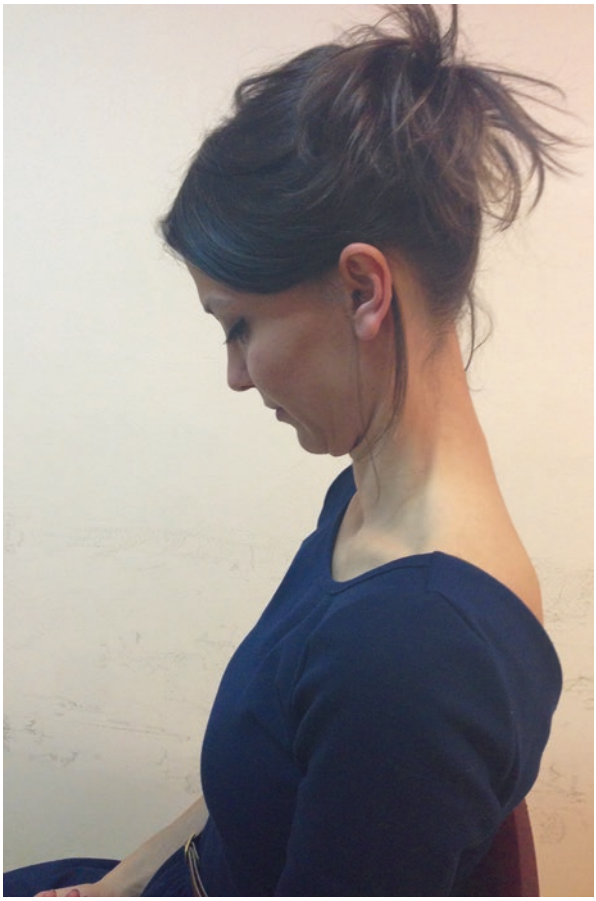

Fig. 9.1 Chin down posture

chin down maneuver could be used in dysphagic patients with delay in the swallowing trigger, reduced laryngeal elevation, and difficulties to swallow liquids [35].

Chin Up The chin up posture (Fig. 9.2) is used in patients with poor lingual mobility for oral bolus transportation. The use of this posture also requires sufficient airway closure and pharyngeal clearance to prevent any laryngeal penetration and/or aspiration during swallowing with chin up posture [36].

Head Tilt Head tilt posture (Fig. 9.3) is usually appropriate for problems caused by unilateral oral weakness or unilateral oral and pharyngeal weakness. The head tilt posture requires the patient tilting the head to the unimpaired or less impaired side to provide the bolus to go down the stronger side.

Fig. 9.2 Chin up posture

Head Rotation The head rotation posture (Fig. 9.4) requires the patient to turn the head toward the impaired side to prevent the bolus to transport through the weaker side. This posture also pulls cricoid cartilage away from posterior pharyngeal wall and reduces the resting pressure in upper esophageal sphincter. The head rotation posture can be used if there is a unilateral laryngeal, pharyngeal, and cricopharyngeal dysfunction.

It was reported that in patients with unilateral pharyngeal paralysis secondary to lateral medullary syndrome, head rotation to the paralyzed side could effectively close the hemipharynx on that side. Serial computed tomography of the pharynx showed that hemipharyngeal closing occurred at the level of the hyoid bone or the hypopharyngeal cavity above the pyriform sinus [37]. Dysphagia limit improved significantly in 67% of patients with unilateral lower cranial lesions when the head was rotated toward the paretic side [36].

Fig. 9.3 Head tilt posture

9.2.4.2 Swallowing Maneuvers

Compensatory maneuvers including Mendelsohn maneuver, Masako maneuver, effortful swallowing, and supra and super-supraglottic swallowing are used in swallowing rehabilitation because they alter timing, bolus flow, and duration of physiological swallow events. The Mendelsohn maneuver, Masako maneuver, and effortful swallowing are also used as swallowing exercises to increase muscle strength. The effectiveness of the swallowing maneuver during instrumental swallowing examination should also be considered during selection of the appropriate maneuver for a

Fig. 9.4 Head rotation posture

patient. Patients should also have enough cognitive abilities such as attention, comprehension, and memory to intentionally increase muscle effort and to carry out the instructions during swallowing.

Mendelsohn Maneuver The Mendelsohn maneuver, which is also used as an exercise to increase strength and ROM, can improve the duration of maximum anterior and superior movement of hyoid and impact the duration of cricopharyngeal opening [38]. The patients who exhibit reduced laryngeal movement and consequent reduced cricopharyngeal opening will benefit from the Mendelsohn maneuver. It can be performed either with or without a bolus. The patient is asked to hold the larynx (Adam's apple/voice box) at the peak level of the swallowing before it begins to descend during performing the Mendelsohn maneuver.

Masako Maneuver The Masako maneuver is also called as tongue-holding maneuver [39]. The passive load while performing a dry swallow will increase muscular work and improve oral lingual strength. A patient is asked to swallow while holding the tongue between the teeth anteriorly. Patients who exhibit reduced tongue base/pharyngeal wall movement will benefit from the Masako maneuver.

Effortful Swallowing Patients who exhibit reduced tongue base retraction or decreased pharyngeal constriction will benefit from the effortful swallowing. The effortful swallowing provides increased base of tongue retraction and reduced laryngeal penetration during swallowing in patients with neurologic dysfunction [40]. The patient is asked to swallow normally but squeeze very hard with his/her tongue and throat muscles throughout the swallow. Excessive effort should be clearly visible in his/her neck during the swallow.

Supraglottic and Super-Supraglottic Swallowing Maneuvers The supraglottic and super-supraglottic swallowing maneuvers are designed to close the airway voluntarily. These techniques are effective in patients who have delayed initiation of pharyngeal swallow, decreased hyolaryngeal elevation, incomplete pharyngeal clearance, and incomplete airway closure [41]. The supraglottic swallow provides airway protection at the level of the true vocal cords. The patient is asked to take a deep breath and hold it; he/she then swallows while still holding his/her breath and immediately coughs after swallowing. The super-supraglottic swallow provides airway protection at the level of the laryngeal vestibule. The patient is asked to take a breath, hold it tightly, and swallow hardly. Then the patient is asked to swallow while still holding the breath and cough immediately after the swallow. These techniques require good comprehension and memory due to the multiple steps and endurance throughout the duration of a meal; thus, the clinician should consider these points while using these techniques in patients with neurogenic dysphagia.

9.2.4.3 Bolus Volume, Viscosity, Taste, and Temperature Adjustments

Bolus volume, viscosity, temperature, and taste modifications during swallowing are used as compensatory strategies to ensure safe swallowing by providing sensory modulation.

Bolus Volume The 3, 5, 10, and 20 ml liquid volumes are recommended for testing purposes during instrumental swallowing evaluation. The swallowing test begins with small-volume boluses, and the volume is increased depending on the patient's ability to manage the previous bolus volume safely. Volume regulation prevents aspiration with large liquid volumes secondary to reduced lingual control or delayed pharyngeal swallow. Volume regulation may be more beneficial for patients with cognitive impairment, which prevents them to self-regulate their volume intake [23].

Bolus Viscosity Bolus viscosity adjustment is one of the most used compensatory strategies in swallowing rehabilitation. Thickening liquids is more likely to be tolerated by patients with delayed pharyngeal swallow initiation, because the thickened liquids fall into laryngeal inlet slowly during the delay and provide more sensory

stimulation to initiate pharyngeal swallow. It was found that increasing bolus viscosity reduces bolus penetration and aspiration risk in patients with stroke [42]. Another study which investigated the effect of bolus viscosity on swallowing function in neurogenic dysphagia showed that increasing bolus viscosity to nectar increased efficacy and safety of oropharyngeal swallowing with a maximal improvement at pudding viscosity [43]. Bolus viscosity would probably provide stronger improvement on swallowing function when combined with other more complex swallowing therapies, such as postural changes, active maneuvers, sensory input enhancement, or functional rehabilitation [43]. Diet standardization by increasing bolus viscosity may also increase the liquid and caloric intake in safe conditions and help to reduce pneumonia rates in patients with neurogenic dysphagia.

Bolus Taste and Temperature Bolus temperature adjustment is one of the sensory techniques. Sensory input is crucial for the initiation and modulation of swallowing and provides changes in neuronal circuits. Sensory problems during swallowing reduce both the sensory feedback and cortical control of swallowing [44]. Thus, bolus taste and temperature adjustments are also used as sensory techniques to provide effective and safe swallowing. Cold temperature is the most commonly used bolus temperature adjustment, which is based on the idea that it reduces the time of the pharyngeal phase in individuals with oropharyngeal dysphagia. A study, which investigated the effects of temperature on swallowing, showed that temperature adjustments have minimal effects on pharyngeal peristalsis, duration of true vocal cord closure, and elicitation of a pharyngeal swallow [45]. Taste is another important sensory stimulus for swallowing. Sour is the most studied taste, which increases preswallowing sensory inputs to the cortex and brainstem and reduces the swallowing threshold response. The reduced threshold may cause reduction in oral transit time and facilitation of pharyngeal response time, which may decrease the laryngeal penetration and/or aspiration risk [46].

Conclusion

There are many rehabilitative techniques for oropharyngeal dysphagia in patients with neurological disorders. It is critical that dysphagia clinicians should evaluate each patient individually and select the appropriate treatment protocol according to the assessment results during the clinical decision-making process, evidence based on research literature, and factors related to patient's environment and family.

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Neuronutrition: An Emerging Concept

10

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10.1 Introduction

"Neuronutrition" is an emerging field incorporating the concept of "functional food" into the management of neurological diseases. It is one of the main subchapters of "nutritional neuroscience," which is a well-recognized scientific discipline focusing on the effect of foods, with a broad meaning including diet, products, and additives, on the peripheral and central nervous system (CNS). It has several subdivisions including, but not limited to, nutritional neurochemistry, nutritional neurobiology, nutritional neurocognition, nutritional behavioral neurology, and nutritional epigenetics. Neuronutrition itself has several subdivisions such as developmental neuronutrition, geriatric neuronutrition, and neuromuscular neuronutrition.

The terminology related to the products used for the purposes of neuronutrition is also complex and not standardized. A functional food can be described as food manufactured by adding new ingredients or increasing and/or changing the available composition of their ingredients with a specific aim such as treatment or prevention of a disease or just promotion of health status. The term "health functional food," which replaced the term "health food supplements" in 2002, is reserved for products manufactured in a form of tablet, capsule, powder, granule, liquid or pill, etc., with ingredients or components possessing the functionality useful for human body. This term is used interchangeably with "dietary supplements" in the United States, "food for specific health use (FOSHU)" in Japan, and "food supplements" in Europe. Currently, innumerable (more than 50,000) type of health functional foods have been claimed, and even marketed, for neurological health and diseases. The term "nutraceutical" was coined in 1989 by Dr. Stephen L. DeFelice, by combining

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the parts of the words "nutrition" and "pharmaceutical." The term is not legally recognized in the United States, while it is considered equivalent to functional food in Canada. The defining nature of nutraceuticals is however that regardless of being a food or supplement, they should aid in treatment or prevention of a disease, like a pharmaceutical. Nutraceuticals have been classified into about 60 groups of compounds. The number of medically important nutraceuticals is currently higher than 1000 [1]. A nutraceutical with documented activity in the peripheral nervous system or CNS can also be called as "neuro-nutraceutical" [2].

This chapter, of course, cannot cover every facet of all neuro-nutraceuticals. Instead, selected examples of this colossal group are summarized with specific interest for their current position in stroke, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and migraine prophylaxis and treatment.

10.2 Antioxidant Vitamins

Diets with high antioxidant content are believed to improve health via preventing cancer and atherosclerosis-related vascular diseases such as coronary heart disease and stroke. Albeit dietary modification rather than supplementation is generally promoted, a lot of antioxidant preparations are marketed currently. However, this huge market has not been adequately backed by scientific data. A large number of clinical trials testing antioxidant supplements suggested that these products have no major effect on both global health and any neurological disease; instead, they resulted in a small but quantifiable increase in mortality especially in elderly or other vulnerable populations. This inconsistency between the positive vascular effect of dietary antioxidants and supplementary antioxidant products is called as "antioxidant paradox." The exact cause of this paradox has not been explained completely, but probably includes dosage and collateral pathway issues.

In brief, oxidative stress is described as an imbalance of pro-oxidants over antioxidants in the body. Pro-oxidant substances consist primarily of free radicals, like reactive oxygen species (ROS) and reactive nitrogen species, and non-radical pro-oxidants, like hydrogen peroxide, peroxynitrite, and nitrite. Endogeneous antioxidants include superoxide dismutase (SOD), catalase, glutathione (GSH), GSH oxidase, uric acid, and thioreductase. Exogenous or dietary antioxidants include vitamin A, vitamin C, vitamin E, polyphenols, and minerals such as selenium. It is accepted that some level of oxidative stress is a must for well-being. Low-level oxidative stress activates endogenous adaptive defenses, which result in this seemingly paradoxical beneficial effect. One clear evidence for this assumption comes from the fact that caloric restriction and physical activity, the top efficacious interventions for health improvement, induct ROS production within mitochondria [3].

Multi-substance, or cocktail, approach is a preferred method in antioxidant studies and usually includes major antioxidant vitamins and vitamers such as vitamin C, vitamin E, and beta-carotene. In this context, it is important to state that none of the multivitamin pills are useful for management of neurologic diseases but may even be harmful unless there is a presence of documented deficiency.

10.2.1 Vitamin C

Vitamin C, ascorbic acid or simply ascorbate, is a water-soluble vitamin and is considered to have vasculoprotective effects attributed to its strong antioxidant properties [3]. In several large-scale studies including the EPIC trial [4], plasma levels of vitamin C were inversely correlated with vascular mortality. EPIC data also demonstrated 20% reduction in cardiovascular disease and mortality by increased intake of dietary vitamin C. A recent meta-analysis showed an inverse relationship between dietary vitamin C intake or serum vitamin C concentration and stroke risk [5]. However, this beneficial effect has not been replicated by randomized controlled trials [6]. Vitamin C supplementation has also no effect in reducing overall mortality in presumably healthy populations [7]. These all indicate that vitamin C supplementation on top of a diet containing the recommended amount of fresh fruit and vegetable is not justifiable to prevent vascular events.

The large prospective studies of both dietary intake and supplemental use of vitamin C have not documented a significant positive effect in AD risk [8]. Ascorbic acid is concentrated in human brain in normal conditions. Patients with AD have lower serum ascorbic acid levels than those explainable by age and diet. In early stages of the disease, the cerebrospinal fluid (CSF) to serum concentration ratio of vitamin C is high and decreases over time by disease progression. However, the underlying mechanism by which vitamin C affects cognition and neurodegeneration has not been uncovered yet. Some initial findings suggested promotion of cholinergic system and attenuation of amyloid beta oligomerization (but not total amyloid beta load) by vitamin C [8]. Similar to AD, vitamin C has no preventive role on the risk and progression of PD [9]. However, it is important to note that vitamin C increases gastrointestinal absorption of L-DOPA, which may be useful in PD patients with poor or unstable L-DOPA bioavailability [10].

10.2.2 Vitamin E

Vitamin E is a group name of eight compounds known as tocopherols and tocotrienols. Gamma-tocopherols are the most abundant isoforms found in regular Western diet, while alpha-tocopherol is the most potent antioxidant in the group.

Vitamin E is the most extensively evaluated antioxidant in large-scale cardiovascular protection studies [3]. In the CHAOS trial [11], vitamin E supplementation significantly reduced the risk of nonfatal myocardial infarction (MI) in patients with coronary heart disease, albeit with a slight and nonsignificant increase in overall mortality rates. This placebo-controlled study included 1035 patients assigned into high or low-dose (800 and 400 IU, equal to 720 mg and 360 mg, respectively) vitamin E and a third group of 967 patients receiving placebo. Plasma alpha-tocopherol concentration doubled in the 800 IU group [11]. However, the HOPE trial [12] produced resolutely negative results indicating no effect of vitamin E on cardiovascular outcomes in patients with high vascular risk or diabetes mellitus. In this study, 16.2% of 4761 patients assigned to 400 IU/day vitamin E had a composite rate of

MI, stroke, and vascular death over 4.5 years, in comparison to 15.5% of the 4780 patients receiving placebo [12]. Subsequent seminal trials including but not limited to GISSI [13] (300 mg), Physicians Health [14] (400 IU) and Women's Health studies [15] (600 IU) showed absolutely no benefit of vitamin E supplementation on combined vascular outcomes. Furthermore, a Cochrane analysis documented that vitamin E supplementation led to an inclination for elevated all-cause mortality [7]. Another meta-analysis of 13 randomized controlled studies with specific interest to stroke-centered outcomes indicated no benefit of vitamin E supplementation in prevention of ischemic stroke, hemorrhagic stroke, and fatal or nonfatal stroke [16]. In conclusion, laboratory evidence of anti-atherosclerotic effect of vitamin E has not translated into a clinically demonstrable benefit.

A wide interest about the effect of vitamin E to enhance cognition in normal persons, to decrease the risk of cognitive impairment or dementia in risky populations, and even slow the progression of AD showed confusing results. In ADCS trial [17], vitamin E (2000 IU) and/or selegiline showed a small but significant delay, or decrease, in combined end points of death, institutionalization, loss of ability to perform daily living activities, or progression to severe dementia in patients with AD of moderate severity. Because of more severe disease stages in the placebo group, the results have not been uniformly accepted as positive. Furthermore, several cognitive evaluations included in the secondary outcome parameters showed indifferent results. In the recent TEAM-D VA cooperative randomized trial [18], vitamin E supplementation (2000 IU/day) showed again a small but significant beneficial effect in terms of slowing the progression of disease in patients with AD of mild to moderate severity. In this study [18], Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) inventory score was 3.15 points less in the vitamin E group compared to placebo at the end of the 2.2 years. This effect translated into a 19% delay in yearly clinical progression, or nearly 6 months over the whole study follow-up period. Of note, there was no difference in "memantine only" and "memantine-vitamin E combination" groups. Moreover, there was again no difference with respect to any of the cognitive tests measuring secondary end points. This study has been criticized based on the extremely high rate (42%) of study completion failure. Although both studies indicated "some" effectiveness in slowing AD progression, aforementioned concerns together with the reported increase in all-cause mortality and heart failure in vascular studies prevented wide recognition of the results. Finally, a Cochrane meta-analysis indicated that evidence stating that vitamin E is of benefit in the treatment of AD is not convincing [19].

Oxidative stress has a widely recognized role in the degeneration of substantia nigra in PD. A meta-analysis showed that dietary vitamin E has a protective potential in PD, while no such effect was seen for vitamin C and beta-carotene [20]. However, vitamin E has no effect on disease progression in patients with established PD [21]. In the randomized controlled DATATOP trial [22], vitamin E (2000 IU/day) did not delay the onset of disability mandating L-DOPA initiation in patients with early PD. American Academy of Neurology does not recommend vitamin E for neuroprotection in PD [23].

Oxidative injury is one of the major mechanisms involved in development of sporadic ALS. Some autosomal-dominant ALS forms are caused by mutations in the Cu-Zn-SOD (SOD-1) gene. In transgenic mouse models with human SOD-1 mutation, supplemental life-long vitamin E delayed development of overt disease. In secondary analyses of large-scale vascular protection studies, high dietary vitamin E intake or higher baseline vitamin E serum levels have been linked to lower ALS risk [24–26]. However, alpha-tocopherol supplementation did not produce any detectable protective effect on ALS risk. In addition, while a meta-analysis suggested that an increase in the duration of vitamin E supplementation is linked to decreased ALS rates [27], another one showed absolutely no effect in any dimensions [28]. Effect of vitamin E in patients with ALS has been evaluated in several small-scale studies: In 160 patients with ALS, megadose vitamin E (5000 mg/day for 1.5 years) showed no effect in slowing disease progression when added to riluzole [29]. In 289 patients on riluzole, high-dose vitamin E (1000 mg/day) did not appear to affect survival or motor function [30]. Overall, no effect was seen on a meta-analysis [28].

Vitamin E is suggested for treatment of menstrual migraine [31]. This type of migraine is associated with increased prostaglandin levels in the endometrium. Vitamin E inhibits release of arachidonic acid and synthesis of prostaglandins. The use of vitamin E (400 mg/day for 5 days) has been found to be effective in menstrual migraine [32].

10.2.3 Vitamin A

Vitamin A can be found in two broad forms in foods. The first group, retinol, is included as retinyl acetate or retinyl palmitate in commercial preparations. The second group is carotenes and carotenoids. Of note, not all compounds belonging to carotene family have vitamin A activity. Major compounds in this group are alpha-carotene, beta-carotene, gamma-carotene, beta-cryptoxanthin, lutein, zeaxanthin, and lycopene. Lycopene is the precursor of beta-carotene and many other carotenoids. Carotenes are significant antioxidants. Beta-carotene and lycopene can directly lower plasma cholesterol levels via inhibition of HMG-CoA reductase, like statins. Increase of macrophage LDL receptor activity contributes to LDL lowering effects of beta-carotene and lycopene. A large body of evidence suggests that reduction of inflammation and endothelial dysfunction in addition to antioxidant effects may contribute to carotenoids' presumed cardiovascular protective properties. Beta-carotene and lycopene are the most studied compounds in this regard [33].

Beta-carotene is a precursor of vitamin A and has a probable vasculoprotective effect. Subjects with high serum and adipose tissue levels of beta-carotene were shown to have lower incidence of atherosclerotic events, such as MI in several studies [34, 35]. However, beta-carotene supplementation showed an inverse correlation with the risk of cardiovascular disease in several studies [7]. As mentioned above, this status of apparent disparity is not rare in terms of dietary factors. Several investigators suggested that beta-carotene is not a vasculoprotective compound

itself, but only a marker reflecting high proportion of vegetables and fruits in the diet [3]. In addition, dosage and preparation issues may contribute to this paradox as well.

As with the case of other nonenzymatic antioxidants, plasma and/or CSF levels of beta-carotene, and also vitamin A, have been reported to be lower in patients with AD [36]. Beta-carotene has been shown to inhibit amyloid beta fibril oligomerization and destabilization in in vitro studies. Furthermore, vitamin A decreases cerebral amyloid beta deposition, tau phosphorylation, and neuronal degeneration and increases memory in several animal models of AD [37]. However, supplemental vitamin A and beta-carotene were found to be noneffective for the prevention and improvement of symptoms of AD [37].

The relationship between plasma level of carotenoids and PD risk has not been documented thoroughly. Some studies indicated higher concentration of these vitamers in PD and potential harmful effects of their supraphysiological supplementation [38]. On the other hand, similar to observations with AD, patients with ALS have lower serum levels of carotenoids [39], and the risk of ALS is negatively correlated with dietary intake of beta-carotene [40]. Unfortunately, the effect of beta-carotene supplementation in ALS has not been evaluated satisfactorily. There are currently no neurological indications where beta-carotene could be suggested.

Lycopene, a pigmentous phytochemical giving red color to tomatoes and other red fruits, is a well-known member of carotenoid family. Lycopene has no vitamin A activity. It is a very potent singlet oxygen scavenger. Pharmacologically, its antioxidant capacity is higher than that of beta-carotene and vitamin E. However, its bioavailability and therefore relative contribution to the total body antioxidant pool is lower. Lycopene is highly lipid soluble and accumulates in several fat-rich tissues such as prostate and liver. It reduces inflammation and oxidative stress markers in healthy and overweight persons. It improves endothelial function and reduces platelet aggregation [3, 41].

Serum and adipose tissue lycopene concentrations have been linked to reduced risk of MI and vascular mortality in some [35, 42], but not all [43], studies. In KIHD cohort, a connection between lower levels of serum lycopene and higher risk of stroke was found [44]. No association was observed with alpha-carotene, beta-carotene, alpha-tocopherol, and retinol in this study, where 1031 Finnish men aged 46–65 years were followed approximately for 12 years.

Patients with AD have lower serum lycopene concentrations. Moreover, lower lycopene levels were linked to higher AD and dementia risk. Higher serum lycopene and also lutein plus zeaxanthin levels were found to be associated with a lower risk of AD-related mortality [45]. In addition to its antioxidant properties, lycopene can have a more direct beneficial effect in AD pathogenesis because experimental studies documented that lycopene can inhibit amyloid beta formation, secretion, deposition, and fibril generation [46, 47]. Data on the protective and therapeutic effect of lycopene in patients with AD are very limited. In a prospective but small-scale Japanese study, a combination of omega-3 polyunsaturated fatty acid (FA), *Ginkgo biloba*, and lycopene was linked to lower risk of AD [48]. No data is currently available on its effectiveness on AD progression.

Serum levels of lycopene were not found to be significantly decreased in patients with PD in small studies [49]. No study has investigated the effect of supplemental lycopene regarding PD risk and progression. However, lycopene was found to be neuroprotective in experimental models of PD [50]. Further studies are needed to clarify the value of lycopene in PD.

10.2.4 Antioxidant B Vitamins (Pyridoxine, Folate, and Cobalamin)

B group vitamins include eight members. They are usually marketed in combination form and known as "vitamin B complex." They are critical in the synthesis of GSH, which is one of the most important natural antioxidant. For the sake of completeness, other members of this group are summarized in the following section.

Albeit no convincing data are available, a link between low vitamin B6 (or pyridoxine) level and high risk of migraine, chronic pain, depression, and seizures were found in some studies. There is no evidence that short-term supplementation with vitamin B6 is beneficial in depression, carpal tunnel syndrome, and diabetic neuropathy. Pyridoxine has been used empirically for autism (usually with magnesium) and cognitive dysfunction including AD [51].

Connection between pyridoxine and PD deserves a specific mentioning. Several epidemiological studies linked high dietary pyridoxine levels to decreased risk of PD [52–54]. Again, vitamin B6 supplementation was not useful to decrease the risk or progression of PD. It is important to note that exogenous pyridoxine antagonizes effectiveness of L-DOPA in PD. In the absence of peripheral DOPA decarboxylase inhibitors such as carbidopa, pyridoxine decreases L-DOPA levels via activating its metabolism through induction of peripheral DOPA decarboxylase [55].

Another important aspect of pyridoxine use from the perspective of neuronutrition is its combinative use with vitamin B9 (folic acid or folate) and B12 (cobalamins). All these three vitamins are involved in homocysteine metabolism. Homocysteine is metabolized via two pathways; the first, trans-sulfuration to cysteine, which is catalyzed by cystathionine beta synthase, requires pyridoxal phosphate (vitamin B6) as cofactor. The second is re-methylation to methionine, which is catalyzed by methionine synthase and requires methylcobalamin (a vitamin B12 derivative) as cofactor. Methyl donor in this reaction is 5-methyl tetrahydrofolate, which is converted from 5,10-methylene-tetrahydrofolate by methylenetetrahydrofolate reductase (usually abbreviated as MTHFR) requiring riboflavin (vitamin B2) as cofactor [56]. Dietary deficiency of folate or vitamin B12 leads to elevated homocysteine levels. Hyperhomocysteinemia (>15 μg/L) is an independent risk factor for cardiovascular diseases including stroke [57]. US Preventive Services Task Force meta-analysis showed any 5 μmol/L increase of homocysteine level was related to 20% increase in coronary artery disease risk independent of Framingham's risk score [58]. Hyperhomocysteinemia is also one of the most prevalent and important acquired causes of both arterial and venous thrombosis. Homocysteine induces oxidative stress, endothelial dysfunction, and vascular inflammation, induces

development and then progression of atherosclerosis, and reduces nitric oxide and GSH availability at the tissue level.

Combined and individual low levels of folate, vitamin B12, and vitamin B6 are risk factors for any type of cardiovascular disease including stroke [56]. Homocysteine mediates this elevated risk to some extent. Supplementation of these three vitamins reduces homocysteine levels significantly. Suggested daily doses are 1 mg for folate, 0.4 mg for vitamin B12, and 10 mg for vitamin B6 [56]. It is important to note that supplementation aimed to decrease homocysteine levels failed to show any benefit on prevention of stroke, MI, and vascular death rates in most of the primary and secondary cardiovascular protection studies [59]. There are two large-scale studies performed in patients with stroke in this regard. In the VISP trial [60], no significant protective effect of high-dose combined supplementation of folate (2.5 mg), hydroxyl-cobalamin (0.4 mg), and pyridoxine (25 mg) on incidence of stroke recurrence, MI, and vascular death was observed over a 2-year period in 3680 patients with nondisabling stroke. Control group took the recommended dose of folate (20 μg), hydroxyl-cobalamin (6 μg), and pyridoxine (200 μg) in combination in this study. Of note, average decrease of total plasma homocysteine level was quite moderate (2 μmol/L) in high-dose group in comparison with low-dose group [60]. In the VITATOPS [61] study, combination of folic acid (2 mg), vitamin B6 (25 mg) and vitamin B12 (0.5 mg) was found to be noneffective in decreasing the primary composite outcome consisting of stroke, MI and vascular death during 3.4 years follow-up of 8164 patients with history of stroke or transient ischemic attack in comparison with placebo. As a result, germane data do not support the routine use of homocysteine-lowering B-vitamin combinations to prevent recurrent stroke.

There is a considerable interest for the use of homocysteine-lowering vitamins in the field of cognitive neurology [62]. Many cross-sectional studies demonstrated lower serum levels of folic acid and vitamin B12, with resultant hyperhomocysteinemia, in patients with cognitive decline [63, 64]. Several prospective studies showed that low levels of vitamin B12 and folate together with high levels of homocysteine are risk factors for cognitive decline [65]. Levels of these vitamins were usually found to be proportional to global cognition and executive scores. Vitamin B6 is usually associated with better performance on attention tests [66]. Protective effect of high levels of vitamin B12 and folate against dementia was also found in some studies [62] but not as a uniform finding [64, 67]. Effect of supplementation with homocysteine-lowering vitamins, alone or in combination, on cognitive functions was studied in patients with mild to moderate AD and also in normal persons [68, 69]. The results are negative in almost all studies [68, 70]. In other words, supplementation with folate, vitamin B6, and vitamin B12, alone or in combination, does not slow cognitive decline in patients with mild to moderate AD and mild cognitive impairment [69, 70] and does not show any positive effect on cognitive capacity in normal populations [68]. However, studies with more sensitive surrogates indicate significant benefits. For example, high-dose vitamin B treatment (0.8 mg folic acid; 20 mg vitamin B6; 0.5 mg vitamin B12) decreased effectively (7 times) whole brain gray matter volumes over a 2-year period in patients with AD and high homocysteine [71]. Furthermore, recent animal experiments indicated that homocysteine

excess induces amyloid pathology and elevates amyloid beta levels and deposition via activating gamma-secretase pathway [72]. In addition, homocysteine can increase insoluble fraction of tau and its phosphorylation via cdk5 pathway [72].

Relation of dietary intake of vitamin B6, folate, and vitamin B12 with PD risk is an underexplored subject. Several studies indicated that only dietary vitamin B6 amount seemed to have a direct proportional association with PD risk and progression, while no association was present for dietary folate and vitamin B12 [52, 54]. No supplementation of these vitamins was trialed in L-DOPA naive Parkinson patients. It is important to note that, L-DOPA treatment increases homocysteine concentrations significantly, and this occurs more severely in the setting of vitamin B12, folate, and pyridoxine deficiency. Therefore, monitoring of homocysteine levels and supplementation when needed is a good strategy in PD patients on L-DOPA treatment. COMT-inhibitors also attenuate L-DOPA-induced hyperhomocysteinemia effectively [73].

Several small-scale cross-sectional studies showed increased serum homocysteine levels in patients with ALS [74]. A single study demonstrated elevated CSF homocysteine concentrations in ALS patients [75]. There have been no clinical trials investigating the utility of supplementation with pyridoxine, folate, and vitamin B12 in ALS [76].

10.3 Other B Vitamins

Vitamin B1, thiamine, serves as a coenzyme in amino acid and sugar metabolism. Thiamine deficiency results in beriberi, Wernicke's encephalopathy and Leigh's syndrome [77]. Thiamine supplementation is aimed only to treat its deficiency. No additional benefit of supplementation to supraphysiological levels is demonstrated in neurodegenerative diseases.

Vitamin B2, riboflavin, is a precursor of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), which function as cofactors in citric acid cycle and beta-oxidation of FAs and are integral parts of complex I and complex II located in the mitochondrial electron transport chain. Several small-scale studies indicated efficacy of high-dose (400 mg/day, taken in morning-time) riboflavin in prevention of migraine [78, 79]. Currently, riboflavin is included into some combination preparations marketed for migraine prophylaxis [80]. However, more studies utilizing doses ranging from 50 to 400 mg remained negative [81, 82]. Theory underlying this effect relies on the possible presence of mitochondrial energy depletion in migraineurs. Riboflavin can increase FAD and FMN for electron transport system and decrease this defect. Experience with riboflavin in other neurological conditions is limited or inconclusive.

Vitamin B3, niacin or nicotinic acid, is a precursor of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate, both of which are involved in glucose and lipid metabolism, lipid and nucleic acid synthesis, citric acid cycle, and electron transport system. Niacin is a well-established hypolipidemic agent. It decreases total and LDL cholesterol effectively in moderately high

doses (1–3 g/day) and therefore has been in use to prevent and treat atherosclerotic cardiovascular events for years. Recent data indicate attenuation of neuroinflammation by niacin via its specific cellular receptors. This can open a new door to its use in multiple sclerosis and PD [83]. Increase in the amount of dietary niacin was shown to be protective against AD in Chicago Study [84], while no such effect was observed for folate, vitamin B12, and vitamin B6 [85]. No data are available on supplemental use of niacin in AD.

No conclusive data are available on the effects of isolated supplementation of vitamin B5 (pantothenic acid) or vitamin B7 (biotin) for the purposes of neuronutrition.

10.4 Vitamin D

Vitamin D is a fat soluble secosteroid. Major source of vitamin D is dermal synthesis of vitamin D3 (cholecalciferol) from 7-dehydrocholesterol. Vitamin D2 (ergocalciferol) and vitamin D3 from dietary sources or internal synthesis are first converted into 25-hydroxyvitamin D (abbreviated as 25OH vitamin D; also called as calcidiol) in the liver, then to 1,25-dihydroxyvitamin D (abbreviated as $1,25OH_2$ vitamin D; also called as calcitriol) by 1-alpha-hydroxylase in the kidney. 25OH vitamin D is the major form in the serum, and $1,25OH_2$ vitamin D is the active form.

Subclinical vitamin D deficiency, defined as serum 25OH vitamin D lower than 20 ng/mL (equal to 50 nmol/L), is highly prevalent and seen almost in one-third of the population older than 20 years of age. Subclinical vitamin D deficiency is connected to an increased risk of fall and fracture in the elderly and muscle weakness at all ages. But, the strength of this connection has several weaknesses: First, there is no unanimously accepted optimal serum calcidiol level for bone or extra-skeletal health. Evaluation of parathyroid hormone levels in addition to 25OH vitamin D may be helpful but does not produce a net solution [86]. Blind supplementation, described as giving vitamin D without measuring serum level, is not recommended. Second, no clear-cut positive effect of vitamin D supplementation on fall, muscle strength, and fracture was found in randomized controlled trials and systematic reviews [87, 88]. Furthermore, several randomized trials showed an increase in the risk of falls with intermittent high-dose vitamin D schedules [89].

Recent interest on the extra-skeletal functions of vitamin D is notable. Vitamin D receptors are found in almost all nucleated cells in the body. Vitamin D is involved in regulation of a number of cellular processes such as gene expression. Of note, approximately 3% of human genome is controlled by calcitriol. Cardiovascular effect is one of the most studied extra-skeletal subjects. Observational studies pointed an association between subclinical vitamin D deficiency and increased risk of hypertension, diabetes mellitus, metabolic syndrome, obesity, and cardiovascular disease including stroke [90, 91]. However, vitamin D supplementation did not show any significant benefit in any of these diseases including stroke [92, 93].

Available epidemiological data on the association between serum vitamin D levels and “overall” mortality rate is also inconclusive. Both the absence and presence

of correlation was documented. Furthermore, the shape of the correlation was heterogeneous: U-shaped and reverse J-shaped correlations in addition to linear proportional associations were found [90]. In studies providing cause-specific mortality rates, a more reliable association between "low" serum 25OH vitamin D levels (<21 ng/mL) and "increased" cardiovascular and cancer mortality were documented [94, 95]. Unfortunately, randomized trials testing the effect of vitamin D supplementation on mortality rates as a primary end point are not available yet. Meta-analyses of studies with data on mortality as a secondary end point documented a small, sometimes even statistically significant, reduction in mortality with vitamin D supplementation [96]. It is obvious that further research is needed to determine the place of vitamin D in the prevention and treatment of vascular diseases; until then vitamin D is not recommended for cardiovascular protection or longevity.

There is a widespread expression of vitamin D receptors and 1-alpha-hydroxylase throughout the brain. Vitamin D has major role on brain development via its effects in neuronal proliferation, differentiation, migration, and apoptosis. Vitamin D also has neurosteroid actions. There is a large body of experimental evidence documenting that binding of vitamin D to its receptors is neuroprotective against AD-related degenerative processes, including anti-inflammatory and antioxidant effects, regulation of neuroglial intracellular calcium homeostasis, and improvement of neurotrophic factor functions [97]. Furthermore, vitamin D is involved in attenuation of amyloid beta accumulation via stimulation of its phagocytosis and efflux transport and increase of choline acetyltransferase activity and choline synthesis [97]. In line with these experimental findings, serum vitamin D levels are usually documented to be lower in patients with AD. A proportional correlation between disease severity, assessed with mini-metal status examination score, and vitamin D concentrations were found in some studies [98]. However, the observed association appears to have uncertain clinical significance in most of the other studies. Furthermore, no randomized controlled large-scale study testing the effect of vitamin D supplementation in patients with AD is yet available. Nevertheless, open-label and small-scale studies suggest some benefits of supplementation, mainly for executive function and processing speed [97]. This level of evidence led several authorities to suggest replenishment of vitamin D in AD patients with low serum concentrations [97]. We should note that this strategy is not fully evidence based and further research is definitely needed.

The role of vitamin D in symptom development and deterioration in the setting of PD is more tentative compared to AD. Vitamin D was demonstrated to decrease motor deficits in experimental PD models [99]. It was shown to upregulate glial cell line-derived neurotrophic factor, which decreased pathological changes via promoting dopaminergic axonal outgrowth, increasing GSH and decreasing nitric oxide synthase levels [99]. Several cross-sectional and prospective cohort studies indicated an inverse relationship between vitamin D levels and PD risk [100]. Yet, no dependable evidence about taking extra vitamin D to change the risk and deterioration of PD is present on records.

Vitamin D regulation of intracellular calcium and potentiation of several neurotrophic factors are thought to have potential implications in ALS [76]. In a

retrospective study, poor vitamin D status was linked to higher rates of early mortality in ALS [101]. In another small-scale study, vitamin D supplementation was found to be safe with some advantages [102]. These initial observations suggest measurement of vitamin D concentrations and replacement when found to be low as a reasonable strategy [76].

The relationship between vitamin D and multiple sclerosis has recently become very popular. Vitamin D was found to activate innate immune system, particularly monocytes and macrophages, but inhibits acquired immune systems [90]. Low level of 25OH vitamin D has been suggested as a risk factor for multiple sclerosis [103]. However, effectiveness of vitamin D supplementation to reduce the risk of multiple sclerosis or to decrease disability or attack frequency/severity has not been explored in patients with multiple sclerosis. The other popular subject is depression. Patients with depression have usually been documented to have poor vitamin D status. However, a meta-analysis of nine vitamin D supplementation trials in 4923 depression patients found no significant reduction of depression symptoms. It is important that most studies included mild to moderately severe depression cases and sufficient levels of vitamin D. In other words, the effect of correction of poor vitamin D status has not been documented well [104].

10.5 Polyphenolic Compounds

More than 8000 polyphenolic substances have been identified. Polyphenolic compounds consist of two large classes. The first one is flavonoids, which includes flavonols, flavones, isoflavones, flavanones, flavanols (also known as flavan-3-ols), and anthocyanins. *Isoflavones* include daidzein, glycit(e)in, and genistein, which is found in legumes such as soybean. *Flavonols* include quercetin, which are well-known examples of flavonols found in onion, leaks, broccoli, capers, apples, blueberries, and green tea. Other important flavonols are kaempferol and myricetin. *Flavones* include apigenin, which are abundant in celery, parsley, rosemary, and chamomile along with luteolin, tangeritin, nobiletin, and sinensetin. *Flavanones* include naringenin, which is abundant in grapefruits, oranges, and other citrus fruits, mints, and tomatoes. Other compounds in this group are hesperetin, hesperidin, homoeriodictyol, and naringin. *Flavanols* include catechins and are found in cocoa, chocolate, vinegar, peaches, some berries, and cherries. Black and green teas are very rich sources of catechin. Other significant molecules in this subgroup are epicatechin, gallocatechin, and epigallocatechin. *Anthocyanins* include delphinidin, which is found in blackberries, black currant, grapes, and cranberries. The other compounds are cyanidin, malvidin, pelargonidin, peonidin, and petunidin. Major sources of the latter are various fruits, red wine, some cereals, eggplants, cabbage, beans, onions, and radishes [3, 105, 106].

The second polyphenolic compound class is non-flavonoids. There are at least three subgroups as stilbenes, lignans, and phenolic acids. *Stilbenes* include resveratrol, which is found in grapes peel, red wine, blueberries, and blackberries. Of note, resveratrol is produced in colorful edible fruits as a response to fungal infection

indicating importance of organic farming [107]. *Lignans* include pinoresinol, podophyllotoxin, steganacin, and secoisolariciresinol, which are found in linseed, sesame seed, cereals, and grains. *Phenolic acids* include two subgroups; the first is *hydroxybenzoic acids* such as *p*-hydroxybenzoic acid, vanillic acid, gallic acid, ferulic acid, *p*-coumaric acid, sinapic acid, and caffeic acid, which is found in kiwi and coffee. *Tannins* are also included in this group. Tannin group contains castalin, pentagalloyl-glucose, and pyocyanidins. Foods, which are rich tannin sources are tea, berries, wine, cocoa, and chocolate [3, 106].

Albeit a significant variation exists between compounds, polyphenols have significant antioxidant properties as a class effect. Some investigators argue that polyphenols cannot have significant "direct" in vivo antioxidant activity because of their low bioavailability; the amount reaching to plasma is usually less than 1% of the ingested amount, preventing them to reach the supraphysiological concentration enabling scavenging of oxygen species. Instead, their "indirect" antioxidant activity via induction of endogenous systems is much more effective [3]. These compounds modulate expression of the genes of a wide variety of antioxidant and detoxifying enzymes. Some polyphenols such as gallic acid, protocatechuic acid, vanillic acid, caffeic acid, quercetin, and catechin have smoldering pro-oxidant activity especially in the presence of heavy metals. Major examples of foods in this category are green tea, black tea, and apple extracts. This degree of oxidant activity may inversely be useful by induction of endogenous antioxidant defense mechanisms. Polyphenols improve endothelial function (e.g., red grapefruit). These molecules inhibit angiogenesis, blood vessel proliferation, and platelet aggregation (e.g., anthocyanins from purple grapefruit juice). Their anti-atherogenic effect includes prevention of LDL peroxidation (e.g., pomegranate juice, red wine) and its uptake by macrophages, increasing local availability of nitric oxide via increasing expression of endothelial nitric oxide (e.g., resveratrol, cinnamic, and hydroxycinnamic acids), anti-inflammatory (e.g., resveratrol), and anti-apoptotic (e.g., delphinidin and quercetin) properties [3, 106].

As a group, polyphenols are protective in cardiovascular disease. Albeit not explained completely and not relevant for all individual compounds, direct and indirect antioxidant effects, anti-inflammatory activity, and antithrombotic properties seem to be the three major mechanisms involved in this vasculoprotective effect [108]. In Rotterdam study, dietary total flavonoid amount—particularly black tea—is linked to decrease in MI incidence [109]. However, a vast majority of the polyphenol studies have usually utilized surrogate markers such as improvement of endothelial dysfunction (e.g., epicatechin), arterial stiffness (e.g., isoflavones), decrease of blood pressure (e.g., quercetin), decrease of LDL and increase of HDL (e.g., quercetin), and carotid atherosclerotic disease (e.g., cocoa) instead of reporting risk for and death from cardiovascular disease [110]. In addition to their heterogeneity, these categories of pathophysiological studies are not conclusive for clinical decision-making.

Lay media has an extensive interest in nutritional interventions with foods rich in polyphenolic compounds such as red wine, green tea, black tea, and chocolate. *Red wine* is a rich source of flavonoid and non-flavonoid polyphenols including

resveratrol. Resveratrol, found in red wine and itadori tea, is suggested to have cardiovascular protective effects. The significantly lower cardiovascular mortality rate against high rate of fat consumption and smoking in France, so-called French paradox, has long been attributed to high red wine, and resveratrol, intake. Furthermore, Copenhagen City Heart Study showed a significant decrease of vascular mortality in populations drinking moderate amounts (3–5 glasses/day) of red wine [111]. Accumulating, relatively convincing, evidence has led to wider acceptance of beneficial effects of moderate red wine drinking on cardiovascular mortality.

Data on vasculoprotective effects of *green tea* [a rich source of flavan-3-ols such as catechin, epicatechin, epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG), L-theanine, and myricetin], *black tea* (which contains thearubigin, theaflavin, theaflavin-3-gallate, methylxanthine, caffeine, and several other isoflavones), and *chocolate and cocoa* (containing significant amounts of catechin and epicatechin) are relatively limited.

Polyphenolic substances have neuroprotective effects related but not limited to their antioxidant and anti-inflammatory properties. A wide variety of additional mechanisms of actions have been proposed for various polyphenols [62, 99, 107, 112–115]. Examples of neuroprotection mechanisms primarily targeting AD are improvement of synaptic plasticity with quercetin, epicatechin, and blueberry anthocyanins; limitation, decrease, and reversal of amyloid beta-mediated neuronal injury with apigenin, quercetin, and curcumin; decrease of amyloid beta production, formation, and aggregation with curcumin, oxyresveratrol, and epicatechin; promotion of clearance of amyloid beta with resveratrol; inhibition of secretase-1 with oxyresveratrol and curcumin; increase of choline uptake and acetylcholine release and/or decrease of acetylcholine esterase activity with daidzein, glycitin, genistein, and curcumin; increase of hippocampal neurogenesis with anthocyanidins; and modulation of expression of cAMP response element-binding protein in response to amyloid beta with anthocyanidins, EGCG, and quercetin. Several examples of additional neuroprotective mechanisms involved in PD are inhibition of monoaminoxidase-B with resveratrol, inhibition of alpha-synuclein aggregation with curcumin and curcuminoids, attenuation of decrease in dopamine uptake and loss of tyrosine hydroxylase with luteolin, enhancement of mitochondrial autophagic turnover with kaempferol, and upregulation of mitochondrial complex-1 activity with quercetin.

Supporting this potpourri of mechanistic studies, a variety of experimental studies suggested significant and promising effects of “most” of these polyphenolic compounds such as apigenin, isoflavones, oxyresveratrol, tea polyphenols (including EGCG, curcumin, sulforaphane), and blueberry anthocyanidins against cognitive decline including AD [116, 117]. Furthermore, several epidemiological studies documented lower risk of cognitive impairment in people taking higher amounts of “some” of these compounds such as green tea, red wine, and blueberry [62, 117, 118]. Small supplementation studies with “a few” of these compounds such as soy phytoestrogens showed some improvement in cognitive function such as learning ability and memory. However, no large-scale randomized controlled studies have been performed with supplementation of these agents in patients with AD or cognitive impairment. Small-size case-control studies, e.g., with curcumin, remained as

negative [62, 119]. Of note, SUN-AK study testing the efficacy of EGCG (Sunphenon®-EGCG) in early stages of AD has been completed, but the results have not been announced yet [117]. A modicum of randomized controlled studies performed in cognitively normal people showed globally negative results, such as supplementation of soy [120].

Current status of polyphenols is similar in PD. In other words, no conclusive clinical trial data testing their efficacy in patients with PD is available, albeit a salient evidence indicating multifaceted neuroprotective properties. Indeed, nobiletin, anthocyanin, proanthocyanidin, curcumin, cuercetin, baicalein (huang qin), resveratrol, luteolin, and EGCG were reported to have neuroprotective effects in diverse animal models of PD [99, 121–123]. However, effect of dietary consumption of total flavonoids and risk of PD is not clear in epidemiological studies. In a combined cohort of Health Professionals and Nurses' Health Study, dietary flavonoid (tea, berries, apples, red wine, and orange) consumption reduced PD risk in men but not in women [124]. On the contrary, the Finnish Mobile Clinic Survey did not show any positive association either in men or women [125].

10.6 Fatty Acids

Fatty acids are basically carboxylic acids with an aliphatic hydrocarbon tail and are classified into four groups as "short-chain" (<6 carbon) FA (SCFA), "medium-chain" (6–12 carbons) FA (MCFA), "long-chain" (13–21 carbons) FA (LCFA), and "very long-chain" (>22 carbon) FA (VLFA) according to the length of hydrocarbon tail. FAs are further classified into two groups as "saturated" FAs, which have no carbon-to-carbon double bonds, and "unsaturated" FAs, which have one ("monounsaturated" FAs, MUFAs) or more ("polyunsaturated" FAs, PUFAs) double bonds. Unsaturated FAs are described as "cis" or "trans" according to configuration of the two sides of chain attached to the double bond. Another nomenclature used in FA classification takes into consideration the location of double bond(s), which can be performed referencing "the first" carboxyl carbon or terminal methyl carbon (omega). FAs that are required to be obtained exogenously from foods are called as "essential" FAs. Linoleic acid and alpha-linolenic acid are two important essential FAs. Both are luckily abundant in plant oils. Because of the limited capacity of transformation of alpha-linoleic acid into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), EPA and DHA are also considered essential for humans. Both are present plentifully in fish oil.

10.6.1 Short-Chain Fatty Acids

Acetic acid (2C), propionic acid (3C), and butyric acid (4C) are the representative examples of this group. SCFAs are not essential and are produced via colonic anaerobic fermentation of non-digestible dietary fibers by the gut microbiota. Butyrate is a competitive inhibitor of histone deacetylase with probable beneficial

epigenetic effects such as improvement of glycemic regulation. Acetate is an abundant product of microbiota and regulates appetite centrally. Propionate increases intestinal glucagon-like peptide 1 and neuropeptide-Y secretion. Partially based on these mechanisms, diet containing high amounts of fiber is speculated to have protective effects in AD and therapeutic effects in insulin resistance and obesity [126].

Butyric acid is on the market as sodium butyrate "dietary supplement" capsules. Sodium butyrate was shown to have neuroprotective and therapeutic effects in AD, PD, and Huntington's disease animal models. Histone deacetylase inhibition with butyric acid is useful to correct aberrant histone acetylation, which is an important mechanism implicated in these neurodegenerative diseases. No human studies are available yet. It is important to note that SCFAs are not devoid of side effects, given the reported connection of propionate, and to a lesser degree of butyrate, with non-genetic autism spectrum disorders [126].

10.6.2 Medium-Chain Fatty Acids

Caprylic acid (8C) and lauric acid (12C) are the principal MCFAs. The main source of MCFAs is diet. Coconut oil, mainly containing saturated lauric acid, is the most common source of dietary MCFAs. MCFAs are metabolized into ketone bodies such as acetate, acetoacetate, and hydroxybutyrate in the liver, which are critical elements of neuronal energetics.

In AD, glucose transport through blood brain barrier (BBB), such as via glucose transporter 1, is dysfunctional, but ketone body transport remains normal until late stages of the disease [127]. Therefore, supplementation with ketone bodies in the form of MCFAs is suggested to compensate the relative energy depletion occurring early in AD. Potential of MCFAs in treatment of AD include reduction of amyloid beta formation [128], toxicity, and antioxidant and anti-inflammatory effects [126]. Caprylic triglyceride (Axona®), an example of MCFAs derived from coconut oil, was studied in patients with AD and marketed as a medical food (see Sect. 10.10 for details).

10.6.3 Long and Very Long-Chain Fatty Acids

Polyunsaturated omega-3 and omega-6 FAs are common examples of LCFAs. Omega-3 polyunsaturated FAs include alpha-linolenic acid (18C), stearidonic acid (18C), EPA (20C), and DHA (22C), and omega-6 polyunsaturated FAs include linoleic acid (18C), gamma-linolenic acid (18C), arachidonic acid (20C), and adrenic acid (22C). Source of long/very long-chain FAs is diet. Fish oils include EPA and DHA; algae are rich sources of arachidonic acid and DHA. Some supplements on the market contain algae-based DHA. The vast majority contains fish oils, which is usually marketed in gelatin capsules containing high amounts of EPA and smaller amounts of DHA. Omega-6 FAs are found abundantly in plants such as palm,

soybean, rapeseed, and sunflower. Other sources include poultry, eggs, nuts, cereals, whole grain breads, and most vegetable oils. It is important to note that an increased ratio of omega-6 to omega-3 PUFAs in diet has several negative health effects. The average ratio of omega-6 to omega-3 PUFAs is about 15–20 in typical western diet; however, the optimal ratio is suggested as 4 or lower.

DHA is the most extensively studied omega-3 FA. It is one of the primary constituents of cell membrane like phospholipids, involved in the control of membrane fluidity and found abundantly in neuronal and retinal cells. Preclinical studies indicate that DHA has anti-inflammatory, neuroprotective, and antioxidant effects [126, 129]. Supplementation of DHA and/or EPA can improve memory, decrease amyloid beta burden and toxicity, and inhibit hyperphosphorylation of tau in experimental AD models [130, 131]. In addition, postmortem studies documented lower levels of DHA in brains of patients with AD [132]. Furthermore, dietary amount of fish oil was inversely correlated with the risk of AD in some studies [126, 131, 133]. A meta-analysis documented 11% decrease in AD risk with every 100 g increase of fish oil in weekly diet [134]. However, another meta-analysis did not find any form of dose-response relation including a linear one [133].

Some observational studies showed enhancement of learning and memory with DHA supplementation in cognitively normal individuals and people with age-related cognitive decline [135–137]. However, randomized controlled studies are usually negative in this respect. For example, in a randomized controlled trial, 26 weeks 1800 mg/day DHA and 400 mg/day EPA combination was observed to have no overall effect on cognitive performance in 302 cognitively healthy individuals [138].

Supplementation with EPA and/or DHA, in various schedules, failed to show any benefit in cognitive status, mood, and functionality in comparison to placebo (usually olive oil) in patients with AD and non-AD dementia [139–141]. In one of the earliest randomized, double-blind, placebo-controlled trials, 18 months supplementation with algal DHA at a dose of 2 g/day was found to be ineffective in slowing of cognitive deterioration in 295 individuals with mild to moderate AD [142]. In the more widely known omega AD study, 6 months of daily combination of 1.7 g DHA and 0.6 g EPA was found to be unsuccessful in delaying disease progression in 204 patients with mild to moderate AD [143], even with the presence of a significant increase in their CSF levels [144]. In the latest Cochrane meta-analysis, no benefit from DHA/EPA was found with standardized clinical scales such as Alzheimer's disease Assessment Scale-Cognitive subscale (ADAS-Cog) in 3 high-quality trials including 632 patients with mild to moderate AD followed between 6 and 18 months [139].

It is noteworthy that AD patients have lower plasma concentrations of EPA and DHA [131, 145]. Therefore, replacement might be rational in patients with documented deficiency. DHA is the major component of Souvenaid®, an oral supplement designed for memory improvement in AD. Souvenaid® studies showed quite modest improvements in memory function among patients with very early AD. Positive effect was however not perceivable at the functionality level. Details of Souvenaid® treatment is discussed in Sect. 10.10.

From the perspective of PD, supplementation with DHA/EPA was found to reduce apoptosis in nigral dopaminergic neurons and elevate dopamine levels. Furthermore, it was shown to alleviate Parkinsonian symptoms in experimental models [121, 129, 146, 147]. Against these various documented mechanism of actions, epidemiological studies have not disclosed any positive data about supplementation of DHA/EPA on PD risk. Combined analysis of Health Professionals and Nurses' Health studies linked high dietary intake of PUFAs to lower risk of PD [99]; however, this relationship has not been replicated in another large cohort, the Rotterdam Study [148]. There is no study in patients with PD addressing therapeutic effects of DHA/EPA supplementation [129].

Antioxidant, anti-neuroexcitotoxicity, anti-neuroinflammation, and anti-apoptotic activities of polyunsaturated FAs make them research targets promoting neuroprotection of ALS. However, supplementation with high dose of EPA was found to have no effect on motor function and survival in SOD-1 mutant mice [149]. Instead, EPA accelerated disease progression with motor neuron vacuolization in this model. This finding has not been replicated in further studies and is in contradiction with the result of a recent pooled analysis of more than 1 million cases enrolled in five well-known cohort studies including Health Professionals Study [150], which has revealed an inverse relationship between high dietary intake of marine omega-3 polyunsaturated FAs and alpha-linoleic acid and ALS. On the other hand, omega-6 polyunsaturated FAs were not found to be associated with reduced risk of ALS in this analysis. No study assessing the effect of omega-3 FA supplementation in ALS is currently available. Further research is needed to define protective and therapeutic effects of omega-3 polyunsaturated FAs in ALS; given instability of supporting data and potential inadvertent harm, omega-3 FAs should not be given as treatment for ALS.

Apart from these studies, DHA and EPA, alone or in combination as "fish oil," were tested in patients with traumatic brain injury, autism spectrum disorder, and depression in small-sized underpowered studies and failed to show any significant symptomatic improvement [126]. Finally, increased dietary intake of DHA and EPA has been linked to decreased cardiovascular risk. Fish oil supplementation is promoted as a protective agent in cardiovascular diseases. The mechanisms involve lowering of plasma triglycerides, decreasing heart rate and blood pressure along with improvement of cardiac functions [151]. However, studies with supplemental fish oil have failed to show also any significant effect in prevention of cardiovascular diseases. In this context it is important to highlight that there is significant heterogeneity in the amount of DHA and EPA within various prescription and supplement formulations of omega-3 PUFA in the market. This issue is critical as the triglyceride-lowering effects of fish oil are primarily related to EPA, while DHA might elevate LDL levels—an unwanted effect in terms of vascular protection. Further details of omega-3 PUFAs associated vasculoprotection are summarized in Sect. 10.9. These vasculoprotective properties can also contribute to the speculated beneficial effects in neurodegenerative diseases.

10.7 Cellular Energetic Modulators

Cellular energetic modulators can be separated into two major groups as mitochondrial function modulators and others. Mitochondrial dysfunction, resulting in reduction of oxidative phosphorylation and ATP production, is one of the key mechanisms involved in aging and also in a variety of chronic neurodegenerative diseases [152]. Mitochondrial dysfunction can be due to inadequate number of mitochondria, loss of maintenance of the electrochemical transmembrane potential of the inner mitochondrial membrane, dysfunction of electron transport chain and ATP synthesis machinery, or inability to supply critical compounds and substrates to this machinery [152]. These critical compounds are called as "mitochondrial energy modulators" and include coenzyme Q10, L-carnitine, alpha-lipoic acid, nicotinamide adenine dinucleotide (NADH), membrane phospholipids, and riboflavin among many others. Other substances involved in cellular energetics include creatine and magnesium. All of these are also known as "mitochondrial (function) enhancer compounds" and are summarized herein. Of note, mitochondrial dysfunction itself can be clinically symptomatic such as causing fatigue in addition to its pathophysiological role in disease processes.

10.7.1 Alpha-Lipoic Acid

Alpha-lipoic acid (thioctic acid; 1,2-dithiolane-3-pentaoic acid) has antioxidant, transition metal chelating, redox transcription regulative, and anti-inflammatory effects. Given its low bioavailability at the tissue level, the main mechanism behind the antioxidant effect of alpha-lipoic acid is not a direct effect and most probably is related to induction of GSH activity [152]. Alpha-lipoic acid is found in almost every food, but the amount is usually very low. The majority of daily need is provided by metabolism. Supplemental forms are also chemically synthesized, rather than being produced from natural foods.

It is well demonstrated that oxidative stress-associated mitochondrial dysfunction is one of the major mechanisms in early stages of AD. Furthermore, amyloid beta itself and ROS decrease performance of mitochondrial electron transport chain. Theoretically alpha-lipoic acid can attenuate this stress at the mitochondrial level in the setting of AD. In addition, it increases acetylcholine by activation of choline acetyltransferase directly and production of more acetyl-CoA due to increased glucose utilization [153]. Therefore alpha-lipoic acid was trialed in AD in several open-label case series or case-control studies [154, 155]. Against several positive effects noted in these studies, no randomized controlled decisive trial has been performed yet. Furthermore, there is no evidence that alpha-lipoic acid supplementation may have positive effects on mitochondrial disease, multiple sclerosis, or ALS. On the other hand, alpha-lipoic acid oral supplement (200–600 mg/day) is widely used for diabetic polyneuropathy and chronic fatigue syndrome [156].

10.7.2 L-Carnitine

L-carnitine, 3-hydroxy-4-*N*-trimethylaminobutyrate, is a transporter of FAs into the mitochondrial matrix for beta-oxidation. Carnitine is found abundantly in red meat. It can also be found, but significantly in lower amounts, in nuts, seeds such as pumpkin and sunflower, legumes, beans, peas, lentils, green leafy vegetables, and fruits such as apricot and banana, rye, and whole wheat. Acetylated form of L-carnitine, also called as Alcar, is a dietary supplement. It is hydrolyzed into L-carnitine in blood. Therefore, its effects are almost equal to those of L-carnitine. Bioavailability of Alcar is probably better than L-carnitine, and it also increases intramitochondrial acetyl-CoA availability more effectively.

Several studies documented physical performance enhancement by L-carnitine supplementation. The rationale of this effect is suggested to be the principal dependence of energy production to fats during high-level exercise. However, this mechanism alone cannot fully explain its effectiveness because no increase in striated muscle carnitine levels is observed after L-carnitine supplementation. Its antioxidant properties with scavenging of superoxide and hydrogen peroxide, along with decrease of mitochondrial injury and apoptosis, may also be contributory [157]. In addition, several studies showed that L-carnitine may have some beneficial effects in diabetes mellitus, sepsis, and cardiomyopathy, where carnitine levels are relatively lower [152]. L-carnitine is also marketed with the claim of antiaging effect, which is an underexplored topic, but probably includes improvement of fatigue, increase of physical and cognitive activities, increase of mobility and endurance, and thereby decrease of fat and increase of muscle mass.

Albeit quite limited, both L-carnitine and Alcar were investigated in dementia [158] and PD [159]. They were unsubstantiated and are not currently recommended for this purpose. At present there is no clinical study documenting positive effects of carnitine supplementation in patients with stroke and migraine [160], as well.

L-carnitine supplementation for ALS and neuropathic pain is a matter of debate. L-carnitine was demonstrated to delay disease onset and progression in transgenic mice with human SOD-1 gene mutation [161]. A small-scale randomized controlled study showed that 42 ALS patients taking 3 g/day Alcar had slower progression rate and better median survival times compared to 40 patients taking placebo [162].A phase III trial to replicate these preliminary findings is needed before a firm suggestion can be made [76]. Similarly, Alcar has a potential for treatment of peripheral neuropathic pain. A meta-analysis of 4 studies (523 patients) documented that Alcar moderately but significantly reduced VAS scores (mean 1.2) in patients with polyneuropathy [163]. Again, a phase III trial is needed.

Finally, L-carnitine is not harmful in epileptic patients in contrast to the public fear. It is important to note that valproic acid decreases carnitine concentrations significantly, and replacement is suggested to prevent or reverse valproate-related hepatotoxicity and hyperammonemic encephalopathy.

10.7.3 Coenzyme Q10

Coenzyme Q10, ubiquinone, is a vitamin-like compound. It is not essential for humans and synthesized from phenylalanine and tyrosine. It serves as an electron carrier, transferring electrons from complexes-I and -II to cytochrome-c in the mitochondrial electron transport system. Furthermore, its reduced form is a strong antioxidant [99, 164]. Therefore, it is a candidate molecule for the prevention and treatment of neurodegenerative diseases.

In AD animal models, coenzyme Q10 was shown to delay brain atrophy and beta-amyloid plaque pathology [152]. However, an antioxidant cocktail including vitamin E (800 IU), vitamin C (500 mg), alpha-lipoic acid (900 mg), and coenzyme Q10 (400 mg) failed to influence CSF amyloid beta 42, tau, and phosphorylated-tau concentrations in 98 patients with AD. No significant clinical benefit has also been observed in AD [165].

Several experimental studies showed that coenzyme Q10 had a potential to prevent decay of dopaminergic neurons in MPTP-induced PD model [147]. But, clinical studies proved that coenzyme Q10 supplementation is noneffective in decreasing the risk and preventing the progression of PD [99, 166]. A Cochrane meta-analysis initially declared but later withdrew the positive statement about the benefit of coenzyme Q10 supplementation in PD [167]. A decisive phase III randomized controlled trial performed in 267 patients showed that neither 1200 nor 2400 mg/day coenzyme Q10 administered in addition to 1200 mg vitamin E had any clinical benefit [168]. Similarly, coenzyme Q10 (600 mg/day along with remacemide for 30 months) has failed to improve total functional capacity in patients with Huntington's disease [169].

Coenzyme Q10 resulted in a modest increase in survival duration in SOD1 transgenic mice [76]. A multicenter, placebo-controlled phase II trial showed that 9-month duration 2700 mg daily coenzyme Q10 administration failed to modify functional deterioration in 185 ALS patients [170]. No phase III trial was pursued after these disappointing results.

Plasma level of coenzyme Q10 is not related to future cardiovascular risk [171]. Coenzyme Q10 improves exercise capacity modestly in normal persons. It has antihypertensive activity (10 mmHg decrease of mean arterial pressure on average). Effect of coenzyme Q10 on heart failure is popular, albeit data are not convincing. Information about coenzyme Q10 supplementation and stroke risk is limited. It is important to note that statins decrease the level of coenzyme Q10. This decrease has been connected to statin intolerance and statin-induced myopathy. Albeit still a matter of discussion, coenzyme Q10 supplementation is recommended in the management of patients with myogenic symptoms after statin use [172].

Finally, coenzyme Q10 was evaluated in migraine prophylaxis and found effective in some small-scale studies [173]. Some studies pointed higher anti-migraine activity in patients with plasma level of coenzyme Q10 lower than normal [174].

10.7.4 Nicotinamide Adenine Dinucleotide (NADH)

NADH is a cofactor in more than 200 redox reactions. It is the major carrier of electrons within the mitochondrial electron transport system released during metabolism. Its reduced form is a potent antioxidant. Oral supplementation preparations include niacin, nicotinic acid, nicotinamide, or stabilized NADH [152]. NADH supplementation has been used in neurodegenerative diseases including AD and PD with the hope of delaying progression.

NADH was first used in several open-label studies with small number of patients with AD and found to be safe with some beneficial effects in some [175], but not in others [176]. A controlled trial disclosed 10 mg/day stabilized oral NADH was not associated with better scores of tests for memory and attention or lower dementia severity scale scores in 26 patients with AD after 6 months use [177]. Better scores in tests for verbal fluency and visual construction were not found to be clinically relevant. No further and larger-scale studies have been pursued since then.

Mitochondrial complex I, which consists of NADH-ubiquinone oxidoreductase, NADH-coenzyme Q reductase, and NADH dehydrogenase, removes two electrons from NADH and transfers them to coenzyme Q. Several studies indicated that patients with PD had defective complex I. Importantly, NADH stimulates endogenous dopamine production [178]. These observations led to human studies of NADH in PD. In an open-label study, NADH administered either intravenously or orally resulted in some degree of improvement in almost three-fourth of 800 patients with PD [179]. However, these findings have not been replicated in controlled and larger studies.

10.7.5 Creatine

Creatine-associated neuroprotection is usually attributed to intracellular creatine phosphate increase, which plays a role in energy supply in settings of high ATP demand like muscle tissue. It is an antioxidant agent with neuroprotective effects against toxicity of glutamate, amyloid beta, and malonate [147].

Creatine supplementation was found to reduce the loss of dopaminergic neurons in PD animal models [99]. In a placebo-controlled proof-of-concept trial performed in 60 PD patients, 2-year duration creatine supplementation (initiated at a loading dose of 20 g/day, then by 2 g/day for 6 months and 4 g/day for the remaining period) decreased dosages of L-DOPA required and also found to be beneficial in associated mood disorders. However, no positive effect was found on Unified Parkinson's Disease Rating Scale or dopamine transporter SPECT abnormalities [180]. In a Cochrane meta-analysis of 194 cases, no clear positive effect on motor function and ADL was noted after 2 years of supplementation [181]. A NINDS sponsored, decisive, long-term randomized clinical trial, named as NET-PD Investigators Group Study, aimed to determine the efficacy of creatine in mitigating progression of PD was unfortunately terminated prematurely for futility based on results of a planned interim analysis with 955 patients. The median follow-up was 4 years then, and no signal was seen for usefulness of creatine [182].

Preclinical studies with transgenic mouse models of ALS showed discordant results about the effect of creatine supplementation on muscle strength and bulk, weight maintenance, and survival [76]. A meta-analysis of 3 randomized controlled studies involving 386 patients showed that creatine supplementation in the range of 5–10 g/day did not have any significant benefit in disease progression rate and survival. In contrast, a trend of forced vital capacity worsening was noted [183].

Experience with creatine is limited in AD and other types of dementia.

10.7.6 Magnesium

Magnesium functions as a cofactor in more than 300 enzymatic reactions including protein metabolism and DNA/RNA synthesis [184]. Magnesium is vital as a cofactor for adenosine triphosphatase (ATPase). Furthermore, magnesium is the physiological antagonist at NMDA channels, which have significant role in neuronal excitability. A variety of preparations with medical and supplemental purposes are currently on the market [184].

Parenteral magnesium is used in various clinical conditions such as treatment of torsades de pointes-type ventricular arrhythmias, eclampsia, and delirium tremens. Oral preparations are also used as laxatives (magnesium sulfate, magnesium hydroxide) and antacids (magnesium hydroxide). Majority of available supplemental preparations include magnesium chloride, magnesium gluconate, magnesium ascorbate, and magnesium citrate. These are suggested for a variety of neurological diseases albeit the absence of positive trials [185]. The main support for their use comes from observations of low levels of magnesium in AD, stroke, migraine, attention deficit hyperactivity syndrome, restless leg syndrome, and also in diabetes mellitus and hypertension [184].

10.8 Miscellaneous Nutraceuticals

10.8.1 Saffron

Saffron, *Crocus sativus,* is a spice with charming color and taste. It has been used in oriental folk medicine with quite wide purposes including sedation and improvement of learning capabilities. More than 150 compounds have been identified in saffron mound. The carotenoid pigments of saffron are crocin and crocetin. Saffron's bitter taste comes from its picrocrocin and safranal content [186].

It is suggested to be useful in coronary artery disease and hypertension. Small-sized but randomized double-blind clinical trials indicated that saffron supplementation is beneficial in patients with depression. Usual dose is 30 mg/day for 6 weeks in these studies [187]. Both saffron and its compounds were found to be neuroprotective in experimental PD and other neurodegeneration models [188]. It was shown to reduce dopamine utilization, inhibit apoptosis, increase GSH synthesis, decrease nitric oxide and glutamate toxicity, and inhibit sphingomyelinase, syncytin-1, and

ceramide formation [189]. It was also demonstrated that trans-crocin-4, a saffron compound, decreases amyloid beta fibrillogenesis and inhibits acetylcholine esterase activity moderately. In a small-sized study, saffron (15 mg twice a day) was found as effective as donepezil for treatment of mild to moderate AD [190].

10.8.2 Carnosine

Carnosine is beta-alanyl-L-histidine. Carnosine is marketed for bodybuilding or geroprotection effects based on uncorroborated claims from unreviewed studies. It has antioxidant properties. Carnosine is also an anti-glycating compound and reduces the rate of formation of advanced glycation end products (AGEs), which are toxic molecules originating as by-products of metabolism or high-temperature processed foods. Main AGEs are hemoglobin-A1c, 3-deoxyglucosone, pentosidine, malondialdehyde, and methylglyoxal. There is a considerable body of evidence supporting significant contribution of AGEs to aging, AD, stroke, PD, diabetes mellitus, and several other conditions [191, 192]. Carnosine can scavenge most of these substances such as methylglyoxal, which was shown to be involved in PD pathology. However, no clinical study has been conducted to document its efficacy in these diseases [193].

10.8.3 Garlic

Garlic, *Allium sativum*, extract is used for vasculoprotection. Garlic preparations have marginal lipid-lowering effects; the average decrease is 11–23 mg/dL in total cholesterol and 3–15 mg/dL in LDL cholesterol after 2 months use [194]. Albeit garlic supplementation is widely suggested and used for blood pressure control, this effect has not been subjected to high-quality studies. Furthermore, there is no evidence supporting reduction of cardiovascular mortality and event rate by garlic supplementation [195]. Garlic was reported to reduce platelet aggregation in some, but not all, studies. It is suggested that patients taking anticoagulants should be cautioned against consuming garlic in big amounts. Active ingredients playing role in garlic-associated presumed positive vascular effects are allicin, adenosine, and paraffinic sulfide.

10.8.4 Chitosan

Chitosan is isolated from shellfish and sea crustaceans. Many health-related beneficial effects including lipid reduction, blood pressure control, and weight loss are alleged to chitosan, without support from trials with sufficient quality. For example, lipid-lowering effect of chitosan is marginal. Chitosan, 1–6 g/day in 2 or 3 divided doses, has decreased total cholesterol in the range of 10 mg/dL and increased HDL-cholesterol by about 10%, but there was no significant effect on LDL cholesterol

levels [196]. In theory, chitosan increases sense of satiety by increasing gastrointestinal bulk and viscosity and inhibits absorption of dietary lipids.

10.8.5 Glucomannan

Glucomannan is a soluble fiber obtained from konjac. It is used as a thickener and nutritional supplement for obesity, hyperlipidemia, and diabetes mellitus. It was authorized for appetite reduction and weight loss in some countries. Average decrease of weight with glucomannan supplementation is about 1 kg, while total cholesterol decreases by 19 mg/dL, triglyceride by 11 mg/dL, and LDL cholesterol by 16 mg/dL [197]. It is important to note that glucomannan is not devoid of side effects and may also reduce bioavailability of oral medications when taken simultaneously.

10.9 Neuronutritional Aspects of Ischemic Stroke

Albeit not much scientific evidence exists, various nutraceuticals, functional foods, and supplements are widely used not only for the purposes of primary and secondary prevention of stroke but also directly for acute-phase treatment. The most frequent mechanisms of stroke are directly or indirectly related to atherothrombosis. Therefore, control of atherosclerosis risk factors such as diabetes mellitus, hypertension, dyslipidemia, metabolic syndrome, and smoking is of critical importance in stroke prevention. Therapeutic lifestyle changes including diet with low cholesterol, saturated fat and salt, regular physical activity, weight loss, quitting smoking, and reducing stress is usually suggested. Mediterranean diet and DASH (Dietary Approaches to Stop Hypertension) diet and their components are associated with decreased stroke risk [198, 199].

Claimed protective and therapeutic properties of the foods and supplements suggested for stroke are multidimensional and act primarily by decreasing oxidative stress and inflammation as noted in previous sections. Products with lipid-lowering properties, antihypertensive effects, and antiplatelet/anticoagulant activities are herein summarized. Detailed discussion about cardiovascular effect of vitamin C, vitamin E, beta-carotene, lycopene, vitamins involved in homocysteine metabolism, vitamin D, and polyphenols can be found in their subsections.

Food supplements and products with antiplatelet effect include omega-3 PUFAs, olive oil, borage oil, garlic, onion, polyphenols such as resveratrol, feverfew, taurine, flavonol-rich cocoa (dark chocolate), policosanol, glucosamine, lycopene, L-arginine, magnesium, and vitamin E [200–203]. Vitamin E had observable antiplatelet effect only with doses higher than 800 IU/day. Some fruits (usually in the range of 1 mg per kg) such as cranberry, grapes, nectarine, and tangerine and some spices (usually in 20–30 mg per kg range) such as cinnamon, turmeric, curry powder, peppermint, ginger, dill, and oregano contain salicylate and therefore reduce platelet aggregation. Plants and dietary supplements containing coumarin

derivatives include aniseed, cassia cinnamon, celery seed, dandelion, licorice root, red clover, and parsley [202]. Against being commonly cited, *Ginkgo biloba*, ginseng, and *Panax* ginseng, ginger products, and Pycnogenol® (proanthocyanidines extracted from French maritime pine bark) appear to have no, or very little, antiplatelet or anticoagulant effect at regular doses [200, 201]. Cranberry, danshen, ginkgo, ginseng, Japanese green tea, and St. John's wort can potentiate effects of warfarin [200]. Of note, knowledge about the anticoagulant and antiplatelet properties of supplements and herbal products, as well as their interaction with antiplatelet and anticoagulant medicines, is of utmost importance to avoid excessive risk of bleeding especially in patients taking these agents.

Nutraceuticals with lipid-lowering effects include plant sterols (sitosterol, campesterol) and stanols (sitostanol, campestanol), berberine, fish oil, EGCG, spirulina, anthocyanins such as delphinol, niacin, beta-glucan, and curcuminoids. Hypolipidemic effects of garlic (allicin as the main putative hypolipidemic ingredient), resveratrol, sour tea (roselle, *Hibiscus sabdariffa*), flaxseed oil, turmeric, ginger, holy basil, yarrow, artichoke leaf extract, policosanol, red yeast rice, gugulipid, chitosan, glucomannan, and rosemary extract are controversial or absent [204, 205]. The lipid-lowering mechanism of nutraceuticals is multifactorial: stanols/sterols, chitosan, and EGCG interfere with intestinal absorption of cholesterol. Spirulina, beta-glucan, guggul, and chitosan interfere with reabsorption of intestinal bile acids and increase fecal excretion of cholesterol. Policosanol and some polyphenols such as EGCG inhibit HMG-CoA reductase. EGCG inhibits FA synthase. Berberine and EGCG enhance hepatocyte LDL receptor expression and biliary excretion of cholesterol. Berberine also decreases LDL receptor turnover [204].

Among others berberine, stanols/sterols, and fish oils are discussed more widely in the germane literature. Berberine is a plant alkaloid with strong yellow color. It is proposed to treat diabetes mellitus, hyperlipidemia, and metabolic syndrome along with various neurodegenerative diseases, but its poor oral bio-absorption is a limiting factor. Berberine supplementation, with its usually suggested dose of 500–1000 mg per day, decreases total cholesterol (average by 23 mg/dL), LDL cholesterol (average by 25 mg/dL), and triglyceride (average by 40 mg/dL) and also increases HDL (average by 2 mg/dL). Its hypolipidemic effect is additive to statins [205].

Stanols and sterols are found in vegetable oils, nuts, breeds, seeds, and cereals. Average daily intake of stanols/sterols is 200–400 mg in regular western diet. Stanols/sterols decrease plasma total cholesterol, LDL cholesterol (8–10%), and triglyceride (6–9%) levels. There is no effect on HDL-cholesterol [205]. Plant sterol/stanols (usually 2 g/day) are recommended for hypolipidemic purposes in patients intolerant or poorly responsive to statins [206].

Albeit a signal toward cardiovascular protection can be seen in several randomized trials, more studies have concluded that omega-3 PUFAs do not reduce cardiovascular events including stroke [207]. Protective effect, if present, could be due to antiplatelet, hypolipidemic, and antihypertensive properties of PUFAs. Fish oil (EPA/DHA) reduces triglyceride levels significantly (between 20 and 50%, average

by one-third) by decreasing hepatic VLDL-triglyceride synthesis and secretion, enhancing triglyceride clearance from VLDL in bloodstream, increasing beta-oxidation and plasma lipoprotein lipase activity, and inhibiting acyl-CoA-1,2-diacylglycerol acyltransferase. This effect is greater in patients with significantly elevated baseline triglyceride levels. Several fish oil-based formulations such as Vascepa® (capsules contain 1 g of icosapent ethyl which is ethyl ester of EPA; usual dose 4 g per day) and Lovaza® (1 g capsules contain 465 mg EPA ethyl ester and 375 mg DHA ethyl ester; usual dose 4 g per day) have FDA clearance for hypertriglyceridemia management. While there was no significant safety concern in randomized trials, it is well known that omega-3 PUFAs (higher than 3 g per day) can increase risk of bleeding and may interact with antiplatelets and warfarin. FDA recommendations state that only consuming of 3 g of combined DHA and EPA per day is safe.

Many nutraceuticals and functional foods are currently marketed with the claim of treatment of hypertension. Without exception, the effect size of these agents on systolic and diastolic blood pressure levels is usually small, and they are not suggested as stand-alone treatments in hypertension [208]. There is relatively larger body of evidence for potassium, L-arginine, coenzyme Q10, melatonin, vitamin C, coca flavonoids, beetroot juice, and garlic extract [208]. In hypertensive patients, average reduction of systolic and diastolic blood pressure is 6 and 3.5 mmHg for doubling potassium intake [208], 5.4 and 2.7 mmHg for oral L-arginine [209], 3.7 and 2 mmHg for coenzyme Q10 [210], 6.5 and 3.1 mmHg for controlled release melatonin [211], 4.9 and 1.7 for vitamin C [212], 6 and 3.3 mmHg for soy isoflavone [213], 3 and 2 mmHg for cocoa flavonoids [214], 4.4 and 1.1 mmHg for beetroot juice [215], and 8.4 and 7.3 mmHg for aged garlic extract [216]. As noted above, antihypertensive properties of omega-3 PUFAs contribute to their alleged vasculoprotection effects. The amount of systolic and diastolic blood pressure reduction by omega-3 PUFAs is usually about 4 and 2 mmHg, respectively. Antihypertensive effect of omega-3 PUFAs is attributed to enhanced nitric oxide generation, prostaglandin synthesis, parasympathetic stimulation, and suppression of renin-angiotensin-aldosterone system [208].

Cardiovascular protection by some nutraceuticals and medicinal foods is mainly due to their effect on lowering fasting and postprandial plasma glucose, improvement of overall blood glucose control, and insulin sensitivity. For example, resveratrol, which has significant protective effects on cardiovascular risk including stroke, was shown to have no influence on blood pressure and lipid profile but appeared to provide cardiovascular benefits just due to its positive effects on glycemia control and insulin sensitivity in type 2 diabetes mellitus [205]. Of note, this effect is not clear in people without diabetes mellitus. Among others, the mechanism attributed to this effect of resveratrol is mimicking caloric restriction by activating several metabolic regulators such as AMP-kinase. Potential benefits on glucose and insulin metabolism can contribute to alleged vasculoprotection by anthocyanins, lycopene, beta-carotene, quercetin, kaempferol, cytrolin, epicatechin, and phloridzin [217].

10.10 Neuronutritional Aspects of Alzheimer's Disease

A long list of medical foods is currently on the market with the claim of preventing or delaying the progression of AD and other dementias. Much more is promoted as memory enhancers for normal populations. Most of these agents are devoid of information about safety and effectiveness. Peer-reviewed literature remains very restricted in comparison with lay literature. Most information in the Internet is not scientific and includes opinions, beliefs, traditions, and a small body of nonstandardized research. These agents are not subject to strict and well-developed approval procedures similar to prescription drugs. Effectiveness, safety, and purity are usually unknown. A significant prevalence of side effects and interaction with prescribed medications is also a concern.

We herein restricted the subject to peer-reviewed literature. Detailed information about homocysteine-lowering vitamins, vitamin E, vitamin C, vitamin A, beta-carotene, lycopene, vitamin D, polyphenols, alpha-lipoic acid, coenzyme Q10, and omega-3-FAs can be found in the related parts of the chapter. Because of limited space, we do not discuss several nutraceuticals, including grape juice, chromium picolinate, *S*-adenosylmethionine, Perceptiv® (combination of 3-deaza-adenosine, *N*-acetyl-L-cysteine, and *S*-adenosylmethionine), Brain Up10® (Andean compound plus complex B vitamins), *Bacopa monnieri, Centella asiatica,* vinpocetine, and *Salvia miltiorrhiza*, which were found to have statistically significant positive effects on at least one cognitive domain in either only a single study or multiple but contrasting studies [218–220]. Souvenaid®, caprylic triglyceride (coconut oil, Axona®), *Ginkgo biloba*, tramiprosate, phosphatidylserine, crocin, and huperzine A are discussed in more detail in this section.

10.10.1 Souvenaid®

Souvenaid® is a medical liquid food designed for treatment of early AD. It is marketed as a daily 125-cc drink and includes a cocktail (registered as Fortasyn Connect®) of EPA 300 mg, DHA 1200 mg, phospholipids 106 mg, choline 400 mg, uridine monophosphate 625 mg, vitamin E 40 mg, vitamin C 80 mg, vitamin B12 3 μg, vitamin B6 1 mg, folic acid 400 μg, and selenium 60 μg. This combination is aimed to increase the concentration of substances taking place in the synthesis of phosphatidylcholine, the major ingredient of synaptic membranes. Increase in phosphatidylcholine is presumed to promote synapse formation and function and thereby reduce cognitive symptoms occurring in the setting of AD. Souvenaid® indeed leads to sufficient elevations in serum concentrations of uridine, choline, selenium, folate, vitamin B6, vitamin B12, and vitamin E along with DHA and EPA after 3 months of treatment [145]. It is however important to note that all of the Souvenaid® studies excluded subjects consuming enough amount of dietary fish oil (more than twice a week) or using regular supplementation of omega-3 FAs. Therefore, the study populations had lower levels of DHA and EPA than usual cohorts.

Against this logical theoretical background and promising experimental data, randomized controlled trials testing effect of Souvenaid® failed to show a significant positive effect on progression of cognitive decline in patients at various stages of AD [221–224]. In the Souvenir I trial, 12 weeks of Souvenaid® treatment resulted in a significant improvement in the delayed verbal recall, but not in other cognitive domains in 225 drug naive patients with mild AD [221]. The Souvenir II trial which evaluated Souvenaid® intake for 24 weeks showed a modest improvement of the memory function domain Z score of the neurophysiological test battery, but not in other cognitive parameters in 259 Alzheimer's patients [222]. In S-Connect study, 24-week Souvenaid® treatment resulted in no significant effect on cognitive deterioration in 527 mild to moderate AD patients [223]. In LipiDiDiet study no significant benefit of 24-weeks of Souvenaid® treatment was observed in the cognitive composite score in 311 patients with prodromal or predementia stage of AD. MRI-based atrophy rate, which was one of the secondary end points, was however less in the Souvenaid® group [225].

In conclusion, clinically discernible benefit of Souvenaid® in patients with early AD is quite modest, if not none. This therapeutic option is currently not suggested for nonselected patients with AD.

10.10.2 Caprylic Triglyceride (Axona®)

Caprylic triglyceride (CTG) is a medical food marketed in 2009 for patients with mild to moderate AD. It is originally coconut oil, which is a medium-chain triglyceride, fractioned to form the product with brand name of Axona®. It is also known as "Alzheimer's milkshake" in the lay literature. It has no approval for treatment of AD but is classified into GRAS (generally recognized as safe) category by FDA. It is sold only by prescription.

The scientific evidence for use of CTG is not very tangible. In theory, brain glucose uptake is impaired in the early periods of AD. This energy defect can partially be restored with ketone bodies, principally beta-hydroxybutyrate and acetoacetate. CTG can provide beta-hydroxybutyrate to the Alzheimer brain given that ketone uptake is not impaired apparently in contrast to glucose in AD.

In the single small-sized industry-sponsored index study, 90-day use of CTG resulted in a small but statistically significant difference in ADAS-Cog in 152 apolipoprotein E4-negative subjects diagnosed with mild to moderate AD [226]. Further small-sized studies have also shown similar positive results [227, 228]. It is obvious that this area requires large-scale dependable studies. None of the professional authorities, including Alzheimer's Association, does not recommend the use of medical foods, including Axona®, for the treatment of AD for now.

10.10.3 *Ginkgo biloba*

Extract of the leaf of *Ginkgo biloba* is on the market as a dietary supplement with the allegation of enhancement of cognitive function in normal populations, albeit

the absence of any ascertainable positive effect except for one study [229]. A standardized and special preparation, called as Egb176, has also been marketed as a medicine (usually as an over the counter medication) for a long time. This agent has been extensively studied in patients with cognitive dysfunction including those with AD. Although germane evidence indicates the absence of any reliable and consistent clinically significant effect, the subject is still a matter of ongoing discussion [230, 231]. *Ginkgo* leaves contain several active ingredients such as phenolic acids, proanthocyanidins, flavonoid glycosides, biflavons, alkylphenols, and polyphenols. Putative neuroprotective and cognitive-enhancing activity of *Ginkgo biloba* leaf extract include antioxidant, anti-apoptosis, and anti-inflammatory mechanisms, protection against mitochondrial dysfunction, and improvement of cerebral blood flow. Reduction of amyloidogenesis and amyloid beta aggregation, modulation of tau phosphorylation, and induction of growth factors are also suggested [232].

10.10.4 Tramiprosate (Homotaurine)

Tramiprosate, also called as homotaurine, is an 3-amino-1-propanesulfonic acid and is a natural compound of red algae. It is a GABAergic compound with GABA receptor (both A and B types) partial agonistic activities. Therefore, it has anticonvulsant, muscular relaxant, and hypothermic properties. Tramiprosate was demonstrated to bind soluble amyloid beta and inhibit its aggregation [233]. Therefore, tramiprosate was first studied in AD. However, the Alphase study, a phase III double-blind randomized controlled trial, failed to show any beneficial effects [234]. In this trial, 78-week use of tramiprosate (100 or 150 mg bid) did not improve, or stabilize, the clinical status in 1052 patients with AD. The manufacturer has then chosen to market tramiprosate as a medical food (Vivimind®) instead of medicinal drug [235]. Of note, *N*-acetyl derivative of homotaurine, acamprosate, has been approved for use in alcohol dependence.

10.10.5 Phosphatidylserine

Phosphatidylserine was initially derived from cattle brain cells. However, after the epidemic of bovine spongiform encephalopathies in the 1990s, soybean and cabbage became the source to extract phosphatidylserine for supplementation. These plant-derived phosphatidylserines are claimed to reduce AD risk and enhance memory or other cognitive functions in demented or non-demented elderly, but the evidence supporting these claims is quite limited [236].

The theory behind supplementation with phosphatidylserine for the purposes brain health is logical. Aging and other factors coincide with neurotransmission impairment due to biochemical and/or structural deterioration. Phospholipids such as phosphatidylserine are responsible for cell membrane polarity. Under normal circumstances, phosphatidylserine is located at the inner side of cell membranes. This is achieved by an active process and involves several enzymes such as flippases and scramblases. In cellular deterioration, phosphatidylserine flips to the outer

surface due to problems of these enzymatic processes. Extracellular appearance of phosphatidylserine activates apoptosis. Amyloid beta-associated disruption of phosphatidylserine holding contributes significantly to its toxicity, even though not being a primary mechanism in AD [237]. Satisfactory gastrointestinal absorption and BBB passage of supplemental phosphatidylserine results in sufficient tissue levels that might help in reversing all this deterioration. Phosphatidylserine is recommended as 200 mg, 3 times daily. There is also a high interest about phosphatidylserine in sport nutrition, where it is used for performance and endurance improvement and muscle protection.

10.10.6 Crocin

Crocin is the main ingredient of saffron. It exerts anticonvulsive, antidepressant, and cognitive-enhancing activities. Saffron inhibits amyloid beta fibrillation and acetylcholine esterase activity [187]. In a small-scale randomized controlled trial including 55 subjects with mild to moderate AD, effect of saffron extract (15 mg bid) was similar to donepezil (5 mg bid) in terms of slowing the cognitive decline during 22 weeks of treatment [190]. In another small study with 68 patients with moderate to severe AD, 1-year treatment with saffron extract (30 mg/day) was found to be equal to memantine (20 mg/day) in terms of slowing cognitive deterioration [238]. No large-scale randomized controlled study is available yet.

10.10.7 Huperzine A

Huperzine A is a firmoss (*Huperzia serrata*) extract, and biochemically a sesquiterpene alkaloid. It has been used in traditional Chinese medicine for centuries. It has reversible acetylcholine esterase inhibiting and NMDA receptor antagonistic activities. More recently its central muscarinic and nicotinic ACh receptor, mainly α7 and α4β2 nicotinic types, activities were demonstrated [239]. Therefore, it also has anti-inflammatory effects by decreasing interleukin-1β, tumor necrosis factor-α, and nuclear factor kappa B (NFκB) signaling. It can cross the BBB and also has anticonvulsive effects via potentiation of GABAergic transmission [239].

Huperzine A has been used in treatment of AD, epilepsy, and myasthenia gravis. A meta-analysis of 8 AD (733 patients) and 2 vascular dementia (92 patients) studies indicated significant improvement in the scores of mini-mental state examination and ADL [240]. Huperzine A is a well-tolerated compound with low frequency of side effects mostly related to cholinergic activity such as nausea, vomiting, and diarrhea. However, poor quality and nonstandardized properties of the studies together with the small sample size and individual inconclusive results suggest that huperzine A should not be recommended routinely for dementia patients until high-quality positive evidence becomes available [241]. Furthermore, it should be noted that no evidence, even weak, is found for mild cognitive improvement or as a cognitive enhancer in normal people [242].

10.11 Neuronutritional Aspects of Parkinson's Disease

PD is a highly prevalent and disabling neurodegenerative disease. No curative treatment is currently available. Several neuronutritional approaches targeting various mechanisms are proposed and examined for both to decrease the risk and stop deterioration of the disease. Neuronutritional strategies can provide neuroprotection with scavenging of free radicals and ROS, chelation of iron, modulation of cell-signal pathways, and inhibition of neuroinflammation, apoptosis, and mitochondrial dyshomeostasis [99, 243]. Several of selected nutraceuticals such as vitamin A, vitamin E, vitamin B groups, vitamin D, coenzyme Q10, creatine, and saffron were reviewed above in detail; some additional aspects of other molecules are summarized briefly herein.

10.11.1 Genistein

Genistein is a phytoestrogen primarily found in soybean isoflavone. In experimental PD models, it was shown to have some neuroprotective effects such as inhibition of microglial activation and apoptosis along with restoration of tyrosine hydroxylase and dopamine transporter [129]. Unfortunately, no studies testing the efficacy of dietary enrichment or direct supplementation of soy on the progression and risk of PD exist in humans.

10.11.2 Caffeine

Major caffeine sources are coffee, black tea, energy drinks, and chocolate. Several epidemiological studies reported an inverse association between PD risk and caffeine intake [121]. Furthermore, a dose-response relationship was proposed where maximum protection by coffee occurred at approximately three cups per day [244]. Caffeine is putatively neuroprotective in various animal models of PD, primarily related to antagonism of several subtypes (A1, A2a, A2b, A3) of adenosine receptors, inhibition of glutamate transmission, neuroinflammation and microglial activation, and downregulation of nitric oxide production. In addition to its stimulant effect, caffeine may have positive effects on motor problems in patients with PD [245]. Of note, several lines of evidence indicated that neuroprotective effect of caffeine decreases with estrogen; in other words, the effect is less in women, and additionally when combined with creatine [129, 246].

10.11.3 Tea

Increased tea intake is linked to a lower risk of PD in some, but not all, epidemiological studies [129]. These cohort and case-control studies usually tested "general" tea consumption rather than green or black tea separately. Both black tea theaflavin and green tea EGCG were found to be neuroprotective in rodent models of PD

[129]. Especially, EGCG can pass the BBB thoroughly and produce CNS concentrations enough to produce putative neuroprotection. Neuroprotective activity spectrum of tea polyphenols is quite wide and multidimensional including, but being not limited to, iron chelation, free-radical scavenging, anti-apoptotic properties, protein kinase C regulation, endogenous antioxidant capacity, adenosine monophosphate-activated protein kinase activation, and mitochondrial biogenesis promotion [99, 122, 147]. In addition, catechin and EGCG inhibit catechol-o-methyltransferase, and EGCG decreases MAO-B activity and acts synergistically to rasagiline, an MAO-B inhibitor, in MPTP models of PD. Green tea polyphenols also decrease alpha-synuclein oligomer levels in the striatum. L-theanine of green tea increases neurotrophic factors in rotenone models of PD. Black tea polyphenols suppress expression of proinflammatory markers such as inteleukin-1 beta [122]. Nonetheless, data from large prospective studies investigating general tea consumption and PD prevalence are not conclusive. Of note, no connection between green tea intake and PD risk was observed in Singapore Chinese Health Study [247]. In conclusion, we do not have enough data to suggest tea for neuroprotection in PD currently.

10.11.4 Canonical Effects of Nutraceuticals in Parkinson's Disease

In addition to nutraceutical protection and treatment efforts in PD, several other neuronutritional issues merit discussion. The first is symptomatic treatment with natural L-DOPA sources. *Mucuna pruriens* (velvet bean) and *Vicia faba* (broad bean or fava bean) are well-known plants containing L-DOPA. Commonly used *Mucuna* seed powder at a dose of 45 g per day corresponds to 1.5 g L-DOPA. Several studies claimed similar degrees of anti-Parkinsonian effect and tolerability compared to regular L-DOPA preparations. *Mucuna* has faster onset of action and longer duration of effect with lesser dyskinesia and peripheral dopaminergic side effects [248]. In addition to L-DOPA, *Mucuna* seed powder contains NADH and coenzyme Q10, both of which are potentially neuroprotective in PD models [99].

The other neuronutritional issue in PD is the modulation of L-DOPA pharmacokinetics. Some nutraceuticals may reduce the side effect of L-DOPA or increase its bioavailability at the gastrointestinal absorption stage. One example is vitamin C which increases the efficacy of L-DOPA via enhancing its gastrointestinal absorption in elderly with PD [10].

10.12 Neuronutritional Aspects of Amyotrophic Lateral Sclerosis

There is a consensus about positive influence of weight stabilization on prognosis of ALS. However, opinions about the best dietary modification are quite variable. Diets with high carbohydrates, diets with high fat, ketogenic diet, or just hypercaloric diets are all suggested without finalizing evidence [249]. In addition to dietary

modification, direct supplementary use of vitamins, minerals, and other nutraceuticals is very popular and reported in up to 75% of patients with ALS [76, 250]. Common products used in this setting include vitamin E, pyridoxine, vitamin B12, folate, *Ginkgo biloba*, green tea extract, coenzyme Q10, grape seed extract, zinc, melatonin, and creatine [118]. A "wide" variety of cocktails of functional food and supplements are also currently on the market for ALS without sufficient scientific background. Examples of well-known products are Deanna protocol [251] and Mototab oral supplement [252]. Deanna protocol includes arginine-alpha-ketoglutarate, NADH, GABA, GSH, idebenone, coenzyme Q10, vitamin B12, folate, R-lipoic acid, acetyl-L-carnitine, phosphatidylserine, bee propolis, 5-hydroxy-tryptophan, creatine, *Ginkgo biloba*, glycine, magnesium, methyl-folic acid, OptiZinc, phosphatidylcholine, taurine, theanine, vitamin D3, and vitamin D [251]. Mototab consists of magnesium murakab, zinc murakab, *Berberis Aristata* extract, egg shell calcium, sulfur, and substituted olive oil [252]. The vast majority of these agents have not been studied with scientific methods. It is not easily lucid why these substances might be useful in patients with ALS. We herein evaluated only neuro-nutraceuticals with scientific data about the use in ALS. Of note, clinical and preclinical data assessing the status of omega-3 FAs, vitamins, L-carnitine, coenzyme Q10, and creatine were summarized in the previous sections. Catechins, resveratrol, medium-chain triglycerides, and caffeine are reviewed in this section in more detail.

10.12.1 Catechins

These compounds are effective constituents of green tea, blueberries, red wine, and *Ginkgo biloba*. EGCG, green tea extract, was shown to extend survival and retard the onset of disease in SOD1 mutant mice probably as a result of decrease in glutamate excitotoxicity in motor neurons, microglial activation, and caspase-3 activity [253]. No human study is available.

10.12.2 Resveratrol

Resveratrol, as mentioned above, is the health-effective constituent of blueberries, grapes, and red wine. Its positive effect on mitochondrial bioenergetics and autophagy is suggested to provide neuroprotection in ALS [254]. Resveratrol activates intracellular survival pathways such as sirtuin-1 and AMP-activated protein kinase. Supplementation showed delay in disease onset and extent of survival in SOD1 transgenic mouse models [254]. There is no human study performed.

10.12.3 Medium-Chain Triglycerides

Medium-chain triglycerides are metabolized into acetyl-CoA which can be used an alternate energy source for motor neurons [250]. Similar to ketogenic diet, 10% caprylic triglyceride was shown to improve motor function without any benefit in

survival rate in ALS mice [255]. No human study has been performed to test this symptomatic effect yet.

10.12.4 Caffeine

Caffeine is suggested to have neuroprotective effects in ALS by adenosine receptor antagonism. However, epidemiological studies did not support any correlation of caffeine, coffee, or tea intake with ALS risk [256]. No human supplementation study is available to us.

10.13 Neuronutritional Aspects of Migraine

Rate of use of complementary or alternative medicines is highly prevalent among migraineurs. A significant amount of data is not present in peer-reviewed sources but instead documented in the lay literature and therefore difficult to evaluate. Data meriting discussion includes mitochondrial function modulators (riboflavin, coenzyme Q10), magnesium, *Petasites*, feverfew, and melatonin.

10.13.1 Riboflavin

Riboflavin was found to be effective in several studies, but negative in more. Despite the weak quality of evidence, American Academy of Neurology has still labeled riboflavin as a "probably effective" treatment in migraine prophylaxis [257]. The Canadian Headache Society went further and had put a definite positive recommendation statement for riboflavin use in adult migraine [258]. There is however no indication for riboflavin in pediatric migraine [79]. Its suggested mode of use is 400 mg daily taken in the morning. However this once-daily regimen is criticized due to the short (approximately 1 h) half-life of riboflavin [79].

10.13.2 Coenzyme Q10

Coenzyme Q10 was studied in several small-scale trials for prophylaxis of migraine attacks; however, evidence remained rather weak. However, American Academy of Neurology again considers coenzyme Q10 as a "probably effective" migraine prevention compound [257]. Canadian Headache Society recommends its use in migraine prevention [258]. The advised regimen is a daily 300 mg morning dose.

10.13.3 Magnesium

Magnesium supplementation was evaluated in both prevention and acute attack treatment settings. The evidence in terms of prevention is not conclusive as stated by a meta-analysis [259]. The Canadian Headache Society recommends 600 mg/

day elemental magnesium for prophylaxis but gives more importance to extra advantages of increased dietary magnesium consumption [258]. Absorption of certain magnesium formulations such as magnesium glycinate and other amino acid chelated forms are better than others [260]. Efficacy of intravenous magnesium to abort acute migraine attacks is an understudied subject, and this agent cannot be recommended as an attack abortive medicine currently.

Of note, a combined preparation including magnesium (600 mg), riboflavin (400 mg), and coenzyme Q10 (150 mg) is currently in the market for migraine prevention (Migravent® in Europe, Dolovent® in the USA). This agent was tested in a randomized controlled trial in 130 adult migraineurs with three or more attacks per month. During the 3-month active period, migraine days decreased by 0.8 days with this compound (migraine days: baseline 6.2; active 4.4; placebo 5.2; $p = 0.20$) [80].

10.13.4 *Petasites*

Experience with *Petasites hybridus* (butterbur, pestilence wort) is worth of discussion. *Petasites* has antihistaminic properties and inhibits leukotriene synthesis [79]. Furthermore, it inhibits calcium channels. It is on the US market but withdrawn from British and German markets due to severe hepatotoxicity risk. Its purified form (Petadolex®) has been evaluated in prevention of migraine in three small studies. In the first study [261] 100 mg butterbur showed significant benefit in 120 patients; it decreased migraine days by 1.6 with a response rate of 45% (placebo 15%). In the second study, Petadolex was not useful in 58 patients [262]. The third study [263] again documented significant benefit of butterbur 75 mg bid with a decrease in migraine days by 1.7 and response rate of 68% (placebo 49%). Of note, butterbur 50 mg bid was not found to be effective in this study. Albeit igniting a substantial controversy, this evidence led American Academy of Neurology to state that butterbur is an effective treatment with class A evidence in the prophylaxis of migraine [257]. But, this argument has not been endorsed by European societies based on the modest level of effectiveness and rare (1/175,000) but significant hepatic toxicity [79].

10.13.5 Feverfew

Feverfew is *Tanacetum parthenium*. Its appearance is reminiscent of typical daisy, but it grows within small bushes instead of grass. The active ingredient is parthenolide and sesquiterpene lactones. It is marketed in various forms such as dried leaf extract, tea, or purified pill preparations. It is used for migraine prevention; however, the exact mechanism of action has not been clarified. Parthenolide, inhibits NFκB, which is involved in migraine pathophysiology. NFκB plays a role in cortical spreading depression-related inducible nitric oxide synthase induction and dural neurogenic inflammation. In addition, feverfew was shown to inhibit calcitonin gene-related peptide release in the trigeminovascular system via its partial agonistic effects on transient receptor potential channel ankyrin-1 [264].

The effect of parthenolide-purified feverfew (MIG99) on migraine prophylaxis was studied in two randomized trials. In the first study [265], 3-month use of three dosages (2.08 mg; 6.25 mg; 18.75 mg, all tid) of "feverfew alone" was compared with placebo in 147 patients. Feverfew was found to be neutral in terms of reducing the number of migraine attacks, duration and severity of attacks, number of migraine days, number of days with inability to work, and type and amount of rescue medications. A combination of feverfew (100 mg) with magnesium (300 mg) and riboflavin (400 mg) was compared to placebo containing 25 mg riboflavin in 49 patients enrolled into the second study [266]. This study was also negative in terms of primary outcome measure, which was at least 50% or more decrease in migraine attack frequency (occurred in 42% in active and 44% in placebo groups). However, both groups showed a significant reduction of migraine attack number, migraine days, and migraine index. This effect was apparently higher than those observed in usual migraine studies. These observations and overall negative findings can be attributed to the design where riboflavin 25 mg was utilized as placebo but seemingly acted as an active comparator.

The latest Cochrane analysis of feverfew migraine studies included 561 patients in 6 studies [267]. After noting low quality, significant heterogeneity, and small sample sizes, this analysis indicated a difference in favor of feverfew against placebo with 0.6 attacks less per month. Based on this evidence, American Academy of Neurology labeled feverfew as a "probably effective" treatment for migraine prevention [257].

Feverfew was also studied in acute treatment of migraine episodes. A combined preparation of feverfew and ginger (LipiGezic®M sublingual liquid) has been tested in treatment of 208 acute migraine attacks in 59 patients [268, 269]. At the end of the second hour, pain-free rate was significantly higher in the active group (32%) compared to placebo (16%). Medication was generally well tolerated and devoid of significant adverse effects except for perioral paresthesia.

10.13.6 Melatonin

Melatonin's antinociceptive effects are primarily modulated via spinal melatonergic receptor activation. Other spinal and supraspinal mechanisms involving opioid, benzodiazepine, adrenergic, serotonergic, and cholinergic receptors have also a role [270]. Melatonin supplementation showed variable response for pain management in fibromyalgia, irritable bowel syndrome, postoperative conditions, and cluster headache. The use of melatonin in prevention of migraine is also a matter of debate. In a small-sized (48 subjects) but well-conducted randomized trial [271], extended release melatonin at a dose of 2 mg taken 1 h before bedtime for 2 months was found to be neutral in comparison with placebo. However, in a recent three-arm randomized controlled trial [272], comparing melatonin 3 mg, amitriptyline 25 mg, and placebo in 196 patients with migraine suffering from 2 to 8 attacks per month, melatonin was found to be significantly more effective than placebo and definitely more tolerable than amitriptyline. The efficacy of melatonin and amitriptyline was comparable.

10.14 Epilogue

The relationship between diet and prevention/treatment of neurological diseases is not a new notion but unfortunately has not developed at the required level. For example, currently there is still no official definition for the term "neuro-nutraceutical." We can note that it is a misconception that (neuro)nutraceuticals are just fortification of diet in one or more aspects. It is important to be aware that (neuro)nutraceutical compounds are not placebos and, importantly, are not devoid of adverse effects. In other words, it is a dangerous myth that "(neuro)nutraceuticals have no effects and no side effects." This incorrect opinion is apparently not an uncommon belief in the medical communities. In accordance, very little interest is directed to (neuro)nutraceuticals by the "contemporary" systems of medical education and practice. However, the general public has a very different point of view, probably via the influence of commercial media. They are usually informed about "magical" efficacy without provision of any scientific evidence. Side effects are not mentioned at all. In this context, protection of our patients when needed requires radical changes of the current status. The most critical step is certainly the advancement of individual interest and knowledge of physicians about these products.

The one big truth is that the effect of supplementation with many, if not all, (neuro)nutraceuticals on neurological diseases and on global health is uncertain. Tentative results and expert opinion/expectations have been awaiting confirmation with randomized controlled trials. It is critical to keep in mind that the process of development of a (neuro)nutraceutical should obey the same rules traditionally coined for clinical drugs. First, the effect of a nutraceutical should be established, or at least presumed, on the biological basis after sufficient number of experimental studies. Simultaneously or later, case-control and cohort studies are needed to determine the level of a nutrient in a population with a certain disease. These studies cannot produce solid evidence for efficacy, as low blood levels are usually the result of disease rather than being the cause in these kinds of studies. Therefore, dependable information can only be obtained from population based prospective cohort studies. However, prospective studies performed in this context should examine dietary habits and make use of laboratory investigations to demonstrate the increase of the nutrient level after supplementation. All of these steps would still be not enough to prove causality and treatment efficacy, unless a clinical benefit is clearly documented. An example is the connection of vitamin D to dementia. Vitamin D inadequacy is very prevalent in elderly demented patients. But, this may be alternatively as a result of reduced physical activity and/or exposure to sunlight, rather than a causal dietary factor. Of note, taking additional vitamin D does not always lead to a significant increase in its plasma level in this population. In addition, randomized trial(s) produced inconsistent results about its clinical benefit. Against a plenty of biological, experimental, and case-control studies suggesting a causal relationship, vitamin D supplementation cannot be currently recommended for dementia. All this experience in the field highlights the fact that the conventional evidence categories for determining therapeutic effect is also applicable for

(neuro)nutraceuticals without exception. The problem is that most of the evidence about (neuro)nutraceuticals falls into class III (nonrandomized but controlled trials) and class IV (other studies not meeting class I, II, or III including consensus reports, guidelines, and expert opinions) evidence categories, rather than class I (at least one randomized, controlled clinical trial with masked or objective outcome assessment in a representative population) or class II (randomized controlled trials that lack at least one of the criteria for studies providing class I evidence) category.

It is important to note that the beneficial role of (neuro)nutraceuticals is apparently rather modest. Accessible evidence is mostly not in the peer-reviewed literature, instead in lay broadcastings such as blogs, newspapers, or open or nonmedical journals. In contrast to other parties, these sources are not utilized by regular physicians to modify their own clinical strategies. Pressure from functional food industry, financial extent of the local and global markets, and the absence of directly involved governmental or societal regulatory agencies can affect objectivity of the information provided by these lay sources. An example is the story of tramiprosate used in AD. A phase III trial with this compound has remained inconclusive. The investigators tried to work with the FDA for further analysis and research, but the manufacturer abandoned development of the product as a prescription drug and later marketed it on the Internet as a medical food. In other words, tramiprosate took its place on the shelves in stores for the customers albeit the verified inefficacy in the trial. Like a lot of other compounds, tramiprosate is not subject to same level of FDA regulation as clinical drugs.

The other overlooked truth is "nutraceutical paradox." This paradox defines an asymmetry between results of supplementation studies and dietary modification studies. An important example is antioxidants. Dietary modification to reduce oxidative stress load is rather efficacious; however, antioxidant supplementation is not. Indeed, a large number of clinical trials testing antioxidant supplements suggested that these products either have no major effect on global health or any neurological disease; instead, they result in a small but quantifiable increase in mortality especially in elderly or other vulnerable populations. This inconsistency between the positive vascular effect of dietary antioxidants and the negative results of supplementary antioxidant products is called the "antioxidant paradox." The exact cause of this paradox has not been explained completely but probably includes dosage and collateral pathway issues. Against this paradox, a plenty of antioxidant preparations have been marketed currently.

In conclusion, (neuro)nutraceuticals are a reality. Our patients are using them and will continue to use them. Therefore, we cannot remain indifferent to these compounds. We are, of course, aware that scientific evidence is too limited currently but also know that it is expanding geometrically. Many of the (neuro)nutraceuticals we focused in this chapter will be subjects of wider discussions in the near future. For now, equivocal evidence permitting no recommendation on their use should not prevent our efforts to learn about them. This is going to be beneficial at least to decrease their adverse effects.

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