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Review / Derleme

Nutritional Approach and Treatment in Patients with Stroke, An Expert Opinion for Turkey

İnme Hastalarında Nütrisyonel Yaklaşım ve Tedavi, Türkiye İçin Uzman Görüşü

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Abstract

Cerebrovascular diseases comprise the most common category of inpatient cases taken care by neurologists. Dysphagia and malnutrition are not rare after stroke. It is strongly recommended for neurologists to screen and treat swallowing disturbances and malnutrition in stroke patients. However, present scientific literature lacks clear evidence with regards to nutritional treatment strategies for stroke patients. This review and recommendation paper is written with the aim to standardize nutritional screening and treatment algorithms during acute and chronic phases of cerebrovascular diseases and guide neurologists in Turkey for their daily practice.

Keywords: Stroke, nutrition, malnutrition, dysphagia

Öz

Beyin damar hastalıkları nöroloji uzmanlarının en çok yatırarak izlemek durumunda kaldığı hasta grubunu oluşturmaktadır. İnme sonrası disfaji ve beslenme bozukluğu nadir değildir. Akut dönemde ve taburculuk sonrasında inme hastalarının malnütrisyon ve yutma bozukluğu açısından izlemi ve tedavisi nöroloji uzmanları tarafından gerçekleştirilmelidir. Ancak mevcut literatür ve kaynaklarda inme hastalarının nütrisyonel tedavisi ile ilgili net veriler yoktur. Bu gözden geçirme ve öneri makalesi, Türkiye özelinde beyin damar hastalığının akut ve kronik fazlarında nütrisyonel yaklaşım ve tedavi yöntemlerini standardize hale getirebilmek ve nöroloji uzmanlarına rehberlik etmesi amacıyla hazırlanmıştır.

Anahtar Kelimeler: İnme, nütrisyon, malnütrisyon, disfaji

Introduction

There is no specific evidence revealing how nutritional evaluation should be made in patients with cerebrovascular disease and which nutritional therapy should be preferred. The daily practice applied for these patients basically depends on scientific data obtained from general intensive care units and geriatric patient populations. Some countries and nutrition societies developed their own national guidelines to compensate for this deficit. Five national specialists in fields of stroke, neuro-intensive care, nutrition and swallowing disorders collaborated to create basic proposals on clinical significance of nutrition and dysphagia in stroke patients, the diagnosis and treatment of malnutrition and swallowing disorders, enteral nutrition products, application principles and complications, considering national conditions.

A scientific search was performed in medical databases (Pubmed and Embase) by using the keywords "stroke, cerebrovascular disease, malnutrition, malnutrition screening, malnutrition assessment, nutrition, enteral nutrition, parenteral nutrition, oral supplements, dysphagia, dysphagia diagnosis, dysphagia screening, dysphagia treatment". The resulting articles were evaluated by each expert and preliminary assesment was carried out by online communication. Consensus decisions on contraversial and unclear issues were made following 3 meetings each lasting for 8 hours. The principles of nutritional assessment and treatment in patients with stroke were summarized in 19 questions and the relevant answers.

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1. Is malnutrition a common problem after stroke?

Malnutrition is defined as "a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat free mass) and body cell mass resulting with diminished physical and mental function and impaired clinical outcome from disease. Malnutrition may also occur as the result of a disease state and ageing (1). Patients with stroke may lose their eating and drinking abilities due to disorders of consciousness, swallowing problems, postural instability, decreased mobilization, limitations in communication, fatigue, depression and visuo-spatial deficits. Nearly 90% of stroke patients have a risk of malnutrition (2).

Malnutrition rates reported in stroke patients differ greatly according to the evaluation methods used and the patient population taken under consideration. Malnutrition rate determined among acute stroke patients at admission is reported as 3.8-32%; this ratio reaches up to 7.5-35% at the end of second week of hospitalization. Prevelance of malnutrition development within two-weeks after stroke is increased by nearly two-fold (3-15). Malnutrition is very common in patients especially in rehabilitation centers, and malnutrition rate may increase up to 30-49% in chronic phase (16-22).

Malnutrition is not a rare event in the acute phase after stroke; its frequency increases gradually in subsequent weeks.

2. What is the frequency of dysphagia after stroke?

The frequency of dysphagia varies greatly according to evaluation method used. The rate of dysphagia is 30-65% in the acute phase of ischemic and hemorrhagic stroke (23-28). When detailed examination is performed for the diagnosis of dysphagia by videofluoroscopy or fiberoptic endoscopy, it increases up to 64-78% (29). Its frequency decreases to 22% in the subsequent weeks (11). At the end of the sixth month, 13% of patients have not yet started to eat normally; dysphagia becomes permanent in nearly 3% of patients, and they require continuous enteral feeding (25,26,30).

Dysphagia is a common problem following stroke, but recovers in majority of patients within time.

3. How is energy metabolism affected after stroke?

Patients in acute phase following stroke are not in a high hypermetabolic state as patients with other critical diseases. In the first week after stroke, basal energy requirement is increased only by 7-26% of normal; it is not markedly elevated as in traumatic brain injury, sepsis or burns. Energy requirement at rest is found to be slightly increased in intracranial hemorrhage than in ischemic stroke cases (19,31-33).

After stroke, plasma catecholamine, cortisol, glucagon levels, interleukins, and acute phase reactants are found to be increased as a component of acute stress response. This systemic response causes both a rapid catabolism and degradation of fat-free body mass, namely muscle tissue, and fats. However, it is not clear how much this systemic response plays a role in the development of malnutrition.

In the case of fasting, all fat storages are degraded, and fatty acids are released to produce energy. Since fatty acids cannot pass through the blood-brain barrier, they cannot be used as an energy source for the brain. Even the ketone bodies produced from fatty acids in the liver can pass through the blood-brain barrier, but are not a good and effective energy source for neurons. If blood glucose is not replaced in stroke patients whose oral intake is reduced, rapid muscle protein degradation starts in order to expose amino acids as an energy source. This process, accompanied by other factors such as hormonal deficits, inflammation and immobility, rapidly leads to a clinical picture with the potential of development of sarcopenia (34,35).

Intestinal wall integrity not only depends on the mesenteric blood flow, but also the presence of nutrient products in the bowel lumen. Restriction of oral intake in a stroke patient leads to rapid atrophy of intestinal villi and crypts, increase in intestinal wall permeability and translocation of pathogenic intestinal bacteria via bowel wall. All of these processes culminate in an increased risk for sepsis (36,37).

Patients with inadequate food intake after stroke start to lose their muscle tissue rapidly. Additionally, lack of nutrients in the oral enteral route causes a risk of intestinal epithelial atrophy.

4. Does development of dysphagia and malnutrition after stroke contribute to unfavorable outcome?

Mortality is higher in patients who have malnutrition at admission (38). The Barthel index score on day 30 is lower, mortality is higher at the end of the first week, and complications are more frequent in patients whose nutritional parameters were deteriorated after stroke. Duration and costs of hospitalization are higher in patients with malnutrition (10,13,23). Patients who are not fed adequately and develop malnutrition during the period of hospitalization, have worse prognosis at the end of third month during follow-up (11,14). This unfavorable effect of malnutrition continues till the sixth month after stroke (23).

The major complications of dysphagia related with stroke may be listed as aspiration and aspiration pneumonia (29), dehydration (39), prolonged hospitalization (40), longer rehabilitation period, and healthcare requirements (41). These complications cause a decrease in the physical and social well-beings of stroke patients, and quality of life of patient and their relatives (26). The presence of dysphagia increases the risk of malnutrition (25,29,40,42-44).

Dysphagia and malnutrition after stroke increase mortality, morbidity, and costs.

5. Is nutritional support beneficial in patients with stroke?

There are limited number of scientific evidences indicating that the correction of nutritional status and providing adequate energy intake in post-stroke patients, have positive effects on clinical recovery (15,45-47). As there would be an ethical problem to feed a group of post-stroke patients without feeding the other group, this issue cannot be completely tested by a controlled clinical

trial. In line with studies and scientific evidences indicating that nutritional support in the general patient population has favorable effects on prognosis, it is generally accepted that the correction of nutritional parameters in post-stroke patients would also contribute positively in clinical prognosis.

6. How is nutritional state of stroke patients evaluated and followed up?

Nutritional state and fluid intake of stroke patients should be evaluated at admission and thereafter with regular intervals, and the best nutritional plan should be prepared for patients (9). Clinical scales, anthropometric measurements, laboratory tests, and functional tests can be used to evaluate the nutritional state of stroke patients (10,48). Some clinical scales are developed for screening malnutrition, whereas others are developed both for screening and evaluation; in other words for defining the severity of malnutrition.

Screening tests developed to screen patients with malnutrition or at the risk of malnutrition are listed as NRS-2002 (Nutrition Risk Screen-2002), MNA-SF (Mini Nutrition Assessment-Short Form), MUST (Malnutrition Universal Screening Test), MST (Malnutrition Screening Tool) and SNAQ (Short Nutrition Assessment Questionnaire). Acute stroke patients, especially patients who cannot be fed orally, are under increased risk of malnutrition (49,50). It is recommended that malnutrition is intermittently screened during the chronic phase of stroke (51-54). Screening tests can be performed in a short time by nurses or physicians.

There are three validated tests for the evaluation of nutrition. These are the Subjective Global Assessment (SGA), Mini-Nutritional Assessment (MNA) (56) and "informal evaluation" of nutritional state, that is evaluation of patients by visual observation (49,57). There is no standard screening and evaluation test for stroke patients. The most commonly used tests are MNA and SGA (52). SGA is an evaluation test for nutritional state developed to evaluate complication risks in patients scheduled for surgery (55). MNA is developed as a screening and evaluation tool in geriatric patients (56,58). Both tests contain anthropometric measurements. MNA is a test with two steps. While MNA-SF is used in malnutrition or malnutrition risk screening, the application of complete test can assess the severity of malnutrition. The MNA and SGA tests show moderately significant correlations with biochemical parameters and anthropometric measurements in chronic stroke patients (for MNA r: 0.520, for SGA r: 0.449) (50). The power of these tests may be increased by biochemical markers (3).

Anthropometric measurements which may be used in nutritional state assessment are body weight, body mass index, triceps skin thickness, and the arm and calf circumference measurements. The measurements of body weight and body mass index are difficult in immobilized patients. Triceps skin thickness or mid-arm circumference may be measured in immobilized patients, but it should also be considered that these measurements may be misleading results because of the presence of edema and atrophy in stroke patients. The hand grip test (with hand dynamometer) may be performed at the bedside as a functional test. However, none of these assessments are validated for evaluation of nutritional status in patients with stroke.

Other investigations that may be used to evaluate body composition include bioelectrical impedance analysis (BIA), Dual energy X-ray Absorptiometry (DeXA), computerized tomography, ultrasonography and magnetic resonance imaging.

There is no an ideal biochemical marker to demonstrate the nutritional state of stroke patients. Cut-off values of biochemical parameters are debatable. Malnutrition rates differ greatly according to methods used and cut-off values (49). Biochemical markers used during follow-up can be listed as albumin, pre-albumin, transferrin, retinol binding protein, serum iron level, total cholesterol, leukocyte count, lymphocyte count, hemoglobin level, vitamin B12 level and folic acid. There are also studies indicating that lower serum albumin level (<3,5 mg/dl) is related with poor prognosis after stroke (59-61), and that albumin level is not related to the amount of protein and calorie intake (62). Blood levels of biochemical markers cannot be routinely used in the quantitative evaluation of malnutrition, because their levels can change enormously with several factors such as patient's age, acute stress, systemic inflammation and infections, hepatic functions, catabolic processes, and accompanying diseases (63).

Diagnostic criteria for malnutrition were re-defined in 2015 by the European Society of Parenteral and Enteral Nutrition (ESPEN) (Table 1) (1).

Stroke patients are generally under the risk of malnutrition. Malnutrition which adversely affects prognosis should be evaluated right from the acute phase, and a nutritional plan should be implemented accordingly.

There is not a single method recommended to evaluate malnutrition in stroke patients; MNA and SGA tests which have been shown to be valid for other patient groups can be used. Anthropometric measurements and laboratory investigations indicating body composition may be used in the diagnosis and follow-up of patients with malnutrition. There is no standard biochemical test which can be used in the evaluation of the nutritional state of patients with stroke.

Nutrient and fluid intake of all stroke patients, especially those with problems of oral feeding should be followed up during the acute phase, and their nutritional states should be evaluated weekly. Malnutrition screening and follow-up are also important in stroke patients during the chronic and rehabilitation phases. MUST, MST, NRS-2002, SNAQ or MNA-SF may be used as screening tests.

Table 1. Malnutrition diagnostic criteria according to ESPEN

Definition 1	BMI <18.5 kg/m^2
Definition 2 (1+ one of the remaining)	1. >10% involuntary weight loss at any time or >5% weight loss in the last 3 months 2. <70 years old, BMI <20 kg/m^2 ≥70 years old, BMI <22 kg/m^2 3. Fat-free body mass index Females <15 kg/m^2 Males <17 kg/m^2

7. Which tests are used for the screening and evaluation of dysphagia in stroke patients?

The diagnosis of dysphagia can be made in stroke patients by bedside screening and clinical assesment tests. Specific equipment is essential for the advanced evaluation of dysphagia. During clinical examination, potential indicaators of dysphagia include impaired consciousness, NIHSS>12, aphasia, hypophonia, dysarthria, severe neurological deficit, marked facial paralysis, decreased pharyngeal sensation and wet sound, cough and change of voice after swallowing. On the other hand, risk factors for aspiration in patients with stroke are reported as presence of brainstem lesion, bihemispheric infarcts, accumulation of intraoral secretion, soft palate dysfunction, delay in swallowing reflex, marked facial paralysis, history of recurrent pulmonary infection, smoking and COPD, weak spontaneous cough, dysphonia, voice change, wet sound and wet coughing after swallowing. It is not always possible to diagnose aspiration by clinical examination. Nearly half of the patients with dysphagia aspirate, and pneumonia is reported to develop in 1/3 of these cases. Silent aspiration is passage of swallowed material below the vocal cords without coughing. Under videofluoroscopy, the incidence of aspiration is 30-51% in acute stroke patients, whereas silent aspiration is reported as 8-27% (64-66).

Early diagnosis of dysphagia is important in stroke patients to prevent complications, mainly pneumonia. It has been shown that the incidence of pneumonia is higher in stroke patients not screened for swallowing than in screened cases (29,67,68).

The level of consciousness and cooperation of the patient, postural control (ability to sit straight with help), oral hygiene and secretion control, and voluntary cough should be evaluated before the screening test.

Screening tests should include water swallowing tests together with clinical evaluation. Moreover, there are swallowing evaluation tests in which patients are given fluids of different textures, and bolus amounts. Different evaluation methods such as the Toronto Bedside Swallowing Screening Test (69), Gugging Swallowing Screen (GUSS) (70), Mann Assessment of Swallowing Ability (MASA) and its modified form (mMASA) (71), and the Barnes Jewish Hospital Stroke Dysphagia Screening (72) can be used for the screening of dysphagia in stroke patients. The prefered swallowing screening test should be validated, reliable, with high sensitivity. There is no study indicating the superiority of one of these tests over the other. There is no consensus or recommendation about which test is the best for stroke patients in systematic reviews and guidelines (73-75).

The water contents and methods differ among most commonly used water swallowing tests. Water content changes between 5 and 100 ml. Some procedures include re-swallowing boluses with a volume of 3 or 5 ml, others include only sequential water swallowing from a glass, while some others include both re-swallowing of small amounts and sequential water swallowing. There is no consensus neither in the optimal water swallowing test nor ideal water amount for the screening of dysphagia (76-78). However, the most commonly preferred method in the evaluation of swallowing is to start with small amounts and increase gradually (78).

Dysphagia screening should be performed in every stroke patient before initiation of oral feeding and drug administration by using a simple and valid bedside swallowing test, and the aspiration risk should be defined. This test may be performed by an experienced nurse or healthcare professional. The dysphagia screening test should be performed within the first 24 hours. Screening test may be repeated in the subsequent days if necessary, according to the neurological condition of the patient. Oral feeding may be initiated carefully in patients who passed the test, but patients should be followed up thereafter for aspiration.

Weak palatal movement, dysarthria, abnormal voice, inadequacy of voluntary coughing, presence of abnormal pharyngeal sensation, observation of cough and voice change (wet voice) after swallowing 5 ml of water three times and 50 ml of water from a glass are high-sensitive bedside clinical markers in dysphagia screening (Figure 1) (79). Monitorization of oxygen saturation from the finger during swallowing evaluation by using a peripheral probe may increase sensitivity of the screening test (80-82).

In addition to a screening test, clinical evaluation of swallowing performed by an experienced physician or speech therapist may determine the presence of aspiration and dysphagia. In clinical assesment, the appropriate method and treatment options and the possible risk of aspiration is determined in the light of symptoms and signs. Oro-linguo-pharyngeal sensorimotor examination involves the test of food and water swallowing with different

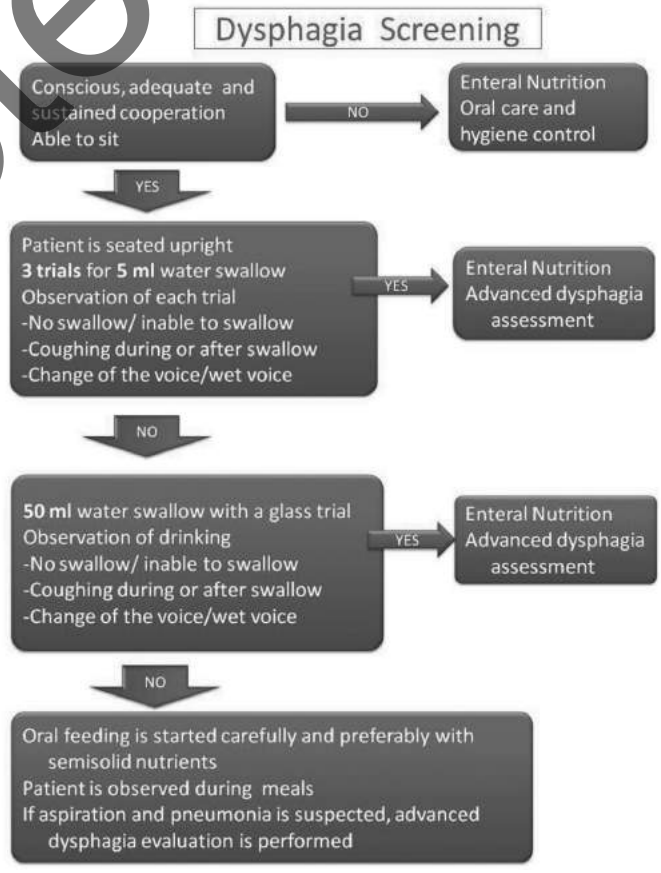


Figure 1. Recommended algorithm to determine the presence of dysphagia in stroke patients

consistency. Although there is no generally accepted validated clinical swallowing evaluation method for stroke patients, a standardized protocol or clinical evaluation test developed by Logemann can be used (Annex 1) (83).

Patients who cannot pass the screening test, and those with dysphagia and aspiration risk which have lasted for longer than one week, may require further instrumental methods according to hospital and patient conditions. Advanced dysphagia evaluation is performed in patients with suspected silent aspiration or in patients who cannot pass screening tests, and provides to determine the consistency of foods, the way of swallowing therapy and rehabilitation method. Therefore, it is recommended that further dysphagia evaluation should be performed by an experienced physician or speech therapist. Videofluoroscopy (VFS) and Fiberoptic endoscopic evaluation (FEES) may be used for this purpose. All phases of swallowing, aspiration, penetration or oropharyngeal residual materials can be shown radiologically by using VFS. Its disadvantages include requirement of complete patient cooperation,

Annex 1: Clinical swallowing assessment (Logemann) which can be used in stroke patients

Clinical Swallowing Assessment

	Safe	Not safe
Medical History		
1. Recurrent pneumonia		
2. Frequent high fever		
3. Aspiration pneumonia		
4. Long-term intubation (>1 week) or tracheotomy (>6 weeks)		
Cognitive condition		
5. Alertness/awareness		
6. Cooperation / agitation		
7. Attention / communication level		
8. Awareness of swallowing problem		
9. Awareness of secretions		
10. Ability to manage secretions		
Major motor function		
11. Postural control		
12. Fatigue		
Oral motor tests		
13. Oral, pharyngeal, laryngeal anatomy and function		
14. Level of obeying orders		
15. Dysarthria		
16. Facial weakness		
17. Oral apraxia		
18. Oral sensation		
19. Pharyngeal wall contraction during gag reflex		
20. Ability to swallow saliva		
21. Voluntary coughing and throat cleaning		
Observations during swallowing trials with 1 cc thin fluid, 1 cc pudding, a quarter biscuit		
22. Swallowing apraxia		
23. Oral residue		
24. Coughing and throat cleaning		
25. Delayed pharyngeal swallowing		
26. Decreased laryngeal elevation		
27. Wheezing voice		
28. More than one swallowing trial for one bolus		

need for a sitting position, and low dose of radiation. FEES is a swallowing evaluation performed by a short flexible endoscope. Patients swallow solutions with different consistencies and a mixture of food dyes. FEES is easy to perform by the bedside and available for follow-up, it is cheap and has no risk of irradiation. However, oral and esophageal phases are not visible during FEES, patients may feel uncomfortable, it may cause irritation. Also requirement for experienced staff is an other disadvantage (84,85). Another test is the dysphagia limit, which determines the presence and level of dysphagia during neurological practice by using EMG (86). Its disadvantages include the fact that patient should be in the sitting position, and should be cooperative (86).

All acute stroke patients should be screened for dysphagia before being given oral medication, food, and fluid. The risk of aspiration pneumonia may be decreased by formal screening test and the evaluation of dysphagia. A valid screening test should be performed by an experienced/trained healthcare professional. Dysphagia screening should be performed within the first 24 hours. Patients who pass the test are allowed for oral feeding, but if the patient deteriorates, re-evaluation and follow up for aspiration should be performed in all the patients.

Patients, who cannot pass the screening test, are not allowed to be fed orally. Since it is highly possible for dysphagia to recover during the first weeks, it is suggested that patients are re-evaluated at least twice in a week for passage to oral feeding.

Further instrumental swallowing evaluation may be performed in patients who do not pass the screening test according to hospital and patient conditions. Enteral nutrition is started until VFS or FEES are performed. After VFS and FEES have been performed, a plan is prepared for enteral nutrition process or dysphagia treatment.

8. How is dysphagia managed?

The treatment of dysphagia should be managed by a team including a neurologist, physiotherapist, speech/language therapist, swallowing therapist, dietitian, occupational therapist, and a stroke nurse. Dysphagia treatment includes restorative methods, compensational techniques and adaptive methods (84,87).

The aim of restorative methods is to facilitate improvement in the swallowing function. Restorative methods include maneuvers and exercises to strengthen swallowing muscles and oropharyngeal coordination. Sensorimotor exercises, tongue-chin exercises, chewing exercises, and laryngeal adduction exercises can be given as examples. Biofeedback systems, oral thermal, electrical and vibration sensory stimuli may also be used for this reason (43,84). There is no adequate evidence to show whether transcutaneous/neuromuscular electrical stimulation (TES/NMES) affects the function and safety (aspiration) of swallowing. There are evidences indicating that repetitive transcranial magnetic stimulation, which is one of the non-invasive cranial stimulation applications, has positive effects on the swallowing function, and decreases aspiration. There are no adequate data for transcranial direct stimulation (tDCS), and further studies are required (88). Consistent and adequate benefits have not been obtained in drugs studies (nifedipine, cilostazol, cabergoline, ACE inhibitors, amantadine) conducted on swallowing function, so further studies are also required (87).

The aim of compensation methods is to increase safety of swallowing without correction of the underlying neuromuscular deficiency, and prevention of aspiration. Examples of posturel manuplations are maneuvers like "Chin tuck", head flexion and turning the head to pharyngeal weak side (hemiplegic side). Multiple swallowing, forced swallowing, supraglottic swallowing, super supraglottic swallowing, Mendelsohn maneuver, and laryngeal elevation are some examples of compensatory mechanisms (43,84).

There are no prospective controlled studies demonstrating the efficacy of these methods in patients with swallowing disorders, and favorable effects are reported only from observational and anecdotal reports, and from personal experiences. There are studies reporting that long-term and high intensity programs are better than short-term and low intensity studies (89,90).

Attempts are made to provide patient adaptation to swallowing disorder by using adaptive methods, external support and dietary regulation. Diet regulation, dietary enrichment, thickeners, enteral tube feeding, and feeding with PEG are methods for adaptation (43,84,91). Dietary regulation in dysphagic patients who can be fed orally is directed to adequate nutrient and fluid intake, and to decrease possible aspiration. There are studies indicating that thickened fluids are safer for swallowing and the risk of aspiration is less when compared with thin fluids. However, further studies are required to investigate the benefits of thickeners. Apart from these approaches, it has been shown that approaches for patient's oral hygiene and dental health have positive effects in stroke patients (92,93).

The most ideal treatment for dysphagia should be performed by a team composed of neurologists, speech therapists, physiotherapists, dietitians, and stroke nurses. While teaching maneuvers and exercises for strengthening oropharyngeal coordination, helpful postures and compensation maneuvers should be shown to prevent aspiration. It is recommended that swallowing rehabilitation should be started in a cooperative stroke patient with dysphagia after one week.

Other treatment approaches are thickeners, diet modification (switching to soft diet and enriched diet, etc.), and initiation of enteral feeding without delay if daily calorie and protein requirements cannot be met via oral route.

Applications directed to oral hygiene (oral and tooth care, etc.) should be performed in stroke patients to protect against aspiration pneumonia, and other infections.

9. Which stroke patients are initiated on enteral feeding?

Enteral feeding should be initiated in every stroke patient who cannot be fed orally due to impaired consciousness, dysphagia or severe neurological deficit, because they are highly prone to be at a high risk of developing malnutrition and pneumonia. Patients with detoriation in consciousness state, lack of cooperation, aphasia, swallowing apraxia, 9th-10th and 12th nerve palsies, and pseudobulbar palsy may require enteral nutrition. Nutritional tube feeding has been shown to reverse malnutrition under conditions where stroke patients cannot be orally fed despite the absence of dysphagia (19,94). Since dysphagia due to stroke can improve in the first couple of weeks, enteral feeding may be initiated just

for this time period, and it may be switched to oral feeding after improvement of dysphagia (12,95).

Regardless of the underlying reasons, enteral nutrition should be employed in all stroke patients who cannot be fed orally, unless it is contraindicated.

10. When is enteral nutrition initiated in stroke patients?

The main data about the time to start enteral feeding in stroke patients are obtained from the novel randomized controlled clinical trial, FOOD. In this study which has some limitations, stroke patients who could not feed orally were randomized into two groups; one with early enteral feeding as soon as possible, and the other which started enteral feeding on the seventh day after the stroke. Physicians were allowed to decide which type of enteral feeding (NG or PEG) would be administered. No statistically significant difference was found in the modified Rankin Score (mRS) and mortality rates between early and late onset enteral feeding groups (46).

Considering the negative effect of malnutrition in the prognosis of stroke patients, it is clear that protein and calorie targets should be reached as soon as possible. If only low calorie fluids are infused intravenously in comatose stroke patients, the levels of protein and albumin are decreased as 1.5 g/dL and 1.2 g/dL, respectively (96). "Early enteral feeding", which means initiation of enteral nutrition within the first 24-48 hours of intensive care unit admission, decreases infective complications and length of hospital stay in patients with traumatic brain injury and in medical intensive care unit patients (97). If there is no severe metabolic disorder such as hemodynamic instability, diabetic ketoacidosis, or hepatic coma, severe nausea and vomiting or intestinal distention, then early enteral nutrition should be started. Even at lower doses, early enteral feeding has valuable effects on the preservation of intestinal mucosal integrity, and the continuation of barrier function and immune system of the body. Trophic feeding (10-20 ml/hour) may be sufficient to prevent intestinal mucosal atrophy (98-100).

Enteral feeding should be accepted as a part of stroke management. Although there are no supportive data in randomized studies about stroke, in the light of data obtained from other fields, enteral feeding should be initiated in acute stroke treatment as early as possible after hemodynamic stabilization is preserved. This time period should not be longer than 48-72 hours.

11. Which route is preferred for enteral feeding?

Feeding tubes are used for enteral nutrition in stroke patients. The route of feeding tube may be nasogastric (NG), nasoduodenal (ND) or nasojejunal (NJ). If nasal tube insertion is impossible, then the oral route (orogastric/oroenteral) can be used. There is no study which has tested the superiority of these routes on each other during the acute phase in stroke patients. Although the use of postpyloric feeding has been shown to decrease aspiration risk in critical patients in some studies, this has not been approved in others (101-103). As a result, postpyloric feeding is the primary objective, however enteral feeding should not be delayed if the tube stays in gastric area.

Location of tube may be controlled by a chest X-ray or checking the pH of aspiration material via the tube. If the pH of the liquid aspirated is below 5 (shown by using a Turnusol paper), it is supposed to be inserted in the stomach. However, only pH measurement may cause faulty results, if the tube is in esophagus or when drugs affecting gastric acidity are used. The diameter of commonly used feeding tubes is 6-10 Fr; if diameter of the inserted tube has 8 French (1 Fr= 0.33 mm), then it is suitable. Feeding should not be performed by nasogastric drainage catheter. Radiopaque tubes should be preferred, because they are easily detected in chest and abdominal X-rays. Displacement of nasoenteral tubes is the main common issue mentioned in studies. It is recommended that nasal loop should be used to prevent this (104).

It has not been shown that early Percutaneous Endoscopic Gastrostomy (PEG) insertion after stroke is not superior to nasoenteric approach in survival and neurological recovery. It is reported that PEG insertion within the first week after stroke was only helpful to reach nutritional targets, and it decreased ventilator-associated pneumonia risk in one study (105). Long-term nasogastric nutrition has risks such as displacement of tube, traumatic insertion, pressure ulcers, gastric and duodenal ulcers, aspiration and pneumonia, inadequate feeding or dehydration. It is believed that such problems are less frequently encountered in feeding with PEG (98,99,106).

As a standard, enteral feeding is initiated by using tubes reaching the enteral system via the nasal route. Initially, nasogastric or nasoduodenal accesses are targeted. Nasojejunal tube may be used in patients with the risk of high aspiration and recurrent aspirations. If enteral feeding requirement is longer than four weeks, then opening PEG is recommended. No definite benefit has been shown in the opening of PEG during the early phase. However, if it is considered from the beginning that dysphagia and enteral feeding will last for long period, early PEG insertion may be reasonable.

12. How are calorie, protein, and fluid requirements of stroke patients calculated, and what is the dose of nutritional product?

Indirect calorimetry is the best way to calculate the daily calorie need of a stroke patient. Indirect calorimetry depends on the hypothesis that all of oxygen taken into the body is used to oxidize energy sources in the body, and all of the carbon dioxide produced during this time interval is released through expiration. The energy content that an individual needs at rest is calculated by using a closed spirometry system which captures oxygen used and carbon dioxide produced in a defined time interval. Measured volumes are converted to daily calorie requirement by using the Weir Formula. It is a non-invasive and cheap method. It calculates the metabolic rate with an error rate of 1%. There are different indirect calorimetric devices with different designs (108,109). However, since there are difficulties with its practical use in intensive care units, and hospitalized patients, formulas obtained from test results of hospitalized patients (Penn State, Ireton-Jones, Swinamer) or healthy volunteers (Harris-Benedict, Mifflin-St Jeor) are preferred. All these equations may be affected from various confounders like obesity, asthenia, treatments given, body temperature, and comorbid conditions (109). The superiority of energy calculation considering ideal body weight by using height and gender (20-30 kcal/kg/day) to the above mentioned formulas

is its simplicity. It can be used in stroke patients.

There is no specific study investigating initiation dose of enteral feeding, or the duration to reach the calorie target. It is recommended that enteral feeding is started at 20 ml/hour infusion rate, and if there is no complication, then the infusion rate will be increased 10-20 ml/hour in every 8-12 hours to reach the targeted calorie. To provide efficient enteral feeding, 80% of the targeted calorie and protein contents should be given within the first 48-72 hours.

Daily protein requirement is calculated as 1-1.5 gr/kg/day. Protein requirement especially in patients who require intensive care unit hospitalization may reach up to 2 gr/kg/day. Protein is an important macronutrient for wound healing, supporting immune functions, and preservation of body mass index. However, it has not been shown that protein-supported enteral solutions provide superior nutritional condition than in stroke patients who have received standard enteral solutions (102). There are no data proving the efficacy of serum albumin, pre-albumin, transferrin, and CRP measurements to follow up the adequacy of protein support (103,110).

Daily fluid requirement is calculated as 30 ml/kg/day. To reach this target, and prevent dehydration, it should be considered that there is 69-86% of free water in nutritional products.

Indirect calorimetry is the most reliable method to calculate calorie requirement, but calorie calculations considering ideal body weight is a frequently used practical method. Daily calorie requirements in stroke patients may be calculated as 20-30 kcal/kg. It is aimed to start nutrition at 20 ml/hour, and to reach target dose at least within 48-72 hours.

13. Which enteral product to chose?

Enteral nutritional products are divided into four groups as polymeric, oligomeric, elemental, and disease-specific modified products. Standard polymeric products are preferred in all stroke patients. Osmolarities vary between 265 and 320 mOsm. Energy content is provided by 15-20% of protein, 30-35% of fat, and 49-54% of carbohydrate. A standard 500 ml product contains 20 g protein, 16-20 g fat, and 60-70 g carbohydrate. One mL of a standard polymeric product provides 1 kcal of energy, and its pH value is between 6.5-7.0.

Protein content is increased to 29-31 g, fat content is increased to 20-31 g, while the carbohydrate content is increased to 93-100 g in high energy products, so that 1 mL of the formulation can provide 1.5-2.0 kcal energy. High energy products have a high osmolarity and low fluid content. They can be used in patients who should have fluid restriction. Physicians should be cautious about the dehydration of patients while administering these products. These products may cause osmotic diarrhea due to high osmolarity.

Protein content in every 500 ml of high protein products is increased to 32-34 g, so that 20-22% of energy is provided from proteins. High protein ratio causes the high osmolarity value to reach 290-474 mOsm. It helps to meet protein requirement with lower calorie content.

In high fiber products, non-digested and non-absorbed fiber ratios are increased without changing the ratios of protein, fat, and carbohydrate. The osmolarity of these products varies between 210-360 mOsm.

Disease-specific products are used for special conditions by changing their contents. Products high in branched chained amino acid (valine, leucine, isoleucine), low in aromatic acids (tyrosine, phenylalanine, methionine, tryptophan) are manufactured for hepatic failure cases, whereas protein restricted and only essential amino acid and histidine containing products are developed for renal failure cases. Use of these products may not be convenient for dialysis patients. For diabetic patients, there are products with a low carbohydrate ratio, increased protein and fat ratios, and containing monounsaturated fatty acids (MUFA). Their osmolarities are high. These products are more commonly recommended in diabetic patients without blood glucose regulation rather than for routine use. There are not consistent and adequate data about the clinical benefits of disease-specific products.

Elemental and semi-elemental products are low molecular weight compounds with minimal digestion and almost complete absorption. Fats constitute only 1-12% of the energy content. They decrease pancreatic, biliary, and intestinal secretions, and the amount of feces. They may be used in diseases which deteriorate digestion or absorption capacity.

Modular products are used as products in addition to nutrients to change the general energy and nutritional composition, and they are only composed of glucose polymers, protein, or lipids. They are preferred in patients who require fluid restriction,with electrolyte imbalance, or in need of specific nutrients (106,111-113).

Although scientific evidences are inadequate, depending on practical long-term experiences, the most commonly employed nutritional products in stroke patients are polymeric standard formulas. Diabetic products may be administered if blood glucose levels are uncontrolled; fiber rich products can be given in diarrhea and constipation cases. High calorie products can be administered in patients with fluid restriction or whose energy requirements cannot be provided. Products high in protein can be given to patients with protein deficiency.

14- How should enteral feeding be administered?

Enteral tube feeding may be performed by either continuous infusion through special pumps or by intermittent bolus administration. There are data obtained from studies conducted on patients in the general intensive care units about intermittent feeding or continuous infusion. These data indicate that continuous infusion decreases the risk of aspiration, pneumonia, and diarrhea, decrease contamination risk of products, and prevent spending of unnecessary assistant healthcare professional work-force. Therefore, continuous infusion is preferred in hospitalized stroke patients. Intermittent enteral feeding may be preferred in patients who are mobilized, at the stage of discharge, and who are planned to receive enteral feeding at home. However, before switching to intermittent feeding, the patient should have reached targeted calorie levels by using continuous infusion (106,114-116).

The head of the bed should be raised at 30-45 degrees to decrease the risk of aspiration during infusion of nutritional product. Routine use of prokinetic agents is not recommended. There are no data indicating that they decrease the risk or increase tolerance of the risk of aspiration pneumonia. Prokinetic agents

(metoclopramide, domperidone) can be used under conditions such as gastric distention, nausea, vomiting, regurgitation, and constipation. Prokinetic agents can also be used to facilitate passage of feeding tube through the postpyloric region (106,112,113).

Oral hygiene performed at least twice daily by using oral antiseptics such as chlorhexidine decreases the risk of pneumonia in stroke patients with enteral feeding requirement. Bacterial contamination of aspirated saliva is important in respiratory tract infections associated with aspiration. Therefore, oral hygiene should be provided carefully in stroke patients (117,118).

Although there is no study conducted on stroke patients investigating gastric residual volume (GRV), it has been shown in studies conducted on intensive care unit that there is no correlation between GRV and the incidence of pneumonia and aspiration. In addition, it is not recommended to perform GRV follow-up during routine practice, because it causes interruption of enteral feeding, it prevents reaching protein and calorie goals, and it may lead to the contamination of enteral products. GRV measurement is not valid in the presence of post-pylorically located enteral feeding tube (119,123).

GRV follow-up is performed only in patients who cannot tolerate enteral nutrition, and have nausea, vomiting, distention and decreased intestinal sounds.

Continuous enteral nutrition is preferred in acute stroke patients who are followed up in the hospital. It is not recommended to routinely check gastric residual volume, and initiation of prokinetic agents. Oral hygiene decreases the risk of pneumonia, and it should be performed twice daily.

15. What are the complications of enteral nutrition in stroke patients, and how are they treated?

Diarrhea: It is defined as daily number of defecation of more than three times with more than 250 ml volume. During enteral nutrition, it may arise due to bolus administration, rapid or high dose infusion, the use of products with high osmolarities, cold solutions, bacterial contamination, gastrointestinal infection and malabsorption. The first thing to do in the presence of diarrhea is to check the enteral nutrition scheme of the patient. Decreasing infusion rate, switching to products with lower osmolarity or products high in fiber are the first step treatment options. Drugs which may cause diarrhea such as antibiotics, prokinetic agents, antacids, and atropine should be reviewed.

Presence of fecal incontinence should also be considered. Causes of infectious diarrhea should be ruled out by performing fecal culture and direct microscopic examination. If there is a suspect for malabsorption, then the patient should be consulted to certain departments. If the problem is still persisting despite these precautions, it should be switched to parenteral feeding.

Nausea-vomiting: If nausea and vomiting develop during enteral nutrition, firstly the infusion rate is decreased. Sedative drugs should be discontinued. Prokinetic agents may be used.

Constipation: Immobilization, pain and stress, previous abdominal surgery, accompanying systemic diseases such as diabetes and pancreatitis, drugs such as opioids, anticholinergics, erythromycin, and benzodiazepine may decrease gastrointestinal motility. It should be ensured that adequate hydration is preserved in constipated patients with nausea and vomiting. Products high in insoluble fiber content may be started. Discontinuation of drugs causing hypomotility, and dealing with problems of immobilization may solve the problem. If the condition continues, then stool softeners or intestinal stimulants may be required. In resistant cases, mechanical and paralytic ileus should be ruled out. If intestinal passage cannot be provided enteral nutrition should be discontinued, and it should be switched to parenteral feeding.

Refeeding syndrome: It is observed when high calorie nutrients are administered rapidly in patients who are malnourished for a long-time. Refeeding syndrome presents itself with impaired consciousness, deteriorated medical status, or seizures. Signs of cardiac failure may develop. Hypophosphatemia, hypomagnesemia, hypokalemia, and fluid retention may develop. When refeeding syndrome develops electrolyte deficiencies and circulation volume should be carefully corrected. 50-250 mg of thiamin should be administered especially during glucose infusion. Thiamin support may be required until the patient is stabilized. Intravenous replacement is performed with 40-80 mmol/day of phosphate, 8-16 mmol/day of magnesium, and 80-120 mmol/day of potassium. Since diuretics may increase the intensity of hypokalemia, they should be carefully used. At most 50-75% of the targeted calorie should be administered to patients who have developed refeeding syndrome. It is important to prevent this fatal complication in patients with the risk of refeeding syndrome development by starting enteral nutrition at very small amounts, and gradually increasing the volume (118,124-126).

Metabolic complications of feeding with NG tube, PEG, and enteral nutrition are given in tables 2,3 and 4.

16. How are oral drugs administered in patients fed by enteral route?

There may be problems in enterally fed patients who should receive oral drugs. Parenteral forms of drugs should be used in these patients when they are especially hospitalized. Tablets are suspended in 30 ml water after crushing. They are given through tubes by using 50 cc syringes. If required, contents of capsulated

Table 2. Complications of nasogastric enteral feeding

Gastrointestinal (30-38%)	**Mechanical (2-10%)**
Nausea-vomiting	Agitation, irritability
Esophageal reflux	Rhinitis, otitis, parotitis
Diarrhea	Epistaxis
Gastrointestinal bleeding	Nasopharyngitis, esophagitis
Abdominal cramps	Nasopharyngeal edema, ulcer
Abdominal distention and constipation	Malposition or displacement of tube
Perforation	Aspiration and edema
Malabsorption	Esophageal erosion and stricture
Elevated hepatic enzymes	Obstruction of tube

drugs may be emptied in hot water and the granules should be given through PEG tubes. Oral drugs should never be added into the feeding bag. Crushed tablets or opened capsule contents may have physical and chemical interaction with the feeding tube wall, and decrease the administered dose, so drug absorption may change. When slow release forms are crushed, this characteristic is lost, and drug bolus is administered at high dose. Different drugs should not be mixed in the same syringe. Before and after drug administration with a syringe, feeding tube should be washed with 15-50 cc of warm water. Thirty minutes before drug administration through feeding tube, enteral feeding should be discontinued, and it should be re-started 30 minutes after drug administration (127-133).

Table 3. Complications of PEG

During the procedure	After the procedure
Aspiration	Peristomal infection
Hemorrhage	Stomal leakage
Abdominal organ damage	Bumper embedding syndrome
Delayed ileus	Fistula tracts
Cardiopulmonary complications associated with sedation	Malposition or displacement of PEG Gastric ulcer
Systemic complications associated with general anesthesia	Peritonitis

Table 4. The most common metabolic complications and their solution methods for enteral feeding

Complication	Cause	Solution
Hyponatremia	Excessive hydration	Change the product Restrict fluids
Hypernatremia	Inadequate fluid intake	Increase amount of free fluid
Dehydration	Diarrhea Inadequate fluid intake	Investigate causes of diarrhea Increase free fluid intake
Hyperglycemia	Excessive energy intake Inadequate insulin	Evaluate energy intake Adjust insulin dose
Hypokalemia	Refeeding syndrome Diarrhea	Potassium replacement Investigate causes of diarrhea
Hyperkalemia	Excessive potassium intake Renal failure	Change the product
Hypophosphatemia	Refeeding syndrome	Phosphate replacement Decrease administered calorie amount
Hyperphosphatemia	Renal failure	Change the product

Rules to administer some drugs which are commonly used in neurological practice through enteral tube are given in annex 2.

Annex 2: Important characteristics for some orally administered drugs in stroke patients with tube feeding.

Drug	Observation	Alternative
Atenolol	Inadequate plasma concentration	IV esmolol
Amiodarone	Very low plasma concentration	IV amiodarone
Carbamezapine	Effective plasma concentration can be reached very late, or cannot be reached	Frequent serum level measurement
Ciprofloxacin	Plasma level cannot be estimated Chelation with enteral product (27-67%)	IV ciprofloxacin Twice the dose
Kinapril	Magnesium carbonate content increases pH, and destroys the drug	
Lansoprazole, Omeprazole	No stability of gastric acidity Bioavailability decreased by 33-39%	Pantoprazole +Bicarbonate

Drug	Observation
Clopidogrel	300 mg loading given via NG tube provides more rapid and higher bioavailability than by oral route
Amlodipine	Since it is rapidly denatured after crushing and diluting, it should be administered rapidly
Aspirin	Although enteric tablets are crushed, they may not be completely absorbed in the stomach. No need for fear of gastric side effects.
Carbidopa +L-dopa	Case reports indicating it is effective in the perioperative period
Duloxetine	Tablet dissolves when mixed with apple juice and it provides as much effective blood level as capsules
Warfarin	It sticks to the feeding tube, so 35% of the dose reaches stomach. Dose should be reduced when feeding is switched to oral route
Dabigatran	cannot be placed down an enteral feeding tube
Rivaroxaban	may also be given to patients via feeding tube if the tube is placed within the stomach
Apixaban	Crushed forms suspended in distilled water can be administered via a feeding tube
Epdantoin	89% is adsorbed. It should be well-diluted. It binds to proteins in nutritional products and calcium salts (±2 hours)
L-dopa	Its absorption decreases when protein amount increases above 1.4 g/kg/day. It is not administered by continuous infusion.

17. How are enterally fed patients followed up?

Follow-up in the first week is especially important in patients who are fed enterally. Urine volume should always be surveyed. Close blood glucose follow-up is performed. Urea, creatinine, electrolytes and liver enzymes should be surveyed every day whereas, Ca, Mg and PO4 supervised twice a week. Body weight should be checked at reasonable time intervals (106,114-116).

Since dysphagia may improve, it should be evaluated twice in the first week, once a week in weeks 1-4, in the first month after discharge, and 3-6 months after the first follow-up to test whether patients still require enteral nutrition. Enteral tube is withdrawn in patients with safe swallowing.

18. In which stroke patients should oral nutritional support products be used?

Oral nutritional support products are sterile compounds formulized as liquid, semisolid or powder forms, which are prepared to be given orally and include different amounts of micro and macronutrients. Studies have been conducted about their use in different clinical settings to support daily calorie and nutrient intake, and these studies highligted positive effects in terms of functional (increased grasping strength, etc.), nutritional (weight gain, achieving daily protein and calorie targets, etc.), and clinical (decrease in pressure ulcer incidence and mortality, shortening of hospitalization duration, etc.) end-points especially in geriatric individuals with malnutrition by use of oral nutrition support products (134-138).

There are a limited number of studies conducted to investigate whether there are similar effects in stroke patients. The most important of these was a multicenter randomized controlled study named FOOD which was performed on a total of 4023 patients (46). In this study, oral nutritional support was not shown to be significantly effective on mortality and functional outcome in stroke patients. This study had certain methodological drawbacks in desing, like evaluation of nutritional state only by clinical observation in 63% of patients, and underrepresentation of malnourished patients, constituting only 8% of the overall cohort. In this subset of patients with malnutrition, there was evidence for a non-significant decrease in mortality and functional dependency. Overall, taking into consideration other additional studies which are very heterogeneous in terms of the products used and study design, various nutritional goals were attained by using oral nutritional support products, but no consistent clnical benefit was shown in stroke patients (15,16,46,139).

Use of oral nutritional support products on a routine basis is not recommended in stroke patients. In stroke patients with malnutrition or risk of malnutrition where adequate protein and calorie requirements cannot be provided by normal nutritional schemes, oral nutritional support products can be initiated, if oral intake is safe. Oral nutritional support treatment may contribute to the improvement of nutritional parameters in this patient group. However, there is no consistent evidence indicating their positive effects on clinical end-points.

19. In which stroke patients should total parenteral nutrition (TPN) be administered?

There is no study about the effects of total parenteral nutrition (TPN) specifically on stroke patients; therefore the use of TPN in these patients can be deduced under the light of data obtained from other clinical settings. Parenteral nutritional is not clearly superior to enteral nutrition in terms of mortality, functional outcome, and length of hospitalization in patients with functional gastrointestinal tracts. It is not considered as the first line of nutritional treatment because of its possible complications and cost. Parenteral treatment comes up as an option when enteral nutrition is contraindicated or treatment targets are not reached by enteral nutrition (140-142).

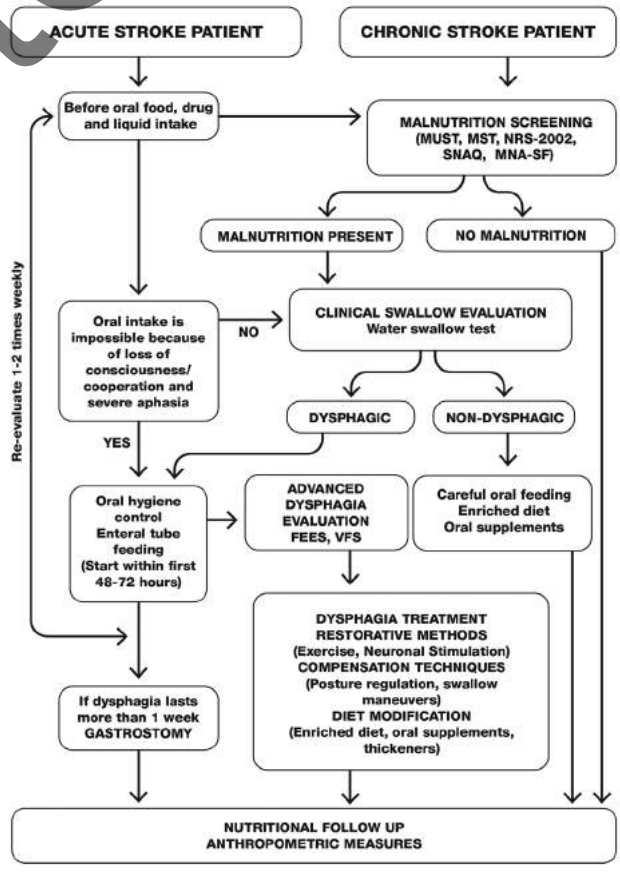
Parenteral nutrition is not recommended routinely in stroke patients.

Parenteral nutrition should be considered only when oral or enteral nutritional treatments are contraindicated or these treatments cannot provide the required treatment targets.

If TPN has to be initiated, every measure should be taken to prevent treatment related complications, mainly hyperglycemia and infection,, and nutritional support should be switched to oral or enteral regiments in the shortest time interval possible.

A nutrional aproach algorithm for stroke patients is given in annex 3 to gether with three prescription examples regarding basic nutritional requirements (Annex 4).

Annex 3: Algorithm for the approach to patient with stroke in the acute and chronic phases



Annex 4: Basic requirements in enteral nutrition

BASIC REQUIREMENTS IN ENTERAL NUTRITION

WATER	ENERGY	PROTEIN
30 ml/kg	20-30 kcal/kg	1.0-1.5 gr/kg

INITIAL INFUSION RATE 20 ml/hour
INFUSION RATE IS INCREASED TO 10-20 ml/hour AT 8-12 HOURS INTERIMS
IT IS EXPECTED TO REACH NUTRITIONAL GOALS WTIHIN 48-72 HOURS

EXAMPLE
MALE PATIENT WITH IDEAL BODY WEIGHT 70 kg

REQUIREMENTS	2100 cc WATER	1750 kcal ENERGY	100 gr. PROTEIN

TIME	INFUSION RATE
0-12.hour	20 ml/hour
12-24.hour	30 ml/hour
24-36.hour	40 ml/hour
36-48.hour	50 ml/hour
48-72.hour	60 ml/hour
After 72 hours	80 ml/hour

ALTERNATIVE 1	CONTENT		
PRODUCT	VOLUME	ENERGY	PROTEIN
STANDART	2000 cc	2000 kcal	80 gr
TOTAL	2000 cc	2000 kcal	80 gr

ALTERNATIVE 2	CONTENT		
PRODUCT	VOLUME	ENERGY	PROTEIN
HIGH PROTEIN	1000 cc	1000 kcal	60 gr
HIGH ENERGY	500 cc	750 kcal	20 gr
TOTAL	1500 cc	1750 kcal	80 gr

ALTERNATIVE 3	CONTENT		
PRODUCT	VOLUME	ENERGY	PROTEIN
HIGH PROTEIN	1000 cc	1000 kcal	60 gr
STANDARD	500 cc	500 kcal	20 gr
FIBER	500 cc	500 kcal	20 gr
TOTAL	2000 cc	2000 kcal	100 gr

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