

QUARTERLY MEDICAL REVIEW

Vol. 70, No. 2

April - June 2019

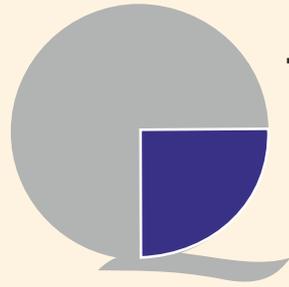
Loss of Appetite: Challenges and Considerations

Published and issued by :

RAPTAKOS, BRETT & CO. LTD., 21 A, Mittal Tower, A Wing, 210, Nariman Point, Mumbai 400 021. INDIA.
www.raptakos.com

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Review:

Loss of Appetite: Challenges and Considerations

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Introduction

Most countries have a common health problem of appetite related issues regarding nutrition. Appetite is an issue for children below 5 years of age, elderly, during any grade of illness, those undergoing major depressive disorder, hemodialysis and major surgery. Anorexia is defined as a loss of appetite and/or reduced food intake.⁽¹⁾ It is a type of eating disorder that perpetuate the biochemical changes marked by an inability to maintain a normal healthy body weight, often dropping below 85% of ideal body weight (IBW), ketosis and starvation illness. Ventromedial hypothalamic nucleus is called satiety center. Serotonin stimulates satiety center and lead to loss of appetite and weight loss.⁽¹⁾ Loss of appetite and ensuing weight loss is a key feature of severe illnesses. Severe acute malnutrition (SAM) contributes significantly to the adverse outcome of these conditions. Loss of appetite, regardless of cause, is a significant symptom that may cause extreme weight loss in older patients. The consequences of anorexia include muscle wasting, weakness, depression, increased susceptibility to disease complications, and decreased immunocompetence.

Different population affected by Anorexia

Childhood malnutrition is a result of multidimensional factors such as intrauterine undernutrition, lack of exclusive breast feeding, inappropriate complementary feeding, repeated attacks of infectious illnesses, inadequate food intake, and micronutrient deficiencies (Hidden Hunger).⁽²⁾ Its prevalence is 20% and 32% irrespective of low, middle or high-income countries.^{(3),(4)} The developing countries struggle with diet scarcity and/or lack of appetite. An effective, safe and accessible medical treatment should intervene anorexia before it can impact on child's cognitive and potential growth. Reduced appetite and low food intake is a leading cause of mortality in childhood.⁽⁵⁾ Anthropometric parameters such as weight and height are important health indicator in children. These are regulated in human by neuropeptide Y, serotonin, and glucagon like peptide 1, tumor necrotizing factor- α , some hormones like insulin, antihistamines and leptin.⁽⁶⁾

Anorexia is a true geriatric syndrome with its multifactorial origin and associated multiple negative health outcomes.⁽⁷⁾ Anorexia of aging and consequent weight loss are very common problems of hospitalized and nursing home residents.⁽⁸⁾ The major causes are pulmonary and cardiac diseases, cancer, dementia, alcoholism, depression, and medications and last but not least due to aging per se. Accumulating evidence indicates that a significant number of frail elderly people fail to ingest an amount of food that meets essential energy and nutrient needs.⁽⁸⁾ The accumulated effects of impairment in multiple systems make the older subject more vulnerable to adverse health events. The diagnosis is based on the physical exam, a history of weight loss, and a review of dietary intake. Treatment strategies include managing GI disturbances, encouraging physical activity and socialization, reducing fatigue and food aversions, and adding high-calorie supplements to the diet.⁽⁹⁾

Hemodialysis (HD) if accompanied by anorexia; presents with poor health-related quality of life as well as higher risks of hospitalization and mortality.⁽¹⁰⁾ Anecdotal accounts of physicians and patients; strongly correlate experience of pain to decrease or loss of appetite.⁽¹¹⁾

Patients with major depressive disorder exhibit marked heterogeneity in appetite, with approximately 48% of adult depressed patients exhibiting depression-related decrease in appetite, while approximately 35% exhibit depression-related increase in appetite.⁽¹²⁾ In fact, across large depressed cohorts, appetite and weight changes are often some of the most discriminating symptoms in latent class analyses of depression subtypes. These changes in appetite and weight are 75-85% stable across depressive episodes, suggesting that they may

be trait markers of how depression is manifested within a particular individual.⁽¹³⁾

Appetite loss is commonly reported by patients following major surgery, including total joint arthroplasty (TJA). A number of studies have examined related problems, particularly in relation to physiological responses to surgery.⁽¹⁴⁾ Nutrition positively influence convalescence and recovery time. Understanding the natural history of postoperative appetite loss is important for the surgeon.

Physiological causes of the anorexia

Many mechanisms are involved in the regulation of appetite and, consequently, food intake. The anorexia of aging may result from numerous physiological factors associated with aging, including changes in perception of the hedonic qualities of food and central and peripheral mechanisms regulating hunger and satiety.

Older adults often have less hunger and experience earlier satiety. As a result, they consume less food comparing to younger adults, eat smaller meals at a slower rate, drink less, and snack less between meals.⁽¹⁵⁾ All of these result into a reduction in calorie intake. One study reported a 25% decrease in daily calorie consumption from 40 to 70 years of age.⁽¹⁶⁾ This decline in energy intake is predominantly due to a decrease in fat calories with a small increase in the percent of calories ingested as carbohydrate. Similar changes in healthy counterparts with adequate food supply indicate physiological anorexia of aging. Possible explanation is physiological changes result from a decline in total energy expenditure (TEE) due to a decline in physical activity and decreased resting metabolic rate. Lowered lean body mass (LBM) further reduce caloric intake.⁽¹⁷⁾

Food intake affects hunger to a lesser extent in older compared to younger subjects. In healthy elderly, anorexigenic signals prevail over orexigenic signals, and they contribute to prolonged satiety and inhibition of hunger.⁽¹⁸⁾ The fluctuation in food intake and inability to regulate weight proves impaired homeostasis of regulatory mechanisms.

Children and adolescent's diet is regulated by a number of factors, including age, puberty, sex, race, and body composition, may contribute to differences in satiety, food intake, and appetite-related peptides. These peptides include the orexigenic peptide ghrelin and anorexigenic gut peptides peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). For example, lower fasting ghrelin levels, lower postprandial ghrelin suppression, and blunted PYY and GLP-1 responses to food intake could contribute to a dysregulation of appetite in already obese children and adolescents. Changes observed in these peptides during puberty could facilitate growth.⁽¹⁹⁾

Decline of senses

Aging and failure in senses are very commonly associated. It result from loss of sensory cells, loss of their sensitivity, but also from poor oral hygiene. Perception of the hedonic qualities of food (its odor and taste) lessens when people get older due to physiological changes in smell and taste. Thus taste is less appreciated and consequently-affect food choice and limit type and mount of food eaten. More than 60 % of people aged 65 to 80 have major olfactory impairment, and after the age of 80, more than three-quarters evidence major gustatory impairment.⁽²⁰⁾ The high rate of anosmia is consequence of changes in the olfactory epithelium, reduced mucus secretion, changes in airway structure or epithelial thickness, and reduced regeneration rate in olfactory receptors. The number and sensitivity of taste papillae is reduced with aging.⁽²¹⁾ Reduced fat intake (and consequently reduced amount of body fat) in the elderly is partly due to inability of fat to affect hedonic qualities of food.⁽²²⁾

The increase in odor and taste thresholds suggests a need for "richer" tastes of food for older persons. Salt test being most affected as to sweet. Taste and smell enhancers can reverse the decreased enjoyment of food in some older persons.⁽²³⁾ These alterations also mean that

improving visual presentation of food (e.g., meals that are familiar and recognizable-not mashed together). It may be an easy and effective intervention in prevention and treatment of the anorexia of aging.

Regulation of appetite

The central site for appetite regulation, the appetostat, is located in the hypothalamus. Within the hypothalamus, appetite is regulated by several nuclei. Appetite is a complex interactions between ventromedial hypothalamic nucleus (satiety center), lateral hypothalamus (hunger center), and arcuate nucleus. Its physiological reduction with aging is regulated by changes in activity of and sensitivity to peptides regulating appetite and feeding. The exact nature of these changes is poorly understood. However, a general pattern is; decline of central feeding drive with age.⁽¹⁷⁾

Exercise

Physical activity not just control energy balance by induced energy expenditure but also energy intake and appetite. Although the mechanisms involved remain uncertain. Many studies have assessed both post-exercise energy intake and appetite but have mainly focused on food consumption. So, the analysis remains unclear whether changes in appetite provide an accurate reflection of changes in energy intake.⁽²⁴⁾

Opioids

The endogenous opioid peptides, b-endorphin, enkephalin, and dynorphin, stimulate feeding behavior. They preferentially increase ingestion of a high-fat diet through the b receptor.⁽²⁵⁾ A physiological decline in the opioid feeding system can explain lower fat consumption in elderly, although data from human studies are limited. Since drinking is probably under control of the b receptor, little is known whether there is a similar diminished role of opioids.⁽²¹⁾

Neuropeptide Y

Neuropeptide Y (NPY) is a 36-amino acid neuropeptide; produced at various sites, including the hypothalamus. NPY is one of the most potent orexigenic agents. Its effects are predominantly on carbohydrate-rich food.⁽¹⁷⁾

Orexins

Orexin activity is inhibited by leptin (through the leptin receptor pathway) and activated by ghrelin and hypoglycemia. Orexin-A and orexin-B, also named hypocretin-1 and hypocretin-2 are involved mainly in sleep, but also increase the craving for food.⁽¹⁷⁾ Cocaine - and amphetamine-regulated transcript (CART) is a neuropeptide produced mainly by hypothalamic neurons. Its anorexigenic activity is regulated by inhibition of NPY neurons. There might be aging-related increase of CART activity in males. However, a very recent study showed that CART peptide expression in the nucleus accumbens is stable in adults and does not change with age.⁽²⁶⁾

Agouti-related protein (AgRP) This is a neuropeptide produced in the brain by the AgRP/NPY neurons. AgRP is co-expressed with NPY. It works by increasing appetite and decreasing metabolism and energy expenditure.⁽¹⁷⁾

Nesfatin-1 is expressed in both central and peripheral tissues and links metabolic alterations. It is the satiety molecule associated with melanocortin signaling in hypothalamus. It decreases food intake in a dose-dependent manner. The effect of nesfatin-1 on appetite has been studied in several metabolic diseases, such as epilepsy, diabetes mellitus inflammatory

stimulation and cancer. Nesfatin-1 might also have an important role in regulation of food intake and pathogenesis of loss of appetite in children.⁽²⁷⁾

Leptin Leptin is a hormone secreted by the adipose tissue; that regulates amount of fat stored in body. It not just decrease sensation of hunger and food intake, but also adjust energy expenditures.⁽¹⁷⁾

Galanin Galanin is a neuropeptide produced in the brain as well as peripherally. It has orexigenic activity which is hypothesized to decline with age in women.⁽¹⁷⁾ In underweight children, decreased vaspin and apelin levels should be considered in the etiology of anorexia.⁽²⁸⁾

Gastrointestinal tract & Delayed gastric emptying stretch of the antrum is the major gastrointestinal satiety signal.

With aging, gastric emptying is significantly delayed, resulting in more rapid feeling of satiation. Early satiation in the older person appears to involve signals predominantly arising in the stomach. Age-related changes in other parts of the gastrointestinal tract seem to have less important impact on satiety signaling. This leads to reduced appetite.⁽²⁹⁾ Reduced compliancy (receptive relaxation) of the gastric fundus lead to more rapid antral filling which in turn impart sensation of fullness. The reduction in compliancy is probably a result of diminished effect of nitric oxide.

It is speculate age-related changes in the cellular mechanisms control gastrointestinal smooth muscle contraction.⁽³⁰⁾

Gastrointestinal hormones

All major appetite-regulating gastrointestinal hormones and their age-dependent changes in peripheral factors regulating appetite have an impact on anorexia of aging.⁽³¹⁾ Many observed changes are not directly related to aging, but to changes in body composition.

Cholecystokinin

Cholecystokinin (CCK) is a satiating hormone. It causes bile release, stimulates secretion of pancreatic enzymes, and inhibits food intake. Concentration of CCK is increasing with age. This may be explained by an increase in circulating fatty acids in aging humans.⁽³²⁾ Additionally, since CCK slows gastric emptying, increased CCK concentration may mediate aging-related changes in gastric emptying.

Glucagon-like peptide 1

Glucagon-like peptide 1 (GLP-1) is a potent inhibitor of food intake. GLP-1 lowers blood glucose levels by stimulating insulin secretion from pancreatic b-cells in a glucose-dependent manner. Its action slows gastric emptying, suppresses appetite, reduces concentrations of glucagon, increases insulin sensitivity, and stimulates glucose disposal.⁽³³⁾ The short-term postprandial concentrations of GLP-1 are similar in both young and older healthy subjects after the isoenergetic duodenal infusion of glucose or lipid. However, in healthy elderly people, high-fat diet increases the satiety signal from GLP-1. This consequently decreasing hunger through increasing insulin sensitivity of certain brain areas, including the hypothalamus, which in turn mediates the onset of anorexia.⁽¹²⁾

Ghrelin

Ghrelin is a peptide produced by P/D1 cells in the gastrointestinal tract. It is a potent anorexigenic hormone, also regulating fat distribution and rate of use of energy. Ghrelin administration increased the levels of nitric oxide synthase in the hypothalamus. This fact supports the role of nitric oxide in central regulation of food consumption. The activity of nitric oxide synthase diminish in aging (although human data are not conclusive). The older

persons have lower activity of ghrelin. Acylated (orexigenic) ghrelin is low compared to desacylated (anorexigenic, although this is controversial) ghrelin. The plasma ghrelin concentrations are higher in the undernourished older women than well-nourished older as well as young women. Ghrelin concentrations decreased more after food ingestion in the older compared with the young subjects.⁽³⁴⁾

Amylin

Amylin is a peptide hormone co-secreted with insulin from the b-cells in response to a meal. Peripherally, it is a potent anorexigenic agent, producing its effects (e.g., slowed gastric emptying) through the nucleus tractus solitarius. In humans, amylin secretion exhibits a U-shaped curve with greater secretion in young and old subjects than in middle-aged persons.⁽¹⁷⁾ However, aging is also associated with changes in glucose metabolism due to increasing insulin resistance. Amylin may merely be acting as a marker of impaired glucose metabolism.

Peptide YY

Peptide YY (PYY) is released in the ileum and colon in response to feeding and reduces appetite. Some evidence suggests that with advancing age there is an increase in postprandial, but not in fasting PYY levels.⁽³⁵⁾ However, its concentration did not differ significantly between older and younger subjects. This rejects any relationship between circulating PYY concentrations and anorexia of aging.⁽³⁶⁾

Zinc

Zinc has role in many physiological functions, such as growth, immune function, and reproduction in human. So its deficit induces a number of physiological problems, including anorexia, growth retardation, dermatitis, taste disorder, and hypogonadism.

Zinc stimulates food intake in short-term zinc-deficient rats through the afferent vagus nerve with subsequent effects on hypothalamic peptides associated with food intake regulation. Oral zinc rapidly stimulates food intake through orexigenic peptides coupled to the afferent vagus nerve using rats during early-stage zinc deficiency without decreased zinc concentrations in plasma and tissues. Zinc-sufficient diet containing zinc chloride acutely stimulated food intake after short-term zinc deprivation. Orally administered zinc sulfate increased the expression of NPY and orexin mRNA.⁽³⁷⁾ Specific and profound anorexia observed in experimental animals, cannot be extrapolated to humans.

Pathological mechanisms of the anorexia

Depression

Depression is one of the most common reversible causes of anorexia and weight loss in elderly persons.⁽³⁸⁾ Corticotropin-releasing factor (CRF) is a very potent centrally acting anorectic agent. Lack of appetite in depressed patients is associated with increased concentrations of serotonin and CRF. It is probably due to increased ghrelin secretion caused by the stimulation of serotonin 5-HT_{2B} and 5-HT_{2C} receptors.⁽³⁹⁾ Elderly subjects suffering from depression exhibit a greater amount of dysregulation of the hypothalamic-pituitary-adrenal axis activity compared with younger adults. So a depressed elderly consequently eat less.⁽⁴⁰⁾

Constipation is a common symptom of elderly patients with depression. It adds to decreased appetite due to a feeling of fullness. Patients with severe depression may also refuse to eat and drink due to suicidal thoughts.

Patients with psychotic disorders, such as schizophrenia, paranoia, delirium, or psychotic

depression (when symptoms of depression coexist with hallucinations and delusions), may experience various psychotic symptoms limiting their food consumption. Examples of such symptoms are auditory hallucinations ordering them not to eat, persecutory delusions that food is poisoned, gustatory hallucinations affecting food taste, and cenesthetic hallucinations that the gastrointestinal tract is congested or obstructed.

Dementia

Dementia particularly of the Alzheimer's type, are associated with loss of appetite and weight. ⁽⁴¹⁾ Patients may experience indifference to food, loss of appetite and/or forget to eat. Detailed biological mechanisms of anorexia in demented patients are unknown. Probably they have altered mechanisms regulating appetite and metabolism. It also affect processing of olfactory stimuli and enhance physiological decline in smell. ⁽⁴²⁾

Apraxia of swallowing and reduction of taste and smell are especially marked in Parkinson syndromes. They may also play a significant role.

Chronic kidney disease

Inadequate nutritional intake is a classic manifestation of chronic kidney disease (CKD) in adults and children. This is believed to be secondary to a variety of mechanisms, including nausea, early satiety due to delayed gastric emptying, altered taste, and, in some patients, the need to drink large volumes of fluid to keep up with high urine output. In adults with CKD, self-reported decreased appetite is associated with a variety of poor outcomes, including decreased quality of life, and increased hospitalizations and mortality in hemodialysis patients. Self-reported appetite in children with CKD worsens with lower i.e. GFR and is correlated with clinical outcomes, including hospitalizations and quality of life. ⁽⁴³⁾

Comorbidities

Any disease that impairs instrumental activities of daily living is associated with increased risk of anorexia. ⁽⁴⁴⁾ Pathologic anorexia of aging may also be secondary to comorbidities, such as cancer (driven by anorexigenic cytokines released by tumor cells, see below), chronic pulmonary obstructive disease (causing shortening of breath during food consumption), abdominal angina (manifested by abdominal pain after a meal), and constipation (causing a feeling of fullness). Important and frequent causes of both anorexia and cachexia are kidney and heart diseases, mainly chronic kidney disease and chronic heart failure.

Arthritis, stroke, Parkinson's disease, and many other neurological disorders may impair mobility, and thus affect activities of daily living, such as doing shopping, preparing food, and feeding. Also, many diseases may cause gastroparesis and thus reduce appetite.

These include the following: autonomic neuropathy in diabetes, Parkinson's disease, scleroderma, Ehlers-Danlos syndrome.

Gastrointestinal diseases may lead to anorexia, but also cause malabsorption syndromes, with micronutrient deficiencies and increased energy and protein requirements. Differential diagnosis of the anorexia of aging must also include alcoholism and hypermetabolic conditions (e.g., hyperthyroidism) with secondary weight loss.

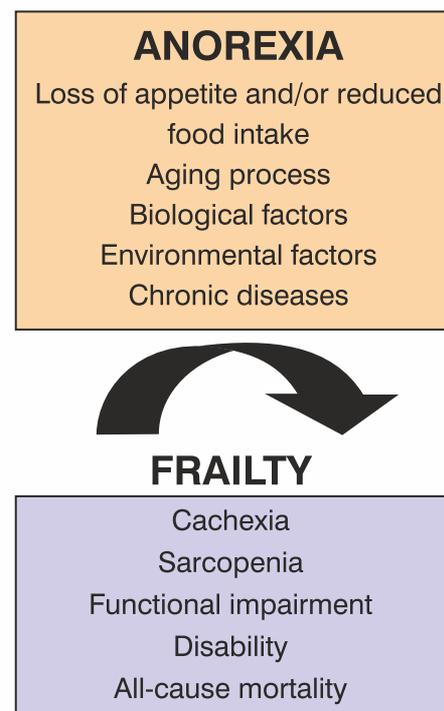


Figure 1: Anorexia as a geriatric syndrome.

Acute illness, such as viral or bacterial infections, is often associated with a spontaneous loss of appetite despite increased energy and nutrients requirements. Inadequate food intake may partly contribute to a reduced nutritional status and increase the occurrence of hospitalization in a vulnerable group of elderly people. Therefore, there is a bidirectional association between acute illness and loss of appetite. Cancer is a model disease for disease-associated loss of appetite and weight. Several factors are considered to mediate anorexia, including hormones, e.g., leptin; neuropeptides (NPY); proinflammatory cytokines (IL-1 and IL-6); and tumor necrosis factor (TNF)-alpha; and neurotransmitters (serotonin and dopamine).

Mechanisms through which cytokines alter appetite include the following: release of leptin; activation of the leptin receptor; stimulation of the corticotropin-releasing factor; inhibition of orexigenic peptides, such as NPY, dynorphin, galanin, and melanin-concentrating hormone (MCH); increase of highly anorexigenic prostaglandin E1b.⁽⁴⁵⁾ Increased expression of cytokines disturbs physiological response of the hypothalamus to peripheral signals, by persistent activation of anorexigenic and inhibition of orexigenic pathways. For example by acting on the glucose-sensitive neurons of the hypothalamic satiety and hunger sites.⁽⁴⁶⁾ As a matter of fact, elevated circulating cytokines may both result in pathological anorexia of aging, but can also directly contribute to the development of physiological anorexia of aging.

C-reactive protein (CRP) level is also higher in free living or hospitalized subjects with the anorexia of aging.⁽⁴⁴⁾ Raised CRP level may be an indicator of acute inflammation, but also may affect appetite more directly, via changes of testosterone levels. Chronic low-grade inflammation may also suppress appetite by activating serotonin system via increased level of tryptophan.

Others gastrointestinal problems that occur in aging and may affect appetite are as follows: impaired motility, reduced gastric and intestinal secretion, reduced intestinal absorptive surface, all leading to malabsorption of carbohydrates, lipids, amino acids, minerals, and vitamins.⁽⁴⁷⁾ Hypercalcemia may cause anorexia, while gallstones may produce early satiety. Experienced gastrointestinal symptoms (e.g., dyspepsia, gastroesophageal reflux) may also limit food intake. Bacterial overgrowth is more common in the elderly and may cause both anorexia and malabsorption.⁽⁴⁸⁾ Increased damage susceptibility of the elderly gastrointestinal tract may also affect nutrition via reduced absorption of nutrients. Chronic constipation is reported in up to 25 % of the population over 65 and also play a role here.

Zinc deficiency and Taste Disturbances

According to the National Health and Nutrition Examination Survey III, 35% to 45% of adults 60 years of age or older had zinc intakes below the estimated average requirement of 6.8 mg/day for elderly females and 9.4 mg/day for elderly males. Zinc deficiency may lead to loss of appetite, impaired immune function, weight loss, delayed healing of wounds, eye and skin lesions, and smell and taste disturbances. Older adults are especially affected by changes in taste sensations because of age-related gustatory dysfunction, use of multiple medications, increased frailty; all leading to zinc deficiency.⁽⁴⁹⁾ Correction of zinc deficiency improves taste and smell disturbances and the appetite.

Medications

Numerous commonly prescribed medications can cause dry mouth, metallic taste, nausea, vomiting, constipation, and diarrhea. They can also affect taste and appetite and may cause

malabsorption of nutrients or gastrointestinal symptoms or lead to drug-food interactions.⁽⁵⁰⁾ This is a significant problem, particularly because polypharmacy is common in the elderly. Appetite-affecting medications include antianxiety agents, antibacterials, antidepressants, antiepileptics, antifungals, antihistamines and decongestants, antihypertensives and cardiac medications, anti-inflammatory, antimigraine, antineoplastics, antiparkinsonic and antiviral agents, bronchodilators, CNS stimulants, hypnotics, lipid-lowering agents, muscle relaxants, pancreatic enzyme preparations, smoking cessation aids, and thyroid drugs and it seems whole pharmacopia.⁽⁵⁰⁾

The evaluation of pharmacological therapies is required to identify drugs that may decrease appetite and/or favor weight loss. The most frequently prescribed drugs that may hinder appetite comprise: (1) cardiovascular drugs such as digoxin, amiodarone and spironolactone; (2) psychiatric drugs such as phenothiazines, lithium, amitriptyline, fluoxetine and other selective serotonin reuptake inhibitors; and (3) anti-rheumatic drugs such as non-steroidal anti-inflammatory agents. Other medications can contribute to weight loss by causing malabsorption (e.g., laxatives) or increasing metabolism (e.g., theophylline).

Oral-health status

Impairments of the masticatory functions, poor dentition, and ill-fitting dentures may influence food choice and limit the type and quantity of food eaten. This is a result of altered food choice in order to circumvent the effort involved in chewing using dentures.⁽⁵¹⁾ There is significantly more food avoidance among the subjects with chewing problems, discomfort with dentures, or ill-fitting dentures. The presence of chewing problems is associated with lower intake of specific nutrients, including fibers, vitamins, calcium, and proteins, and with a higher intake of fats and cholesterol (Figure 2).⁽⁴¹⁾ The same effect may be observed in people with the reduced function of salivary glands. Therefore, correction of oral-health problems may improve food intake.

Swallowing problems may also limit the amount and type of food consumed. Common complaints reported by patients with dysphagia are as follows: difficulty keeping liquids in the mouth, coughing after drinking or eating, shortness of breath while drinking or after eating, voice change after drinking or eating, food getting stuck in the mouth/throat when eating, and difficulty with saliva.⁽⁵²⁾

Medical Diagnoses

All possible medical causes that can contribute to weight loss need to be evaluated and specifically addressed. These comprise swallowing disorders (e.g., dry mouth, tooth loss, lesions or sores in the mouth), dyspepsia (e.g., gastritis and ulcers), malabsorption syndromes (e.g., bacterial overgrowth, gluten enteropathy, pancreatic insufficiency), neurological causes (e.g., stroke with residual swallowing deficits), endocrine disorders (e.g., hypercalcemia), psychiatric disorders (e.g., depression, delirium), respiratory diseases (e.g., COPD), and cardiovascular diseases (e.g., CHF).

Appetite measures are often recorded by visual analogue scales (VAS), and are assumed to reflect central nervous system (CNS) perceptions and sensations. Appetite ratings differ according to age, gender, and physical activity and to a lesser degree for smoking habits and menstruation cycle. Appetite ratings is influenced by BMI and diet/weight concern.⁽⁵³⁾

Nutritional risk screening

Considering the clinical relevance of anorexia, several tools have been proposed for screening in the general population. Questionnaires and visual analog scale (VAS) are most commonly used. Anorexia specifically reflects loss of the "desire" to eat; and food intake may not be affected in anorexic patients. Nevertheless, in daily practice, reduced food intake is frequently used as a surrogate marker of presence of anorexia and its severity.

Recent evidence obtained in a large European survey shows that hospitalized patients reporting reduction of food intake, as assessed by intake at each meal over the most recent day, were at higher risk of mortality within 30 days, even more than patients reporting involuntary body weight loss.⁽⁵⁴⁾ More recently, patients who reported reduced food intake during the most recent lunch (eating half, a quarter, or nothing) were at particularly high risk of adverse outcomes.⁽¹⁰⁾

In patients with positive findings on history or physical examination, further testing should be focused on confirming the suspected diagnosis. When the history and physical examination do not indicate a likely diagnosis, a basic diagnostic evaluation should include:

1. Laboratory testing: Complete blood count with differential, chemistries (electrolytes, glucose, calcium, renal and hepatic function, thyroid stimulating hormone), hemoglobinA1c, urinalysis, stool occult blood test(OBT), and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).
2. Diagnostic imaging: Chest radiograph.
3. If a GI cause is suspected, endoscopy and colonoscopy with biopsies may be helpful

It is not recommended CT scanning in the initial workup, although CT scan may be indicated based on history or physical examination. Further studies should be based on results of these initial tests. Despite an appropriate initial evaluation, a clear cause for anorexia is often not found. Watchful waiting for one to six months is preferable to a battery of testing with low diagnostic yield. As organic disease is rarely found in patients with a normal physical examination and initial diagnostic testing, a waiting period of one to six months is unlikely to result in an adverse outcome. On follow-up, careful attention should be paid to dietary history, possibility of psychosocial causes, surreptitious drug intake, and new manifestation of occult illness.

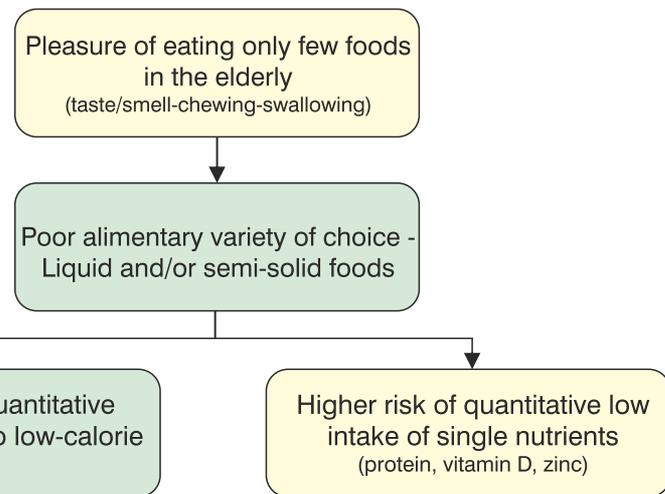


Figure 2: Anorexia and risk of malnutrition

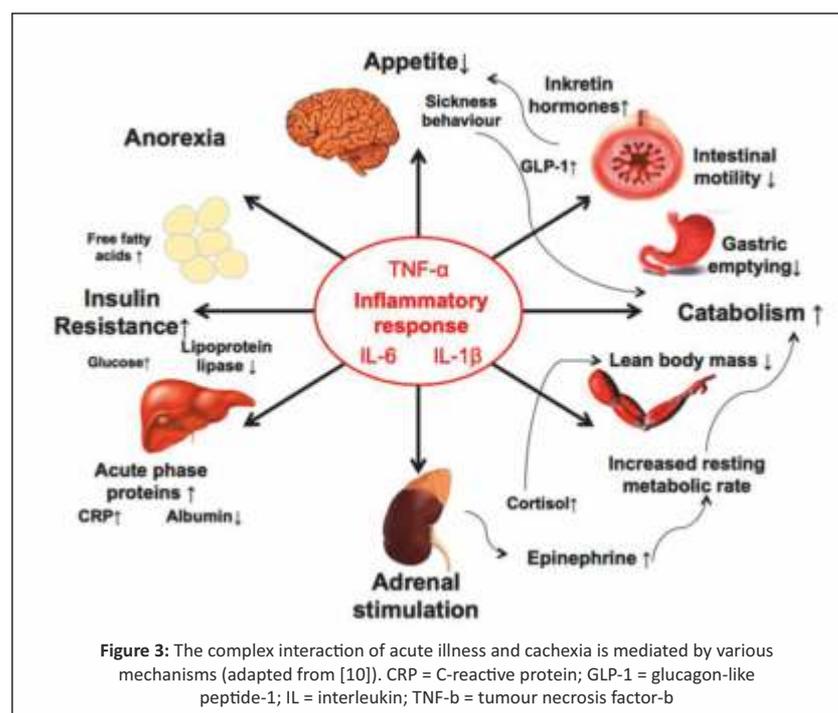


Figure 3: The complex interaction of acute illness and cachexia is mediated by various mechanisms (adapted from [10]). CRP = C-reactive protein; GLP-1 = glucagon-like peptide-1; IL = interleukin; TNF-b = tumour necrosis factor-b

Validated screening tools are available to identify older persons with anorexia or at risk of developing it. Visual analogue scales can reveal decreased spontaneous food intake. Specific questionnaires can document nutrient intakes lower than 70% of estimated needs. The Simplified Nutritional Assessment Questionnaire (SNAQ) is a simple screening tool with good predictive ability for future weight loss and protein-energy malnutrition.⁽⁵⁵⁾ Moreover, the section AC/S-12 of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire may be used to recognize anorexia-related symptoms and grading the severity of each of them scoring from 0 (worse score) to 4 (better score). A score of 24 has been proposed as diagnostic for anorexia.⁽⁵⁶⁾

Multidimensional programs that aim to identify and address risk factors for anorexia of aging. The first step in the management of anorexia is the identification of persons at risk of developing the condition by using second- and third-generation geriatric assessment tools (e.g., MDS-interRAI tools).⁽⁵⁷⁾ The interRAI system is comprised of a suite of comprehensive geriatric assessment instruments that are able to identify clinical, psychological, socioeconomic, and environmental conditions across different healthcare settings.⁽⁵⁷⁾ Modifications in feeding patterns may be sufficient in milder cases, whereas the correction of specific deficiencies and/or a systematic dietary revision may be needed in more advanced cases. When a specific and individualized intervention is established, follow-up assessments should be performed to estimate the effectiveness of the treatment plan. The interRAI system is particularly suited for this purpose as it permits encompassing individualized nutritional interventions across different healthcare settings.

Treatment of loss of Appetite

The prevention and treatment of anorexia may be accomplished through multi-stimulus interventions, including food manipulation, correction of environmental and pharmacological risk factors, and treatment of underlying medical causes.

Food Manipulation

This approach involves the enhancement of food texture and palatability, flavor improvement, provision of dietary variety, and feeding assistance as needed.

Children served themselves more with larger plates and bowls and consumed nearly 50% of the calories that they served. This provides new evidence that children's self-served portion sizes are influenced by size-related facets of their eating environments, which, in turn, may influence children's energy intake.⁽¹⁹⁾ Consuming an egg-based breakfast significantly reduced short-term, but not longer-term, energy intake in children in the absence of differences in appetite ratings.⁽⁵⁸⁾

In older subjects, intraduodenal protein at low doses increased overall energy intake, which supports the use of protein supplements in undernourished older people.

Fish oil supplementation: has a positive effect on appetite level, caloric intake and mid upper arm muscle circumference among children.⁽⁵⁹⁾

Multi-micronutrient supplementation: for six months seems to significantly improve the appetite of HIV-infected children.⁽⁶⁰⁾

An ideal appetite stimulant or tonic should have the following characteristics:

- No potential and hazardous effects on body
- Restores taste
- High nutritive value

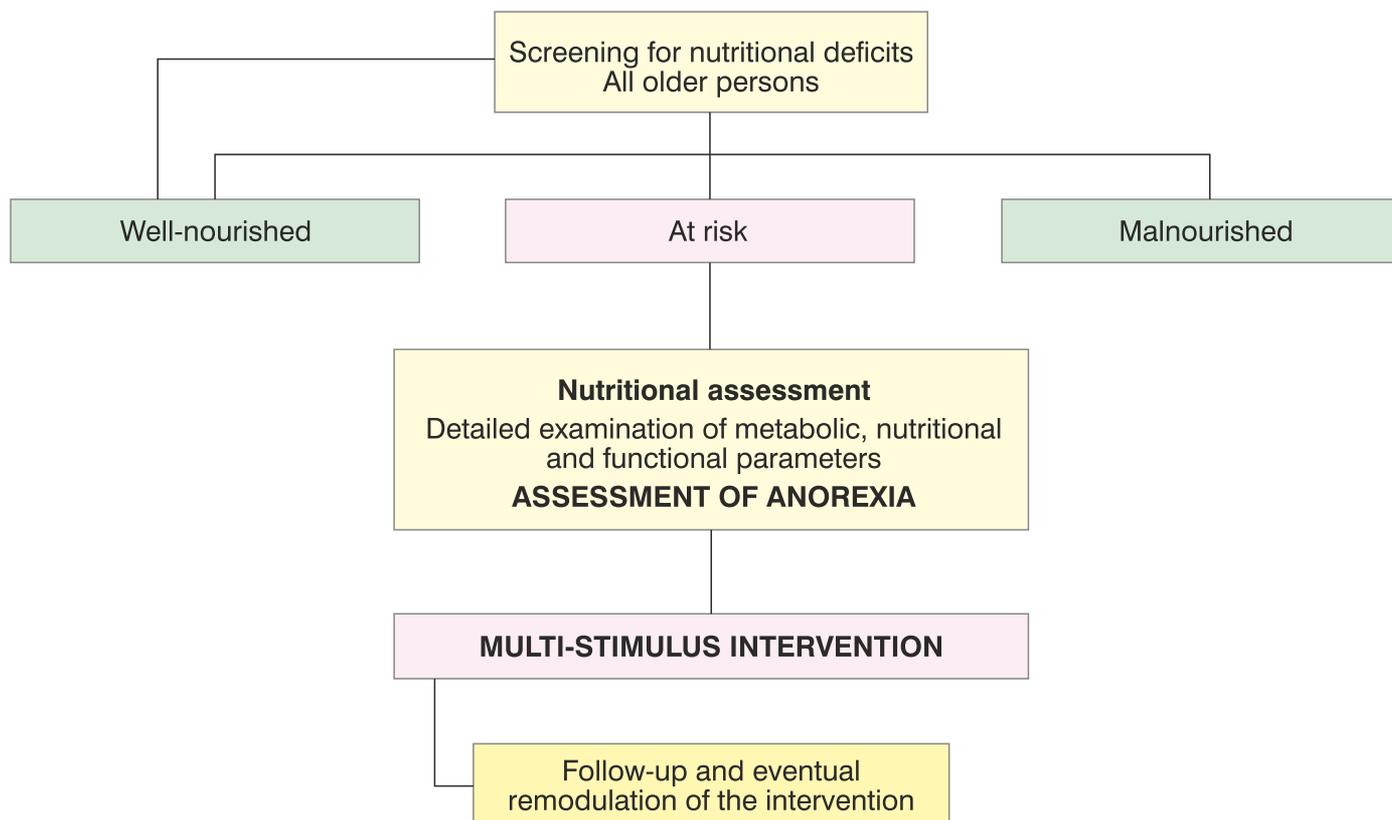


Figure 4: Assessment of anorexia of aging and malnutrition.

- Stimulate salivary secretion
- Stimulate secretion of acid & pepsin
- Enhances liver functions
- Normalize metabolism

Environmental adaptation

This intervention is aimed at preventing social isolation and endorsing conviviality, particularly in nursing home residents. Physical highly intensive exertion, results in a temporary reduction in the subjective sensation of hunger but leads to an increased food intake.⁽⁶¹⁾

Specific Treatments

Presently, no specific therapeutic agents have shown to be clearly effective in treating anorexia. Nutritional supplementations do not directly cure anorexia of aging but only its consequences, such as weight loss and energy-protein malnutrition. A small number of studies have demonstrated positive effects from energy supplementation in malnourished older adults. Nevertheless, the heterogeneity of the supplementation protocols adopted hinders their applicability to routine patient care. The only clear evidence is currently limited to protein supplementation. According to the position paper from the PROT-AGE Study Group, a daily intake in the range of at least 1.0–1.2 g protein per kilogram of body weight is required to reduce the loss of muscle mass. It maintain strength and prevent development of frailty.⁽⁶²⁾

Multivitamin supplementation: Several vitamins have been examined to stimulate appetite in older adults, but none of them is actually recommended in routine clinical practice.

Folic acid has a positive effect on appetite enhancement and consequently growth in children. A clinical trial assessed the effect of folic acid on the appetite of 127 preschool children 3 to 6

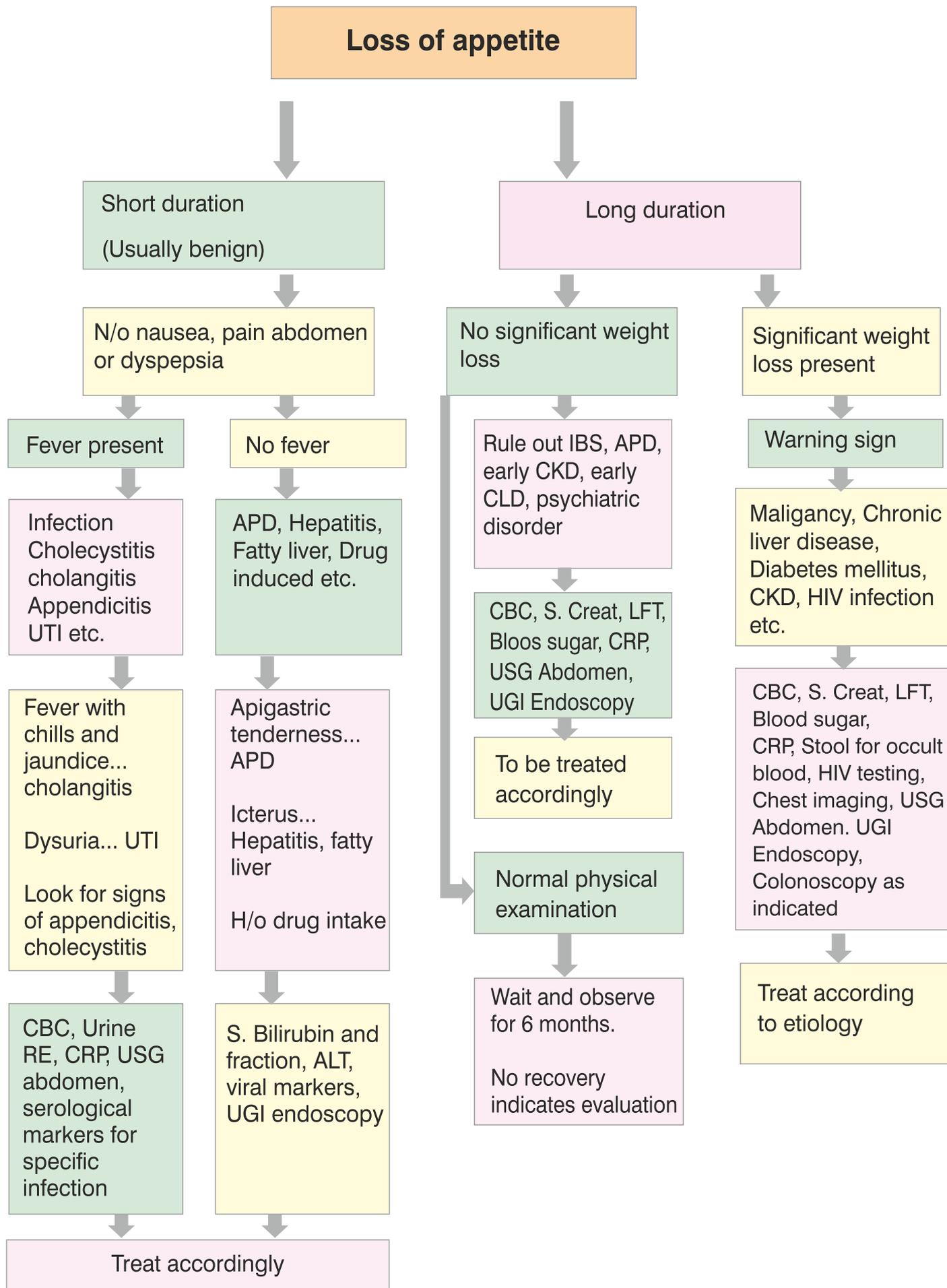


Figure 5: Algorithmic approach to loss of appetite

years old. It was found that after controlling for the potential confounders, in a statistical ordinal logistic model, serum folate showed a significantly positive effect on appetite. A small but positive effect was detected by fuzzy logistic regression.⁽⁵⁾

Corticosteroids increase body weight, primarily through increases in fat mass and fluid retention.

Growth hormone also produces weight gain in malnourished older persons, but does not improve any physical and functional outcomes.

Anabolic steroids (e.g., testosterone and oxandrolone) have been tested in older people with some positive results, but they have numerous adverse effects, such as cardiovascular events and liver dysfunction.

Metoclopramide may control the symptoms correlated to the early satiety; however, its long-term use is associated with important negative side effects, namely extra-pyramidal symptoms.

Megestrol acetate (MA) is an appetite stimulant with efficacy in promoting weight gain in adults with cancer-associated anorexia-cachexia. In children with high-risk malignancies, MA resulted in significant increases in mean percent weight change compared to placebo.⁽⁶³⁾

Dronabinol: When taken for 3 months to 1 year, dronabinol significantly improves appetite and reverses weight loss in patients living with HIV/AIDS.⁽⁶⁴⁾

Rivastigmine: It has inhibitory effects on not only acetylcholinesterase (AChE), but also on butyrylcholinesterase (BuChE). BuChE is known to inactivate ghrelin, a potent orexigenic hormone secreted by stomach in the hunger state to increase appetite and promote food intake. Rivastigmine treatment significantly improved appetite in patients with mild to moderate Alzheimer disease treated with even rivastigmine patch.⁽⁶⁵⁾

Cyproheptadine: is an anti-histaminic drug with antiserotonergic activity. It was first invented as drug for pruritis and other allied conditions. Later on it was recognised as an appetite and growth stimulant. The simulation of its appetite effect is probably due to serotonin antagonism which antagonizes the satiety stimulation effect of serotonin on satiety center. Intake finds clinical application in children with increased growth, weight gain and regulation of secretion growth hormone for enhancement of height and weight in those who suffer from weight loss.⁽⁶⁶⁾

Clinical evidence

A randomized, double-blinded controlled trial included 77 evaluable children, aged 24–64 months with undernutrition. They received cyproheptadine (CH) with multivitamin, or multivitamin over a period of four weeks. The weight, height and body mass index were measured at the baseline, four weeks after intervention and four weeks after discontinuation. A significant higher body mass index was observed among CH-treated patients after 8 weeks intervention with cyproheptadine compared with the control group ($P < 0.041$). Mean weight gain after eight weeks was 0.11 kg in the control group and 0.60 kg in the CH group. There were no significant differences at study termination in changes of weight and height velocity across the study between CH-treated and control group. Thus cyproheptadine promotes increase in body mass index in children with mild to moderate undernutrition after four weeks treatment.⁽⁶⁷⁾

A phase IV clinical study was conducted for evaluating the efficacy and safety of combination of Cyproheptadine in the treatment of undernutrition or anorexia in infants and children. Out of 322 patients, 279 patients completed the study. Safety assessment was made by inspecting the adverse events during trial. Efficacy assessment was made by analysis of increase in appetite and meal frequency. Result documented average increase in meal frequency and change in meal quantity (very low/low/moderate/high/very high) at three visit. As compared to

baseline visit, appetite shifted from very low and low to moderate and high appetite. Some patients even had very high appetite. The average meal frequency improved. Cyproheptadine is proved effective for the treatment of undernutrition or anorexia in infants and children by this trial.⁽¹⁾

Cyproheptidine HCl when prescribed for a patient with growth hormone insensitivity syndrome (GHIS) for increasing appetite, his height growth was surprisingly increased. Therefore, a study investigated the effect of Cyproheptidine on growth parameters of the patients with GHIS. Twenty patients were enrolled in two prospective cohorts at two different times. Fifteen cases were observed for 1.17 ± 1.3 years without treatment (observation period, OP). Then, Cyproheptidine was administered for 2.2 ± 2.7 years (treatment period, TP), and growth parameters were compared within these two periods. It was found that that cyproheptidine caused height growth in the patients with GHIS.⁽⁶⁸⁾

In a retrospective study it was found that use of cyproheptidine in combination with a specialized multidisciplinary interventional program is a safe and effective therapy in infants and young children with low appetite and poor growth.⁽⁶⁹⁾ Of the 127 patients in treatment owing to poor weight gain who received the cyproheptidine, 82 took the medication regularly. Of these, majority of parents (96%) reported a positive change in mealtime and feeding behaviors. A significant improvement in mean weight-for-age z scores (WtZ) was observed after starting Cyproheptidine when compared with the WtZ before treatment for those patients regularly receiving the medication. This effect was independent of patients' age and/or presence of an underline medical problem. No significant differences in mean WtZ were observed over time within the comparison group.

Use of cyproheptadine in cystic fibrosis patients was well tolerated, showing a significant weight gain and a significant increase in BMI after 12 weeks. A clinically relevant effect size for weight/age (z score) and body mass index for age (z score) was found. Such findings suggest that the prescription of cyproheptadine can be an alternative approach for patients who need nutritional support for a short period of time.⁽⁷⁰⁾

Conclusion

The management of anorexia depends on the specific underlying cause. Treatment strategies include, but are not limited to, pharmacologic therapy (e.g., infections, endocrinopathies), surgery/radiation (e.g., malignancy), behavioral therapy (e.g., depression, anorexia nervosa) and/or nutritional support (e.g., dementia, dysphagia). In addition to the prescription drugs, fish oil (eicosapentaenoic acid EPA), multivitamins, high protein and calorie diet has been recommended as an alternative or complementary treatment for improving the loss of appetite.

However some children are fussy eaters. Even though they do not have any disease they do not love to consume from family pot. Majority times we prescribe so called appetite stimulant which are Lysine containing multivitamin and minerals, nevertheless they are truly better placebo. It's an opportunity to go for anthelmintic as well. Proper nutritional advise, encourage active feeding and counseling are the major pillar to manage lack of appetite in children.

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Dear Doctor,

The increasing older adult population has led to encounter patients requiring treatment for unintended loss of appetite and weight loss. Another set of population who suffer from loss of appetite are children. It is crucial to know how to assess for, and diagnose unintended loss of appetite and weight, as well as understand the treatment options.

It is indeed a pleasure to present to you this QMR issue by Dr. Sunil Agarwalla, renowned pediatrician. In this issue, he is enlightening us on 'Loss of Appetite: Challenges and Considerations'.

I sign off by once again reminding you to continue sending in your comments and suggestion regarding the QMR. Do write to me at balaji.more@raptakos.com with your write ups, notes or tidbits on various topics of interest that can make for informative and interesting reading.

With best regards,

Dr. Balaji More

Vice President - Medical



Feedback form: April - June 2019
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