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Mechanisms of the anorexia of aging—a review

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Abstract Many, even healthy, older people fail to adequately regulate food intake and experience loss of weight. Aging-associated changes in the regulation of appetite and the lack of hunger have been termed as the anorexia of aging. The etiology of the anorexia of aging is multi-factorial and includes a combination of physiological changes associated with aging (decline in smell and taste, reduced central and peripheral drive to eat, delayed gastric emptying), pathological conditions (depression, dementia, somatic diseases, medications and iatrogenic interventions, oral-health status), and social factors (poverty, loneliness). However, exact mechanisms of the anorexia of aging remain to be elucidated. Many neurobiological mechanisms may be secondary to age-related changes in body composition and not associated with anorexia per se. Therefore, further studies on pathophysiological mechanisms of the anorexia of aging should employ accurate measurement of body fat and lean mass. The anorexia of aging is associated with protein-energy malnutrition, sarcopenia, frailty, functional deterioration, morbidity, and mortality. Since this symptom can lead to dramatic consequences, early identification and effective interventions are needed. One of the most important goals in the geriatric care is to optimize nutritional status of the elderly.

Keywords Elderly · Anorexia of aging · Appetite loss · Weight loss

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Introduction

Overweight and obesity remain a serious and growing problem in adult population. Meanwhile, the main concern in the elderly, especially in those of very advanced age and with multiple comorbidities, is reduced food intake and weight loss. The anorexia of aging is defined as age-related reduction in appetite and food intake, which occurs even in illness-free adults and in the presence of adequate food supply. It may result from physiological, pathological, and social factors and was first described by John Morley in 1988 (Morley and Silver 1988). The anorexia of aging is also present in healthy elderly persons (Rolls et al. 1995; Wurtman 1988). There is a distinctive difference between the anorexia of aging and anorexia nervosa. The latter is usually found in children and adolescents, is volitional and ego-syntonic, and leads to obsessional preoccupation with body image and body weight.

The anorexia of aging is a frequent condition in older people, occurring in approximately 20 % of this population (Donini et al. 2013). In developed countries,

approximately 85 % of long-term care residents, between 23 and 62 % of hospitalized elderly patients, and 15 % of community-dwelling older adults suffer from malnutrition (Ahmed and Haboubi 2010; Donini et al. 2003). The anorexia of aging, defined by the presence of decreased food intake or the presence of poor appetite, was found in more than 12 % of the older persons living in an Italian nursing home (Landi et al. 2013). In various geriatric settings of Italy, the overall prevalence of anorexia, based on estimates of low food intake, was 21.2 %, with higher values among hospitalized patients (34.1 % women and 27.2 % men in long-term facilities; 33.3 % women and 26.7 % men in rehabilitation and geriatric wards; 3.3 % women and 11.3 % men living in the community) and in the oldest persons (Donini et al. 2011). In another study in acute-ward and rehabilitations settings, Donini et al. found the prevalence of anorexia to be 33.3 % in women and 26.7 % in men (Donini et al. 2008).

Loss of appetite may lead to protein-energy malnutrition and weight loss. In older people, these are associated with numerous poor health outcomes (Soenen and Chapman 2013), including increased mortality. In the elderly, weight loss is associated with impaired muscle function, falls, decreased bone mass, immune dysfunctions, anemia, pressure ulcers, reduced cognitive functions, poor wound healing, delayed recovery from surgery, functional decline, and increased morbidity and mortality (MacIntosh et al. 2000). The decrease in food intake associated with anorexia leads to the frailty syndrome (Martone et al. 2013), which includes weakness, slowing, decreased energy, and lower activity and is associated with an elevated risk of catastrophic declines in health and functions.

While the anorexia of aging may have dramatic consequences, its mechanisms are still poorly understood. While several reviews on the anorexia of aging are already available (MacIntosh et al. 2000; Chapman 2004; Hays and Roberts 2006; Soenen and Chapman 2013), this article gives up-to-date information on a complex combination of low- (molecular) and high- (clinical) level mechanisms involved in the pathogenesis of the anorexia of aging.

Methods

The aim of this literature review is to present a summary of current knowledge on the physiological, pathological, and social mechanisms of the anorexia of aging. First, we have searched the EBSCO Medline and PubMed databases using the keywords anorexia and aging/ageing. No time limits were used. Two hundred seventy-three articles were identified (August, 2014). Next, additional publications were identified from the references of papers identified from the search and additional searches for individual queries. One of the authors was responsible for selecting the papers according to the inclusion criteria. We included articles on people above 65 years of age that assessed physiopathology, epidemiology, mortality, and treatment of the anorexia of aging. Also, articles on pathological causes of anorexia in the elderly and social causes of the anorexia of aging were included. As regards physiopathology, we included articles that studied age-related changes in appetite regulation, secretion of hormones related to appetite, the regulation of ingestion or intestinal motility, and age-related deterioration of senses. Studies on anorexia nervosa were excluded.

General mechanisms of the anorexia of aging

With advancing age, there is a decline in energy consumption (Wakimoto and Block 2001; de Boer et al. 2013), and depending on energy expenditure and on energy balance, older people may lose weight. It seems that there are two general mechanisms involved in the development of the age-related decline in appetite: (1) reduced drive to eat (hunger) resulting from lower energy requirements, and (2) more rapidly acting or more potent inhibitory satiety signals. During aging, reduced energy needs and expenditures lead to physiological reduction of energy intake. These changes are associated with alterations in body composition, with an increased proportion of body fat and decreased lean muscle mass and body water (Noel and Reddy 2005). However, in many older people, the reduction in energy intake (resulting from the loss of appetite) is higher than the reduction of energy expenditure, thus leading to weight loss. This transition from "physiological" to "pathological" anorexia is often associated with the occurrence of various pathological and social factors. It may also manifest problems associated with the regulation of energy homeostasis and the control of food intake. Next, the anorexia of aging leads to protein-energy malnutrition, further weight loss, and secondary complications (sarcopenia, frailty, comorbidities, and

finally—an increased mortality). A summary of mechanisms involved (individually or in combinations) in the development of the anorexia of aging (with non-physiological problems becoming increasingly frequent with aging) is shown in Table 1.

Physiological causes of the anorexia of aging

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 (De Castro 1996), drink less, and snack less between meals (Nieuwenhuizen et al. 2010). All of these translate into a reduction in calorie intake. One study reported a 25 % decrease in daily calorie consumption from 40 to 70 years of age (Di Francesco et al. 2007). 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 (Morley 1997). These changes are also found in healthy older people, in the presence of adequate food supply. Therefore, they indicate the presence of the physiological anorexia of aging. Most probably, these physiological changes result from a decline in total energy expenditure (TEE) with aging (Roberts et al. 1995) and lower lean body mass (LBM) resulting in lower caloric intake. Reduced TEE is due to a decline in physical activity and decreased resting metabolic rate.

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 (Di Francesco et al. 2006). When given a preload, older persons reported greater satiation, even when the preload consists of water, suggesting a failure of the energy-sensing mechanisms (Rolls et al. 1995). Clarkston et al. found that overnight fasted older individuals were less hungry, and after a standardized meal, they demonstrated a higher level of satiation than did young persons (Clarkston et al. 1997). Following underfeeding, young men developed hyperphagia and regained the weight loss, while older persons failed to increase food intake and failed to regain the body mass lost during underfeeding (Roberts 2000). Little is known why older people have reduced ability to increase their food intake appropriately after a period of limited food consumption (e.g., after a surgery, acute infection, or due to psychological factors, such as grief). Compared with younger adults, elderly people do not show a decrease in pleasantness of the eaten food taste ("sensory-specific satiety") (Rolls 1999). All these

Table 1 Mechanisms of the anorexia of aging

Physiological	Pathological	Social
Age-associated changes in taste and smell	Depression	Low income and poverty
Diminished appetite:	Dementia	Loneliness and social isolation, especially at mealtimes
• Changes in appetite-regulating peptides	Anxiety	Physical and psychological abuse
• Changes in gastrointestinal hormones	Psychosis and delirium	
Delayed gastric emptying	Behavioral disorders	
	Comorbidities:	
	• Gastrointestinal diseases	
	• Malabsorption syndromes	
	• Hypermetabolism (e.g., hyperthyroidism, acute and chronic infections)	
	• Other diseases (cardiovascular, respiratory, kidney, cancer)	
	Medications	
	Poor dentition	
	Ill-fitting dentures	
	Swallowing problems	
	Dietary interventions (low-fat, low-salt diets)	

evidences indicate that older people are less able to regulate weight when food intake is fluctuating and prove impaired homeostasis in a number of regulatory mechanisms.

Decline of senses

Perception of the hedonic qualities of food (its odor and taste) lessens when people get older due to physiological changes in smell and taste that occur with aging (Schiffman and Graham 2000). They result in food being less tasty and thus—less appreciated and consequently—affect food choice and limit type and amount of food eaten (Mulligan et al. 2002). Aging changes in the senses are very common and result from loss of sensory cells, loss of their sensitivity, but also from poor oral hygiene. 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 impairment (Doty et al. 1984). The high rate of anosmia in the elderly is suspected to be due to several factors, such as changes in the olfactory epithelium, reduced mucus secretion, changes in airway structure or epithelial thickness, and reduced regeneration rate in olfactory receptors (Welge-Lussen 2009). Also, the number and sensitivity of taste papillae is reduced with aging (Morley 1997). Reduced fat intake (and consequently reduced amount of body fat) in the elderly may be partly explained by the fact that fat affects the hedonic qualities of food to a lesser degree compared to younger adults (Kohl et al. 2013).

The increase in odor and taste thresholds (with sweet taste being less and salt test being most affected) that occurs with aging suggests a need for "richer" tastes of food for older persons. Taste and smell enhancers can reverse the decreased enjoyment of food in some older persons (Essed et al. 2009). These alterations also mean that improving visual presentation of food (e.g., meals that are familiar and recognizable—not mushed together) may be an easy and effective intervention in prevention and treatment of the anorexia of aging (Nijs et al. 2009).

Regulation of appetite

Due to limited space, we will briefly present physiological aspects of mechanisms involved in the 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 and complex interactions between the ventromedial hypothalamic nucleus (satiety center), the lateral hypothalamus (hunger center), and the arcuate nucleus. Detailed review of mechanisms involved in the regulation of appetite is available (Kalra et al. 1999) and is beyond the scope of this paper. We would like to focus on age-related changes, with a summary of changes in appetite-regulating mechanisms shown in Table 2. A thorough review of age-related changes in the secretion of hormones related to appetite was published by Malafarina et al. (2013). Changes in activity of and sensitivity to peptides regulating appetite and feeding are important factors of physiological reduction of appetite in aging. The exact nature of these changes is poorly understood; however, a general pattern is that the central feeding drive declines with age.

Opioids

The endogenous opioid peptides, β-endorphin, enkephalin, and dynorphin, stimulate feeding behavior and preferentially increase the ingestion of a high-fat diet through the κ receptor (Chang et al. 2007). As shown by Kavaliers and Hirst, the opiate-stimulated food consumption is reduced in older mice (Kavaliers and Hirst 1985), probably due to an age-related reduction in the number of opioid receptors. Younger rats are 10–100 times more sensitive than older animals to the suppressive effects of naloxone on feeding (Gosnell et al. 1983). A physiological decline in the opioid feeding system with aging may be responsible for the decline in fat intake that occurs in old humans, although data from human studies are limited. Silver and Morley demonstrated a decline in the effectiveness of naloxone to block fluid ingestion in older humans (Silver and

Table 2 Aging-related changes in peptides regulating appetite

↓ Sensitivity to opioids (β-endorphin, enkephalin, and dynorphin)[a]
↓ Expression and number of receptors for neuropeptide Y (NPY)[a]
↓ Expression and number of receptors for orexins[a]
↓ Expression of agouti-related protein (AgRP)[a]
↑/= Expression of cocaine- and amphetamine-regulated transcript (CART) (in men)
↑ Concentration of leptin (in men)
↓ Concentration of galanin (in women)

[a] Results mostly from animal studies; human studies are inconclusive

Morley 1992). However, since drinking is probably under control of the μ receptor, while the κ receptor is responsible for feeding control (particularly for fatty feeding drive (Morley 1997)), little is known whether there is a similar diminished role of opioids in appetite with aging.

Neuropeptide Y

Neuropeptide Y (NPY) is a 36-amino acid neuropeptide that is produced in various locations, including the hypothalamus. NPY is one of the most potent orexigenic agents and its effects are predominantly on carbohydrate-rich food. Results of studies on changes in NPY secretion with aging are inconclusive. NPY mRNA expression declines with aging in rats (Wolden-Hanson et al. 2004) and older rats show altered feeding responses to NPY (Blanton et al. 2001). It has been found that aging decreased the feeding and drinking effects of NPY in rats (Pich et al. 1992), but not in mice (Morley et al. 1987). While mRNA levels of NPY Y1 and Y5 receptors do not change in aging of rats, immunohistochemistry indicates that the number of hypothalamic neurons staining for Y1 receptor protein was greater in young compared with old rats (Coppola et al. 2004). Therefore, a decreased expression and number of Y1 or Y5 receptors in the hypothalamus cannot explain the attenuated responsiveness of old rats to NPY. In humans, NPY levels in the cerebrospinal fluid may be increasing with aging in women, but not in men (Taniguchi et al. 1994). However, other researchers observed a decline in plasma NPY levels in humans that significantly correlated with increasing age (Chiodera et al. 2000). In general, as compared to certain animal species, NPY seems to play less important role in the development of the anorexia of aging in humans.

Orexins

Two orexins (orexin-A and orexin-B, also named hypocretin-1 and hypocretin-2) are involved mainly in sleep, but also increase the craving for food. Their activity is inhibited by leptin (through the leptin receptor pathway) and activated by ghrelin and hypoglycemia. The function of the orexin system is diminished in old rats (Kappeler et al. 2003), probably due to age-related loss of orexin neurons (Kessler et al. 2011) and the decrease in the orexin-A receptor protein level in the hypothalamus (Takano et al. 2004). However, some authors found no age-related changes (Matsumura et al. 2002). No data from human studies are available.

Cocaine- and amphetamine-regulated transcript

Cocaine- and amphetamine-regulated transcript (CART) is a neuropeptide produced mainly by the hypothalamus neurons. Its anorexigenic activity results from the inhibition of NPY neurons. Results for age-related changes are inconclusive: some authors reported increased CART mRNA expression (Wolden-Hanson et al. 2004), while others found no changes (Kappeler et al. 2003). As shown by Sohn et al., testosterone may lower hypothalamic CART mRNA levels (Bender et al. 2014). Therefore, there might be aging-related increase of CART activity in males. However, a very recent study Armbruszt et al. showed that CART peptide expression in the nucleus accumbens is stable in adults and does not change with age (Armbruszt et al. 2015).

Agouti-related protein

Agouti-related protein (AgRP) is a neuropeptide produced in the brain by the AgRP/NPY neurons. AgRP is co-expressed with NPY and works by increasing appetite and decreasing metabolism and energy expenditure. Animal studies indicate that the expression of AgRP is decreased in older rats (Lin et al. 2014). Other authors found that fasting-induced changes in gene expression of AgRP is attenuated with aging, but older animals are more sensitive to the effects of AgRP than younger animals (Wolden-Hanson et al. 2004). No data for aging-related changes in AgRP levels are available for humans.

Leptin

Leptin is a hormone secreted by the adipose tissue and regulates the amount of fat stored in the body. Leptin decreases the sensation of hunger and food intake, but also adjusts energy expenditures. Carrascosa et al. published an in-depth review of the changes in the neuroendocrine control of energy homeostasis by leptin during aging (Carrascosa et al. 2009). Animal studies showed reduced anorexic and thermogenic effects of centrally administrated leptin in obese aged rats (Shek and Scarpace 2000). Results of human studies on changes in leptin concentration with aging are conflicting. Donini et al. found no differences in leptin levels

between older patients with or without anorexia (Donini et al. 2013). Perry et al. found increases leptin levels in middle age women, followed by a decline in older women (Perry et al. 1997). However, testosterone levels are inversely correlated with leptin concentration (De Maddalena et al. 2012), and in aging males, testosterone level decrease (and is strongly related with the development of sarcopenia) (Maggio et al. 2013). These results suggest a possible role for leptin in the physiological anorexia of aging in males, but not in females. Another possibility is that leptin levels are increased due to physiological increase in adiposity in older people.

Galanin

Galanin is a neuropeptide produced in the brain, but also peripherally, that has orexigenic activity. In rats, levels of circulating galanin do not change with aging (McShane et al. 1999) or may be increased in male rats (Kappeler et al. 2003). In humans, plasma galanin levels in postmenopausal women, both lean and overweight, were significantly lower than in young women (Baranowska et al. 2000). It was demonstrated that compared to younger subjects, older women but not older men have lower increase of growth hormone secretion after galanin treatment (Giustina et al. 1993). Therefore, it may be hypothesized that in women orexigenic activity of galanin diminishes with aging.

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 (Brogna et al. 2006). Age-related changes in other parts of the gastrointestinal tract seem to have less important impact on satiety signaling (MacIntosh et al. 2000) and early satiation in the older person appears to involve signals predominantly arising in the stomach (Morley et al. 1999). Therefore, increased satiation (resulting in reduced appetite) in response to a meal that is observed in older persons is predominantly due to signals from the stomach. Reduced compliancy of the gastric fundus underlies more rapid antral filling and earlier antral stretch (Sturm et al. 2004), which is the major factor responsible for sensation of fullness. The reduction in compliancy is probably a result of diminished effect of nitric oxide (Smits and Lefebvre 1995). Some authors state there are age-related changes in the cellular mechanisms controlling gastrointestinal smooth muscle contraction (Bitar and Patil 2004). Also, reduced receptive relaxation of the gastric fundus may play a role (MacIntosh et al. 2000). Overall, studies support the concept that reduced gastric relaxation resulting in early antral filling is a major factor responsible for early satiation in the elderly.

Gastrointestinal hormones

An excellent review of all major appetite-regulating gastrointestinal hormones was published by Murphy and Bloom (2006). Also, Atalayer et al. summarized age-dependent changes in peripheral factors regulating appetite in regards to their role in the etiology of anorexia of aging (Atalayer and Astbury 2013). Therefore, we will only briefly discuss the physiological role of these hormones and focus on the effect of aging on them. A summary of gastrointestinal mechanisms of the anorexia of aging is shown in Table 3. Similarly to other hormones and neuropeptides, studies of mechanisms discussed below must involve accurate body composition analysis due to strong correlations between body fat and levels of these substances. It is possible that many observed changes are not directly related to aging, but to changes in body composition.

Cholecystokinin The best-studied satiating hormone is cholecystokinin (CCK). It causes bile release, stimulates secretion of pancreatic enzymes, and inhibits food intake. Concentration of CCK is increasing with age, both in animals (Miyasaka et al. 1995) and in humans (Sturm

Table 3 Gastrointestinal mechanisms of the anorexia of aging

↓ Synthesis and muscle-relaxing effect of nitric oxide
↓ Fundus compliance and ↑ antral stretch
↑ Absorption of glucose and fatty acids
↑ Concentration of cholecystokinin
↑ Concentration of glucagon-like peptide 1 (GLP-1)
↑ Resistance to ghrelin
↓ Proportion of acylated to desacylated ghrelin (↓ orexigenic activity)
↑ Concentration of amylin
↑/= Concentration of peptide YY (PYY)

et al. 2003). This may be explained by an increase in circulating fatty acids in aging humans (Parker and Chapman 2004), which contributes to the increase in circulating CCK. Rodent studies have also demonstrated an increased satiating effect of cholecystokinin-octapeptide (CCK-8) in older animals (Silver et al. 1988). This effect was also confirmed in aging humans (Chapman et al. 2002, Tai et al. 2010). 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 β-cells in a glucose-dependent manner, slows gastric emptying, suppresses appetite, reduces concentrations of glucagon, increases insulin sensitivity, and stimulates glucose disposal (Lee and Jun 2014). 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, consequently decreasing hunger through increasing insulin sensitivity of certain brain areas, including the hypothalamus, which in turn mediates the onset of anorexia (Di Francesco et al. 2010). However, no difference between younger and older subjects in GLP-1 levels after intraduodenal infusions of lipid and glucose was also reported (MacIntosh et al. 2000).

Ghrelin Ghrelin is a peptide produced by P/D_1 cells in the gastrointestinal tract. It is a potent anorexigenic hormone, also regulating fat distribution and rate of use of energy. Levels of circulating ghrelin are lower in older compared to younger persons (Schneider et al. 2008), although some studies showed no differences (Vilarrasa et al. 2005). Donini et al. did not find differences in ghrelin levels between older patients with or without anorexia (Donini et al. 2013). Ghrelin administration increased the levels of nitric oxide synthase in the hypothalamus, which also supports the role of nitric oxide in central regulation of food consumption (Gaskin et al. 2003). Since the activity of nitric oxide synthase is diminished in aging (although human data are not conclusive), it may explain lower activity of ghrelin in older people. Another finding is that older persons have lower levels of acylated (orexigenic) ghrelin compared to desacylated (anorexigenic, although this is controversial) ghrelin (Rigamonti et al. 2002). Sturm et al. found that plasma ghrelin concentrations were much higher in the undernourished older women than in well-nourished older women and well-nourished young women, and ghrelin concentrations decreased more after food ingestion in the older compared with the young subjects (Sturm et al. 2003). The authors concluded that ghrelin activity is reduced in undernourished, older subjects due to marked ghrelin resistance or increased concentrations of inactive ghrelin.

Amylin Amylin is a peptide hormone co-secreted with insulin from the β-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 solitarus. In humans, amylin secretion exhibits a U-shaped curve with greater secretion in young and old subjects than in middle-aged persons (Citrome 2011). However, aging is also associated with changes in glucose metabolism due to increasing insulin resistance, and amylin may merely be acting as a marker of impaired glucose metabolism. Insulin is unlikely to play a role in the anorexia of aging in humans since insulin infusions within the physiologic range fail to alter food intake (Chapman et al. 1998).

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 (Di Francesco et al. 2005). However, plasma PYY concentrations did not differ significantly between older and younger subjects, indicating that changes in circulating PYY concentrations are unlikely to contribute to the anorexia of aging (Park and Bloom 2004).

Pathological mechanisms of the anorexia of aging

Depression

Depression is one of the most common reversible causes of anorexia and weight loss in elderly persons (German et al. 2011). Corticotropin-releasing factor (CRF) is a very potent centrally acting anorectic agent and thus may play an important role in the development of anorexia in this group of patients. Lack of appetite in

depressed patients is associated with increased concentrations of serotonin and CRF, probably due to increased ghrelin secretion caused by the stimulation of serotonin 5-HT_{2B} and 5-HT_{2C} receptors (Takeda et al. 2013). Older people suffering from depression show a higher degree of dysregulation of the hypothalamic-pituitary-adrenal axis activity compared with younger adults (Belvederi Murri et al. 2014) and consequently they eat less when depressed (Roberts and Rosenberg 2006).

Constipations are common in the elderly patients with depression (Simon et al. 1999). They may additionally contribute to decreased appetite due to a feeling of fullness. 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. Patients with severe depression may also refuse to eat and drink due to suicidal thoughts.

Finally, depression (especially in the older age group) is often associated loss of social networks, grief, and loss. This deterioration of social networks may lead to loss of appetite through various social factors, which will be discussed below.

Dementia

Dementias, particularly of the Alzheimer's type, are associated with loss of appetite and weight, with a nearly twofold increased risk of anorexia compared with non-demented subjects (Landi et al. 2013). Patients with dementia may experience both loss of appetite and/or forget to eat. Dementia may also affect processing of olfactory stimuli (Marine and Boriana 2014) and enhance physiological decline in smell. Also, demented patients may be indifferent to food. Many patients with dementia experience behavioral problems, commonly termed as the Behavioral and Psychological Symptoms of Dementia (BPSD) and occurring in up to 90 % of demented patients (Taemeeyapradit et al. 2014). Eating problems are one of the symptoms within this complex (van der Linde et al. 2014). Detailed biological mechanisms of anorexia in demented patients are unknown, but probably are associated with altered mechanisms regulating appetite and metabolism. A reduction of taste and smell, especially marked in Parkinson syndromes (Lang et al. 2006), may also play a significant role. Apraxia of swallowing is also seen. Important finding in various studies is that weight loss is present early in disease or even precedes dementia, suggesting weight loss as a preclinical marker of dementia (Salva et al. 2009).

Comorbidities

Any disease that impairs instrumental activities of daily living is associated with increased risk of anorexia (Donini et al. 2013). 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 constipations (causing a feeling of fullness). Important and frequent causes of both anorexia and cachexia are kidney and heart diseases, mainly chronic kidney disease (Luis et al. 2014) and chronic heart failure (Invernizzi et al. 2014). 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. Gastroparesis may also be caused by excessive consumption of alcohol, tobacco, and damage to the vagus nerve during abdominal surgery (Hasler 2008). 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.

Acute illness, such as viral or bacterial infections, is often associated with a spontaneous loss of appetite despite increased energy and nutrients requirements. Biochemical mechanisms of this phenomenon will be discussed in the next paragraph. It has been found, however, that 65 % of elderly men and 69 % of elderly women had an insufficient energy intake already in the month before hospitalization (Mowe et al. 1994). The

authors have found that this 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 (Laviano et al. 2002); neuropeptides, e.g., NPY (Laviano et al. 2008); proinflammatory cytokines, e.g., IL-1 and IL-6, and tumor necrosis factor (TNF)-alpha (Laviano et al. 2003); and neurotransmitters, e.g., serotonin and dopamine (Meguid et al. 2004). 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 $E_{1\alpha}$ (Morley 2001). 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 (Jiang et al. 2008). C-reactive protein (CRP) level is also higher in free living (Donini et al. 2013) or hospitalized subjects with the anorexia of aging (Donini et al. 2008). Raised CRP level may be an indicator of acute inflammation, but also may affect appetite more directly, via changes of testosterone levels. Del Fabbro et al. found an inverse correlation between testosterone and CRP levels in cachectic men with cancer (Del Fabbro et al. 2010). Chronic low-grade inflammation may also suppress appetite by activating serotonin system via increased level of tryptophan (Capuron et al. 2011).

The role of cytokines in the development of the anorexia of aging is additionally confirmed by the fact that many medications used or tested for treatment of this condition produce their effects by modulating cytokine production and/or activity (Thomas 2009). For example, thalidomide and pentoxifylline reduce levels of TNF-alpha by its inhibition and degradation. Oxandrolone reduces levels of TNF-alpha, IL-1, and IL-6. Treatment with megestrol is associated with a decrease in IL-6, soluble IL-2 receptors, and TNF receptor-p75. Also, apart from downregulating proinflammatory cytokines, megestrol may increase NPY levels (Deans and Wigmore 2005). Usually, these changes correlate significantly with weight gain. Finally, aging itself is a form of chronic stress and may be associated with low-grade inflammation (termed as *inflammaging*). 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.

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 (Dunn-Walters et al. 2004), all leading to malabsorption of carbohydrates, lipids, amino acids, minerals, and vitamins (Woudstra and Thomson 2002). Hypercalcemia may also cause anorexia, while gallstones may produce early satiety. Experienced gastrointestinal symptoms (e.g., dyspepsia, gastroesophageal reflux) may also limit food intake. Chronic constipations (reported in up to 25 % of the population over 65) also play a role here. Bacterial overgrowth is more common in the elderly and may cause both anorexia and malabsorption (Parlesak et al. 2003). Increased damage susceptibility of the elderly gastrointestinal tract (Newton 2004) will also affect nutrition via reduced absorption of nutrients. Oral tolerance (where oral feeding of a certain antigen can result in down-regulation of the response upon subsequent systemic challenge with the same antigen) is more frequently compromised in the elderly; a thorough review of this issue is available (Fujihashi and McGhee 2004). Effects of aging on intestinal permeability is sparsely documented; there is evidence to suggest that intestinal permeability is easily affected (e.g., by stress, diet, drug use) and therefore the aging gut will certainly be at risk of permeability dysregulation.

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 (Akamine et al. 2007). This is a significant problem, particularly because polypharmacy is common in the elderly (Gokce Kutsal et al. 2009). 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. A detailed list of these medications and a review of mechanisms involved in drug-induced taste disorders was published by Naik et al. (2010).

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 as a result of altered food choice in order to circumvent the effort involved in chewing using dentures (Donini et al. 2013). There are consistent decreases in the levels of nutrition seen in edentate individuals as compared to those who have full or partial retention of their teeth (Walls and Steele 2004). There is also significantly more food avoidance among the subjects with chewing problems, discomfort with dentures, or ill-fitting dentures (Altenhoevel et al. 2012). 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 (Boczko 2006). The most common cause of swallowing problems is stroke. Stroke and other neurological diseases (such as Parkinson's disease) may also affect manual dexterity, thus limiting abilities to prepare a variety of foods and requiring help when feeding.

Dietary interventions

Dietary interventions may also be another important iatrogenic factor contributing the development of the anorexia of aging. The presence of fat and salt in food is required for its taste and palatability. Therefore, restrictive diets, commonly prescribed by physicians, may have a detrimental effect on appetite. While such diets are important for younger adults, their efficacy and safety is questionable for the elderly, particularly in the light of age-related changes in taste threshold.

Social factors of the anorexia of aging

Improper food quality may limit its intake (Kim et al. 2010). These problems may often affect food served to nursing home residents. However, Johnson et al. demonstrated that residents fed with regular or pureed diets met recommended dietary allowances and diet consistency did not affect nutrient intakes (Johnson et al. 1995). Health status of an aging person has a direct effect on poor foods choice or availability—the more frail and physically disabled the person, the less able they are to shop or prepare food needed for a healthy diet. As demonstrated by Donini et al., some older people have inadequate dietary patterns and the variety of food consumed by older people is sometimes poor (low consumption of meat, fruits, and vegetables) (Donini et al. 2013). In many countries, poverty may be a major cause of such limitations. Age-associated dysregulation of the immune system of the gastrointestinal tract may affect tolerance to vegetables and fruits and thus limits their consumption. Also, low level of education and common incorrect beliefs regarding dietary restrictions may lead to poor selection of food.

Social environment may significantly affect meals size. People living alone and nursing care residents often miss company, conversation, and pleasant atmosphere during mealtimes. Meals eaten in the presence of more people, during weekends are larger by up to 40 % (de Castro 1991). Older people living alone, particularly men, eat less and have a significantly increased risk of poor nutrition (Hsieh et al. 2010). Recent bereavement, even if not complicated with depression, may alter the social meaning of eating and produce negative effects on eating behaviors and nutrient intakes (Fields and Goran 2000). This may trigger chronic and progressive loss of appetite since older people have reduced ability to increase their food intake appropriately after a period of limited food consumption. Thus, congregate meals and improved social context of food consumption may improve nutrient intake.

Important and often neglected cause of appetite and weight loss is elder abuse, which can also present with anorexia (Lindbloom et al. 2007). Verbal mistreatment was self-reported by 38 % of older adults (Fulmer et al. 2014), while it may also include other forms:

psychological abuse, physical abuse, financial exploitation, and caregiver neglect (Dong and Simon 2013).

Conclusions

Many, even healthy, older people fail to adequately regulate food intake. The etiology of the anorexia of aging is multi-factorial. Better understanding of the mechanisms of the anorexia of aging should enable the development of preventive and therapeutic strategies, leading to improved health and quality of life of older people. The differential diagnosis of appetite and weight loss in the elderly should include known physiological, pathological, and social causes of the anorexia of aging. However, the exact mechanisms of the anorexia of aging remain to be elucidated. Many neurobiological mechanisms may be secondary to age-related changes in body composition and not associated with anorexia per se. Therefore, further studies on pathophysiological mechanisms of the anorexia of aging should employ accurate measurement of body fat and lean mass, such as magnetic resonance, dual-energy X-ray absorptiometry, or body impedance analysis. Altered regulation of appetite in older people may result in serious consequences, such as protein-energy malnutrition, sarcopenia, frailty, functional deterioration, morbidity, and mortality. Therefore, careful monitoring and immediate preventive actions are required. Assessment of nutritional status is important to identify and treat patients at risk. For screening, the Mini Nutritional Assessment (MNA) is commonly used in clinical practice.

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Conflict of interest None to declare

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