REVIEW

Anorexia of Aging: Metabolic Changes and Biomarker Discovery

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Abstract: The age-associated decrease in appetite and food intake is referred to as "anorexia of aging". Older adults with anorexia show changes in the quantity/quality of energy supplied to the organism which eventually may cause a mismatch between ingested calories and physiological energy demands. Therefore, a state of malnutrition and impaired metabolism may ensue which renders older people more vulnerable to stressors and more prone to incur negative health outcomes. These latter cover a wide range of conditions including sarcopenia, low engagement in physical activity, and more severe consequences such as disability, loss of independence, hospitalization, nursing home placement, and mortality. Malnutrition has been recognized by the European Society of Clinical Nutrition (ESPEN) among the chief risk factors for the development of frailty. Frailty refers to a state of increased vulnerability to stressors stemming from reduced physiologic reserve, and according to ESPEN, is also nutrition-based. Alike frailty, anorexia is highly prevalent among older adults, and its multifactorial nature includes metabolic changes that develop in older age and possibly underly the condition. Circulating factors, including hormones (eg, cholecystokinin, ghrelin, leptin, and inflammatory and microbial mediators of gut dysbiosis), have been proposed as biomarkers for this condition to support early identification and develop personalized nutritional interventions. Additional studies are needed to untangle the interrelationship between gut microbiota and appetite regulation in older adults operating through brain–gut crosstalk. Furthermore, the contribution of the genetic background to appetite regulation and specific nutritional needs warrants investigation. Here, we provide an overview on anorexia of aging in the context of age-related metabolic changes. A special focus is placed on candidate biomarkers that may be used to assist in the early identification of anorexia of aging and in the development of personalized nutritional counseling.

Keywords: frailty, geroscience, inflammation, muscle, nutrition, sarcopenia

Introduction

Decreased appetite and reduced food intake are commonly observed in older adults. The term "anorexia of aging" has been introduced to refer to this phenomenon that renders older people more vulnerable to stressors and more prone to incur negative health outcomes (eg, poor quality of life, reduced survival).[1,2]

The age-associated decrease in food intake results in changes in the quantity/quality of energy supplied to the organism that may ultimately cause a mismatch between ingested calories and physiological energy demands. Therefore, a state of malnutrition and impaired metabolism may ensue with several negative health-related consequences. These cover a wide range of conditions spanning from declines in muscle mass/strength and low engagement in physical activity to more severe consequences, such as disability, loss of independence, hospitalization, nursing home placement, and mortality, with an overall increase in healthcare burden.[3–5]

The European Society of Clinical Nutrition (ESPEN) has recognized malnutrition among the chief risk factors for the development of frailty, a state of increased vulnerability to stressors stemming from reduced physiologic reserve,[6] thus making this condition also nutrition-based.[7,8]

Considering the high prevalence of anorexia in frail older adults and its multifactorial nature, we will frame anorexia of aging in the context of metabolic changes occurring in older age and possibly underlying this condition. A special focus will be placed on candidate biomarkers that may help support early identification of anorexia of aging and develop personalized nutritional counseling.
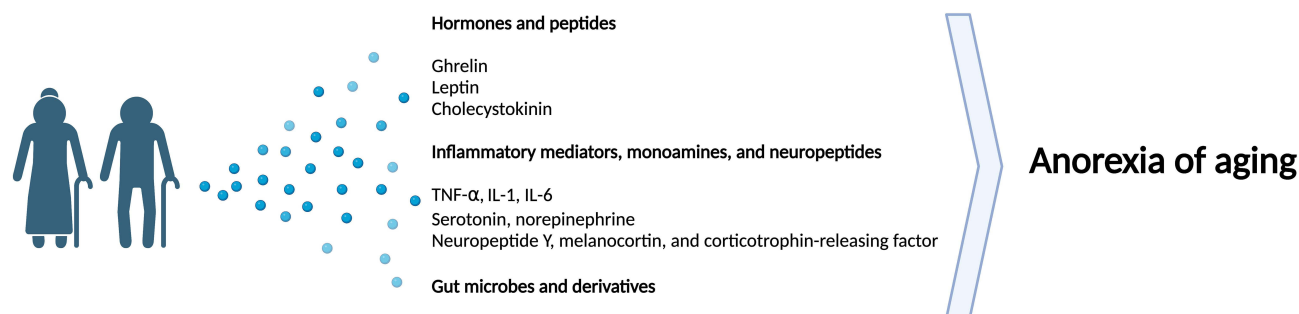
Anorexia of Aging: Prevalence, Causes, and Risk Factors

The prevalence of anorexia in older adults is rated at about 20% and varies according to setting, gender, and comorbidities.[9] A higher prevalence of anorexia is observed among people older than 65 living in long-term institutions, hospitalized, or suffering from neurological disorders and/or inflammatory conditions.[5,10] Anorexia has a multifactorial etiology encompassing both age-associated changes in peripheral and central physiological processes and the co-occurrence of pathological conditions.[2,5,11] Declines in sight, smell, and taste occurring during aging are only a few of the age-related changes implicated in the development of anorexia.[12] Factors related to poor oral health such as inadequate dentition, poor fitting dentures, inflammatory diseases of the oral cavity, and difficulties in chewing and swallowing limit food choices and contribute to reducing food intake in older adults.[2] Socioeconomic factors (eg, living alone, low-income status) and the associated downside of reduced psychological well-being may also contribute to the development of anorexia of aging. However, recent evidence suggests that malnutrition in older adults is not necessarily dependent on socioeconomic factors.[13] Psychological factors (ie, depression) negatively impact the quality and quantity of food being consumed.[14] The Avoidant Restrictive Food Intake Disorder (ARFID) has been reported among older people and associated with avoidance of specific foods for different reasons (eg, fear of choking).[14]

As a whole, these factors are crucial for the assessment and management of anorexia of aging. However, endocrine, metabolic, and nutritional changes that accompany aging have emerged as relevant factors that may allow a better framing of anorexia in the context of age-associated metabolic milieu and will be discussed in more detail in the next sections.

Metabolic Changes of Anorexia of Aging: A Role for Cholecystokinin, Ghrelin, Leptin, and Gut Dysbiosis

Modifications occurring at the gastric level during aging lead to altered regulation of appetite-related signaling.[15] The physiology of the gastrointestinal tract becomes compromised with age, with a decrease in muscular tone and motility as well as reduced activity of visceral neurons and altered distension of the stomach (ie, fundus and antrum). The delay in gastric emptying observed in older people may explain longer-lasting satiety, which in turn contributes to reduced appetite.[15] The reduced digestive ability of the stomach may further aggravate the lack of appetite and reduced food intake in older persons. As part of the changes occurring in the gastrointestinal system during aging, hormonal alterations have been observed and likely modulate the function and activity of brain circuits that regulate appetite/satiety (Figure 1).[2,5,11] Among the age-associated hormonal perturbations are those related to the circulating levels of several gastrointestinal mediators including cholecystokinin (CCK), peptide tyrosine (PYY), glucagon-like peptide 1 (GLP1), gastric inhibitory polypeptide (GIP), and ghrelin.

Hormones and peptides

Ghrelin
Leptin
Cholecystokinin

Inflammatory mediators, monoamines, and neuropeptides

TNF-α, IL-1, IL-6
Serotonin, norepinephrine
Neuropeptide Y, melanocortin, and corticotrophin-releasing factor

Gut microbes and derivatives

Anorexia of aging

Figure 1 Schematic representation of major biological factors involved in anorexia of aging. Created with BioRender.com, accessed on 11 November 2022.
Abbreviations: IL, interleukin; TNF-α, tumor necrosis factor alpha.

Studies have reported a significant increase in circulating levels of CCK in older adults.[16,17] CCK, also called pancreozymin, is an appetite-regulating peptide hormone that stimulates digestion of fat and proteins and regulates satiety. CCK is produced by the enteroendocrine cells of the first segment of the small intestine following the transit of lipids and proteins into the stomach. CCK is considered to be a major player in appetite loss in aging. In particular, a study investigating the effects of infusion of exogenous CCK in young and old individuals indicated that CCK induced a greater satiety effect in older than younger adults.[16] Older people also showed higher endogenous levels of CCK during fasting and following low-calorie meals. Despite high levels of CCK, older adults retain sensitivity to the satietogenic effects of CCK, thus indicating that higher CCK activity may compromise appetite in older adults.[16] In light of these observations, CCK antagonists have been proposed as therapeutic strategies that may help improve appetite in anorexia of aging.[16]

Reduced secretion of the orexigenic hormone ghrelin by the enteroendocrine cells of the gastrointestinal mucosa may also have an impact on dietary habits and behaviors of older adults. Ghrelin is secreted by the stomach, and its synthesis and release are triggered by fasting. Ghrelin release is under the control of ghrelin O-acyltransferase (GOAT) that acts on pro-opiomelanocortin neurons and the agouti-related protein neurons/neuropeptide Y-containing cell bodies of the hypothalamic arcuate nucleus. Albeit plasma concentrations of total ghrelin and acyl-ghrelin do not show variations with aging,[18] positive effects of the non-peptide, orally active ghrelin agonist anamorelin on appetite stimulation and body composition have been described.[19] Mitigation of lack of appetite and muscle loss have also been reported in tumor-bearing mice via the same signaling pathway.[20] Results of anamorelin administration to cancer patients with cachexia are mixed.[21,22] The possibility to exploit ghrelin agonists as a therapeutic strategy in anorexic older adults warrants further investigation.

The release of ghrelin is negatively modulated by circulating levels of leptin and insulin which may be higher in older adults due to central and peripheral resistance to these hormones.[2,5,11,23] Leptin is a hormone released by adipose cells and enterocytes of the small intestine that can signal at the level of central nervous system. Leptin is a marker of energy storage, and high circulating levels of this mediator indicate overt adiposity. Leptin signaling is involved in long-term control of food intake.[24] Older adults show higher circulating levels of leptin during fasting compared with younger people and no changes in serum levels of this mediator in post-prandial conditions.[25] Although young and old participants were not matched by body mass index (BMI), BMI values were not significantly different between age groups.[25] Moreover, while hunger feeling was inhibited after the prandial period in older adults, ghrelin levels remained unchanged.[25] A recent study on the effects of short-term administration of the recombinant leptin analogue metreleptin in patients with anorexia nervosa indicated that this molecule was able to favor weight gain and increase appetite, possibly through amelioration of cognitive and emotional symptoms.[26] Additional studies are needed to confirm this finding and explore whether the potential benefits of therapeutics based on leptin analogues can also be obtained in anorexia of aging.

Among the so-called hallmarks of aging, chronic low-grade inflammation involving high levels of pro-inflammatory interleukins (ILs) (ie, IL-1 and IL-6) and tumor necrosis factor alpha (TNF-α), is a major determinant. These mediators of inflamm-aging have been implicated in appetite reduction via regulatory pathways operating both at central and peripheral levels.[27,28] Their involvement in the reduction of gastric emptying and intestinal motility while conveying anorexigenic signals at the level of the hypothalamic neurons and other orexigenic brain areas has been reported.[27–29] Therefore, dysregulation in IL-1, IL-6, and TNF-α signaling can be considered a promoter of nutritional disarrangements and, ultimately, anorexia of aging (Figure 1).[29] An association between poor appetite and reduced food intake with inflammation has also been documented in hospitalized older adults, indicating that inflammation may be a relevant mediator in the development of malnutrition in this setting.[30] More recently, the growth and differentiation factor 15 (GDF15), a cytokine member of the transforming growth factor beta family, has been associated with anorexia, weight loss, and reduced survival in cancer patients and tumor-bearing rodents.[31] Circulating levels of GDF15 increase during aging, which has been linked with reduced physical performance and physical frailty.[32] Whether these associations are, at least partly, mediated by the anorexic effect of GDF15 needs to be established. Other mediators such as monoamines (ie, serotonin and norepinephrine), neuropeptides (ie, neuropeptide Y, melanocortin, and corticotropin-releasing factor) have

also been included among the central regulators of appetite.[33,34] Perturbations in circulating levels of these mediators during aging may contribute to anorexia.[33,34]

Alterations in gut microbiota have gained increasing attention as per their implication in age-related appetite dysregulation (Figure 1).[35] Gut microbes influence a large set of body activities (eg, host–gut functions, endocrine and immune system) via gut–brain crosstalk.[36,37] Among the major changes observed in gut microbiota during aging are the shift in taxonomic composition and decrease in microbial richness and diversity which have been associated with frailty and malnutrition.[38–41] Variations in gut microbiome composition have also been associated with appetite status in older adults living in the community.[42] Associations between alterations in gut microbiota and poor appetite have also been reported in people with eating disorders (ie, anorexia nervosa, bulimia) or cancer,[43,44] and bacterial products have been attributed relevant roles in modulating satiety via the activation of arcuate pro-opiomelanocortin neurons.[45,46] Metabolic fluctuations over the 24 hours that are observed in physiological systems and thus under the control of intracellular circadian clocks have been reported to be altered during aging and should be taken into account while studying anorexia of aging.[47,48] For instance, circadian dysfunction of leptin has been linked to leptin resistance,[49] a possible contributor to anorexia of aging.

The modulation of low-grade inflammation has been indicated as a therapeutic target to improve nutritional disarrangements in older people. Although more conclusive studies are needed, a set of nutraceuticals including omega-3 fatty acids and vitamins (ie, vitamin B12 and D) have been tested for their potential to attenuate inflammation.[5] Results from a systematic review and meta-analysis have indicated that, more than one specific compound, the Mediterranean dietary patterns, which include foods rich in fat and dense in nutrients administered in a moderate volume, is associated with lower inflammation in older adults and contributes to healthy aging.[50,51]

Additional studies also evaluating the interrelationship between gut microbiome and appetite in older adults likely acting through brain–gut axis are needed. As a new frontier in the evaluation of these changes, the advent of next-generation sequencing approach enabling the identification of the genetic profile of individuals and how this may contribute/relate to nutritional needs (ie, nutrigenomics) holds promise for the field.

Biomarkers of Anorexia of Aging: Differences and Similarities with Other Age-Associated Conditions

Aging is a major risk factor for the development of multiple diseases, which may have a direct or indirect impact on nutritional status. Indeed, chronic and acute disease conditions (eg, acute and chronic inflammatory conditions, hyperthyroidism, chronic obstructive pulmonary disease, cancer, heart failure, gastrointestinal diseases with or without malabsorption) may induce nutritional disarrangements that may lead to appetite suppression, inflammatory load, malabsorption and micro- and macronutrient deficiencies, and/or increase in body energy needs.[2,52]

The co-existence of several disease conditions in older people requires consumption of multiple medications that may have negative effects on appetite, food intake, and nutritional status.[53] For instance, cancer chemotherapy agents are well-documented inducers of lack of appetite, nausea, and vomiting. Also, therapeutics for rheumatoid arthritis (ie, penicillamine) decrease gastrointestinal tract absorption and zinc bioavailability and cause dysgeusia. Antacids, including aluminum hydroxide and calcium carbonate, may lead to gastrointestinal problems in older persons. Mobility limitations also impact food consumption through interfering with independent grocery activities, cooking, and eating.[3,54] Hearing and vision impairments may further reduce the functional abilities of older people[55] and, therefore, impinge on their nutritional status.[56,57] However, data on the relationship between sensory impairments and anorexia of aging are not conclusive and the subject needs to be further explored.[58]

As previously mentioned, frailty has been linked to anorexia of aging. Frailty develops independent of chronological aging or specific diseases and can culminate into negative health-related events.[59] Conceptualizations of frailty continue to emerge.[60] However, its theoretical framework has been developed mainly based on two seminal models. The first, by Fried et al,[61] is built on five pre-defined elements: 1) unintentional weight loss; 2) dynapenia; 3) fatigue; 4) poor mobility; and 5) inactive lifestyle.The second, by Rockwood et al,[62] is based on the deficit accumulation paradigm and, in its original formulation, includes 70 items. Regardless of the assessment tool, clinical manifestations of frailty arise from multi-system

dysregulations.[6] In particular, stress-response and metabolic signaling are progressively lost in efficiency as we age[63] and, passed a specific threshold, can compromise resilience and impair function.[6] The unintentional weight loss that marks frailty is also a feature of anorexia of aging and the two conditions largely overlap. For instance, frailty was observed in over 20% community-dwelling older adults with anorexia, while only 8.4% of the older people without anorexia were frail.[8] In another study, the association between frailty and malnutrition was explored in community-dwelling older people from the Singapore Longitudinal Aging Study 1.[64] Prefrailty or frailty was associated with malnutrition in 23% of the participants. Notably, frail participants with malnutrition had higher rates of disability, poor quality of life, and mortality compared with those without nutritional problems.[64] Finally, anorexia of aging has also been associated with sarcopenia in old community-dwellers.[65]

A set of cellular processes originally introduced as pillars of aging (ie, genomic and epigenetic instability, telomere attrition, altered nutrient sensing, loss of proteostasis, mitochondrial dysfunction, cellular senescence, decreased stemness, and altered intercellular signaling) are now recognized as mechanisms contributing to the pathophysiology of frailty and sarcopenia.[63] Efforts have been made towards the incorporation of as many markers as possible pertaining to these processes in complex statistical models that may help identify pathways involved in the pathophysiology of frailty and sarcopenia.[66,67] With a similar intent, a recent systematic review and meta-analysis on shared biomarkers between frailty and sarcopenia in older adults was performed.[68] As a result of this analysis, biomarkers belonging to inflammatory, metabolic, hematologic pathways were retrieved as the most relevant mediators associated with frailty and sarcopenia that may explain their clinical overlap.[68]

The early identification of older adults at risk of or with malnutrition is crucial to mitigate the impact nutritional deficits on health status and quality of life. The analysis of metabolic mediators associated with anorexia of aging through comprehensive approaches like those tested in other geriatric conditions (ie, frailty and sarcopenia) may provide great support.

Conclusion

Anorexia is a highly prevalent condition among older adults, and its multifactorial etiology includes a set of metabolic changes that accompany the aging process. Circulating mediators, such as cholecystokinin, ghrelin, leptin, and inflammatory and microbial mediators of gut dysbiosis, have been proposed as biomarkers for the condition and may help identify anorexia of aging at an early stage and develop personalized nutritional counseling. Studies investigating the interrelationship between gut microbiota and appetite regulation in older adults as well as establishing whether the genetic background may influence the nutritional needs are highly sought after.

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