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Review

Endocrinological and Nutritional Implications of Anorexia of Aging

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Abstract: Poor appetite—known as anorexia—is a common condition in aging and is associated with poor outcomes, including reduced survival and impaired quality of life. The anorexia of aging is mainly the result of several complex endocrinological, metabolic, and nutritional changes occurring with later age. The modulation of different peptides and hormones has been identified as an important determinant for the development of low appetite; in particular, an altered imbalance of plasma ghrelin, leptin, and cholecystokinin and increased inflammatory markers are implicated in its pathophysiology, and robust evidence of their involvement in anorexia of aging has been produced in the clinical setting. More recently, researchers identified that the gut microbiome composition significantly varies according to the appetite status. Other important clinical factors may worsen the symptoms of the anorexia in the elderly, in particular the potential concomitant presence of chronic catabolic comorbidities. Importantly, data indicate that anorexia is prevalent in frail older adults, negatively impacting body composition and specifically in altering muscle mass and function. For all these reasons, a prompt and early diagnosis of anorexia in the elderly is crucial to implement personalized metabolic and nutrition interventions to improve the outcomes and ameliorate quality of life.

Keywords: anorexia of aging; appetite; hormones; peptides; inflammation; sarcopenia; frailty

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1. Introduction—Prevalence and Impact of Anorexia of Aging

Anorexia of aging is considered an unvoluntary progressive loss of appetite affecting food intake and therefore negatively impacting on nutritional and metabolic status [1]. In community old dwellers, the loss of appetite is particularly frequent with a prevalence ranging between 9% and 25% [2–4]. The prevalence of anorexia increases in older adults hospitalized, accounting for approximately 56% [5] and is a symptom present during several chronic and acute diseases, including cancer, chronic kidney disease, and infections. In this case, the loss of appetite is generally known as "secondary anorexia" or "disease-associated anorexia", which may overlap with an already existing low appetite and further decrease it in the elderly population, although it represents a phenomenon determined by changes in different metabolic patterns, which are mainly driven by the underlying disease [6]. According to the "ESPEN guidelines on definition and terminology of clinical nutrition", anorexia is a common clinical manifestation of both the diseases-related malnutrition (DRM) with inflammation and without inflammation [1]. Importantly, anorexia of aging is associated with worse outcomes including decreased survival [3] and poor quality of life [7]. In particular, poor appetite represents a risk factor for the development of frailty [8], i.e., a geriatric syndrome characterized by a state of vulnerability with reduced capacity of response to stress [1]. Frailty, as well as anorexia of aging, is highly associated with advanced age, even though it is possibly influenced by lifestyle changes, such as implementation of diets. In this light, the European Society of Clinical Nutrition (ESPEN) has considered frailty a nutrition-related condition [1].

The anorexia of aging represents one of the multiple factors determining metabolic, endocrinological, and nutritional derangements in older adults associated with a worse prognosis. A greater understanding of the endocrinological and nutritional implications of poor appetite in older people may help to develop effective therapeutic strategies to counteract metabolic derangements in this setting.

By the present narrative review, we aimed to analyze robust evidences available on the most relevant endocrinological and metabolic changes occurring during anorexia of aging and how poor appetite in this setting may affect clinical outcomes.

2. Endocrinological and Metabolic Changes Promoting Anorexia of Aging

The pathogenesis of poor appetite in the elderly is multifactorial, including endocrinological and metabolic alterations as well as psychological and social aspects that can all coexist with other pathological conditions [7,9].

The modulation of several hormones and peptides represents a crucial point for the development of anorexia of aging, as shown in Figure 1.

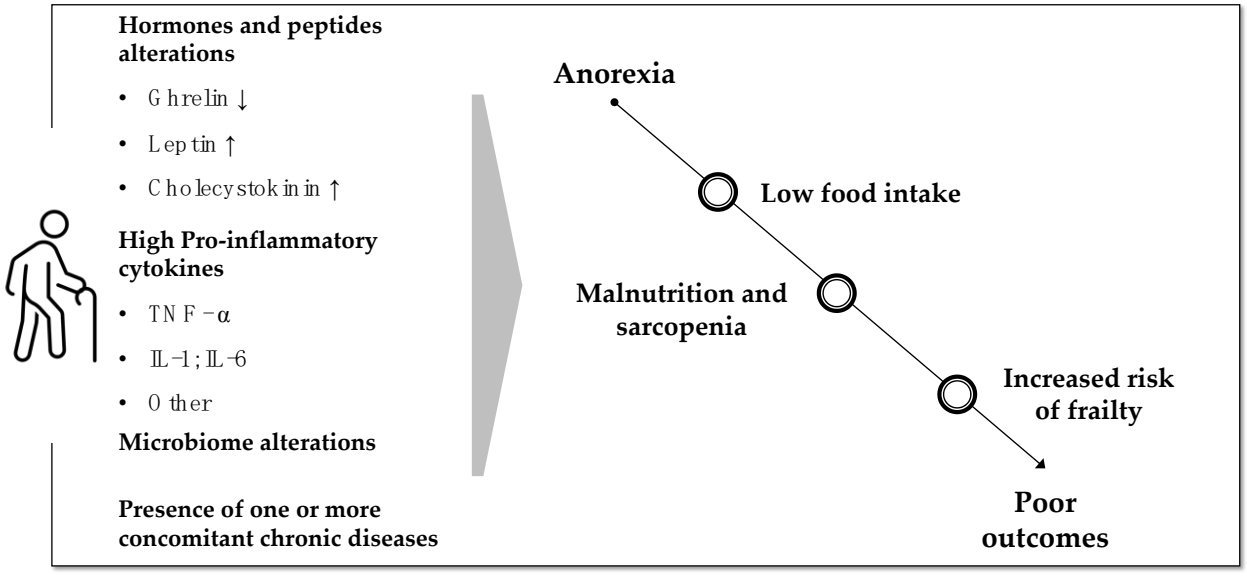

Figure 1. Summary of the main mechanisms determining the anorexia of aging and the clinical consequences.

2.1. Ghrelin

Ghrelin is considered an important orexigenic hormone, and the comprehension of its metabolic pathways appears fundamental for the development of novel and effective therapies for the treatment of anorexia in particular during wasting diseases [10]. In physiological conditions, it is secreted by the fundus of the stomach, and fasting promotes its synthesis and release. In particular, ghrelin is acylated by the ghrelin O-acyltransferase (GOAT), and this form determines the orexigenic stimulation acting on arcuate pro-opiomelanocortin (POMC) and AgRP/NPY neurons [11]. The circulating levels of ghrelin presented circadian fluctuation associated with mealtimes, increasing during the pre-prandial period and, in turn, decreasing after a meal [12]. There is a paucity of data available in the literature on the role of ghrelin in healthy older adults.

Hickson et al. produced results on the concentration of total ghrelin and acyl-ghrelin in plasma of healthy adults, observing no differences in ghrelin or acyl-ghrelin levels according to the age of the participants [13]. However, there are robust evidences on the efficacy of molecules acting as ghrelin agonist drugs, such as anamorelin, in increasing food intake and ameliorating body composition, in particular increasing muscularity, although in disease-associated wasting [12]. Experimental data have shown important effects of a ghrelin agonist not only on appetite stimulation but also on the mitigation of muscle

loss in tumor-bearing mice [14]. However, in patients with cancer, anamorelin showed limited effects on lean body mass improvement and no effects on muscle functionality (e.g., hand grip strength) [15]. In this light, the possibility to use ghrelin agonists in anorexic older people might represent a therapeutic strategy to implement nutritional status in this population, but additional clinical data are needed to consider the use of ghrelin agonists in this setting.

2.2. Leptin

Leptin is a cytokine mainly produced by the adipocytes acting on the central nervous system as a sign of adequate energy storage. In fact, increased circulating leptin levels physiologically are indicators of abundant adiposity [16]. Importantly, leptin is considered to be more involved in long-term food control rather than in short-term reduction of food intake [16]. In humans, circulating fasting leptin levels were observed to be significantly increased in older healthy adults when compared to younger people [16]. Di Francesco et al. [17] investigated the serum leptin and ghrelin levels after a meal and their relation with appetite, observing that healthy older adults presented with an increased concentration of circulating leptin with respect to younger adults, but no changes in serum levels were detected after a meal. Although hunger sensation was inhibited after the prandial period in older adults, ghrelin levels resulted not affected [17].

Interestingly, novel data on metreleptin, an analogue of human leptin, showed that this molecule was effective on modulating positively appetite in anorexia nervosa [18]. Although these preliminary data were obtained in a very different setting [18], further research may focus also on the potential implication(s) of leptin analogues in anorexia of aging.

2.3. Cholecystokinin

In different clinical studies evaluating appetite modulation, cholecystokinin (CCK) was observed significantly elevated in elderly [19–21]. CCK is an appetite-regulating hormone that stimulates satiety. It is produced by the small intestine mainly in response to lipids and proteins transiting in the stomach. In this light, CCK was considered crucial in the development of the loss of appetite during aging. Macintosh et al. considered two groups of individuals (younger vs. older adults) receiving an infusion of exogenous CCK, and they observed [19] that in older adults, CCK induced a greater satiety effect compared to younger subjects. Moreover, the older group showed higher endogenous CCK levels both during fasting and after a low-calorie meal with respect to younger adults [19]. In addition, it was shown that despite higher circulating CCK levels, older adults are able to retain their sensitivity to the satietogenic effects of exogenous CCK, suggesting that enhanced CCK activity may worsen appetite in the elderly [19]. In this light, Macintosh et al. speculated that there may be a potential therapeutic role for CCK antagonists to ameliorate appetite in the elderly [19].

2.4. Inflammation

In the field of "geroscience", a pivotal aspect inducing several metabolic changes is represented by increased inflammatory status [22]. In fact, inflammation is considered a "mechanistic pillar" of geroscience [22], i.e., a mechanism contributing to the aging process, as well as stress and epigenetics alterations [22]. Inflammation in the elderly, also known and "inflammaging", is considered of low-grade and not provoked by infective or non-infective diseases [19]. In the hospital setting, recent data showed an association between high C-reactive protein levels and low appetite, and also inflammation was independently associated with anorexia and low food intake [5]. As biohumoral indicators of low chronic inflammation, in older adults, we often observe increased levels of different cytokines, including TNF-alpha, IL-1, and IL-6, which may negatively affect appetite homeostasis [23], promoting anorexia of aging and several nutritional derangements [24]. In fact, orexigenic hypothalamic neurons can be stimulated by these cytokines, in particular

by IL-1 [23]. Understanding the role of these inflammatory pathways may be relevant for the comprehension of the pathophysiology of the anorexia of aging and to target these factors to tackle malnutrition in older subjects. In this light, there are several data in the literature indicating that the modulation of low-grade inflammation appears crucial to improve appetite, in particular by using some nutraceuticals that may be useful in the elderly, including omega-3 fatty acids and multivitamins, in particular vitamin B12 and vitamin D [25].

2.5. Microbiome

Recently, changes in the microbiome have been indicated as possible contributing factors in the development of low appetite in aging [26,27]. In particular, Cox et al. firstly observed that in old community-dwellers, the gut microbiome composition varied according to the appetite status [27]. The association between poor appetite and microbiota alterations was also observed in other conditions, such as anorexia nervosa, bulimia, and cancer [28,29]. In particular, it was shown that bacterial products, such as the caseinolytic peptidase B protein homologue (ClpB) may modulate satiety signals by the activation of POMC neurons [26,30].

2.6. Thyroid Function and Other Factors

Modifications in thyroid hormone levels may be present in older adults. In particular, it is well-known that an age-associated increase in serum TSH is frequent in older individuals who may not apparently present thyroid diseases [31]. However, hypothyroidism is often associated with loss of appetite in the elderly and with changes in body composition in particular with increased fat mass accumulation [32]. The hypothalamic–pituitary–thyroid axis plays a crucial role on energy expenditure, in particular influencing directly food intake and body weight not only by the peripheral effects of thyroid hormones but also through their direct action on the central nervous system, modulating the activity of POMC and AgRP/NPY neurons [33]

Based on these data, anorexia of aging may be considered as the result of deep changes, among others, of hormones (including thyroid), peptides, as well as inflammation and alterations in intestine bacterial products whose mechanisms of action and their potential interaction should be further clarified.

In particular, Kamva et al. [34] described the complex relation between anabolic hormones, glucocorticoids, and low vitamin D levels on nutritional and performance status in aging unrevealing potential implications of these hormones in appetite dysregulation.

We should also consider that anorexia of aging may be, at least in part, determined by the negative effect of multiple drugs on appetite regulation that are very frequently administered in this setting.

3. Differences and Overlap between Anorexia of Aging and Disease-Associated Anorexia in the Elderly

The anorexia of aging was considered as a "physiological syndrome" that is not determined by a specific underlying disease but due to several factors belonging to the advanced age [35]. However, the loss of appetite is a particularly frequent condition during the course of many chronic and acute diseases. In this light, anorexia of aging belongs to the DRM without inflammation, although it may be present also during chronic or acute diseases (often associated with inflammation), worsening the appetite status of older individuals. The disease-associated anorexia was extensively investigated in several catabolic conditions in terms of its pathophysiology and clinical impact. In specific conditions, such as cancer, anorexia may represent a strong indicator of poor prognosis. Differently from anorexia of aging, cancer anorexia recognizes different factors driven by tumor metabolism as triggers of this condition, such as pro-inflammatory cytokines [6], growth differentiation factor-15 [36], and lipocalin-2 [37]. Moreover, in advanced cancer patients, the worsening of nutritional status may be refractory to nutritional intervention [38]. This aspect represents one of the main differences between disease-associated anorexia and anorexia of aging,

which is the form of poor appetite where the nutritional intervention is often more effective. In fact, in wasting conditions, anorexia is associated with body weight loss, and for this reason, it may be considered as the result of a high grade of inflammation, including neuroinflammation, and of the catabolic stimulus underlying the disease, whereas anorexia in older age, without an associated catabolic disease, may be considered the main driver of low food intake determining, in turn, body weight loss.

In summary, although the nutritional intervention is crucial in both conditions, in older adults with anorexia of aging, we may expect a greater response to the nutritional intervention with respect to patients with the same phenotype (i.e., loss of appetite and clinical signs of malnutrition) but with the presence of a wasting chronic disease that may induce a clinically relevant catabolic state.

4. Can We Consider Anorexia of Aging a Component of Frailty?

All the endocrinological and metabolic alterations previously described are considered the main causes of anorexia in older adults and, in turn, low food intake. The main consequence of low food intake is the reduction in total energy and protein intake (named as hypophagia), leading to poor nutritional status. As we previously indicated, this form of malnutrition was considered by ESPEN as the one "without inflammation", although we believe that low-grade inflammation may play some role in the development of this phenotype.

In the elderly population, a large number of individuals can be defined as frail [39]. Frailty is considered as the reduction over time in the efficacy of homeostatic systems determining increased vulnerability and poor outcomes [39]. The phenotype model is one of the most used in the clinical setting, taking into consideration five items: weight loss, exhaustion, low energy expenditure, slow gait speed, and reduced grip strength [40]. Prefrail is defined with the presence of one or two of these aspects, whereas people with $\geq$3 of these are considered frail [40]. Considering that anorexia is one of the main causes of body weight loss, we may assert that anorexia of aging appears, at least in part, related to frailty. In fact, in a cohort of community old-dwellers frailty was present in 20.3% of dwellers with anorexia, whereas it was present only in 8.4% in the group without anorexia [8]. In the same cohort, older adults with appetite loss presented with increased prevalence of disability with respect to those without anorexia [8]. Importantly, the anorexia of aging may affect disability by an indirect relationship via frailty [8].

Wei et al. [41] investigated the association between frailty and malnutrition in 2804 community-dwellers in Singapore. Patients with both a status of malnutrition or risk of malnutrition (assessed by Mini Nutritional Assessment—Short Form) and prefrail or frail constituted 23%. Individuals in this group presented an increased rate of disability, poor quality of life, and increased mortality with respect to fit people with a normal nutritional status [41]. Importantly, the authors indicated that the majority of the reported negative outcomes attributed to malnutrition often seemed to be more associated with the presence of frailty [41]. Therefore, it was suggested that prefrail/frail older individuals with altered nutritional status might be targeted for nutritional treatment to improve the outcomes [41] (as we summarized in Figure 1).

Indeed, when body weight loss is present, we expect that changes in body composition may occur. In the elderly, anorexia of aging was observed to be independently associated with the presence of sarcopenia [4]. A study by Landi et al. confirmed that anorexia was independently associated with sarcopenia in community-dwellers [42]. Indeed, sarcopenia represents one of the most common geriatric syndromes, which was defined by the European Working Group on Sarcopenia in Older People as a muscle disease characterized by an increased risk of poor outcomes [43]. An inadequate food intake is a leading cause of altered muscle mass and function [43] (Figure 1).

Moreover, recent evidences highlighted the role of anorexia of aging in contributing to reduced mobility and altered cognitive function, representing a clinically relevant determinant of disability [44,45]. In particular, anorexia is the major cause of reduced

energy and protein intake and synthesis contributing to muscle and bone alterations, i.e., sarcopenia and osteoporosis, which are frequently observed in the frailty syndrome [45].

According to the aforementioned evidence, we believe that the identification of patients with the anorexia of aging and sarcopenia/osteoporosis appears pivotal to early improve nutritional status.

5. Diagnosis of Anorexia and Malnutrition in the Elderly and Guidelines for Nutritional Interventions

Older adults represent a cohort of population that is often at risk of malnutrition due to several factors, including comorbidities, polypharmacy therapy, social aspects, and anorexia [46]. The ESPEN published in 2019 the guidelines on clinical nutrition and hydration in geriatrics that represent an important guide for physicians [47].

To establish early an appropriate nutritional intervention, physicians should early diagnose the presence of malnutrition. In this light, the Global Leadership Initiative on Malnutrition (GLIM) set the criteria for the diagnosis of malnutrition based on the presence of at least one phenotype aspects of malnutrition, such as unvoluntary bodyweight loss, reduced BMI and/or muscle mass, and one etiology criterion (e.g., low food intake and/or severe illness with inflammation) (Figure 2) [48].

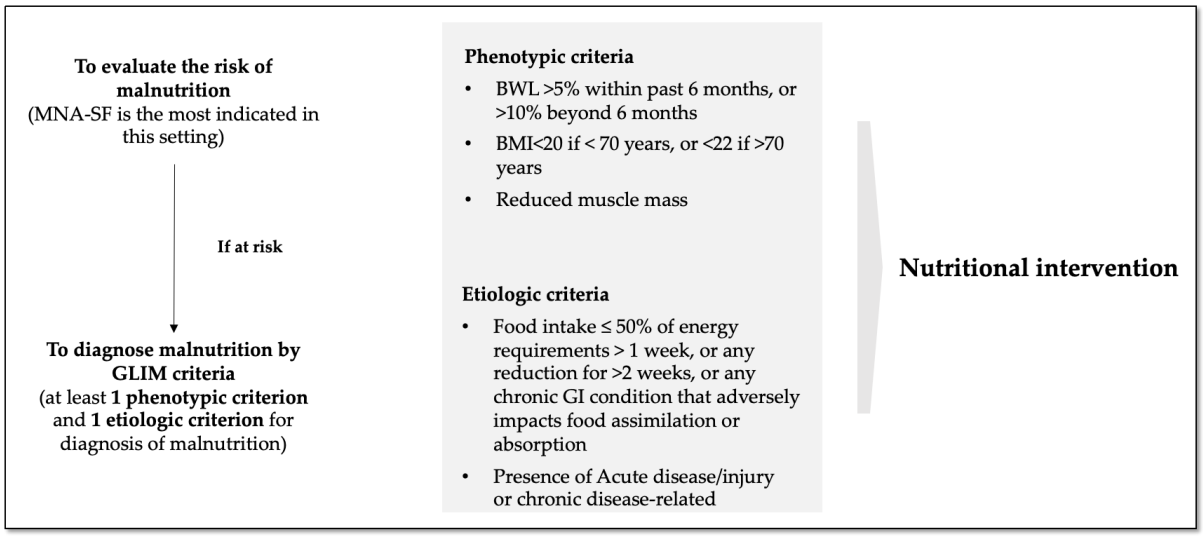

Figure 2. Summary of the diagnostic criteria of malnutrition according to GLIM [48].

Considering the appetite status, several tools, including questionnaires, are available for the evaluation of anorexia also in older patients. Importantly, specific appetite tools have been validated in different settings including patients with chronic diseases [49,50]. The Visual Analog Scale (VAS) is one of the most frequent used appetite tools allowing an evaluation of anorexia objectively and allowing a quantitative follow-up measure. It consists of a 100 mm line where the extremes are anchored to "no hunger", i.e., "I had no appetite at all" (0 mm) and "hunger", i.e., "my appetite was very good" (100 mm), and the patients can mark on the line where they scored their current appetite. Recent evidence suggested a cut-off value of $\leq$50 mm for the diagnosis of anorexia, in particular disease-associated. In addition, several questionnaires were proposed for the assessment of anorexia of aging, such as the Disease-Related Appetite Questionnaire (DRAQ), which evaluates 10 aspects of anorexia of aging using a five-point Likert scale for each domain. Domains included several aspects of the appetite modulation in the elderly, including daily variations in the appetite and food tastes, the number of meals per day, and the presence of nausea. A total score of 50 corresponds to a good appetite [51].

In the elderly, as food intake is reduced, different factors also influence liquid intake, determining a high risk of dehydration. The ESPEN guidelines highlighted the relevance

of hydration in geriatric patients, which is usually impaired due to several mechanisms, including reduced renal function, reduced thirst response, comorbidities, and the use of diuretics [52]. The improvement of nutritional and hydration status in the elderly is crucial to maintain physical function and quality of life. The main nutritional endpoints to reach by nutritional interventions are to stabilize body weight and ameliorate body composition in order to improve morbidity, mortality, and quality of life. The main nutritional interventions include the delivery of the correct macro and micronutrient intake.

However, the presence of anorexia severely limits the possibility to eat the correct amount of nutrients. In this light, it appears essential to provide a tailored nutritional counseling provided by a nutritionist and by a trained dietitian who are able to suggest the preferred and more palatable food (likely providing a high amount of energy and protein) and to indicate, if necessary, the use of oral nutritional supplements [47].

In particular, a total of 30 kcal/kg body weight and at least 1 g protein/kg body weight should be indicated according to individual characteristics, such as comorbidities and according to the underlying nutritional status (e.g., sarcopenia, chronic diseases, etc.) [47]. For instance, older patients with associated chronic conditions may require a greater amount of energy and protein intake due to the increased energy expenditure.

In this light, the different clinical guidelines may overlap in one patient with different diseases. For this reason, the nutritional interventions have to be strictly targeted to patient's specific needs.

Although these guidelines appear clear and evidence-based, we acknowledge that it is not simple for many older adults with anorexia to reach the calorie and protein goals due to several reasons, including the absence of caregivers or a difficult food access for social problems that highly limit the implementation of the nutritional needs.

6. Conclusions

Anorexia is a frequent condition in older adults independently of the presence of a concomitant chronic disease. Anorexia determines low food intake, known as hypophagia, and in turn, unvoluntary body weight loss. All these conditions represent a phenotype of malnutrition, which is a condition associated with changes in body composition, in particular sarcopenia. Therefore, anorexia represents a risk factor for negative outcomes in older adults and the implementation of a correct and prompt diagnosis and nutritional intervention appear essential to improve the outcomes in the elderly.

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Abbreviations

BWL	Body weight loss
GI	Gastrointestinal
GLIM	Global Leadership Initiative on Malnutrition
MNA-SF	Mini Nutritional Assessment-Short Form

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