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Review

The anorexia of ageing: Physiopathology, prevalence, associated comorbidity and mortality. A systematic review☆

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ABSTRACT

The physiological processes of ageing and factors prevalent in the elderly such as comorbidities and polypharmacy often cause loss of appetite in the elderly, which we call anorexia of ageing. Social factors, together with changes in the sensory organs, can be important causes of a reduction in both appetite and ingestion. This review assesses the regulation of appetite in the elderly and the development of anorexia of ageing. It also examines the prevalence of this type of anorexia, its associated comorbidities and mortality rates. We have reviewed 27 studies, with a total of 6208 patients. These reported changes in the secretion and response of both central and peripheral hormones that regulate appetite. Anorexia, very prevalent among hospitalized and institutionalized elderly people, is associated with comorbidity and represents a predictive factor for mortality. No treatment for it has been proved to be effective. The mechanism regulating ingestion in elderly people is complex and difficult to resolve. Comorbidity as a cause or a consequence of anorexia of ageing has become a research field of great interest in geriatrics. A correct nutritional evaluation is a fundamental part of an integrated geriatric assessment.

Contents

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1. Introduction

The changes in the regulation of appetite and the lack of hunger frequently observed in association with ageing have been described as anorexia of ageing (AA) [1].

The main factors associated with the onset of AA can be split into three main groups: (1) physiological; (2) psychological and social; and (3) medical. Among the physiological factors, we may list those related to the process of ageing itself, including: (a) loss of acuity in taste, smell and sight; (b) changes in the secretion and peripheral action of the hormones that regulate the wish to eat, hunger and satiation; (c) changes in gastrointestinal motility; (d) changes to the central control of ingestion; and (e) chronic low-grade inflammation [2,3]. Poverty, isolation and changes to a person's environment are the main psychological and social causes. The third group comprises medical causes, among which we can list certain pathologies and drugs [4].

Fig. 1 is a simplified and schematic representation of the appetite regulation system.

The importance of knowledge and, especially, diagnosis of AA is related to the fact that it represents a major cause of loss of weight and malnutrition, as well as of sarcopenia and fragility [5,6].

The main aim of this review is to describe and summarize the physiopathological factors at the root of AA. Secondary aims are to assess the prevalence of AA, to report on associated comorbidities and mortality rates, and to assess possible treatments for AA.

2. Methods

We performed this review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [7,8]. The protocol of the present review was registered with PROSPERO, which is an international database of prospectively registered systematic reviews in health and social care. PROSPERO is funded by the UK National Institute for Health Research. See http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002893.

2.1. Search strategy

A search was carried out in PubMed, limited to the title or the abstract and using the following terms and term associations: anorexia, ageing/aging/older person/elderly/senile, loss/regulation of appetite, dietary intake, feeding, nutrient/food/fluid intake, gastrointestinal hormones, treatment, megestrol acetate/loxiglumide/dronabinol. We limited the search to articles published between January 1987 and June 2012. We then reviewed the bibliographies of all the papers identified from the search, as another bibliographical source.

2.2. Inclusion and exclusion criteria

We included studies on people above 65 years of age that assessed the physiopathology, prevalence, comorbidities, mortality or treatment of AA. As regards physiopathology, we included articles that studied the secretion of the hormones related to appetite, the regulation of ingestion or intestinal motility. We discarded studies on anorexia nervosa or on anorexia secondary to acute pathologies. Despite AA being a cause of involuntary weight loss, studies on this aspect were considered to be beyond the remit of the present review, although we have not dismissed the possibility of undertaking a future review on this problem.

2.3. Selection and quality assessment

One of the authors was in charge of selecting the papers according to our inclusion criteria. We read the abstract of all potentially eligible papers and where it was not clear from the abstract whether the inclusion or exclusion criteria had been met, we read the full text. Doubts the authors had were resolved by joint critical assessment of the papers.

The quality of the included papers was evaluated subjectively according to the DRAFT criteria [9].

2.4. Data abstraction

We extracted from every paper the design of the study, where it was carried out, the demographic characteristics of included subjects and their division into groups, the body mass index (BMI) of the subjects, and the study's exclusion criteria and main results. The main characteristics of the studies are summarized in Table 1.

3. Results

3.1. Study characteristics and quality assessment

We included 27 studies, with a total population of 6208 patients. Fig. 2 presents a flow chart showing the paper selection process.

None of the protocols of the studies included in this revision was registered in any international registers.

We considered 11 studies to be good, 12 fair and 4 wanting. The main area which caused papers to be evaluated as 'wanting' was their statistical analysis, whether because an incorrect test was chosen or because the test that would best represent the data was not used, thereby causing confusion and complicating the assessment and interpretation of results. A low number of subjects, the fact that part of the sample populations had been used in earlier studies, often not specified, and an incomplete presentation of results are other reasons for studies to be judged as being of lower quality.

None of the studies specified how the sample size was chosen.

3.2. Outcomes measured

We employed a fourfold classification of the results of the 27 studies: (1) physiopathology; (2) prevalence and comorbidity; (3) mortality; and (4) treatment.

3.3. Physiopathology

3.3.1. Hormones related to appetite regulation

Cholecystokinin (CCK) is secreted by cells in the duodenum and jejunum in response to certain foods. It inhibits appetite at a central level and at a peripheral level it delays gastric emptying and the production of ghrelin [10].

Statistically higher levels of CCK in fasting conditions were observed in elderly people compared with younger people in a number of studies [11–14], while a further study reported a difference that was not statistically significant [15]. One study found

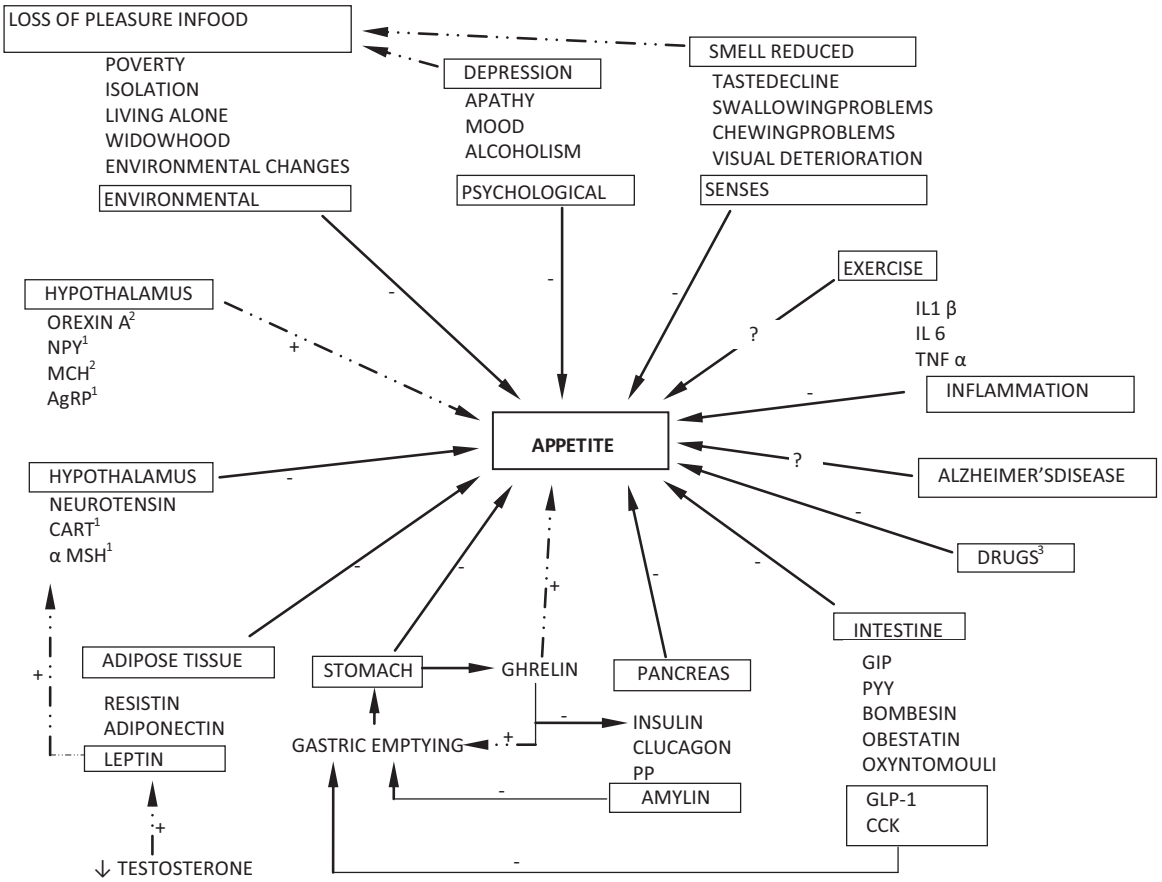

Fig. 1. pathogenesis of anoxia of ageing. Central and peripheral hormones, psychological and environmental factors, medical and pharmacological factors and habits linked to the regulation of appetite in elderly people. [1]Neurons in the hypothalamic arcuate nucleus. [2]Neurons in the lateral hypothalamic area. [3]Morley JE. American Journal of Clinical Nutrition 1997;66:760–73. α MSH, alpha melanocyte-stimulating hormone; AgRP, agouti-related protein; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide; IL-1 β, interleukin-1 β; IL-6, interleukin-6; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; PYY, peptide YY; TNF-α, tumour necrosis factor-alpha. The solid line indicates inhibition, the dashed line indicates stimulation.

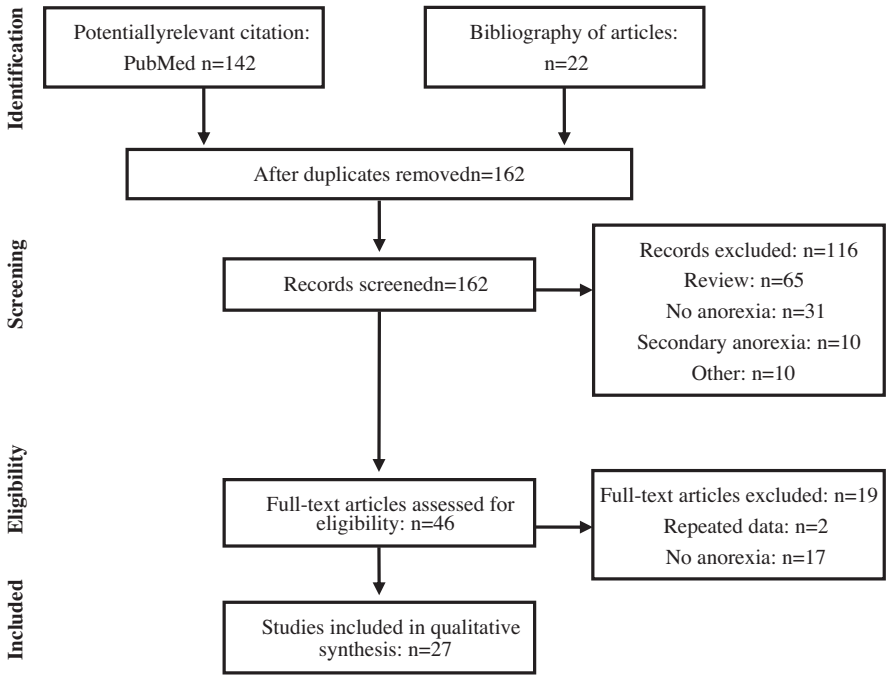

Fig. 2. Flow-diagram of literature search.

Table 1
Physiopathology and prevalence of anorexia of ageing: author, year, cohort characteristics, aim and main outcomes of reviewed studies.

Authors Publ. year Origin	Aim	*n* and population characteristics	Age, years (sex M/W) [BMI mean ± SD] kg/m^2	Exclusion criteria	Experimental design and intervention	Results
Landi F 2012 Italy [34]	Relationship between anorexia and mortality	2787 elderly living in the community	80.4 ± 7.5 (1110/1677) [NA]	<65 years	Longitudinal, prospective, cohort study using data from the National Silver Network project. Follow-up for at least 12 months	Prevalence of anorexia 26.7%. 17% of the entire sample died. Subjects with anorexia were more likely to die, RR 1.83
Donini LM 2011 Italy [35]	Prevalence and factors associated with anorexia	218 free-living 213 long-term 96 acute wards	>65 (208/319) [25.8]	Parenteral or enteral nutrition; severe comorbodity	Cross-sectional	Prevalence of anorexia was 21.2% in whole group
Serra-Prat M 2010 Spain [39]	Long-term relationship between ghrelin and nutritional status and functional capacity	313 elderly living in the community	77.0 ± 5.9 (153/160) [28.1 ± 4]	In nursing homes, <70 years	Longitudinal population-based cohort study, 2 years follow-up	13% of men and 20% of women showed a >5% weight loss. In men low basal ghrelin was negatively correlated with weight loss.* Women who died had lower levels of basal ghrelin*
Landi F 2010 Italy [36]	Relationship between anorexia and physical performance, muscle strength and functional status	364 elderly living in the community	85.8 ± 4.8 (120/244) [25.6 ± 4.5]	Born after January 1st 1924	Cross-sectional, using data from the ilSIRENTE study	Prevalence of anorexia 21%. SPPB, walking speed and grip strength associated with anorexia#. ADL and IADL not associated with anorexia
Vázquez-Valdez 2010 Mexico [37]	Association between anorexia and disability	1247 elderly living in the community	69.9 ± 7.8 (511/736) [NA]	NA	Cross-sectional, using data from SABE study	Prevalence of anorexia was 30.1%. Anorexia was associated with all types of disability (NS). Interaction between anorexia and depression**
Bauer JM 2010 Germany [18]	Secretion pattern of ghrelin, and correlation with hunger and satiety	15 young 19 elderly	35.4 ± 6.4 (10/5) [25.3 ± 5.1] 80.7 ± 5.6 (5/14) [26.4 ± 5.6]	DM, cancer, advanced chronic disease, taking corticosteroids	One day, intervention repeated measurement, 4 h after breakfast, before and after oral meal test (420 kcal)	No difference in basal ghrelin. After meal ghrelin declined only in the younger
Serra-Prat M 2009 Spain [15]	Assess whether ghrelin and CCK responses to a standard nutritional load are relate to age and frailty	17 healthy young 10 elderly non-frail 15 elderly frail	39.7 ± 9.8 (7/10) [25.2 ± 3.3] 80.0 ± 8.4 (6/4) [26.7 ± 3.0] 83.0 ± 7.3 (5/10) [28.7 ± 6.6]	For elderly: <75, dementia, gastrectomy, active cancer, severe dysphagia	Intervention repeated measurement, after 10 h overnight fast, between 8:00 and 9:00 am, before and after oral meal 380 kcal	In the young, ghrelin concentration reduction during the 1st h* and recovery until the 4th h.*** In the non-frail, inhibitory response* but not recuperation phase. In the frail, no inhibitory but a recuperation phase.* Fasting CCK was similar in 3 groups. In the young, threefold increase and in elderly, twofold at 0.5 h and in young decreased after 3rd h
Schneider SM 2008 France [19]	Effect of age, malnutrition and refeeding on ghrelin secretion	10 UN young 10 WN young 11 UN elderly 9 WN elderly	26.0 ± 6.0 (2/8) [15.4 ± 2.2] 34.0 ± 8.0 (5/5) [22.5 ± 2.9] 80.0 ± 6.0 (5/6) [17.5 ± 2.1] 76.0 ± 9.0 (3/6) [23.6 ± 1.8]	Ongoing infection, wasting disease, PCR>10 mg/L, taking steroids, antibiotics or drugs that influence GI motility	First cross-sectional phase, followed by an intervention phase in 14 UN subjects (7 young and 7 elderly), with enteral nutrition for 21 days	Fasting ghrelin was higher in young UN compared to WN. Effect of refeeding on total weight and leptin in young*
Yukawa M 2006 USA [32]	Ghrelin before and after diet-induced weight loss	21 healthy young 18 healthy elderly	25.5 ± 5.0 (8/13) [24.7 ± 3.0] 75.4 ± 4.0 (7/11) [26.9 ± 3.0]	Renal or hepatic insufficiency, severe pulmonary disease, CHF, thyroid dysfunction, DM, malabsorption, terminal disease, weight loss, hospitalized within 3 months before, cognitive dysfunction	Prospective, diet intervention 2 weeks of weight-maintaining diet, 2 weeks of a diet with 30% fewer total calories, 4 weeks of ad libitum diet	In the young caloric intake remained below their weight maintenance level,* increased in the elderly (NS). Ghrelin increased after caloric restriction,* and decreased after ad libitum diet*
Di Francesco V 2006 Italy [20]	Dynamics of leptin and ghrelin and effect on appetite	8 young 8 elderly	29.5 ± 1.0 (4/4) [22.5–25.7] 78.0 ± 1.0 (4/4) [22.1–29.4]	GI illness, medication or surgery, DM, neurologic, cardiac, renal or respiratory disease, cancer, acute disease, BMI <18.5 or >30	One experimental day, intervention repeated measurement. After overnight fast, before and after oral meal (800 kcal)	Fasting leptin and insulin was higher in the elderly,* basal ghrelin did not differ

Reuben DB 2005 USA [40]	Optimal dosage of megestrol acetate for impaired appetite	47 elderly recently discharged (3 weeks)	83.5 (16/31) [22.6]	Normal appetite, taking megestrol acetate or mirtazapine, cancer, TE or hepatic or renal or GI or dental disease, feeding tube or TPN, glucocorticoid therapy, MMSE <20	RCT, placebo or megestrol acetate 200 mg, 400 mg or 800 mg daily for 9 weeks	No different on appetite. At 20 days greater prealbumin increases in 400 and 800 mg[#], lower cortisol[#]. At 63 days greater prealbumin for 400 mg[#]. Thromboembolism occurred in two megestrol participants
Cornali 2005 Italy [38]	Whether anorexia could be a predictor of mortality	316 elderly community living	81.0 ± 7.2 (68/248) [NA]	Severe cardiopulmonary, GI, hepatobiliary and renal disease, cancer	Longitudinal prospective cohort study, 10.5 months follow-up	Prevalence of anorexia 15.8%. Mortality was higher for anorexia[#]. Anorexia HR 2.9 and BI HR 1.1 independent predictors of mortality
Sturm K 2003 Australia [11]	GI hormones response to an oral mixed nutrient preload	8 WN young 8 UN elderly 8 WN elderly	22.0 ± 1.3 (0/8) [20.5 ± 0.40] 80.4 ± 2.6 (0/8) [16.9 ± 0.57] 77.0 ± 0.9 (0/8) [23.7 ± 0.80]	Alcohol abuse, GI symptoms or medications affect GI, abnormal amylase, lipase or TSH, cancer, DM, MMSE<25, GDS>11	Two studies on separate days. After 12-h overnight fast, oral preload 143 g vanilla ice-cream (280 kcal), or no preload	Insulin was higher in WN elderly than in both UN elderly and WN young[#]. CCK was higher in elderly than young[#]. Ghrelin was higher in UN elderly than WN elderly and young
Rigamonti AE 2002 Italy [22]	Ghrelin concentration in ageing and in physiopathological conditions	12 healthy young 7 healthy elderly 6 anorexia nervosa 7 morbid obesity	33.4 ± 1.0 (NA) [21.2 ± 0.9] 79.8 ± 2.1 (NA) [25.0 ± 1.7] 17.5 ± 0.5 (NA) [13.1 ± 0.5] 26.9 ± 2.7 (NA) [39.7 ± 2.5]	NA	Cross-sectional	Mean ghrelin was higher in anorexic and lower in obese and in elderly than in young.[*] Insulin were higher in obese and in elderly and lower in anorexic than in young[**]
McIntosh CG 2001 Australia [33]	Effects of naloxone on appetite and food intake	12 healthy young 12 healthy elderly	23 (5/7) [25.0 ± 0.5] 72 (5/7) [24.7 ± 0.7]	EI < 1000 kJ/day, smokers, serious illness, GI disease or surgery, medication influence on appetite	Three studies on separate days. After 10-h overnight fast, intravenous treatment infusion of: 0.9% saline (control), naloxone 144 μg/kg (LD) or 288 μg/kg (HD)	No effect of age or treatment on ratings of hunger, fullness or drowsiness[a]. Effect on EI of age[#], and of treatment[#]
McIntosh CG 2001[a] Australia [25]	Effect of intestinal nutrient infusion on appetite and GLP-1, GIP and insulin secretion	13 healthy young 13 healthy elderly	23.7 ± 1.4 (13/0) [23.9 ± 0.6] 72.0 ± 1.6 (13/0) [23.5 ± 1.0]	Smokers, GI disease or surgery, medication influence GI motility	Single blind, randomized on three separate days, at 8:00 am. After 12 h overnight fast, ID infusion of saline (control), glucose or lipid, with the same volume 3 ml/min and for glucose and lipid 2.9 kcal/min, during 120 min (348 kcal totals)	During glucose infusion greater rise in blood glucose and insulin in elderly[#]. GLP-1 and GIP higher during glucose and lipid infusion compared to control infusion[#]
McIntosh CG 2001 Australia [12]	Effect of iv CCK-8 on appetite and GI hormones secretion	12 healthy young 12 healthy elderly	22.6 ± 1.2 (6/6) [23.5 ± 0.8] 71.2 ± 1.3 (6/6) [24.1 ± 0.7]	Smokers, GI disease, DM medication influence GI motility	Three studies on separate days. After 12-h overnight fast, oral preload and iv infusion of saline (control), CCK 1 ng/kg per min (LD) or CCK 3 ng/kg per min (HD)	CCK-8 suppresses EI. Inverse relationship between EI and CCK-8 concentration.[#] Greater Glu increase in elderly.[#] CCK-8 reduces plasma insulin concentration after meal.[#] No effect on leptin concentration
Zandstra EH 2000 The Netherlands [29]	Short-term regulation of food intake	30 healthy children 33 healthy young 24 elderly	4.5 ± 0.6 (18/12) [16.0 ± 1.2] 22.0 ± 1.9 (5/28) [23.3 ± 2.3] 75.5 ± 5.0 (6/18) [26.6 ± 3.5]	Medication influence appetite	Intervention repeated measurement, five different randomized days. Four oral preloads yoghourts: (1) low fat, low COH, low E; (2) high-fat; (3) high-COH; (4) high-fat, high-COH, high E, and one no-preload condition	All groups ate less after high-fat and high COH compared to no-preload.[#] Elderly ate less after high COH compared to no-preload[#]
McIntosh CG 1999[a] Australia [13]	Effect of ageing on CCK, GLP-1 and PYY	8 healthy young 8 healthy elderly	27 (8/0) [26.8 ± 1.2] 70 (8/0) [25.8 ± 1.3]	Smokers, GI disease or surgery, medication influence GI motility	After 12 h overnight fast, at 9:00 am, two studies on separate days. ID infusion of glucose or triacylglicerol emulsion, 2.9 kcal/min during 120 min	Greater increase of CCK in elderly than in young.[#] No significant effect of age on GLP-1 or PYY. During ID lipid infusion hanger rating was inversely related to CCK and GLP-1 in younger
Clarkston WK 1997 USA [28]	Examine potential link between anorexia and gut transit	19 healthy young 14 healthy elderly	30 (10/9) [25.3 ± 3.4] 76 (5/9) [25.2 ± 1.7]	Significant medical illness, GI symptoms or surgery, atrophic gastritis, pernicious anaemia, medications affect GI transit	At 8:00 am intervention repeated measurement study. Before and after oral test meal: solid (389 kcal), liquid 150 ml (67 kcal)	Prolonged gastric emptying in elderly,[*] no difference in orocecal or total gut transit time

Table 1 (*Continued*)

Authors Publ. year Origin	Aim	*n* and population characteristics	Age, years (sex M/W) [BMI mean ± SD] kg/m^2	Exclusion criteria	Experimental design and intervention	Results
Rolls BJ 1995 USA [30]	Adjust food intake to preloads.	16 healthy young 16 healthy elderly	24.3 ± 1.2 (16/0) [22.7 ± 0.5] 68.9 ± 1.6 (16/0) [26.2 ± 0.9]	Smokers, medication influence GI motility, chronic health problem, motor impairment, swallowing or chewing problems	Four studies on separate randomized days. No-preloads day. Three oral preloads yoghurts: (1) low fat, low COH (230 kcal); (2) high-fat (510 kcal); (3) high-COH (510 kcal)	In no-preloads lunch in young was higher than elderly.# Elderly overate compared with their baseline intake
Roberts SB 1994 USA [31]	Investigate the effects of ageing on the control of energy intake	17 healthy young 18 healthy elderly	22.7 (17/0) [22.8] 68.0 (18/0) [25.1]	Smokers, recent illness, endocrinopathy, taking medication	Not randomized, sequentially, dietary intervention study. Phase 1, 10 days, maintenance diet, phase 2, 21 days, group 1 overfeeding (+1000 kcal/d) and group 2 underfeeding (−800 kcal/d). Phase 3, 46 days, ad libitum diet	Group 1 increase in body weight and in phase 3, the young lose the weight gained but the elderly do not.** Group 2 decrease in body weight and in phase 3 the young increase body weight but the elderly do not**
Martinez M 1993 Spain [16]	Role of satiety neuropeptides and stimulants feeding in anorexia of ageing	14 anorexic elderly 10 healthy elderly	78 ± 8 (6/8) [18.4 ± 0.6] 74 ± 9 (6/4) [22.7 ± 0.6]	Dementia, depression, medication, smoking	Phase 1, cross-sectional, with retrospective control group. Phase 2, in 5 anorexic patients, longitudinal prospective intervention study with 480 mg/d of megestrol acetate during at least 6 months	Phase 1: BMI decreased in anorexics.*** Senile anorexia showed higher plasma CCK8,* increased CSF NPY** and reduced somatostatin and **β**-endorfin.* Phase 2: increased of **β**-endorphin in CSF*
Cook CG 1997[a] Australia [27]	Effects of small intestinal nutrient infusion on appetite and pyloric motility	7 healthy young 8 healthy elderly	27 (8/0) [26.8] 70 (8/0) [25.8]	EI < 1500 kcal/d, smokers, GI disease or surgery, medication influence GI motility	After 12 h overnight fast, at 9:00 am, two studies on separate days. ID infusion of glucose or triacylglicerol emulsion, 2.9 kcal/min during 120 min	No effects on appetite in elderly. Frequency of IPPWs was greater in the elderly*
Di Francesco 2010 Italy [21]	Effect on satiety of oral macronutrient	12 healthy young 12 healthy elderly	28.2 ± 2 (6/6) [18.9–26.5] 75.2 ± 6 (5/7) [21.1–28.3]	Malnutrition, weight loss, oral, swallowing or chewing problems, GI disease or surgery, DM, neurological, respiratory, cardiac or renal disease, malignancies. 18.5 < BMI > 30	Two studies on separate days. After overnight fast oral test 20% fat meal or 40% fat meal (800 kcal)	Serum GLP-1 higher in older after 40%FM*
Di Francesco 2008 Italy [23]	Fasting and postprandial serum acylated ghrelin (A-Ghr)	11 healthy young 11 healthy elderly	28.1 ± 0.7 (4/7) [18.9–24.5] 75.2 ± 1.8 (4/7) [21.1–28.3]	NA	One study day, intervention repeated measurement. After overnight fast oral test 20% fat meal (800 kcal)	Acylated ghrelin was lower in elderly in fasting conditions*
Di Francesco 2005 Italy [14]	Postprandial gastric emptying, cholecystic contraction, CCK and PYY levels	9 healthy young 10 healthy elderly	32 ± 8 (4/5) [22.7–28.1] 77 ± 3 (5/5) [23.5–29.3]	Abdominal surgery, cholelitiasis, DM, neurological disease, pregnancy, GI disease, Malignancies, acute ongoing disease	One experimental day, intervention repeated measurement. After overnight fast, oral meal (800 kcal)	In elderly delayed gastric emptying,** lower gallbladder contraction,* higher basal and sustained rise of CCK.* PYY values were similar in fasting condition but after 2 h higher in elderly**

BI, barthel index; CCK, cholecystokinin; CHF, congestive heart failure; COH, carbohydrate; CSF, cerebrospinal fluid; CyEN, cyclic enteral nutrition; DM, diabetes mellitus; E, energy; EI, energy intake; HD, high dose; GDS, geriatric depression scale; GI, gastrointestinal; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; Glu, glucose; IPPWs, isolated pyloric pressure waves; HR, hazard ratio; ID, intraduodenal; LD, low dose; MMSE, mini mental state examination; NA, not available; NPY, neuropeptide Y; NS, non-significant; PYY, peptide YY; RCT, randomized clinical trial; RR, relative risk; SABE, study multicenter health, well being and ageing study; SPPB, short physical performance battery; TE, thromboembolic; TPN, total parenteral nutrition; UN, undernourished; WN, well-nourished.

[a] Share part of the sample.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

statistically higher values in anorexic elderly people than in non-anorexic elder people [16].

An increase in basal values was observed in both younger and older subjects following a preload meal. The differences were not statistically significant in one study [11], whereas in three studies the increase observed was statistically higher in older subjects [12–14]. Serra Prat et al., conversely, observed a statistically greater increase in younger subjects than in older ones [15].

Ghrelin is the main orexigenic hormone, secreted by the cells at the bottom of the stomach. Ghrelin levels increase in fasting conditions and fall rapidly after the ingestion of food [17]. The levels of ghrelin observed in the studies varied greatly. In general, the studies did not specify whether they measured total ghrelin, the acylated (active) form or the non-acylated (inactive) form. Most of the studies observed similar levels of ghrelin in young and elderly subjects [18–21], although one found minimally higher levels in elderly people [15] and another lower levels in elderly people than in young subjects [11]. Two studies found plasma ghrelin concentration in older subjects to be significantly lower than that in younger people [22,23]. Two studies observed no difference in basal levels of ghrelin following a preload meal [20], and a further study observed no changes in elderly subjects and a reduction of ghrelin levels in young subjects [18]. Some of the authors observed a decrease in ghrelin levels following a preload meal compared with fasting levels, with the difference not being significant in one case [11] and significant in another [15]. One study reported slightly conflicting results, with an increase of ghrelin compared with fasting values only in young subjects, although the differences were not statistically significant [23].

Serra Prat et al. present the results of a study with repeated measurements design type after two years [39]. The authors observe that low baseline levels of ghrelin are associated with a loss of strength, as measured by the hand grip, with a worsening of the Barthel index, and an increased risk of malnutrition, calculated using the Mini Nutritional Assessment-Short Form (MNA-SF). Although the authors do not present the data about the number of deaths, commented that the women who died during the two years had baseline ghrelin lowest of women still alive, which is not observed in men.

Glucagon-like peptide-1 (GLP-1) is a hormone produced by the small intestine in response to food intake, especially carbohydrates; it delays gastric emptying and inhibits appetite [24]. The various studies diverge in their observations: some have shown similar fasting levels in elderly and young patients [11,14,21], while others have reported slightly lower values in elderly subjects [25] or even higher levels [13], although the differences were not statistically significant in the latter two studies. Almost all of the studies agree that GLP-1 levels increase after a preload meal in both elderly and young people [11,13,21,25] and in two cases the levels were statistically higher in elderly subjects than in young ones [14,21].

Insulin, in addition to being one of the principal hormones involved in glucose metabolism, acts, like leptine does, at the hypothalamic level, reducing appetite by inhibiting cells in the arcuate nucleus and stimulating the lateral hypothalamic area [26]. Several studies assessed fasting levels of insulin and the changes in these levels following various stimuli – for example oral or intraduodenal food administration or intravenous CCK – and obtained slightly differing results. Some authors observed similar basal values in elderly and young subjects [15,18,21,25], while others showed statistically higher levels in elderly subjects compared with young ones [11,20,22,23], and MacIntosh et al. observed statistically higher basal levels of insulin in young subjects [12]. Of the six studies that examined insulin levels following a preload meal, three observed an increase in both elderly and young subjects [11,21,25] and the other three found statistically higher levels in elderly subjects [15,18,20]. Again, the study conducted by MacIntosh et al. diverged from the rest of the studies, as they observed that, following intravenous CCK, insulin levels were statistically higher in young subjects than in elderly subjects [12].

Martínez et al. studied two groups of elderly people with and without anorexia and found, in the anorexic group, statistically higher levels of CCK in plasma and lower levels of **β**-endorphin, and statistically lower levels of somatostatin and **β**-endorphin in cerebrospinal fluid (CSF) [16]. Levels of neuropeptide Y (NPY) were statistically higher in both the plasma and the CSF of the anorexic subjects.

There are few data regarding elderly people and three appetite-inhibiting hormones: leptine, produced by the adipose tissue, the glucose-dependent insulinotropic peptide (GIP) and peptide YY (PYY), produced in the intestine.

3.3.2. Motility

Studies on intestine transit have demonstrated an increase in frequency and amplitude of isolated pyloric pressure waves (IPPWs) [27] in elderly people compared with younger people, an increase in the time gastric emptying takes [28] and a decrease in maximum contraction of the gallbladder [14]. All these factors may contribute to the feeling of satiation following a meal. The complete intestine transit time does not change with age.

3.3.3. Regulation of ingestion

In two studies was assessed caloric intake in basal conditions and after a test meal [29,30]. The authors observed that the intake in the elderly was lower after the test meal. Even so the total amount of calories consumed the amount of calories of the meal test plus the calories of the free meal were statistically larger than the calories ingested in the baseline situation. Data are conflicting on medium-term and long-term regulation. Young people recover weight lost during a period of restrictive dieting and lose weight gained during a hypercaloric diet by regulating their ingestion thereafter, whereas this was not observed in elderly people [31]. Nevertheless, another of the reviewed papers reported how, following a restrictive diet that brought about weight loss, elderly subjects soon were back to basal levels of ingestion and tended to recover the weight they lost, which was not observed in young subjects [32].

It is known that activation of opiate receptors in the brain stimulates appetite and ingestion, although their role in the feeling of thirst and in the regulation of water ingestion is not clear [10].

MacIntosh et al. found a decrease in ingestion as a response to naloxone infusion in young people and elderly men, but not in elderly women [33].

3.4. Prevalence and comorbidity

The prevalence of AA among elderly people living in the community has been reported to range between 15% and 30%, with an overall higher prevalence in women [34–37]. Prevalence is higher in elderly people in nursing homes, at 31% (27% of men and 34% of women), and in hospitalized patients, at 31.5% (26.7% men and 33.3% women) [35]. Cornali et al. observed a prevalence of 15.8% in elderly people discharged from hospital [38]; of those diagnosed as having AA, 18% were men and 82% were women.

There is agreement that AA is more prevalent in older age [34–38] and that it tends to occur in people with disabilities and dependency for the activities of daily living (ADL) [34,35,37], as well as in people with a higher comorbidity index [35–37]. Anorexic elderly people overall seem to have worse cognitive deterioration [34–37], worse oral health (expressed as fewer natural teeth and more difficulty in chewing) [34,35], and more depression [34–38]. Table 2 is a summary of the main comorbidities associated with AA.

Table 2
Comorbidity associated with anorexia of ageing.

Author	Age (mean ± SD)		ADL		Cognitive impairment		Depression		Comorbidity index	
	Anorexia	No anorexia	Anorexia	No anorexia	Anorexia	No anorexia	Anorexia	No anorexia	Anorexia	No anorexia
Landi 2012 [34]	81.0 ± 7.8	80.1 ± 7.4**	Score, mean ± SD 5.3 ± 2.4	4.5 ± 2.7***	CPS (mean ± SD) 2.7 ± 2.2	2.3 ± 2.1***	(%) 61	56**	NA	NA
Donini 2011 [35]	83.0 ± 7.0	76.6 ± 8.0*	>2 lost ADL (%) 55.5	31.8*	MMSE (mean ± SD) 18.5 ± 9.0	23.8 ± 5.0*	GDS, (mean ± SD) 6.7 ± 5.0	4.7 ± 4.0*	(mean ± SD) 2.4 ± 2.0	2.1 ± 2.0*
Landi 2010 [36]	86.8 ± 4.6	85.6 ± 4.9 NS	NA	NA	CPS (mean ± SD) 1.1 ± 1.8	0.8 ± 1.5 NS	(%) 36.5	22.4*	Number of disease 2.4 ± 1.3	2.1 ± 1.2*
Vázquez 2010 [37]	NA	NA	(%) 29.2	13.2***	NA	NA	NA	NA	NA	NA
Cornali 2005 [38]	81.0 ± 7.2	76.5 ± 6.8**	BI (mean ± SD) 60.0 ± 29.2	67.9 ± 23.6NS	MMSE (mean ± SD) 21.7 ± 5.9	22.7 ± 5.6 NS	GDS (mean ± SD) 6.4 ± 3.5	6.2 ± 3.4 NS	BDS (mean ± SD) 9.9 ± 4.3	9.1 ± 3.5 NS

ADL, activities of daily living (score range 0–7, a higher number indicates higher impairment); BDS, burden of disease score; BI, barthel index; CPS, cognitive performance scale (range 0–6, a higher number indicates higher impairment); GDS, geriatric depression scale; MMSE, mini mental state examination; NS, non-significant; NA, not available.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

3.5. Mortality

AA has proven to be an independent mortality factor in elderly people.

Two studies found elderly people with AA to have elevated mortality rates. In one of these the corrected relative risk (RR) was 1.83 (95% confidence interval, CI, 1.45–2.31) [34]. The same study found that the RR was 1.45 (CI 1.01–2.19) when anorexia was not associated with weight loss, and 1.89 (CI 1.53–2.54) when it was associated with weight loss. The other study observed a RR of 2.9 (95% CI 1.1–7.4) at 10.5 months [38].

3.6. Treatment

We found few clinical studies of the treatment of AA. Megestrol acetate is a synthetic hormone (progestogen) currently indicated for treatment of loss of appetite associated with weight loss in HIV-positive patients who have cancer. It is the most studied drug in this field but results have not demonstrated its efficacy in treating AA and its side-effects limit its use [16,40].

Dronabinol is a synthetic form of delta-9-tetrahydrocannabinol, a natural component of the plant *Cannabis sativa*, approved for the treatment of anorexia associated with weight loss in patients with AIDS, and as an anti-emetic in cancer patients undergoing chemotherapy. We have found no prospective randomized studies with dronabinol.

CCK inhibitors such as loxiglumide or dexloxiglumide may potentially be used as treatment for AA, but they are still at an experimental stage.

4. Discussion

There is much diversity in the results of studies on the hormones that regulate appetite. This confirms the complexity of the peripheral and central regulation of appetite. Nonetheless, research must continue along these lines, with particular attention to anorexic elderly people.

One of the most interesting aspects for geriatricians is the high comorbidity observed in elderly people and how it influences their clinical state and, more especially, their functional state. Despite the fact that the observational studies included in this review do not allow us to establish causal relationships, they do pose interesting questions about mechanisms potentially related to AA, which may serve as a basis for future research. The high comorbidity associated with AA is a subject of great clinical interest, but here again, more research is required, especially to show which of these comorbidities are causes and which are consequences of AA.

The response to naloxone indicates that opiate regulation is still important and may be a therapeutic target but there is evidence only for elderly males.

AA is a clinical problem recognized by geriatricians, but its diagnosis, complications and possible treatments are difficult to resolve [41]. It is recognized as a geriatric syndrome, but the factors influencing appetite in elderly people are so many and so prevalent that research into its physiopathological mechanisms is difficult.

Nutritional intervention in elderly patients is a matter currently under discussion. For it to be used appropriately, it is imperative that it is based on an important premise: nutritional intervention should begin with the assessment and narrowing down of the possible causes of malnutrition in an elderly person, and dietary supplementation should be instituted only when it has been shown to be necessary should [42].

Before clinicians give dietary advice, they must be aware that elderly people have slower gastric emptying although they maintain normal complete intestinal transit times. Such consideration

may help to improve the tolerance of and adherence to nutritional treatment.

Although an active lifestyle and physical exercise have been shown to be effective in preventing functional deterioration and loss of muscle mass, it seems there is no relation between physical exercise and appetite [43–46].

The main limitations of this review are the broad variety in the designs of the included studies, their varying objectives, the characteristics of the populations studied and, in the intervention studies, the broad variety of preload meals used in terms of nutritional characteristics, administration route and volume.

5. Conclusions

Almost all the included studies assessed the secretion of peripheral hormones related to appetite control in healthy elderly people and compared this with secretion in younger people. Future studies should assess the differences between elderly people with and without anorexia, to give a better understanding of the physiopathological mechanism at the root of appetite loss.

Environmental factors (such as isolation), sensory alterations, poor oral hygiene and polypharmacy are potential targets for interventions aimed at improving ingestion and reducing the risk of malnutrition in elderly people. Research into the treatment of AA should not focus exclusively on the search for yet another drug to stimulate appetite, in order to add it to the existing long list of treatments of elderly patients. Rather, it should focus on an integrated geriatric assessment, including a nutritional evaluation.

Provenance and peer review

Commissioned, externally peer reviewed.

Contributors

Dr. Vincenzo Malafarina conceived the idea of the review, performed the bibliographic search and wrote the manuscript. Dr. Francisco Úriz-Otano, Dra Lucía Gil-Guerrero and Raquel Iniesta helped interpreting the data and making comments on the final version of the manuscript.

Competing interest

The authors declare no conflict of interest.

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References

[1] Morley JE, Silver AJ. Anorexia in the elderly. Neurobiology of Aging 1988;9(1):9–16.
[2] Franceschi C, Capri M, Monti D, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mechanisms of Ageing and Development 2007;128(1):92–105.
[3] Hays N, Roberts S. The anorexia of aging in humans. Physiology Behavior 2006;88(3):257–66.
[4] Morley JE. Anorexia of aging: physiologic and pathologic. American Journal of Clinical Nutrition 1997;66(4):760–73.
[5] Malafarina V, Uriz Otano F, Iniesta R, Gil-Guerrero L. Sarcopenia in the elderly: diagnosis, physiopathology and treatment. Maturitas 2012;71(2):109–14.
[6] Degens H, Korhonen M. Factors contributing to the variability in muscle ageing. Maturitas 2012;73(3):197–201.
[7] Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine 2009;151(4):W64, 264,9.
[8] Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of Internal Medicine 2009;151(4):W65–94.
[9] Agency for Healthcare Research and Quality. Methods reference guide for effectiveness and comparative effectiveness reviews, version 1.0 [draft posted October 2007]. Rockville, MD. Available from: http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf
[10] de Boer A, Ter Horst G, Lorist M. Physiological and psychosocial age-related changes associated with reduced food intake in older persons. Ageing Research Reviews 2012;12(1):316–28.
[11] Sturm K, MacIntosh C, Parker B, Wishart J, Horowitz M, Chapman I. Appetite, food intake, and plasma concentrations of cholecystokinin, ghrelin, and other gastrointestinal hormones in undernourished older women and well-nourished young and older women. Journal of Clinical Endocrinology and Metabolism 2003;88(8):3747–55.
[12] MacIntosh CG, Morley JE, Wishart J, et al. Effect of exogenous cholecystokinin (CCK)-8 on food intake and plasma CCK, leptin, and insulin concentrations in older and young adults: evidence for increased CCK activity as a cause of the anorexia of aging. Journal of Clinical Endocrinology and Metabolism 2001;86(12):5830–7.
[13] MacIntosh CG, Andrews JM, Jones KL, et al. Effects of age on concentrations of plasma cholecystokinin, glucagon-like peptide 1, and peptide YY and their relation to appetite and pyloric motility. American Journal of Clinical Nutrition 1999;69(5):999–1006.
[14] Di Francesco V, Zamboni M, Dioli A, et al. Delayed postprandial gastric emptying and impaired gallbladder contraction together with elevated cholecystokinin and peptide YY serum levels sustain satiety and inhibit hunger in healthy elderly persons. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2005;60(December (12)):1581–5.
[15] Serra Prat M, Palomera E, Clave P, Puig Domingo M. Effect of age and frailty on ghrelin and cholecystokinin responses to a meal test. American Journal of Clinical Nutrition 2009;89(5):1410–7.
[16] Martinez M, Hernanz A, Gómez Cerezo J, Peña JM, Vazquez JJ, Arnalich F. Alterations in plasma and cerebrospinal fluid levels of neuropeptides in idiopathic senile anorexia. Regulatory Peptides 1993;49(2):109–17.
[17] Morley J. Pathophysiology of the anorexia of aging. Current Opinion in Clinical Nutrition Metabolic Care 2013;16(1):27–32.
[18] Bauer JM, Haack A, Winning K, et al. Impaired postprandial response of active ghrelin and prolonged suppression of hunger sensation fin the elderly. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2010;65(3):307–11.
[19] Schneider S, Al Jaouni R, Caruba C, et al. Effects of age, malnutrition and refeeding on the expression and secretion of ghrelin. Clinical Nutrition 2008;27(5):724–31.
[20] Di Francesco V, Zamboni M, Zoico E, et al. Unbalanced serum leptin and ghrelin dynamics prolong postprandial satiety and inhibit hunger in healthy elderly: another reason for the "anorexia of aging". American Journal of Clinical Nutrition 2006;83(5):1149–52.
[21] Di Francesco V, Barazzoni R, Bissoli L, et al. The quantity of meal fat influences the profile of postprandial hormones as well as hunger sensation in healthy elderly people. Journal of the American Medical Directors Association 2010;11(3):188–93.
[22] Rigamonti AE, Pincelli AI, Corrà B, et al. Plasma ghrelin concentrations in elderly subjects: comparison with anorexic and obese patients. Journal of Endocrinology 2002;175(1):R1–5.
[23] Di Francesco V, Fantin F, Residori L, et al. Effect of age on the dynamics of acylated ghrelin in fasting conditions and in response to a meal. Journal of the American Geriatrics Society 2008;56(7):1369–70.
[24] Visvanathan R, Chapman I. Undernutrition and anorexia in the older person. Gastroenterology Clinics of North America 2009;38(3):393–409.
[25] MacIntosh CG, Horowitz M, Verhagen MA, et al. Effect of small intestinal nutrient infusion on appetite, gastrointestinal hormone release, and gastric myoelectrical activity in young and older men. American Journal of Gastroenterology 2001;96(4):997–1007.
[26] Moss C, Dhillo WS, Frost G, Hickson M. Gastrointestinal hormones: the regulation of appetite and the anorexia of ageing. Journal of Human Nutrition and Dietetics 2012;25(1):3–15.
[27] Cook CG, Andrews JM, Jones KL, et al. Effects of small intestinal nutrient infusion on appetite and pyloric motility are modified by age. American Journal of Physiology 1997;273(2):R755–61.
[28] Clarkston WK, Pantano MM, Morley JE, Horowitz M, Littlefield JM, Burton FR. Evidence for the anorexia of aging: gastrointestinal transit and hunger in healthy elderly vs. young adults. American Journal of Physiology 1997;272(1):R243–8.
[29] Zandstra EH, Mathey MF, Graaf C, van Staveren WA. Short-term regulation of food intake in children, young adults and the elderly. European Journal of Clinical Nutrition 2000;54(3):239–46.

[30] Rolls BJ, Dimeo KA, Shide DJ. Age-related impairments in the regulation of food intake. American Journal of Clinical Nutrition 1995;62(5):923–31.
[31] Roberts SB, Fuss P, Heyman MB, et al. Control of food intake in older men. Journal of the American Medical Association (Chicago, IL) 1994;272(20):1601–6.
[32] Yukawa M, Cummings D, Matthys C, et al. Effect of aging on the response of ghrelin to acute weight loss. Journal of the American Geriatrics Society 2006;54(4):648–53.
[33] MacIntosh CG, Sheehan J, Davani N, Morley JE, Horowitz M, Chapman IM. Effects of aging on the opioid modulation of feeding in humans. Journal of the American Geriatrics Society 2001;49(11):1518–24.
[34] Landi F, Liperoti R, Lattanzio F, et al. Effects of anorexia on mortality among older adults receiving home care: an observation study. The Journal of Nutrition, Health Aging 2012;16(1):79–83.
[35] Donini LM, Dominguez LJ, Barbagallo M, et al. Senile anorexia in different geriatric settings in Italy. The Journal of Nutrition, Health Aging 2011;15(9): 775–81.
[36] Landi F, Russo A, Liperoti R, et al. Anorexia, physical function, and incident disability among the frail elderly population: results from the ilSIRENTE study. Journal of the American Medical Directors Association 2010;11(4):268–74.
[37] Vázquez-Valdez O, Aguilar Navarro S, Avila-Funes J. Association between anorexia of aging and disability in older community-dwelling Mexicans. Journal of the American Geriatrics Society 2010;58(10):2044–6.
[38] Cornali C, Franzoni S, Frisoni G, Trabucchi M. Anorexia as an independent predictor of mortality. Journal of the American Geriatrics Society 2005;53(2):354–5.
[39] Serra Prat M, Palomera E, Roca M, Puig Domingo M. Long-term effect of ghrelin on nutritional status and functional capacity in the elderly: a population-based cohort study. Clinical Endocrinology 2010;73(1):41–7.
[40] Reuben D, Hirsch S, Zhou K, Greendale G. The effects of megestrol acetate suspension for elderly patients with reduced appetite after hospitalization: a phase II randomized clinical trial. Journal of the American Geriatrics Society 2005;53(6):970–5.
[41] Landi F, Laviano A, Cruz Jentoft A. The anorexia of aging: is it a geriatric syndrome? Journal of the American Medical Directors Association 2010;11(3):153–6.
[42] Malafarina V, Uriz Otano F, Iniesta R, Gil-Guerrero L. Effectiveness of nutritional supplementation on muscle mass in treatment of sarcopenia in old age: a systematic review. Journal of the American Medical Directors Association 2013;14(1):10–7.
[43] Dermott M, McDaniel J, Weiss E, Tomazic T, Mattfeldt Beman M. Is physical activity associated with appetite? A survey of long-term care residents. Journal of Nutrition for the Elderly 2009;28(1):72–80.
[44] Valenzuela T. Efficacy of progressive resistance training interventions in older adults in nursing homes: a systematic review. Journal of the American Medical Directors Association 2012;13(5):418–22.
[45] Ferrari CKB. Functional foods and physical activities in health promotion of aging people. Maturitas 2007;58(4):327–39.
[46] Yu R, Yau F, Ho S, Woo J. Cardiorespiratory fitness and its association with body composition and physical activity in Hong Kong Chinese women aged from 55 to 94 years. Maturitas 2011;69(4):348–53.