Editorial

Anorexia and Weight Loss in Older Persons

John E. Morley

Division of Geriatric Medicine, Saint Louis University School of Medicine, and Geriatric Research, Education, and Clinical Center, VA Medical Center, St. Louis, Missouri.

“No fear can stand up to hunger, no patience can wear it out, disgust simply does not exist where hunger is...It’s really easier to face bereavement, dishonour and perdition of one’s soul than this kind of prolonged hunger.”

—Heart of Darkness, Joseph Conrad

UNINTENTIONAL weight loss represents a cardinal symptom of frailty in older persons (1–6). Even a small decline in body mass in older persons is associated with mortality (7). Protein energy malnutrition is associated with anemia, pressure ulcers, sarcopenia, bone loss and hip fractures, declining immune function, impaired immune response to vaccinations, infections, cognitive impairment, functional decline, and poor quality of life (8–17). Weight loss is a sentinel event in long-term care facilities and associated with particularly poor outcomes (18,19). Despite this, aggressive nutritional management when weight loss is well established is often not associated with improved outcomes (20–24). For this reason, it is important that geriatricians increase their understanding of the pathophysiological processes that underlie weight loss in older persons (25) and increase their vigilance to detect early weight loss and institute-appropriate preventive and health promotion measures (26,27).

In this issue of the Journals, Paquet et al. (28) demonstrate the importance of emotional state on food intake in older persons undergoing geriatric rehabilitation. Positive emotions at the time of eating increased food intake, while anxiety, depression, and anger had negative effects on food intake. While previously depression has been shown to have a major negative effect on food intake (29,30), this study extends these findings to demonstrate that much smaller fluctuations of mood at the time of the meal produce major effects on the amount of food ingestion. de Castro (31) found that, in older persons living in the community, social facilitation at mealtimes and palatability were major factors in the amount eaten. He suggested that increasing the number of people present at a meal could enhance food intake. This was found to be true in persons receiving Meals on Wheels by Suda et al. (32), who found that when the meal deliverer stayed while the meal was eaten, nutritional risk and dysphoria were decreased.

When staff members spend more time feeding residents in the nursing home and utilize more verbal and physical prompts, food intake increased (33). Under these circumstances, it took an average of 38 minutes to feed a resident compared to 9 minutes under usual conditions. Because of the importance of food intake, it is critical that nursing staff are trained to be able to make accurate estimations of calorie intake in older persons (34).

Enhancing the environment in which meals are eaten has been shown to improve food intake (32). Older persons eat more in the morning (31), and this circadian shift is even more marked when they develop cognitive impairment (35). Thus, it is recommended that older persons receive more food at breakfast (36). Increasing palatability of meals later in the day also improves food intake (37). For these reasons, the Clinical Guide to Prevent and Manage Malnutrition in Long-Term Care provides a number of hints to improve social facilitation of eating at mealtimes (38).

It has been suggested that weight loss is more likely to occur in older persons who are lifelong practitioners of dietary restraint, i.e., the intentional restriction of food intake to prevent weight gain (39,40). In some older persons, this has been associated with recurrence of anorexia nervosa toward the end of their life. In a normal-weight older population, Bathalon et al. (41,42) found no major differences between persons who practiced dietary restraint and those who did not. They did, however, have lower hemoglobin levels. Lower hemoglobin levels have been associated with an increase in frailty (43). Some older persons, when made aware of the studies on caloric restriction and longevity in animals, excessively restrain their food intake and develop malnutrition (44–48). Similarly, malnutrition is seen in older persons attempting to lower their cholesterol to prevent heart disease. This condition is known as “cholesterol phobia” (49). In 1988, we suggested that there was a physiological anorexia of aging that universally affected all older persons (50). The existence of a decline in caloric intake over the life span is now well established by multiple epidemiological studies (51). We postulated that this age-related physiological anorexia placed older persons at particular risk for developing malnutrition when they developed a disease process. Roberts et al. (52) showed that older persons had a deregulation of feeding regulation such that they struggled
to alter their food intake either upward or downward in response to perturbations of body mass. Over the last decade, much research has explored the factors involved in the physiological regulation of food intake (53,54). As we originally postulated in the early 1980s, much of the normal feeding system is redundant, with multiple fail-safe mechanisms to ensure that hunger and the desire to intake continues and, therefore, that the individual survives (55).

The development of the physiological anorexia of aging appears to be predominantly due to altered gastric signals resulting in early satiation (56). With aging there is a decrease in the ability of the fundus to accommodate
large volumes of food (57). This appears to be due to the failure of food in the fundus to release nitric oxide, resulting in a failure of smooth muscle relaxation (58,59). This leads to early antral filling, resulting in satiation signals being generated as the antral diameter increases (60,61). In addition, cholecystokinin, a gastrointestinal peptide that decreases hunger, circulates in higher levels in older compared to young persons (62,63) and is a more potent anorectic agent in older humans and other animals (64,65).

The role of antral nervous system neurotransmitters with aging is less clear and based predominantly on studies in rodents. The kappa opioid receptor modulator, dymorphin, has been shown to be less effective at increasing food intake in older rodents (66). However, a study in humans failed to demonstrate a clear effect of altered opioid tone in the pathogenesis of the anorexia of aging (67). Neuropeptide Y (NPY) is an important orexigenic agent. Older animals maintain their responsiveness to NPY stimulation of food intake (68), but have a reduction in NPY gene expression in response to starvation in older animals (69). Within the central nervous system, nitric oxide appears to play an important coordinating role in the production of feeding due to a variety of orexigenic neuropeptides such as orexin, neuropeptide Y, ghrelin, and agouti-related peptide (70,71). There is evidence that, with aging, there is a decline in the efficacy of the nitric oxide-synthesizing mechanisms related to feeding (59).

Leptin (from the Greek for “thin”) is a peptide hormone produced by adipose cells that results in a decreased food intake and an increase in metabolic rate (72). With aging in men, there is a decline in testosterone levels (73–75), and this is associated with an increase in leptin levels out of proportion to fat loss in older males (76,77). However, another study failed to show a correlation between leptin levels and involuntary weight loss in older humans (78). This may be due, in part, to the development of leptin resistance with aging (79). In older animals, testosterone deficiency is associated with an increase in the anorectic peptide, cocaine-amphetamine-regulated transcript (CART) peptide, and a decrease in NPY, which could be reversed by the administration of testosterone (80).

Recently ghrelin, an orexigenic peptide produced by the fundus of the stomach, has been isolated (81). Its feeding-enhancing effects are antagonized by a metabolite of peptide YY, PYY$_{3-36}$ (82). Peptide YY has been shown to produce weight loss when administered peripherally (83). Ghrelin also produces growth hormone release, which has been used to treat malnutrition in older persons (84,85). These agents may well prove to be important mediators of the gastric-induced satiation component of the anorexia of aging. The complex interactions of these neurotransmitters in the pathophysiology of the anorexia of aging are outlined in Figure 1. However, as pointed out in the pages of the Journals, long-term use of growth hormone is unlikely to enhance longevity (86–88).

As so eloquently attested to by Blumenthal (89) in a recent issue of the Journals, the aging-disease dichotomy is often an inseparable conundrum. This is particularly true when anorexia and weight loss are accelerated in older persons when they develop one or more disease processes. Thus, cancer and end-stage heart disease can lead to “the cancer anorexia-cachexia syndrome” and the “cardiac cachexia syndrome,” respectively (90–92). Cachexia is derived from the Greek words kakos meaning “bad” and hēsis meaning “condition.” The development of these cachexia syndromes appears to be related to the release of cytokines by the diseased tissues (93). Tumor necrosis factor α, interleukin-1, interleukin-6, and ciliary neurotrophic factor appear to be particularly potent cytokines responsible for anorexia, muscle mass loss, and low albumin levels (94,95). Cytokines decrease albumin levels by decreasing production of albumin and producing extravariation of albumin outside of the intravascular space (95–97). In addition, cytokines activate nuclear factor kappa B, which reduces the formation of Myo D, and thus decrease muscle repair (98). Cytokines can produce their effects peripherally on multiple tissues, but they also produce effects on the central nervous system either directly by crossing the blood-brain barrier or secondarily by stimulating ascending fibers of the autonomic nervous system (99).

The majority of pathological causes of weight loss are reversible. For the clinician, these causes are easily remembered by using the “MEALS-ON-WHEELS” mnemonic (Table 1; 100). Depression is the major reversible cause of weight loss (28,30,101). Therapeutic diets remain a common cause of weight loss, and their utility in older persons, particularly those in nursing homes, continues to be of questionable value (102–104). If caloric supplements are to be used, they should be administered at least 1 hour before the meal or their major effect is mainly to reduce the size of the meal the elderly person would have eaten (105).

There is increasing enthusiasm for the use of orexigenic agents in the treatment of anorexia and weight loss in older persons. Megestrol acetate increases weight in older persons (106,107) most probably by decreasing cytokine production. Unfortunately, this is associated with a decline in testosterone levels, resulting in a decline in lean mass while increasing fat mass (108, and see 109 in this issue of the Journal). Testosterone can increase muscle mass in older persons (110,111), and its decline with aging is associated with a decline in muscle mass, strength, and functional status (112,113). Testosterone replacement may enhance function in older persons during rehabilitation (114).

Table 1. MEALS-ON-WHEELS Mnemonic for Reversible Causes of Weight Loss

| Medications (e.g., digoxin, theophylline, cimetidine) |
| Emotional (e.g., depression) |
| Alcoholism, elder abuse, anorexia tardive |
| Late life paranoia |
| Swallowing problems |
| Oral problems |
| Nasocomial infections (tuberculosis, clostridium difficile, helicobacter pylori) |
| Wandering and other dementia-related behaviors |
| Hyperthyroidism, Hypercalcemia, Hyperadrenalism, Hyperglycemia |
| Enteral problems (e.g., gluten enteropathy) |
| Eating problems |
| Low salt, low cholesterol, and other therapeutic diets |
| Stones (cholecystitis) and shopping problems |
Potential Pharmacological Approaches To Treatment of Anorexia and Weight Loss in Older Persons

Antidepressants → Limbic System

Hypothalamus

NPY Agonist
Other Orexigenic Agonists
CRF Antagonist
Other Anorectic Agonists
NSAIDS

Serotonin Antagonists

Blood-Brain Barrier

Dronabinol
Progestagens

Ghrelin Agonists
Nitrates
CCK Antagonist
PYY$_{3-36}$ Antagonist

Leptin Antagonists

Prokinetic Agents

Testosterone Anabolic Steroids

Pentoxyfillin
Thalidomide
Megestrol Acetate
NSAIDS

Cytokine Antagonists

Figure 2. Potential pharmacological approaches to treatment of anorexia and weight loss in older persons. NPY = neuropeptide Y; CRF = corticotropin-releasing factor; NSAIDS = nonsteroidal anti-inflammatory drugs; CCK = cholecystokinin; PYY = peptide YY.
Appetite stimulation and a feeling of general well-being are well-recognized effects of marijuana (115). Dronabinol, a cannabis derivative, is available and has been shown to enhance appetite and mood in patients with end-stage dementia, cancer, and AIDS (116–118). This agent can also inhibit vomiting and decrease pain, making it an excellent agent for use in end-of-life care (119). This drug appears to produce its effect through the endogenous CB1 cannabinol receptor. The function of endogenous cannabinoids is regulated by leptin (120).

The effects of the antiserotonergic agent, cyproheptadine, have been disappointing. Thalidomide inhibits cytokine release and may prove to be an excellent agent for treatment of cachexia syndromes (121). An approach to the development of drugs for the anorexia of aging is given in Figure 2.

Weight loss is considered a sentinel event in nursing homes. Enormous strides have been made in the understanding of weight loss and anorexia over the last decade. Clinicians should be regularly screening for nutritional risk using tools such as the Mini-Nutritional Assessment Short Form (122), SCREEN [Seniors in the Community: Risk Evaluation for Eating and Nutrition] Questionnaire (123), or the Appetite Questionnaire (119). When older persons who are at nutritional risk are detected, the guidelines for nutritional management published in the Journals should be consulted (18).

REFERENCES


