Review

Rational Approach to Patients With Unintentional Weight Loss

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Unintentional weight loss is a problem encountered frequently in clinical practice. Weight loss and low body weight have potentially serious clinical implications. Although a nonspecific observation, weight loss is often of concern to both patients and physicians. There are multiple potential etiologies and special factors to consider in selected groups, such as older adults. A rational approach to these patients is based on an understanding of the relevant biologic, psychological, and social factors identified during a thorough history and physical examination. The goal of this article is to discuss the clinical importance, review potential pathophysiology, and discuss specific etiologies of unintentional weight loss that will enable the clinician to formulate a practical stepwise approach to patient evaluation and management.

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AIDS = acquired immunodeficiency syndrome; BMI = body mass index

Body weight is determined by a complex interaction of caloric intake, absorption, and utilization. Multiple factors (age, health status, medications, etc) influence this interaction. Among healthy people, total body weight tends to peak in the fifth to sixth decade of life.[1-3] Once weight has peaked, there is relative stability, with longitudinal studies of physique changes demonstrating a decrease of only 1 to 2 kg per decade thereafter.[2,3]

Clinically important weight loss can be defined as the loss of 10 lb (4.5 kg) or more than 5% of the usual body weight over a period of 6 to 12 months, especially when progressive. Weight loss greater than 10% is considered to represent protein-energy malnutrition, which is associated with impaired physiologic function such as impaired cell-mediated and humoral immunity.[4] Weight loss in excess of 20% implies severe protein-energy malnutrition and is associated with pronounced organ dysfunction.[5] Weight loss may also be characterized by the decrease in lean body mass relative to body fat. Excessive loss of lean body mass results in skeletal and cardiac muscle wasting and loss of visceral protein.[6] Accompanying nutrient deficiencies also have clinical implications.

As a cumulative effect, low body weight and weight loss are powerful predictors of morbidity (eg, wound healing, infectious complications, pressure sores, performance status), response to medical therapy, and mortality.[6-11] Weight loss is usually a concern for both patients and physicians; however, weight loss is a nonspecific finding with broad diagnostic possibilities. Indeed, the etiology can be multifactorial or idiopathic. Unintentional weight loss is encountered frequently in clinical practice, identified in up to 13% of elderly outpatients[12] and 50% to 65% of nursing home residents.[13,14] Some patients may be undisturbed by their weight loss, may welcome it, and may mistakenly attribute it to their attempts to lose weight. Therefore, routine determination of weight is an important strategy in any primary care practice.

Given the prevalence of unintentional weight loss, particularly among older adults, and the associated clinical importance of weight loss and low body weight, the clinician must address several important questions. Does the patient have an underlying malignancy or other serious illness? What are the immediate clinical implications of the weight loss (eg, operative morbidity) for this patient? What is the best way to proceed with an evaluation? How should this patient be treated?

PATHOPHYSIOLOGY OF WEIGHT LOSS

The precise mechanism of weight loss is unknown in many patients. Caloric intake, absorption, utilization, and loss are key components that determine an individual's weight. Alteration in the balance of these components affects a patient's ability to maintain weight. For example, caloric intake may be modified by altered smell or taste, anorexia, nausea, abnormal satiation, etc. Absorption may be modified by altered gastrointestinal motility, exocrine pancreatic function, mucosal absorptive capacity, luminal bacteria, and medications, among other factors. Utilization is primarily affected by the metabolic rate, which is affected

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by the systemic inflammatory response of various medical conditions. In addition to primary gut disease, excessive loss of calories can be secondary to diseases of the skin and kidneys. Mediators of anorexia and weight loss include cytokines such as cachectin (tumor necrosis factor) and interleukins, humoral substances (eg, bombesin-like substances, hypersensitivity to cholecystokinin), and proposed anorectic agents such as corticotropin-releasing factor.[15,16]

ETIOLOGIES OF WEIGHT LOSS

Whereas dieting and eating disorders (ie, anorexia nervosa and bulimia nervosa) explain most cases of intentional weight loss, unintentional weight loss can be divided into organic, psychosocial, and idiopathic etiologies. Additionally, selected groups (eg, older adults) often have multiple etiologies to explain their weight loss. Three studies that have evaluated the etiologies of unintentional weight loss, defined as more than 5% of usual body weight, are summarized in Table 1.[17-19] Although each study can be challenged for methodological bias, several key concepts emerge: (1) among organic etiologies, cancer is most common; (2) the etiology of weight loss is evident without an extensive evaluation in most patients; and (3) psychiatric illness and nondiagnostic evaluations are common.

Similar studies from France[20] and Mexico[21] have reported a higher prevalence of psychiatric etiologies (primarily depression and stress), prompting the authors to encourage a thorough search for psychiatric disorders. Of note, although patients with involuntary weight loss have higher mortality rates than those without weight loss, the prognosis appears to be better for those in whom no organic cause of weight loss is identified.

Organic Etiologies of Unintentional Weight Loss

The organic etiologies most commonly identified in patients presenting with unintentional weight loss are listed in order of decreasing frequency.[4,17-21]

Cancer.—Malignancies account for approximately one third of all patients presenting with unintentional weight loss. Signs and symptoms suggesting malignancy may be nonspecific or subtle but are often identified by history and physical examination. Metabolic derangements, often coupled with the production of anorectic agents, have been implicated as pathophysiologic mechanisms. Malignancies to consider include gastrointestinal, hepatobiliary, hematologic, lung, breast, genitourinary, ovarian, and prostate.

Gastroenterological Disorders.—Gastroenterological disorders are the most common nonmalignant organic etiologies identified in patients with unintentional weight loss, accounting for about 15% of cases in published series. Peptic ulcer disease, inflammatory bowel disease, dysmotility syndromes (eg, gastroparesis and pseudoobstruction), chronic pancreatitis, celiac disease, constipation, atrophic gastritis, and oral problems (eg, poor dentition, periodontal disease, and xerostomia) are some of the potential etiologies that can precipitate weight loss. A thorough history and physical examination will usually reveal signs or symptoms suggestive of a primary gastrointestinal etiology.

Endocrine Diseases.—Diabetes mellitus, hyperthyroidism, and hypothyroidism are the most common endocrinopathies that cause unintentional weight loss. Less common diagnoses include pheochromocytoma, panhypopituitarism, adrenal insufficiency, and hyperparathyroidism.

Infection.—Tuberculosis, fungal disease, parasites, subacute bacterial endocarditis, human immunodeficiency virus, and other hidden infections can occasionally cause unintentional weight loss. Asking about risk factors, including travel, occupation, living arrangements, lifestyle, and history of exposure, is essential. Patients with the acquired immunodeficiency syndrome (AIDS) may develop AIDS wasting syndrome, one of the most common AIDS-defining illnesses.

Medications.—Frequently overlooked, medications are an important potential etiology of unintentional weight loss, particularly in elderly patients. Adverse effects, including anorexia, nausea, diarrhea, and dysgeusia, can alter the intake, absorption, and utilization of nutrients.

Cardiovascular Diseases.—Cardiovascular diseases can lead to unintentional weight loss via multiple mechanisms, but the primary mechanisms are increased metabolic demand and decreased appetite and caloric intake. Cachexia is a frequent complication of severe congestive heart failure (ie, cardiac cachexia). Routine dietary restrictions for patients with cardiac disease may further accentuate weight loss. Mesenteric ischemia is relatively uncommon but should be considered. Affected patients present with sitophobia (fear of eating). Inadequate blood flow to the gut postprandially precipitates abdominal discomfort, termed *intestinal angina*, that improves following revascularization.

Neurologic Illness.—Nervous system injury or degeneration (eg, stroke, quadriplegia, multiple sclerosis, and dementia) can contribute to visceral dysfunction (ie, dysphagia, constipation) and other functional limitations that impair caloric intake. One such example is Parkinson disease, which has been associated with intestinal dysmotility, defecatory dysfunction, and increased caloric demands. In addition, prescribed medications often cause xerostomia, anorexia, and early satiety, which further compromise nutrient intake. Cognitive dysfunction, such as dementia, frequently diminishes interest in nutritional intake, which can lead to unintentional weight loss.

Table 1. **Published Studies of Unintentional Weight Loss**

Study	Marton et al[17]	Rabinovitz et al[18]	Thompson & Morris[19]
Design	Prospective	Retrospective	Retrospective
Population	70% Inpatient	Inpatient	Outpatient
Study size (No. of patients)	91	154	45
Mean age (y)	59	64	72
Male:female ratio	90:1	1.2:1	1:2
Weight loss (time)	>5% (6 mo)	>5% (unspecified)	>7.5% (6 mo)
Mortality (follow-up)	25% (18 mo)	38% (30 mo)	9% (24 mo)
Diagnosis (%)			
Cancer	19	36	16
Organic (not cancer)	50	30	40
Psychiatric	9	10	20
Idiopathic	26	23	24

Pulmonary Diseases.—As with cardiac diseases, unintentional weight loss may be a secondary manifestation of pulmonary diseases. Severe chronic obstructive pulmonary disease can lead to an increase in metabolic demands secondary to the increased use of accessory muscles of respiration. Dyspnea, aerophagia, and adverse effects of medication often produce anorexia, early satiety, bloating, and dyspepsia—all factors that may contribute to reduced nutrient intake.

Renal Disease.—Uremia often produces anorexia, nausea, and vomiting. Protein loss in the urine, as seen in patients with nephrotic syndrome, often leads to a negative caloric balance. Hemodialysis is accompanied by swings in metabolic balance that have been associated with losses in lean body mass over time.

Connective Tissue Diseases.—Acute and chronic inflammatory diseases increase metabolic demand, and associated anorexia may also disrupt nutritional balance. In addition, connective tissue diseases that affect the gut (eg, scleroderma) may produce various motility disturbances, including dysphagia, delayed gastric emptying, pseudoobstruction, and constipation. Resultant bacterial overgrowth may exacerbate nutrient malabsorption. All these sequelae can compromise the intake, absorption, and utilization of nutrients.

Psychosocial Etiologies of Unintentional Weight Loss

Blazer and Williams[22] reported that 15% of elderly people have depressive symptoms, with approximately 4% meeting criteria for major depression. In addition, 2% to 3% of patients aged 65 to 79 years have dementia; this increases to 20% in those older than 80 years.[16] Depression and dementia, which are poorly recognized in clinical practice, may lead to apathy, an inability to care for oneself, and a decreased recognition for the need to eat, all of which lead to weight loss. In fact, weight loss may not just be a late manifestation of dementia but may be one of the most apparent presenting symptoms.[23]

In a longitudinal study of patients with Alzheimer disease, White et al[24] found that nearly twice as many patients experienced a weight loss of 5% or greater compared with controls. This finding of weight loss was confirmed in a review of 8 international studies on nutrition in patients with Alzheimer disease.[25] The presence of altered affect or cognition should also prompt an evaluation for associated medical conditions (eg, thiamin, folate, or vitamin B_{12} deficiency) that may present with symptoms similar to depression or dementia.[7,26-29]

Anxiety has been associated with several functional gastrointestinal disorders, including rumination syndrome and nonulcer dyspepsia. Weight loss may accompany these disorders.[30,31] Treatment directed at the psychological cause is often helpful. Other psychosocial issues include alcoholism, physical isolation, poverty, and other barriers to obtaining adequate nutrition. These functional limitations are frequently underappreciated by physicians and family members.

Older adults represent a select group of patients in whom multiple medical, pharmacological, and psychosocial issues can lead to weight loss. Since lean body mass declines with age, weight loss in the elderly population may be of greater clinical importance. Several excellent reviews have outlined special considerations in the evaluation and management of weight loss in older adults.[7,32-35] Identification of weight loss in the elderly population should prompt a thorough evaluation that includes an assessment of specific age-related factors (impaired smell and taste, dementia, social isolation, etc) and common organic etiologies. Robbins[33] nicely summarized many of these considerations in his "nine D's" of weight loss in the elderly population (Table 2).

Table 2. **The Nine D's of Weight Loss in the Elderly**

Dentition	Depression
Dysgeusia	Dementia
Dysphagia	Dysfunction
Diarrhea	Drugs
Disease (chronic)	

Reprinted with permission from Robbins.[33]

EVALUATION OF UNINTENTIONAL WEIGHT LOSS

In most patients, the etiology of unintentional weight loss is identified through a detailed history and physical examination. Key concepts of the evaluation include: (1) document weight loss—in up to 50% of patients, weight loss cannot be documented[13]; (2) perform a detailed history—medical, psychosocial, and dietary—and physical examination; (3) perform tests based on history and physical findings in conjunction with limited standard tests; and (4) establish appropriate follow-up to assess response to management.

A rational stepwise approach to the patient presenting with unintentional weight loss is outlined in Figure 1. If targeted investigations fail to reveal a diagnosis, completion of a limited standard testing panel, to include age-dependent cancer screening, is indicated. Given the high prevalence of gastroenterological disease, evaluation of the upper and lower gut should be considered, particularly in patients with gastrointestinal symptoms. Several factors, including age, patient tolerance, and presence or absence of anemia or diarrhea, will help the clinician in determining the diagnostic yield of endoscopy vs radiographic studies.

Assessment of study results and reevaluation of the patient should be followed by a definitive plan. Patients with a negative evaluation are unlikely to have a serious organic explanation for weight loss. The clinician should be cognizant of relevant psychosocial issues that may have a role in the patient's presentation. Additional studies should be performed for specific concerns or to follow up abnormalities identified on initial testing (Table 3). If a satisfactory evaluation is negative (in about 25% of patients), one should establish a management plan that includes a predetermined follow-up in 3 to 6 months because some causes of weight loss can be subtle and may be revealed with time and continued vigilance. Additionally, many patients' nutritional status should be monitored even if a specific etiology of weight loss cannot be determined.

MANAGEMENT PRINCIPLES

Early intervention based on the findings of the diagnostic evaluation provides the greatest opportunity for success. The severity of weight loss should be determined by a nutritional assessment, including a biochemical analysis combined with a thorough dietary history, evaluation of the patient's psychosocial situation, and consideration of anthropometric or other qualitative evaluations. A simple and common anthropometric evaluation is the body mass index (BMI). The BMI is defined as body weight (kilograms)/height (meters^2). A BMI lower than 17 is consistent with undernutrition.

The specific etiologies of weight loss should be treated accordingly, with medications, structural or functional modifications (eg, gut revascularization, dentistry), nutritional supplementation, psychosocial modulation, or multimodal therapy. These treatments are also beneficial for patients with no specific diagnosis because low body weight and weight loss are risk factors for morbidity and mortality regardless of the underlying etiology.[40]

Nutritional Therapy

Nutritional therapy, including dietary education and/or use of dietary supplements supervised by a dietitian, is beneficial for most patients. One should consider reducing dietary restrictions instituted for an underlying disease if they are further aggravating nutritional balance. The goal of nutrient intake in patients with low body weight and pronounced weight loss should be 30 to 35 kcal/kg per day with 20% or greater protein content. For malnourished elderly patients and those with mild to moderate illness, a goal of 40 kcal/kg per day should be used.[35] High caloric snacks and nutritionally complete supplements are useful; however, one should be mindful of the timing of supplement delivery (snacks between rather than with meals) and the type of supplement prescribed (composition, patient tolerance, etc).[34] Nutritional supplementation should be enteral, with the oral route preferred. For patients who are unable to ingest adequate calories, tube feeding, either with a temporary nasojejunal tube or more permanent access with a percutaneous gastric or jejunal tube, should be considered.[41-46] The addition of a daily multivitamin will help restore deficient micronutrients. Parenteral nutrition should be reserved for highly selected patients.

Pharmacological Therapy

Various agents[4,47] that have been used to stimulate appetite and promote weight gain are listed in Table 4. Although some studies involving selected patients (eg, those with AIDS and cancer) suggest efficacy manifested as improved appetite and weight, studies demonstrating improvement in long-term survival are not available. Some of these drugs have serious potential adverse effects and should be used with caution. Any therapeutic trials with these agents necessitate close supervision.

Additional Considerations for Older Adults

As mentioned previously, psychosocial issues are prevalent in older adults. In addition to the aforementioned

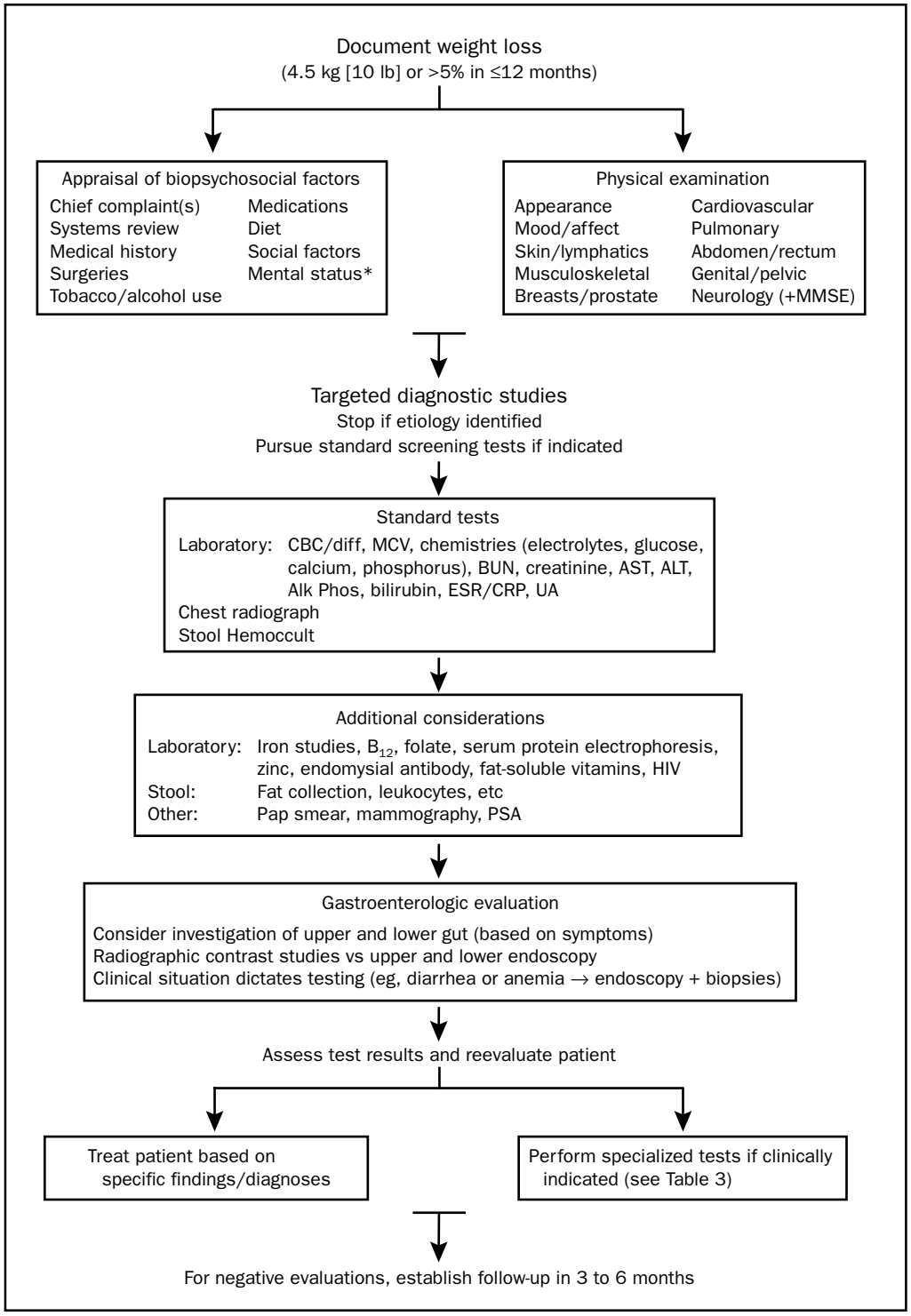

Figure 1. Stepwise approach to patients with unintentional weight loss. Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood cell count; CRP = C-reactive protein; diff = white blood cell count differential; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; MCV = mean corpuscular volume; MMSE = Mini-Mental State Examination[36]; Pap = Papanicolaou; PSA = prostate-specific antigen; UA = urinalysis. *Depression inventories may be useful.[37-39]

Table 3. **Specialized Testing to Consider in Patients With Unintentional Weight Loss***

Structural investigations	Small bowel x-ray film (inflammatory bowel disease, diarrhea, malabsorption, obstruction) Body CT scan (malignancy, abscess, chronic pancreatitis, intestinal complications, etc) Mesenteric Doppler ultrasonography vs angiography (intestinal ischemia)
Functional investigations	Scintigraphic assessment of gastrointestinal/colonic transit (dysmotility)
Laboratory studies	RPR, PPD, LDH, growth hormone, testosterone
Histopathology	Small bowel (malabsorptive process), colon (diarrhea), amyloid staining, etc
Psychosocial issues	Formal testing, psychology or psychiatry consultation

*Based on clinical concerns or preliminary findings. CT = computed tomography; LDH = lactate dyhydrogenase; PPD = purified protein derivative; RPR = rapid plasma reagin.

standard management, clinicians should discuss the following factors[48] with their elderly patients when appropriate: maintain companionship during meal preparation and intake; optimize meal preparation (eg, receive meals from meals-on-wheels); maximize caloric intake during the favorite meal of the day; take medication with meals to limit adverse effects such as anorexia, nausea, and early satiety; avoid gas-forming foods and beverages; manage bowel movements to avoid constipation and diarrhea; increase physical activity to stimulate appetite and improve sense of well-being; and promote oral health.

SUMMARY

Body weight, as determined by several key components, remains relatively stable over time. Unintentional weight loss, defined as a decrease of more than 5% of usual body weight during a 6- to 12-month period, is an important predictor of morbidity and mortality. However, weight loss is a nonspecific finding with multiple possible etiologies, including organic, psychosocial, and idiopathic. A rational stepwise approach based on relevant data extracted from the history and physical examination, with special attention to psychological and social issues, is highly effective in establishing a diagnosis and determining effective management. Treatment should be based on the results of the tests and each patient's clinical situation.

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Table 4. **Agents Used to Stimulate Appetite and Promote Weight Gain**

Category	Examples
Orexigenic agents	
Corticosteroids	Dexamethasone, methylprednisolone
Progestational agents	Megestrol acetate, medroxyprogesterone acetate
Dronabinol	Marinol
Serotonin antagonist	Cryoheptadine
Anabolic agents	
Growth hormones	Growth hormone, insulin-like growth factor
Androgen therapy	Testosterone, dihydrotestosterone, testosterone analogues
Anticatabolic agents	
Dietary anticytokine	ω-3 Fatty acids
Methylxanthine derivative	Pentoxyifylline
Inhibitor of gluconeogenesis	Hydrazine sulfate
Proposed anticytokine activity	Thalidomide, melatonin

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