

Unintentional Weight Loss: etiology, Clinical Characteristics, Predicting Factors of Malignancy and Outcomes.

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Abstract

Background: Unintentional weight loss (UWL) is associated with increased morbidity and mortality. Etiology is wide and there are no specified predicting factors for underlying malignancy. Our objective is to examine the etiologies, characteristics, mortality, and need of hospital admissions in a cohort of outpatients with UWL.

Methods: We retrospectively reviewed patients referred to an outpatient quick diagnosis consultation for evaluation of UWL. A standard baseline evaluation with laboratory tests, chest X-ray, and abdominal ultrasonographic examination were performed in all patients. Patients without initial diagnosis were followed up for 6 months, and all patients for 5 years or death using electronic medical records.

Results: Overall 145 patients (mean age 70 [17.6] years; 50.3% males) were included. Predominant etiologies were non-malignant organic disorders (48.2%, mainly digestive diseases), malignancies (31%), and psychosocial disorders (10.4%). Malignancies, smoking, higher level of ESR, CRP, LDH, abnormal chest X-ray, and mortality were higher in males and patients aged ≥ 65 years. Patients with malignancies had a higher mortality rate and needed hospitalization more frequently than other groups. After initial work up, 10.4% patients remained without diagnosis. Elderly, male sex and the need of hospital admission were related to a final diagnosis of malignancy and the presence of an abnormal physical examination with early mortality.

Conclusion: Patients with UWL are mostly older, with non-malignant organic disorders, especially digestive diseases. Risk factors for underlying cancer are male sex, high level of ESR, CRP, LDH, and aged ≥ 65 years. Outpatient consultation seems to be the optimal setting to assess patients with UWL and few patients need hospital admission in our study. Mortality rate is high, especially in those patients with malignancy. Follow up is needed in patients with initially normal work up.

Introduction:

Unintentional weight loss (UWL) is an important challenge for every clinician. Most published case series studies define UWL as weight loss of 5% or greater as compared to the usual body weight in six months to a year(1-3), while other studies use a criterion of up to 7.5% or 10% of weight loss (1,2,4). Irrespective of the criterion used, it is important that the patient does not purposefully set out to lose weight. It may be present as the patient's chief complaint or may be found by observation by a clinician or family member, and requires comprehensive evaluation to determine its cause.

The prevalence of UWL ranges from 15% to 20% in older adults and it has been associated with increased morbidity and mortality (5). The yearly incidence varies between 0.6% and 7.3% (1,6,7). UWL is a non-specific condition and there are no published guidelines for evaluation, appropriate work-up and management. The rate of diagnosis after the initial work-up ranges from 33% to 60% (8,9).

The path physiology of UWL is poorly understood. Body composition is known to changes with age, and should be kept in mind with older patients. The total body weight usually peaks at 60 years of age, with small decreases of 0.1 to 2 kg per year after the age of 70 years. Thus, substantial weight changes should not be attributed to the normal anorexia of aging (10). In older adults, the most common etiologies are malignancies (19% to 36%), nonmalignant gastrointestinal disease (9% to 19%), and psychiatric disorders such as dementia and depression (9% to 24%). Nonmalignant disease is therefore a more frequent cause than malignancy (11,12). Other common etiologies include endocrine, neurological, rheumatic, and cardiovascular, alcohol-related, or infectious diseases. Financial constraints, lack of assistance in obtaining and preparing meals, and impairment in activities of daily living also play an important role in some patients.

Even when an appropriate work-up has been performed, the etiology remains unknown in 6% to 28% of patients (11,12). Some studies have focused on the role of inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 β , tumor necrosis factor α (TNF- α), gut hormones (such as glucagon-like peptide, cholecystokinin, and ghrelin), but at present their relationship with UWL is not clearly established (13).

The aim of our study was to assess the etiology, and the clinical, laboratory, and complementary exploration characteristics, as well as the mortality of a group of patients with UWL and to investigate possible differences between malignant and non-malignant etiologies.

Material and Methods:

Setting: The creation of alternatives to hospitalization, such as hospital-based outpatient's rapid diagnosis consultations has contributed to decreasing emergency department referrals from primary physicians and has ensured higher patients' satisfaction scores and significant cost savings. This type of consultation ensures a time-to-diagnosis similar to conventional hospitalization for the same evaluable condition, if the patient's medical status allow it (14,15). We therefore performed our study using rapid diagnosis consultations.

Study design and population: In this retrospective study, the inclusion criteria were an age older than 18 years, with $\geq 5\%$ reduction in the usual body weight during the last 6 - 12 months, with UWL being the only or dominant feature of disease. We excluded patients with intentional weight loss, known malignancy because one objective was to find predictors of malignancy in these patients, eating disorders, or hospitalization for any cause within the previous 3 months. Patients were referred by family physicians or emergency department physicians for a rapid diagnosis consultation at the hospital. Patients with a combination of UWL plus asthenia and/or anorexia were referred. The general status of the patients was sufficiently good to travel to hospital and back home for visits and complementary explorations. The study was performed from August 1st 2012 until December 31st 2012.

Evaluation: Medical record-takings (using electronic medical records [EMR]), anamnesis, and thorough physical examination (searching for physical examination abnormalities such as lymph node, liver or spleen enlargement, palpable abdominal mass...) were performed in all patients by a consultant internist. Initial tests were carried out as appropriate, according to the clinical evaluation. Minimal investigations included standard laboratory tests, such as hemogram, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum biochemistry (including basic metabolic panel, liver function tests, thyroid function tests, lactate dehydrogenase [LDH]), serum protein electrophoresis (proteinogram), fecal occult blood tests, urinalysis, chest X-ray, and abdominal ultrasound studies. Other examinations, such as additional laboratory or microbiological tests, computed tomography, PET (positron emission tomography) scanning, endoscopies, and biopsy/cytology studies, were ordered when needed.

Follow-up: All patients were followed-up for 5 years or until death, by checking the electronic medical records. Clinical follow-up, in patients with an initially normal work-up, consisted of 2 or 3 medical consultations during the next 6 months.

Statistical analysis: To compare categorical data, the chi-square test or the Fischer's exact test, when appropriate, was used and expressed as absolute frequencies (%). The *t*-test was used to compare continuous variables with a normal distribution, which were expressed as means with standard deviation (SD). To assess normality we used the Kolmogorov-Smirnov test. The Mann-Whitney U test was performed to compare continuous variables with skewed distributions. Statistical significance was established at 0.05. Multivariable linear regression models were used to determine the association between final diagnosis of cancer or mortality (as dependent variables) and the demographic, health-related or biological data. Analyses were performed using SPSS software (version 22.0) (SPSS, Chicago, USA).

Ethics: Using the Galician Health Services Authority online tool, it was determined that Galician Research Ethics Committee Approval was not required for this study. As this was a retrospective study, an informed consent for the medical record reviews was not obtained.

Results:

General characteristics of study population:

A total of 145 patients with UWL were included in the study; 50.3% were males and mean age was 70 (17.6) years. The estimated weight loss was 7.2 (3.5) kg. Self reported mean time for weight loss was 4.6 ± 6.1 months. Smoking and drinking status, mean time-to-diagnosis, and abnormal physical assessment results are shown in Table 1.

Causes of UWL:

After a complete initial work-up, in 89.7% of patients, the etiology of UWL could be established, and only 10.3% of patients remained with unexplained UWL. For analysis purposes, 4 main groups were established: malignancy (n= 45 [31%]), nonmalignant organic disorder (n = 70 [48.2%]), psychosocial disorder (n = 15 [10.4%]), and unexplained UWL (n = 15 [10.4%]) (Tables 2 and 3).

Malignancy: Underlying cancer was diagnosed in 45 (31%) patients. Over all, digestive cancers were the most frequent cause of malignancy-related UWL (n = 21 [46.6%]). Among these, colorectal cancer was the most common (49%) followed by pancreatic cancer (28%), and gastric cancer (18%).

Non-malignant organic disorders: non-malignant organic disorder was the most frequent etiology overall in our study (n = 70). The most common disorders were digestive conditions (n = 43 [29.7%]), followed by infections, endocrinopathies, and respiratory diseases.

Psychiatric disorders and social factors: Psychiatric causes were diagnosed in 13 (9.1%) patients. The most frequent cause was depression followed by anxiety. Social factors were responsible in 2 (1.4%) patients; in both cases, this was related to economic circumstances.

Differences according to groups:

Patients with malignancies were older ($p=0.026$), mostly men ($p=0.016$), had higher levels of CRP ($p=0.022$), ESR ($p=0.003$) and more frequently had anemia ($p=0.020$) and thrombocytopenia ($p=0.021$). Abnormalities on physical assessment ($p=0.008$), renal failure ($p=0.005$), higher levels of tumor markers ($p=0.001$), and LDH ($p=0.004$). Abnormal results on chest X-ray ($p=0.029$), abdominal ultrasonography ($p=0.001$), computed tomography ($p=0.001$), upper digestive endoscopy ($p=0.019$) and colonoscopy ($p = 0.001$) were also more frequent in patients with final diagnosis of malignancy. Multivariate analysis, after adjusting for age and sex, showed that age (OR 1.1 IC 95% 1.02-1.14; $p=0.01$), male sex (OR 5.6 CI 95% 1.4-23; $p=0.015$), and the need of hospital admission (OR 29 IC 95% 5-171; $p=0.001$) were predictors of malignancy.

Differences according to sex:

Underlying malignancy, smoking, alcohol intake, higher ESR, LDH, CRP, abnormal protein gram, abnormal chest X-ray, and anemia were more frequent in men than in women (Table 4).

Differences according to age:

When comparing patients aged <65 years ($n = 47$) to those aged ≥ 65 years ($n = 98$), several significant differences were found. Older patients more frequently had a final diagnosis of cancer, were smokers, and had higher levels of ESR and LDH, abnormal chest X-ray, as well as a higher mortality rate (Table 4).

Clinical outcome according to groups:

A total of 50 (34.5%) patients died during follow-up. Cancer patients had the highest mortality rate (66%). Half of the patients died in the first year after diagnosis. Hospital admission was required in 21 (14.5%) patients. The main causes were a rapid clinical deterioration, leading to the need for hospitalization (8 patients) or the need for further in-hospital medical explorations (8 patients) (Table 5). Multivariate analysis, after adjusting for sex, showed that the presence of an abnormal physical examination (OR 4.6 IC 95% 1.5-14.1; $p=0.008$) was a predictor of early mortality.

Discussion:

We here reported a cohort of patients with UWL. While the main etiologies of UWL generally agreed with those described in previous studies, the incidence of malignancies was very high in our study without differences regarding to sex, but most patients were elderly (mean age: 70 years).

Non-malignant organic disorders were the most frequent etiology (60.1%). Similar to previous reports (8, 9, 12, 16), digestive disorders predominated (29.7%), followed by infectious diseases (5.5%).

The second leading cause was malignancy, which accounted for nearly one-third of UWL patients overall, which is in accord with previous reports (6,16). The most common cancer was colorectal cancer followed by pancreatic cancer. Patients with cancer were older and were mainly men. Patients with malignancies lost a greater amount of body weight, had more related symptoms, had abnormal physical examinations, and had more laboratory test, chest X-ray, and abdominal ultrasonographic abnormalities, after the initial work-up, as compared with the other etiological groups.

Psychological disorders, mainly depression and anxiety, explained UWL in 10.4% of patients. The initial cause of UWL was not identified in 10.4% of patients.

There were some sex differences in our study. Several variables, such as tobacco and alcohol intake, abnormal chest X-ray, abnormal protein gram, the presence of anemia, and higher levels of ESR, LDH, and CPR were more frequent in men than in women. Men also had a greater probability of UWL related to underlying malignancy.

UWL has been more extensively investigated in elderly individuals than in younger patients (5, 11, 17-20). Some reports have indicated that 15–20% of patients aged ≥ 65 years have UWL (5-17). Similar to other studies, non-malignant organic disorders, malignancies, and psychological disorders were more common in the older subjects in our study. In our study, patients aged ≥ 65 years were most frequently smokers, had higher level of ESR, and LDH, and had abnormal results in a chest X-ray examination. The probability of being diagnosed with cancer, as well as the mortality rate, was also higher in elderly patients. In fact, advanced age, male sex, and the need of hospital admission were predictors of underlying malignancy.

Psychiatric disorders are an important cause of UWL, in up to 10–20%, in elderly people (5). In our study, depression and anxiety were the most frequent psychological conditions associated to UWL without differences between sexes or age.

Compared with those with psychological disorders, patients with UWL due to non-malignant organic disorders, were mostly men, were more symptomatic, and demonstrated physical examination, laboratory tests, chest X-ray, and abdominal ultrasonographic abnormalities. For this reason, we propose that abdominal ultrasonography should be included in the initial work-up of patients with UWL.

Although drugs and polypharmacy represent a significant etiologic factor of UWL in some studies (5, 11, 17, 18), only 2 patients in our study had this etiology, and the use of digoxin was involved in both cases.

It has been reported that patients with UWL with an initially normal work-up have favorable outcomes (2, 8, 11, 12). However, some authors have claimed that serious “occult” disorders,

mostly cancer, could escape early detection, based on case series studies with small sample sizes, without a defined follow-up period, and with very few autopsy examinations of deceased patients (1, 2, 6, 12). Nevertheless, it remains unclear how long clinicians should follow-up patients with UWL after the initially normal work-up. Bosch et al. reported malignancies in 19 (5%) of 375 patients with initially unexplained UWL. These malignancies were diagnosed between 6 and 28 months' follow-up (21). In our study, after the initial work-up, the etiology remained unexplained in 10.4% patients, but after a 5-year follow-up, etiology was determined in 5 (33%) of these patients. Malignancy was diagnosed in 4 patients (1 renal carcinoma, 1 pancreatic cancer, 1 thyroid carcinoma, and 1 non-Hodgkin lymphoma), and vasculitis in the remaining patient. Two of the patients with unknown etiology died during the first year of follow-up.

Death and the need for hospital admission have also been studied in the context of UWL. Most patients who died were in the group with malignancies, followed by patients with non-malignant organic disorders, in our study. Mortality was similar to that reported in the literature (1, 8, 12, 21). Patients who required hospital admission were mostly those diagnosed with cancer; they were hospitalized because of the need for a quicker diagnosis or due to clinical impairment. The presence of an abnormal physical examination was associated with early mortality.

Our study had some limitations. First, the study lacked oral cavity examinations; oral cavity dysfunction may affect the oral intake in some patients. Moreover, it has been reported from USA and Canada that people living in nursing homes have a higher rate of UWL (18,22). Traditionally, nearly all of these patients in Galicia, northwest of Spain, live with their relatives at home, but the rates of UWL in nursing homes in this country have not yet been reported. The influence of severity of gastrointestinal symptoms on food intake was not assessed. Additionally, no autopsies were performed on the patients who died during follow-up in this study.

Conclusion:

In this study, UWL in most patients were due to non-malignant organic disorders, followed by malignancies and psychosocial disorders, with significant differences according to sex and age. In a small percentage of patients, "occult" malignancies were diagnosed some years after the initially normal work-up.

Clinicians should therefore be aware of the possibility of an underlying malignancy, particularly if the patient with UWL is male, smokes, and presents with increased ESR, LDH, or CRP levels. To increase our knowledge of this disorder, more autopsies are needed in patients who died without a defined etiology. Patients with unexplained UWL should be followed-up regularly, searching for early clinical signs and symptoms of disease, or changes in basic laboratory tests.

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Legends to tables:

- 1.- General characteristics of study patients.
- 2.- Specific causes of unintentional weight loss.
- 3.- Characteristics of patient groups according to etiology. MDs: malignant disorders; NMDS: non-malignant disorders; PSDs: psychosocial disorders; UE: unexplained. WL: weight loss; PE: physical examination; SD: standard deviation. P-value less than 0.05 was considered significant.
- 4.- Differences according to sex and age.

ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase. p-value less than 0.05 was considered significant.

5.- Need of hospital admission and mortality in the different groups. MDs: malignant disorders; NMDS: non-malignant disorders; PSDs: psychosocial disorders; UE: unexplained.

Table 1

Characteristic	Patients (n = 145)
Age (years), mean (SD)	70 (15.6)
Sex, n (%)	
Females	72 (49.7)
Males	73 (50.3)
Active smoker, n (%)	36 (24.8)
Active drinker, n (%)	44 (30.3)
Time from onset of symptoms to medical assessment n (%)	
Less than 2 months	51 (35.2)
2-6 months	73 (50.3)
More than 6 months	21 (14.5)
Abnormal physical assessment n (%)	30 (20.7)
Estimated weight loss (Kg over 6-12 months), mean (SD)	7.2 (4.5)
Unintentional weight loss of known origin, n (%)	130 (89.7)
Initially unexplained weight loss, n (%)	15 (10.3)

Table 2

Cause	Patients (n, %)
Malignant disorders	45 (31)
Non-malignant organic disorders	70 (48.2)
1.- Digestive disorders	43 (29.7)
2.- Infectious diseases	8 (5.5)
3.- Endocrinopathies	4 (2.8)
4.- Respiratory diseases	4 (2.8)
5.- Nervous system disorders	2 (1.4)

6.- Autoimmune diseases	3 (2.1)
7.- Kidney diseases	1(0.7)
8.- Cardiovascular disorders	3 (2.1)
9.- Drug intolerance	2 (1.4)
Psychosocial disorders	15 (10.4)
1.- Psychological disorders	13 (86.6)
2.- Social conditions	2 (13.4)
Unknown	15 (10.4)

Table 3

CHARACTERISTIC	MDs 1	NMDs 2	PSDs 3	UE 4	P value					
	(n = 45)	(n = 70)	(n = 15)	(n = 15)	1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Age (years), mean (SD)	74.3 (11.4)	68.2 (17.2)	68.2 (15.7)	67.5 (17.5)	<0.001	<0.001	<0.001			
Sex, n (%)					<0.001	<0.001	<0.001	<0.001	<0.001	0.231
Females	16 (35.6)	34 (48.5)	11 (73.3)	11 (73.3)						
Males	29 (64.4)	36 (51.5)	4 (16.7)	4 (16.7)						
Estimated WL (Kg), (mean SD)	10.6 (6.3)	7.9 (4.6)	7.7 (3.6)	7.4 (3.9)	<0.001	<0.001	<0.001	0.326	0.056	0.338
Accompanying symptoms, n (%)	39 (86.6)	44 (62.8)	8 (53.3)	4 (26.6)	<0.001	<0.001	<0.001	<0.001	<0.001	0.283
PE abnormalities, n (%)	16 (35.5)	13 (18.5)	1 (6.6)	0 (0)	<0.001	<0.001	<0.001	<0.001	<0.001	0.332
Lab. Abnormalities, (n %)	44 (97.7)	51 (72.8)	3 (20)	4 (26.6)	<0.001	<0.001	<0.001	<0.001	<0.001	0.143
Chest X-ray abnormalities, n (%)	10 (22.2)	4 (5.7)	1 (6.6)	0 (0)	<0.001	<0.001	<0.001	<0.001	<0.001	0.295
Abdominal ultrasonographic abnormalities, n (%)	16 (35.5)	7 (10)	0 (0)	0 (0)	<0.001	<0.001	<0.001	<0.001	<0.001	0.251

MDs: malignant disorders; NMDs: non-malignant disorders; PSDs: psychosocial disorders; UE: unexplained.

Table 4

Variables predominant in men (p-value)	Variables predominant in patients aged ≥65 years (p-value)
Cancer diagnosis 0.024	Cancer diagnosis 0.032
Tobacco 0.002	Tobacco 0.001
Alcohol intake 0.001	
Higher ESR 0.037	Higher ESR 0.001
Higher LDH 0.004	Higher LDH 0.004
Abnormal proteinogram 0.023	
Anemia 0.032	
Abnormal chest X-ray 0.041	Abnormal chest X-ray 0.041
Mortality 0.007	Mortality 0.007

Table 5

Outcome	MDs 1 (n,%)	NMDs 2 (n,%)	PSD 3 (n,%)	UE 4 (n,%)
Deaths (n=50)	30 (66.6)	16 (22.8)	2(13.3)	2 (13.3)
Hospital admission (n=21)	17 (37.7)	4 (5.7)	0	0