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Weight loss and Alzheimer's disease: temporal and aetiological connections

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The intermediate and advanced stages of Alzheimer's disease (AD) are frequently associated with weight loss (WL), but WL may even precede the onset of cognitive symptoms. This review focuses on the possible aetiological and temporal relationships between AD and WL. When WL occurs some years before any signs of cognitive impairment, it may be a risk factor for dementia due to deficiency of several micronutrients, such as vitamins and essential fatty acids, and consequent oxidative tissue damage. The leptin reduction associated with WL may also facilitate cognitive decline. The mechanisms potentially inducing WL in AD include lower energy intake, higher resting energy expenditure, exaggerated physical activity, or combinations of these factors. A hypermetabolic state has been observed in animals with AD, but has not been confirmed in human subjects. This latter mechanism could involve amyloid assemblies that apparently increase the circulating cytokine levels and proton leakage in mitochondria. WL may be caused by patients' increased physical activity as they develop abnormal motor behaviour (restlessness and agitation) and waste energy while trying to perform daily activities. During the course of AD, patients usually find it increasingly difficult to eat, so they ingest less food. AD-related neurodegeneration also affects brain regions involved in regulating appetite. The caregiver has an important role in ensuring an adequate food intake and controlling behavioural disturbances. In conclusion, WL is closely linked to AD, making periodic nutritional assessments and appropriate dietary measures important aspects of an AD patient's treatment.

Weight loss: Alzheimer's disease: Dietary intake: Energy expenditure: Malnutrition

Alzheimer's disease (AD) is the most common neurodegenerative disease of the brain, representing more than 50% of all dementia cases⁽¹⁾. It is characterized by multiple cognitive deficits and progressive deterioration in functional performance, and leads to increasing disability and mortality. AD is frequently associated also with nutritional disorders and weight loss (WL), which is considered as one of the criteria for the clinical diagnosis of dementia⁽²⁾.

The loss of body weight gives rise to loss of muscle mass and strength, and a greater risk of falls, functional dependence and worsening quality of life⁽³⁾. To prevent these negative consequences, it is important for clinicians to detect weight variations early and plan appropriate nutritional intervention.

The majority of studies report that AD patients lose weight especially in the intermediate and advanced stages of the disease⁽⁴⁾, but some studies suggest that WL may start even several years before dementia sets in, and others indicate that it may occur just before the cognitive symptoms become manifest⁽⁵⁾. This variability in the onset of WL *vis-à-vis* the clinical signs of dementia, combined with the long latency period of AD, makes it difficult to ascertain the relationship between WL and AD. The question is not only whether WL comes before or after the onset of AD but also whether the former represents a risk factor for the latter, whether WL is an early sign of AD or a consequence of the related behavioural disturbances.

This review focuses on the link between WL and AD, and aims to define the temporal relationship between the

Abbreviations: AD, Alzheimer's disease; REE, resting energy expenditure; WL, weight loss.

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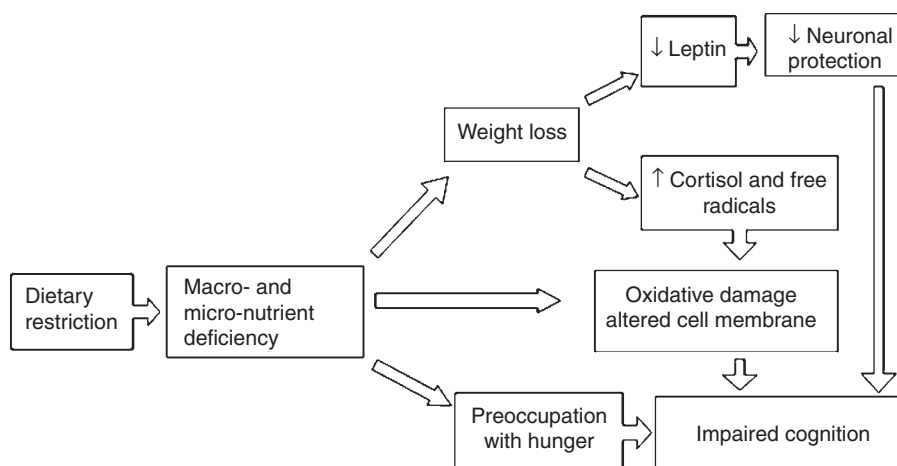


Fig. 1. Possible mechanisms explaining the relationship between weight loss and risk of Alzheimer's disease.

two, and to investigate their possible aetiological connections.

The relationship between Alzheimer's disease and weight loss: how can it best be studied?

The relationship between WL and AD is complex and has yet to be fully elucidated. To clarify their temporal and aetiological links and to help us to identify the initial signs of cognitive symptoms of AD and weight changes with a reasonable degree of reliability, only observational studies conducted for an adequately long time with frequently scheduled cognitive and nutritional visits (e.g. every 3 or 6 months) should be considered. In the literature, however, either the studies are not long enough or the follow-up visits are scheduled at excessively long intervals, so they enable no definite conclusions to be drawn.

Given the lengthy latency period of AD, it is hard to define a maximum time interval that could elapse between the onset of WL and cognitive impairment for the WL to be considered as risk factors for dementia or one of its signs. WL starting more than a year before the onset of dementia could feasibly be seen as a risk factor for the latter.

Weight loss as a potential risk factor for Alzheimer's disease

Although overweight and obesity in middle age are notoriously associated with cerebro- and cardiovascular events, there is some evidence to suggest that WL may be a risk factor for both AD and mild cognitive impairment⁽⁶⁾. Dietary restrictions have been associated with a decline in vigilance, slower reaction times and worsening immediate memory^(7,8).

WL may contribute to cognitive impairment in various ways (Fig. 1). First, it can worsen cognitive performance by causing a deficiency in several micronutrients, including vitamins and essential fatty acids⁽⁹⁾. The possible mechanisms behind this effect could relate to the protective effect

of vitamins against tissue oxidative damage⁽¹⁰⁾, and the biophysical effects of essential fatty acid on neuronal membrane structure⁽¹¹⁾. WL could also impair cognitive performance by raising serum cortisol and free radical levels⁽¹²⁾.

In recent years, leptin has also been attracting more interest because it seems to be implicated in the pathogenesis of AD. Leptin is produced in the subcutaneous and visceral adipose tissue and its levels drop when a person loses weight. This adipokine seems to improve axon growth, synaptogenesis and cell survival, protecting against glutamatergic cytotoxicity and oxidative damage, and promoting the proliferation of hippocampal progenitor cells⁽⁸⁾. Data from the Framingham study indicate that people with leptin levels in the lowest quartile have a 4-fold higher risk of developing AD than those in the highest quartile after a 12-year follow-up⁽¹³⁾.

WL could affect cognitive performance too, because preoccupation with hunger and anxiety caused by energy restriction may reduce and interfere with working memory capacity^(14,15).

Previous epidemiological studies suggested that, in middle age, people who eventually develop AD weigh the same as their peers who do not, and they begin to lose weight later on at a faster rate than subjects who remain cognitively intact. Data from the Honolulu-Asia Aging Study⁽¹⁶⁾ on 1890 individuals monitored for 32 years identified an accentuated WL starting 6 years prior to the diagnosis of dementia. This finding is consistent with other reports⁽¹⁷⁾ and with the results of the Indianapolis-Ibadan Dementia Project⁽⁴⁾, which reported that individuals with incident dementia had a BMI similar to that of people with normal cognition up to 9 years before dementia was diagnosed, but then lost weight between the ninth and the sixth years before any signs of cognitive impairment became apparent. The Religious Order Study⁽¹⁸⁾ also showed that a loss of one point on the BMI per year coincided with a 35% higher risk of developing AD than in subjects whose BMI remained stable, and with an 80% higher risk than in people gaining 0.6 points a year on their BMI.

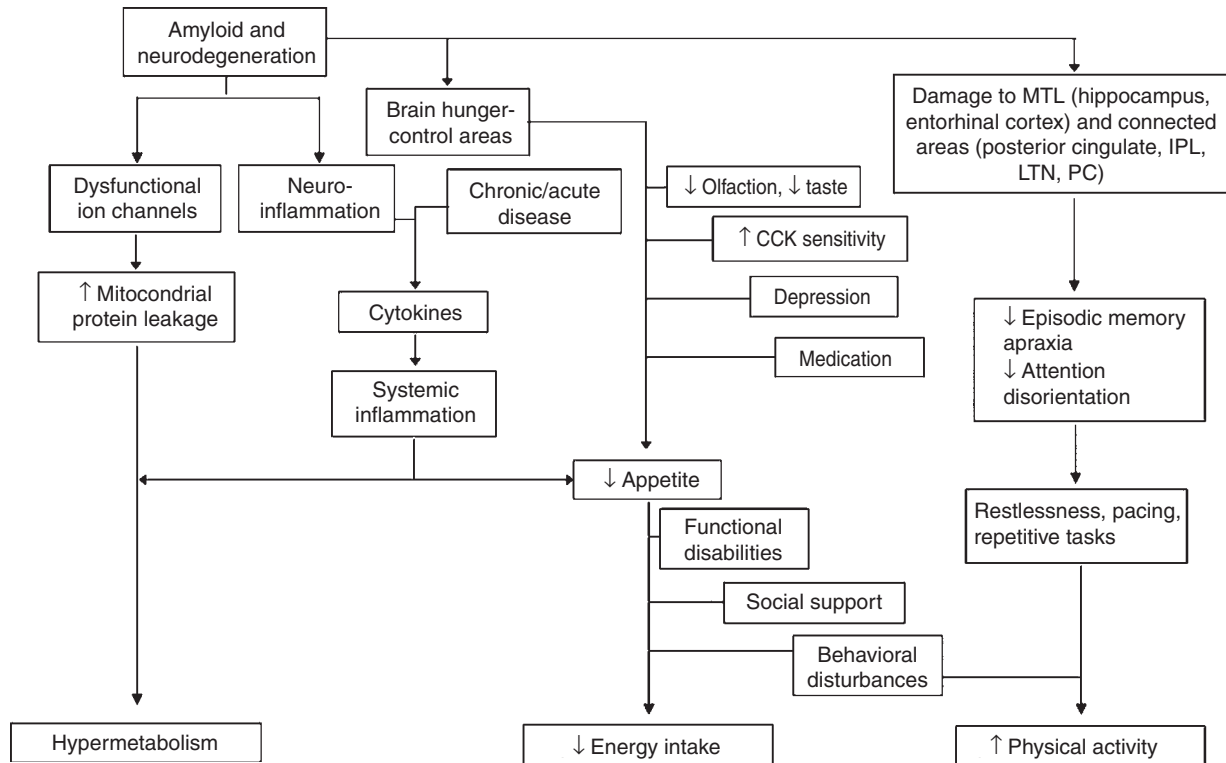


Fig. 2. Possible mechanisms inducing weight loss in Alzheimer's disease. MTC, medial temporal cortex; ACC, anterior cingulate cortex; MTL, medial temporal lobe; IPL, inferior parietal lobe; LTN, lateral temporal neocortex; PC, prefrontal cortex; CCK, cholecystokinin.

Involuntary weight loss as a sign of Alzheimer's disease

Involuntary WL in people with AD is not infrequent, reportedly preceding the diagnosis of AD by only a few years. As Johnson *et al.* reported⁽⁵⁾, elderly AD patients seem to exaggerate the physiological WL accompanying ageing a year before their cognitive decline sets in. WL continues, however, with the progression of dementia, becoming accentuated in the advanced stages leading up to cachexia and death.

According to the laws of energy balance, WL may be caused by a lower energy intake or a higher energy expenditure due to a hypermetabolic state (with a higher resting energy expenditure (REE)) or an increased physical activity. Fig. 2 shows the various mechanisms that can lead to WL in subjects with AD.

The possible mechanisms by means of which AD could cause WL may be different in the various stages of dementia. Logically, the main cause of WL in the early stages of AD would be an increased REE or exaggerated physical activity, whereas in the advanced stages the major determinant of WL is likely to be a lower energy intake.

Involuntary weight loss due to a hypermetabolic state

A condition of hypermetabolism, defined as a more than 10% higher REE than in healthy individuals of the same sex, age and body composition, could contribute to WL in AD. It is uncertain, however, whether patients with AD have an abnormal metabolism because the condition has

reportedly been associated with increases, reductions and no change in energy metabolism^(19–22); the studies involved were conducted on small samples, however, and some have been judged unreliable⁽²³⁾.

The existence of a hypermetabolic state has nonetheless been suggested in animal models of AD overexpressing amyloid-precursor protein. Vloeberghs *et al.*⁽²⁴⁾ found that transgenic amyloid-precursor protein mice has a higher energy intake and a lower body weight than their wild-type litter-mates, and hypermetabolism was demonstrated in amyloid-precursor protein mice by Knight *et al.*⁽²⁵⁾ using calorimetric cages, and it was confirmed by a higher than expected WL after energy restriction⁽²⁶⁾. On the other hand, these studies fail to explain whether the hypermetabolism is attributable to an increased REE or physical activity because it is impossible to create a physiological resting condition in mice. The exact reason for a higher REE is still not known, but it may have something to do with amyloid (Fig. 2), which can form membrane pores and dysfunctional ion channels, increasing proton leakage within mitochondria as a consequence⁽²⁷⁾. In addition, astrocytes and microglia activated by amyloid deposits (neuro-inflammation)⁽²⁸⁾ increase circulating cytokine levels, thus adding to the catabolic state^(29,30).

Involuntary weight loss due to increased physical activity

Involuntary WL may also result from an increased energy expenditure due to an abnormal motor behaviour.

Disruptive behavioural symptoms are common in AD right from the early stages and become more severe with the progression of dementia⁽³¹⁾. One of the first clinical hallmarks of AD is episodic memory impairment⁽³²⁾, which leads to the ineffective consolidation and storage of new information⁽³³⁾. Patients frequently become restless, engage themselves in repetitive tasks^(34,35) and use a large amount of energy in trying to complete the activities of daily living. Constructional apraxia and temporo-spatial disorientation (which contribute to an intensified physical activity and excessive pacing), and anxiety due to the perception of an impaired performance, also contribute to a greater energy expenditure.

In advanced stages of AD, patients often present psychotic behavioural symptoms, such as agitation and aggressiveness⁽³¹⁾, and such symptoms have been found associated with WL^(36,37), leading to a loss of 5 kg or more over a 6-month follow-up⁽³⁸⁾.

Involuntary weight loss due to a lower energy intake

As AD progresses, patients usually also develop dietary problems, neglecting or forgetting to eat or becoming averse to some foods, and this can lead to a lower oral intake and a consequently accelerated WL⁽³⁹⁾. A decline in food consumption has been observed right from the first stage of AD⁽⁹⁾, probably due to early changes in the appetite-regulating mechanisms. The exact reasons for a lower food intake have yet to be clearly defined, but changes in the brain regions involved in hunger control, a declining sense of smell and taste⁽⁴⁰⁾, and an earlier satiety due to a greater sensitivity to cholecystokinin⁽⁴¹⁾ are all potential contributors. In particular, some brain areas are known to have a role in regulating food intake, as medial temporal cortex, anterior cingulate cortex and olfactory epithelium, are frequently involved in amyloid deposition^(42–44).

Concomitant chronic diseases, depressed mood and several types of medication could also contribute to a lower food intake by determining anorexia, constipation and an altered sense of smell and taste^(45,46). In addition, pro-inflammatory cytokines and chemokines (TNF α , IL-1 and IL-6), the levels of which are higher than normal in AD due to neuro-inflammation⁽⁴⁷⁾, may mimic the action of appetite-regulating peptides and suppress feeding by taking effect directly on the glucose-sensitive neurons in the hypothalamic sites of satiety and hunger^(30,48).

As the dementia progresses and the related functional impairment becomes more severe, patients' remaining abilities and the availability of adequate family/social support become more important in assuring an adequate energy intake. Hansen *et al.*⁽⁴⁹⁾ showed that living alone, having a restricted social network and having lost competency in preparing meals or grocery shopping raised the risk of WL in patients with AD. Difficulties in bringing food to the mouth and chewing also correlated significantly with the loss of body weight over a 2-year follow-up⁽⁴⁾. An excessive burden on caregivers would also make them unable to invest sufficient resources in helping the patient to eat^(50,51).

Table 1. Strategies to minimize weight loss

Objective	Actions
Early detection of malnutrition	Periodic nutritional assessment: <ul style="list-style-type: none"> – anthropometry: body weight, height, BMI – biohumoral values – dietary intake – feeding behaviour
Improvement of dietary intake	<ul style="list-style-type: none"> – Energy supplements, medical foods, vitamins (B, D, E, folic acid) – Attention to adverse gastrointestinal effects of drugs – Consideration of patient's preferences and eating times
Support for patient's functional disabilities	<ul style="list-style-type: none"> – Grocery shopping, preparing meals – Adapting food consistency and dimensions – Thickening fluids
Reduction of energy expenditure due to repetitive tasks	<ul style="list-style-type: none"> – Treatment of behavioural problems

WL in advanced dementia could be likened to what happens in the terminal phase of several chronic diseases and stems from multiple causes. At this stage, patients become unwilling to eat and dysphagia often makes oral feeding difficult. Hypermetabolic states relating to newly contracted diseases, and muscle atrophy⁽⁵²⁾ due to prolonged immobilisation also accelerate WL, ultimately leading to cachexia.

Strategies to minimise weight loss

Given the impact of WL on cognitive performance, cognitive evaluation alone is clearly not enough in the follow-up of patients with AD; a multidimensional and multidisciplinary approach is needed. Periodic nutritional assessments should include anthropometric measures, biohumoral tests (haemochrome, albumin and prealbumin)⁽⁵³⁾ and an assessment of food intake and eating behaviour⁽⁵⁴⁾. The possible actions that can be taken to contain WL are summarized in Table 1.

Since AD patients have multiple nutritional deficiencies, a number of energy supplements, vitamins and medical foods (i.e. foods intended to provide specific nutritional requirements for patients with certain diseases) have attracted interest for the adjuvant treatment of AD in recent years. Administering flavonoids, herbal supplements, phosphatidylserine, essential fatty acid and vitamins may improve cognition, offering some degree of neuroprotection⁽⁵⁵⁾.

As the patients' ability to perform activities of daily living diminishes, the role of their caregivers becomes crucial. They should try to compensate for the patient's difficulties in performing tasks, be it in purchasing food, preparing meals, or changing a food's consistency to make it easier to swallow. Attention should also be paid to the patients' preferences, and their chewing and swallowing times must be respected. Every effort should also be made to control any behavioural disorders responsible for an excessive and purposeless energy expenditure. Finally, the

patients' medication should be reviewed to avoid the use of drugs known to cause nausea, vomiting, anorexia or other gastrointestinal symptoms; in the choice between equally effective alternative drugs, those stimulating the appetite should be preferred.

Conclusions

WL not only represents a risk factor for AD, it is also so closely connected to the disease that it can be considered as one of its clinical signs. WL may start early in AD (even before the related cognitive impairment becomes overt), and it is associated with the progression of the dementia. It has numerous causes that differ in the various stages of dementia, attributable to hypermetabolism, a lower energy intake and a greater physical activity. It is consequently important to focus not only on an AD patient's cognitive performance, but also on their nutritional assessment and the prescription of appropriate dietary measures. A correct approach to the treatment and the adequate support of a caregiver are crucial to the identification and treatment of nutritional problems with a view to limiting WL and its consequences, i.e. frailty and disability.

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