# Psychophysiological, cognitive and behavioral aspects of malnutrition in Alzheimer's disease: a review

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## Abstract

Alzheimer's Disease is characterized by a progressive loss of cognitive and behavioral functions, also caused by changes to the neuroendocrine system and eating behaviors, and can lead to patient malnutrition and result in a nutritional imbalance with consequent malnutrition, affecting the overall health condition in patients, causing organic complications and influences in the evolution of dementia. The study obiective present some information relating to the main factors involved in weight loss in AD patients reported in previous studies. As method use non-systematic review of the literature in the period 1988-2014, with search conducted in MEDLINE, LI-LACS and SciELO electronic library. Results 58 scientific articles reviewed and subdivided in categories for discussion, like cognitive losses, psychological symptoms, dysphagia and others. Conclude that

unfulfilled nutritional needs associated with increased energy demands and various alterations can lead to a rapid, undesirable, and sharp decline in nutritional status in patients with AD.

Keywords: Dementia. Nutritional Status. Weight Loss. Quality of life.

## Introduction

Dementia is one of the most common health problems among the elderly and is also one of the leading causes of disability in this age group (PILOTTO et al., 2009). Alzheimer's disease (AD) is the most common type of dementia (THOMAS et al., 2008) responsible for over 50% of dementia cases in the elderly aged 65 years and older (HERRERA et

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al., 2002). It is estimated that the prevalence of AD doubles every five years after this age reaching from 26% to 45% in patients over 85 years old (PILOTTO et al., 2009). Currently, more than 24 million people are affected worldwide and 4.6 million new cases are recorded per year making AD an important public health problem (IRVINE et al., 2008).

AD is a neurodegenerative disease characterized by the progressive loss of cognitive and behavioral functions (IR-VINE et al., 2008) it progresses through an insidious installation and presents multifactorial etiology (HERRERA et al., 2002). Several studies indicate possible risk factors for dementia such as age, hypercholesterolemia, diabetes type 2, hypertension, physical inactivity, smoking, obesity, ethnicity, gender, and genetic factors (KIVIPELTO et al., 2005; RUSANEN et al., 2011).

The pathophysiology of AD includes severe neuronal loss, impaired neurotransmission, and the emergence and proliferation of amyloid plaques (senile plaques) in the neuronal interstice of neurofibrillary tangles in the cytoplasm of neurons (THOMAS et al., 2008; WALDAU; SHETTY, 2013). These alterations lead to a decline in cognitive functions by causing a series of biochemical and structural changes in the brain.

Cognitive losses and neuropsychiatric changes arising from brain atrophy seem to contribute to weight loss and nutritional deficit in AD patients (GILLETTE-GUYONNET et al., 2000). Weight loss occurs in approximately 40% of AD patients. It can often precede the disease onset and even assist in the cli-

nical diagnosis of the disease (GUÉRIN et al., 2005). However, the Body Mass Index (BMI) is mostly compromised at the most advanced stages of the disease. On the other hand, low BMI or low weight is associated with increased risk of developing AD (STEWART et al., 2005), and its severity and speed of progression (GILLETTE-GUYONNET et al., 2000; GRUNDMAN, 2005).

In the Alzheimer's Disease, the feeding habits are affected, and eating becomes increasingly difficult during the disease's evolution (STEENHAGEN; MOTTA, 2006). However, weight loss may arise not only from memory problems, food refusal, and progressive difficulty related to food intake, but also from an increased energy demand associated with ambulation and unintended moves. Moreover, the presence of infections and consequent elevation of the basal metabolism can also contribute to weight loss (SPACCAVENTO et al., 2009).

The speed of weight loss can vary. It can be sharp with the dropping of several pounds in a short period of time, or moderate but steady according to the disease progression (GUÉRIN et al., 2005; SPACCAVENTO et al., 2009). According to Guérin et al. (2005), the weight loss kinetics in AD patients varies with the severity of the disease. These authors conducted a study with 395 patients and observed steady weight loss in most of the patients (about 33.4%) and severe weight loss (greater than or equal to 5 kg in 6 months) in fewer patients (10.2%). Sharp weight loss in a short period could result from acute diseases, hospitalization, institutionalization, and changes in living conditions.

In the study by Spaccavento et al. (2009), AD patients presenting risk of malnutrition demonstrated greater cognitive impairment, greater difficulties in performing daily activities, and greater motor deficit when compared to patients with eutrophic nutritional status, which seems to have a protective effect on the development of AD. Weight loss and consequent malnutrition causes a series of complications that lead to infections, respiratory failure, and heart failure, increasing disease severity and patient mortality (GUÉRIN et al., 2005).

Other serious complications related to malnutrition include reduced immune function, deficient wound healing, depression, apathy, compromised intestinal integrity, hypothermia, decreased hepatic protein synthesis, glomerular filtration, and production of gastric juice (SAUNDERS; SMITH; STROUD, 2011).

Before the changes related to malnutrition, cited above, we present some information on the main factors involved in weight loss in patients with AD, as reported by previous studies.

## Materials and methods

Considering high malnutrition rates in patients with Alzheimer's disease, both in Brazil and worldwide, the aim of this paper is to review the causes for this increase noted in the scientific literature. The study conducted through non-systematic review of literature in the period 1988-2014, resulted in 58 reviewed scientific articles. Inclusion criteria were the bibliographic search words such as Alzheimer's disease, loss

of weight, agnosia, apraxia, memory loss, behavioral symptoms, dysphagia, leptin, neuroinflammation, seeking causal aspects of malnutrition in case to alert the public policies and health professionals. This study was conducted between the years 2011 to 2014. The searches occurred in MEDLINE, LILACS and SciELO electronic library.

## Results

After reviewing the 58 articles, subdivided into six items for discussion of malnutrition in patients with AD.

# **Cognitive losses**

Epidemiological studies indicate a complex relationship between the proportions of fat and lean mass and cognition in all ages (GUSTAFSON et al., 2003; WHITMER et al., 2005). According to Hsu-Ko et al. (2006), loss of lean mass is associated with worse cognitive performance in the elderly.

It has been observed that the BMI is lower among elderly individuals with dementia than in elderly without impaired cognition (GUSTAFSON et al., 2003; FAXÉN-IRVING; BASUN; CEDERHOLM, 2005). A positive association between cognitive dysfunction and reduced muscle mass in AD patients is generally identified as sarcopenia (NOURHASHÉMI et al., 2002). In these cases, a direct relationship between total brain volume and body composition is observed; brain atrophy is suggested to be directly related to the loss of lean mass observed in AD patients (BUCH-MAN et al., 2006).

As discussed by Muñoz, Agudelo e Lopera (2006), some of the characteristic symptoms present in AD, such as agnosia and apraxia, can cause decreased food intake and, consequently, increased weight loss. Patients with agnosia might not recognize food and silverware, while patients with apraxia appear to have difficulties using silverware and/or problems swallowing (SANDMAN; NORBERG, 1988).

Memory loss may affect the preparation of food and its consumption; patients can forget to eat, refuse food, or even repeat the same meal (SAND-MAN; NORBERG, 1988; VELOSO, 2004). Memory loss can also affect the perception of basic needs such as thirst, hunger, and satiety, which can lead to the patient spending a whole day without ingesting food and water, and thus losing weight and becoming dehydrated (CALDAS, 2001).

Changes in the sense of smell also occur in AD patients, especially in the early stages of the disease, and may affect food consumption (GILBERT; BARR; MURPHY, 2004). Olfaction and other senses (vision and gustation) are necessary to initiate salivation and motion to start eating (FURKIM, 1999). These patients tend to prefer soft, moist, paste and liquid foods, and sometimes tend to increase the amount of salt and sugar in their diet due to changes in their tasting abilities (SILVA et al., 2008).

Executive dysfunction interferes in many aspects such as choosing food, feeling satisfied, and the duration of the meal (GILLIOZ et al., 2009). Speaking and understanding impairments also hinder feeding because patients might have difficulty in naming what they want to eat and understanding the meaning of words from those assisting them (ATHLIN et al., 1990)

The caregiver is often unable to identify the source of the aversion to food. In many cases, the bite reflex can be erroneously interpreted as a rejection to food. These circumstances make the patient increasingly dependent. Around 50% of AD patients lose the ability to feed themselves within eight years of disease diagnosis (VOLICER et al., 1989).

# Psychiatric and behavioral disorders

In AD, the behavior changes are part of the clinical status and occurs in 90% of cases (GARCÍA-ALBERCA; MUÑOZ; TORRES, 2010). Among the most common disorders are depression and apathy; irritability; verbal and physical aggression; anxiety; disinhibition; repetitive behaviors; walk incessant; delusions; hallucinations; changes in sleep-wake cycle and eating patterns (BURNS; JACOBY; LEVY, 1990). However, the three groups of symptoms described most often are: depressive symptoms, agitation and psychotic symptoms (WEINER et al., 1996).

Behavioral disorders may predispose patients with AD to weight loss through at least two ways: (1) increased energy expenditure (eg, agitation, repetitive movements) and (2) reducing calorie intake (eg, distraction, agitation, depression) (WHITE et al., 2004).

Isolated depressive symptoms can be found in up to 87% of patients with

AD at some stage in the disease, while major depression is less common appearance, around 24%. One of the most common manifestations of depression is loss of appetite and weight (WESTIN et al., 1988; THOMPSON; MORRIS, 1991; MORLEY; KRAENZLE, 1994; BLAUM et al., 1995). Depression was associated with weight loss in 30% to 36% of outpatients or remain in nursing home (MORLEY; KRAENZLE, 1994). Thus, appetite changes due to depression may be another factor associated with malnutrition in those patients.

## Motor disorders — Dysphagia

Swallowing depends on a complex sensorimotor mechanism controlled by the CNS, which includes voluntary and involuntary components. Previous studies showed that cognitive deficits found in neurological diseases, such as AD, can cause an interruption in the present and necessary preparatory actions for swallowing (CORREIA et al., 2010).

This swallowing impairment may result in dysphagia, which is a common clinical manifestation in patients with dementia of the Alzheimer's type (28 to 32%) (MUÑOZ; AGUDELO; LOPERA, 2006). Dysphagia may be present since the early stages of AD (CORREIA et al., 2010) and leads to nutritional and social consequences that impact the quality of life of the individual.

The main changes in swallowing found in these patients are lingual motor dysfunction, delay in firing the swallowing reflex, failure of the oral motor control of food mass, retention of food in the vallecula and pyriform sinus, food penetration and aspiration, mainly for liquids, and absent mastication. Commonly, it is verified that masticatory movements become slower and uncoordinated, making swallowing difficult and causing nutritional disorders (CAMPOS et al., 2000).

Furthermore, dysphagia can lead to inadequate dietary intake driven by the consistency of foods. Some individuals change the consistency of preparations by adding large amounts of water to adapt the food to their symptoms; however, this reduces the total caloric value of the food and contributes to increased weight loss. The difficulty in swallowing thin liquids, including saliva, requires progressively greater coordination and control on the part of the AD patient, which increases the risk of aspiration pneumonia and recurrent respiratory tract infections (SMITH, 2006). The most severe phases of dysphagia are usually associated with aspiration pneumonia. Communication difficulties are also associated with dysphagia in many cases (SANDMAN; NORBERG, 1988).

# **Endocrine alterations**

Nutrient intake and metabolism are influenced by the functioning of a set of neural structures and specific neurochemical and neuroendocrine systems. Leptin and insulin are the main energy signaling factors in the neuroendocrine control of energy metabolism. (HALLS-CHMID et al., 2008). These two hormones act both peripherally and in the CNS where they interact as hypothalamic receptors (REAGAN, 2007).

Leptin is a protein found in adipose tissue that acts as a hormone controlling food consumption through receptors found in the hypothalamus. This hormone is involved in control of body fat (storage and mobilization), reproductive and immune systems, bone homeostasis, insulin sensitivity, and neuronal activity. Leptin receptors have been identified in both peripheral tissues and neurons, including in the hippocampus which is particularly vulnerable to AD(HOLDEN et al., 2009).

In Borer (2014), it was shown that obesity induces hyperleptinemia suppressing insulin lipogenic action and inhibits bone mineral ability, suggesting that leptin has important factors with regard to maintenance of skeletal stability lean mass and even body's own fat.

Reduced leptin levels are positively associated the risk of AD, but not the severity of the dementia. A large-scale prospective study that followed about 3.000 elders for approximately four years demonstrated that participants with low leptin levels showed a greater cognitive decline compared to individuals with higher levels of leptin (HOLDEN et al., 2009).

Insulin exerts metabolic, neurotrophic, neuromodulatory, and neuroendocrine functions in the brain and participates in synaptic plasticity. Several studies in humans identified insulin receptors in brain regions such as in the olfactory bulb, hypothalamus, hippocampus, and cerebellum. Insulin also regulates hypothalamic participation in food intake, smell in the olfactory bulb, and body weight control (PLIQUETT et al., 2006). The effect of hyperglycemia and insulin resistance on the hippo-

campus has been demonstrated to lead to losses in hippocampal plasticity and cognition impairment (REAGAN, 2007). In addition, hyperglycemia can be a contributing factor to the incidence of AD (RAFFAITIN et al., 2009).

Decreased food intake in AD patients can also result from decreased orexigenic peptides such as the neuropeptide Y and norepinephrine. Other hormones such as ghrelin, orexin, cholecystokinin, and oxyntomodulin combine with other signals to control food intake by acting on hypothalamic centers (REAGAN, 2007).

Thus, the interconnected operation between neural, physiological, endocrine, and behavioral responses participates in the control of food intake and is involved in the ontogeny of weight loss (LANDEIRO; QUARANTINI, 2011).

# Inflammatory activity

Neuroinflammation, mainly triggered by the deposition of proteins such as the  $\beta$ -amyloid peptide, is observed in AD patients (DENG et al., 2006). The hyperactivation of microglia cells and astrocytes produces a high amount of inflammatory cytokines such as the Tumor Necrosis Factor (TNF), interleukins, and interferon, which lead to chronic inflammatory responses especially in the neocortex, hippocampus, and cerebellum. This chronic inflammation predisposes the development of AD through an increased accumulation of  $\beta$ -amyloid (BLASKO et al., 1999).

Studies show that patients with AD exhibit elevated levels of TNF- $\alpha$  and interleukin-6 in the brain, in the cerebrospinal fluid (CSF) and blood (TAR-

KOWSKI et al., 1999; SWARDFAGER et al., 2010).

The presence of  $\beta$ -amyloid in the CNS, increasing local inflammatory response leading to the formation of pro-inflammatory cytokines (TNF and IL-6), these cytokines that increase the enzymatic process of APP and therefore to increased production of  $\beta$ -amyloid, which is known as cytokine cycle (BIESSELS; KAP-PELLE, 2005; WATSON; CRAFT, 2006).

Some studies showed also that interleukin 4 and interleukin 10 serum concentrations were higher in patients with lower caloric intake. This finding deserves consideration because this promoted humoral mediated immunity (CATAPANO et al., 2008).

Moreover, the causes of weight loss in this patients are multifaceted and include loss of appetite secondary to deterioration of brain regions (SMITH; GREENWOOD, 2008). This loss of appetite, in the Carrero et al. (2007) study, was associated with increased inflammation, or higher concentrations in interleukin serum and poor nutritional status (lower serum concentrations of insulin-like growth factor).

# Alterations in energy needs

An important factor that can lead to weight loss is the increase in energy needs in AD patients due to some exacerbated psychomotor agitation (MUÑOZ; AGUDELO; LOPERA, 2006).

AD patients can also exacerbate their energy loss through infectious processes that lead to elevated basal metabolism. AD also affects organic needs of protein and calories, because the changes in the

dynamics of deglutition, causing losses in nutritional aspects of hydration and metabolism of patients (STEENHAGEN; MOTTA, 2006).

The deregulation of the energetic metabolism and food intake is also observed in AD patients due to CNS impairment. The brain atrophy observed in AD can unbalance the patient's appetite and metabolic processes involved in body weight control (MUÑOZ et al., 2006).

Therefore, it is suggested that low food intake coupled with increased energy needs cause a nutritional unbalance that triggers substantial weight loss leading patients to a stage of malnutrition (REAGAN, 2007; POEHLMAN; DVORAK, 2000; WHITE et al., 2004).

### Final considerations

The inability to feed itself is a determining factor for the diagnosis of dementia according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (DUBOIS et al., 2007). In this way, the food supplement becomes an important strategy for maintaining the nutritional and cognitive state of patients. The Souvenaid® formulation (Nutricia NV, Zoetermeer, Holanda), which contains nutrients were combined in order to contribute to the formation and functioning synapses in AD patients, as having positive results compared to other nutritional formulations (WILDE et al., 2011).

This food supplement is composed of fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), uridine

monophosphate (UMP), choline, phospholipids, folic acid, vitamins B6, B12, C, E and selenium, which are forming precursors neuronal membranes. Preclinical studies have shown increased phospholipid synthesis, dendritic growth and synaptic proteins (CANSEV et al., 2014) and clinical studies have shown that Souvenaid® preserves the memory and to maintain the functional organization of the brain when evaluated by electroencephalogram in patients with AD (WAAL et al., 2014).

## Conclusion

Before our findings in the literature, the conclusion refers to the results already referenced. Unfulfilled nutritional needs associated with increased energy demands and alterations that are physiologic, cognitive, psychological, behavioral, endocrine, and inflammatory can lead to a rapid, undesirable, and sharp decline in nutritional status in patients with AD diagnosis. Malnutrition can affect the development of dementia and AD affects food intake and nutritional balance due to cognitive and motor disorders. Malnutrition in AD patients results in serious impairments in their general health and well-being that can lead to increase morbidity and mortality. Moreover, the nutritional status appears to be a good indicator of quality of life in these patients.

# Aspectos psicofisiológicos, cognitivos e comportamentais da desnutrição na doença de Alzheimer: revisão de literatura

#### Resumo

A doença de Alzheimer (DA) é caracterizada por uma perda progressiva das funções cognitivas e comportamentais, causadas por alterações no sistema neuroendócrino e nos comportamentos alimentares que podem levar à desnutrição do paciente e resultar em um desequilíbrio nutricional, afetando o estado geral de saúde dos pacientes, provocando complicações orgânicas e influências na evolução da demência. Este estudo objetiva apresentar algumas informações relativas aos principais fatores envolvidos na perda de peso em pacientes com DA relatados em estudos anteriores. Como método, utiliza-se uma revisão não sistemática da literatura, no período 1988-2014, com pesquisa realizada no Medline, Lilacs e na biblioteca eletrônica SciELO. Essa pesquisa resulta de 58 artigos científicos que foram revisados e subdivididos em categorias para discussão, como as perdas cognitivas, os sintomas psicológicos, a disfagia, e outros aspectos. Conclui-se que não cumpridas as necessidades nutricionais associadas com aumento da demanda de energia, várias alterações podem levar a um declínio rápido, indesejável e nítido no estado nutricional em pacientes com DA.

Palavras-chave: Demência. Estado Nutricional. Perda de peso. Qualidade de vida.

## Conflict of interests

The author(s) declare(s) that there is no conflict of interests regarding the publication of this article.

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