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Prodiet Journal

Alzheimer's Disease Edition

Background

Dementia is a comprehensive term for several diseases affecting memory or other cognitive and behavioral skills that significantly interfere with a **person's ability to perform daily activities.**

Its prevalence increases exponentially with aging, doubling every 5.5 years. In Latin America, the prevalence goes from 1.3% at age 60 to 63.9% after age 90[1,2]. Although age is the most well-known risk factor for dementia, it is not a normal part of aging. In addition, dementia does not exclusively affect older people, with cases such as the early onset dementia (defined as the onset of symptoms before age 65), which represents up to 9% of cases[3]. Currently, the number of people living with dementia in the world is approximately 50 million, with the prospect of reaching 152 million in 2050[4]. In Brazil, 55 thousand new cases of dementia are estimated every year[5].

One of the causes of dementia is the Alzheimer's disease (AD), which accounts for 60% to 80% of the cases[6]. There are two forms of AD, sporadic (usually of late onset, after age 65) and familial (usually of early onset, before age 65), which represents 5% of AD cases[7,8]. The most common form of AD is the amnestic impairment, which affects recent memory and the ability to learn new facts. There may be non-amnestic impairment related to language (remembering words), executive functions (affecting reasoning, judgment and problem solving), and visual-spatial function (loss of the ability to identify objects or people, disturbance in the sense of sight and reading)[9,10].

AD can have different stages: mild, moderate, and severe, depending on the progress of the disease and the impairment of cognitive ability and daily activities[11]. The clinical manifestations of dementia in AD go through a stage called mild cognitive impairment (MCI) and the preclinical phase[10,12]. Patients in the MCI stage do not necessarily progress to dementia; however, the risks for this population increase substantially compared to the population without MCI, reaching a conversion rate for dementia of 10% per year[13, 14].

Pathophysiology of AD

Before the MCI phase, AD enters the preclinical phase, which can take years, even decades, before the clinical diagnosis of dementia[10,12,15]. The onset of AD seem to occur in a cascade of events, with mutations in the genes of enzymes that cleave a neuronal transmembrane protein, the amyloid precursor protein (APP), leading to extracellular production and deposition of ß-amyloid peptides. These peptides become neurotoxic through structural reorganization, forming oligomers that aggregate and form senile plaques, differently from what would happen under normal conditions, in which APP cleavage would generate protein fragments that would protect the neuronal metabolism[16]. ß-amyloid peptides and their oligomers change the structure and the synaptic transmission[17] and can **quickly block the mechanism of new memory formation, changing synaptic plasticity**[18].

Another protein, called tau protein, is also involved in AD pathological changes. This protein, which supports the neuronal cytoskeleton, is normally soluble, but in AD cases it becomes hyperphosphorylated and transforms into an insoluble filamentous polymer. This process destabilizes the microtubules, protein structures that are part of the cytoskeleton, leading to their degradation and, consequently, to the death of neurons. This happens because these microtubules transport nutrients and information on neuronal extensions to their cell body and vice versa[20, 21]. As a result of tau protein hyperphosphorylation, the anatomical pathology of AD identifies intraneuronal neurofibrillary tangles[21] that impair axonal transport, resulting in synaptic function deficit and neuronal death[22].

Thus, the deposition of ß-amyloid in senile plaques and the tau protein accumulated in neurofibrillary tangles define AD as a unique neurodegenerative disease among the different disorders that can lead to dementia[23]. In addition to these changes, cerebral glucose hypometabolism is observed decades before the onset of symptoms[24,25].

Glucose Hypometabolism

The human brain weighs about 2% to 3% of the weight of an adult and uses approximately 20% to 23% of the daily energy requirement[24]. Most of the glucose consumed is used to maintain the pre- and postsynaptic ion gradient necessary for glutamatergic neurotransmission[26]. Glucose transporters (GLUTs) are responsible for glucose uptake. GLUT1, located in the blood-brain barrier, and GLUT3, located in the neurons, are the main GLUTs in the brain. These transporters are not sensitive to insulin, and the glucose uptake process is correlated to its concentration on both sides of the blood-brain barrier (BBB)[27]. On the other hand, GLUT4 is insulin dependent, being present in different regions of the brain related to memory and cognition[28].

In the human brain affected by AD, glucose transport is reduced in most metabolically active brain regions, such as the cortex and hippocampus[29, 30]. Post-mortem brain analysis of AD patients showed decreased levels of GLUT1 and GLUT3 in the cerebral cortex[31], with significant loss of the neuronal glucose transporter GLUT3. These lower levels are associated with the most severe AD pathology[32], which decreases glucose uptake by neurons[33].

Furthermore, some studies have shown that cerebral insulin signaling may be impaired in AD patients[34,35] when compared to control subjects[36]. The Rotterdam study, published in 1996, demonstrated that patients with type 2 diabetes mellitus (DM2) had twice as much AD as healthy subjects[37]. Since then, there has been a growing number of studies associating DM2 to DA[38-45], with inflammation, insulin resistance, and mitochondrial dysfunction being common signs in both diseases[35].

Insulin resistance and, consequently, reduced glucose uptake and use, decrease neuronal cell energy, homeostatic functions, and synaptic connection[46]. Thus, a decreased glucose metabolism results in decreased cholinergic

transmission and nerve cell atrophy. This is because acetylcholine synthesis (ACh) is extremely sensitive to glucose metabolism in the brain, since it occurs exclusively in the glycolytic pathway, impairing synapses and, consequently, neurotransmission[47]. At the cellular level, AD is associated with reduced ACh in the synaptic process, decreasing cholinergic neurotransmission[48]. The low availability of glucose is also related to tau protein hyperphosphorylation[49,50] and unbalanced homeostatic functions, such as increased oxidative stress and mitochondrial dysfunction with the generation of reactive oxygen (ROS) and reactive nitrogen (RNS) species[51].

Brain glucose uptake and metabolism are assessed using the cerebral glucose metabolic rate (CGMR)[24]. Some studies indicate a 20% to 25% reduction in CGMR in AD, with earlier reductions in the hippocampal area (related to the processing of new information for long-term memory). CGMR reduction is also seen in areas related to space, sound and language interpretation and orientation, such as the parietal and temporal lobes[52,53]. In addition, there is a relationship between decreased CGMR and worsening cognitive status in AD patients[54].

As already discussed, the pathophysiology of AD is complex, and, so far, the treatment can delay disease progression, but cannot cure it. Thus, the search for other nonpharmacological measures has increased in recent years with the objective of contributing, at least partially, to slow the disease progression, especially if performed early. Based on the hypotheses that explain AD, it is possible to investigate nutritional mechanisms that can clinically benefit these patients.

• Alternative Energy Pathway

Although the brain's primary fuel is glucose, it is important to highlight that this organ can easily use ketone bodies during periods of prolonged fasting, which can be considered the main source of fuel in these situations[55-58]. Decreased plasma glucose and insulin levels, as occurs in periods of fasting or intense carbohydrate reduction, release free fatty acids that are beta-oxidized in the mitochondria. Excess acetyl-CoA increases ketone body production since there is extra acetyl-CoA to be used in the Krebs cycle[58].

The comparison between the cerebral metabolic rates of glucose (CMRG) and ketone bodies, such as the cerebral acetoacetate metabolic rate (CAMR), in patients with or without AD shows a decreased CGMR in the gray matter of mild AD patients, **while the CAMR presents no difference between groups**[59,60]. In addition, there is a linear relationship between the plasma concentration and brain uptake of ketone bodies in these patients[58,60], **suggesting that ketone bodies can compensate for the energy deficit in AD patients**[24,58] **and be a great strategy to improve cerebral energy metabolism**[61].

• Caprylic and Capric Acids

Caprylic (C8:0) and capric acids (C10:0) are medium-chain fatty acids recognized for their ability to form ketone bodies[58,62,63] **even when added to a regular meal.** This happens due to a rapid absorption by the portal system and beta-oxidation in the liver, generating excess acetyl-Coa, which leads to ketone body formation[58,64].

Acetoacetate is the first ketone body produced[65], followed by beta-hydroxybutyrate (BHB), considered the main ketone body[66]. Ketone bodies cross the blood-brain barrier[67], enter neurons and generate ATP by oxidative phosphorylation in the mitochondria[58].

BHB acetoacetate levels reach 0.010 to 0.015 mM in the postprandial period[68]. Supplementation with 12 grams of caprylic acid combined with eight grams of capric acid, twice a day, brought BHB levels to 0.6 mM[69], indicating that the consumption of caprylic and capric acids safely induces mild to moderate ketonemia without the need for prolonged fasting or consumption of high fat content, as in the classic ketogenic diet. In addition, caprylic and capric acids do not stimulate fat deposition[63].

In AD patients, when plasma BHB levels are around 0.1 mM, ketone bodies provide more than 5% of brain energy, providing about 10% to 15% when reaching 1 mM[58]. The daily supplementation of 30 grams of capric acid combined with caprylic acid, or just caprylic acid, in mild to moderate AD patients, **decreased the brain energy deficit by 23%** due to an increased supply of ketone bodies, without changing the use of cerebral glucose[61]. Another study reported that, in addition to the increased plasma concentration of ketone bodies, the ingestion of 20 grams of capric acid combined with caprylic acid resulted in **cognitive improvements assessed through memory tests in participants with mild to moderate AD**[70].

One dose of **Instanth® NEO** provides
20 g of caprylic acid and 15 g of capric acid.

• Phosphatidylserine

Synaptic dysfunction is an important factor that increases cognitive impairment in AD[71]. Neuropathological analyses of AD patients show a strong association between degrees of cognitive impairment and synaptic changes[72]. **One of the causes may be related to the composition and function of neuronal membranes.**

Post-mortem brain analyses of AD patients showed changes in the composition of neuronal membranes, such as decreased phospholipid content, when compared to control subjects of the same age, who presented changes mainly in the hippocampus and cerebral cortex[73,74,76-78].

Among phospholipids, decreased phosphatidylserine (PS) in neuronal membranes has been associated with

impaired memory and deficits in mental cognitive abilities[75], since PS plays a fundamental role in neuronal membrane functioning[76-78].

Oral supplementation of PS crosses the blood-brain barrier, increasing the supply of this compound to the brain[79], which is related to increased interneuronal communication due to an increased fluidity of cell membranes[80-82]. PS is also related to cholinomimetic action, inhibiting cholinesterase, an enzyme that degrades ACh, in addition to being related to glucose metabolism[76]. Probable AD subjects presented an increase of 15% in CGMR after three weeks of PS supplementation (500 mg/day)[83].

A randomized double-blind controlled study on patients diagnosed with probable AD, receiving supplementation of 200 mg of PS daily for three months, reported significant improvements in memory, information processing, and the ability to perform daily activities compared to the placebo group[84]. In another study, patients diagnosed with AD who received supplementation of 300 mg of PS daily for five months presented increased cognitive assessment scores in vocabulary and image memory tests after treatment[85].

One dose of **Instanth® NEO** provides 300 mg of PS and 459 mg of choline.

PS is a constituent of neuronal membranes that protects cell membranes against oxidative damage[86]. In AD patients, PS seems to inhibit the oxidation of cell membrane phospholipids caused by ROS[87]. **Choline is an important nutrient in the metabolism of phospholipids** that also plays a role in cholinergic dysfunction and in synaptic membrane functioning[88]. In AD, the need for choline increases due to the high brain levels necessary to correct synaptic dysfunction[89]. In this context, post-mortem research documented lower levels of choline and phospholipids in the brain of AD patients compared to controls of the same age[90]. In animal models, choline supplementation increased free choline and ACh concentrations in the cortex and hippocampus, indicating improved cognitive deficits and anxiety, and decreased ß-amyloid deposition[91].

• Docosahexaenoic acid (DHA)

Brain cell membranes are rich in Ω3 polyunsaturated fatty acids, such as DHA. However, in AD, DHA levels are decreased[92] and there is significant experimental evidence that DHA deficiency or enrichment in the hippocampus is associated, respectively, with decreased or increased learning related to memory skill[93].

In addition, about 20% to 30% of the PS content in the gray matter is combined with DHA[94.95]. A reduction in PS DHA content in the cerebral cortex is associated with the progression of mild cognitive impairment to AD[86,96]. Consequently, the incorporation of PS into human membranes depends on the availability of PS itself, but also of DHA[86,94]. DHA positively modulates PS biosynthesis and reserves in neuronal cells that promote survival and inhibit apoptosis, in a PS-dependent manner. In addition, the combined supplementation of DHA and PS significantly reduced nitric oxide (NO) levels (which demonstrated antioxidant activity), in the brain tissue of animals, being more efficient than the supplementation of DHA or PS alone[97].

A double-blind placebo-controlled trial investigating the safety of using 300 mg of PS combined with 79 mg of Ω3 for 15 weeks showed that this supplementation was safe and well tolerated[98]. Another double-blind placebo-controlled study showed that the same dose of PS combined with DHA improved cognitive performance in older patients with memory complaints[99].

One dose of **Instanth® NEO** provides 180 mg of DHA.

• Hyperhomocysteinemia and AD

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One dose of **Instanth® NEO** provides 6.8 mcg of vitamin B12, 289 mcg of folic acid, and 20 mg of vitamin B6.

• Vitamin D

Vitamin D deficiency can impact the development of several diseases and accelerate aging[115], since this vitamin is related to neuronal protection[116]. Vitamin D receptors (VDR) are widely expressed throughout the central nervous system (CNS), with greater expression in the hippocampus, hypothalamus, thalamus, cortex, subcortex, and substantia nigra, essential areas for cognition[117].

Vitamin D has an anti-inflammatory action that can reverse age-related changes in the hippocampus in an animal model[118]. The neuroinflammation caused by ß-amyloid accumulation plays a key role in AD pathogenesis and progression[119], being represented by the increased expression of pro-inflammatory cytokines released by the non-neuronal cells astrocytes and microglia, auxiliary cells that support the SNC operation[120,121].

The probable neuroprotective mechanism of action of vitamin D occurs through the suppression of cerebral proinflammatory cytokines[122] and the recovery of the ability of macrophages to phagocyte ß-amyloid[123] - with its increased brain efflux - and, consequently, decrease the number of amyloid plaques[124,125].

In AD patients, hypovitaminosis D is associated with faster cognitive decline[126,127], which demonstrates the potential benefit of supplementing this nutrient.

One dose of **Instanth® NEO** provides 41 mcg of vitamin D.

• Mix of Antioxidant Vitamins and Minerals

Older people present decreased antioxidant levels in brain regions related to AD[128]. In AD, oxidative stress is closely related to mitochondrial dysfunction due to a defect in the electron transport chain and an increased production of free radicals[129], which increase neurodegeneration[130]. Thus, a combination of antioxidant vitamins and minerals must be present in the diet of AD patients.

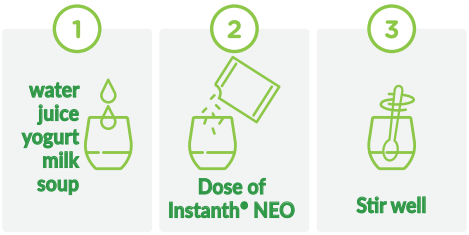
One dose of **Instanth® NEO** provides antioxidant vitamins and minerals: vitamins C and E, selenium, zinc, and magnesium.

• **Instanth® NEO** is a unique combination of nutrients for brain nutrition in Alzheimer's patients. Caprylic and capric acids increase ketone body formation, partially compensating for the energy deficit observed in AD patients. Phosphatidylserine plays a fundamental role in neuronal membrane functioning, supporting cognitive functions. However, the incorporation of phosphatidylserine in the membranes is mediated by DHA, which also supports the proper functioning of synapses. The combination of vitamins and minerals with anti-inflammatory and antioxidant properties present in **Instanth® NEO** supports the brain nutrition.

4-week adaptation (28 days): 2 boxes with 37 sachets (13.75 grams each).

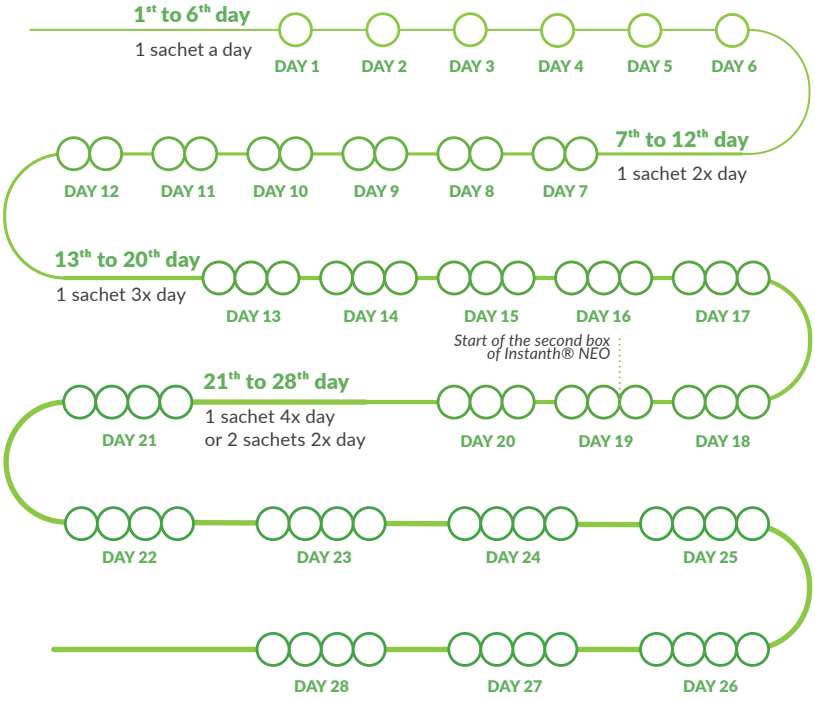
Adaptation period	Duration	Quantity	Number of sachets for the period
1st to 6th day	6 days	1 sachet 1x day	6 sachets
7th to 12th day	6 days	1 sachet 2x day	12 sachets
13th to 20th day	8 days	1 sachet 3x day	24 sachets
21st to 28th day	8 days	1 sachet 4x day or 2 sachets 2x day (2 to 4 days)	36 sachets

How to use:



During the adaptation period, **Instanth® NEO** should be consumed after meals.

Consumption guidance for the adaptation period



Continuous use after the adaptation period:

4 sachets of 13.75 g consumed preferably together, or 2 sachets of 13.75 g twice a day.

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