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Smoking as a triggering factor for alzheimer's disease: an integrative review

Tabagismo como fator desencadeante para a doença de alzheimer: uma revisão integrativa

El tabaquismo como factor desencadenante de la enfermedad de alzheimer: una revisión integradora

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Abstract

More than 50 million people worldwide suffer from dementia, with Alzheimer's being the most common, especially in smokers. The objective was to identify studies that related

smoking to Alzheimer's. The methodology was an integrative literature review to respond to the PICO strategy (P: smokers; I: cigarette; C: non-cigarette users; O: cigarette as a triggering factor for Alzheimer's Disease): Smoking can be a triggering factor of Alzheimer's? The results showed smoking as a risk factor for the disease, in addition to chronic, recreational or passive smoking being associated with increased cerebral oxidative stress. Heavy consumption in middle age increased the risk of dementia by more than 100% compared to non-smokers. Thus, it is important to have measures and policies that guide about the risks and the reduction of cigarette consumption, contributing to greater development and quality of life for the population.

Keywords: Dementia; Alzheimer disease's; Medicine; Neurology; Tobacco products.

Resumo

Mais de 50 milhões de pessoas no mundo sofrem com demência, sendo o Alzheimer a mais comum, especialmente associado ao tabagismo. O objetivo foi identificar estudos que relacionassem o tabagismo com o Alzheimer. A metodologia foi uma revisão integrativa da literatura para responder a estratégia PICO (P: fumantes; I: cigarro; C: não usuários de cigarro; O: cigarro como um fator desencadeante para a Doença de Alzheimer): O tabagismo pode ser fator desencadeante do Alzheimer? Os resultados demonstraram o cigarro como fator de risco para a doença, além do tabagismo crônico, recreativo ou passivo estarem associados ao aumento do estresse oxidativo cerebral. O consumo intenso na meia idade aumentou em mais de 100% o risco de um quadro demencial comparado aos não fumantes. Desta forma, é importante medidas e políticas que orientem sobre os riscos e a redução do consumo de cigarro, contribuindo para maior desenvolvimento e qualidade de vida da população.

Palavras-chave: Demência; Doença de Alzheimer; Medicina; Neurologia; Produtos do tabaco.

Resumen

Más de 50 millones de personas en todo el mundo padecen demencia, siendo el Alzheimer el más común, especialmente asociado con el tabaquismo. El objetivo fue identificar estudios que relacionaran el tabaquismo con el Alzheimer. La metodología fue una revisión integradora de la literatura para responder a la estrategia PICO (P: fumadores; I: cigarrillos; C: no consumidores de cigarrillos; O: cigarrillos como factor desencadenante de la enfermedad de Alzheimer): El tabaquismo puede ser un factor desencadenante de ¿Alzheimer? Los resultados mostraron que el tabaquismo es un factor de riesgo para la

enfermedad, además de que el tabaquismo crónico, recreativo o pasivo se asocia con un mayor estrés oxidativo cerebral. El consumo excesivo en la mediana edad aumentó el riesgo de demencia en más de un 100% en comparación con los no fumadores. Por ello, es importante adoptar medidas y políticas que orienten sobre los riesgos y la reducción del consumo de cigarrillos, contribuyendo a un mayor desarrollo y calidad de vida de la población.

Palabras clave: Demencia; Enfermedad de Alzheimer; Medicina; Neurología; Productos del tabaco.

1. Introduction

More than 50 million people worldwide suffer from dementia, with nearly 10 million new cases reported each year. The World Health Organization (WHO) estimates that the number of people with dementia will reach 82 million by 2030 and 152 million by 2050, mainly in low- and middle-income countries. Alzheimer's disease (AD) is the most common form of dementia, comprising up to 60 to 70% of cases, representing a major public health problem, which mainly affects elderly individuals (World Health Organization, 2019).

The name of the disease is related to the German neurologist Dr. Alois Alzheimer (1864– 1915), who observed in 1906 changes in the brain tissue of a woman, who he considered to have died from a rare mental illness. It is known today that these abnormal changes in brain tissue are characteristic of Alzheimer's disease (Cayton et al, 2016, p. 17).

AD is a progressive, multifactorial neurodegenerative disease manifested by cognitive and memory deterioration, with progressive impairment of activities of daily living, associated with a variety of neuropsychiatric and behavioral symptoms. The disease settles insidiously and develops slowly and progressively over the years (Querfurth & LaFerla, 2010). The initial symptoms are barely noticeable, and the first years of the disease go unnoticed. Only when their evolution begins to harm the activities of daily living do family members observe that something is wrong with their family member. The first symptom, and the most characteristic, is recent memory loss. With the progression of the disease, more serious symptoms such as the impairment of remote memory (i.e., the older facts) appear, as well as irritability, language failures, impairment in the ability to orient one's orienting itself in space and time. Among the main signs and symptoms of Alzheimer's are: lack of memory for recent events; repetition of the same question several times; difficulty in following complex conversations or thoughts; inability to develop strategies to solve problems;

difficulty in driving a car and finding familiar paths; difficulty in finding words that express ideas or feelings; irritability, unjustified suspicion, aggressiveness, passivity, misinterpretations of visual or auditory stimuli, tendency to isolation (Ministério da Saúde, 2018).

Since the 1980s, the cholinergic system and Alzheimer's dementia have been linked, which has been identified through observations of primary neurochemical changes in this system. Then, the brain demonstrates cholinergic dysfunction involved in changes in memory, learning, attention and other common cognitive processes affected in these patients. Other alterations have been reported, such as the amount of muscarinic receptors in several brain regions in intracellular signaling induced by these receptors, indicated by the presence of high concentrations of a protein-induced low molecular weight endogenous inhibitor (IEBP). The IEBP provides an endogenous antagonism to muscarinic cholinergic receptors in these patients, which seems to be related to the clinical manifestations observed in this degenerative neuropathy (Cummings & Back, 1998).

An external factor that may be related to AD is smoking. Studies show that smokers are more susceptible to the development of problems in the circulatory system, such as atherosclerosis, when the arteries undergo inflammatory process and deposition of fat plaques on their walls. Over time, these plaques calcify, decreasing the caliber of the vessels and causing the brain to receive less blood, oxygen and nutrients. This vascular involvement can lead to brain injury, gradually progressing to a dementia (Engelhardt et al., 2011). In addition, in a study conducted at King's College London, it showed consistent evidence that smokers tend to have a higher risk of cognitive decline compared to nonsmokers (Dregan et al, 2013).

One of the studies related AD to smoking followed more than 21,000 people during 23 years, with profiles among smokers, nonsmokers and former smokers. They were submitted to several questionnaires at different periods of their lives. They concluded that smoking more than two packs a day, mainly between 50 and 60 years of age, increased the risk of developing Alzheimer's by 157%. Smoking also contributes to oxidative stress and inflammation, which is estimated to be important for the development of AD (Rusanen et al, 2011).

Cigarette smoke contains several toxic substances to the body. Among the main ones are nicotine, carbon monoxide, and tar. The intense and constant use of cigarettes increases the probability of occurrence of some diseases such as pneumonia, lung cancer, coronary problems, chronic bronchitis, in addition to cancers in the throat, tongue, larynx and esophagus, regions of the body that come into direct contact with cigarette smoke. The risk of

myocardial infarction, angina and stroke is higher in smokers when compared to nonsmokers (Brazilian Psychotropic Drug Information Center, 2015).

In 2016, 20% of the world's population used tobacco, with 1.1 billion adult smokers registered worldwide, a number that has remained virtually unchanged since 2000 (World Health Organization, 2019).

The objective of this study was to analyze scientific studies on Alzheimer's disease and smoking and establish the relationship between diseases.

2. Methodology

The present study is configured as an integrative review of literature of qualitative and exploratory nature. Qualitative, because it stimulates the analysis and allows the development of concepts and ideas from the patterns of the data obtained, and exploratory because it has the objective of contributing to a greater understanding of the theme studied. According to Souza, Silva and Carvalho (2010), the integrative review is a methodology used to synthesize the results of studies already conducted, democratizing access and allowing constant updating on the theme of interest. It is an important tool, making it possible for the reader to improve and instill new practices in their professional routine. According to Pereira, Shitsuka, Parreira and Shitsuka (2018), qualitative methods are those in which the interpretation by the researcher with his opinions on the phenomenon under study is important. While the fundamental objective of an exploratory research is to describe or characterize the nature of the variables one wants to know (Koche, 2011).

To elaborate this review, the methodological path was subdivided into six stages: identification of the theme and selection of the research question; establishing inclusion and exclusion criteria; identification of pre-selected and selected studies; categorization of the selected studies; analysis and interpretation of the results; and presentation of the review/synthesis of knowledge.

These aspects facilitated the identification of the relevant results, of the gaps, which point to the development of research, besides assisting the professional in the choice of conducts and decision-making, providing critical knowledge.

Type of study

An integrative review of the medical literature was elaborated using the PICO strategy (Patient, Intervention, Control, "Outcome" (control)) to formulate the clinical question of this

study, which is: Patients: Smokers; Intervention: Cigarette; Control: No cigarette users; Result: "Outcome": Smoking as a triggering factor for Alzheimer's disease.

So, to guide the study, the guiding question was defined: Can smoking be a triggering factor for Alzheimer's disease?

Search criteria

The bibliographic survey was conducted through electronic search in the databases: Latin American and Caribbean Literature on Health Sciences (LILACS), USA National Library of Medicine (MEDLINE/PubMed), ScienceDirect and the Scientific Electronic Library Online (SciELO). The descriptors, selected through the Health Sciences Descriptors (DeCS), were: "neurology" AND "tobacco products" AND "Alzheimer disease" OR neurologia AND produtos do tabaco AND doença de Alzheimer.

Eligibility criteria

The articles searched by 4 authors. First, each author analyzed the studies found in the databases separately and after the initial collection, they met to discuss the filtered articles and complete their selection. The included studies were randomized clinical trials, integrative reviews, systematic meta-analyses, experimental and cohort study, published between 2011 and 2020 and available in full.

Data extraction

Data extraction was performed from the complete reading of the studies extracted from the databases indicated. The results from this reading were organized in a spreadsheet containing six dimensions of analysis, in order to enable their categorization. The dimensions of analysis were: year of publication, source of publication, type of study, sample, objectives, main results. In addition, as part of the analysis of the recovered articles, the level of scientific evidence of each of them was determined through the GRID system (Diretrizes Metodológicas, Ministério da Saúde, 2014).

3. Results and Discussion

The searches performed on the research platforms resulted in 116 articles, 84 of which were excluded because they did not present a relationship between smoking and Alzheimer's disease. By reading the abstracts, 18 studies were not directly related to the theme and, according to the reading of the full text, 12 other articles were also excluded. At the end of the selection, 6 articles comprised the study because they met the inclusion criteria. To better elucidate the findings, Table 1 shows the distribution of the studies found.

Table 1. Absolute number (N) and percentage (%) of all articles found by database analyzed.

Search site	N	%
PubMed	76	65,5
Scielo	38	32,7
Lilacs	2	1,8

Source: Authors.

Of the 116 studies found, the majority were found in the PubMed database, with 76 articles (65.5%), while in Lilcas only 2 were found.

The distribution of the articles included is presented in Table 2, together with their respective title, year of publication, country and level of evidence. While Table 3 presents the studies according to the type of study, sample, objectives and main results.

Table 2. Studies included according to their authors, title, year and country of publication and classification of the level of evidence.

Authors	Title	Year	Country	Level of evidence
Durazzo et al	Cigarette smoking is associated with cortical thinning in anterior frontal regions, insula and regions showing atrophy in early Alzheimer's Disease	2018	USA	B (A3)
Wallin *et al.*	Alzheimer's disease and cigarette smoke components: effects of nicotine, PAHs, and Cd(II), Cr(III), Pb(II), Pb(IV) ions on amyloid-β peptide aggregation	2017	Sweden	B (A3)
Toda & Okamura.	Cigarette smoking impairs nitric oxide-mediated cerebral blood flow increase: Implications for Alzheimer's disease	2016	Japan	A (B1)
Durazzo *et al.*	Active Cigarette Smoking in Cognitively-Normal Elders and Probable Alzheimer's Disease is Associated with Elevated Cerebrospinal Fluid Oxidative Stress Biomarkers	2016	USA	A (B1)
Durazzo et al.	Smoking and Increased Alzheimer's Disease Risk: A Review of Potential Mechanisms	2014	USA	A (B1)
Rusanen *et al.*	Heavy Smoking in Midlife and Long-Term Risk of Alzheimer Disease and Vascular Dementia	2011	USA	B (A2)

Fonte: Os autores

The studies found correspond to the years 2011 to 2018, representing 3 different countries, four in the USA and the other two in Japan and Sweden. The level of evidence was divided with half A and the other half B, being B1, the least relevant qualis.

Table 3. Studies included according to their authors, type of study and sample, objectives and main results.

Authors	Study type/Sample	Goals	Main results
Durazzo et al	Control case N= 82 patients (41 smokers and 41 nonsmokers)	To investigate the effects of smoking in relation to changes in cortical thickness	Cortical thinning in smokers, in relation to nonsmokers and directly proportional to the number of cigarettes/year of use; as well as symptoms: impulsivity, worse decision-making and risk decisions
Wallin *et al.*	In vitro experiment between Aβ peptidemonomers and the substances studied	Investigate in vitro the effects of cigarettes (nicotine, polycyclic aromatic hydrocarbons (PAH) and metal ions Cd (II), Cr (III), Pb (II) and Pb (IV) on beta-amyloid aggregation (Aβ)	PAH and metal ions modulated the aggregation process of Aβ. Unloaded nicotine (molecular form) and hydrophilic form showed no direct interactions with Aβ, nor did it affect the aggregation of Aβ
Toda & Okamura	Integrative Review N= 139 studies	Summarize the possible mechanisms of action of active and passive smoking and nicotine on cerebral vascular endothelial function, the nitrergic nerve and blood flow in reference to cognitive failure and AD	The possible mechanisms of action are (1) in impairing nitric oxide (NO) synthesis in cerebral vascular endothelial cells and nitrergic nerves, leading to interference stems from cerebral blood flow and glucose metabolism in the brain. (2) smoking-induced cerebral hypoperfusion is triggered by impaired synthesis and actions of NO mediated by the inhibitory pathway of the endothelial nitric oxide synthase enzyme, and by increased free radical production, resulting in decreased no actions on the vascular smooth muscle. (3) harmful (acute and chronic) action of nicotine on endothelial NO and inhibiting nitrergic nerve function in chronic use. (4) impairment in cerebral blood supply promotes amyloid synthesis β which accelerates the decrease in local blood flow

Durazzo *et al.*	Cohort Study N=83 (Cognitively normal elderly smokers and nonsmokers) N=164 (Elderly with mild cognitive impairment) N=101 (Elderly with probable Alzheimer's disease)	To evaluate the association of active smoking with f2-isoprostane concentration in cognitively normal elderly, with mild cognitive impairment and probable Alzheimer's disease (AD)	The smoker with probable AD showed the highest concentration of iPF2α-III among the groups. Elderly with mild cognitive impairment, both for smokers and nonsmokers, did not differ in the concentration of iPF2α-III. No group showed apparent difference in concentration of 8.12, iso-iPF2α-VI but in those with probable AD, higher levels in 8.12, iso-iPF2α-VI were related to smaller volumes of the left and total hippocampus
Durazzo et al.	Systematic Review N= 260 studies	To investigate the association between smoking and increased risk of AD in the preclinical and human literature. To relate smoking, nicotine exposure and neuropathology related to AD	Cigarette smoke is associated with neuropathology of AD in preclinical and human models. Smoke-related cerebral oxidative stress is a potential mechanism that promotes ad pathology and increases the risk of AD
Rusanen *et al.*	Cohort Study N=21,123 patients	Investigate the association between smoking in middle age and the risk of dementia, Alzheimer's disease (AD) and vascular dementia (VaD)	A total of 5367 people (25.4%) was diagnosed with dementia (including 1,136 cases of AD and 416 cases of VaD) during 23 years of follow-up. Compared to nonsmokers, those who smoked more than 2 packs per day had a high risk of dementia (adjusted risk ratio [RR]: 2.14; confidence interval [CI]: 95%, 1.65-2.78), AD (adjusted RR: 2.57; CI: 95%, 1.63- 4.03) and VaD (adjusted RR: 2.72; CI: 95%, 1.20-6.18)

Fonte: Os autores

According to the types of study presented in Table 3, one case-control, two cohorts, one experimental in vitru, an integrative review and a systematic review were found.

Active use of cigarettes for long years may be associated with brain changes reaching its morphology, blood flow and consequent biochemical functions. It achieves structural integrity and the different functionality of the cognitive domain. Thus, there is an increased

risk of developing AD after continued exposure to cigarette toxins, such as nicotine and compounds present in smoke such as hydrocarbons and metals. Thus, Rusanen et al (2011) reported that the use of more than 40 cigarettes per day increases the risk of dementia, in addition to the high intensity of use in middle age for causing serious consequences to the brain.

Wallin et al (2017) experienced the action on brain biochemistry of five aromatic hydrocarbons and four metal ions in cigarette smoke that can affect the peptide aggregation process of the myeloid beta (Aβ). They showed that toluene alter the oligomeric and hydrophobic (tetropera) form of Aβ. Among the metals, they reported that Pb (IV) seems to affect the formation of dummers and trimers of Aβ.

Another change, caused by the chronic use of cigarettes, is in the formation of free radicals that trigger oxidative stress on the phospholipids of neuron membranes. Accelerated brain metabolism increases cellular susceptibility to oxidative stress and the action of oxidizing agents associated with low levels of anti-oxidant enzymes. The greatest predisposition is between neurons in the hippocampus. A biomarker of oxidative and free radical-induced stress is IsoprostanE F2, present in neuronal and glial tissue of the brain. This marker assists in the evaluation of tissue damage in neurodegenerative diseases, atherosclerosis, lung diseases and in chronic smokers. They also demonstrated that recreational and passive use increased oxidative stress and impaired cerebral vasodilation with consequent decreased blood flow as risk factors for memory disturbance and AD (Durazzo et al., 2016).

4. Final Considerations

It is concluded that cigarettes are one of the main causation agents of chemical dependence of society and its persistence, over the years, is related to numerous diseases, besides being an important factor of poor prognosis in several comorbidities. In relation to Alzheimer's disease, it was possible to identify a significant influence of smoking, in which oxidative stress, derived from the substances that compose it, is extremely harmful to brain structures. It can directly affect neuronal tissue or indirectly compromising cerebral blood flow, which contributed to dementia as well as Alzheimer's disease. Moreover, it was seen that intense smoking in middle age increased by more than 100% the risk of developing a lack of education when compared to non-smokers, making clear the importance of social measures and policies in both primary care and society, which guide and clarify the risks and reduce

cigarette consumption, contributing to a greater development and quality of life for all.

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