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What is the Relationship Between Sleep and Alzheimer's Disease? A Narrative Review

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Abstract

Introduction: Alzheimer's disease (AD) is the most common neurodegenerative disorder, impacting 55 million people worldwide. With rates on the rise, research is continually being conducted to examine risk factors that are contributing to its growing prevalence. There is growing evidence showing a bidirectional relationship between sleep and AD, where poor sleep contributes to the development of AD, and conversely, AD pathology impairs patients' sleep quality and quantity.

Methods: A narrative review was conducted in a systematic fashion using the databases PubMed, Embase and the Cochrane Library. After performing a literature search, high-quality relevant sources are selected, and data were extracted and analyzed to explore the relationship between AD and lack of sleep.

Results: A bi-directional relationship was suggested based off evidence which was gathered from longitudinal studies and cross-sectional studies. As well as experimental studies which was focused on the mechanisms of AD, including tau protein aggregation and beta-amyloid accumulation.

Discussion: Results showed that there could be a potential bi-directional relationship when discussing AD and sleep. In AD, metabolic waste known as beta-amyloid creates neurotoxic plaques which form in the spaces between neurons. Studies suggest that Aβ has an important role to play in sleep as increased sleep disturbances are present with Aβ accumulation. Conversely, after losing one night of sleep, there is an increase in beta-amyloid, highlighting the role of sleep in metabolite clearance. Another AD protein associated with sleep is tau. Poor sleep is associated with clumping of tau, forming toxic tangles inside neurons which injure tissues nearby and contributes to cognitive impairment. However, it still difficult to conclude the directionality of sleep and AD due to limitations on the current technologies used to detect amyloid-beta and tau.

Conclusion: This narrative review concludes that a bi-directional relationship may be present between sleep abnormalities and AD. Management of poor sleep quality should be further considered as a potential prophylactic intervention against AD.

Keywords: sleep deprivation; Alzheimer's disease; cognitive decline; beta-amyloid; tau protein; lack of sleep.

Introduction

Dementia refers to neurodegenerative disorders associated with memory impairment, difficulty in planning and problem solving, inability to learn new things, and shortened attention span, and affects more than 55 million people worldwide [1]. Alzheimer's disease (AD) is the most common form of dementia, accounting for about 70% of cases [2]. AD is a progressive neurological disease which results in the deterioration of various cognitive functions, including significant memory impairment. With numbers on the rise, AD and dementia are becoming a growing concern globally. It is anticipated that approximately 70 million people worldwide will develop AD by 2030, and this number is expected to nearly double by 2050 [3]. In Canada alone, over 747,000 Canadians are currently living with AD or other dementias, and this number is expected to increase to 1.4 million people by 2031 [1,4].

One seldom discussed factor in AD is the role of sleep. Sleep disturbance is a common complaint reported in individuals with AD [5]. AD pathology may damage certain neural pathways that control and regulate sleep, as sleep quality tends to deteriorate significantly as the disease progresses [6]. Additionally, poor sleep may also be a risk factor for the development of AD as observational evidence suggests that disrupted sleep is related to cognitive impairment and the development of neurodegenerative diseases. Thus, there may be a bi-direction relationship between AD and sleep as sleep is a risk factor to AD pathology, and sleep deterioration and disturbances are a marker of AD [7,8]. It is hypothesized that a bidirectional relationship exists between sleep and the pathogenesis of

AD as the accumulation of beta-amyloid (Aβ) negatively impacts sleep behaviour. Likewise, poor sleep may increase Aβ aggregation and promote the deposition of tau protein in the brain [9]. Therefore, the aim of this manuscript is to review and examine the literature surrounding the bidirectional relationship between AD pathology and varying aspects of sleep.

Methods

This narrative review took a systematic approach to find (48) relevant literature. Databases used included PubMed, Embase and the Cochrane Library. The keywords that were used in the search were: "Alzheimer's disease" OR "Alzheimer's dementia", "Early-onset Alzheimer's disease", late-onset Alzheimer's disease", "cognitive decline", "pathogenesis of Alzheimer's disease," AND "lack of sleep" OR "sleep deprivation", "insomnia", "insufficient sleep" , "sleep disturbance", "sleep complaints", "sleep disorders "AND "tau protein" OR "beta-amyloid", "tau", "amyloid beta". Results were filtered to the last 20 years and high-quality, relevant sources were selected, and important data is extracted and analyzed to determine a potential correlation between AD, cognitive decline, and poor sleep.

Results

Evidence for the bi-directional relationship sleep and AD in humans comes from both longitudinal studies and cross-sectional studies. There was also evidence for the role of AD pathologies, beta-amyloid and tau, as possible mechanisms contributing to sleep disturbances and AD.

Longitudinal Studies

Longitudinal evidence demonstrates that poor and disrupted sleep earlier in life is associated with cognitive difficulties years later. In a pivotal study by Lim et al., poor sleep quality was associated with cognitive health of older adults, as those with the greatest sleep fragmentation (Interrupted sleep) had a 1.5-fold risk in developing dementia. Additionally, greater sleep fragmentation was associated with a greater annual rate of cognitive decline. This suggests that short interruptions during sleep was associated with increased risk for cognitive decline and the development of AD [10].

For example, having insomnia earlier in life is associated with the development of AD [11]. Osorio et al. used a subset of 346 healthy older adults, and compared between healthy older adults who then progressed to develop AD and those who did not develop AD. [11]. After 7.7 years, it was found that having insomnia at baseline was associated with an increased risk of developing AD [11]. Similarly, Yaffe et al. examined the association between sleep-disorder breathing, a condition which significantly lowers sleep quality in elderly women [12]. Women with sleep-disordered breathing were 31.1% more likely to develop mild cognitive impairment (MCI), a predormal stage of AD 44.8% more likely to develop dementia [12]. These studies demonstrate that sleep disorders like insomnia and sleep-disordered breathing increases the likelihood of cognitive decline and dementia.

Additionally, a similar relationship has been observed between sleep duration and dementia. Sabia et al. explored the association between sleep duration in middle and older age and the incidence of cognitive impairment [13]. After 25 years, there was an increased risk of developing dementia in older adults ages 50-60 years old who slept six hours or less compared to the those who had seven hours of sleep [13]. Furthermore, older adults between 50 to 70 at baseline who were identified as "persistent short sleepers" had a 30% risk of developing dementia, which was not associated with behavioural or cardiometabolic factors. This recent study provides preliminary evidence that short sleep duration in middle adulthood may increase the risk of dementia later in life.

Interestingly, there may be an inverted U-shape relationship between sleep duration and cognitive decline. In a pooled cohort study, Ma et al. found that individuals who self-reported their sleep to be less than four hours or greater than 10 hours per night had faster rates of cognitive decline than those who reported seven hours of sleep per night [14]. Similar results have been found when looking at the amount of time in bed (TIB). Bokenberger et al. classified participants into three groups: those with short TIB (less than six hours), extended TIB (more than nine hours), and an intermediate reference group (7 hours per night) [15]. At baseline, it was found that those with longer TIB had lower cognitive functioning. After 17 years, participants with short or extended TIB had higher incidences of dementia. Researchers suggested that a longer TIB could be a prodromal feature of AD as it was associated with poorer cognition at baseline and at follow up. In contrast, shorter TIB may be a risk factor for developing cognitive impairment [15]. In summary, much longitudinal research has suggested that short sleep duration and lower sleep quality may lead to an increased risk of AD development.

Cross-Sectional Studies

Over the last decade, many cross-sectional studies have examined the relationships between cognitive decline, AD, and sleep. For example, using objective measures of sleep, Blackwell et al. found that poor sleep quality was associated with impaired global cognition and executive functioning in elderly women [16]. Furthermore, Miller et al. found similar results when looking at memory[17]. Using data from the English Longitudinal Study of Aging., Miller et al. separated participants into two groups: a younger group (aged 50-64) and an older group (ages 65+ years). Sleep and cognitive functions (categorized as amnestic and non-amnestic cognitive functions) were examined [17]. In the older group there was a greater association between sleep quality and amnestic cognitive functions compared to

the younger group, where older adults had significantly worse amnestic cognitive functions with poor sleep. These results suggest the relationship between sleep disturbances and cognitive function increases with age [17]. Additionally, there was evidence of the inverted U-shape relationship between sleep duration and cognition in the younger age group, as both short (less than 6 hours) and long (more than 8 hours) and long sleep durations were associated with poorer cognition.

Moreover, the prevalence of sleep disturbance may be higher in people with mild cognitive impairment. 431 Individuals with MCI were enrolled in 10 different neurological centres for dementia, and interviews were conducted with these individuals in order to investigate their sleep quality. Over 60% of people said that they had one or more sleep disturbances per night. Similar to the previous, this supports that sleep disturbances are frequent in people with cognitive impairment or dementia, suggesting a relationship between the two [18]. These results are further supported by a recent systematic review and meta-analysis looking at sleep disturbances in care home residents with dementia. This systematic review found that out the 20% of participants who had been diagnosed with dementia, 70% of them also had disturbed sleep [19]. Overall, some cross-sectional studies propose that poor sleep quality and longer sleeping times may be associated with AD.

Possible Mechanisms – Amyloid Beta and Tau

Cross sectional and longitudinal study propose an association between sleep, cognitive impairment, and AD. The mechanisms underlying this association may be related to the two hallmarks of AD pathology: the accumulation of amyloid-beta (Aβ) in the brain and the degree of phosphorylation of the tau proteins within neurons [20].

Aβ is a large membrane protein that normally plays an essential role in neural growth and repair. Aβ peptides are cleaved off by the larger precursors, consequently forming neurotoxic insoluble plaques [20]. According to the Aβ cascade hypothesis, these Aβ plaques trigger a series of processes that initiate AD pathogenesis, such as toxic accumulations triggering neurodegeneration [21]. However, once Aβ starts to accumulate, AD progression may continue independently to the amount Aβ accumulated. New imaging technologies such as Aβ imaging agents may be used; however, these tools are not able to distinguish pathological from non-pathological forms of Aβ [20].

Sleep serves as an important biological mechanism during which the brain is able to clear the Aβ produced throughout the day [22]. Studies have found that one night of unrestricted sleep resulted in a 6% decrease of Aβ amounts, while complete sleep deprivation achieved the opposite. These results are further supported by Chen et al., in which samples of cerebrospinal fluid (CSF) were taken to determine the levels of Aβ in individuals with chronic insomnia [23]. CSF-Aβ levels were significantly higher in individuals with chronic insomnia when compared to healthy controls [23]. Additionally, rest-activity rhythm fragmentation is linked to preclinical AD depending on certain factors such as age and sex. It was concluded that aging was associated with circadian dysfunction that was unrelated to AD pathology, but only in men. There is a presence of abnormalities in the circadian rhythm at the preclinical phases of individuals with AD which suggests that it could serve as a biomarker for the disease [23].

The second critical hallmark of AD is hyperphosphorylated tau proteins. Typically, tau proteins are abundant in nerve cells and glial cells, including oligodendrocytes and astrocytes [24]. Tau protein's primary functions are to stabilize neuronal microtubules under normal physiological conditions [25]. Increased phosphorylation of tau proteins results in helical tangles, also known as neurofibrillary tangles. The accumulation of misfolded hyperphosphorylated tau protein has been linked to neuronal loss, although it is unclear how this related to neuronal degeneration. Early in the development of AD, tau protein accumulation begins in certain parts of the brain such as the hippocampus, a region critical for learning and memory, potentially contributing to cognitive impairment [26].

Animal models conducted by Di Meco et al. and Rothman et al. revealed evidence that changes in the sleeping cycle may increase levels of hyperphosphorylated tau protein accumulation in the brain [27–29]. Di Meco et al. found that after a night of sleep deprivation, there was a significant increase of about 17% of tau levels in the blood [27]. Moreover, evidence in animal models suggest that after a couple of months of restricted sleep, there is about a 50% increase of insoluble tau in the brain [30] [27].This suggests that insoluble tau proteins form following periods of restricted sleep durations which affect cognitive function. These mechanisms of Aβ deposition and tau protein accumulation indicate that restricted or disrupted sleep may have an effect on AD pathogenesis [7].

Discussion

When examining the relationship between sleep and AD, the research suggests the two are interconnected. From the aforementioned results, longitudinal research has suggested that short sleep duration and lower sleep quality may lead to an increased risk of AD. Whereas, recently conducted cross-sectional studies have proposed that poor sleep quality as well as long TIB may be associated with AD. However, it remains unclear the true nature of this relationship; does disrupted sleep cause AD to develop, or does AD pathogenesis result in sleep disturbance? The answer is likely both, where a bi-directional relationship between sleep and AD may exist.

There are several mechanisms by which poor sleep would contribute to an accumulation of Aβ in the brain and increased phosphorylation of tau. The deposition of soluble Aβ is a normal result of synaptic activity [31]. During

wakefulness, there is constant neuronal activity which increases Aβ between neurons [32,33], but during sleep, changes in CSF dynamics clear out Aβ [34]. However, following sleep deprivation, we do not see this clearance of Aβ; a potential consequences of this may be the accumulation of Aβ and which progressively become insoluble plaques [35–37]. This imbalance between the deposition and removal of Aβ is a plausible mechanism as to why insufficient sleep is associated with excessive of Aβ deposition in the brain [9,38]. Similarly with tau, there are significant increases in tau proteins ollowing one night of sleep deprivation or chronic sleep restriction [27,28]. Additionally, poor sleep alters tau proteins through hyperphosphorylation and truncation, resulting in the formation of toxic neurofibrillary tangles and contributing to AD pathology [7].

Studies have provided crucial advancement on the mechanisms of sleep and cognitive decline outlining an intriguing bidirectional relationship between sleep and Aβ. Conversely, a relationship can be observed between Aβ and its effect on sleep. In healthy older adults, Aβ accumulation has been shown to disrupt slow wave sleep, which is a phase of sleep where Aβ clearance occurs [22,39]. Additionally, accumulated Aβ could lead to synapse loss, hypometabolism, and synaptic disconnection further impairing sleep [40]. However, further research is needed in order to completely understand the mechanisms associated with AD development, which will also help to explore potential preventative interventions. As Strooper and Karran proposed, AD is a complex disorder consisting of fluctuating and unpredictable responses [41].Overall, the research suggests that disrupted sleep increases the likelihood of Aβ accumulation and the development of AD, and conversely, AD-related Aβ may further disrupt sleep.

Rodent studies have been used to understand how the brain clears metabolic waste. During sleep, CSF is able to diffuse deep into the brain and mix with interstitial fluid, removing the waste products including Aβ [22]. As sleep time augments, the lymphatic system's actions of clearing Aβ and from the brain increases compared to when ones awake [22]. When a person lacks sleep, there is an accumulation of Aβ which in turn, is not cleared out the brain because this mechanism naturally occurs during sleep. This suggests that lack of sleep may increase in Aβ, as one of the functions of sleep is to clear metabolic waste from the brain. This may also be true for tau as the brain's lymphatic system has also been proven to contribute to the clearance of tau protein, based off rat trials [42]. It is also likely that misfolded hyperphosphorylated tau protein leads to neuron loss which could also affect sleep. It has been shown that people with dementia are awake for longer periods of time and often stay awake during the night [43]. In a report by McCullough et al., older healthy people were determined to have increased levels of tau tangles as measured by positron emission tomography scans and were reported to have less slow-wave and deep sleep [44].

Over time, the increased amount of soluble Aβ would accumulate and form soluble and insoluble plaques in the brain regions which are the most active, while the formation of hyperphosphorylated tau protein interferes with the normal function of the brain [20]. The insoluble plaques are toxic to the brain, potentially leading to cognitive decline. The accumulation of Aβ and hyperphosphorylation of tau protein could therefore affect sleep quality and quantity, while in the same way could contribute to AD development. On the other hand, a relationship could also be observed between how AD can interfere with both sleep quality and quantity, suggesting a bi-directional relationship between the two factors.

Conclusions

Although there is promising evidence for the bi-directional role of sleep and AD pathology, there are several limitations to the evidence discussed here. First, many studies are dependent on the use of self-reported measures of sleep. Although this is a convenient measure of sleep, these self-report measures do not have high agreement with more objective measures of sleep, suggesting these may capture different aspects of sleep [45]. Increasing the use of objective measures for sleep such as laboratory-based polysomnography, would provide more accurate and reliable results.

Although there have been significant advancements in the technologies used to track AD pathology in humans, these tools often invasive and expensive. Additionally, they are not able to differentiate between the pathological Aβ, and other forms of Aβ associated with normal aging, making it challenging to draw definitive conclusions. It is also difficult to identify adults with AD in the preclinical stages or when the pathology first appears, as identifying AD biomarkers is still an ongoing investigation [46]. Evidence suggests there are decades between the onset of AD pathology and the presence of cognitive symptoms [20]. Given the delay between the AD pathology and symptoms, as well as the lack of clear biomarkers, longitudinal study designs starting before the onset of AD pathology would be advantageous for studying neurodegenerative diseases like AD.

In conclusion, this narrative review compiles evidence from recent studies that suggest a relationship between sleep and AD, whereby poor sleep may contribute to the development of AD, and conversely, AD pathology may further disrupted sleep. The mechanisms for this bi-directional relationship could be related to Aβ plaques and tau neurofibrillary tangles, both of which are markers of AD and are associated with disrupted sleep. Furthermore, since AD is a complex and multifactorial disorder, other proteins may contribute to its pathogenesis [47]. Future research should continue to focus on the role of Aβ and tau, and also consider the various contributing factors of AD pathogenesis and progression.

List of Abbreviations Used
AD: Alzheimer's disease
Aβ: beta-amyloid
MCI: mild cognitive impairment
TIB: time in bed
CSF: cerebrospinal fluid

Conflicts of Interest
The authors declare that they have no conflict of interests

Ethics Approval and/or Participant Consent
This study did not require ethics approval and/or participant consent as it is a review.

Authors' Contributions
SG: made substantial contributions to the conception and design of the work and drafting the manuscript and revising it critically for important intellectual content. They also gave their final approval of the version to be published.
GR: made substantial contributions to the conception and design of the work and drafting the manuscript and revising it critically for important intellectual content. They also gave their final approval of the version to be published.

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