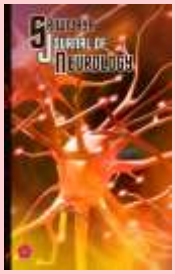

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Beyond Amyloid: Investigating the Role of Tau Oligomers in Alzheimer's Disease Progression in Medan, Indonesia

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A B S T R A C T

Introduction: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive decline and memory impairment. While amyloid plaques have been a central focus of AD research, increasing evidence suggests that tau oligomers play a crucial role in disease progression. This study aimed to investigate the relationship between tau oligomers, cognitive function, and disease severity in AD patients in Medan, Indonesia. **Methods:** An observasional case series study was conducted involving 50 AD patients diagnosed according to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria. Cerebrospinal fluid (CSF) samples were collected and analyzed for tau oligomers using an enzyme-linked immunosorbent assay (ELISA). Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) scale. Correlation analyses were performed to examine the relationship between tau oligomer levels, cognitive performance, and disease severity. **Results:** The mean tau oligomer level in AD patients was 120.5 ± 35.2 pg/mL. A significant negative correlation was observed between tau oligomer levels and MMSE scores ($r = -0.65$, $p < 0.001$), indicating that higher tau oligomer levels were associated with poorer cognitive performance. Furthermore, tau oligomer levels were positively correlated with CDR scores ($r = 0.58$, $p < 0.001$), suggesting a link between tau oligomers and disease severity. **Conclusion:** This study provides evidence for the involvement of tau oligomers in AD progression in the Indonesian population. Elevated CSF tau oligomer levels are associated with cognitive decline and disease severity in AD patients. These findings highlight the potential of tau oligomers as a therapeutic target and emphasize the need for further research to develop effective interventions.

1. Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that primarily afflicts the elderly population, causing progressive and irreversible cognitive decline. It is the most common form of dementia, accounting for 60-80% of cases, and its prevalence is increasing at an alarming rate due to the aging global population. The disease is characterized by a gradual deterioration of memory, thinking, behavior, and the ability to perform daily activities, ultimately leading to severe disability and dependence. The neuropathological hallmarks of AD are the accumulation of amyloid plaques and neurofibrillary tangles (NFTs) in the brain. Amyloid plaques are extracellular deposits of amyloid-beta (Aβ) peptides, while NFTs are intracellular aggregates of

hyperphosphorylated tau protein. These pathological changes disrupt neuronal function, leading to synaptic dysfunction, neuronal loss, and ultimately, cognitive decline.[1-3]

For decades, the amyloid cascade hypothesis has been the dominant theory in AD research. This hypothesis posits that the accumulation of Aβ peptides is the primary event in AD pathogenesis, triggering a cascade of events that lead to tau pathology, neurodegeneration, and cognitive impairment. However, recent research has challenged this hypothesis, highlighting the crucial role of tau pathology in AD progression. Tau is a microtubule-associated protein that plays a critical role in neuronal function. It stabilizes microtubules, which are essential for axonal transport, neuronal signaling, and maintaining the structural integrity of neurons. In AD, tau becomes hyperphosphorylated, leading to its detachment from microtubules and the formation of NFTs. These NFTs disrupt neuronal function and contribute to neurodegeneration.[4-6]

Recent research has focused on tau oligomers, soluble aggregates of tau protein that precede the formation of NFTs. Tau oligomers are believed to be more toxic than mature NFTs and play a critical role in synaptic dysfunction, neuronal loss, and cognitive impairment in AD. Studies have shown that tau oligomers can impair synaptic plasticity, disrupt neuronal signaling, and induce neuroinflammation. The majority of AD research has been conducted in Western populations, and there is limited data on the role of tau oligomers in AD in other populations, including the Indonesian population. Indonesia has a rapidly aging population and a growing prevalence of dementia, making it crucial to understand the underlying mechanisms of AD in this context.[7-10] This study aims to investigate the relationship between tau oligomers, cognitive function, and disease severity in AD patients in Medan, Indonesia.

2. Methods

This study employed an observational case series design to investigate the relationship between tau oligomers, cognitive function, and disease severity in patients with Alzheimer's disease (AD). The study was conducted at a private hospital in Medan, Indonesia, over a period of one year, from January 2022 to December 2022.

The study included 50 patients who had been diagnosed with AD according to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria. These criteria are widely accepted and utilized in research and clinical practice to establish a diagnosis of AD. The diagnosis of AD was not solely based on these criteria but was also supported by a comprehensive clinical evaluation, neuropsychological testing, and neuroimaging findings. This multi-faceted approach ensured the accurate identification and selection of AD patients for the study. Individuals with other neurological or psychiatric disorders, significant medical comorbidities, or those who were unable to provide informed consent were excluded from the study. This exclusion criterion aimed to minimize the potential confounding effects of other conditions on the relationship between tau oligomers, cognitive function, and disease severity in AD. The study was reviewed and approved by the Ethics Committee of CMHC Indonesia. All participants, or their legal guardians, provided written informed consent before enrollment in the study, in accordance with ethical guidelines for human subject research.

Lumbar puncture, a minimally invasive procedure, was performed to collect CSF samples from each participant. CSF is a clear fluid that surrounds the brain and spinal cord, providing cushioning and removing waste products. It is a valuable source of biomarkers for various neurological disorders, including AD. CSF samples were immediately processed and stored at -80°C until analysis. This immediate processing and low-temperature storage helped preserve the integrity of the samples and minimize any potential degradation of tau oligomers, ensuring the accuracy of the measurements. Tau oligomer levels in CSF were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Tau Oligomer ELISA Kit, #KHB0041, Invitrogen, Waltham, MA, USA). ELISA is a widely used laboratory technique for detecting and quantifying specific proteins, such as tau oligomers, in biological samples. The ELISA kit used in this study specifically

detects tau oligomers and has been validated for use in human CSF, ensuring the reliability and validity of the measurements.

Cognitive function, a critical aspect of AD, was assessed using two well-established instruments: the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) scale. The MMSE is a brief, widely used screening tool for cognitive impairment. It assesses various cognitive domains, including orientation, attention, memory, language, and visuospatial skills. MMSE scores range from 0 to 30, with lower scores indicating greater impairment. The CDR is a clinician-rated scale that provides a more comprehensive assessment of cognitive and functional performance. It evaluates six domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. CDR scores range from 0 to 3, with higher scores indicating greater severity of dementia.

Data were analyzed using SPSS software version 26 (IBM Corp., Armonk, NY, USA), a powerful statistical software package commonly used in research. Descriptive statistics were used to summarize demographic and clinical characteristics of the study participants. These statistics included measures of central tendency, such as mean and median, and measures of dispersion, such as standard deviation and range. Pearson correlation analyses were performed to examine the relationship between tau oligomer levels, MMSE scores, and CDR scores. This type of correlation analysis assesses the linear relationship between two continuous variables, in this case, tau oligomer levels and cognitive function measures. A p-value of less than 0.05 was considered statistically significant. This threshold is commonly used in research to determine whether an observed effect is likely due to chance or represents a true effect.

3. Results

Table 1 provides a detailed overview of the sociodemographic and clinical characteristics of the 50 Alzheimer's disease (AD) patients participating in the study. The average age of the participants was 72.5 years, with a standard deviation of 8.3 years. This is consistent with AD typically affecting older adults. The sample had a slightly higher proportion of females (56%) compared to males (44%). This is in line with the general trend of higher AD prevalence in women. Half of the participants were married, while 30% were widowed. This reflects the age group of the participants, where widowhood becomes more common. The majority of participants had received some level of education, with 40% having completed secondary school. A small percentage (10%) had no formal education. A diverse range of occupations was represented, with homemakers being the most common (36%), followed by laborers (20%) and farmers (16%). This provides insight into the participants' backgrounds before retirement. Most participants (70%) lived with their spouse or family, indicating that they had some level of social support. The majority of participants (60%) had a monthly income of less than 5,000,000 Indonesian Rupiah, suggesting that a significant proportion of the sample belonged to lower socioeconomic strata. The mean MMSE score was 18.6 (SD = 5.4). This score falls within the range typically observed in individuals with mild to moderate AD, indicating moderate cognitive impairment. The average CDR score was 1.8 (SD = 0.7), further supporting the presence of mild to moderate dementia in the study population. The mean tau oligomer level in the CSF was 120.5 pg/mL (SD = 35.2). This value provides a baseline measure for comparing with cognitive function and disease severity.

Table 2 presents the correlation analysis between tau oligomer levels in cerebrospinal fluid (CSF) and cognitive function, as measured by the Mini-Mental State Examination (MMSE) score, in the group of AD patients. A strong negative correlation ($r = -0.65$) was observed between tau oligomer levels and MMSE scores. This indicates that higher levels of tau oligomers in the CSF are associated with lower MMSE scores, signifying poorer cognitive performance. The correlation was statistically significant ($p < 0.001$). This means that the observed relationship between tau oligomers and MMSE scores is highly unlikely to be due to chance alone. This finding provides compelling evidence supporting the role of tau oligomers in cognitive decline in AD. The strong negative correlation

suggests that tau oligomers may be a key driver of cognitive impairment in AD patients. As tau oligomer levels increase in the CSF, cognitive function, as measured by the MMSE, tends to worsen. This result aligns with the growing body of research that highlights the importance of tau oligomers in AD pathogenesis. It suggests that these soluble aggregates of tau protein may be more directly related to cognitive decline than previously thought. The statistically significant correlation further strengthens the validity of this finding. It indicates that the observed relationship is likely a true reflection of the biological processes involved in AD progression. This table provides valuable insights into the relationship between tau oligomers and cognitive function in AD. It underscores the potential of tau oligomers as a therapeutic target for interventions aimed at slowing or preventing cognitive decline in AD.

Table 1. Sociodemographic and clinical characteristics of AD patients (n=50).

Characteristic	Mean (SD) or Frequency (Percentage)
Sociodemographic	
Age (years)	72.5 (8.3)
Gender	
- Female	28 (56%)
- Male	22 (44%)
Marital Status	
- Married	25 (50%)
- Widowed	15 (30%)
- Divorced/Separated	5 (10%)
- Never Married	5 (10%)
Education Level	
- No formal education	5 (10%)
- Primary school	15 (30%)
- Secondary school	20 (40%)
- Tertiary education	10 (20%)
Occupation (before retirement)	
- Homemaker	18 (36%)
- Laborer	10 (20%)
- Farmer	8 (16%)
- Trader/Business owner	7 (14%)
- Government employee/Professional	7 (14%)
Living Arrangement	
- With spouse/family	35 (70%)
- Alone	5 (10%)
- With caregiver	10 (20%)
Monthly Income (in Indonesian Rupiah)	
- < 5,000,000	30 (60%)
- 5,000,000 - 10,000,000	15 (30%)
- > 10,000,000	5 (10%)
Clinical	
MMSE score	18.6 (5.4)
CDR score	1.8 (0.7)
Tau Oligomer levels (pg/mL)	120.5 (35.2)

Table 2. Correlation between tau oligomers and cognitive function.

Group	Tau Oligomers (pg/mL)	MMSE Score
AD Patients	120.5 (35.2)	18.6 (5.4)
r	-0.65	
p	< 0.001	

Table 3 illustrates the correlation analysis between tau oligomer levels in the cerebrospinal fluid (CSF) and disease severity, as measured by the Clinical Dementia Rating (CDR) score, in the group of AD patients. A moderate positive correlation ($r = 0.58$) was found between tau oligomer levels and CDR scores. This indicates that higher levels of tau oligomers in the CSF are associated with higher CDR scores, which signifies greater disease severity. The correlation was statistically significant ($p < 0.001$). This means that the observed relationship between tau oligomers and CDR scores is very unlikely to be due to chance alone. This result provides further evidence for the role of tau oligomers in AD progression. The positive correlation suggests that tau oligomers may contribute to the worsening of disease severity in AD patients. As tau oligomer levels increase in the CSF, the severity of dementia, as measured by the CDR, tends to increase as well. This finding supports the idea that tau oligomers are not merely a byproduct of AD but actively contribute to the disease process. It suggests that these soluble aggregates may play a role in the neurodegenerative cascade that leads to the clinical manifestations of AD. The statistically significant correlation reinforces the validity of this finding, indicating that the observed relationship is likely a true reflection of the underlying biological mechanisms in AD. This table offers valuable insights into the relationship between tau oligomers and disease severity in AD. It highlights the potential of tau oligomers as a marker for disease progression and a potential target for therapeutic interventions aimed at slowing or halting the progression of AD.

Table 3. Correlation between tau oligomers and disease severity.

Group	Tau Oligomers (pg/mL)	CDR Score
AD Patients	120.5 (35.2)	1.8 (0.7)
r	0.58	
p	< 0.001	

4. Discussion

Synaptic plasticity, the brain's inherent ability to modify the strength of connections between neurons, is a cornerstone of learning and memory. It's a dynamic process that allows the brain to adapt and fine-tune its circuitry in response to experiences, essentially sculpting itself to accommodate new information and skills. Tau oligomers, however, disrupt this delicate balance, acting as insidious agents that sabotage the brain's ability to learn and remember. Synapses, the junctions between neurons, are the sites where communication occurs. They're not static entities but rather dynamic structures that can strengthen or weaken over time, depending on the frequency and pattern of activity. This ability to change, known as synaptic plasticity, is essential for encoding new information and storing it as memories. Synaptic plasticity manifests in two primary forms, long-term potentiation (LTP) and long-term depression (LTD). LTP is a persistent strengthening of synapses based on recent patterns of activity. It's like turning up the volume of communication between two neurons, making it easier for them to "hear" each other. LTD, on the other hand, is a long-lasting weakening of synaptic strength. It's like turning down the volume, making it harder for neurons to communicate. LTP and LTD work in concert, like a finely tuned orchestra, to shape the brain's circuitry and encode memories. LTP strengthens connections that are frequently used, while LTD weakens those that are less active. This delicate balance ensures that the brain's resources are used efficiently and that memories are stored effectively. Tau oligomers, however, disrupt this harmonious dance of synapses. They interfere with the intricate molecular machinery involved in synaptic plasticity, hindering the ability of synapses to strengthen or weaken appropriately. This disruption can lead to a loss of synaptic connections, compromising the neural networks that underpin cognitive function. N-methyl-D-aspartate Receptor

(NMDAR) is a type of glutamate receptor that plays a critical role in synaptic plasticity. They act as molecular gatekeepers, controlling the flow of calcium ions into neurons. Calcium influx through NMDARs triggers a cascade of signaling events that lead to LTP or LTD. Tau oligomers, however, can disrupt NMDAR function, impairing calcium signaling and hindering synaptic plasticity. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor (AMPAR) is another type of glutamate receptor that plays a key role in synaptic plasticity. They mediate the majority of fast excitatory synaptic transmission in the brain. The trafficking of AMPARs into and out of synapses is a critical mechanism for regulating synaptic strength. Tau oligomers can interfere with AMPAR trafficking, disrupting the dynamic regulation of synaptic strength and impairing plasticity. The actin cytoskeleton is a dynamic network of protein filaments that provides structural support and plays a crucial role in synaptic plasticity. The actin cytoskeleton undergoes constant remodeling to accommodate changes in synaptic strength. Tau oligomers can disrupt the actin cytoskeleton, impairing its ability to remodel and hindering synaptic plasticity. The postsynaptic density (PSD) is a protein-rich structure located on the receiving end of a synapse. It serves as a scaffolding platform for various signaling molecules involved in synaptic plasticity. Tau oligomers can disrupt the PSD, displacing key signaling molecules and impairing plasticity. The disruption of synaptic plasticity by tau oligomers has profound consequences for cognitive function. Synaptic plasticity is essential for encoding new information and storing it as memories. Disrupted plasticity can hinder the ability to learn new skills and form new memories. The inability of synapses to strengthen or weaken appropriately can lead to a loss of synaptic connections, compromising the neural networks that underpin cognitive function. The cumulative effect of impaired learning and memory and loss of synaptic connections can contribute to the progressive cognitive decline observed in AD. Imagine the brain as a vast network of interconnected roads. Synaptic plasticity is akin to the ability to adjust the traffic flow on these roads, optimizing routes based on demand. Tau oligomers, in this analogy, act like roadblocks, disrupting the smooth flow of traffic and hindering efficient communication across the network. Beyond their detrimental effects on synaptic plasticity, tau oligomers also wreak havoc on neuronal signaling pathways, the intricate communication networks that orchestrate brain activity and underpin cognitive function. These pathways, akin to the bustling communication channels of a city, rely on the precise transmission of chemical messengers across synapses, the junctions between neurons. Tau oligomers, however, disrupt these delicate signaling networks, causing a breakdown in communication that contributes to cognitive decline. Neurons, the fundamental units of the nervous system, communicate with each other through a symphony of chemical messengers called neurotransmitters. These neurotransmitters are released from one neuron, the presynaptic neuron, and travel across the synapse to bind to receptors on the receiving neuron, the postsynaptic neuron. This binding triggers a cascade of signaling events that ultimately lead to a change in the postsynaptic neuron's activity. This intricate process of neuronal signaling is essential for coordinating brain activity and ensuring proper cognitive function. It allows the brain to process information, form memories, make decisions, and control movement. Tau oligomers, however, disrupt this delicate communication system, impairing the transmission of signals between neurons. Tau oligomers can bind to and disrupt the function of neurotransmitter receptors, the protein molecules that receive and interpret chemical signals from other neurons. This disruption can impair the ability of neurons to respond to neurotransmitters, hindering communication. Tau oligomers can also interfere with intracellular signaling pathways, the intricate networks of molecular interactions that relay signals within neurons. This interference can disrupt the flow of information within neurons, impairing their ability to process and transmit signals. Synaptic vesicles are small sacs within neurons that store and release neurotransmitters. Tau oligomers can disrupt the function of synaptic vesicles, impairing the release of neurotransmitters and hindering communication between neurons. Mitochondria are the powerhouses

of cells, providing energy for cellular processes. Tau oligomers can disrupt mitochondrial function, leading to energy deficits that can impair neuronal signaling. The disruption of neuronal signaling pathways by tau oligomers has profound consequences for cognitive function. Neural circuits are ensembles of interconnected neurons that perform specific functions, such as processing sensory information, forming memories, or controlling movement. Disrupted neuronal signaling can impair the function of these circuits, leading to cognitive deficits. The cumulative effect of impaired neural circuit function can contribute to the progressive cognitive decline observed in AD. Chronic disruption of neuronal signaling can also contribute to neurodegeneration, the progressive loss of neurons in the brain. Picture a bustling city with a complex communication network of phone lines and internet connections. Tau oligomers, in this scenario, act like disruptions to these communication channels, causing static on phone lines and interrupting internet service. This breakdown in communication hinders the city's ability to function efficiently. Businesses cannot communicate with clients, emergency services cannot coordinate responses, and transportation systems cannot operate smoothly. Similarly, in the brain, disrupted neuronal signaling impairs the ability of different brain regions to communicate with each other. This can lead to a breakdown in cognitive function, as different brain regions are unable to coordinate their activity effectively. In addition to their direct assault on synapses and neuronal signaling, tau oligomers also play a role in fueling neuroinflammation, a chronic inflammatory response in the brain that can contribute to neuronal damage and loss. Neuroinflammation is a complex process, a double-edged sword that can be both beneficial and detrimental. While it is a necessary part of the brain's immune response to injury and infection, chronic neuroinflammation can spiral out of control, contributing to neurodegenerative processes. Tau oligomers, in this context, act as insidious instigators, triggering and exacerbating neuroinflammation, further compromising cognitive function in AD. The brain, like any other organ, has its own immune system, a network of cells and molecules that protect it from harmful invaders and repair damage. Microglia, the brain's resident immune cells, are the primary guardians of this delicate ecosystem. They constantly patrol the brain, scavenging for pathogens, cellular debris, and other threats. When microglia encounter a threat, they become activated, transforming into fierce defenders that engulf and destroy the invaders. This activation also triggers the release of inflammatory molecules, such as cytokines and chemokines, which recruit other immune cells to the site of injury and promote healing. Neuroinflammation, the activation of the brain's immune response, is a necessary process for maintaining brain health. It's like a controlled burn in a forest, clearing out deadwood and promoting regrowth. However, when the fire rages uncontrolled, it can cause widespread damage to the ecosystem. Chronic neuroinflammation, the persistent activation of the brain's immune response, can be detrimental, contributing to neurodegenerative processes. It's like a wildfire that burns out of control, damaging healthy trees and disrupting the delicate balance of the ecosystem. Tau oligomers, in this context, act like sparks that ignite the wildfire of neuroinflammation. They can trigger the activation of microglia, leading to the release of inflammatory molecules that can damage neurons and synapses. This chronic inflammatory state can further exacerbate cognitive decline in AD. Toll-Like Receptor (TLR) are a family of pattern recognition receptors that play a crucial role in the innate immune response. They recognize molecular patterns associated with pathogens and cellular damage, triggering the activation of immune cells. Tau oligomers can activate TLRs on microglia, leading to their activation and the release of inflammatory molecules. The NLRP3 inflammasome is a multiprotein complex that plays a key role in the innate immune response. It activates caspase-1, an enzyme that cleaves pro-inflammatory cytokines, such as IL-1β and IL-18, into their active forms. Tau oligomers can activate the NLRP3 inflammasome, leading to the release of these potent inflammatory molecules. Reactive Oxygen Species (ROS) are highly reactive molecules that can damage cellular components. Tau oligomers can induce the production

of ROS, contributing to oxidative stress and inflammation in the brain. Inflammatory molecules released during neuroinflammation can damage neurons and synapses, contributing to their dysfunction and loss. Neuroinflammation can also disrupt synaptic plasticity, impairing the ability of synapses to strengthen or weaken appropriately. The cumulative effect of neuronal damage, synaptic dysfunction, and impaired neuronal signaling can contribute to the progressive cognitive decline observed in AD. The detrimental effects of tau oligomers on synaptic plasticity, neuronal signaling, and neuroinflammation are not isolated events but rather interconnected processes that form a vicious cycle, accelerating cognitive decline in Alzheimer's disease (AD). This self-perpetuating cycle underscores the critical role of tau oligomers in AD pathogenesis and highlights the urgent need for therapeutic interventions that can disrupt this destructive cascade. As discussed earlier, tau oligomers disrupt synaptic plasticity, the brain's ability to modify the strength of connections between neurons. This disruption impairs the ability of synapses to strengthen or weaken appropriately, leading to a loss of synaptic connections and a weakening of neural networks. The consequences are far-reaching, as weakened neural connections hinder communication between neurons, compromising cognitive function. Impaired neuronal signaling further exacerbates the problem. Tau oligomers interfere with the intricate signaling pathways that neurons use to communicate with each other. This disruption leads to a breakdown in neural circuits, the ensembles of interconnected neurons that perform specific cognitive functions. As neural circuits falter, cognitive processes such as learning, memory, and decision-making become increasingly compromised. Adding fuel to the fire, tau oligomers also induce neuroinflammation, a chronic inflammatory response in the brain that can damage neurons and synapses. Neuroinflammation further disrupts synaptic plasticity and neuronal signaling, creating a vicious cycle that accelerates cognitive decline. Tau oligomers disrupt synaptic plasticity, weakening neural connections and impairing communication between neurons. Impaired communication between neurons disrupts neuronal signaling, further compromising neural circuits and cognitive function. Tau oligomers also induce neuroinflammation, which further damages neurons and synapses, exacerbating synaptic dysfunction and neuronal signaling impairment. This vicious cycle continues, leading to progressive cognitive decline and the eventual manifestation of AD symptoms. The vicious cycle of tau-mediated neurotoxicity highlights the urgent need for therapeutic interventions that can target these toxic aggregates. By breaking this cycle, it may be possible to slow or even halt the progression of AD. Immunotherapy approaches aim to stimulate the immune system to clear tau oligomers from the brain. Small molecule inhibitors are designed to block the formation or aggregation of tau oligomers. Gene therapy approaches aim to reduce the production of tau protein or enhance its clearance from the brain.[11-14]

The positive correlation between CSF tau oligomer levels and Clinical Dementia Rating (CDR) scores in this study provides compelling evidence for the pivotal role of tau oligomers in the overall progression of Alzheimer's disease (AD). This finding suggests that these soluble aggregates of tau protein are not merely bystanders in the neurodegenerative cascade but active contributors to the worsening of cognitive and functional deficits that characterize AD. Unlike the Mini-Mental State Examination (MMSE), which primarily focuses on cognitive function, the CDR offers a more comprehensive and nuanced assessment of disease severity. It evaluates an individual's functional performance across six domains, memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. This multi-dimensional approach provides a more holistic picture of the impact of AD on an individual's daily life. Memory, this domain assesses the ability to recall recent and past events, as well as the capacity to learn new information. It reflects the core deficit in AD, the progressive erosion of memory function. This erosion can manifest in various ways, from forgetting appointments and misplacing items to losing track of conversations and struggling to learn new skills. The impact on daily life can be profound, affecting

everything from maintaining independence to sustaining relationships. Orientation, this domain evaluates awareness of one's surroundings, including orientation to time, place, and person. Disorientation is a common feature of AD, reflecting the disruption of neural networks involved in spatial and temporal processing. Individuals may become lost in familiar places, struggle to keep track of the date or time, or even fail to recognize loved ones. This disorientation can lead to anxiety, confusion, and a sense of isolation. Judgment and problem-solving, this domain assesses the ability to make sound decisions and solve problems in everyday situations. This encompasses a wide range of skills, from evaluating risks and making choices to planning and executing tasks. Impaired judgment and problem-solving abilities can have significant consequences for an individual's safety and independence. They may make poor financial decisions, struggle to manage household tasks, or put themselves at risk in social situations. Community affairs, this domain evaluates the ability to participate in community activities and manage daily affairs, such as shopping, using transportation, and handling finances. These activities require a complex interplay of cognitive and social skills, which are often compromised in AD. Individuals may struggle to navigate public transportation, manage their finances, or engage in social interactions, leading to a loss of independence and social isolation. Home and hobbies, this domain assesses the ability to manage household tasks and engage in hobbies and leisure activities. These activities are essential for maintaining a sense of purpose and quality of life, but they can become increasingly challenging as AD progresses. Individuals may struggle to maintain their home, prepare meals, or engage in hobbies they once enjoyed, leading to a loss of identity and a sense of helplessness. Personal care, this domain evaluates the ability to perform basic self-care tasks, such as dressing, bathing, and grooming. These tasks are fundamental for maintaining personal hygiene and dignity, but they can become increasingly difficult as AD progresses. Individuals may struggle to dress appropriately, maintain their personal hygiene, or even feed themselves, leading to a loss of independence and a decline in self-esteem. By assessing these six domains, the CDR provides a comprehensive picture of an individual's functional abilities and the overall impact of AD on their daily life. The positive correlation between CSF tau oligomer levels and CDR scores suggests that tau oligomers contribute to the global decline in cognitive and functional abilities that characterizes AD progression. The finding that higher levels of tau oligomers are associated with greater disease severity implicates these soluble aggregates as key orchestrators of the neurodegenerative symphony in AD. As tau oligomers accumulate, they trigger a cascade of events that disrupt neuronal function, leading to synaptic loss, neuronal death, and ultimately, the clinical manifestations of AD. The story begins with the hyperphosphorylation of tau, a microtubule-associated protein that normally stabilizes the structure of neurons. In AD, tau becomes abnormally phosphorylated, a process akin to adding too many phosphate groups to a protein. This hyperphosphorylation disrupts tau's normal function, causing it to detach from microtubules and form clumps called tau oligomers. These soluble aggregates of tau protein are highly neurotoxic and disrupt various neuronal processes. They act like molecular saboteurs, interfering with synaptic plasticity, neuronal signaling, and triggering neuroinflammation. This creates a toxic environment within the brain, accelerating the neurodegenerative process. Tau oligomers disrupt the delicate balance of synaptic plasticity, the brain's ability to strengthen or weaken connections between neurons. This impairment hinders communication between neurons, leading to synaptic loss and a weakening of neural networks. The consequences are far-reaching, as weakened neural connections compromise cognitive function, contributing to memory loss and other cognitive deficits. Tau oligomers also interfere with neuronal signaling pathways, the intricate communication networks that orchestrate brain activity. This disruption further compromises neural circuit function, contributing to the decline in cognitive and functional abilities. Imagine a city with disrupted communication networks – emergency services cannot coordinate responses, businesses

cannot communicate with clients, and transportation systems falter. Similarly, in the brain, disrupted neuronal signaling impairs the ability of different brain regions to communicate effectively, leading to a breakdown in cognitive function. Tau oligomers trigger neuroinflammation, a chronic inflammatory response in the brain that can damage neurons and synapses. This inflammatory state further exacerbates neuronal dysfunction and contributes to the progression of AD. Neuroinflammation is like a wildfire in the brain, initially intended to clear out debris and promote healing but ultimately causing widespread damage if left unchecked. The cumulative effect of synaptic dysfunction, neuronal signaling interference, and neuroinflammation leads to neuronal loss and brain atrophy. As neurons die and brain regions shrink, cognitive and functional deficits become increasingly pronounced. This is like losing essential workers in a city – as more and more workers are lost, the city's ability to function efficiently declines. The loss of neurons and synapses, coupled with the disruption of neural circuits, results in cognitive decline and functional impairment, the hallmarks of AD. These deficits manifest as memory loss, disorientation, impaired judgment, difficulty with daily activities, and personality changes. The individual's ability to live independently and engage in meaningful activities diminishes, leading to a decline in quality of life and an increased need for care.[15-17]

The findings of this study illuminate a promising path forward in the fight against Alzheimer's disease (AD), highlighting the potential of tau oligomers as both valuable biomarkers and promising therapeutic targets. The robust association between CSF tau oligomer levels and cognitive decline and disease severity suggests that these soluble aggregates could revolutionize the way we diagnose, monitor, and treat AD. A biomarker is a measurable indicator of a biological state or condition. In the context of AD, biomarkers can be used to detect the presence of the disease, monitor its progression, and predict the response to treatment. Tau oligomers, with their strong association with cognitive decline and disease severity, hold immense promise as a valuable biomarker for AD. One of the most significant advantages of tau oligomers as biomarkers is their potential for early detection. Research suggests that tau oligomers may be detectable in the cerebrospinal fluid (CSF) even before the onset of significant cognitive decline. This early detection could allow for earlier intervention, potentially delaying or even preventing the progression of the disease. Imagine a world where AD could be detected in its earliest stages, allowing individuals to take proactive steps to protect their cognitive health and maintain their independence. Tau oligomer levels may correlate with the severity of AD and its progression over time. This monitoring could help clinicians track the disease's course, providing valuable insights into the rate of cognitive decline and functional impairment. This information could be used to adjust treatment strategies, personalize care plans, and provide more accurate prognoses. Tau oligomer levels may also be used to evaluate the effectiveness of potential AD treatments. By monitoring changes in tau oligomer levels in response to treatment, clinicians can assess whether the treatment is slowing or reversing the disease process. This could lead to more personalized treatment approaches, where therapies are tailored to an individual's specific needs and response. Amyloid-beta (Aβ) plaques are measured in the CSF or detected using positron emission tomography (PET) imaging. Aβ plaques are extracellular deposits of amyloid-beta peptides, one of the hallmarks of AD. Tau tangles are measured in the CSF or detected using PET imaging. Tau tangles are intracellular aggregates of hyperphosphorylated tau protein, another hallmark of AD. Brain atrophy is measured using magnetic resonance imaging (MRI). Brain atrophy, or shrinkage, is a common feature of AD, reflecting the loss of neurons and synapses. Cognitive decline is assessed using neuropsychological tests. These tests evaluate various cognitive domains, such as memory, attention, and language, providing a measure of cognitive function. While these biomarkers have provided valuable insights into AD, they each have limitations. Aβ plaques and tau tangles, while indicative of AD pathology, do not always correlate well with cognitive decline. Brain atrophy is a late-stage marker of AD, often occurring after significant neuronal loss has

already occurred. Cognitive decline, while a key feature of AD, can be influenced by various factors, making it difficult to attribute solely to AD pathology. Tau oligomers, with their strong association with cognitive decline and disease severity, could complement these existing biomarkers, providing a more comprehensive and dynamic picture of the disease process. The study also highlights tau oligomers as a promising therapeutic target for AD. By developing interventions that can reduce tau oligomer levels or neutralize their toxic effects, it may be possible to slow or even halt the progression of AD. Immunotherapy involves stimulating the immune system to clear tau oligomers from the brain. This can be achieved through active immunization, where the individual is vaccinated with a tau oligomer-based vaccine, triggering the production of antibodies against tau oligomers. Alternatively, passive immunization involves administering pre-formed antibodies against tau oligomers, providing immediate protection. Small molecule inhibitors are drugs designed to block the formation or aggregation of tau oligomers. These inhibitors could prevent the accumulation of tau oligomers in the brain, reducing their neurotoxic effects. Imagine a drug that could prevent tau proteins from clumping together, preventing the formation of these toxic aggregates and protecting neurons from damage. Gene therapy aims to reduce the production of tau protein or enhance its clearance from the brain. This could be achieved by delivering genes that silence tau expression or promote its degradation. Gene therapy holds the promise of correcting the underlying genetic defects that contribute to tau oligomer formation, potentially preventing the disease process altogether. Tau oligomers form when tau detaches from microtubules, the structural supports within neurons. Promoting microtubule stability could prevent tau oligomerization and reduce their neurotoxic effects. Oxidative stress, an imbalance between free radicals and antioxidants in the body, can contribute to tau oligomerization. Reducing oxidative stress could prevent tau oligomer formation and protect neurons from damage. Autophagy is a cellular process that degrades and recycles cellular components, including misfolded proteins like tau oligomers. Enhancing autophagy could promote the clearance of tau oligomers from the brain, reducing their toxic effects. Tau oligomers are not unique to AD and can be found in other neurodegenerative diseases. Developing biomarkers and therapeutic strategies that specifically target tau oligomers in AD is crucial to avoid off-target effects and ensure treatment efficacy. Delivering therapeutic agents to the brain is challenging due to the blood-brain barrier, a protective barrier that limits the passage of substances from the bloodstream into the brain. Developing effective delivery methods for tau oligomer-targeting therapies is essential to ensure that these therapies reach their intended targets in the brain. Rigorous clinical trials are needed to evaluate the safety and efficacy of tau oligomer-targeting therapies. These trials will require careful design and implementation to ensure meaningful results and pave the way for regulatory approval.[18-20]

5. Conclusion

In conclusion, this study underscores the pivotal role of tau oligomers in the progression of Alzheimer's disease (AD) within the Indonesian population. Our findings demonstrate a significant association between elevated CSF tau oligomer levels and both cognitive decline and disease severity in AD patients. The strong negative correlation between tau oligomer levels and MMSE scores indicates that higher levels of these toxic aggregates are associated with poorer cognitive performance. This observation is consistent with the growing body of research implicating tau oligomers as key drivers of cognitive dysfunction in AD. Furthermore, the positive correlation between tau oligomer levels and CDR scores suggests that these soluble aggregates contribute to the overall worsening of cognitive and functional deficits that characterize AD progression. This finding is particularly noteworthy as the CDR scale provides a comprehensive assessment of disease severity, evaluating an individual's functional performance across six domains, memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. The implications of our study are far-reaching. First, it highlights the potential

of tau oligomers as a valuable biomarker for AD. Their strong association with cognitive decline and disease severity suggests that they could be used to detect the presence of the disease, monitor its progression, and predict the response to treatment. Second, our study reinforces the importance of targeting tau oligomers in the development of therapeutic interventions for AD. By reducing tau oligomer levels or neutralizing their toxic effects, it may be possible to slow or even halt the progression of AD. While our study provides compelling evidence for the role of tau oligomers in AD progression, it is not without limitations. The relatively small sample size and the cross-sectional nature of the study warrant further investigation with larger, longitudinal studies to confirm our findings and explore the causal relationship between tau oligomers and AD progression. Additionally, future research should focus on developing standardized assays for measuring tau oligomers and establishing their clinical utility as biomarkers for AD. Despite these limitations, our study contributes to the growing body of knowledge implicating tau oligomers as key players in AD pathogenesis. It highlights the need for further research to fully elucidate their role in the disease process and to develop effective therapeutic strategies that target these toxic aggregates. The fight against AD is a global challenge, and it is through collaborative research efforts that we can move closer to finding a cure for this devastating disease.

6. References

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