Journal of Clinical Practice and Medical Case Report

Genesis-JCPMCR-1(2)-13
Volume 1 | Issue 2
Open Access
ISSN: 3048-8206

Discovery of Urinary Biomarker: Urine Amyloid Beta as a Non-Invasive Biomarker for Early Alzheimer's Disease and Cognitive Impairment - A Study of 24 Patients with Cognitive Decline

Kris Ke Shyang See[2*], Miew Leng Khoo[2], Kishan Kannan Yogaratnam[1], Wai Hong Cheang[1], Amarpreet Kaur Sarjit Singh[1], Low Jun Kuang[1], Kalichandren Arumugam[1], Khang Lyn Tan[1], Romel Mario Soyza[1], Hui Ying Teh[1], Nik Nassyiradina Putri Binti Nik Ahmat[1], Norizan Binti Hassan[1], Ananyaa Sreekumar[1], Nicolette Wei Mei Wong[1], Imelda Jing En Lee[1], Lim Yi Za Isabelle[1] , and Yashvardhan Servai Elangeswaran[1]

[1] Osel Clinic, Osel Group, Malaysia

[2] Osel Diagnostics, Osel Group, Malaysia

[*]**Corresponding author:** Kris Ke Shyang See, Osel Diagnostics, Osel Group, Malaysia

Citation: See SKK, Khao LM, Yogaratnam KK, Cheang WH, et al. Discovery of Urinary Biomarker: Urine Amyloid Beta as a Non-Invasive Biomarker for Early Alzheimer's Disease and Cognitive Impairment - A Study of 24 Patients with Cognitive Decline. J Clin Pract Med Case Rep. 1(2):1-7.

Received: October 23, 2024 | **Published:** November 10, 2024.

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative illness characterized by the accumulation of tau tangles and amyloid beta (Aβ) plaques in the brain, ultimately leading to dementia and cognitive impairment [1-2].

Early detection is essential for the effective intervention and management of AD, but current diagnostic methods, such as cerebrospinal fluid (CSF) analysis and positron emission tomography (PET) scans, are either excessively expensive or invasive [3].

As a result, urine biomarkers have started to attract a lot of attention due to the increasing demand for easily accessible, non-invasive, and reasonably priced screening and early detection techniques [4]. Specifically Aβ, a protein fragment that is essential to the pathophysiology of AD, has been investigated as a possible urine-detectable biomarker [5]. Consequently, this paper explored the potential of urine Aβ as a screening tool for early AD and cognitive impairment, based on a study of 24 patients with cognitive decline, where 18 patients tested positive for urinary Aβ. The results of the study demonstrated a 75.0% positivity rate for urinary Aβ, particularly Aβ42, in patients with cognitive decline, thereby indicating its potential as a useful screening tool. However, a few patients in this study presenting with either mild, moderate, or more severe cognitive impairment did not test positive for urinary Aβ42, thereby suggesting that further research is needed to determine the overall accuracy and efficacy of this biomarker as well as its specific utility in the very early stages of AD.

Keywords

Alzheimer's disease (AD); Urinary amyloid beta (Aβ); Amyloid beta peptide; Cognitive impairment; Non-invasive biomarker.

Background

Aβ peptides, especially Aβ42, misfold and aggregate in the pathophysiology of AD, resulting in the development of plaques in the brain [6]. These plaques cause neuroinflammation, impair synaptic function, and ultimately lead to neuronal death. The presence of Aβ in the brain is one of the characteristics of AD, which emphasizes the significance of detecting it early for a speedier diagnosis, management, and treatment of AD [7]. Traditionally, Aβ has been measured in cerebrospinal fluid (CSF) through lumbar punctures or visualized using PET imaging. However, these methods are either invasive, expensive, or impractical for large-scale screening [8]. As urine is a readily available and easily collectible biological fluid, it has emerged as an alternative biomarker for detecting AD [3]. Furthermore, although urine contains lower concentrations of Aβ than CSF, improvements in detection techniques like mass spectrometry and enzyme-linked immunosorbent assay (ELISA) have made it possible to test urine Aβ with greater accuracy [9].

Consequently, recent research has increasingly investigated the potential of urine Aβ as a biomarker for AD, even though the majority of the literature concentrates on the role of Aβ in the plasma or CSF of AD patients. These studies have found that AD-related changes are often present in the urine before the blood or CSF, as urine is not regulated by homeostatic changes [10]. Moreover, the literature on the topic indicates that Aβ levels in the urine tend to correlate with cognitive decline in AD patients [4]. For example, a study by Takata et al found that urine may be a viable diagnostic medium, as it identified substantial variations in urinary Aβ levels between AD patients and healthy controls [5]. This analysis also highlights the potential value of urine Aβ as a non-invasive screening method for the early detection of AD [11].

DOI: https://doi.org/10.52793/JCPMCR.2024.1(2)-13

However, existing literature on the topic has also frequently highlighted the difficulties that still exist in relation to the biological variability present in urine samples and the standardization of urinary Aβ readings. For example, urine composition can be influenced by dietary components, hydration levels, physical activity, and medications, and physiological factors can change the concentrations of all urine biomarkers, including urinary Aβ levels [12]. In order to overcome these issues, some of the literature has suggested standardized procedures for urine collection, storage, and analysis; this could improve the reliability and accuracy of urinary Aβ as a biomarker for detecting AD [12]. These studies also urge further investigations to confirm these methods, techniques, and strategies. Therefore, even if preliminary evidence supports the use of urinary Aβ as a possible biomarker for AD, more research is required to establish standardized procedures and clarify the underlying mechanisms that govern Aβ excretion in urine.

Methodology

Building on the existing literature, clinical trials, and evidence on the potential of urinary Aβ as a noninvasive biomarker for detecting AD, this study aims to evaluate the feasibility of using this urinary biomarker in detecting AD in patients presenting with different levels of cognitive impairment. It specifically focuses on whether urinary Aβ can be used to identify early-stage AD that often goes undiagnosed, evaluating the scope, benefits, and wider applicability of this method of AD detection. Patients selected for urine testing were from 35 to 75 years of age and were of mixed gender. They were selected by simple random sampling from a larger subset of individuals who all demonstrated different levels of cognitive impairment. Consequently, every patient chosen for this study exhibited signs of cognitive deterioration.

Clinical evaluations and cognitive function tests like the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to measure and confirm cognitive impairment in the patients. These tests were selected for this study due to their sensitivity, specificity, accuracy, and extensive usage. For instance, because of its high sensitivity and specificity rate, the MMSE is the most widely used instrument for evaluating cognitive decline in dementia [13]. Similarly, the MoCA scale, which has gained popularity recently, was selected for this study because of its specific sensitivity in identifying milder types of cognitive impairment [14]. As a result, both scales were used to confirm cognitive impairment and determine varying degrees of cognitive decline in the selected patients who were then sent for urinary testing.

Each of the 24 patients then provided individual urine samples for analysis. The following steps were taken to minimise variations in the samples and to address any potential limitations:

1. **Urine sample collection:** Urine samples were collected in the morning after overnight fasting to minimize variability in the Aβ concentrations due to dietary factors.
2. **Aβ detection:** The urine samples were then analyzed using a sensitive ELISA kit specifically designed to detect Aβ42 peptides. A positive result was determined based on a predefined cutoff value for Aβ42 concentration in the urine.

Results

According to the findings, 18 of the 24 patients had positive urine Aβ tests, indicating the presence of Aβ peptides in their urine samples. Among these 18 patients, six demonstrated mild cognitive decline, while 18 exhibited moderate to severe cognitive decline based on their cognitive assessments. Out of the six patients with mild cognitive decline, five tested positive for urinary Aβ and one tested negative. Simultaneously, out of the 18 patients with moderate to severe cognitive decline, 13 tested positive for urinary Aβ and five tested negative.

As evident from Table 1, the results suggest a strong correlation between cognitive decline and the presence of Aβ in urine. While urinary Aβ42 levels were found in 13 patients with moderate to severe cognitive impairment, they were also present in five patients with milder symptoms. This highlights the potential role and scope of urinary Aβ42 in detecting early-stage AD. However, the absence of Aβ42 in the urine of six patients, including those with more moderate to severe cognitive decline, raises questions about the overall sensitivity of urinary Aβ detection for AD and whether it should be used in combination with other testing methods to maximize reliability, accuracy, and validity.

Subject Group	Number of Patients	Aβ Positive	Aβ Negative
Mild Cognitive Decline	6	5	1
Moderate to Severe Cognitive Decline	18	13	5
Total	24	18 (75.0%)	6 (25.0%)

Table 1: Urinary Aβ Test Outcomes in Patients with Different Degrees of Cognitive Decline

Discussion

This study supports the hypothesis that urinary Aβ can serve as a non-invasive biomarker for AD and cognitive impairment. The results demonstrated a 75.0% positivity rate for urinary Aβ in patients with cognitive decline, thereby indicating its potential as a useful screening tool for AD. Moreover, as Aβ accumulation begins years before the clinical symptoms of Alzheimer's manifest, urine-based tests are expected to offer a window for early detection and intervention. However, the variability in Aβ detection in this study, amongst those with both milder and those with more severe cognitive symptoms, highlights the requirement for further research into the sensitivity and specificity of this biomarker. Yet, it is important to note that this variability may also have been due to improper urine handling and collection when submitting the samples, the patients' individual lifestyle, physiological functions and medications, inaccurate assessments of cognitive decline, or the selection of patients presenting with cognitive impairment unrelated to AD.

Lastly, the study's design and results have also demonstrated the overall advantages of urine Aβ testing. Compared to CSF analysis, for instance, it is a straightforward and non-invasive technique that may be

appropriate for routine screening and long-term cognitive function monitoring [15]. Furthermore, urine-based assays are more affordable and are therefore useful for screening large populations as they are substantially less expensive than neuroimaging methods like PET scans [16]. Additionally, urine can be readily obtained in a variety of locations, including clinical labs and through home sample collections, thereby offering flexibility in screening practices [17]. Therefore, these considerations also highlight the potential of urine Aβ testing in improving early diagnosis of AD across diverse populations, by making AD screening more affordable and accessible.

Limitations of the Study

Although this paper has highlighted valuable findings that can be further expanded upon in future research, there were a few limitations that should also be acknowledged and addressed in further studies. For example:

- **Small sample size:** The sample size of 24 patients is considerably small, limiting the generalizability of the findings. To confirm the findings and improve the utility of urine Aβ as a screening tool, larger studies are required to increase the scope and applicability of the findings.
- **Techniques for detecting low levels of Aβ in the urine:** As urine contains far less Aβ concentration than CSF or blood, detection techniques need to be refined to increase their sensitivity and to accurately identify Aβ in the earliest phases of AD-related cognitive impairment [18].
- **Lack of standardization:** It is currently challenging to compare the findings of various studies due to the absence of a defined procedure for measuring Aβ in the urine. Clinical implementation requires the establishment of consistent testing procedures and cutoff criteria [19].

Future

The clinical utility and applicability of urinary Aβ as a diagnostic biomarker, particularly in the very early stages of AD, requires further investigation. Validating the results of this study and determining if urine Aβ levels can predict cognitive deterioration in the preclinical phases of AD should be the main goals of large-scale, longitudinal research in the future [10]. Furthermore, the accuracy of non-invasive diagnostic tests may be improved by combining urinary Aβ testing with additional biomarkers, such as tau proteins or neurofilament light chains (NfL) [18]. Additionally, further research should also aim to investigate the biological processes that underpin the excretion of Aβ in urine [20]. It is essential to comprehend how Aβ peptides are removed from the brain, moved through the bloodstream, and filtered by the kidneys for urine-based biomarker testing to be improved further [20].

Conclusion

In conclusion, a promising non-invasive technique for screening individuals at risk for AD and cognitive impairment is the detection of Aβ in their urine. This study analysed the urine Aβ levels of 18 patients with varying degrees of cognitive impairment. The results of the study indicated that higher urine Aβ levels were present in 75.0% of the study participants, all of whom showed signs of cognitive deterioration. This also reinforces the potential utility of urine Aβ as a readily available and reasonably

priced biomarker for early AD detection.

The results of this study also contribute to existing literature on the topic, focusing on the scope, value, and benefits of this biomarker in assessing and diagnosing AD. However, as a few of the patients with either mild or more severe cognitive decline tested negative for urinary Aβ in this study, longitudinal studies with a larger sample size need to be conducted to assess the sensitivity and accuracy of this biomarker and to evaluate whether it can truly detect AD at its earliest stages when cognitive decline is still mild [7]. Additionally, general challenges surrounding this topic remain, especially in terms of sensitivity, specificity, and standardization of detection methods. Further research is needed to validate these findings and to develop and refine urine-based tests that can reliably identify AD at its earliest stages.

References

1. Kang JH, Korecka M, Figurski MJ, Toledo JB and Blennow k, et al. (2015) The AD neuroimaging initiative 2 biomarker core: a review of progress and plans. Alzheimer's Dement.11(7):772-91.
2. Mayeux R and Stern Y, (2012) Epidemiology of Alzheimer's disease. Cold Spring Harb Perspect Med. 2(8): a006239.
3. Blennow K and Zetterberg H, (2018) Biomarkers for Alzheimer's disease: current Status and Prospects for the Future. J Intern Med. 284(6):643-63.
4. Kurbatova N, Garg M, Whiley L, Chemkeneva E and Jimenez B et al. (2020) Urinary metabolic phenotyping for Alzheimer's disease. Sci Rep. 10(21745).
5. Takata M, Nakashima M, Takehara T, Baba H and Machida K et al. (2008) Detection of amyloid beta protein in the urine of Alzheimer's disease patients and healthy individuals. Neurosci Lett. 435(2):126-30.
6. Villemagne VL, Burnham S, Bourgeat P, Brown B and Ellis KA, et al. (2013) Amyloid β deposition, beurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol. 12(4):357-67.
7. Sperling RA, Aisen PS, Beckett LA, Bennet DA and Craft S, et al. (2011) toward defining the preclinical stages of Alzheimer's disease: recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 7(3):280-92.
8. Hampel H, O'Bryant SE, Molinuevo JL, Zetterberg H and Masters Cl. (2018) et al. Blood-based biomarkers for Alzheimer's disease: mapping the road to the clinic. Nat Rev Neurol. 14(11):639-52.
9. Zhang F, Wei J, Li X, Ma C and Gao Y. (2018) Early candidate urine biomarkers for detecting Alzheimer's disease before amyloid-β plaque deposition in an APP (swe)/PSEN1dE9 transgenic mouse model. J Alzheimers Dis. 66(2):613-37.
10. Nakamura A, Kaneko N, Villemagne VL, Kato T and Doecke J et al.(2018) High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature. 554(7691):249-54.
11. Dubois B, Feldman HH, Jacova C, Hampel H and Molinuevo JL et al. (2014) Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 13(6):614-29.
12. Balhara N, Devi M, Balda A, Phour M and Giri A. (2023) Urine; a new promising biological fluid to act as a non-invasive biomarker for different human diseases. URINE. 5:40-52.
13. Su Y, Dong J, Sun J, Zhang Y and Ma S et al. (2021) Cognitive function assessed by mini-mental state examination and risk of all-cause mortality: a community-based prospective cohort study. BMC Geriatr. 21(1):524.

14. Thomann AE, Berres M, Goettel N, Steiner LA and Monsch AU. (2020) Enhanced diagnostic accuracy for neurocognitive disorders: a revised cut-off approach for the montreal cognitive assessment. Alzheimer's Res Ther. 12(1):39.
15. Molinuevo JL, Blennow K, Dubois B and Engelborghs S et al. (2014). The clinical use of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's biomarkers standardization initiative. Alzheimers Dement. 10(6):808-17.
16. Gunes S, Aizawa Y, Sugashi T, Sugimoto M and Rodrigues PP. (2022) Biomarkers for Alzheimer's Disease in the Current State: a Narrative Review. Int J Mol Sci. 23(9):4962.
17. Lockwood GM and Sharp VA. (2020) Going with the flow: proper urine testing methods for clinical practice. In: Sharp VA, Antes L, Sanders M, Lockwood GM, eds. Urine Tests. Springer. 25-47.
18. Zetterberg H and Burnham SC. (2019) Blood-based molecular biomarkers for Alzheimer's disease. Mol Brain. 12(1):26.
19. Vanderstichele H, Van Kerschaver E, Hesse and Buyse MA et al. (2000) Standardization of measurement of beta-amyloid (1–42) in cerebrospinal fluid and plasma. Amyloid. 7(4):245-58.
20. Tian DY, Cheng Y, Zhuang ZQ, He CY and Pan QG et al. (2021) Physiological clearance of amyloid-beta by the kidney and its therapeutic potential for AD. Mol Psychiatry. 26:6074-6082