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Research Article

Plasma β-Amyloid, Tau Protein, and Gut Microbiota Alterations in Mild Cognitive Impairment and Alzheimer's Disease, A comparative analysis of anti- amyloid therapy

Muhammad Ali[1], Sheikh Muhammad Junaid Ur Rehman[2], Abdul Aleem[3], Nida Ayesha[4], Farah Asad[5], Rafiq Ahmed Siddiqui[6]

[1] MD, Our Lady Hospital, Navan, Ireland.
[2] Senior Demonstrator, Pharmacology, DGKhan Medical College, DGKhan.
[3] Senior Registrar, Neurology Department, Post Graduate Medical Institute, Quetta.
[4] Assistant Professor, Pharmacology Department, Jinnah Sindh Medical University.
[5] Professor, Department of Pharmacology, Jinnah Sindh Medical University.
[6] Associate Professor, Biochemistry, Services Institute of Medical Sciences, Lahore.
Corresponding author: Muhammad Ali

Abstract: The progressive accumulation of β-amyloid and tau pathology is central to cognitive decline, yet peripheral biomarkers and gut microbiota alterations remain insufficiently integrated into therapeutic response evaluation. This experimental study aimed to comparatively assess plasma β-amyloid, total tau protein, and gut microbiota composition in individuals with mild cognitive impairment and Alzheimer's disease receiving anti-amyloid therapy versus untreated counterparts, alongside cognitively healthy controls. A total of 160 participants were enrolled and stratified into four groups. Plasma biomarkers were quantified using enzyme-linked immunoassays, while gut microbiota diversity and relative abundance were analyzed through 16S rRNA sequencing. Anti-amyloid–treated Alzheimer's disease participants demonstrated significantly reduced plasma β-amyloid ($p<0.001$) and tau levels ($p=0.002$) compared to untreated patients, accompanied by partial restoration of microbial diversity indices. Mild cognitive impairment cases showed intermediate biomarker profiles with significant correlations between microbiota dysbiosis and plasma tau concentrations. These findings indicate a statistically significant biochemical and microbial modulation associated with anti-amyloid therapy. The study introduces integrated peripheral and microbiome-based biomarkers as novel indicators of therapeutic response and disease stratification, providing mechanistic insight into the gut–brain axis in neurodegeneration and supporting biomarker-guided intervention strategies.

Keywords: β-Amyloid, Tau protein, Gut microbiota

Introduction

Neurodegenerative disorders characterized by progressive cognitive decline represent a growing global health challenge, with Alzheimer's disease occupying a dominant position due to its prevalence, socioeconomic burden, and lack of curative therapy. Mild cognitive impairment constitutes a prodromal

stage with heterogeneous trajectories, ranging from stable cognitive performance to rapid progression toward dementia. Although amyloid and tau pathology have long been recognized as pathological hallmarks, increasing evidence suggests that Alzheimer's disease is a systemic disorder with peripheral biochemical and metabolic signatures that precede overt neurodegeneration. The identification of accessible biomarkers capable of reflecting disease stage and therapeutic response remains a critical unmet need.[1-3]

Plasma β-amyloid and tau protein have emerged as minimally invasive indicators of central pathological processes. Advances in assay sensitivity have enabled reliable detection of subtle biomarker fluctuations, rendering blood-based markers suitable for longitudinal monitoring. However, inconsistencies in their clinical interpretation persist, particularly in the context of disease-modifying therapies. Anti-amyloid agents have demonstrated the capacity to reduce amyloid burden, yet their peripheral biochemical effects and downstream biological implications remain incompletely understood. Evaluating plasma biomarker dynamics alongside therapeutic exposure offers an opportunity to refine patient stratification and treatment monitoring.[4-7]

Parallel to biochemical investigations, the gut microbiota has gained recognition as a key modulator of neuroinflammation, synaptic plasticity, and amyloid aggregation. Alterations in microbial diversity and composition have been consistently reported in cognitive disorders, suggesting a bidirectional gut–brain interaction. Dysbiosis-induced immune activation and microbial metabolite imbalance may accelerate neurodegenerative cascades, thereby influencing disease onset and progression. Despite mounting evidence, the relationship between gut microbiota alterations and established Alzheimer's biomarkers remains inadequately characterized in clinical populations.[8-10]

Anti-amyloid therapy may exert indirect effects beyond amyloid clearance, potentially modulating systemic inflammation and microbial ecosystems. The interaction between therapeutic amyloid reduction, plasma tau dynamics, and gut microbiota remodeling has not been systematically examined within a unified experimental framework. Understanding these relationships is essential for elucidating treatment mechanisms and identifying adjunctive therapeutic targets.[11-12]

Recent investigations have emphasized the necessity of multidimensional biomarker integration to capture the complexity of neurodegenerative disorders. Isolated biomarker assessment fails to account for interdependent biological systems that collectively influence disease expression. By combining plasma biomarkers with microbiota profiling, a more comprehensive representation of disease biology may be achieved, enabling earlier diagnosis and personalized therapeutic strategies.

The present experimental study addresses this gap by comparatively analyzing plasma β-amyloid, tau protein, and gut microbiota alterations in mild cognitive impairment and Alzheimer's disease, with specific emphasis on anti-amyloid therapy exposure. By integrating biochemical and microbial parameters, this work aims to provide novel evidence supporting combined biomarker frameworks for disease monitoring and therapeutic evaluation.

Methodology

This experimental, comparative study was conducted at DGKhan Medical College at pharmacology department, following institutional ethical approval. The study population consisted of individuals aged 55–80 years, categorized into four groups: cognitively healthy controls, mild cognitive impairment, Alzheimer's disease without anti-amyloid therapy, and Alzheimer's disease receiving anti-amyloid therapy for at least six months. Sample size was calculated using Epi Info software, assuming a power of 80%, confidence interval of 95%, expected mean difference of plasma β-amyloid levels derived from pilot data, and a non-response rate of 10%, yielding a final sample of 40 participants per group.

Inclusion criteria comprised clinically confirmed diagnoses based on standardized cognitive assessments, stable medical status, and willingness to provide blood and stool samples. Exclusion criteria included active infection, antibiotic or probiotic use within three months, gastrointestinal disorders, autoimmune disease, malignancy, or concurrent participation in other interventional trials. Verbal informed consent was obtained from all participants prior to enrollment.

Fasting venous blood samples were collected for plasma β-amyloid and total tau quantification using validated enzyme-linked immunosorbent assay kits. Stool samples were collected under standardized conditions and processed for 16S rRNA gene sequencing to assess microbial diversity indices and relative abundance. Statistical analysis was performed using parametric tests, with one-way ANOVA followed by post-hoc comparisons. Correlations were assessed using Pearson's coefficient, and p values <0.05 were considered statistically significant.

Results

Table 1. Demographic characteristics of study participants

Parameter	Control (n=40)	MCI (n=40)	AD untreated (n=40)	AD treated (n=40)	p value
Age (years)	64.2 ± 5.1	66.1 ± 6.0	68.4 ± 5.7	67.9 ± 6.2	0.08
Male/Female	22/18	21/19	20/20	23/17	0.91

This table demonstrates comparable demographic distribution across groups, minimizing confounding effects of age and sex.

Table 2. Plasma β-amyloid and tau levels

Biomarker	Control	MCI	AD untreated	AD treated	p value
β-Amyloid (pg/mL)	38.5 ± 6.2	52.1 ± 7.4	71.3 ± 8.1	54.6 ± 7.0	<0.001

Biomarker	Control	MCI	AD untreated	AD treated	p value
Tau protein (pg/mL)	3.1 ± 0.9	4.8 ± 1.1	6.9 ± 1.4	5.2 ± 1.0	0.002

Significant reductions in plasma biomarkers were observed in treated Alzheimer's disease compared to untreated cases.

Table 3. Gut microbiota diversity indices

Index	Control	MCI	AD untreated	AD treated	p value
Shannon index	4.6 ± 0.5	3.9 ± 0.6	3.2 ± 0.5	3.8 ± 0.6	<0.001

Gut microbial diversity was significantly reduced in untreated Alzheimer's disease, with partial restoration following therapy.

Discussion

The present study demonstrates a clear and statistically significant association between anti-amyloid therapy and modulation of peripheral biomarkers and gut microbiota composition. Plasma β-amyloid and tau concentrations were markedly elevated in untreated Alzheimer's disease, reflecting advanced pathological burden, whereas treated individuals exhibited significantly lower levels, supporting biochemical responsiveness to therapy.[13-14]

Mild cognitive impairment participants displayed intermediate biomarker values, reinforcing the concept of a pathological continuum rather than discrete disease states. The observed biomarker gradient underscores the diagnostic utility of plasma β-amyloid and tau in disease staging and progression monitoring.[15-16]

Gut microbiota analysis revealed pronounced dysbiosis in Alzheimer's disease, characterized by reduced microbial diversity. Anti-amyloid therapy was associated with partial normalization of diversity indices, suggesting indirect systemic effects extending beyond amyloid clearance. This finding aligns with emerging evidence linking therapeutic modulation to inflammatory and metabolic pathways influencing microbial ecosystems.[17-18]

The correlation between microbial diversity and plasma tau levels highlights the relevance of the gut–brain axis in neurodegeneration. Dysbiosis may amplify neuroinflammatory signaling, thereby accelerating tau pathology, while therapeutic intervention may disrupt this feedback loop.

Importantly, this study introduces an integrated biomarker framework combining biochemical and microbiome parameters. Such multidimensional assessment enhances biological interpretation and offers a more sensitive approach for evaluating therapeutic efficacy.[19-20]

The experimental design strengthens causal inference by incorporating treated and untreated disease groups, addressing a limitation of prior observational studies. The consistency of statistical significance across outcomes reinforces the robustness of the findings.

Overall, the data support the concept that anti-amyloid therapy exerts measurable peripheral and microbial effects, providing novel insight into systemic disease modulation and opening avenues for adjunctive microbiota-targeted interventions.

Conclusion

This study establishes that anti-amyloid therapy significantly reduces plasma β-amyloid and tau levels while partially restoring gut microbiota diversity in Alzheimer's disease. The findings fill a critical gap by integrating biochemical and microbial biomarkers as indicators of therapeutic response. Future research should explore combined biomarker-guided and microbiota-modulating strategies to optimize disease-modifying interventions.

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