# PLASMA TAU LEVEL AS A DIAGNOSTIC AID IN PATIENTS WITH ALZHEIMER DISEASE

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**Abstract**

**Background:** Neurodegenerative diseases are significant health concerns with regard to morbidity and social and economic hardship around the world. Many researches in the field of Alzheimer disease have validated the CSF Tau level especially phosphorylated tau (P-tau) in the prediction of conversion of mild cognitive impairment (MCI) to clinically definite Alzheimer disease.

**Objectives:** To study plasma tau level in patient with Alzheimer's disease and elderly patients undergoing normal aging degenerative changes

Patients and Methods: The study enrolled 50 patients with symptomatic AD, or with memory impairment in the consensus of mild cognitive impairment (MCI). They were subjected to cognitive scales and plasma tau assessment.

**Results:** Plasma tau levels assessment revealed that all patients in Alzheimer group had high level of plasma tau and MCI group nearly half of them (47.3%) had high levels meanwhile the control groups did not revealed and high levels of plasma tau, these findings revealed high statistical significance (ρ-value <0.001). Higher levels of plasma tau are consistent with low MMSE scores, MoCA scores and high CDR scale score with high statistically significant differences (ρ-value <0.001).

**Conclusion:** Plasma tau levels can give an overview of pathophysiological changes at the cellular level in patients with Alzheimer's disease, which increases the biomarker's diagnostic value. Achieving a reliable biomarker with adequate sensitivity and specificity is necessary in detecting AD at early stages.

**Keywords:** Plasma tau, MCI, Dementia, Alzheimer disease

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## 1. INTRODUCTION

Neurodegenerative diseases are significant health concerns with regard to morbidity and social and economic hardship around the world. The neurodegenerative processes characteristic of Alzheimer disease (AD) predate the development of clinical dementia by decades. These changes include neuronal loss and the development of amyloid plaques, neurofibrillary tangles and associated gliosis. Persons in this pre-symptomatic stage provide the opportunity to prevent the symptomatic disease and the development of therapeutics that target this early neurodegeneration requires biomarkers that accurately predict the development and progression of clinical dementia.[1]

Many researches in the field of Alzheimer disease have validated the CSF Tau level especially phosphorylated tau (P-tau) in the prediction of conversion of mild cognitive impairment (MCI) to clinically definite Alzheimer disease. Theses findings supported by the pathological evidence from post mortem studies open the way in front of the tau PET scan in Alzheimer disease. P- tau levels may have a promising predictive value if it can be detected in patient serum, given the ease of accessibility in comparison to the need for lumbar puncture. [2]

In this study we would hopefully answer the question whether there is marked difference in plasma tau level and metabolic brain changes measured in patient with Alzheimer's disease and

elderly patients undergoing normal aging degenerative changes and to investigate if these measurable differences could make definite diagnosis of AD at earlier stages possible.

**Aim of the work**

This study would hopefully answer the question whether there is marked difference in plasma tau level and metabolic brain changes measured in patient with Alzheimer's disease and elderly patients undergoing normal aging degenerative changes and to investigate if these measurable differences could make definite diagnosis of AD at earlier stages possible.

## 2. PATIENTS AND METHODS

This is a prospective cross-sectional study. The study was carried in Neurology department, Mansoura university hospital. Fifty Egyptian individuals were enrolled during the study period according to the DSM-5 criteria for major neurocognitive disorders. The Institutional Research Board - IRB Ethics Committee under the code of (**MD.19.01.135.R1**) approved the research protocol. All patients or their surrogated had clearly read the study protocol and an informed written consent were collected from them.

The study enrolled 50 patients with symptomatic AD, or with memory impairment in the consensus of mild cognitive impairment (MCI) diagnosed using the DSM- 5 criteria with age more than 60 years and Mini Mental State Examination score of 24 or less. They were recruited from the Neurology outpatients clinic Department, Neurology department, Mansoura University Hospital between May 2019 and November 2021.

**The exclusion criteria were:** Age less than 60 years, major health problem that can impair cognitive functions e.g. severe renal or hepatic impairment, history of major cerebrovascular stroke, metal implants or pace maker that could hinder radiological investigation and severe cognitive impairment with MMSE score less than 15.

Control group included twenty healthy individuals; age and sex matched subjects with no previous or current suspicion of cognitive affection were recruited in this study.

At initial visit, gender, age and body mass index (BMI) were recorded. Then we collected data about comorbid medical diseases as hypertension, diabetes, AF, thyroid disease, end organ failure, psychiatric illness and medication exposure history.

Then the patient was subjected to psychometric assessment. First, the Mimi mental state examination test (MMSE) which is rapid cognitive assessment tool that include of 30 items that need only five to ten minutes and has an entire score with the range between normal (thirty) to severe affection (zero). Alzheimer disease severity can be stratified according to MMSE examination to: Mild form (MMSE between 21–26); moderate AD (MMSE 15–20); moderately severe to severe (MMSS) AD (MMSE<15 points)

Second, the Montreal Cognitive Assessment (MoCA) test, it has an advantage in detection of MCI or early signs of cognitive affection. MoCA Fully measures short-term memory, visuospatial function, Executive functions, Attention, concentration, working memory and Language. Arabic version of the test was used.[3]

Third, the clinical dementia rating scale (CDR) which is obtained through semi-structured interviews of patients and informants, and cognitive functioning is rated in six domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

A blood sample was obtained from each patient on the first morning (07:00) after being admitted under fasting condition and within 48 hours of clinical onset of stroke. Within 30 minutes, aliquots of plasma and serum underwent separation and were kept at − 80 °C until analysis.

Plasma tau was analyzed with the Tau ELISA Assay Kit (SKU: ARG81145); The Tau ELISA Assay Kit is intended for the quantification of Tau in cell culture supernatant, serum, cell culture extracts, plasma, cerebral spinal fluid. The Tau ELISA assay kit is for research use only and should not be used for diagnostic procedures. Sensitivity: 5.2 pg/ml. Dynamic Range: 31.25-2000 pg/ml. Incubation Time: 3 hours. Samples were analyzed at the Clinical pathology Laboratory, Mansoura University Hospital.

## STATISTICAL ANALYSIS:

All statistical analyses were performed using "Statistical Package for the Social Sciences (SPSS) Statistics version 21.0" (*IBM Corp., Armonk, New York, USA*). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test.

Continuous variables were presented as mean ± SD (standard deviation) for parametric data and Median for non-parametric data. The two groups were compared with Student t test (parametric data) and Mann–Whitney test (non- parametric data). Multivariate logistic regression model to explore the factors associated with outcomes.

## 3. RESULTS

Fifty Egyptian patients diagnosed according to the DSM-5 criteria for major neurocognitive disorders without any pre-morbid handicap who were

enrolled in our study from Neurology outpatients clinic, Mansoura university hospital between May 2019 and August 2021 at Mansoura University Hospital. The association between plasma tau and demographic factors were studied; then the association between P- tau and disease severity using linear regression adjusted.

The studied population age range was 61-72 years (Mean ± SD = 68.35 ± 4.44). Twenty-nine were males and mean BMI was 26.49 ± 4.45 (range was 23-36).

Neuropsychiatric tests revealed that mean MMSE levels among patients with Alzheimer disease diagnose was 15.35 ± 1.73 and 22.43 ± 1.48 among those with MCI diagnosis and these findings showed high statistical significance (ρ-value <0.001). In addition, mean level of MOCA among AD group was 17.95 ± 1.10 and 23.10 ± 1.32 among those with MCI and this had high statistical significance (ρ-value <0.001). Finally clinical dementia rating scale showed significant statistical differences among the three groups with the mean level 2 in AD group and 0.5 among MCI group (ρ-value <0.001). **Table (1).**

**Table (1):** Analysis of MMSE, MOCA, CDR and tau protein in the study groups

| | **AD group N= 20** | **MCI group N= 30** | **Control group N= 20** | **Test of sig.** |
|---|---|---|---|---|
| **MMSE** | 15.35 ± 1.73 | 22.43 ± 1.48 | 26.85 ± 0.75 | F= **347.248** P < 0.001* |
| **MOCA** | 17.95 ± 1.10 | 23.10 ± 1.32 | 29.15 ± 1.14 | F= 429.111 P < 0.001* |
| **CDR** | 2 (2-3) | 0.5 (0.5-1) | **0** | KW= **63.663** P < 0.001* |
| **Tau protein** | | | | |
| **Normal** | 0 (**0**%) | 16 (**5**3.3%) | 20 (100%) | $\chi^2$= 40.109 P < 0.001* |
| **Elevated** | 20 (100%) | 14 (46.7%) | 0 (0%) | |

Quantitative data are expressed as mean ± SD or median (Range); Qualitative data are expressed as number (Percent); F: One-way ANOVA test; KW: Kruskal Wallis test; $\chi^2$: Chi-Square test.

Analysis of routine laboratory results among the three groups revealed no statistically significant differences as regard CBC, liver function tests, renal function tests and thyroid profile **(Table 2).** Lipid profile analysis revealed higher levels of total cholesterol and lower levels of HDL cholesterol among Alzheimer group, and these findings revealed statistically significant difference (ρ-value <0.05). **(Table 3).**

**Table (2):** Analysis of laboratory data in the study groups

| **Variables** | | **AD group N= 20** | **MCI group N= 30** | **Control group N= 20** | **Test of sig.** |
|---|---|---|---|---|---|
| AST | Normal | 18 (90%) | 26 (86.7%) | 20 (100%) | MC= 2.795 P = 0.247 |
| | Elevated | 2 (10%) | 4 (13.3%) | 0 (0%) | |
| ALT | Normal | 18 (90%) | 27 (90%) | 20 (100%) | MC= 2.154 P = 0.341 |
| | Elevated | 2 (10%) | 3 (10%) | 0 (0%) | |
| Urea | Normal | 20 (100%) | 30 (100%) | 20 (100%) | ——— |
| | Hyperuricemia | 0 (**0**%) | 0 (0%) | 0 (0%) | |
| Creatinine | Normal | 20 (100%) | 30 (100%) | 20 (100%) | ——— |
| | Elevated serum creatinine | 0 (**0**%) | 0 (0%) | 0 (0%) | |
| T3 | Normal | 19 (95%) | 28 (93.3%) | 20 (100%) | MC= 1.335 P = 0.513 |
| | Decreased | 1 (5%) | 2 (6.7%) | 0 (0%) | |
| T4 | Normal | 19 (95%) | 28 (93.3%) | 20 (100%) | MC= 1.335 P = 0.513 |
| | Decreased | 1 (5%) | 2 (6.7%) | 0 (0%) | |
| TSH | Normal | 19 (95%) | 28 (93.3%) | 20 (100%) | MC= 1.335 P = 0.513 |
| | Elevated | 1 (5%) | 2 (6.7%) | 0 (0%) | |

Qualitative data are expressed as number (Percent); MC: Monte-Carlo test.

**Table (3):** Analysis of lipid profile in the study groups

| **Variables** | | **AD group N= 20** | **MCI group N= 30** | **Control group N= 20** | **Test of sig.** |
|---|---|---|---|---|---|
| Cholesterol | Normal | 15 (75%) | 28 (93.3%) | 20 (100%) | MC= 7.593 P = 0.022* |
| | Elevated | 5 (25%) | 2 (6.7%) | 0 (0%) | |
| TGs | Normal | 16 (100%) | 28 (93.3%) | 20 (100%) | MC= 5.347 P = 0.069 |
| | Elevated | 4 (**0**%) | 2 (6.7%) | 0 (0%) | |
| LDL | Normal | 18 (90%) | 29 (96.7%) | 20 (100%) | MC= 2.554 P = 0.279 |
| | Elevated | 2 (1**0**%) | 1 (3.3%) | 0 (0%) | |
| HDL | Normal | 15 (75%) | 28 (93.3%) | 20 (100%) | MC= 7.593 P = 0.022* |
| | Decreased | 5 (25%) | 2 (6.7%) | 0 (0%) | |

Qualitative data are expressed as number (Percent)
MC: Monte-Carlo test
*: Statistically significant (p< 0.05).

Plasma tau levels assessment revealed that all patients in Alzheimer group had high level of plasma tau and MCI group nearly half of them (47.3%) had high levels meanwhile the control groups did not revealed and high levels of plasma tau, these findings revealed high statistical significance (ρ-value <0.001). **(Figure 1)**

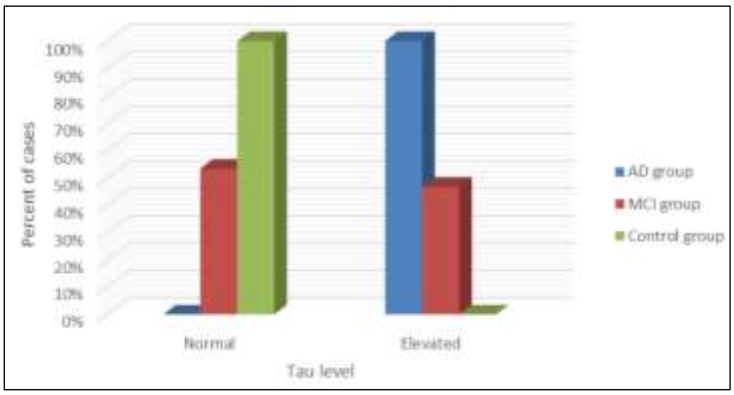
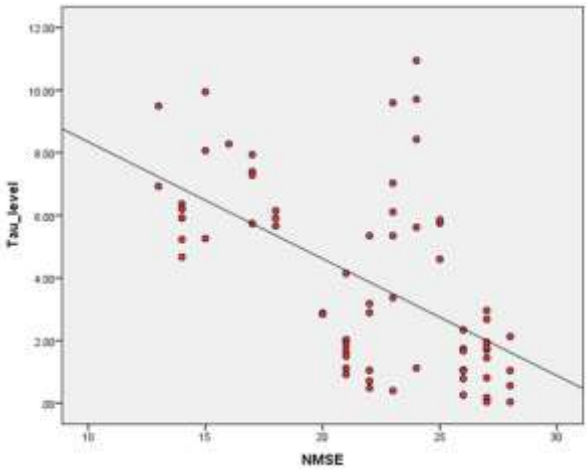



**Figure (1):** Plasma tau protein levels in the study groups

Further assessment of any possible correlation between the plasma tau levels and the neuropsychiatric assessment tools revealed that higher levels of plasma tau are consistent with low MMSE scores, MoCA scores and high CDR scale score with high statistically significant differences (ρ-value <0.001). **(Figure 2)**



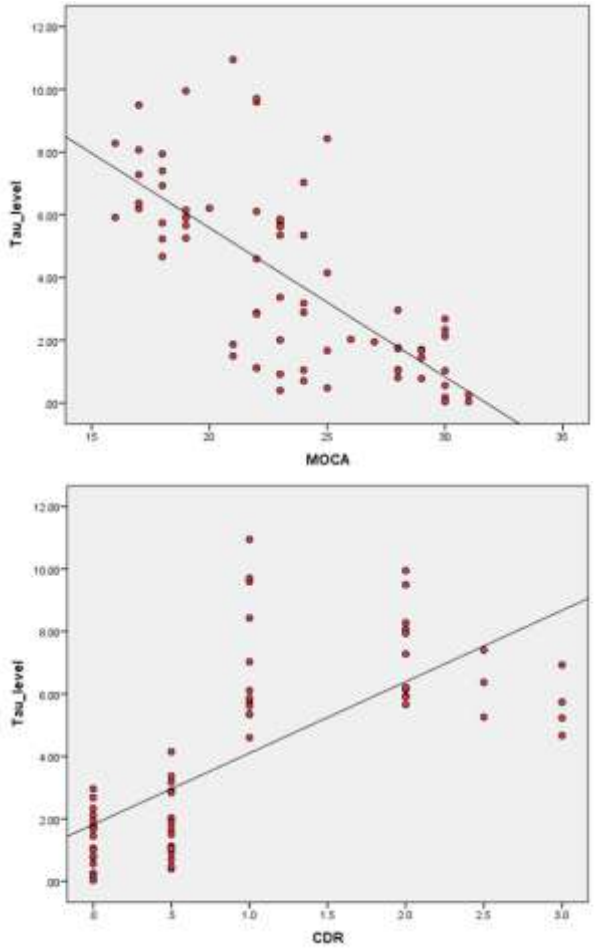



**Figure (2):** Relation between tau protein level with MMSE, MOCA and CDR

## 4. DISCUSSION

Alzheimer disease (AD) have an important and increasing burden on personnel and high social impact which lead to an increase highlighting on diagnosis and management of this cognitive degenerative disease [4]. Thirty years before, a lot of biomarkers were discovered in relation to Alzheimer disease molecular pathology, they gave the conclusion that AD dementia is a chronic condition that progress dozens of years before the clinical presentation become evident. [5]

Alzheimer disease is well-known neurodegenerative disease with well-identified histopathological findings and pathophysiological mechanisms. In addition, diagnosis of AD can be concluded at the clinical presentation only, but the presence of biomarkers eases the early pick up of different cases even at the sub clinical condition or the prodromal phase.[5] These different biomarkers open the road in front of different neurocognitive dilemma diagnosis to be solved especially when there is clinical overlap in their presentations.[6]

A diagnosis of dementia has a profound impact on patients and their families. Determining the cause of dementia is important because this etiologic diagnosis directs treatment and management decisions and provides patients and their families with prognostic information; however, determining the etiology of dementia may be difficult. [6]

Plasma and CSF adequate analysis can reveal the pathophysiological process in neurodegenerative disorders as dementia. Advanced neuroimaging such as PET scan can give us an open vision to assess the degree of pathophysiological changes and progression, but unfortunately, it is costly and more complex. [7]. CSF has higher privilege that make any molecule derived from it an ideal biomarker as it can give an excellent overview about the pathological process in diseased brain. This raise the chance for possible use of less invasive and cheaper procedures. Introduction of the plasma biomarkers in Alzheimer disease is somewhat hopeful as it is less invasive and affordable [2, 7]

In this study we would hopefully answer the question whether there is marked difference in plasma tau level and metabolic brain changes measured in patient with Alzheimer's disease and elderly patients undergoing normal aging degenerative changes and to investigate if these

measurable differences could make definite diagnosis of AD at earlier stages possible.

In our study, patients with the diagnosis of Alzheimer's disease and MCI had higher plasma levels of tau. These findings support the findings of previous researches [8-10]. This can be explained by the theory about tau which suggest its tight relation amyloid plaques in the diseased brain [11]. Findings from different researches reflect an elevation in P-tau in the early stages of sporadic cases and autosomal dominant AD, which can give an importance to P-tau for early detection of preclinical stages of Alzheimer. In addition, patients with normal tau PET scans in early stages of Alzheimer, when they have higher levels of P-tau, tau PET in the entorhinal cortex was increased, indication the close association between them. Also, this association was significant in case of amyloid plaques deposition, suggesting that P-tau may have close relation to amyloid plaques deposition [12, 13].

Some researchers don't consider blood t-tau as an ideal biomarker of AD [14], mainly because of the short half-life in plasma and low specificity across Alzheimer's disease (AD) spectrum [15].

## 5. SUMMARY AND CONCLUSION

Plasma tau levels can give an overview of pathophysiological changes at the cellular level in patients with Alzheimer's disease, which increase the biomarker's diagnostic value. Achieving a reliable biomarker with adequate sensitivity and specificity is necessary in detecting AD at early stages.

## 6. REFERENCES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