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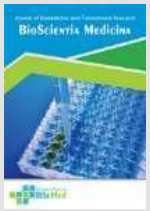

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# Relationship between Serum p-Tau Levels and Impaired Cognitive Function in Type 2 Diabetes Mellitus

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**A B S T R A C T**

**Background:** Type 2 diabetes mellitus (Type 2 DM) is a metabolic disease that causes a global crisis that threatens health and the world economy. Impaired cognitive function is a key factor in reducing health-related quality of life in type 2 DM patients. Phosphorylated Tau (p-Tau) is a microtubule protein that functions in cell signaling, synaptic plasticity, and regulation of genome stability. A malfunction of p-Tau will cause disruption of cell signaling, which can result in impaired cognitive function. This study aims to assess the relationship between serum p-Tau levels and impaired cognitive function in type 2 diabetes mellitus patients. **Methods:** This research is an observational study, comparative analysis with a cross-sectional design with a sample of 60 type 2 diabetes mellitus patients who sought treatment at the endocrine polyclinic at Dr. M. Djamil General Hospital Padang. Cognitive function was assessed using MoCa-Ina. Serum p-Tau levels were measured using the ELISA method. Data analysis was carried out using SPSS. **Results:** The average serum p-Tau level in type 2 diabetes mellitus patients with impaired cognitive function was 542.9 pg/ml. The cut-off point for serum p-Tau levels which is associated with impaired cognitive function in type 2 diabetes mellitus patients is 517.2 pg/ml. There was a significant relationship between serum p-Tau levels and impaired cognitive function in type 2 diabetes mellitus patients (p=0.039). **Conclusion:** There is a significant relationship between serum p-Tau levels and impaired cognitive function in type 2 diabetes mellitus patients.

## 1. Introduction

Type 2 diabetes mellitus (Type 2 DM) is a metabolic disease characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. Type 2 DM is associated with many chronic complications involving multiple organs including the brain and nervous system. Evidence suggests that type 2 DM is strongly associated with reduced performance in several domains of cognitive function. Cognitive function is a cerebral activity in acquiring knowledge that enables a person to carry out daily activities. Recent studies show that there is an increased risk of impaired cognitive function in type 2 DM patients. Severe cognitive function impairment will have an impact on individual independence in daily life and can increase hospitalization rates, health care costs, morbidity, and mortality in type 2 DM patients. 2. However, cognitive impairment in type 2 DM patients is often undiagnosed and does not receive optimal treatment, so early detection and preventive efforts are needed for impaired cognitive function in type 2 DM patients through neurocognitive examination and biomarkers. Several biomarkers have been studied related to the incidence of cognitive impairment in patients with type 2 DM. Type 2 DM sufferers, such as neurodegenerative markers, inflammatory markers,

oxidative stress markers, BDNF, adipokins and MicroRNAs. One of the specific neurodegenerative biomarkers that describes impaired cognitive function in type 2 DM sufferers is phosphorylated Tau (p-Tau) serum.[1-5]

P-Tau is a microtubule protein that is found mostly in central nervous system (CNS) neurons. P-Tau is important for cell signaling, synaptic plasticity, and regulation of genome stability. Named protein malfunctions microtubule-associated protein Tau (MAPT) causes hyperphosphorylation of the Tau protein which is known as tauopathy. Tauopathy resulting in the destruction of microtubules which ultimately leads to their formation of neurofibrillary tangles. The release of p-Tau in the microtubule structure causes the release of tubulins that are polymerized by p-Tau. This causes the microtubules, which are likened to signal-conducting rails, to be damaged, resulting in signal transfer being disrupted which causes dysfunction of intercellular connections which is ultimately followed by cell death. This is one theory of the pathogenesis of impaired cognitive function due to hyperphosphorylation of the Tau protein. Several studies show that p-Tau has a role in impaired cognitive function in type 2 DM patients. Insulin dysfunction that occurs in type 2 DM and changes in glycogen synthase kinase-3β (GSK-3β) signaling in the brain contributes to hyperphosphorylation of tau, thus potentially increasing the risk of occurrence of Alzheimer's disease. A study also showed that there was a significant relationship between impaired cognitive function in type 2 diabetes mellitus patients and Tauopathy and chronic hyperglycemia. Apart from that, other studies show a significant relationship between type 2 DM and mild cognitive impairment. However, in contrast to the studies above, other studies show that there is no significant relationship between impaired cognitive function in type 2 DM patients, where in this study only around 33.7% experienced impaired cognitive function, and 66.3% showed cognitive function. normal. Another study showed that there was no evidence to show any difference in the accumulation of Tau hyperphosphorylation in type 2 DM patients with or without impaired cognitive function. Research on the relationship between serum phosphorylated Tau (p-Tau) levels and impaired cognitive function in type 2 DM patients is still limited. Apart from that, there is still controversy in several studies that have been conducted previously regarding the relationship between levels of phosphorylated Tau (p-Tau) serum with impaired cognitive function in type 2 DM patients.[6-11] This is the background for researchers interested in conducting research on whether there is a relationship between serum phosphorylated Tau (p-Tau) levels and impaired cognitive function in type 2 DM patients.

## 2. Methods

This research is a comparative analysis study with a cross-sectional design conducted by Dr. M. Djamil General Hospital Padang. Data collection, collection, and examination were carried out from April 2023 – May 2024. The study population was all type 2 DM patients who sought treatment at the endocrine polyclinic at Dr. M. Djamil General Hospital Padang. The research sample was taken from a population that met the research inclusion and exclusion criteria. The research sample consisted of 60 Type 2 DM patients. Next, the sample underwent a cognitive function examination using MoCA-Ina and an examination of serum p-Tau levels. Statistical analysis was carried out computerized using SPSS version 25.0 for Windows. Descriptive analysis was carried out on categorical and numerical variables to obtain data regarding the basic characteristics of the research sample. Categorical variables are displayed in the form of frequencies and percentages. The normality test is carried out for numerical variables and is presented in the measure of centrality (*rate,* median) and measures of spread (standard deviation, maximum-minimum). Unpaired categorical comparative analysis will be conducted with chi-squared. Unpaired numerical comparative analysis on normally distributed data was carried out using the unpaired T-test and on data that

was not normally distributed, it was carried out using Mann Whitney test. Results are declared significant if the p-value is <0.05.

## 3. Results

The research sample consisted of 60 patients who had been diagnosed with type 2 DM with or without impaired cognitive function. The basic characteristics of the research sample were grouped based on whether they had cognitive function impairment or without as seen in Table 1. From this table, it can be seen that there were statistically significant differences in the basic characteristics of age (p=0.001) and years of education (p=0.005) between the samples. with impaired cognitive function and without impaired cognitive function, but there were no significant differences in the basic characteristics of gender, duration of suffering from Type 2 DM, BMI (Body Mass Index), and hypertension.

Table 1. Basic characteristics of the research sample based on cognitive dysfunction.

| **Characteristics** | **Cognitive function (MoCA-Ina)** | | |
|---|---|---|---|
| | **Disturbed (n=30)** | **Normal (n=30)** | **p-value** |
| Age | | | 0,001* |
| < 40-59 years | 17 (37,8%) | 28 (62,2%) | |
| ≥ 60 years | 13 (86,7%) | 2 (13,3%) | |
| Gender | | | 0,243* |
| Male | 10 (62,5%) | 6 (37,5%) | |
| Female | 20 (45,5%) | 24 (54,5%) | |
| Length of education | | | 0.005* |
| < 12 years | 7 (100%) | 0 (0%) | |
| ≥ 12 years | 23 (43,3%) | 30 (56,6%) | |
| Long-suffering from DM time | | | 0,152* |
| 5-9 years | 19 (44,2%) | 24 (55,8%) | |
| ≥ 10 years | 11 (64,7%) | 6 (35,3%) | |
| BMI ($Kg/m^2$) ± SD | 26,4 ± 4,8 | 26,5 ± 5,7 | 0,912# |
| Hypertension | | | 0,426* |
| Yes | 13 (56,5%) | 10 (43,5%) | |
| No | 17 (45,9%) | 20 (54,1%) | |

*Chi-square test.
# Independent t-test.

The mean serum p-Tau level in 60 samples with type 2 diabetes mellitus was 498.1 ± 233.5 pg/mL. Where the lowest p-Tau level in the current study was 36 pg/mL and the highest p-Tau level was 1069.5 pg/mL. Serum p-Tau levels between groups with impaired cognitive function and those without impaired cognitive function are shown in Table 2. In this table, the mean value of serum p-Tau levels in the group with impaired cognitive function is 542.9 ± 247.0 pg/mL. The mean serum p-Tau level in the group without impaired cognitive function was 453.3 ± 213.8 pg/mL. The table also shows that serum p-Tau levels in the group with global cognitive function impairment were higher compared to the group without cognitive function impairment. However, the results of bivariate analysis use an independent t-test The serum p-Tau levels of patients with and without impaired cognitive function showed no statistically significant difference (p = 0.138).

Table 2. Differences in serum p-Tau levels in type 2 DM patients with and without impaired cognitive function.

| Variable | Cognitive function (MoCA-Ina) | | |
|---|---|---|---|
| | Disturbed (n=30) | Normal (n=30) | p-value |
| Serum p-Tau levels (pg/mL) ± SD | 542,9 ± 247,0 | 453,3 ± 213,8 | 0,138* |

*Independent t-test.

Provision regarding normal serum p-Tau values in type 2 DM patients still vary. Therefore, calculations were carried out at the cut-off point (COP) using a receiver operating characteristic (ROC) curve so that is obtained area under the curve (AUC) can be used to determine the optimal COP of serum p-Tau levels which is associated with impaired cognitive function in type 2 DM patients. The results of the ROC curve analysis shown in Figure 1 show the optimal COP of serum p-Tau levels between groups with and without disorders. cognitive function was 517.20 pg/mL. The AUC value obtained from the ROC method was 0.59 (95% confidence index, 0.446 – 0.737), sensitivity 63% and specificity 63%.

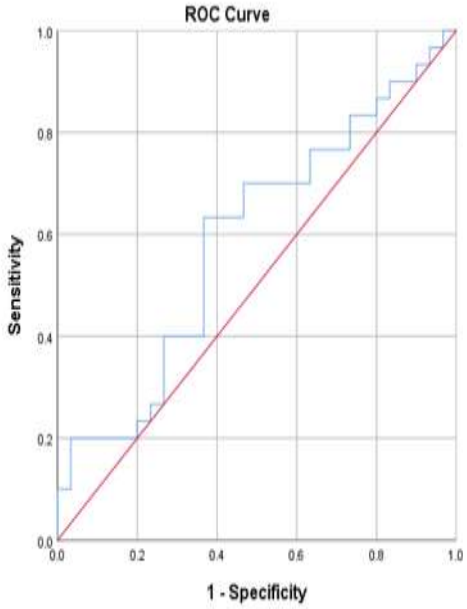


Figure 1. ROC curve of serum p-Tau levels with impaired cognitive function in type 2 DM patients.

In this study there were 30 people (50%) with serum p-Tau levels that were below cut-off point and 30 people (50%) with serum p-Tau levels equal to or above cut-off point. The results of the bivariate analysis and the estimated risk of developing cognitive function disorders are shown in Table 3. In the group with cognitive function disorders, there were 19 people (63.3%) who had serum p-Tau levels above the cut-off point while in the group without global cognitive function impairment, there were 11 people (36.7%) who had serum p-Tau levels above the cut-off point. Chi-square test results showed that there was a significant difference in serum p-Tau levels between groups with and without impaired cognitive function (Odds Ratio [OR]: 2,98; IK 95%, 1,04-8,52; p = 0,039).

Table 3. Relationship between serum p-Tau levels and impaired cognitive function in type 2 DM patients.

| Variable | Cognitive function (MoCA – INA) | | | |
|---|---|---|---|---|
| | Disturbed (n=30) | Normal (n=30) | p-value | OR (I 95%) |
| Serum p-Tau level | | | 0,039* | 2,98 (1,04-8,52) |
| ≥ cut off point | 19 (63,3%) | 11 (36,7%) | | |
| < cut-off point | 11 (36,7%) | 19 (63,3%) | | |

*Chi-square test.

Based on the basic characteristics of the study, it was found that there was a relationship between age and years of education with impaired cognitive function, so we need to assess whether there are differences in serum p-Tau levels with age and years of education to rule out confounding factors in the relationship between serum p-Tau levels and cognitive function disorders in patients type 2 DM. Based on Table 4, it can be seen that there is no significant difference between serum p-Tau levels and age and years of education, where age (p=0.731) and length of education (p=0.07).

Table 4. Differences in serum p-Tau levels with age and length of education.

| Variable | Serum p-Tau levels (pg/mL) ± SD | p-value |
|---|---|---|
| Age | | 0,731* |
| < 40-59 years | 504,5 ± 238,4 | |
| ≥ 60 years | 480,3 ± 225,7 | |
| Length of education | | 0,07* |
| < 12 years | 650,5 ± 274,9 | |
| ≥ 12 years | 478,4 ± 222,8 | |

*Independent t-test.

There are several factors that can be predictors of impaired cognitive function in Type 2 DM patients, namely serum p-Tau levels, age, and years of education. These factors will then be analyzed using a logistic regression test.

Table 5 Multivariate analysis of several risk factors for impaired cognitive function in Type 2 DM.

| Variable | Coefficient | p-value | OR |
|---|---|---|---|
| p-Tau levels | 1,426 | 0.03 | 4,16 |
| Age | 2,731 | 0,00 | 15,34 |
| Length of education | 21,18 | 0,99 | - |

Based on the logistic regression test in Table 5, it was concluded that serum p-Tau levels had a significant effect on impaired cognitive function in Type 2 DM patients, where type 2 DM patients with serum p-Tau levels ≥ 517.20 pg/mL were at 4.16 times the risk. experience impaired cognitive function compared to patients with serotonin levels < 517.2 pg/mL. Apart from that, it was found that age also had a significant effect on the incidence of impaired cognitive function in type 2 DM patients, where patients aged ≥ 60 years had a 15.34 times risk of experiencing impaired cognitive function compared to patients aged 40-59 years.

**4. Discussion**

Bivariate analysis of the age variable in this study showed that as many as 86.7% (13 out of 15 people) of type 2 DM sufferers aged 60 or more suffered from

impaired cognitive function. The results of this study show that there is a significant relationship between age and impaired cognitive function in Type 2 DM patients (p=0.001). Malik's research states that impaired cognitive function often occurs in individuals suffering from type 2 DM, where this is also related to increasing age. Malik's research shows that Type 2 DM patients aged more than and equal to 65 years have a higher incidence of impaired cognitive function. higher compared to patients aged under 65 years p=0.02. During the aging process, oxidative stress increases, hyperglycemia or hypoglycemia and insulin resistance are important risk factors for impaired cognitive function. Type 2 DM can accelerate age-related decline in cognitive function, making patients vulnerable to impaired cognitive function and dementia.[12-15]

This study found a significant relationship between length of education and impaired cognitive function, where patients with a low level of education (less than 12 years) experienced impaired cognitive function by 100% (7 out of 7 people) and patients with a higher level of education (more than and equal to 12 years) showed normal cognitive function in 56.6% (30 of 53 patients) with p = 0.005. This is in accordance with other research which states that a low level of education is significantly related to the degree of impaired cognitive function. Type 2 DM patients with a higher level of education will more easily have the opportunity to access information regarding the management of their disease, including the importance of controlling blood glucose so that they will be able to prevent complications of type 2 DM, one of which is impaired cognitive function.[16-20]

In this study, it was found that the incidence of cognitive dysfunction in men (62.5%) was higher than in women (45.5%). These results are in accordance with other research which states that men have been shown to have a significantly higher incidence of MCI or dementia than women. However, the results of the analysis in this study show that there is no significant relationship between gender and impaired cognitive function in Type 2 DM patients. Based on other research, shows that cognitive function impairment in type 2 DM patients is not related to gender. The results of the current study contradict other studies that show a relationship between the female gender and the emergence of impaired cognitive function in type 2 DM patients. This occurs due to lower levels of education in women, obesity, and cerebrovascular comorbidities which are more often found in women, as well as genetic factors and hormonal factors. The differences obtained in the current study indicate that there are other factors that dominate as causes of impaired cognitive function in type 2 DM patients besides gender.[21-24]

The duration or duration of suffering from type 2 DM is a risk factor for impaired cognitive function in patients, this has been seen in several studies. This study shows that those suffering from type 2 DM > 10 years (64.7%) have a higher risk of suffering from impaired cognitive function compared to those suffering from type 2 DM < 10 years (44.2%), but this is not significantly different. This is in accordance with other research which shows that the duration of suffering from type 2 DM does not affect the degree of impaired cognitive function. Different levels of patient control compliance and ongoing treatment may be one of the factors that cause there to be no significant relationship between the duration of suffering from type 2 DM and impaired cognitive function. Type 2 DM patients with and without impaired cognitive function in the current study had a mean BMI that was not significantly different. The mean BMI of type 2 DM patients with impaired cognitive function in this study was 26.4 ± 4.8 $Kg/m^2$ and in patients without functional impairment cognitive is 26.5 ± 5.7 $Kg/m^2$. This shows that the majority of type 2 DM patients included in this study were obese. Type 2 DM is a risk factor for decreased cognitive function and dementia. However, according to a recent systematic review and meta-analysis of longitudinal studies, obesity is not associated with dementia.[25-29]

As many as 38.3% of type 2 DM patients in this study had hypertension, but this study did not show a significant difference in the incidence of hypertension between groups with or without impaired cognitive

function. The pathophysiology of hypertension in type 2 diabetes mellitus involves maladaptive changes in the autonomic nervous system, vascular endothelial dysfunction, increased activity of the renin-angiotensin-aldosterone system, changes in immune function, and environmental factors.[30]

Phosphorylated Tau is a microtubule-associated protein (MAP) that plays a role in the assembly and stability of microtubules as well as various cellular processes such as cell morphogenesis, cell division, and intracellular trafficking. In addition, p-Tau is involved in neuronal function, especially at the synapse and nuclear levels. Normal levels of phosphorylation are required for optimal tau function, whereas hyperphosphorylation causes tau to lose its biological activity. Abnormal post-translational modifications are the main cause of damage, one of which is abnormal phosphorylation (hyperphosphorylation). Hyperphosphorylated tau protein has an affinity for kinesin and is transported to the distal neuropil causing its formation neurofibrillary tangles in AD. The serum phosphorylated Tau (p-Tau) level in all samples in the current study was 498.1 pg/ml. The serum p-Tau level in type 2 DM patients with impaired cognitive function was 542.9 pg/ml and in type 2 DM patients without cognitive function impairment was 453.3 pg/ml. Currently, there is no standardized normal value for serum p-Tau levels in blood. However, other studies say that the normal value range for tau in CSF is 80 – 450 pg/ml. However, p-Tau levels cannot be compared due to differences in samples from blood serum and CSF.[31-33]

In the current study, it appears that serum p-Tau levels in type 2 DM patients with impaired cognitive function are higher when compared with type 2 DM patients without impaired cognitive function. This is in line with other studies that show that serum p-Tau levels in type 2 DM patients are significantly higher compared to normal patients, and this is associated with impaired cognitive function. In addition, other studies showed that serum CSF t-Tau and p-Tau in type 2 DM patients were significantly increased compared to controls. Because there is no standardized normal value for serum p-Tau levels, researchers looked for a value cut-off point serum p-Tau levels in type 2 DM patients who had impaired cognitive function, and a COP value of 517.2 pg/mL was obtained, sensitivity 63% and specificity 63%. However, other studies say that the normal value range for tau in CSF is 80 – 450 pg/ml. However, p-Tau levels cannot be compared due to differences in samples from blood serum and CSF. The statistical results of this study show that there is a significant relationship between serum p-Tau levels and impaired cognitive function in type 2 DM patients with p= 0.039, where patients with serum p-Tau levels of more than 517.2 pg/mL have a risk of 2.98 times experienced impaired cognitive function compared to patients with serum p-Tau levels < 517.2 pg/mL. Findings in other studies suggest that there is a relationship between p-Tau and insulin signaling and events in Alzheimer's disease, where Tau pathology is said to trigger insulin resistance and insulin deficiency in the brain and peripheral tissues so that it is said to be an initial event in the pathogenesis of impaired cognitive function in Alzheimer disease.[34-36]

Phosphorylated Tau is a protein that plays an important role in cell signaling, synaptic plasticity, and regulation of genomic stability. Hyperphosphorylation of p-Tau causes disruption of its ability to bind to microtubules resulting in the addition of free monomers of p-Tau from missfolded Tau will trigger accumulation, oligomerization, and aggregation. During the aggregation process, the repeating p-Tau domains will form filaments. Tau aggregates are deposited in pathological NFTs called Taupathy which is divided into primary, secondary, and mixed. Tau hyperphosphorylation induces axons in the somatodendritic compartment which is associated with synapse dysfunction and cell death. Tau hyperphosphorylation is an important marker of impaired cognitive function. Some of the kinases and phosphatases of p-Tau are specifically involved in the insulin signaling pathway such as GSK3-β, adenosine monophosphate protein kinase (AMPK), extracellular

signal-regulated kinase (ERK), Jun - N terminal kinase (JNK), PP1, and PP2A. An imbalance of kinases and phosphatases will cause hyperphosphorylation. In type 2 DM patients, there is an increase in GSK-3β activity which triggers a decrease in glucose clearance due to insulin resistance. In addition, increasing GSK-3β activity can increase the production of p-Tau and amyloid-β which causes impaired cognitive function.[37,38]

## 5. Conclusion

There is a significant relationship between serum p-Tau levels and impaired cognitive function in type 2 diabetes mellitus patients.

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