

Serum Levels of Plasminogen Activator Inhibitor-1 in Patients with Parkinson's Disease

Azra Meryem Tanrikulu^a Betul Ozdilek^{b,c} Mehmet Agirbasli^{d,e}

^aClinic of Cardiology, Ministry of Health Maltepe State Hospital, Istanbul, Turkey; ^bDepartment of Neurology, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey; ^cClinic of Neurology, Ministry of Health Goztepe Training and Research Hospital, Istanbul, Turkey; ^dDepartment of Cardiology, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey; ^eClinic of Cardiology, Ministry of Health Goztepe Training and Research Hospital, Istanbul, Turkey

Highlights of the Study

- Elevated plasminogen activator inhibitor-1 levels have been reported in Alzheimer's disease; however, data on plasminogen activator inhibitor-1 levels in Parkinson's disease are limited.
- We found that serum plasminogen activator inhibitor-1 levels were significantly lower in patients with Parkinson's disease than in controls.
- Clinical findings revealed that plasminogen activator inhibitor-1 concentration was marginally positively correlated with the Hoehn and Yahr Scale score.

Keywords

Parkinson's disease · Neurodegeneration · Serum · PAI-1

Abstract

Objectives: The aim of the study was to investigate serum plasminogen activator inhibitor-1 (PAI-1) levels of patients with Parkinson's disease (PD) and their relationship with clinical findings and treatment of disease. **Methods:** The study included 125 PD patients and 48 healthy controls. Patients have been taking effective dopaminergic treatment regularly. The clinical severity of parkinsonism was assessed using the Hoehn and Yahr (HY) staging scale and the Unified PD Rating Scale (UPDRS). PAI-1 level analysis was performed by enzyme-linked immunosorbent assay.

Results: Patients with PD had significantly lower serum PAI-1 levels than healthy controls ($p < 0.001$). Correlations with clinical findings showed only a marginally positive correlation between serum PAI-1 and HY score ($r = 0.170$, $p = 0.05$). In contrast, no significant correlation was demonstrated with the UPDRS score or other clinical parameters. **Conclusion:** This is the first comprehensive analysis of serum PAI-1 levels in patients with PD. The distribution of PAI-1 in PD appears to be complex. The study results implicate that the paradoxical effects of tissue plasminogen activator on the brain parenchyma can be important in the pathophysiology of PD. Future studies are needed to elucidate the role of fibrinolytic system components in PD.

© 2024 The Author(s).
Published by S. Karger AG, Basel

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder (ND) just behind Alzheimer's disease (AD). PD is characterized by neuron death resulting in progressive motor and non-motor dysfunction. Cardinal motor clinical findings are bradykinesia, tremor at rest, rigidity and postural instability. Motor findings, which usually affect one body side at the onset of the disease, spread to the other body side later in the course of the disease, and lead to severe disability [1]. PD remains a poorly understood and incurable disease.

Progressive degeneration of dopaminergic neurons in the substantia nigra and abnormal accumulation of α -synuclein (α -syn) and other proteins; tau and amyloid in the Lewy neurites are biological processes that participate in the pathophysiology of PD [2, 3]. Studies have revealed that genetic mutations, mitochondrial dysfunction, oxidative stress, immunological dysfunction, neuroinflammation, and protein aggregation contribute to the pathogenesis of PD. Recent studies have focused on candidate molecules that can serve as surrogate biomarkers in PD [4–6].

Plasminogen activator inhibitor-1 (PAI-1) has been reported as a biomarker for diagnosis, prognosis, clinical stages, and therapeutic targets of NDs such as PD and AD [7–11]. PAI-1 has been reported in AD [12–14]. PAI-1 is a serine protease inhibitor. It regulates the plasminogen activation system by inhibiting tissue and urokinase-type plasminogen activators (tPA and uPA). PAI-1 is mainly produced from platelets and endothelial cells. PAI-1 inhibits the conversion of plasminogen to plasmin and fibrinolysis. PAI-1 levels and activity have been extensively investigated in thrombotic disorders, atherosclerosis, inflammation, sepsis, cancer, and AD [15–17]. Studies have consistently reported that PAI-1 levels increase in AD [11, 12, 14]. Differences in pathophysiology have been observed between NDs. Although increased PAI-1 levels have been reported in AD, studies on its levels in PD are limited. AD and PD exhibit many similarities and differences in pathogenesis and progression. For instance, vascular risk factors have been implicated in the onset of AD but not in PD. In contrast, cellular death and neuroinflammation are involved in the pathophysiology of PD [4, 5, 8].

Therefore, PAI-1 levels in PD are of clinical interest. The aim of this study was to analyze serum levels of PAI-1 in patients with PD and investigate their relationship with motor and non-motor clinical findings, prognosis and treatment of the disease.

Materials and Methods

Subjects

This study included 125 consecutive patients with PD who attended the Movement Disorders Clinic of Istanbul Medeniyet University, Goztepe Training and Research Hospital, and 48 consecutive healthy subjects who were the spouses of the patients or individuals who volunteered. The participants were between 40 and 80 years old and had a five year-education period at least. Pregnant, post-partum, or breast-feeding women were excluded. All participants agreed and signed informed consent before enrollment in the study.

Inclusion and Exclusion Criteria

An experienced neurologist diagnosed the PD patients based on the Movement Disorder Society Clinical Diagnostic Criteria [18]. Same neurologist followed up the patients in the outpatient clinic regularly. Patients had PD diagnosis for at least 2 years and used effective dopaminergic treatments for the last 6 months regularly. We recorded demographic information, clinical findings, scale scores, and treatment protocols in their databank at each follow-up. Exclusion criteria were as follows: the presence of dementia and/or having scores less than 24 on the mini-mental state test; a psychiatric disorder diagnosed with a structured clinical interview and/or on the Geriatric Depression Inventory, a score of 17 or higher measuring moderate to severe depression; history of comorbidities including diabetes mellitus, cardiovascular disease, cerebrovascular disorder, hyperlipidemia, infectious disease, neoplasm, endocrine disorder, autoimmune, renal, hepatic, and hematologic disorders; use of an anti-inflammatory or immunosuppressive drug; and a history of alcohol and/or substance abuse. Healthy controls with a family history of neurological disorders were also excluded from the control group. Participants with hypertension comorbidity under one drug use only included.

Clinical Evaluation

PD patients were examined “on” periods and disease-related scales were performed the day before collecting blood samples. Clinical data included the onset symptom of PD (tremor or bradykinesia), affected body side (right or left), disease duration, presence of postural and gait dysfunction, motor fluctuations, dyskinesia, hallucination, and family history. The Hoehn and Yahr (HY) staging scale was used for disease severity [19]. Higher stages in this scale ranging from 1 to 5 meant a more severely presented disease. Stage 1 was for unilateral disease, stage 2 for bilateral form without balance difficulties, stage 3 for presence of postural instability, stage 4 for physical dependence, and stage 5 if having wheelchair or without aid being bound in bed. PD patients were categorized according to the HY scale as early stage (stages 1 and 2), moderate stage (stage 3), and late stage (stages 4 and 5), respectively. Clinical symptoms were assessed using the Unified PD Rating Scale (UPDRS). It has four parts: part I for mental function, behavior and mood (4 items by self-assessment), part II for self-determination of the daily activities (13 items), part III for motor examination scored by clinician (14 items), and part IV for motor complications (4 items for dyskinesia, 4 for fluctuation, and 3 for other complications). The patients were asked to rate 39 items in total on a 5-point scale. By adding the scores of the four parts, a total score was obtained [20]. All patients were using effective dopaminergic treatment regularly and levodopa equivalent daily dose (LEDD, mg/day) was recorded [21].

Table 1. Demographic and clinical characteristics of patients with PD and healthy controls

Variables	Patients (n = 125)	Controls (n = 48)	p value
Age, years ^a	63.82±8.41	61.85±7.97	0.163 ¹
Gender, male, n (%)	85 (68)	24 (50)	0.028 ^{2,*}
Education, years ^b	5 [3]	7.5 [9]	0.024 ^{3,*}
History of hypertension, %	29 (23)	11 (23)	0.857 ²
Disease duration, years ^a	8.20±5.72		
HY stage ^a	2.10±0.76		
LEDD, mg/day ^a	878.86±514.79		
UPDRS-I ^a	1.323±1.29		
UPDRS-II ^a	9.27±5.60		
UPDRS-III ^a	12.52±6.39		
UPDRS-IV ^a	2.26±3.57		
UPDRS-total ^a	25.41±14.45		

¹Student's *t* test. ²Pearson's χ^2 test. ³Mann-Whitney U test. ^aData are presented as the mean $\pm$ SD. ^bData are presented as the median [IQR]. *Significance at *p* < 0.05.

Blood Sampling

In the outpatient clinic, blood specimens were collected from all participants early in the morning between 8 and 10 am after 12 h of fasting. Samples were taken into serum vacutainer tubes including gel and clot activator and were then centrifuged for 10 min at 4,000 g. Supernatant serum was stored at -80°C until used for laboratory analysis. Serum PAI-1 levels were determined by using commercially available enzyme-linked immunosorbent assay kits (cat. No: E-EL-H2104; Elabscience, USA), according to the manufacturer's instructions and are expressed as mol/L in unit.

Statistical Analysis

Statistical analyses were performed using SPSS® version 23. All measured variables were subjected to normality testing using the Shapiro-Wilk normality test. Descriptive values were expressed as mean $\pm$ standard deviation (SD), median (interquartile range) and percentage. The following statistical tests were performed: Pearson's χ^2 or Fisher's exact test for categorical variables, Student's *t* test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Spearman's test was used to assess correlations for continuous and ordinal variables. Nonparametric Jonckheere-Terpstra test was used to analyze the differences in median PAI-1 levels between ordinal HY score groups from stages 1 to 4. The *p* value of less than 0.05 was considered significant.

Results

Demographic and Clinical Characteristics of the Study Participants

A total of 173 participants, including 125 PD patients (85 males and 40 females) and 48 healthy controls (24 males and 24 females), were included in the study.

Sociodemographic and clinical variables have been presented in Table 1. There was no significant difference in age between patients and controls (Table 1). Male predominance was found significantly higher in PD patients than in the controls (Table 1). Duration of education was found significantly longer in the control group than in the PD patients (Table 1). All participants were the ones using their right hands. A total of 78 (62%) of PD patients were followed up with tremor-dominant form and 64% of them had right-sided onset of the disease. Besides, 62% of patients with bradykinesia-dominant form had right-sided disease onset. A total of 11 (9%) patients had a family history of PD. As a result of HY scale, 28 (22%) of the patients were distributed into stage 1, 60 (48%) into stage 2, 34 (27%) into stage 3, and 3 (2%) into stage 4, respectively. All patients were treated by effective dopaminergic drugs regularly. Only 7 patients did not use any dopamine agonists and 91 (73%) used an extended-release form of pramipexole treatment, while the others were treated with an extended-release form of ropinirole. A total of 10 (12%) of the patients had dopamine dysregulation syndrome. 11 (9%) of the patients had bilateral subthalamic nucleus deep brain stimulation (STN DBS) surgery.

Serum PAI-1 Levels

Median serum PAI-1 levels were significantly lower in PD patients when compared to those in the healthy controls (8.60 [4.50] vs. 9.40 [1.25], respectively, *p* < 0.001; Fig. 1).

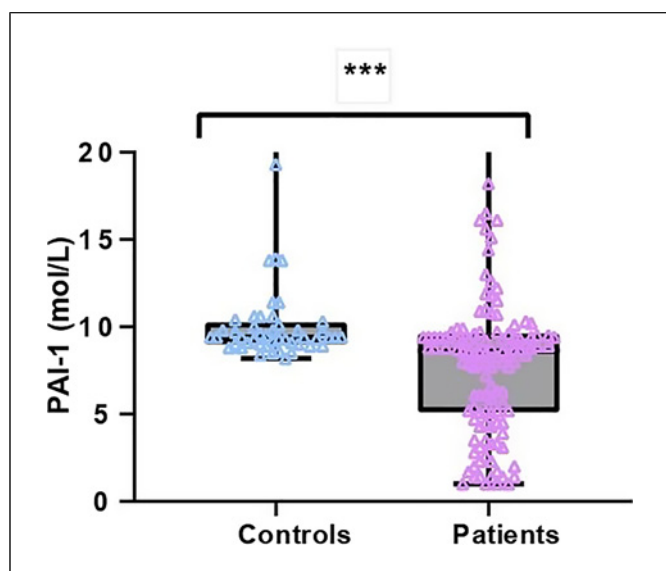


Fig. 1. Scatter plot showing serum PAI-1 levels of patients with PD and healthy controls ($p < 0.001$).

Correlations between PAI-1 Levels and Demographic and Clinical Data

Age, gender, years of education, and presence of hypertension did not show any association with serum PAI-1 levels. We also analyzed the correlation between disease duration, onset type and dominant side of the disease, presence of family history, disease severity (HY score), current clinical status (UPDRS), treatment, and serum PAI-1 levels. Nonparametric Jonckheere-Terpstra test was used to analyze the differences in median PAI-1 serum levels between ordinal HY score groups from 1 to 4 and a borderline significant difference was found between the groups ($p = 0.05$). Based on the results, there was a borderline significant positive correlation between serum PAI-1 levels and HY scores ($r = 0.170$, $p = 0.05$; Fig. 2). Furthermore, serum PAI-1 concentration was only marginally positively correlated with the HY score, which is useful for quick staging and general categorization but primarily focuses on motor symptoms and balance. In contrast, no significant correlation was observed between serum PAI-1 levels and UPRDS, which is a much more comprehensive scale that also accounts for non-motor symptoms and is most often used in research. Similarly, no significant correlations were observed between PAI-1 levels and other clinical characteristics, including disease duration, onset type of PD, complications (e.g., dopamine dysregulation syndrome), psychosis, and treatment (e.g., LEDD, type of dopamine agonist, and STN DBS).

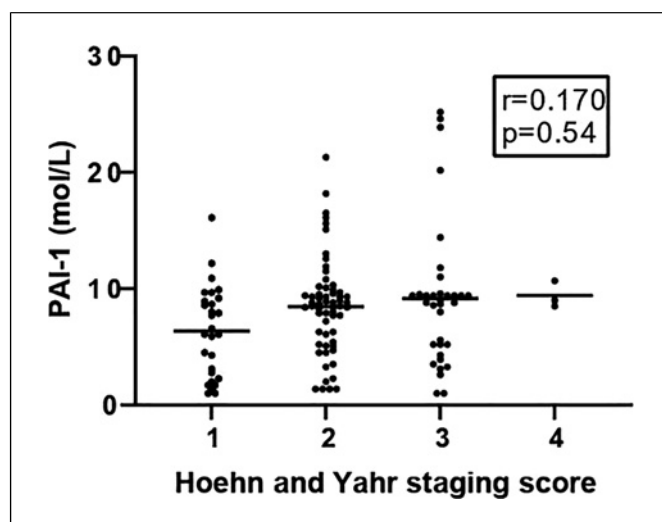


Fig. 2. Correlation analysis between serum PAI-1 levels and HY staging scores in patients with PD (Spearman's correlation test, $r = 0.170$, $p = 0.05$).

Discussion

There is a need for novel surrogate biomarkers in the diagnosis and management of PD. PAI-1 is a potential biomarker for the diagnosis, prognosis, clinical stages and therapeutic targets of NDs such as PD and AD. The role of PAI-1 and fibrinolysis in the PD pathogenesis remains to be elucidated [22, 23]. In our study, we measured the concentration of PAI-1 in the serum of PD patients. We report that PD patients have significantly lower serum PAI-1 levels compared to the healthy controls. There was a positive but weak correlation between PAI-1 levels and the HY score. The study findings contradict the previous report from AD which indicated that PAI-1 is increased in AD [11–14]. In the two most common NDs (AD and PD), PAI-1 levels appear to shift in opposite directions. The findings reported in this study are interesting but require further confirmation in future research.

Fibrinolytic system components such as PAI-1 and tPA exhibit pleiotropic activities beyond hemostasis in the central nervous system (CNS). Several questions remain to be answered about the role of fibrinolytic system components in the pathophysiology of NDs. The balance between plasminogen activators such as tPA and uPA and their principal inhibitor, PAI-1 modulates the fibrinolytic activity. Therefore, measuring the PAI-1 level alone would not be sufficient to assess the total fibrinolytic activity in the CNS. PAI-1 to tPA molar ratio is a better index of overall fibrinolytic capacity. Hence, it would be difficult to draw conclusions from the elevated

PAI-1 levels in AD in the absence of knowledge about the corresponding tPA levels. It is important to note that we did not measure tPA levels in our study. Little is known about the balance or molar ratio of PAI-1 to tPA in AD, PD, or other NDs [24, 25].

PD is a movement disorder with a highly heterogeneous course. The disease course, including motor and non-motor symptoms, varies significantly among patients. The rate of disease progression is also heterogeneous and unpredictable. The pathophysiology of AD and PD remain the topics of extensive investigation. PD and AD exhibit many differences in their pathogenesis. The current hypothesis in AD indicates that the deposits of extracellular amyloid beta proteins and neurofibrillary tangles of accumulated hyperphosphorylated tau protein lead to cognitive and neuropsychiatric symptoms [26]. A variety of evidence demonstrates that vascular risk factors and history of vascular disease increase the risk of AD [27]. Increased PAI-1 levels have been reported in atherosclerosis, chronic inflammatory states, and cardiovascular disease [24, 25].

On the other hand, the effects of PAI-1 in CNS appear to be more complicated than its effects in circulation. It has been reported that tPA has a dual role in the brain; it has a beneficial fibrinolytic effect in the thrombotic vascular occlusion, yet tPA also has a deleterious effect in the brain parenchyma [27, 28]. tPA increases inflammation, blood-brain barrier disruption, and neovascularization [28]. tPA effects brain parenchyma in the absence of the generation of plasmin through various receptors like N-methyl-D-aspartate receptor and the low-density lipoprotein receptor-related protein-1 (LRP-1). The effects of tPA differ in the ischemic versus non-ischemic brain. As a ligand of LRP-1, tPA has proinflammatory effects in the brain. Since neuroinflammation is involved in the pathophysiology of PD, report of low PAI-1 levels in PD can be of clinical interest. A low level of PAI-1 would indicate an increased activity of tPA. As the substrate of PAI-1, tPA is found in abundance in all cellular elements of the brain, and the effects of tPA in the ischemic versus non-ischemic brain are varied. Induction of fibrinolysis, regulation of the permeability of the blood-brain barrier, neuron survival, and neuroinflammation are some of the effects of tPA. Thus, PAI-1 appears to be a checkpoint inhibitor of tPA in various CNS pathologies such as AD and PD. Fibrinolytic system components contribute to the development of neuroplasticity under ischemic and non-ischemic conditions in which tPA affects the disease onset.

We also observed that the serum PAI-1 levels were significantly lower in PD patients treated with STN DBS

compared to the controls. Furthermore, there was a borderline significant positive correlation between serum PAI-1 levels and HY stages of the disease. It is important to note that in this study, all PD patients were effectively treated with dopaminergic drugs and STN DBS treatment. The results show that serum PAI-1 levels in PD patients vary widely with the disease-related indices. Confirmatory studies are needed to assess the role of PAI-1 levels as a potential biomarker of dopamine treatment efficacy in PD.

Pan et al. conducted a study on the role of PAI-1 levels in the diagnosis and prognosis of PD [22]. They reported that plasma PAI-1 levels in PD patients were higher than in the control group across all clinical stages of PD (mild, moderate, and severe). However, PD patients who underwent STN DBS had lower plasma PAI-1 levels. Treatment with DBS significantly decreased plasma PAI-1 levels in PD patients compared to the controls. Additionally, Pan et al. [22] observed increased plasma PAI-1 levels in the worsening clinical stages of PD.

The study findings add to the nascent body of literature on fibrinolytic systems in PD. There are studies that report conflicting results regarding serum/plasma PAI-1 levels and polymorphisms in PD patients [22, 23]. Further studies are required to elucidate the effects of dysregulated fibrinolysis neurodegeneration in PD.

The study has several limitations. We examined a representative sample of PD patients from Istanbul, Turkey, also the sample size is small and cross-sectional. PAI-1 levels and stability vary widely in the general population. There are differences in treatment algorithms for PD among various countries. We cannot exclude confounding effects of genetic and environmental risk factors. Preanalytical and analytical factors can also affect the levels for PAI-1. For instance, serum levels are obtained in the morning hours from patients with PD as diurnal variations can affect the PAI-1 levels. PD phenotype can change significantly between populations. Naturally, the diagnostic and prognostic forecast value of biomarkers would also change according to the PD phenotype. There is also a need to measure tPA levels to describe overall fibrinolytic balance in addition to PAI-1 levels.

Conclusion

The distribution of PAI-1 in NDs appears to be complex, depending on the disease, treatment, presence of ischemia, and corresponding tPA levels. Having a better understanding of the mechanisms in which fibrinolytic system components, such as PAI-1, contribute to

the development of novel therapeutic strategies to modify the disease course in NDs is important. The findings reported in this study showed that PAI-1 levels were low in patients with PD and changed with treatment. Finally, studying the role of PAI-1 in PD can pave the way for the treatment of NDs and PD with novel therapeutics.

Statement of Ethics

All procedures performed in this study were approved by Istanbul Goztepe Training and Research Hospital Institutional Review Boards (Approval No. 2020/0569). All participants agreed and signed informed consent before enrollment in the study.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Funding Sources

The authors declare that this study and publication has received no financial support.

Author Contributions

Conceptualization, protocol development, and data curation: Azra Meryem Tanrikulu, Betul Ozdilek, and Mehmet Agirbasli. Data analysis and interpretation and critical insights and refinement of the manuscript: Betul Ozdilek and Mehmet Agirbasli. Preparation of the first draft of the manuscript: Azra Meryem Tanrikulu and Betul Ozdilek. All authors have read and approved the final version of the manuscript.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding authors upon request.

References

- Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkman J, et al. Parkinson disease. *Nat Rev Dis Primers*. 2017;3:17013. <https://doi.org/10.1038/nrdp.2017.13>
- Michel PP, Hirsch EC, Hunot S. Understanding dopaminergic cell death pathways in Parkinson disease. *Neuron*. 2016;90(4):675–91. <https://doi.org/10.1016/j.neuron.2016.03.038>
- Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. *Clin Geriatr Med*. 2020;36(1):1–12. <https://doi.org/10.1016/j.cger.2019.08.002>
- Johnson ME, Stecher B, Labrie V, Brundin L, Brundin P. Triggers, facilitators, and aggravators: redefining Parkinson's disease pathogenesis. *Trends Neurosci*. 2019;42(1):4–13. <https://doi.org/10.1016/j.tins.2018.09.007>
- Nolan YM, Sullivan AM, Toulouse A. Parkinson's disease in the nuclear age of neuroinflammation. *Trends Mol Med*. 2013;19(3):187–96. <https://doi.org/10.1016/j.molmed.2012.12.003>
- Grünblatt E. Parkinson's disease: molecular risk factors. *Parkinsonism Relat Disord*. 2012; 18(Suppl 1):S45–8. [https://doi.org/10.1016/S1353-8020\(11\)70016-5](https://doi.org/10.1016/S1353-8020(11)70016-5)
- Reuland CJ, Church FC. Synergy between plasminogen activator inhibitor-1, α -synuclein, and neuroinflammation in Parkinson's disease. *Med Hypotheses*. 2020;138:109602. <https://doi.org/10.1016/j.mehy.2020.109602>
- Mehra A, Ali C, Parcq J, Vivien D, Docagne F. The plasminogen activation system in neuroinflammation. *Biochim Biophys Acta*. 2016;1862(3):395–402. <https://doi.org/10.1016/j.bbdis.2015.10.011>
- Liu R-M, Van Groen T, Katre A, Cao D, Kadisha I, Ballinger C, et al. Knockout of plasminogen activator inhibitor 1 gene reduces amyloid beta peptide burden in a mouse model of Alzheimer's disease. *Neurobiol Aging*. 2011;32(6):1079–89. <https://doi.org/10.1016/j.neurobiolaging.2009.06.003>
- Barker R, Kehoe PG, Love S. Activators and inhibitors of the plasminogen system in Alzheimer's disease. *J Cel Mol Med*. 2012; 16(4):865–76. <https://doi.org/10.1111/j.1582-4934.2011.01394.x>
- Angelucci F, Čechová K, Průša R, Hort J. Amyloid beta soluble forms and plasminogen activation system in Alzheimer's disease: consequences on extracellular maturation of brain-derived neurotrophic factor and therapeutic implications. *CNS Neurosci Ther*. 2019;25(3):303–13. <https://doi.org/10.1111/cns.13082>
- Angelucci F, Veverova K, Katonová A, Vyhnaek M, Hort J. Serum PAI-1/BDNF ratio is increased in Alzheimer's disease and correlates with disease severity. *ACS Omega*. 2023;8(39):36025–31. <https://doi.org/10.1021/acsomega.3c04076>
- Guo C, Wang T, Zhang D, Ge X, Li J. Plasminogen decreases A β 42 and Tau deposition, and shows multi-beneficial effects on Alzheimer's disease in mice and humans. *Biochem Biophys Res Commun*. 2023;654: 102–11. <https://doi.org/10.1016/j.bbrc.2023.02.078>
- Angelucci F, Veverova K, Katonová A, Piendel L, Vyhnaek M, Hort J. Alzheimer's disease severity is associated with an imbalance in serum levels of enzymes regulating plasmin synthesis. *Pharmaceuticals*. 2022;15(9):1074. <https://doi.org/10.3390/ph15091074>
- Dupont DM, Madsen JB, Kristensen T, Bodker JS, Blouse GE, Wind T, et al. Biochemical properties of plasminogen activator inhibitor-1. *Front Biosci*. 2009;14(4): 1337–61. <https://doi.org/10.2741/3312>
- Yamamoto K, Takeshita K, Saito H. Plasminogen activator inhibitor-1 in aging. *Semin Thromb Hemost*. 2014;40(6):652–9. <https://doi.org/10.1055/s-0034-1384635>
- Rein-Smith CM, Church FC. Emerging pathophysiological roles for fibrinolysis. *Curr Opin Hematol*. 2014;21(5):438–44. <https://doi.org/10.1097/MOH.0000000000000068>
- Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30(12):1591–601. <https://doi.org/10.1002/mds.26424>
- Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement disorder society task force report on the hoehn and yahr staging scale: status and recommendations. *Mov Disord*. 2004;19(9): 1020–8. <https://doi.org/10.1002/mds.20213>
- Fahn S, Elton RL. UPDRS program members. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. *Recent developments in Parkinson's disease*. Florham Park NJ: Macmillan Health-care Information; 1987. Vol. 2; p. 153–63.
- Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord*. 2010;25(15):2649–53. <https://doi.org/10.1002/mds.23429>

- 22 Pan H, Zhao Y, Zhai Z, Zheng J, Zhou Y, Zhai Q, et al. Role of plasminogen activator inhibitor-1 in the diagnosis and prognosis of patients with Parkinson's disease. *Exp Ther Med*. 2018;15(6):5517–22. <https://doi.org/10.3892/etm.2018.6076>
- 23 Xu Q, Lai Q, Wang J, Zhuang L, Cheng L, Mo Y, et al. Association between plasminogen activator inhibitor-1 gene polymorphisms and susceptibility to Parkinson's disease in Chinese patients. *Acta Neurol Belg*. 2022;122(6):1557–66. <https://doi.org/10.1007/s13760-021-01843-7>
- 24 Vaughan DE, Rai R, Khan SS, Eren M, Ghosh AK. Plasminogen activator inhibitor-1 is a marker and a mediator of senescence. *Arterioscler Thromb Vasc Biol*. 2017;37(8):1446–52. <https://doi.org/10.1161/ATVBAHA.117.309451>
- 25 Agirbasli M. Pivotal role of plasminogen-activator inhibitor 1 in vascular disease. *Int J Clin Pract*. 2005;59(1):102–6. <https://doi.org/10.1111/j.1742-1241.2005.00379.x>
- 26 Yarns BC, Holiday KA, Carlson DM, Cosgrove CK, Melrose RJ. Pathophysiology of Alzheimer's disease. *Psychiatr Clin North Am*. 2022;45(4):663–76. <https://doi.org/10.1016/j.psc.2022.07.003>
- 27 Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? *Neurology*. 2009;72(4):368–74. <https://doi.org/10.1212/01.wnl.0000341271.90478.8e>
- 28 Yepes M. Fibrinolytic and non-fibrinolytic roles of tissue-type plasminogen activator in the ischemic brain. *Neuroscience*. 2024;542:69–80. <https://doi.org/10.1016/j.neuroscience.2023.08.011>