Peripheral Detection of α-Synuclein in Parkinson's Disease: A Systematic Review of Minimally and Noninvasive Biomarkers

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Background:
α-synuclein (αSyn) aggregation is a pathological hallmark of Parkinson's Disease (PD), yet current diagnostic practices remain limited by reliance on invasive cerebrospinal fluid (CSF) analysis or postmortem confirmation. These constraints restrict timely diagnosis, early intervention, and patient recruitment for clinical trials. Consequently, there is growing scientific interest in the detection of αSyn in peripheral tissues and fluids as a minimally or noninvasive alternative for diagnostic and prognostic purposes.

Objective:
This review aims to systematically evaluate the diagnostic performance, accuracy, sensitivity, and specificity of minimally and noninvasive peripheral biomarkers for detecting α-synuclein in Parkinson's disease. It aims to evaluate these peripheral approaches as viable, patient-friendly alternatives to CSF analysis.

Methods:
A systematic search of PubMed, Scopus, and Web of Science was conducted for literature published up to 2025. Only English-language, peer-reviewed human studies evaluating αSyn detection in peripheral samples regarding diagnostic performance, clinical relevance, or methodological feasibility were included in the review.

Results:
Peripheral biomarkers of αSyn have emerged as promising tools for early PD diagnosis. Among these, skin biopsy has gained traction due to its ability to detect phosphorylated αSyn in dermal autonomic nerve fibers. Such findings are consistently absent in healthy individuals [1,2]. Further enhancements in diagnostic precision have been achieved with the

Real-Time Quaking-Induced Conversion (RT-QuIC) assay, which is sensitive enough to detect prodromal Parkinson's like isolated REM Sleep Behavior Disorder [3,4]. This technique offers a promising alternative to cerebrospinal fluid (CSF) analysis, potentially enabling earlier intervention.

In parallel, salivary αSyn, particularly in total and oligomeric forms, has been shown to distinguish PD patients from healthy populations [2]. Advanced methods like RT-QuIC have demonstrated a robust capacity to detect prion-like aggregation in saliva. Nonetheless, challenges remain due to variability in salivary αSyn concentrations, and confounding factors such as oral hygiene, medication, and collection protocols complicate the establishment of reliable diagnostic thresholds [2,3,5].

RT-QuIC assays targeting the olfactory mucosa have shown high diagnostic accuracy for early Parkinson's Disease, offering a minimally invasive method via nasal sampling [6,7].Olfactory mucosa sampling, owing to its anatomical proximity to the CNS and involvement in early disease stages, has also demonstrated diagnostic potential. Additionally, the involvement of autonomic pathways supports the olfactory route's utility in disease detection and monitoring[4,7].

The GI tract also presents a vital area for early detection, as it is affected early in the pathological timeline of PD. This supports the notion of a prolonged prodromal phase, during which intervention might be possible before motor symptoms appear. Emerging evidence suggests αSyn aggregates may originate in the enteric nervous system and ascend to the CNS via retrograde vagal transport [8,9].

Additionally, αSyn has been identified in peripheral fluids such as plasma, serum, and tears. Blood levels may reflect peripheral or erythrocyte-derived αSyn, indicating systemic involvement [3]. Plasma exosomal αSyn has shown a significant correlation with disease severity, making it a potential marker for disease progression. Tear fluid studies report a significant increase in oligomeric forms in Parkinson's patients versus controls yet findings are constrained by small cross-sectional cohorts, and high methodological heterogeneity [10].

Conclusion:

Peripheral detection of αSyn presents a promising direction for improving the diagnostic landscape of PD. While limitations such as assay standardization and overlapping pathology remain, integrating αSyn with other markers may enhance diagnostic accuracy. Future research should emphasize the development of standardized, reproducible methods and multi-marker panels for early, accurate, and widely accessible PD diagnostics.

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