UNIVERSAL JOURNAL OF MEDICAL AND NATURAL SCIENCES
ISSN 2992-8826
https://sr-journals.org/index.php/UJMANS

Advanced approaches in microbiome analysis and biomarker discovery for parkinson's disease

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Introduction. Parkinson's disease (PD) is a progressive neurodegenerative disorder with high early-stage misdiagnosis rates due to reliance on subjective clinical assessment. Recent research highlights the role of the "oral-gut-brain" axis, where oral dysbiosis and pathogens such as Porphyromonas gingivalis may contribute to neuroinflammation and α-synuclein aggregation. Therefore, saliva has gained attention as a non-invasive source of potential PD biomarkers. Modern diagnostic methods include metagenomic sequencing, RT-qPCR for periodontal pathogens, ELISA detection of α-synuclein and Heme Oxygenase-1 (HO-1), and ultrasensitive RT-QuIC assays. Together with multi-omics and machine learning approaches, these technologies show strong potential for early and accurate PD diagnosis.

Keywords: Parkinson's diseas, periodontal pathogens, salivary biomarkers, saliva diagnostics, oligomeric α-synuclein, heme oxygenase-1, extracellular vesicles, 16s rrna sequencing, shotgun metagenomic sequencing, real-time pcr, rt-quic, machine learning.

Materials and Methods. A systematic literature review was conducted according to PRISMA guidelines using PubMed/MEDLINE, Scopus, and Web of Science databases. Study selection followed the PI(E)COS framework and included peer-reviewed clinical studies, systematic reviews, and meta-analyses investigating oral dysbiosis, periodontal pathogens, and salivary biomarkers in Parkinson's disease (PD). Priority was given to studies using advanced diagnostic methods such as 16S rRNA sequencing, metagenomic sequencing, PCR assays, and salivary multi-omics approaches. Studies without healthy controls, focused only on the gut microbiome, or involving other neurodegenerative diseases were excluded. Independent investigators performed title/abstract and full-text screening. Extracted data included study design, participant characteristics, diagnostic samples, laboratory methods, and diagnostic performance indicators such as sensitivity, specificity, and AUC. Study quality and risk of bias were assessed using NIH Quality Assessment Tools.

Results. Recent diagnostic methodologies for Parkinson's disease (PD) have transitioned towards advanced high-throughput technologies. Whole-genome shotgun metagenomic sequencing has emerged as a superior modality over traditional 16S rRNA sequencing, offering species-level resolution and the ability to elucidate functional metabolic pathways. Targeted molecular diagnostics, such as the RT-qPCR-based Perio-Ident 12 test, effectively quantify 12 high-risk periodontal pathogens directly from gingival crevicular fluid. For host-derived salivary biomarkers, while total α-synuclein is generally decreased, oligomeric α-synuclein is significantly elevated, and the oxidative stress marker Heme Oxygenase-1 (HO-1) demonstrates excellent predictive value (AUC of 0.848). A major breakthrough is the application of ultrasensitive Real-Time Quaking-Induced Conversion (RT-QuIC) assays to saliva, which detects minute traces of misfolded α-synuclein with high diagnostic accuracy (AUC 0.844–0.914) and successfully differentiates PD from atypical parkinsonian syndromes like Multiple System Atrophy. Furthermore, the integration of multi-omics profiling—including metabolomics (via NMR), proteomics (via LC-MS/MS), transcriptomics (specifically specific salivary miRNAs like miR-153 and miR-29a-3p), and epigenetics—has identified specific disease signatures in the oral environment. Finally, the isolation

of salivary small extracellular vesicles (sEVs) via Nanoparticle Tracking Analysis achieves exceptional diagnostic accuracy (AUC up to 0.967) for α-synuclein detection. Incorporating these complex functional datasets into machine learning algorithms, such as random forest classifiers, yields robust predictive models (AUC = 0.88) that significantly outperform standard taxonomic data models.

Discussion. The emergence of modern diagnostic technologies has shifted the focus toward the complex oral-brain axis, utilizing saliva and gingival crevicular fluid as non-invasive windows into local dysbiosis and central neurodegeneration. In microbial profiling, whole-genome shotgun metagenomics combined with machine learning significantly outperforms traditional 16S rRNA sequencing by providing species-level functional data. For targeted clinical applications, the Perio-Ident 12 PCR test rapidly detects high-risk pathogens, though it cannot evaluate phenotypic antibiotic resistance or newly emerging pathobionts. Regarding host-derived biomarkers, detecting elevated oligomeric α-synuclein shows tremendous promise. Ultrasensitive assays like RT-QuIC effectively evaluate α-synuclein seeding activity, yielding high diagnostic accuracy (AUC up to 0.914) and successfully distinguishing PD from atypical parkinsonian syndromes. Furthermore, capturing small extracellular vesicles (sEVs) via Nanoparticle Tracking Analysis boosts the predictive value of α-synuclein detection to an AUC of 0.967. Despite these breakthroughs, clinical translation is hindered by significant methodological challenges, including unstandardized saliva collection protocols and inconsistent diagnostic criteria for periodontitis. Most importantly, the reliance on cross-sectional study designs restricts the ability to establish definitive temporal causality—whether oral dysbiosis triggers neuroinflammation or is merely a secondary consequence of PD-related motor deficits that impair daily oral hygiene. Future research must prioritize large-scale, longitudinal prospective studies and multi-omics integration to overcome these barriers and enable personalized interventions.

Conclusion. The link between oral dysbiosis and Parkinson's disease (PD) is increasingly recognized as an important factor in neuroinflammation, making saliva and gingival crevicular fluid valuable non-invasive diagnostic sources. Modern microbial profiling methods, including 16S rRNA sequencing and metagenomics, help identify PD-associated microbial and metabolic changes, while PCR-based assays detect high-risk periodontal pathogens. Salivary biomarkers such as oligomeric α-synuclein and heme oxygenase-1 (HO-1), together with ultrasensitive RT-QuIC assays, show strong potential for early PD diagnosis and differentiation from atypical parkinsonism. Emerging technologies, including extracellular vesicle analysis, CRISPR-based biosensors, and machine learning integrated with multi-omics data, further improve diagnostic accuracy. Overall, oral microbiome and salivary biomarker analysis represent promising non-invasive tools for early detection, monitoring, and personalized management of PD.