Dermatology Practical & Conceptual

Dermatological Manifestations and Sebum Composition in Parkinson's Disease

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Key words: Parkinson's disease, Dermatological manifestations, Sebum composition, Volatile organic compounds, Malassezia

Citation: Paz M, Lio P. Dermatological Manifestations and Sebum Composition in Parkinson Disease. *Dermatol Pract Concept.* 2025;15(1):4921. DOI: https://doi.org/10.5826/dpc.1501a4921

Accepted: November 11, 2024; **Published:** January 2025

Funding: None.

Competing Interests: MP has no conflicts of interest to disclose. PAL reports research grants/funding from AbbVie, AOBiome, and Regeneron/Sanofi Genzyme; is on the speaker's bureau for AbbVie, Eli Lilly, Galderma, Hyphens, Incyte, LEO Pharma, L'Oreal, MyOR Diagnostics, ParentMD, Pfizer, and Regeneron/Sanofi Genzyme; and reports consulting/advisory boards for AbbVie, Almirall, Amyris, AOBiome, Arbonne, ASLAN Pharmaceuticals, Burt's Bees, Castle Biosciences, Codex Labs, Concerto Biosciences (stock options), Dermavant, Eli Lilly, Exeltis, Galderma, IntraDerm, Johnson & Johnson, LEO Pharma, L'Oreal, Menlo Therapeutics, Micreos, Pfizer, Pierre-Fabre, Regeneron/Sanofi Genzyme, Theraplex, and Unilever. In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid, and is a Board member and Scientific Advisory Committee Member of the National Eczema Association. MP reports no conflicts of interest.

Authorship: All the Authors contributed equally to this work.

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ABSTRACT

Introduction: Parkinson disease (PD) is a multifaceted neurodegenerative disorder known for its hallmark motor symptoms. However, nonmotor manifestations, specifically dermatological changes, precede motor symptoms and may thus serve as vital early indicators of PD.

Objectives: This article explores the skin-related changes associated with PD, focusing on alterations in sebum composition, microbial dysbiosis, and the potential for leveraging dermatological assessments as early, noninvasive diagnostic markers for PD.

Methods: A comprehensive literature review was conducted to investigate dermatological manifestations of PD, focusing on sebum changes in affected individuals. Research explored the clinical relevance of altered lipid profiles, volatile organic compound (VOC) contributions, and microbiome dysbiosis in those with PD.

Results: Individuals with PD exhibit excess sebum production characterized by altered lipid profiles, including elevated short-chain fatty acids (SCFAs) and disruptions in sphingolipid metabolism. The lipid-rich environment also promotes overgrowth of *Malessezia* yeast, contributing to varied

dermatological symptoms in those with PD. VOCs identified in sebum have been linked to unique odors and serve as biomarkers for diagnostic potential. These findings support the potential for early PD diagnosis through dermatologic assessment and sebum analysis.

Conclusion: Dermatological manifestations in PD offer promising noninvasive biomarkers for early diagnosis. Future research should aim to further elucidate the mechanisms underlying sebum dysregulation in PD and validate the clinical relevance of these biomarkers in larger populations.

Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative conditions, characterized mainly by the loss of dopaminergic neurons in the substantia nigra [1]. Despite extensive exploration, the exact etiology of PD remains elusive. However, it is widely acknowledged that a combination of genetic predisposition, environmental factors, medications, trauma, oxidative stress, and infectious agents contribute to the onset of PD [2]. Similarly, the diagnosis of PD remains limited, utilizing patient history and clinical presentation [3]. Clinically, PD manifests through motor symptoms including resting tremor, rigidity, bradykinesia, postural instability, and gait abnormalities. Growing research has highlighted a plethora of nonmotor symptoms in PD, including olfactory dysfunction (such as anosmia or hyposmia), autonomic instability, skin changes, and sleep disruptions. Interestingly, these symptoms often appear before the more noticeable motor symptoms of the disease [1,4].

Certain dermatological disorders have been associated with PD. Seborrheic dermatitis (SD), bullous pemphigoid, and melanoma have been overrepresented in those with PD [5]. Many different explanatory models for this connection have been suggested, including shared disease pathogenesis and side effects of therapies. Of particular interest is the utility of leveraging the cutaneous manifestations as a tool for early diagnosis of PD [6]. Recent studies have explored skin nerve changes and cutaneous sebum-producing microbiota as promising avenues for developing diagnostic tools for PD [7,8].

Nonmotor changes in PD, especially skin changes, offer a noninvasive diagnostic opportunity for early diagnosis of PD [4,9]. This study aimed to further explore the dermatological manifestations of PD and how these skin changes could be used as early diagnostic tools for PD.

Neurological Changes in PD

The neurological changes in PD shed light on the pathophysiology of the disease. Atrophy of the cortex and basal ganglia can be seen in the brains of those with PD [10]. This is believed to be caused by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta of the basal ganglia, the main macroscopic feature associated with PD [10,11]. The subsequent denervation disrupts the nigrostriatal pathway and thus the striatum, which modulates motor functions. Although the true mechanism of the nerve damage and disruption is uncertain, evidence suggests that inflammation, oxidative stress, and mitochondrial defects may contribute to this pathology [12]. Nevertheless, the loss of dopaminergic neurons has been hypothesized as the main underlying neurological mechanism for the motor symptoms of PD [13].

The substantia nigra further exhibits pathological changes in those with PD through changes in pigmentation in individuals with PD, however, the substantia nigra pars compacta appear depigmented, correlating with disease severity [14,15].

The microscopic neurological hallmark of PD is the presence of the Lewy bodies, which are insoluble intraneuronal aggregates of the protein α-synuclein [11]. Mutations in the *SNCA* gene, which encodes α-synuclein, lead to the abnormal accumulation of this protein within neurons. This accumulation disrupts normal cellular processes and contributes to the neuronal degeneration seen in PD [11,16]. Not only does this provide valuable insight into the pathophysiology of PD, but it also establishes a genetic explanation for the disease [11].

Dermatological and Nonmotor Symptoms of PD

Dermatological manifestations of PD often present before the onset of motor symptoms, demonstrating their potential utility in early detection of PD and thus enhancing patient care [9]. For example, seborrheic dermatitis, melanoma, bullous pemphigoid, and rosacea are not only prevalent in the general population but are also notably common among those with PD (Figure 1) [1,17]. Such associations raise the question of whether these dermatological conditions could serve as early indicators of PD and warrant potential further diagnostic testing. Increasing the scope of testing, however, also raises concerns regarding the practicality of expanding diagnostic efforts. Future research should investigate the

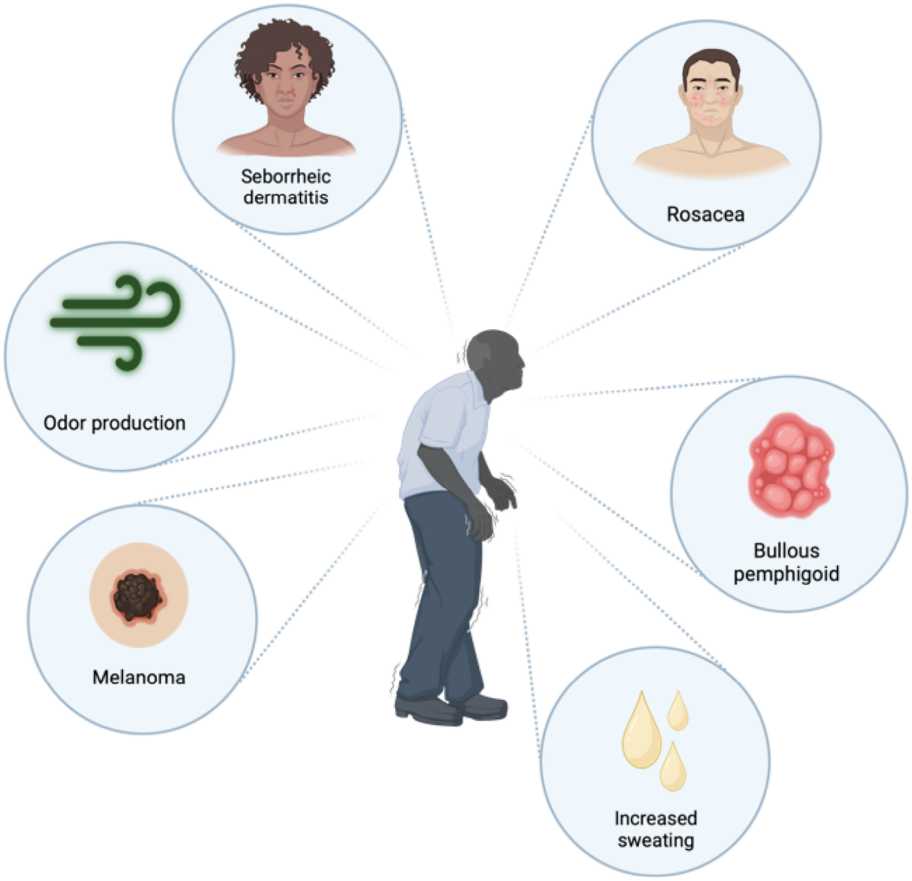

Figure 1. Dermatological manifestations in Parkinson's disease. The various skin conditions commonly associated with Parkinson's disease include seborrheic dermatitis, rosacea, bullous pemphigoid, increased sweating, melanoma, and odor production. These symptoms illustrate the broad spectrum of skin-related issues that can accompany Parkinson's disease, reflecting both primary disease processes and secondary complications

validity of such testing and whether early detection of PD could be improved by routine dermatological evaluations in patients with these conditions.

Pathological changes in the skin composition of those with PD highlight some underlying dermatological manifestations of this neurological disease. Notably, phosphorylated α-synuclein deposits and decreased cutaneous nerve endings have been found in the skin of PD individuals [18,19]. Moreover, metabolic changes in sebum have shed light on cutaneous alterations in those with PD, including decreased long-chain acyl carnitines, disrupted sphingolipid metabolism in skin fibroblasts, and dysregulation of ceramide levels [18,20].

Individuals with PD often present with "oily skin" due to the characteristic excessive secretion of sebum [18,20]. Although the mechanism of this hypersecretion is not well established, researchers have hypothesized that dopaminergic dysfunction may be a possible mechanism: the decrease in dopamine leads to a downstream increase in α-melanocyte-stimulating hormone (α-MSH), which in turn stimulates sebum production [1,21]. Additionally, dopamine loss also causes an increase in prolactin levels, which modulates sebaceous gland function and thus stimulates sebum production as well [18,22]. Peripheral autonomic dysfunction has also been thought to contribute to cutaneous symptoms in PD, altering sweat and sebum production [23,24]. The story of Joy Milne, a woman who could smell PD, emphasizes the significance of sebum changes, as she detected a distinct, musky odor on her husband years before his diagnosis, particularly around his neck and shoulders [9,25].

Sebum changes in individuals with PD extend beyond the quantity produced to include alterations in composition (Figure 2). Studies have identified specific metabolites that vary between PD patients and controls. These biomarkers, termed volatile organic compounds (VOCs), have been identified in sebum and are currently being explored as potential diagnostic tools. VOCs are organic chemicals that are commonly associated with unique odors [9]. Cutaneous VOCs are typically produced by an individual's metabolism, microbial activity on the surface of the skin, and environmental exposures and reactions [26]. For example, Trivedi et al. reported that VOCs like perillaldehyde, eicosane, hippuric

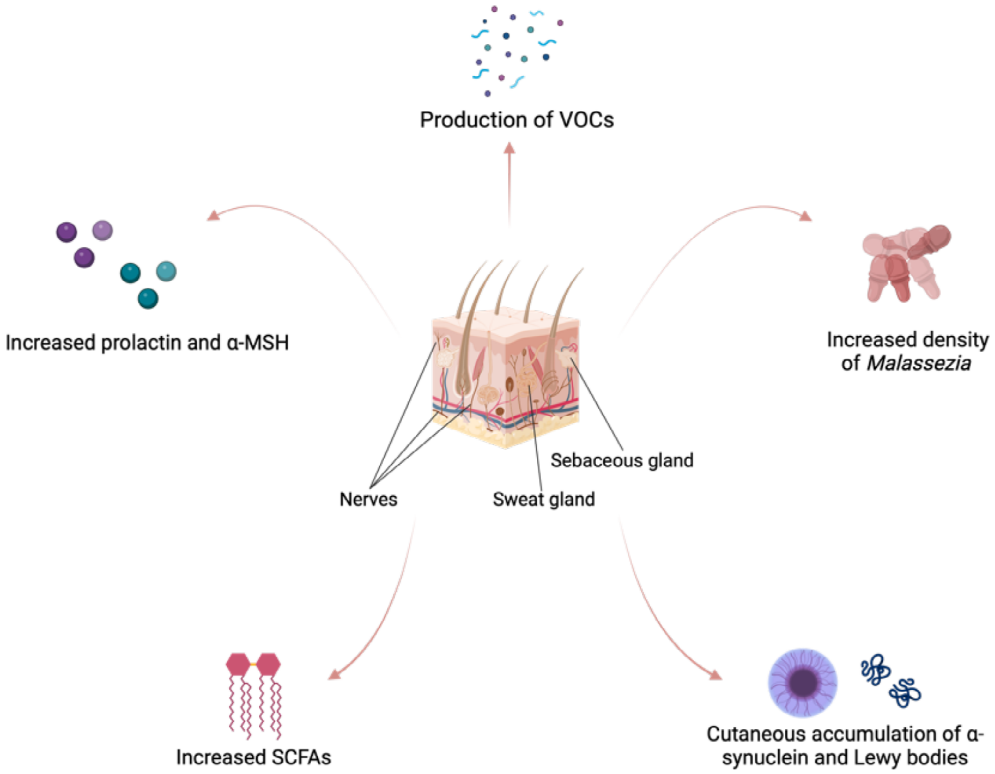

Figure 2. Sebum composition in Parkinson's disease (PD). The alterations in sebum composition in individuals with PD are driven by various factors, including microbial colonization, hormonal changes, immune responses, genetic factors, and environmental influences. Together, these aspects contribute to the altered skin barrier function and various dermatological manifestations observed in PD. These changes contribute to the distinct dermatological manifestations observed in PD patients.

acid, and octadecanal were present in different levels in the sebum of individuals with PD compared to controls [9]. Other studies have found overall increased short-chain fatty-acids (SCFAs) in PD sebum, specifically sapienic acid and palmitic acid. Sapienic acid, a sebaceous-type fatty acid, possesses antimicrobial properties, highlighting the protective role of sebum in maintaining skin health [27]. The dysregulation of these SCFAs in PD patients suggests a disruption in the metabolic processes of sebum production.

Sphingolipids, known for their critical role in neurodegenerative disorders, are essential for cell signaling and regulation, especially in lipid-rich areas like the skin. Research has shown that α-synuclein accumulation impairs sphingolipid metabolism [28]. Proposed mechanisms include that these metabolic disturbances are linked to mitochondrial and lysosomal defects in both fibroblasts and sebum, mirroring the type of nerve damage characteristic of PD pathophysiology. Furthermore, sphingolipids, particularly ceramides, play a direct role in the biosynthesis of cholesterol, a pathway notably altered in PD patients [20].

Quantifying and qualifying sebum odor changes using VOCs offers potential for diagnostic approaches and early detection of PD through noninvasive methods. Certain skin odors involve sebum secretion and bacterial activity on the skin, which together generate VOCs that are perceivable via olfaction [29]. Interestingly, not only are odors by individuals with PD altered, but olfactory function is also significantly impaired. One of the earliest nonmotor presentations of PD is hyposmia or anosmia [30]. Several hypothesized mechanisms for the olfactory impairment have pointed to pathological changes in the olfactory system that mirror that of PD, specifically relating to α-synuclein deposition. Studies have shown that α-synuclein accumulation in the olfactory bulb occurs before other brain regions [31]. As such, changes both in a person's odor and the ability to smell are associated with PD and can be used as early clinical markers of the disease presence and prognosis [30,31].

The increased sebum and altered odor in those with PD are linked to increased *Malassezia* fungus density on the skin [9]. These lipophilic yeasts are a normal constituent of human skin flora but are noted to be present in higher amounts on the skin of PD patients. This species is dependent on exogenous lipids for growth, which explains their predominance on seborrheic skin [32]. In addition to the altered sebum composition and production, the associated immune dysfunction in PD provides an ideal environment for *Malassezia* overgrowth [33,34]. Research has established that individuals with PD present with sebum containing

more colonies of this yeast [23,34,35]. Of note, many VOCs are produced in the presence of *Malassezia*, explaining the associated odor production observed with this yeast [36]. The increased presence of *Malassezia* in patients with PD not only exacerbates dermatological diseases such as dandruff and seborrheic dermatitis but also presents a potential diagnostic approach to PD through its nonmotor symptoms of altered sebum [34].

Conclusion

Exploring dermatological manifestations and sebum composition in PD offers promise for the early detection of this neurodegenerative disease. The high prevalence of skin conditions, such as seborrheic dermatitis, along with pathological changes observed in both the skin and nervous system, emphasizes the connection between the cutaneous and neurological impacts of the disease [5-8]. Most significantly, the distinct metabolic changes in sebum composition, particularly the disrupted sphingolipid metabolism and increased SCFA, present valuable biomarkers for PD [20,27,28]. Unique VOCs in the sebum of PD patients, including perillaldehyde, eicosane, hippuric acid, and octadecanal, highlight the potential for using sebum as an early, noninvasive diagnostic tool [9]. The presence of distinct microbiota, specifically *Malassezia* yeast, and associated cutaneous odor changes underscore the specific dermatological manifestations of the disease that could be leveraged as diagnostic tools. This highlights the fascinating potential for dermatologists to detect PD through olfactory cues, leveraging the altered sebum odor as a novel diagnostic approach [9,23,32-36].

As such, the interplay between sebum production, bacterial activity, and the role of *Malassezia* yeast presents a multifaceted understanding and approach to diagnosing PD. Leveraging dermatological manifestations offers noninvasive, early insight into the neurodegenerative disease, ultimately improving patient outcomes. Future studies should investigate the causes of sebum hypersecretion and the associated skin changes in PD. Research should also aim to add to the comprehensive understanding of metabolic profiles of sebum in PD patients, adding to the identification of novel skin biomarkers and VOCs.

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