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ASSOCIATION BETWEEN CORTISOL AND QUALITY OF LIFE IN PARKINSON'S DISEASE: MAPPING THE AVAILABLE EVIDENCE

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ABSTRACT: Parkinson's Disease (PD) is a progressive neurodegenerative disease that impacts, in addition to motor symptoms, the quality of life (QoL) of patients through non-motor symptoms such as anxiety, fatigue, and sleep disorders. Cortisol, a stress hormone, has been investigated as a biological marker linked to the subjective experience of PD, presenting complex relationships with QoL. This scoping review mapped the evidence on the association between cortisol measures and quality of life in people with PD, through the analysis of original studies that measured both variables simultaneously. We included three studies that demonstrated that altered cortisol levels, especially in salivary samples collected at specific times, are related to worse QoL related to non-motor symptoms such as fatigue and anxiety, with evidence of variations by sex and psychosocial influence between patients and caregivers. The findings highlight the need for standardization of cortisol collection and analysis protocols, as well as the multidimensional assessment of QoL in PD, for a better understanding of the mechanisms and support for future clinical interventions. Despite the limitations due to methodological heterogeneity and the small number of studies available, this synthesis contributes to identifying gaps and guiding further research at the interface between hormonal biomarkers and well-being in PD.

Keywords: Parkinson's disease. Cortisol. Non-motor symptoms. Quality of life. Scoping review.

RESUMEN: A doença de Parkinson (DP) é um distúrbio neurodegenerativo progressivo que afeta negativamente os sintomas motores e não motores, prejudicando significativamente a qualidade de vida dos pacientes. O cortisol, o hormônio do estresse, tem sido investigado como um potencial biomarcador ligado à experiência vivida da DP, mostrando associações complexas com a QV. Esta revisão de escopo mapeou as evidências disponíveis sobre a associação entre medidas de cortisol e qualidade de vida em indivíduos com DP, analisando estudos originais medindo simultaneamente ambas as variáveis. Três estudos incluídos indicaram que níveis alterados de cortisol, especialmente amostras salivares coletadas em horários específicos do dia, estão associados a pior QV relacionada a sintomas não motores, como fadiga e ansiedade, com diferenças entre os sexos e influências psicossociais entre pacientes e cuidadores. Os resultados destacam a necessidade de protocolos padronizados de coleta e análise de cortisol e avaliações multidimensionais de QV na DP, com o objetivo de melhorar a compreensão dos mecanismos subjacentes e intervenções clínicas. Apesar das limitações devido à heterogeneidade metodológica e ao número limitado de estudos, esta síntese identifica lacunas de pesquisa e orienta futuras investigações sobre biomarcadores hormonais e bem-estar na DP.

Palavras-chave: Doença de Parkinson. Cortisol. qualidade de vida. sintomas não motores. revisão de escopo.

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition that, in addition to motor symptoms, causes a wide range of non-motor manifestations that have a decisive impact on the quality of life (QoL) of people with PD and their caregivers (Chaves et al., 2021; Filippin et al., 2014). Population and clinical evidence shows that both motor and non-motor symptoms such as depression/anxiety, sleep disturbances, pain, and fatigue have a strong association with worse QoL scores (Berganzo et al., 2016; Chaves et al., 2021; Filippin et al., 2014). There are also gender-specific nuances, with different impact profiles between men and women, reinforcing the need for gender-sensitive analysis(Balash et al., 2019).

From the point of view of measurement, the Parkinson's Disease Questionnaire, especially the PDQ-39 and its abbreviated version PDQ-8, has established itself internationally as the most widely used instrument for assessing QoL in PD, with a widely disseminated manual for use and interpretation (Jenkinson et al., 1997; Pontes et al., 2017; Silva; Dibai Filho; Faganello, 2011). In addition to capturing multiple domains (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort), there are recent proposals for aligning PDQ-39 cutoffs to clinical severity (Hoehn & Yahr), which can improve decision-making and stratification in studies (Galeoto et al., 2022).

In clinical management, interventions targeting motor circuits can produce tangible gains in QoL and mood. In particular, deep brain stimulation (DBS) has demonstrated a positive impact on QoL when carefully indicated, underlining that QoL is a responsive and clinically relevant outcome (Alves et al., 2018). At the same time, there is a growing interest in biological markers that can be related to the subjective experience of the disease. The hypothalamic-pituitary-adrenal (HPA) axis and its main marker, cortisol, have been investigated in PD, with reports of HPA alterations already in de novo cases (Ibrahimagic et al., 2016) and cortisol variations associated with motor, cognitive, and behavioral aspects (Costa et al., 2019; Soares et al., 2019). Recent conceptual reviews discuss mechanisms by which cortisol (and possibly its interaction with other molecules such as klotho) may be intertwined with the pathophysiology of PD (Luthra et al., 2023).

The association between cortisol and quality of life in PD is complex and scientific evidence is limited indicating that cortisol may affect quality of life, although the exact relationship and mechanisms of action still need to be further studied. It is known that cortisol, a stress hormone, can be dysregulated in PD and contribute to motor and non-motor symptoms, such as anxiety, depression, and social isolation, negatively impacting patients' quality of life (Costa et al., 2019).

In view of this panorama, it is pertinent to map, in a structured way, how the literature has evaluated the association between cortisol measurements (preferably salivary, due to the feasibility of serial collections) and QoL in PD, which cortisol parameters (e.g., baseline, response to awakening, area under the curve, diurnal slope) and which instruments/domains of QoL have been used, in what contexts, and with what direction/consistency of findings (Costa et al., 2019; Jenkinson et al., 1997; Silva; Dibai Filho; Faganello, 2011; Soares et al., 2019). The objective of this study is to map the available evidence on the association between cortisol levels and quality of life in people with Parkinson's Disease, identifying methodologies employed, existing gaps and future research perspectives.

Methodology

Review design

We conducted a scoping review according to the recommendations of the Joanna Briggs Institute (JBI) and the PRISMA-ScR checklist, with the aim of mapping and synthesizing the available evidence on the association between cortisol measures and quality of life (QoL) in people with Parkinson's Disease (PD). This study aims to identify how, in which contexts and with which parameters the cortisol-QoL↔relationship has been investigated, without performing quantitative synthesis of effects (meta-analysis).

Protocol and registration

The protocol was pre-specified and publicly registered on the Open Science Framework platform on 11/10/2025 (File link: https://archive.org/details/osf-registrations-ekbm9-v1; and DOI Registration: 10.17605/OSF. IO/EKBM9). Any deviations from the protocol will be reported transparently.

Research Question (PCC)

Population: people diagnosed with Parkinson's Disease (any gender, age, stage). Concept: Statistical association between cortisol biomarkers (e.g., saliva, serum, urine; baseline morning measurements, arousal response (CAR), area under the curve (AUC), circadian tilt) and quality of life assessed by validated instruments (e.g., PDQ-39/PDQ-8, SF-36, WHOQOL-bref, EQ-5D). Context: any clinical or community settings, without geographical restriction.

Eligibility criteria

Inclusion: (i) original studies in humans with PD; (ii) cortisol and QoL measurement in the same study/sample; (iii) presentation of some statistics on the relationship between cortisol and QoL (correlation, regression, comparison between strata, etc.); (iv) any observational design (cross-sectional, cohort) or baseline arm of trials without cortisol-targeted intervention. Exclusion: reviews (narratives, systematic), preclinical/animal studies, reports/opinions, studies without concomitant measurement of cortisol and QoL or without presentation of an association between these variables.

Sources of information and search strategy

Searches were carried out in MEDLINE/PubMed, Embase, and VHL from the creation of the databases until 10/29/2025, with no language restriction. We also manually searched the reference lists of included studies and citations to identify additional records. The complete strategies by base (Boolean strings, fields and controlled vocabularies such as MeSH/Emtree). Below is an example of a generic string for MEDLINE, to be adapted to each base: ("Parkinson Disease"[Mesh] OR "Parkinson*") AND ("Hydrocortisone"[Mesh] OR cortisol OR "hypothalamic pituitary adrenal" OR "HPA axis" OR glucocorticoid* OR "cortisol awakening response" OR CAR OR AUC) AND ("Quality of Life"[Mesh] OR "quality of life" OR PDQ-39 OR "PDQ-8" OR "SF-36" OR WHOQOL OR "EQ-5D")).

Study selection process

The identified records were exported and deduplicated. The screening of titles/abstracts and the evaluation of full texts were carried out by two reviewers, independently, with resolution of disagreements by consensus or by a third reviewer. Full-text exclusion reasons were categorized (e.g., no QoL, no cortisol, review, duplicate, inadequate population). The PRISMA-ScR flowchart documents all steps.

Data extraction

We developed and piloted a standardized extraction form containing: country/year; study design; sample size; sample characteristics (age, gender, H&Y stage, duration of PD);

cortisol measurement (matrix: saliva/serum/urine; time of collection; parameter: baseline, CAR, AUC, slope; method: ELISA/LC-MS; control of circadian factors/acute stressors); measurement of QoL (instrument/domains: PDQ-39 total and domains; PDQ-8; SF-36; WHOQOL-bref; EQ-5D); association statistics (r, β, OR, 95%CI, p-value) and adjustments for relevant confounders (age, gender, motor symptoms, anxiety/depression, sleep). When applicable, limitations reported by the authors were recorded.

Summary of the data

The findings were synthesized in a descriptive and tabular manner. We constructed an evidence map by crossing cortisol parameters and QoL instruments/domains, indicating the direction and significance of the reported associations. We did not perform a formal assessment of risk of bias or meta-analysis, according to the scope of the method. When studies showed substantial heterogeneity of measurement (e.g., collection times and circadian control), this was highlighted as a limitation of the body of evidence.

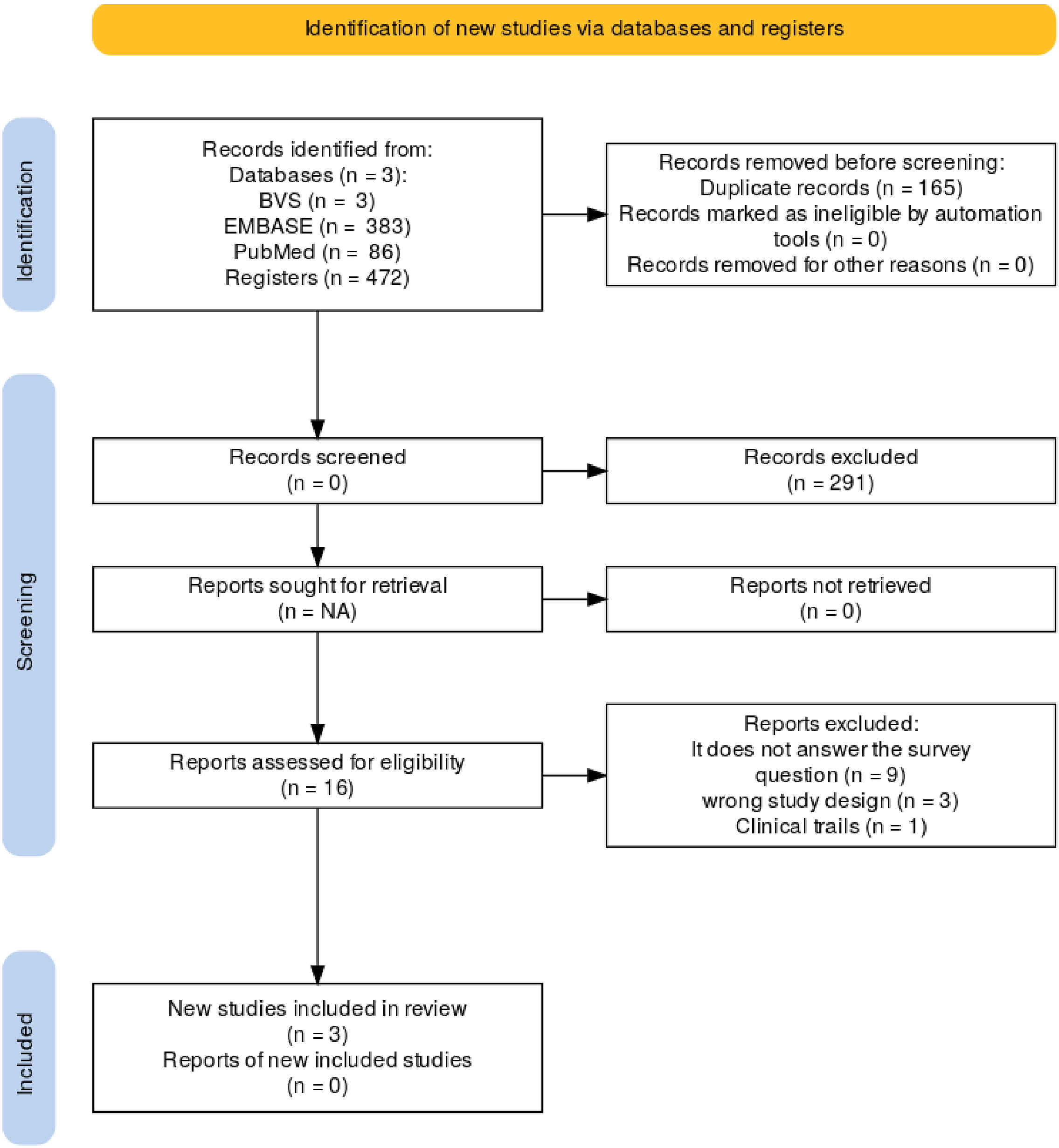
Ethical considerations

As this is a synthesis of published secondary data, ethical approval was not required. There was no specific funding for this review. Conflicts of interest will be declared by the authors.

Findings

We identified 472 articles from bibliographic databases (VHL, n=3; EMBASE, n=383; PubMed, n=86). After the removal of 165 duplicates, screening was carried out, culminating in the evaluation of 16 full-text reports for eligibility. Of these, 13 were excluded because they did not answer the research question (n=9), had an inadequate design (n=3) and clinical trials (n=1). In the end, 3 studies were included in the mapping (Figure 1).

Figure 1: Prism flowchart of the records and studies identified in the scoping review searches.



The studies included in the review (**Chart 1**) that explained the association between salivary cortisol measurements and quality of life (QoL) in people with Parkinson's Disease (PD) demonstrate consistent results and point to complex mechanisms involving non-motor symptoms, such as fatigue and anxiety, that impact this relationship.

The study of Deepa et al., (2022), conducted in India with 50 patients, showed that women with PD had significantly higher levels of salivary cortisol in the morning, which correlated with higher fatigue scores and worse quality of life index assessed by the PDQ-39. This association was especially marked in the physical and emotional domains of QoL, indicating that salivary cortisol, reflecting the activity of the hypothalamic-pituitary-adrenal (HPA) axis, may be a useful biomarker of subjective fatigue, the main non-motor symptom analyzed in this study. Methodological quality included standardized cortisol collection upon awakening and chemiluminescence analysis (ECLIA). The statistical analysis pointed out significant differences between genders and independence of motor severity measured by the Hoehn and Yahr scales, highlighting the clinical relevance of the gender-differentiated assessment.

Phillips et al., (2022) explored a triad composed of PD patients and their caregivers, in a pilot study in the USA. They measured salivary cortisol at multiple times throughout the day and analyzed the diurnal cortisol inclination, finding that patients had higher cortisol levels at sleep and flattened cortisol inclination during the day, associations linked to greater anxiety and poorer physical and mental quality of life (assessed by the SF-36). In addition, dyadic effects were evidenced, as the psychological stress of one member increased the daytime cortisol of the other, suggesting important inter-relational influences for clinical management. The findings reinforce that changes in the daily dynamics of cortisol reflect the impact of non-motor symptoms on the well-being and social functioning of patients.

The randomized and multicenter study of Kwok et al., (2025), in Hong Kong, evaluated the effect of non-pharmacological interventions (meditation and yoga) in 159 patients with PD, measuring plasma cortisol (not saliva), anxiety, motor symptoms, and quality of life (PDQ-8). Although significant improvements were observed in anxiety, motor symptoms, and quality of life in meditation and yoga interventions, there was no robust evidence of change in plasma cortisol in the periods evaluated. This fact suggests that cortisol variability may be more sensitive to collection parameters and biological matrix, in addition to responding differently to psychosocial interventions.

Frame 1: Included studies and data extraction fields from manuscripts.

Field	*Deepa et al. (2022)*	*Phillips et al. (2022)*	*Kwok et al. (2025)*
Study (year, country)	2022, India	2022, USA	2025, Hong Kong
Drawing / N	Transverse, N=50 (25M, 25F)	Pilot, diadico 18 pairs (36 persons)	RCT, 3 arms, N=159
Sample (age; H&Y or duration)	50-80 years; H&Y 1-3; mild to moderate stages	Average age ~63 years; H&Y II-III	64.8 years, H&Y 1-3
Salivary cortisol/time of collection	Morning sample, 5ml, before brushing	9 samples in 3 days: waking, 30min powder, bedtime	Plasma, collection between 2pm-4pm (non-salivary)
Salivary cortisol (Parameter)	Morning basal	Diurnal slope, mean cortisol, bedtime cortisol	Plasma cortisol

Salivary cortisol (Method)	ECLIA	Luminescent immunoassays	ELISA plasma
Quality of life (Instrument)	PDQ-39	SF-36	PDQ-8, HADS, FFMQ
Quality of life (items evaluated)	Total and 8 domains	Total, physical and mental	Total PDQ-8 and mindfulness domains
Association (metric: r/β/OR)	Correlation r, ANOVA, differences $p<0.05$	Actor-Partner Interdependence Models (APIM), t-tests	Linear mixed models, mean differences
Effect / p	Women with PD have ↑ cortisol and worse QoL	Patients with higher cortisol bedtime and lower QoL, $p<0.01$	Meditation and yoga improve QoL and symptoms $p<0.05$
Direction (↑/↓/ns)	Cortisol ↑ associated with QoL ↓ in women	Cortisol bedtime ↑ and QoL ↓ in patients	Plasma cortisol without significant change
Study completion (association?)	Salivary cortisol correlates with fatigue and QoL	Altered salivary cortisol reflects effects of stress and QoL	Interventions improve QoL, impact on cortisol not confirmed
Observations	Cross-sectional study, small, important gender	Dyads reveal crossover psychosocial effect, initial study	Large sample, longitudinal evaluation

Caption 1: N refers to the total number of study participants; H&Y is the Hoehn & Yahr scale to assess the stage of Parkinson's disease; CAR is the cortisol awakening response; AUC indicates the area under the curve, which represents an integrated measure of cortisol levels during the day; ELISA corresponds to Enzyme-Linked Immunosorbent Assay, a laboratory method for cortisol measurement; LC-MS is the Liquid Chromatography technique coupled to Mass Spectrometry used for biochemical analysis; ECLIA stands for Enhanced Chemiluminescence Immunoassay, an advanced method that uses chemiluminescence; PDQ-39 and PDQ-8 are specific questionnaires for assessing quality of life in Parkinson's; SF-36 is a generic instrument for assessing health-related quality of life; r represents the statistical correlation coefficient; β is the beta coefficient resulting from regression analyses; OR stands for odds ratio, or odds ratio in statistical analyses; p indicates the value of statistical significance used to assess the robustness of the results; the up (↑) and down (↓) arrows indicate, respectively, a positive or negative association between cortisol and quality of life; NS identified the absence of a statistically significant association.

DISCUSSION

This scoping review presents a systematic survey of the available evidence on the association between cortisol and quality of life in patients with Parkinson's disease. By bringing together original studies that evaluated these variables together, the review offers an updated and organized view of the theme, contemplating biological and psychosocial aspects relevant to the understanding of this relationship.

Some methodological and clinical dimensions are evidenced by studies to explain the findings on salivary cortisol and quality of life in PD. These studies indicate that the collection of cortisol samples at specific times, upon waking up, 30 minutes after waking up (CAR) and at bedtime, for example, is decisive for capturing the diurnal profile of the hormone, whose alteration is related to non-motor symptoms of PD, such as anxiety and fatigue, negatively impacting quality of life (Deepa et al., 2022; Phillips et al., 2022). This temporal variation in cortisol requires standardized protocols to avoid bias, such as guidelines for patients to avoid eating, brushing their teeth, or being exposed to stress before collection, which can alter the result (Deepa et al., 2022).

Laboratory methods, such as ELISA, ECLIA, and LC-MS, had different sensitivities, influencing the accuracy of the data and making it difficult to compare studies. In addition, the parameters analyzed, such as baseline levels, CAR, AUC, and diurnal tilt, reflect distinct aspects of HPA axis function and bring complementary contributions to the interpretation of the data (Phillips et al., 2022; Kwok et al., 2025).

The mapped studies demonstrate that the association between cortisol and quality of life in patients with Parkinson's Disease mainly addresses non-motor aspects, highlighting the relevance of these symptoms for the well-being of patients. This finding highlights the complexity of the biological and psychosocial interactions involved and suggests that the motor components may be less related to variations in cortisol levels or still little explored in the current literature. However, it is important to note that none of the studies performed an isolated analysis of each domain of quality of life, separating motor from non-motor aspects, which limits the detailed understanding of the specific influence of cortisol on each dimension.

Clinical aspects such as the stage of the disease, as measured by the Hoehn & Yahr scale, and sociodemographic factors, especially gender, modulate cortisol levels and the severity of non-motor symptoms, with women having higher cortisol levels and poorer quality of life (Deepa et al., 2022). Another relevant point refers to psychosocial relationships, especially the role of the caregiver, who modulates the patient's stress response and vice versa, evidencing the complexity of interactions in the context of PD (Phillips et al., 2022).

It is important to highlight cortisol as a potential biomarker for monitoring non-motor symptoms in PD, given the significant impact of these symptoms on the quality of life of patients. Considering that non-motor symptoms, such as anxiety, depression, sleep disturbances, and fatigue, are prevalent and often underdiagnosed, the use of cortisol can offer a useful objective indicator for clinical evaluation and therapeutic follow-up. In addition, the psychosocial interaction between patient and caregiver evidences a dynamic dimension that influences both the response to stress and the results in quality of life, reinforcing the importance of interventions that consider these relationships to optimize the management of the disease. Thus, integrating biological assessments with psychosocial aspects can provide more effective strategies to improve the care and well-being of Parkinson's patients.

This study has some important limitations that should be considered in interpreting the results. First, the methodological heterogeneity of the included studies, especially in relation to the methods and times of collection of cortisol samples, as well as the instruments used to assess quality of life, makes it difficult to directly compare and generalize the findings. In addition, the small number of studies that have specifically investigated the association between cortisol and quality of life in people with Parkinson's disease limits the robustness and scope of the conclusions. The absence of a formal assessment of the risk of bias in the selected studies is also noteworthy, which compromises the evaluation of the reliability of the evidence presented. Another relevant point is the diversity of sample characteristics, including different stages of the disease and demographic variability, which can influence the results and their applicability. These limitations underscore the need for future studies with greater methodological standardization and larger sample sizes to provide more consistent evidence on this association.

CONCLUSION

In view of the above, it is concluded that this mapping carried out in this review evidenced important aspects in the relationship between cortisol and quality of life in patients with Parkinson's Disease, even with a limited number of studies that specifically addressed this association as a biological marker. It was observed that, despite the scarcity of evidence, there is consistency in the presence of modulating factors, such as demographic variations and psychosocial influences, which contribute to the complexity of the phenomenon. These findings highlight gaps and methodological challenges that need to be overcome, indicating the need for standardization of cortisol collection and analysis methods, as well as more systematic assessments of quality of life, to advance the understanding and clinical application of these findings.

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