

**ANALYZING THE CASUAL RELATIONSHIP BETWEEN PHYSIOLOGICAL
BIOMARKERS AND SCALES IN ASSESSING
PARKINSON'S DISEASE-RELATED - FATIGUE:AN ATTEMPT TO OPTIMIZE
THE EXERCISE STRATEGY.**

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Abstract:

Parkinson's Disease is the commonest neurodegenerative disease secondary to Alzheimer's disease, it has taken a pattern of a pandemic affecting cross countries, religions, cultures, and ethnicity. 150 years since its emergence in the medical diagnosis India has been the 13th country to be a contributor to the global publication output in PD among 15 competing countries. 2013 fatigue was reported to be most disabling in the World Parkinson's Congress by the patients who participated in the conference. With the increasing industrialization, aging, and smoking cessation the review article strongly raises the need to do extensive in-depth research on the objective assessment tools like salivary biomarkers as cortisol which can be a benchmark of prognosis for the interventions applied. There is a need for a robust protocol for treating fatigue and it is believed that targeting fatigue as a separate element from the initial stages would reduce the severity of the disease, improving the quality of life of the patients and their caregiver also with a reduction on the financial aspects which has led to increased drops from the therapy sessions.

Introduction:

With motor and non-motor symptoms dominating the disease severity, leading to functional dependence and reduced quality of life^(1,2). Studies show variations in the symptoms, pathophysiology, diagnosis, and intervention among patients with Parkinson's Disease thus leading to very low-quality evidence studies on intervention and managing these symptoms and disability. Parkinson's disease has been emerging as a pandemic due to an increase in life

expectancy, industrialization, and use of chemicals, pesticides it is now the second most common neurological disease globally with a prevalence rate high in china and the USA^(3,4,5).

Globally in 2016, 6.1 million individuals were diagnosed with Parkinson's Disease, the Disability-adjusted life years were 3.2 million, also causing 211296 deaths⁽⁶⁾. Among 580 million elderly population 60% developing countries and 22% in India and the fact that 80 % live in rural India. Bangalore in south Karnataka in 2004 reported to have 33 per 100,000, 2006 in Kolkata 45.82 per 100,000, in Kashmir prevalence was 14.1 per 100,000, Parsi community in Mumbai reported to have 192 per 100,000. A study in south-central India, Warangal, Telangana, between 2004 – 2015 showed 28% from urban, 10 % semi-urban, and 12 % from tribal areas. The first article assessing fatigue was published in 1993 and the first mention about fatigue as an independent symptom was in 1967. The Journal of Neurology in 2013 was the first study to describe the clinical determinants and psychosocial factors associated with fatigue^(5,6,7,8).

India, Mumbai Parsi community have reported having a greater number of cases. With the disease history showing 150 years of documentation yet there is numerous research gap that has created a distance to the road of recovery. With which the patients are leading their life in an utmost compromised situation related to balance, locomotion, postural control, engaging in social activities. Patients have reported being more confined to home rather than in community due to barriers and stigma associated^(5,9, 10). With disease in its early stages the most commonly reported but unattended element among the non-motor symptoms is fatigue. Though fatigue has been a recently common area of interest still studies have shown a very low number of articles providing a gold standard protocol of treating patients with idiopathic Parkinson's disease^(11, 12).

An in-depth literature, survey fatigue shows a strong magnitude of interrelationship with motor and other non-motor symptoms. Paucity in movement, immobility, speech difficulties, tremor, postural instability, frequent fall and injury, cognitive impairment, difficulty attention, depression, sleep disorder are few mentions major symptoms related to fatigue or vice versa^(13,14). Hence, optimizing the physical therapy intervention to alter the fatigue with more objective measurements at the molecular and neural level, can give us more scope in managing the disease course and allowing the patients with a more improved quality of life and less strain on the caregiver. Research is failing to fill this gap even though studies are pointing at its management, whilst the speed at which the disease is progressively making patients vulnerable to frequent hospitalizations leading increase financial strain on the family⁽¹⁵⁾.

Fatigue is a complication symptom with a lack of proper definition which makes it inefficient in measuring accurately and mostly is dependent on the subjective information provided by the patients. Fatigue has been associated with depression, anxiety, mood disorders, and sleep. 35% to 75% of Parkinson's disease patients experience fatigue^(5, 9, 10, 12).

Diagnostic criteria: -

With unknown pathophysiology, there is no standardized diagnosis for fatigue. But an attempt by the Parkinson's disease foundation developed a case definition of Parkinson's disease-related fatigue with Diagnostic and statistical manual IV⁽¹⁶⁾. The core concept of the definition "is a daily or near-daily feeling of significantly diminished energy or an increased perception of effort disproportionate to attempted activities or general activity level"⁽¹⁶⁾. The patient should experience at least 4 out of 9 symptoms mentioned in the criteria sections. Though they are not validated they still find a place in recognizing the debilitating symptom called fatigue⁽¹⁷⁾.

Scales: -

The movement disorder society task force on rating scales for Parkinson's disease conducted a critical review of existing scales for fatigue in 2010^(17,18). 9 scales as fatigue severity scale (FSS)^(19,20,21), The fatigue Assessment Inventory (FAI), Functional assessment of chronic Illness Therapy – the fatigue scale (FACIT-F), The multidimensional fatigue inventory (MFI), The Parkinson's fatigue scale (PFS), the Fatigue Severity Inventory (FSI), Fatigue impact scale for daily use (D- FIS) Visual analog scale (VAS), Clinical global impression scale (CGIS) was rated as recommended, suggested or listed. The FSS scale was rated as recommend for both diagnostic screening and severity of measurement, The MFI was recommended for the severity of measurement but for not diagnosing, FACIT- F, and PFS both were recommended for diagnostic screening but not for measuring the severity, others did not get a recommendation category in either of the criteria proposed during the critical evaluation^(14, 18,22).

These scales could only objectify the subjective fatigue from the perception of the patients in Parkinson's disease. Such quantification is of utmost importance even in the Indian rural population suffering from Parkinson's disease where language, illiteracy, medical facilities are still a barrier. For such a population whose understanding about fatigue related to Parkinson's disease is varied, the physiological and biochemical biomarkers can make a major decision in the prognosis of functional activities, quality of life and also improve the exercise strategies that are directed towards more standardization⁽²²⁾.

Assessing Fatigue: -

The physiological biomarkers reflect the deterioration of the functional systems related to performance, systems associated with the perception of effort and fatigue⁽²²⁾.

Physical measurements: - As the activation levels of maximum voluntary contraction are low, the total amount of fatigue can be quantified by fatigue index which is the ratio of maximum voluntary contraction (MVC) force before versus after fatigue-inducing exercise. This maximum voluntary contraction (MVC) force is displayed on the oscilloscope for feedback. The voluntary activation level and twitch forces were measured using interpolated twitch test, the muscle was stimulated with 200us.

Fatigue Index, as general fatigue Index was calculated as post fatigue maximum voluntary contraction(MVC) to pre-fatigue maximum voluntary contraction (MVC)⁽²⁴⁾. The central fatigue was calculated as the ratio of post-fatigue Voluntary Activation to pre-fatigue Voluntary activation. The peripheral fatigue was calculated as the ratio of post-fatigue twitch force to pre-fatigue twitch force, and values between 0 and 1 indicate fatigue. The limitations of such assessments are confined to a laboratory setup and cannot be a part of assessing the prognosis.

Fatigue biomarker Index: - Is another method found by the Hyperion biotechnology lab, can be considered while performing research clinical trials. The fatigue changes the composition of small molecular weight proteome saliva during a 10-hr session of moderate exertion. This was done on recreationally trained cyclists. The analysis was done using reversed-phase liquid chromatography with mass- spectrometric detection. This study reports being objective salivary measurement. But its higher cost, range of age, interference of other factors affecting fatigue peptides, a laboratory with an advanced level of technology that supports the equipment makes its application limited⁽²⁶⁾.

Physiological measurements: -Cortisol salivary samples can be collected early morning and stored at -20°C . The cortisol levels were higher in the morning and lowered down in the latter part of the day. The increase in cortisol levels has been related to the impulsive compulsive disorder. The salivary cortisol measurement is an excellent indicator of plasma-free cortisol concentration which assesses the Pituitary–Adrenal function, this pathway the Hypothalamic–Pituitary – Adrenal axis is dysfunctional in Parkinson's Disease-causing fatigue symptoms^(23,24).

During stress, the Hypothalamic – Pituitary axis responds by stimulating the production of adrenocorticotrophic hormones which release cortisol in the blood, where it's bound to carriers, and 1-15% of cortisol being free and biologically active. The circulating salivary cortisol also reflects the cortisol in the blood more than 80%. It has its limitations of not completely reflecting the total plasma cortisol levels, nicotine, alcohol, influence the cortisol levels⁽²⁴⁾.

A study was conducted on 101 normal adults, 18 patients with Cushing syndrome, and 21 patients with adrenal insufficiency which indicated that salivary cortisol measurement is a practical approach to assess Pituitary–Adrenal functions. The measurement offers the advantages as no endogenous binding protein, no temperature-dependent, avoiding physiological, pathological, and pharmacological corticosteroid-binding protein (CBG), ease of sampling, it allows multiple samples at home, no needle stick injuries^(25,26,27,28).

In another study which included 111 subjects diagnosed with Parkinson's Disease, patients underwent screening with MDS - UPDRS, FSS, FAS score with serum cortisol measurement, the results concluded that cortisol has a linear predictor effect for fatigue, it promises a significant biomarker for non-motor symptoms. Traditional markers of fatigue like Interleukin – 6 levels in blood a good indicator of fatigue in breast cancer, CD26 has been used to diagnose chronic fatigue syndrome or fibromyalgia, the procedures cause discomfort, have limitations of drawing the blood from the patients and need healthcare professional^(29,30,31).

The interventions are targeted more towards motor symptoms and less with non-motor symptoms like sleep, anxiety, cognitive impairment

Conclusion:

With the difference in male and female fatigue levels, the biomarker cortisol can be a very feasible element in understanding fatigue levels and their response to exercise. It can be used as a method of objective assessment. In-depth research and the intervention may prove to be of future robust rehabilitation protocol for the patients with fatigue-related - Idiopathic Parkinson's disease. The non-motor symptoms have become the major prognostic factors determining the overall disease burden and everyday function, which cannot be ignored. Many authors have researched anxiety, stress, Cushing syndrome, fibromyalgia but research on fatigue related to Parkinson's Disease is yet to be established. With variation in definition, pathophysiology, clinical sign, and symptoms, inability to identify fatigue in novice diagnosed Parkinson's Disease have sped the disease progression and clinical trials are yet under argument for the "highly acceptable" or "highly recommended" objective assessment and a robust intervention targeting only fatigue and its severity in the initial subclinical phase of the disease.

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