BASKENT UNIVERSİTY STUDY PROTOCOL

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PROJECT TITLE: Comparison of Frailty, Physical Fitness Parameters, and Irisin Levels Between Patients with Multiple Sclerosis and Healthy Volunteers

INTRODUCTION AND GENERAL INFORMATION

Multiple Sclerosis (MS) is a chronic, immune-mediated, inflammatory, and neurodegenerative disorder of the central nervous system (CNS), characterized by demyelination and axonal degeneration. The pathological process leads to focal plaques and lesions resulting from inflammation and axonal loss. MS predominantly affects the white matter of the brain, spinal cord, and optic nerves, although gray matter structures, including the cerebral cortex, may also be involved. Disease onset typically occurs between 20 and 40 years of age, and women are affected approximately two to three times more frequently than men. Globally, both the incidence and prevalence of MS have increased in recent decades. This rise is largely attributed to advances in neuroimaging and diagnostic criteria, improved treatment strategies that prolong survival, and more accurate case ascertainment.

Frailty is a significant and increasingly recognized clinical concern in individuals with MS. It is defined as a state of reduced physiological reserve and increased vulnerability to stressors, resulting in impaired ability to maintain homeostasis. Frailty is characterized by weakness, reduced stress tolerance, impaired adaptive capacity, and heightened sensitivity to adverse events. It is a multidimensional construct encompassing physical, cognitive, psychological, social, and environmental domains. Physical frailty is commonly identified by clinical features such as fatigue or exhaustion, unintentional weight loss, decreased physical activity, slowed gait speed, and reduced muscle strength.

Frailty is more prevalent among individuals with MS who have higher levels of disability; however, it is also observed in patients with low scores on the Expanded Disability Status Scale (EDSS), indicating that factors beyond neurological disability contribute to its development. Comparative studies have demonstrated that frailty levels are significantly higher in individuals with MS compared to healthy controls. Furthermore, the Frailty Index has been shown to correlate significantly with EDSS scores, comorbid conditions, educational level, disease duration, and quality of life. Importantly, frailty has also been independently associated with fall history, regardless of age, sex, or disease severity.

A recent systematic analysis published in 2024 examined studies evaluating the prevalence and clinical implications of frailty in MS. Reported prevalence rates ranged from 17% to 66% among outpatient populations. Evidence suggests that frailty develops earlier in individuals with MS compared to the general population. Higher disability levels, longer disease duration, and progressive MS phenotypes are consistently associated with increased frailty risk. Additionally, frailty has been strongly linked to reduced walking performance, poor sleep quality, fatigue, diminished quality of life, increased fall risk, greater healthcare utilization, and mortality. Notably, frailty and disability demonstrate distinct associations with gait parameters, highlighting the need for targeted rehabilitation strategies. Overall, frailty represents a common

yet under-investigated clinical issue in MS, and a better understanding of its mechanisms is essential for early identification and intervention.

Irisin is a 112–amino acid polypeptide hormone first identified in 2012. It is released from skeletal muscle during exercise and plays a role in energy metabolism by promoting the browning of white adipose tissue, thereby increasing energy expenditure. Exercise-induced muscle contraction elevates intracellular calcium (Ca^{2+}) levels, which stimulates AMP-activated protein kinase (AMPK) phosphorylation. This activation triggers irisin production through the AMPK–PGC-1α–FNDC5 signaling pathway. Circulating irisin levels have therefore been proposed as a biomarker of muscle mass and physical performance. Reduced irisin concentrations have been observed in individuals with sarcopenia and pre-sarcopenia compared to non-sarcopenic controls.

The aim of the present study is to investigate the relationship between frailty, physical fitness parameters, and circulating irisin levels in patients with multiple sclerosis.

MATERIAL AND METHOD

Research Type: Designed as a randomized controlled study.

Research Sample: Patients aged 18-65 diagnosed with MS who applied to the Başkent University Alanya Hospital Center Physical Medicine and Rehabilitation outpatient clinic between April 1, 2026, and May 30 2026, and healthy volunteers aged 18-65 years with similar demographic characteristics (age, gender, etc.) will be included.

(Note: Please check the dates in the original text, as 08.2025 to 02.2025 suggests a chronological discrepancy).

Inclusion Criteria:

- Patients aged 18-65 evaluated by neurology and diagnosed with definitive MS via objective methods (MRI, lumbar puncture, etc.).
- Healthy volunteers aged 18-65.
- Being literate in Turkish.
- Participants who provide a consent form to participate in the study.

Exclusion Criteria:

- Being younger than 18 or older than 65.
- Presence of any concomitant neurological disease other than MS.
- Presence of an uncontrolled systemic disease at a level that would affect the evaluation.
- Presence of cognitive impairment or psychiatric illness at a level that would affect the evaluation.
- Having had an MS attack or received steroid treatment in the last month.
- Presence of an orthopedic disability that prevents evaluations.
- Patients and healthy volunteers who do not agree to sign the informed consent form.

Evaluation of Participants:
Demographic data (age, gender, height, weight, occupation, education level, BMI, marital status, disease duration, MS type) will be collected. All participants will be evaluated by an experienced physiatrist using the **Functional Independence Measure (FIM)**, **Frailty Index**, **Berg Balance Scale**, **6-Minute Walk Test**, and **Jamar hand dynamometer** for handgrip strength.
Additionally, blood samples will be taken from all participants at 10:00 AM during the evaluation to measure irisin levels using the **ELISA method**.

Assessment Tools:

 Functional Independence Measure (FIM):

The **Functional Independence Measure (FIM)** is a standardized assessment tool developed in the 1980s by the Uniform Data System for Medical Rehabilitation to evaluate a patient's level of disability and functional independence, particularly in rehabilitation settings. It assesses 18 items across six domains: self-care (eating, grooming, bathing, dressing, toileting), sphincter control (bladder and bowel management), transfers (bed, chair, toilet, tub/shower), locomotion (walking or wheelchair use and stairs), communication (comprehension and expression), and social cognition (social interaction, problem-solving, memory). Each item is scored on a 7-point scale, where 7 indicates complete independence, 6 modified independence (use of device or extra time), 5 supervision or setup, 4 minimal assistance (patient performs 75% or more of the task), 3 moderate assistance (50–74%), 2 maximal assistance (25–49%), and 1 total assistance (less than 25% effort or requires two helpers). The total FIM score ranges from 18 (complete dependence) to 126 (full independence), with higher scores reflecting greater functional ability. It is widely used in inpatient rehabilitation to track patient progress, guide treatment planning, and estimate the level of care required after discharge.

 Fraility index

The **Frailty Index (FI)** is a quantitative measure of frailty based on the concept of "accumulated deficits," first developed by researchers including Kenneth Rockwood and Arnold Mitnitski. It reflects the proportion of health deficits an individual has out of a defined total number assessed. Deficits can include symptoms, diseases, disabilities, cognitive impairments, abnormal laboratory values, or functional limitations, typically numbering 30–70 variables. Each deficit is scored as 0 (absent) or 1 (present), though intermediate values (e.g., 0.5) may be used for partial impairment. The Frailty Index is calculated by dividing the number of deficits present by the total number measured (e.g., 10 deficits out of 40 variables = FI of 0.25). Scores range from 0 to 1, with higher values indicating greater frailty; commonly, <0.10 suggests robustness, 0.10–0.24 mild frailty, 0.25–0.39 moderate frailty, and ≥ 0.40 severe frailty. The FI is widely used in geriatric medicine and research to predict adverse outcomes such as falls, hospitalization, disability, and mortality. In this study 30 variables were included for FI calculation according to Searle et al.'s study. ( )

 6-Minute Walk Test:

Measures functional walking capacity and endurance. It is a simple, practical, and widely used functional exercise test that measures the distance an individual can walk on a flat, hard surface in six minutes. It is designed to assess **submaximal aerobic capacity and endurance**, reflecting daily activity performance rather than maximal exercise capacity. The test is commonly used in patients with cardiovascular, pulmonary, or musculoskeletal conditions, as well as in older adults and those undergoing rehabilitation. Standardized protocols recommend a 30-meter corridor, with patients instructed to walk as far as possible in six minutes at a self-paced speed, allowing rests if needed. The **primary outcome** is the total distance walked (6-minute walk distance, 6MWD), often compared to reference values based on age, sex, height, and weight.

- BERG Balance Scale:

The Berg Balance Scale (BBS) is a widely used clinical tool designed to assess balance and risk of falls in adults, especially older adults and individuals with neurological or musculoskeletal impairments. Developed by Katherine Berg in 1989, the BBS evaluates a person's ability to maintain balance during static and dynamic tasks through 14 functional activities, including sitting to standing, standing unsupported, reaching forward, turning, retrieving objects from the floor, and standing on one foot. Each task is scored on a 5-point scale (0–4), where 0 indicates the lowest level of function and 4 reflects independent and safe performance. The maximum total score is 56, with higher scores indicating better balance. Commonly used cutoffs suggest that a score below 45 may indicate increased fall risk, while lower scores correlate with greater functional impairment.

STATISTICAL EVALUATION

"Student's t-Test" will be used to compare two independent groups if parametric assumptions are met; otherwise, the "Mann Whitney U Test" will be used. Relationships between qualitative variables will be examined with "Chi-Square" or "Fisher's Exact Test." Relationships between quantitative variables will be investigated with Pearson or Spearman Correlation tests. The Type I error probability will be taken as $\alpha=0.05$.

Sample size: Calculated using G*Power 3.1.9.4. To provide 95% power at a 95% confidence level with an effect size of $d=0.84$, a total of 76 individuals (39 per group) must be included (18).

RESEARCH HYPOTHESES

- Although MS patients consist of a young population, frailty is detected more frequently in this group compared to healthy volunteers.
- Irisin levels are significantly lower in participants where frailty is detected.

KEY WORDS: biomarker, functional performance, physical fitness, multiple sclerosis, muscle weakness,