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Message of the President of the P.S.F.

Dear colleagues,

The scientific journal "Physiotherapy", which is an official publication of the Panhellenic Association of Physiotherapists, has comleted more than half a century of uninterrupted presence. Since 1975 it has been a place for scientific dialogue, documentation and the dissemination of knowledge, while recording the evolution of physiotherapy in our country.

The Central Board of Directors of the P.S.F., holding the editorial and publishing responsibility, proceeded with renewal of the composition of the Scientific/Editorial Committee of the journal.

It is with great pleasure that we welcome the new Scientific Director, Dr. George A. Koumantakis, as well as all the members of the new Scientific/Editorial Committee. We congratulate them on taking up their duties and wish them a creative and productive term. The new composition, with the participation of scientists from different academic institutions both in Greece and abroad, creates the conditions for a diverse, extroverted and modern publishing career. We are confident that their scientific training and experience will further enhance the journal's quality, credibility, and international presence.

- This renewal marks a new period, with the main objectives being:
- The scientific and methodological integrity of the published papers
- The timely and constructive evaluation of the submitted articles
- Encouraging young researchers and clinical physiotherapists
- Connecting of scientific research with everyday clinical practice
- International extroversion and the gradual upgrading of the journal's awareness, as well as maintaining free access to scientific knowledge.

At the same time, we recognize and honor the contribution of all the Scientific Directors and members of the Committees who served the journal during its long history and contributed to the maintenance of its uninterrupted publishing presence.

We call on all members of the P.S.F., academics, researchers, young scientists and, especially, colleagues in clinical practice to actively support this new effort. To study and utilize the published scientific work, to participate in the scientific dialogue and to submit their own papers, contributing to the production and dissemination of modern physiotherapeutic knowledge.

The journal "Physiotherapy" belongs to the scientific community of Greek physiotherapists. Its empowerment and development are a shared responsibility and a significant investment in the scientific prestige, professional development and future of physiotherapy in our country.

On behalf of the Central Board of Directors, I wish the new Scientific Director and the members of the Scientific/Editorial Committee every success in their work.

Petros Lymperidis
President of the Panhellenic Physiotherapists' Association

Φysikotherapia

Editorial

A new Editorial Board and a volume on measurement, mechanisms and prevention

The Journal 'Φysikotherapia' has been published without interruption since 1975. To assume its editorial direction, as this Board did in April 2025, is therefore to inherit half a century of continuous publication in Greek physiotherapy — a responsibility we take up with respect for those who preceded us, and with clear targets for the future.

The Editorial Board draws on the Departments of Physiotherapy of Athens, Lamia, Patras and Canada. This composition is deliberate. A national journal serves its profession best when it is neither confined to a single institution nor detached from international standards.

Our aims are straightforward: peer review that is constructive and timely, particularly for authors early in their careers, methodological rigour without gatekeeping, and continued open access, so that what appears here reaches the clinicians for whom it is written.

The three papers in the present volume come from different fields, yet converge on a common question: how do we measure movement, and what exactly changes when we intervene with it.

Papakosta and Lampropoulou (University of Patras) examine how kinetic and kinematic measures of balance and gait relate to the functional scales used daily in Parkinson's disease. The correlations they report are largely moderate — and that is precisely the finding. Instrumented analysis and clinical scales are complementary rather than interchangeable; choosing between them is a matter of disease stage and clinical question, not of technological preference.

Galanopoulos and Kalyviotis (EKA) review the effect of physical activity on bone metabolism in children and adolescents, and locate the window of greatest opportunity before puberty. Their candid handling of the discordant evidence — a transient rise in fracture risk during the first year of intervention, trials finding no effect at all — is exactly what a narrative review should do. The clinical implication extends well beyond paediatrics: exercise in childhood acts as a deposit against fracture decades later.

Mitsiou and colleagues (UNIWA, "Evangelismos" Hospital, NKUA) show that a single session of aerobic exercise mobilises endothelial and haematopoietic progenitor cells and alters microcirculation in patients with chronic heart failure. Small and acute-phase though the study may be, it considers exercise as a biological agent with a traceable mechanism, not merely as a functional intervention.

Collectively, the volume moves from cell (endothelial progenitor cells mobilization), through adaptation in growing bone, to the balance and gait of the person as a whole. The therapeutic tool remains the same at every level; what changes is the resolution at which we observe it.

An invitation to contribute

We invite physiotherapists, and colleagues from allied sciences, to submit their work. Original research, systematic and narrative reviews, and case studies are all welcome, prepared in accordance with the journal's Guidelines for Authors (journal.psf.org.gr). We particularly encourage postgraduate students, doctoral candidates and clinicians, whose findings are useful to highlight.

George A. Koumantakis, PhD, MSc, PT
Editor-in-Chief, on behalf of the Editorial Board

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Associations between Kinetic and Kinematic Parameters and Functional Assessment Methods of Balance and Gait in Parkinson's Disease: A Critical Literature Review

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ABSTRACT

Aim: The present study aims to elucidate the degree to which objective modalities of balance and gait assessment, including kinetic and kinematic analyses, correlate with the functional rating scales routinely employed in clinical practice for the evaluation of patients with PD.

Methods: The present study constitutes a narrative critical review of the literature and does not adhere to a formal PRISMA protocol. Electronic searches were conducted in the PubMed, ScienceDirect, and Google Scholar databases using the keywords "Parkinson's disease", "balance", "gait", "motion analysis", "force platform", "Vicon system" and "functional assessments". Articles published between 2015 and 2025 were considered eligible, provided that they focused on high-precision methods, such as kinetic and kinematic evaluations of postural control and gait in patients with PD, as well as studies that examined the quantitative associations of these measures with functional scales (mini-BESTest, BBS, FGA).

Results: A moderate correlation was observed between kinetic and kinematic parameters and the BBS (r = -0.55), while kinematic parameters recorded via inertial measurement units (IMU's) also demonstrated moderate correlations with the UPDRS (r = – 0.5). Furthermore, the FGA demonstrated a strong correlation with gait speed (r = 0.77) and a moderate correlation with step length (r = 0.54 – 0.59), while an FGA score of ≤ 18 predicted falls within a six-month period (ICC= 0.81).

Conclusions: The integrative application of objective metrics and clinical assessment tools affords a multidimensional and more precise characterization of functional capacity in patients with PD. In early stages (H&Y 1-2), IMU's and force platforms detect subtle deviations, whereas in intermediate and advanced stages, the combined deployment of mini-BESTest/FGA alongside objective measurements is recommended for the timely prevention of falls.

Keywords: Parkinson's disease, gait, balance, functional assessments, motion analysis

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INTRODUCTION

Parkinson's disease (PD) is characterized by a variety of motor disturbances, including impairments in balance and gait, which lead to a markedly increased risk of falls (Bao et al., 2023). It is estimated that approximately 60% of individuals with PD will experience at least one fall, an event directly associated with injury, reduced mobility, and a decline in quality of life (Sotirakis et al., 2024). Consequently, accurate and comprehensive assessment of balance and gait patterns is essential both for fall prevention

and for monitoring disease progression (Bao et al., 2023).

Assessment of static and dynamic balance in patients with PD is typically conducted through clinical methods and standardized tests. Instruments such as the Berg Balance Scale (BBS), the mini-Balance Evaluation Systems Test (mini-BESTest), the Functional Gait Assessment (FGA), and the Timed Up and Go (TUG) test are widely employed to evaluate static and dynamic balance, as well as gait, in patients with PD. (Winser et al., 2019). Although these scales have been established as reliable and valid measures in PD (Bao et al., 2023), the subjective nature of examiner observation and their confinement to controlled laboratory or clinical settings undermine their external validity (Atrsaei et al., 2021). For instance, gait speed during daily activities has been shown to be up to 30% lower than speeds measured in a clinical assessment (Atrsaei et al., 2021). Moreover, functional scales often feature a limited scoring range (e.g. 0-4 or 0-56 points), resulting in ceiling and floor effects. For example, many patients in the early stages of PD obtain the maximum score on the BBS, thereby concealing subtle balance deficits (King et al., 2012). Likewise, 89% of patients with mild symptomatology are rated 0-1 (no/slight impairment) in the gait item of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS), a scale internationally used for assessing disease severity and progression. Nevertheless, measurable gait deviations are recorded which the scale fails to detect (Hill et al., 2021).

With advances in technology, high-precision laboratory methods have been developed for the assessment of balance and gait, such as force platforms for analyzing Center of Pressure (CoP) displacements and wearable inertial measurement units (IMUs) for kinematic gait analysis (Horak et al., 2013). These techniques offer high – resolution quantitative measurements (e.g. centimeter – level accuracy) (Merlo et al., 2025). Studies have demonstrated that quantitative biomechanical parameters can detect balance impairments in the early stages of PD, before they become clinically apparent (Atrsaei et al., 2021; Bao et al., 2023). Specifically, pathological alterations in CoP variability during quiet standing have been documented in early PD, even prior to the emergence of overt symptoms (Taghizadeh et al., 2018). In contrast, conventional clinical tests typically only reveal deficits once they have progressed to a level that visibly impacts functional performance (Wodarski et al., 2023).

The correlation between these sensitive and high-precision assessment methods and functional recording data represents a major scientific concern. By examining this relationship, we can determine the extent to which clinical methods capture (or omit) critical aspects of balance and gait (Wodarski et al., 2023). At the same time, such analysis highlights the shortcomings of clinical tools with respect to the completeness and precision of the information they provide (Merlo et al., 2025). The present review evaluated the latest empirical findings that explore these dimensions in patients with PD.

The aim of the present study was to examine the extent to which objective and high-precision assessment methods for balance and gait, such as kinetic and kinematic analyses and data from specialized recording systems correlate with the functional scales employed in the evaluation of patients with PD. This work seeks to critically delineate the strengths and limitations of clinical instruments in terms of their accuracy and comprehensiveness in capturing the corresponding measurable parameters.

METHODS

The present study adopts a narrative critical literature-review approach, without formal application of a PRISMA protocol, and involves a targeted search of the PubMed, ScienceDirect and Google Scholar databases. English-language keywords («Parkinson disease», «balance», «gait», «motion analysis», «force platform», «Vicon system», «functional assessments»), were used to identify relevant publications from 2015 through 2025. Included articles investi-

gated objective methods for assessing balance and gait in patients with PD, such as three – dimensional kinematic analysis (e.g. Vicon system), indirect force measurement systems (e.g. force platforms), or wearable inertial measurements units (IMUs), as well as studies that investigated the quantitative associations of these objective, high-precision measurements with established functional scales (e.g. mini-BESTest, BBS, FGA). All sources were drawn from peer-reviewed, English-language journals to ensure scientific rigor. Although a full systematic review was not conducted, a careful selection of representative studies spanning the main technological categories and featuring quantitative comparative analyses was performed to guarantee the validity and relevance of the literature synthesis.

RESULTS

High-precision and objective balance assessment versus clinical tests

Patients with Parkinson's disease (PD) frequently exhibit balance impairments, which are clinically evaluated using instruments such as the Berg Balance Scale (BBS), the single-leg stance test, the mini Balance Evaluation Systems Test (mini-BESTest) and the MDS-UPDRS Pull Test (Liu et al., 2020). By contrast, objective and high-precision assessment employs force platforms, which record Center of Pressure (CoP) excursions and ground reaction forces (GRF), and inertial measurement units (IMUs) that capture three-axis accelerations and angular velocities, thereby enabling precise quantification of both static sway and gait kinematics (King et al., 2012; Álvarez et al., 2020). Recent evidence demonstrates that while correlations between selected parameters from these objective and clinical methods are statistically significant, they tend to be moderate in strength (Bao et al., 2023; King et al., 2012; Picardi et al., 2020).

Specifically, the study by Bao et al. (2023), involving 46 patients with mild-moderate PD (H&Y 1-2), compared Berg Balance Scale (BBS) scores with stabilometric CoP indices during quiet standing under eyes - open and eyes - closed conditions on a force platform. The 95% prediction ellipse area of the CoP was negatively correlated with BBS ($r = –0.55$, $p = 0.001$), while the high – frequency slope of the sway power spectrum, reflecting rapid corrective adjustments, showed a moderate positive correlation with BBS ($r \approx 0.48$, $p = 0.001$). Structural metrics, such as the intersection point in the sway scatterplot, also exhibited moderate positive correlations ($r \approx$ 0.40–0,50, $p \leq 0.01$).These findings indicate that the BBS explains only about 25% of the total variance in laboratory-derived measures, with clear clinical implications: although the functional scale broadly reflects balance ability, it fails to detect subclinical instabilities revealed by objective metrics, potentially delaying intervention and increasing fall risk. Similar results were reported by Liu et al. (2023), who found $r \approx 0.55$ between CoP ellipse area and BBS, while experimental interventions demonstrated that a reduction in sway corresponded to a clinically meaningful improvement of + 2.3 points on the Mini Balance Evaluation Systems Test (mini-BESTest) (Giardini et al., 2018). Additionally, regarding balance parameters, the study by Hasegawa et al. (2019), reported moderate correlations between the mini-BESTtest and stabilometric indices of CoP sway, with values ranging from r= 0.5 to r = 0.58. Furthermore, the "Sensory Orientation" subscale of the mini-BESTest demonstrated a moderate association with sway variability during quiet standing ($r = 0.45$), whereas the "Reactive Postural Control" subscale exhibited moderate correlations with parameters derived from the "Push and Release test" which evaluates automatic postural responses (r = 0.4-0.55). These findings highlight that, although the mini-BESTest represents a reliable and widely utilized clinical tool for balance assessment, its associations with biomechanical parameters remain moderate. This underscores the value of integrating laboratory-based measurements, which may provide complementary insigths and enrich the clinical evaluation of postural control in PD. Nevertheless, despite the exceptional precision of force platform for recording CoP and GRFs, their

use is severely limited by high cost and space requirements, specialized laboratory facilities and trained personnel for calibration and operation are mandatory. Additionally, their limited portability confines measurements to brief trials (10-40 seconds) and precludes assessment in real – world settings (Merlo et al., 2025).

Accordingly, the findings indicate that in the early stages of PD (H&Y 1-2), where functional scales rapidly exhibit ceiling effects, CoP indices obtained through force platforms (Bao et al., 2023; Taghizadeh et al., 2018) capture subtle balance deviations. In intermediate stages (H&Y 2-3), the mini-BESTest, in conjunction with stabilometric indices of CoP displacement, demonstrates moderate yet clinically meaningful associations (Hasegawa et al., 2019). In advance stages (H&Y 3-4), increased postural instability is substantiated by CoP parameters that are directly linked to a heightened risk of falls (Kamieniarz et al., 2018).

High-precision and objective gait assessment versus clinical tests

Gait in PD is characterized by bradykinesia, manifesting as reduced walking speed, shorter step length, prolonged double-support time, and difficulty with gait initiation/termination and dual-task performance (Zhang et al., 2024). In routine clinical practice, gait is quantitatively assessed primarily via timed speed tests (e.g. the 10-Meter Walk Test) and functional gait scales (e.g. the Tinetti gait score), which nonetheless fail to yield detailed quantitative indices of the kinematic and postural control impairments that objective assessment methods can reveal. (De Pasquale et al., 2025).

Specifically, a central question is whether objective gait measurements reflect overall motor severity in PD as captured by the UPDRS and the Hoehn & Yahr stage. In the study by Curtze et al. (2016), 104 patients with mild-to-moderate functional impairment (stage 2-4), as classified by the H&Y, were evaluated on 34 gait and balance parameters using IMUs, and correlations were examined: (a) with subjective motor function (PDQ-39 Mobility, ABC scale) and (b) with clinical severity (UPDRS, Hoehn & Yahr). In the off-medication state, gait speed, turning angular velocity, and stride length exhibited the strongest correlations with UPDRS ($r \approx 0.5$) and with perceived difficulty ($r \approx 0.4–0.5$), whereas CoP variability showed a weaker association. By contrast, in the on-medication state these correlations were attenuated, highlighting the importance of the off-medication assessment to reveal "hidden" deficits. Moreover, Carlson-Kuhta et al. (2019) confirmed an inverse relationship ($r \approx -0.51$) (Beck et al., 2018) between turning angular velocity and stride length with UPDRS scores, while the SPARC index (Beck et al., 2018) offers a quantitative estimate of gait smoothness that corresponds to disease severity.

Several studies have implemented IMUs during Timed Up and Go (TUG) test, placing a sensor at the lumbosacral junction to capture metrics such as sit-to-stand velocity, acceleration at gait initiation, peak turning angular velocity, and double-support time, thereby enhancing the TUG's sensitivity to motor disturbances in PD (Zhang et al., 2024; Di Lazzaro et al.,2020; Bernad-Elazari et al.,2016). Furthermore, Wang et al. (2024) deployed ten body-worn sensors throughout the TUG to differentiate PD subtypes (tremor-dominant versus bradykinetic/instability-dominant) and to explore their relationship with clinical severity (UPDRS). They demonstrated that composite digital markers, such as peak turning angular velocity, can reliably distinguish the instability-dominant subtype from healthy controls at an early stage, while trunk-related measures, such as maximum sit-to-stand velocity, show an inverse correlation with disease severity. These findings underscore the capacity of wearable sensor technology to reveal subclinical gait alterations that conventional clinical tools fail to detect. Moreover, in the study by Hasegawa et al. (2019), which included patients with PD following at least 12 hours of medication withdrawal, measurements obtained via IMUs placed at multiple anatomical sites revealed moderate to strong correlations between the "Dynamic Gait" sub-

scale of the mini-BESTest and kinematic gait parameters. Specifically, strong positive associations were observed with gait speed (r = 0.77) and stride length (r = 0.61), along with a moderate negative correlation with double support time (r = -0.55), indicating that the scale captures essential kinematic aspects of gait. Nevertheless, the overall findings underscore the complementary value of IMUs in detecting subclinical alterations in gait that remain undetected through conventional assessment tools.

However, although IMUs permit monitoring in natural environments through repeated or continuous measurements, they have certain limitations: (a) integrated accelerations accumulate, leading to positional drift unless regular re-calibration is performed, (b) incorrect sensor placement or tilt on the body substantially alters the recorded data, (c) algorithms designed to distinguish phenomena such as freezing of gait (FOG) require training on a broad patient cohort, otherwise yielding increased false positive and false negative rates and (d) while more affordable than laboratory systems, some of the most reliable IMU models are not universally available in all clinical settings (Prisco et al., 2024).

Additionally, in PD the Functional Gait Assessment (FGA) score has been shown to correlate closely with objective gait parameters measured via three-dimensional motion capture systems, the "gold standard" for kinematic gait analysis (albeit with limitations similar to those of force platforms) (Ehrhardt et al., 2020). Specifically, there is a strong positive correlation between gait speed and FGA score ($r \approx 0.77$), as well as moderate positive correlations with step length and cadence ($r \approx 0.54–0.59$) (Eldeeb & Abdelraheem, 2021). Conversely, temporal parameters, such as step duration and double-support time, are significantly and negatively correlated with FGA ($r \approx –0.59$ έως $–0.65$, $p < 0.01$), indicating that lower FGA scores are associated with slower, more prolonged gait patterns (Álvarez et al., 2020). Meanwhile, certain spatial parameters, such as step width, do not show a significant relationship with FGA scores (Pistacchi et al., 2017). The diagnostic utility of the FGA is further underscored by its ability to predict falls: and FGA score of ≤18 predicted the occurrence of falls within six months with 81% sensitivity and 80% specificity (Marques et al., 2021). Collectively, these results validate the FGA as a functional gait assessment tool in PD, mirroring indices of motor severity and fall risk.

Accordingly, the findings suggest that in the early stages of PD (H&Y 1-2), IMUs and 3D motion capture systems can detect subclinical gait alterations that are not readily captured by functional assessment scales (Zhang et al., 2024; McGuirk et al., 2022). In intermediate stages (H&Y 2-3), the use of IMUs during the execution of the TUG highlights moderate-to-strong associations with subscales of the mini-BESTest (Hasegawa et al., 2019; Curtze et al., 2016). In advanced stages (H&Y 3-4), the FGA (Marques et al., 2021), together with data derived from plantar pressure systems and force platforms (Merlo et al. 2025), is closely linked to the increased risk of falls, thereby constituting valuable tools for prognosis and rehabilitation.

DISCUSSION

The present review demonstrates that contrasting objective and clinical methods for assessing balance and gait in patients with Parkinson's disease (PD) reveals distinct strengths and limitations in both approaches.

Many conventional balance assessment scales (e.g. the BBS and the Tinetti scale) were originally developed for older adults at risk of falls and exhibit ceiling effects in early Parkinson's stages (H&Y 1–2) (Krzysztoń et al., 2018) and floor effects in advanced stages (H&Y 4–5) (Schlenstedt et al., 2016), thereby limiting their ability to detect deterioration or improvement beyond certain thresholds (Park et al., 2018). Moreover, their cumulative scoring does not distinguish discrete functional components (dynamic stability, reactive balance, foot-placement accuracy) and is influenced by the examiner's subjective judgment as well as by patient cooperation, fatigue, or stress at the time of testing

(e.g. off-medication versus on-medication state) (Bao et al., 2023). In contrast, objective methods such as stabilography (kinetic recordings of center of pressure displacements) and three-dimensional motion capture systems deliver continuous or repeated high-resolution measurements (millimeters, degrees, milliseconds), capturing both the direction of sway (anteroposterior versus mediolateral) and the frequency spectrum of postural oscillations (high-frequency reflexive corrections versus low-frequency exploratory adjustments), detecting infrequent events (e.g. FOG), and enabling targeted intervention planning (De Pasquale et al., 2025). Among functional clinical tools, the mini-BESTest stands out for assessing a broader range of balance domains, exhibiting reduced ceiling/floor effects and greater sensitivity to clinical change (Krzysztoń et al., 2018). Likewise, the FGA has proven valuable for early fall prediction in PD, with scores ≤ 18 forecasting falls within six months with high sensitivity and specificity (Marques et al., 2021).

Therefore, depending on the severity of motor impairment, it appears that:

(a) In early stages (H&Y 1-2), where functional scales rapidly exhibit ceiling effects, the use of IMUs or three-dimensional motion capture systems enables the detection of subtle gait and balance deviations (Zhang et al., 2024; McGuirk et al., 2022).

(b) In intermediate stages (H&Y 2-3), the mini-BESTest combined with IMUs during the TUG offers a more comprehensive assessment framework, identifying deficits that the functional scale alone might not capture (Curtze et al., 2016; Mancini et al., 2025).

(c) In advanced stages (H&Y 3-4), where fall risk is high, force platforms and pedobarographic systems provide precise fall-risk assessment and facilitate the design of specialized rehabilitation programs (Kamieniarz et al., 2018).

Limitations and future directions

Cost and availability: Many clinical settings, particularly those outside major academic centers, lack the resources to implement large laboratory systems. Further investigation into the cost-effectiveness of IMU devices relative to improvements in fall-prediction accuracy is needed (Mancini et al., 2025; Prisco et al., 2024).

Protocol standardization: The absence of universally accepted protocols (e.g. number and placement of sensors, standardized walking speeds) impedes the comparability of gait data across different cohorts and research centers (Merlo et al., 2025). Development of international guidelines for the collection and analysis of IMU-derived gait metrics is therefore essential.

Large-scale, long-term studies: Most existing investigations involve small cohorts (< 50 patients) and relatively brief follow-up periods (6-12 months). To validate digital gait and balance markers as prognostic indicators of disease progression, prospective studies with larger samples and surveillance exceeding two years are warranted (Curtze et al., 2016; Mancini et al., 2025).

Patient acceptance and adherence: Deploying wearable sensors in everyday settings necessitates comprehensive patient training and ongoing evaluation of device comfort. Without sufficient user compliance, the quality and reliability of the collected data may be compromised (Prisco et al., 2024).

CONCLUSIONS

The incorporation of objective indicators into the assessment process, alongside traditional clinical methods, provides a more comprehensive and precise depiction of functional status in patients with PD. The principal challenge is to maintain an optimal balance between cost, accessibility, and measurement accuracy, with an emphasis on developing standardized protocols that yield comparable and clinically actionable outcomes.

Declarations

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The Effect of Physical Activity/Exercise on Bone Metabolism in Children and Adolescents

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ABSTRACT

Purpose: This review examines the effects of physical activity and exercise on bone mass/density [Bone Mineral Density (BMD), Bone Mineral Content (BMC)], bone size, and fracture risk in children and adolescents of both sexes.

Methods: This is a narrative (non-systematic) review. A literature search was conducted in the PubMed database up to August 2025. Studies evaluating the impact of exercise programs on BMD, BMC, bone size, and fracture risk during childhood, adolescence, and later in adulthood were included.

Results: Most studies reported a significant increase in BMC, aBMD, and bone size in children and adolescents who participated in exercise programs compared with control groups, with the pooled evidence indicating that these effects are concentrated in prepubertal children. Furthermore, regular physical activity during childhood and adolescence was associated with a reduced risk of fractures not only during these life stages but also later in adulthood. A transient increase in fracture risk during the first year of intervention has been reported, and some trials found no effect on fracture incidence.

Conclusions: Physical activity during childhood and adolescence enhances bone mass and bone size and is associated with a lower risk of fractures across the lifespan. These findings support the integration of exercise programs for children and adolescents as a preventive strategy for fractures and for improving bone health.

Key words: physical activity, exercise, bone mass, bone density, bone metabolism, fractures, children, adolescents

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INTRODUCTION

The present review investigates the effects of physical activity and exercise on bone metabolism and fracture risk in children and adolescents. In particular, it focuses on changes in bone mass and density [Bone Mineral Density (BMD), Bone Mineral Content (BMC)], bone size, as well as fracture risk during childhood and adolescence and later in adult life. The analysis is based on data retrieved from the PubMed database up to August 2025 and includes studies examining the effects of physical exercise in children and adolescents of both sexes, before and after the onset of puberty.

Effects of physical activity/exercise on bone metabolism

Exercise influences the function of osteocytes, as well as the osteoblastic and osteoclastic cell lineages that regulate bone modelling and remodelling, that is, the process of bone turnover (1,2). It has a beneficial effect on collagen synthesis and on osteoblast proliferation (cells responsible for bone formation), thereby positively affecting

increases in bone mass and density, in combination with increases in bone size and a reduction in fracture risk (2). Conversely, low levels or the absence of physical activity/exercise are associated with enhanced osteoclastic activity (cells responsible for bone resorption) and inhibition of osteoblastic processes (4), resulting in bone mass loss and an increased risk of fractures. Specifically, physical exercise affects:

Vitamin D levels, by increasing the synthesis of its active metabolite 1,25(OH)-D. The implementation of resistance exercise programmes leads to a significant increase in serum 25(OH)D levels (although not consistently across all studies), by upregulating the expression of the enzyme 1α-hydroxylase, which catalyses the conversion of serum 25(OH)D into the active metabolite 1,25(OH) D of vitamin D, as well as increasing the number of vitamin D receptors in various tissues, including bone tissue (3).It should, however, be noted that athletes participating in several sports (e.g. running, weightlifting, dance, taekwondo, football, hockey, among others) often exhibit lower vitamin D levels (deficiency or insufficiency) compared with individuals of the same sex, skin colour, and age. This finding has been associated with insufficient skin exposure to sunlight, inadequate dietary intake, and other related factors (4,5).

Parathyroid hormone secretion, with an increase in its levels. It has been reported that prolonged, high-intensity exercise leads to increased parathyroid hormone (PTH) secretion, which in turn is associated with anabolic effects on bone. This response is related to the enhanced expression of the enzyme 1α-hydroxylase, which catalyses the conversion of serum 25(OH)D to the active vitamin D metabolite 1,25(OH) D that participates in bone formation, in combination with PTH action via parathyroid hormone-1 receptors [parathyroid hormone 1 receptor (PTH1R)] on osteoblasts. Activation of these receptors enhances osteoblastic activity, ultimately resulting in increased bone formation (6).Conversely, it has also been reported that exercise is associated with an increased rate of bone formation combined with reduced bone resorption (i.e. enhanced osteoblastic activity together with decreased osteoclastic activity), despite a significant reduction in serum parathyroid hormone levels (7).

On the secretion of pro-inflammatory cytokines, which promote inflammation and enhance osteolysis [such as interleukin-1, interleukin-6, among others, as well as tumor necrosis factor-α (TNF-α)], physical exercise exerts an inhibitory effect on their secretion, thereby protecting against bone mass loss (2).

On the RANKL (receptor activator of nuclear factor κB ligand)/RANK (receptor activator of nuclear factor κB)/OPG (osteoprotegerin) system, exercise leads to a reduction in RANKL levels in combination with an increase in osteoprotegerin levels, thereby attenuating the process of osteolysis. This occurs through a decreased rate of differentiation of osteoclast precursors into mature osteoclasts, together with reduced osteoclast activity, ultimately limiting bone mass loss (1).

On the hypothalamic–pituitary–adrenal axis as well as the hypothalamic–pituitary–gonadal axis, exercise enhances the secretion of hormones that exert beneficial effects on the differentiation of osteoblast progenitor cells into mature osteoblasts, leading to an increased rate of bone formation (2).

On the expression of myokines (produced by skeletal muscle fibres during contraction) that exert effects on bone tissue, exercise has been associated with increases in myokines that positively influence bone metabolism—such as reduced myostatin levels and increased levels of irisin, apelin-13, interleukin-6, and insulin-like growth factor—while it may also be associated with reductions in bone mass in specific contexts, for example through increased secretion of interleukin-15 (8–17).

From the above, it emerges that physical activities and exercise (both aerobic and anaerobic) exert inhibitory effects on bone resorption (osteolysis), by suppressing the differentiation of osteoclast precursors into mature osteoclasts and inhibiting their activity, while simultaneously ex-

erting stimulatory effects on bone formation through enhanced osteoblast function and survival, leading to increased bone mass. Conversely, low levels or the absence of physical activity may result in reduced mechanical loading on bone tissue, which is associated with enhanced osteoclastic activity and inhibition of osteoblastic processes, ultimately leading to a reduction in bone mass.

A substantial number of publications (including reviews, meta-analyses, and original studies) have reported greater increases in bone mass and density [Bone Mineral Density (BMD), Bone Mineral Content (BMC)] as well as bone size in children and adolescents of both sexes, before or after the onset of puberty, who received education on physical activity importance or participated in structured exercise programmes, compared with control groups. Importantly, no adverse events related to these programmes were reported (18–35). Not all reports within this body of literature are concordant: one prospective study found that vigorous physical activity was associated with an increased fracture risk in children irrespective of bone mass (27). In these studies, increases in bone mineral density were primarily assessed using dual-energy X-ray absorptiometry (DXA), at the whole-body level, in the lumbar spine (L2–L4), at the hip (predominantly at the femoral neck), and at other skeletal sites such as the forearm and tibia. In many cases, increases in bone mineral density were accompanied by increases in bone size.

Effects of physical activity/exercise on bone mass/density and bone size

Specker B. et al. (2015), in their systematic review and meta-analysis of 22 studies involving children and adolescents aged 3–18 years, reported individual study sample sizes ranging from 16 to 410 participants, examined the effects of physical exercise programmes of 3–36 months' duration. They reported greater increases in bone mineral content (BMC) and areal bone mineral density (aBMD), with no between-group difference in bone area, in children and adolescents who participated in exercise compared with control groups. Mean between-group differences in BMC percent change were 1.7% at the lumbar spine (95% CI 0.4–3.1; p = 0.01), 1.5% at the femoral neck (95% CI 0.5–2.5; p = 0.003) and 0.8% at the whole body (95% CI 0.3–1.3; p = 0.003); the corresponding differences in aBMD percent change were 1.2% at the lumbar spine (95% CI 0.6–1.8) and 0.6% at the femoral neck (95% CI 0.2–1.1; p = 0.006). The authors concluded that exercise produced a 0.6%–1.7% greater annual gain in bone accrual, with effects predominantly among prepubertal children, and that heterogeneity in spine aBMD was reduced when calcium intake and intervention length were entered as covariates (20).

Löfgren B. et al. (2011) studied 446 boys and 362 girls aged 7–9 years who participated in a physical activity education programme lasting 40 minutes per day for 3 years, and compared them with 807 boys and 780 girls of similar age who served as controls and followed the standard Swedish curriculum of 60 minutes of physical activity per week. In a subsample of the intervention group (76 boys and 48 girls) and the control group (55 boys and 44 girls), bone mineral density at the lumbar spine and hip was assessed using DXA. All children were followed prospectively for 36 months. Compared with the control group, no significant differences were observed in fracture incidence [mean rate ratio (RR) = 1.08; 95% CI: 0.71–1.62] or in absolute bone mineral density measurements. However, the mean annual increase in lumbar spine bone mineral density was significantly higher in the intervention group, by 0.9 SD in girls and 0.8 SD in boys (both p < 0.001), compared with controls (21).

MacKelvie K.J. et al. (2003) studied 32 girls who participated in a jumping exercise program for 10 minutes, three times per week, and 43 age-matched girls who served as a control group. Bone mineral content (BMC) was measured using DXA at baseline and 20 months later for the whole body, the lumbar spine, and the proximal femur. The authors found a greater increase in BMC in the exercise group compared with the

control group at the lumbar spine (41.7% vs 38.0%) and at the femoral neck (24.8% vs 20.2%), both significant on analysis of covariance ($p < 0.05$) (22). These figures are gains in bone mineral content, not in bone mineral density.

Linden C. et al. (2006) studied 49 normally developing girls aged 7–9 years who participated in a school-based physical activity program lasting 40 minutes per day (200 minutes per week) and 50 age- and development-matched girls who served as a control group and followed the standard school physical activity curriculum in Sweden (60 minutes per week). All participants were premenarcheal.

Bone parameters were assessed using dual-energy X-ray absorptiometry (DXA), including bone mineral content (BMC, g) and areal bone mineral density (aBMD, g/cm^2). Measurements were performed for the total body (TB), the lumbar spine (L2–L4 and L3), the femoral neck, and the tibia. In addition, volumetric bone mineral density (vBMD, g/cm^3) and bone size were assessed at the femoral neck and L3. Compared with the control group, the intervention group demonstrated a greater annual increase in BMC at L2–L4 (mean difference 3.8 percentage points; $p = 0.007$) and L3 (mean difference 7.2 percentage points; $p < 0.001$); the difference at the tibia did not reach significance (mean difference 3 percentage points; $p = 0.07$). This was accompanied by a significantly greater annual increase in aBMD at the total body (mean difference 0.6 percentage points; $p = 0.006$), L2–L4 (1.2 percentage points; $p = 0.02$), L3 (1.6 percentage points; $p = 0.006$), and the tibia (1.2 percentage points; $p = 0.007$). Furthermore, greater increases in bone size were observed in the intervention group at L3 (mean difference 1.8 percentage points; $p < 0.001$) and at the femoral neck (0.3 percentage points; $p = 0.02$), along with a greater increase in volumetric bone mineral density [mean difference: 0.24 SD; $p = 0.002$] (28).

Bradney M. et al. (1998) studied 20 boys (mean age 10.4 years; range 8.4–11.8 years) who participated in a moderate-intensity weight-bearing exercise training program (30 minutes, three times per week for 8 months) and compared them with 20 age-matched boys who served as a control group. Bone mineral content and bone size were assessed using dual-energy X-ray absorptiometry (DXA) at baseline and at the end of the intervention. The authors observed a significantly greater (approximately twofold) increase in bone mineral content in the exercise group compared with controls at the total body, lumbar spine, and lower extremities ($p < 0.05$). In addition, cortical bone thickness at the femoral diaphysis increased significantly ($p < 0.05$), accompanied by a significant increase in volumetric bone mineral density (vBMD; $p < 0.05$) (30).

Fuchs R.K. et al. (2001) studied 89 prepubertal children aged 5.9–9.8 years who were randomly assigned to either a jumping exercise group (25 boys and 20 girls) or a control group (26 boys and 18 girls) that participated in low-intensity, non–weight-bearing stretching exercises for 7 months. Bone mineral content was assessed using dual-energy X-ray absorptiometry (DXA) at baseline and at the end of the intervention at the lumbar spine and the femoral neck.

Using analysis of covariance (ANCOVA), the authors found a greater increase in bone mass in the exercise group compared with the control group (4.5% vs 3.1% overall), with a trend toward significance at the femoral neck ($p = 0.08$) [the source reports significant gains at both the spine and the femoral neck – figures to be re-checked]. No adverse events related to the exercise program were reported (31).

Valdimarsson et al. (2006) studied 53 girls aged 7–9 years who participated in a school-based exercise program lasting 40 minutes per day and compared them with 50 healthy age-matched girls who followed the standard school physical activity curriculum of 60 minutes per week (control group) for one year. Bone mineral content and bone width were assessed using dual-energy X-ray absorptiometry (DXA) at the lumbar spine, the femoral neck, the tibia, and the total body. The authors reported a significantly greater annual increase in BMC in the intervention group compared with the control group,

amounting to 4.7% at the lumbar spine and 9.5% at L3 (both $p < 0.001$). In addition, the annual increase in bone width was 2.9 percentage points greater in the intervention group than in the control group ($p < 0.001$) (34).

Maintenance of increased bone mass despite reductions in the intensity and frequency of physical activity at later ages

Bass S. et al. (1998) studied 45 premenarcheal girls (mean age 10.4 ± 0.3 years) and 36 retired female gymnasts who had previously participated in regular physical activity, and compared them with 50 women in a control group (mean age 25 ± 0.9 years). Bone mineral density was assessed using dual-energy X-ray absorptiometry (DEXA), including measurements expressed as standard deviations (SD) and Z-scores. Higher bone mineral density was observed in the physically active girls compared with controls, ranging from 0.7 to 1.9 SD ($p < 0.01$), with corresponding Z-scores showing significant correlations ($r = 0.32–0.48$; p values between <0.04 and <0.002). Over a 12-month period, the annual increase in bone mineral density was 30%–85% greater (total body, lumbar spine, and lower extremities) in prepubertal girls engaged in physical activity compared with prepubertal girls in the control group ($p < 0.05$ for all sites). Among the retired gymnasts, greater increases in bone mineral density were also observed compared with women in the control group. Notably, no decline in bone mineral density was detected after retirement (mean 8 ± 1 years since cessation of training, range 1,5-20 years), despite a reduction in the frequency and intensity of physical activity and exercise (29).

Association between increases in bone mineral density and lean body mass in children and adolescents participating in physical exercise programs

McKay H.A. et al. (2000) studied 144 girls from 10 elementary schools who were premenarcheal or in the early postmenarcheal period. Participants were randomly assigned to either an exercise intervention group (n = 63), which primarily involved jumping exercises performed twice weekly, or to a control group (n = 81) that received regular physical activity–related education, for a duration of 8 months. Areal bone mineral density (aBMD) was assessed using dual-energy X-ray absorptiometry (DXA). A significantly greater increase in aBMD was observed in the intervention group compared with the control group at the femoral trochanter (4.4% vs 3.2%; $p < 0.05$). This difference remained significant after adjustment for potential confounders, including dietary calcium intake, baseline aBMD, and changes in height and lean body mass at the end of the study (32).

Similarly, Morris F.L. et al. (1997) investigated 71 premenarcheal girls aged 9–10 years who participated in a high-impact physical exercise program for 10 months (n=38) and compared them with age-matched girls in a control group (n=33). Bone mineral density was measured at the lumbar spine, the hip, and the total body using DXA. Multiple linear regression analysis demonstrated significantly greater increases in bone mineral density in the exercise group compared with controls at all measured sites (lumbar spine: 4.8% vs 1.2%; hip: 12% vs 1.7%; total body: 3.5% vs 1.2%). These increases were associated with a greater increase in lean body mass at the end of the intervention period (33).

Association between the duration of physical activity and annual increases in bone mineral content and vertebral width in children

Lindén C. et al. (2007) studied 81 boys aged 7–9 years who participated in a school-based exercise program lasting 40 minutes per day and compared them with 57 healthy age-matched boys who followed the standard school physical activity curriculum of 60 minutes per week (control group) for one year. Bone mineral content, aBMD and vertebral width were assessed using dual-energy X-ray absorptiometry (DXA) at the lumbar spine, the femoral neck, the tibia, and the total body.

The intervention group demonstrated a sig-

nificantly greater annual increase in BMC at the lumbar spine (mean difference 5.9 percentage points; $p < 0.001$), a greater increase in areal bone mineral density (aBMD) at L3 (mean difference 2.1 percentage points; $p = 0.01$), and a greater increase in vertebral width at L3 (mean difference 2.3 percentage points; $p = 0.001$) compared with the control group.

Overall, exercise duration was positively correlated with greater mean annual increases in bone outcomes at L3, including BMC ($r = 0.26$; $p = 0.003$), L3 aBMD ($r = 0.18$; $p = 0.04$), and vertebral width at L3 ($r = 0.24$; $p = 0.006$) (35).

Reduction in fracture risk in children, adolescents, and adulthood

Participation in physical activity programs during childhood and adolescence has been associated with a reduced risk of fractures during childhood and adolescence, as well as later in young adulthood (25,36–45). Two of these trials, however, reported improved skeletal traits without any accompanying effect on fracture incidence (44,45).

Fritz J. et al. (2016) studied 3,534 children aged 6–8 years who were allocated by school (a prospective controlled, non-randomised design) to either an intervention group (n = 1,339) that participated in moderate-intensity physical activity for 40 minutes per day or a control group (n = 2,195) that followed the standard school physical activity curriculum of 60 minutes per week, over a period of 7 years. In a subsample of 264 children, bone mineral density was assessed using dual-energy X-ray absorptiometry (DEXA). The annual fracture incidence rate ratio (IRR) was lower in the physical activity group compared with the control group ($r = -0.79$, $p = 0.04$), with a marked reduction observed by the seventh year (IRR = 0.52; 95% CI: 0.27–1.01). In addition, a greater increase in lumbar spine bone mineral density was observed in the intervention group compared with the control group (mean difference 0.03 g/cm²) (25). It should be noted, however, that during the initial phase of participation (e.g., the first year), a transient increase in fracture risk compared with control groups may be observed, likely attributable to a higher risk of injuries such as falls (25,36). Subsequently, a progressive annual reduction in fracture risk has been reported (25,36).

Cöster M.E. et al. (2017) analyzed data from 1,339 children who participated in a physical activity program and 2,195 children in a control group (all aged 6–8 years) from five schools in Malmö, Sweden, during the period 1998–2012. The intervention consisted of daily moderate-intensity physical activity for 40 minutes over 8 years. The control group followed the Swedish national physical activity curriculum of 60 minutes per week. Radiographically confirmed fracture risk was assessed using annual fracture incidences and incidence rate ratios (IRRs). During the first year after the start of the intervention, an increased fracture risk was observed in the intervention group compared with controls [IRR = 1.65; 95% CI: 1.05–2.58]. However, in subsequent years, the annual fracture risk decreased by 15.7% per year (95% CI: 5.6%–26.8%) relative to the control group. After 8 years, the intervention group showed a 52% reduction in fracture risk compared with controls [IRR = 0.48; 95% CI: 0.25–0.91] (36). This reduction is likely attributable to a combination of increased bone mineral density [areal bone mineral density (aBMD)] (25,46), enhanced muscle strength (47), and a lower risk of falls/injuries due to improvements in balance and motor control (48).

Notably, reduced fracture risk has also been reported in former athletes (40–43), and the beneficial effects of physical activity are largely maintained over time, although they diminish significantly when exercise is not continued (41,49,50).

Limitations

This is a narrative rather than a systematic review: a single database (PubMed) was searched, no formal inclusion or exclusion criteria were pre-specified, no record counts are reported, and the methodological quality and risk of bias of the included studies were not formally appraised.

Several of the trials cited here (references 21, 25, 28, 34, 35, 36, 44 and 45) originate from the same Malmö Pediatric Osteoporosis Prevention cohort, so the evidence base is less independent than the number of citations suggests. Most interventions were short (7 months to 3 years) relative to the skeletal outcomes of interest, and few reported beyond the end of the intervention. Bone outcomes were assessed almost exclusively by DXA, which yields areal rather than volumetric density and is therefore confounded by the concurrent change in bone size that exercise itself produces; where volumetric density or peripheral quantitative computed tomography data were available they are noted, but such data are sparse. Finally, dietary calcium and vitamin D intake, energy availability and pubertal staging modify the skeletal response to loading and were inconsistently reported across the primary studies.

Practical considerations

The trials summarised here converge on brief, high-impact, weight-bearing loading – typically jumping or circuit activities of 10 to 40 minutes, performed on at least three days per week, integrated into the school curriculum. Effects appear to be site-specific and largest before the onset of puberty. Adequate calcium and vitamin D intake and adequate energy availability should accompany any such programme; in adolescents, and particularly in female athletes, high training loads combined with low energy availability (relative energy deficiency in sport) can reduce rather than increase bone mineral accrual, and this should be screened for.

CONCLUSIONS

Evidence from multiple publications, including reviews, meta-analyses, and original studies, indicates that participation in physical activity or exercise programs leads to greater increases in bone mass/density [Bone Mineral Density (BMD), Bone Mineral Content (BMC)] and bone size in both pre- and postpubertal children and adolescents of both sexes, compared with control groups, without reports of adverse events associated with these programs.

Participation in physical activity during childhood and adolescence has also been associated with a reduced risk of fractures during these periods and later in life. It should be noted, however, that during the initial phase of participation (e.g., the first year), a transient increase in fracture risk may occur compared with control groups, likely due to a higher risk of injuries such as falls.

Furthermore, a positive association has been reported between the duration of physical activity and greater mean annual increases in bone mineral density and bone thickness in children.

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Endothelial progenitor cell mobilization and changes in systematic microcirculation during exercise in patients with chronic heart failure

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ABSTRACT

Purpose: Endothelial progenitor cells (EPCs) consist a cell population that enters the bloodstream from the bone marrow during tissue hypoxia and contributes to angiogenesis. Aerobic exercise induces tissue hypoxia and stimulates the mobilization of progenitor cells facilitating the endothelial function and contributing to the treatment of cardiovascular disease. The aim of this study was to investigate the effect of an aerobic exercise protocol on EPC mobilization and microcirculation in patients with chronic heart failure (CHF) compared to healthy individuals.

Materials and Methods: Patients that participated in the study were referred from the Heart Failure Clinic of the Cardiology Department of "Evangelismos" Hospital. Blood samples were collected before exercise, immediately after exercise, and 40 minutes post-exercise to determine the number of circulating EPCs and hematopoietic progenitor cells (HPCs) using flow cytometry. Changes in microcirculation were assessed using near-infrared spectroscopy before and after exercise.

Results: Sixteen patients (n = 16) with CHF and eleven healthy individuals (n = 11) participated in the study. The continuous aerobic exercise protocol revealed significant effects ($p < 0.05$) on the mobilization of EPCs and HPCs, as well as on endothelial function, in both patients with CHF and healthy individuals.

Conclusion: A single session of aerobic exercise can increase EPCs and HPCs and improve microcirculation in patients with chronic heart failure as well as in healthy individuals. Exercise performed using a low intensity, long-duration protocol stimulates physiological mechanisms that promote progenitor cell mobilization, microcirculatory function, and vascular regeneration.

Keywords: endothelial progenitor cells, hematopoietic progenitor cells, continuous exercise, microcirculation

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INTRODUCTION

Systematic aerobic exercise has anti-atherogenic effects on the vascular system, improves autonomic nervous system function (thereby reducing the risk of arrhythmias), and decreases the risk of myocardial ischemia. Among therapeutic approaches for the management of chronic heart failure (CHF) is the implementation of exercise, both in the form of individual exercise sessions and structured cardiac rehabilitation programs (1). The endothelium exhibits endocrine and paracrine properties and regulates vascular function through vasodilation of smooth muscle cells and its anti-inflammatory actions. Endothelial dysfunction promotes both immediate and long-term effects on the functional capacity of patients

with cardiovascular diseases (2). It is associated with atherosclerosis, thrombosis, and hypertension, which constitute pathological factors contributing to the development of CHF.

Several studies have demonstrated a significant reduction in endothelium -dependent vasodilation in the peripheral arteries of patients with CHF. An important role in improving endothelial function is accomplished by endothelial progenitor cells (EPCs), which, after their release from the bone marrow, contribute to maintaining a vital layer of endothelial cells that promotes angiogenesis. In patients with cardiovascular disease, endothelial ischemia increases circulating levels of endothelial progenitor cells (EPCs) up to 1000-fold, and this increase in their number can be used as a prognostic marker for the assessment of cardiovascular risk (3). In addition, hematopoietic progenitor cells (HPCs), a cellular population related to EPCs, exhibit progenitor-like properties (4), share a common origin with EPCs—the bone marrow angioblast—support the angiogenic process, and facilitate reparative mechanisms in the vascular system.

Following the initial detection of EPCs by Asahara et al. (1997) (5), maximal cardiopulmonary exercise testing (CPET) has been used as an acute stimulus involving intense physical activity to investigate changes in EPC counts. However, although CPET contributes to the diagnosis and evaluation of underlying conditions (6), it is neither recommended nor representative of a true exercise session (7). In patients with cardiovascular disease, the short duration of the test and the inability to achieve high exercise intensity due to symptom limitations appear to be insufficient to induce an increase in EPC numbers. Therefore, it would be important to investigate the EPC response following a prolonged exercise session at different time points in order to accurately determine i) whether EPC numbers increase and ii) the duration for which they remain elevated after exercise.

In contrast, studies have shown that short-duration CPET, even as brief as 10 minutes, can improve microcirculation in healthy individuals. Nevertheless, it is likely that an exercise session of longer duration may induce more pronounced improvements in microcirculation. This was demonstrated in a study in which a 30-minute session of moderate-intensity exercise significantly improved microvascular capillary function (8). Conversely, exercise performed at very high intensity (85% VO max) or of very long duration (90 minutes) did not result in significant improvements in microcirculation in physically active men (9, 10,11). In patients with chronic heart failure (CHF), some studies have suggested that continuous exercise protocols may improve microcirculation by increasing blood flow and oxygen delivery to peripheral tissues (12). However, further studies are required to clarify the effects of exercise on microcirculation in patients with CHF.

As indicated by the aforementioned studies, the exercise stimulus provided by continuous exercise induces increased blood flow and stimulates the release of growth factors and cytokines that can mobilize EPCs from the bone marrow into the circulation. The extent of EPC mobilization appears to depend on exercise-related characteristics, such as exercise duration. However, the evidence supporting the beneficial effects of continuous exercise is primarily derived from studies in healthy individuals and studies including rehabilitation programmes, and data in patients with cardiovascular disease, including those with CHF, are lacking. Moreover, the application of CPET, which represents primarily a diagnostic clinical test rather than a structured exercise session, has yielded inconsistent results in patients with cardiovascular disease. Consequently, the available evidence regarding the effects of a specific exercise session on vascular function and on the mobilization of EPCs and HPCs remains limited. Therefore, the aim of the present study was to investigate the effects of a continuous exercise protocol on the mobilization of EPCs and HPCs and on microcirculatory function in healthy individuals and patients with chronic heart failure.

Methodology

Patients were referred to the research laboratory from the Heart Failure Clinic of the Cardiology Department of "Evangelismos" Hospital. Healthy volunteers of similar age and body mass index also participated.

Inclusion Criteria

Inclusion criteria comprised men and women aged between 18 and 75 years. Patients were required to have stable heart failure with a left ventricular ejection fraction ≤45%. They were receiving stable, optimal medical therapy and were clinically stable, with no hospitalizations during the preceding three months. Neither patients nor healthy participants had taken part in any structured exercise program during the previous six months.

Exclusion Criteria

Exclusion criteria included contraindications to cardiopulmonary exercise testing (according to the American Thoracic Society), as well as unstable angina or recent acute myocardial infarction, and pathological conditions such as cancer, liver disease, or renal disease. Additional exclusion criteria were hypertension, severe vascular disease, severe chronic obstructive pulmonary disease, peripheral arterial disease, and neuromuscular disease. Participants enrolled in the study also had no symptoms indicative of active ischemia**.**

Exercise Protocol

All participants in the study performed an exercise protocol using the continuous method. The protocol began with a 5-minute warm-up and was conducted at a constant intensity of 50% VO_{2peak}, based on the heart rate corresponding to VO_{2peak}. The mean duration of the continuous exercise sessions was 53 minutes for patients with chronic heart failure (CHF) and 62 minutes for healthy participants. The duration of exercise was based on studies investigating the effects of cardiac rehabilitation, which have shown that approximately one hour of continuous exercise promotes the mobilization of progenitor cells during both short-term (13) and long-term (14) rehabilitation programs. However, the effectiveness of continuous exercise during a single exercise session has not yet been investigated. Exercise duration was calculated so that the total workload was equal for all patients and healthy participants, respectively. Basic hemodynamic parameters were recorded three minutes before exercise, during exercise, and for five minutes following the completion of exercise.

Study Sample

The calculation of the appropriate sample size to examine differences before and at two post-exercise time points was based on an effect size of 0.48 reported in the study by Gatta et al. (13). Specifically, with an effect size of 0.48, statistical power of 0.80, and a significance level of $\alpha = 0.05$, the minimum required sample size was calculated to be 14 patients with CHF allocated to the experimental group. Taking into account an estimated dropout rate of 20% and a missing data rate of 7%, the final sample size was set at 16 patients with CHF.

Outcome measures

Participants were familiarized with cycling exercise on an electronically braked cycle ergometer and subsequently underwent maximal CPET in the upright position. They were verbally encouraged to exercise until volitional exhaustion, which was typically defined as maximal lower-limb fatigue or severe dyspnea. Work rate increments were calculated using the equation proposed by Hansen et al. (2004) (15), in order to achieve an optimal test duration of 8–12 minutes, in accordance with the American Thoracic Society guidelines. Prior to each test, the system was calibrated by passing a known volume of air through the pneumotachograph using a 3-L precision syringe. The maneuver was repeated at least three times, and the best of the three flow–volume curves was used for analysis. All metabolic measurements were recorded for two minutes at rest, throughout the incremental exer-

cise phase, and for five minutes during the post-exercise recovery period.

Gas exchange was assessed on a breath-by-breath basis using an online system, while participants breathed through a low-resistance valve with a nose clip in place, using a metabolic cart (Vmax 229; Sensormedics, Yorba Linda, CA). Heart rate was monitored using a 12-lead electrocardiographic recording system (MAX1, Model 2000; Marquette Electronics, Milwaukee, WI). Arterial blood pressure was measured every two minutes. Peak oxygen uptake (VO peak) was determined as the average value obtained during the final 20 seconds of the CPET. Maximal exercise capacity was defined as the highest work rate achieved and maintained at a pedaling cadence of no less than 60 revolutions per minute for at least 20 seconds. Throughout the exercise test, participants inhaled through a mouthpiece connected to a triple-lumen valve and pneumotachograph, while the nose was occluded with a nose clip. Breath-by-breath measurements of oxygen uptake, carbon dioxide production, and airflow were obtained using a dedicated pulmonary and metabolic testing system. Resting oxygen uptake was calculated as the mean VO during the two minutes preceding exercise onset. Peak values of oxygen uptake (VO peak), carbon dioxide production, and respiratory exchange ratio during exercise were calculated as the average of the measurements obtained during the final 20 seconds prior to exercise termination.

CPET results were analyzed and used to individually determine the appropriate exercise intensity and duration for each participant. Measurements of circulating progenitor cells were performed before exercise, immediately after exercise, and 40 minutes post-exercise. Systemic microcirculation was assessed before and after the exercise session.

Blood Sampling and Flow Cytometry

Venous blood samples were obtained from a peripheral vein using an indwelling venous catheter. Blood collection was performed at three time points: 2 minutes before exercise, immediately after exercise, and 40 minutes post-exercise. During sample processing, blood was centrifuged twice at 700 rpm for 20 minutes without braking of the centrifuge. After the second centrifugation, the upper phase of the sample was removed and discarded. The cellular pellet was resuspended, and 2.5 mL were transferred to a separate tube and kept on ice. Simultaneously, 500 µL aliquots of the samples were transferred into sample tubes, and the following monoclonal antibodies were added: 10 µL CD45-PerCP, 5 µL CD133-PE, 3 µL CD34-APC, and 5 µL VEGFR2-PE. Sample processing continued with a third centrifugation at 4 °C at 250 g. All samples were placed in specialized tubes and transferred for analysis using dedicated flow cytometry software.

Boolean gating analysis (16) was applied for data analysis using combinations of specific cell surface markers. Due to the existing inconsistency in the literature regarding the definition and nomenclature of endothelial progenitor cells (EPCs), three different antigen combinations were used for their analysis (17). EPC measurements were based on the surface expression of four antigens—CD34, CD45, CD133 (clusters of differentiation), and KDR+ (kinase insert domain receptor)—and three distinct EPC marker combinations were analyzed. KDR+ represents the extracellular domain of vascular endothelial growth factor receptor-2 (VEGFR2+). The marker combination CD34+/CD45−/CD133+, which defined the EPC_1 population, was considered a general progenitor phenotype due to the expression of early stem cell antigens, but it lacked the endothelial lineage marker VEGFR2+. Depending on the expression of the endothelial antigen and the specific combination of surface markers, the cell populations CD34+/CD133+/KDR+ and CD34+/CD45−/ KDR+ were defined as EPC_2 and EPC_3, respectively.For the assessment of angiogenic progenitor cells (APCs), the marker combination CD34+/CD45−/CD133− was used.

Measurement of Systemic Circulation

Systemic microcirculation was assessed using a vascular occlusion technique for 3 minutes, with simultaneous continuous recording by near-infrared spectroscopy (NIRS) performed 3 minutes before and 3 minutes after exercise. This technique involves placing a small sensor on the skin surface and using near-infrared light to measure tissue oxygenation and blood flow within the microcirculation (18,19).

For the evaluation of microcirculation, the main parameters assessed were: tissue oxygen saturation (StO_2, %); oxygen consumption rate (%/min), calculated from the regression slope of the first minute of StO_2 decline following vascular occlusion; oxygen reoxygenation rate, representing endothelial function (%/s), quantified by the hyperemic response at the thenar eminence after release of vascular occlusion (reflecting endothelial function); and reactive hyperemia, expressed as the percentage change in the signal during arterial occlusion and estimated from vascular reserve.

Statistical Analysis

Study data were expressed as mean ± standard deviation (SD). Normality of data distribution was assessed using the Shapiro–Wilk test. The effects of continuous exercise at the three measurement time points on the mobilization of EPCs and HPCs were evaluated using a two-way repeated-measures analysis of variance (ANOVA) with a 2 × 3 design (protocol × time). The effects of exercise on microcirculation at the two measurement time points were assessed using a two-way repeated-measures ANOVA with a 2 × 2 design (protocol × time). Post hoc multiple comparisons between groups were performed using Sidak's correction. Effect size was calculated using Cohen's *d*, defined as the difference between the means of two groups divided by the pooled standard deviation of the observations (mean difference/SD), and interpreted as small (≥0.2), medium (≥0.5), or large (≥0.8) effects. Statistical significance was accepted at $p \leq 0.05$. All statistical analyses were conducted using SPSS software, version 28 (SPSS Inc., Chicago, IL).

RESULTS

Twenty-three patients with chronic heart failure (CHF) (n = 23) were invited to participate in the study; two did not meet the inclusion criteria, and one patient withdrew prior to the initiation of the experimental procedures. Twenty non-cachectic male outpatients with stable CHF (n = 20) entered the experimental phase, of whom sixteen (n = 16; mean age 49.2 ± 10.7 years; body mass 78.9 ± 18.6 kg; height 175.4 ± 8.6 cm; body mass index [BMI] 27.2 ± 3.1 kg/m²; left ventricular ejection fraction ≤ 45%) completed the continuous exercise protocol. In addition, eleven healthy individuals (n = 11) matched for age and body mass index also participated in the study. All participants were informed about the potential risks and benefits of the study and provided written informed consent in accordance with the Declaration of Helsinki for research involving human subjects. Baseline characteristics of all participants and clinical characteristics of the patients are presented in Table 1.

Mobilization of Endothelial and Hematopoietic Progenitor Cells

Based on the combinations of surface markers used for the identification of progenitor cells, statistical analysis revealed significant effects of continuous exercise on endothelial progenitor cells (EPCs) and hematopoietic progenitor cells (HPCs) immediately after exercise and 40 minutes post-exercise ($p < 0.05$) (Figure 1) in patients with CHF. In healthy participants, EPC_1, EPC_3 and HPCs increased both immediately after exercise and 40 minutes post-exercise ($p < 0.05$), whereas no changes were observed in EPC_2 at any time point following exercise ($p > 0.05$) (Figure 2) (Table 2).

Table 1. Descriptive characteristics of patients with chronic heart failure and healthy participants

	CHF (n = 16)	Healthy (n = 11)
Anthropometry (mean ± SD)		
Age (years)	*46.4 ± 8.6*	*43.4 ± 6.8*
BMI (Kg/m2)	*26.4 ± 3.3*	*26.3 ± 3.3*
Body Mass (Kg)	*81.6 ± 17.9*	71.7 ± 7.6
Body Height (cm)	176.3 ± 8.8	169.2 ± 6.4
VO_{2peak} and KE (mean ± SD)		
VO_{2peak} (ml/kg/min)	15.3 ± 2.4	
KE%	33.2 ± 4.0	
Heart Failure Characteristics [No (%)]		
NYHA Class II	10 (64)	
NYHA Class III	6 (36)	
Non-ischemic	10 (64)	
Ischemic	6 (36)	
Arterial Hypertension	4 (38)	
Diabetes	4 (38)	
Dyslipidemia	2 (11)	
Smoking	—	
Medical Treatment [No (%)]		
B-blockers	11 (68)	
ACE inhibitors	10 (63)	
Nitrates	4 (25)	
Statins	7 (43)	
Anti-arrhythmics	8 (51)	
Anti-coagulants	3 (19)	
Anti-platelets	4 (25)	

CHF, chronic heart failure; LVEF, left ventricular ejection fraction; SD, standard deviation; ACE, angiotensin-converting enzyme; BMI, body mass index; NYHA, New Heart Association

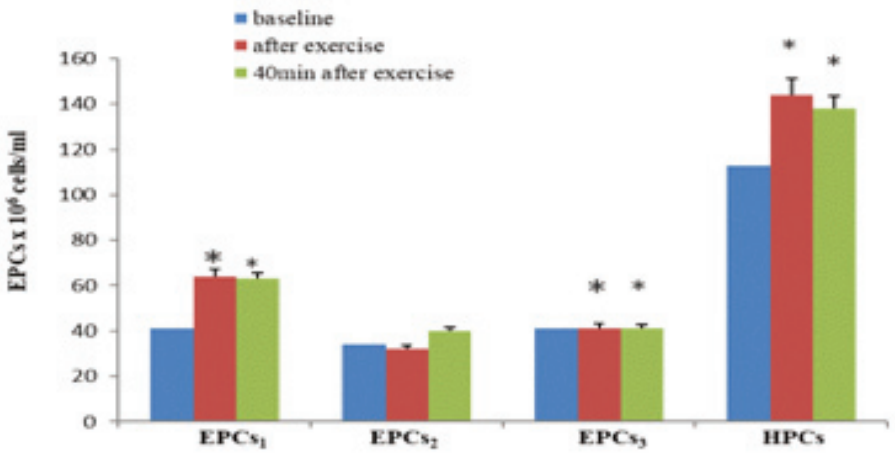

Figure 1. Mobilization of endothelial and hematopoietic progenitor cells in healthy participants EPCs: endothelial progenitor cells, HPCs: hematopoietic progenitor cells

Table 2. Mobilization of endothelial and hematopoietic progenitor cells in patients with chronic heart failure (n = 16) and healthy participants (n = 11)

Continuous exercise	Baseline	After exercise		40 min after exercise	
	Cells•10⁶ enucleated cells	Cells•10⁶ enucleated cells	Effect Size	Cells•10⁶ enucleated cells	Effect Size
Endothelial Progenitor Cells (EPCs) identified by different markers EPCs1 markers: CD34+/CD45-/CD133+					
CHF	19.7 ± 12.2	48.6 ± 34.3[b]	0.87	45.5 ± 41.8[b]	0.79
Healthy	41.5 ± 38.3	64.3.2 ± 52.8[b]	0.71	63.5 ± 51.2[b]	0.82
EPCs2 markers: CD34+/CD133+/VEGFR2+					
CHF	13.1 ± 14.2	16.7 ± 17.4	0.26	15.3 ± 16.1	0.25
Healthy	34.2 ± 26.3	32.9 ± 21.2[b]	0.33	3 9.8 ± 30.2	0.38
EPCs3 markers: CD34+/CD45-/VEGFR2+					
CHF	23.4 ± 26.7	42.3 ± 47.6	0.39	38.4 ± 31.2	0.57
Healthy	41.7 ± 25.2	41.4 ± 33.7	0.19	40.2 ± 28.1	0.23
Hematopoietic Progenitor Cells (HPCs) HPCs markers: CD34+/CD45-/CD133-					
CHF	89.4 ± 49.3	127.5 ± 61.0[a]	0.68	122.9 ± 81.3	0.49
Healthy	113.4 ± 72.6	144.9 ± 78.1	0.89	138.3 ± 86.7[a]	0.80

CHF: chronic heart failure; EPC: endothelial progenitor cells; HPC: hematopoietic progenitor cells; VEGF: vascular endothelial growth factor receptor-2ap ≤ 0.01and bp ≤ 0.05, ± SD: standard deviation

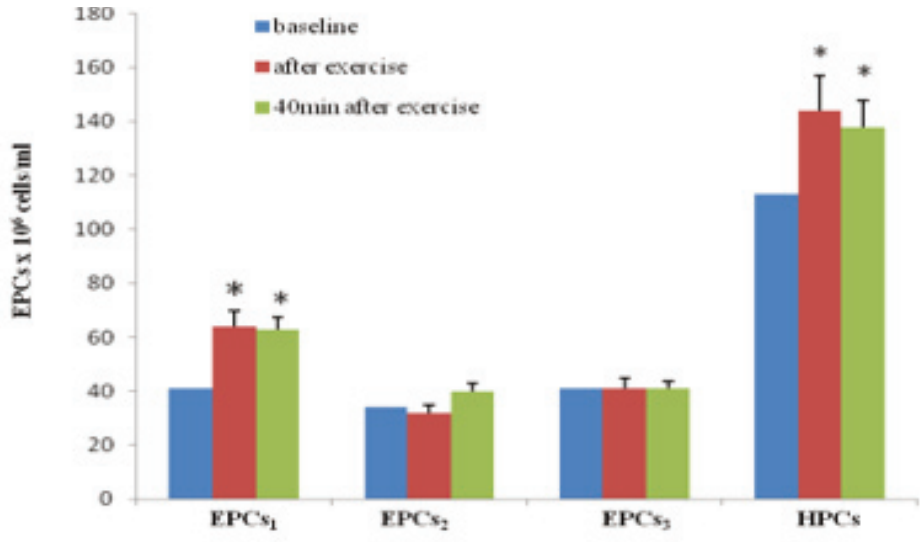

Figure 2. Mobilization of endothelial and hematopoietic progenitor cells in healthy participants EPCs: endothelial progenitor cells, HPCs: hematopoietic progenitor cells

Table 3. Changes in microcirculatory parameters monitored by near-infrared spectroscopy and a vascular occlusion test in CHF patients (n = 16) and healthy individuals (n = 11)

Continuous exercise	Baseline	After exercise	Effect size
Tissue oxygenation (StO2)			
CHF	77.7 ± 3.8	79.2 ± 4.1	0.17
Healthy individyals	81.3 ± 3.1	82.1 ± 3.7	0.14
StO2 downslope (%/minute)			
CHF	10.6 ± 2.2	12.5 ± 1.9[a]	0.69
Healthy individyals	12.3 ± 1.8	12.0 ± 1.8	0.74
StO2 upslope StO_2 (%/second)			
CHF	2.4 ± 0.7	3.1 ± 0.9[a]	0.66
Healthy individyals	3.7 ± 0.6	4.4 ± 0.6[a]	0.78
Time to baseline (seconds)			
CHF	113.2 ± 28.7	103.6 ± 21.3[b]	0.38
Healthy individyals	104.3 ± 22.6	92.4 ± 16.9	0.27

CHF, chronic heart failure; StO2, tissue oxygen saturation;
ap ≤ 0.01and bp ≤ 0.05 compared to baseline. values are expressed as mean ± SD, standard deviation

Systemic Microcirculation

Regarding the effects of continuous exercise on microcirculation, the results demonstrated significant improvements in all four systemic microcirculatory parameters in patients with CHF. Specifically, tissue oxygen saturation, oxygen consumption rate, and the reoxygenation rate following release of vascular occlusion increased significantly after exercise ($p < 0.05$). Recovery time to baseline was also significantly reduced after exercise ($p = 0.05$), concomitantly improving reactive hyperemia (Table 3). In healthy participants, improvements were observed in parameters related to endothelial function, namely the reoxygenation rate after release of vascular occlusion and reactive hyperemia. No changes were detected in tissue oxygen saturation or oxygen consumption rate.

DISCUSSION

The findings of the present study indicate that a single session of continuous, moderate-intensity, long-duration exercise promotes progenitor cell mobilization and improves systemic microcirculation in patients with CHF. In contrast, in healthy participants, although continuous exercise did not induce changes in the number of EPCs overall (with the exception of EPC_1 and HPCs immediately and 40 minutes post-exercise), it did elicit changes in systemic microcirculatory parameters that are indicative of improved endothelial function.

Recent studies have demonstrated that a continuous exercise protocol can increase both the number and activity of EPCs, highlighting the beneficial effects of exercise on endothelial function in healthy individuals. Moderate-intensity aerobic exercise (60–75% HRmax, ~50–68% VO_{2max}) performed for 30–60 minutes leads to the mobilization of circulating EPCs. However, running at a similar relative intensity (~68% VO_{2max}) but of shorter duration (10 minutes) did not induce EPC mobilization (20). In trained athletes, 240 minutes of cycling at approximately

50% VO_{2max} resulted in markedly elevated circulating EPC levels (21). It should be noted that significant mobilization was also observed following a very short exercise session (5 minutes) performed at substantially higher intensity (101 ± 5% HR_max, ~100% VO_{2max}). Conversely, two marathon race studies (~4 hours) reported conflicting results. In the first study, involving nine athletes who completed the marathon in 191 ± 26 minutes, EPC counts were duplicated (22). In contrast, a second study with a considerably larger sample (68 marathon runners) who completed the race in a mean time of 240 minutes showed no statistically significant change in EPC numbers (23). Finally, in ultradistance runners (246 km, with mean running times of 32 h 8 min and 30 h 2 min, respectively), EPC release from the bone marrow was observed as a response to increased nitric oxide bioavailability and tissue hypoxia (24).

Effect of the continuous exercise protocol

In the present study, the increase in EPC levels was associated with a concomitant improvement in endothelial reactivity. The available evidence regarding the effects of continuous exercise during interventional rehabilitation programs on EPC mobilization in patients with cardiovascular disease is limited and inconsistent. Moreover, these studies were not conducted using a single, isolated exercise bout. Continuous exercise as a stimulus for EPC mobilization has been shown to be effective in patients with myocardial ischemia, coronary artery disease, and CHF. Previous studies have reported that exercise sessions of varying duration (20–40 minutes) and intensity (50–75% VO_{2peak}), performed as part of rehabilitation programs, promote EPC mobilization in patients with CHF and are accompanied by parallel improvements in vascular function. However, the effect of a continuous exercise protocol per se in patients with cardiovascular disease, and particularly in those with CHF, had not been clearly established. In the present protocol, the prolonged exercise duration appears to have played a key role by compensating for the moderate exercise intensity, thereby providing a sufficient stimulus to activate progenitor cell mobilization mechanisms and improve endothelial function.

Previous studies have demonstrated the release of EPCs following continuous exercise. Laufs et al. (2005) (20) applied three different exercise protocols in healthy participants and showed that exercise performed at high (80% VO_{2max}) or moderate intensity (68% VO max) with a moderate duration (30 minutes) increased EPC numbers. In contrast, continuous exercise at moderate intensity (68% VO_{2max}) but of short duration (10 min) did not induce changes in EPC counts. The findings of the present study are in agreement with other reports indicating that at least 30–60 minutes of exercise are required to promote EPC mobilization and induce favorable adaptations in vascular function in patients with cardiovascular disease. In the present study, moderate exercise intensity (50% of VO-peak), which can be sustained for a prolonged period, appeared to influence the physiological mechanisms responsible for exercise-induced mobilization and activation of EPCs and HPCs. These molecular mechanisms include increased nitric oxide bioavailability and its antioxidant effects, upregulated expression of matrix metalloproteinase-9, shear stress, and the activation of cytokines and/or chemokines (25-27).

Exercise duration during continuous exercise protocols appears to be a critical factor for increasing EPC numbers in healthy individuals. Studies have shown that longer exercise duration is associated with greater increases in circulating EPCs. For example, one study reported that a 90-minute session performed at constant intensity resulted in a significantly greater increase in EPCs compared with a 30-minute cycling session (28). Similarly, another study demonstrated that a 2-hour running session led to a greater increase in EPCs than a 1-hour running session (29). In the present study, an exercise duration of approximately 1 hour did not appear to be sufficient to stimulate EPC mobilization. In healthy participants, high baseline levels of progenitor cells were observed prior to exercise, and it is possible

that the stimulus of continuous exercise at constant intensity and prolonged duration was insufficient to further increase their numbers or to activate the mechanisms responsible for EPC and HPC release into the circulation.

The prolonged duration of exercise appears to have been a key factor underlying the observed changes in systemic circulation, with improvements noted in patients with chronic heart failure (CHF), while in healthy participants, parameters of microvascular reactivity associated with endothelial function were enhanced. Our findings are consistent with previous studies that employed long-duration exercise to improve vascular function. This study supports prior evidence indicating that continuous exercise at moderate intensity represents a standard approach for promoting cardiorespiratory endurance and enhancing vascular function (30). Future studies should also investigate whether high-intensity interval training can improve cardiorespiratory fitness, promote endothelial integrity, and reverse cardiovascular risk factors (31).

Limitations

One limitation of our study was the difficulty in recruiting a larger number of patients, which is not always an easy task. Patient recruitment was limited to a single center, the Heart Failure Clinic of Evangelismos Hospital. In addition, our results primarily reflect male patients with chronic heart failure (CHF), as the majority of participants were men. Moreover, a control group was not included. However, intervention trials with control groups in patients for whom exercise constitutes a core therapeutic strategy for symptom management are ethically questionable.

Although studies employing specific markers for the identification of endothelial progenitor cells (EPCs) were included, methodological variability could not be avoided, as the optimal combination of antigens that accurately defines EPCs is still under investigation. Moreover, data obtained from a specific population cannot be automatically generalized to all populations. Therefore, consensus regarding the detection markers for EPCs is necessary.

CONCLUSION

Overall, the study shows that the duration of continuous exercise appears to be an important factor for increasing the number of EPCs and HPCs in patients with CHF. The parallel improvement in systemic microcirculatory parameters related to endothelial function indicates that exercise-induced mobilization of EPCs is an important factor for enhancing vascular function in both patients with CHF and healthy individuals.

Declarations

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